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ing data as they accumulate during a trial. Group sequential methods, based on frequentist analysis, are currently the standard used for recommending early termination of a trial when interim data indicate clear benefit or harm from one of the treatments. However, there is no agreed method of calculating a P value or confidence interval for the treatment effect after the use of a group sequential method.[11] Nor are the methods flexible to the emergence of new external data that might influence early termination.[12] Bayesian methods that express prior scepticism about the existence of benefit from a new treatment seem to carry the same advantages of group sequential methods but also take account of new external data in making the final inference.[12] These methods have been used recently for the design, monitoring, and analysis of several cancer trials sponsored by Britain's Medical Research Council.[13]

Another advantage of Bayesian methods involves the interpretation of multiple hypothesis testing. Clinical trials often address the effect of a treatment in different subgroups of patients. Epidemiological studies are often designed to test hypotheses about a range of putative risk factors for a given disease. Frequentist methods aim to control the probability of finding false subgroup effects or risk factors. This means using more stringent significance levels, such as Bonferroni procedures, where the degree of conservatism in the conclusions increases with the number of subgroup effects or risk factors tested. Bayesian methods of dealing with this multiple testing problem depend not on the number of subgroup effects or risk factors but on the prior information regarding the possibility of these effects. The frequentists' idea that conclusions about risk factor W must become more conservative simply because a study also considers risk factors X, Y, and Z makes the Bayesian approach seem scientifically more sensible.[14] Nevertheless, specification of prior distributions in multiple testing problems is difficult, and more research in this area is needed.

Ten years ago, Bayesian calculations were difficult for all but the simplest problems. But advances in statistical computing techniques using Monte Carlo sampling methods[15] have led to an explosion of interest among statisticians. Nowadays, a large proportion of research papers in theoretical statistics journals deal with Bayesian methods. It is only a matter of time before their use becomes more widespread in medicine. To prepare for this, doctors may like to ask their statistical colleagues to teach them about Bayesian methods or read the recently published book by Berry.[16] They will be pleasantly surprised by the natural simplicity of the concepts.

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Better reporting of randomised controlled trials: the CONSORT statement

Authors must provide enough information for readers to know how the trial was performed

Randomised controlled trials are the best way to compare the effectiveness of different interventions. Only randomised trials allow valid inferences of cause and effect. Only randomised trials have the potential directly to affect patient care—occasionally as single trials but more often as the body of evidence from several trials, whether or not combined formally by meta-analysis. It is thus entirely reasonable to require higher standards for papers reporting randomised trials than those describing other types of study.

Like all studies, randomised trials are open to bias if done badly.[1] It is thus essential that randomised trials are done well and reported adequately. Readers should not have to infer what was probably done, they should be told explicitly. Proper methodology should be used and be seen to have been used. Yet reviews of published trials have consistently found major deficiencies in reporting,[2-4] making the task for those carrying out systematic reviews much harder. Almost 50 years after the first publication of a randomised trial,[5] the guarantee of adequate reporting of these important studies is surely long overdue.

In 1994 two groups independently published proposals for requirements for the reporting of randomised trials.[6 7] In an editorial in *JAMA* Drummond Rennie suggested that the two groups should combine to produce a unified statement,[8] and

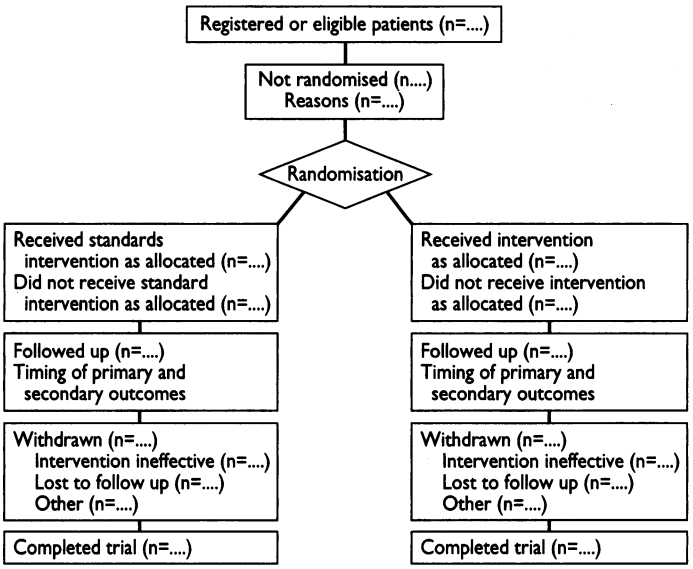

Fig 1—*Flow chart describing progress of patients through randomised trial (reproduced from* JAMA*)*[9]

Table 1—*Items that should be included in reports of randomised trials (reproduced from JAMA)*[9]

Heading	Subheading	Descriptor
Title		Identify the study as a randomised trial
Abstract		Use a structured format
Introduction		State prospectively defined hypothesis, clinical objectives, and planned subgroup or covariate analyses
Methods	Protocol	Describe Planned study population, together with inclusion or exclusion criteria Planned interventions and their timing Primary and secondary outcome measure(s) and the minimum important difference(s), and indicate how the target sample size was projected Rationale and methods for statistical analyses, detailing main comparative analyses and whether they were completed on an intention to treat basis Prospectively defined stopping rules (if warranted)
	Assignment	Describe Unit of randomisation (for example, individual, cluster, geographic) Method used to generate the allocation schedule Method of allocation concealment and timing of assignment Method to separate the generator from the executor of assignment
	Masking (blinding)	Describe Mechanism (for example, capsules, tablets) Similarity of treatment characteristics (for example, appearance, taste) Allocation schedule control (location of code during trial and when broken) Evidence for successful blinding among participants, person doing intervention, outcome assessors, and data analysts
Results	Participant flow and follow up	Provide a trial profile (fig 1) summarising participant flow, numbers and timing of randomisation assignment, interventions, and measurements for each randomised group
	Analysis	State estimated effect of intervention on primary and secondary outcome measures, including a point estimate and measure of precision (confidence interval) State results in absolute numbers when feasible (for example, 10/20, not 50%) Present summary data and appropriate descriptive and interferential statistics in sufficient detail to permit alternative analyses and replication Describe prognostic variables by treatment group and any attempt to adjust for them Describe protocol deviations from the study as planned, together with the reasons
Discussion		State specific interpretation of study findings, including sources of bias and imprecision (internal validity) and discussion of external validity, including appropriate quantitative measures when possible State general interpretation of the data in light of the totality of the available evidence

the outcome of this process was published last week.[9] The new CONSORT statement lists 21 items that should be included in a report (see table 1) as well as a flow chart describing patient progress through the trial (fig 1). In addition, a few specific subheadings are suggested within the methods and results sections of the paper. In the spirit of the times, the recommendations are evidence based where possible, with common sense dictating the remainder.

In essence the requirement is that authors should provide enough information for readers to know how the trial was performed so that they can judge whether the findings are likely to be reliable. The CONSORT statement means that authors will no longer be able to hide inadequacies in their study by omitting important information. For example, at present authors can, and often do, hide their procedures behind the single word "randomised." Authors will now be required to give details of the randomisation procedure. If authors have used an inferior approach, such as alternate allocation, they will have to say so. The *BMJ* has in fact refused to publish trials that were not truly randomised since 1991,[10] a position justified by subsequent empirical findings.[1]

As the authors of the CONSORT statement note,[9] the checklist applies to the most common design of randomised trial—trials with two parallel groups. Some modification is needed for special types of trial such as crossover trials and those with more than two treatment groups. Also, the list should be taken in conjunction with existing general requirements—for example, the requirement to specify all statistical methods used in the analysis. This and other items appear on the checklist for controlled trials that has been used by the *BMJ*'s statistical referees for over 10 years.[11]

Some of the items on the checklist would benefit from greater explanation than is possible in the CONSORT statement. In time a fuller accompanying explanatory paper could be valuable. For example, while the advantages of randomisation have been apparent for several decades, understanding the rationale for it remains poor and so its importance is not fully appreciated by researchers.[12]

The *BMJ* supports the CONSORT statement and is adopting its recommendations. So too are *JAMA*, *Lancet*, and some other journals. Trialists are encouraged to follow the statement right away, but from 1 January 1997 they will be required to do so. Authors should submit with their papers a copy of the completed checklist indicating on which page of the manuscript each item is addressed. The checklist will be used by the editors and supplied to referees. In the published papers the *BMJ* will use the additional subheadings suggested by CONSORT.

It seems reasonable to hope that, in addition to improved reporting, the wide adoption of this new publication standard will improve the conduct of future research by increasing awareness of the requirements for a good trial. Such success might lead to similar initiatives for other types of research.

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ORIGINAL ARTICLE

Efficacy and Safety of the mRNA-1273 SARS-CoV-2 Vaccine

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ABSTRACT

BACKGROUND

Vaccines are needed to prevent coronavirus disease 2019 (Covid-19) and to protect persons who are at high risk for complications. The mRNA-1273 vaccine is a lipid nanoparticle–encapsulated mRNA-based vaccine that encodes the prefusion stabilized full-length spike protein of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the virus that causes Covid-19.

METHODS

This phase 3 randomized, observer-blinded, placebo-controlled trial was conducted at 99 centers across the United States. Persons at high risk for SARS-CoV-2 infection or its complications were randomly assigned in a 1:1 ratio to receive two intramuscular injections of mRNA-1273 (100 μg) or placebo 28 days apart. The primary end point was prevention of Covid-19 illness with onset at least 14 days after the second injection in participants who had not previously been infected with SARS-CoV-2.

RESULTS

The trial enrolled 30,420 volunteers who were randomly assigned in a 1:1 ratio to receive either vaccine or placebo (15,210 participants in each group). More than 96% of participants received both injections, and 2.2% had evidence (serologic, virologic, or both) of SARS-CoV-2 infection at baseline. Symptomatic Covid-19 illness was confirmed in 185 participants in the placebo group (56.5 per 1000 person-years; 95% confidence interval [CI], 48.7 to 65.3) and in 11 participants in the mRNA-1273 group (3.3 per 1000 person-years; 95% CI, 1.7 to 6.0); vaccine efficacy was 94.1% (95% CI, 89.3 to 96.8%; P<0.001). Efficacy was similar across key secondary analyses, including assessment 14 days after the first dose, analyses that included participants who had evidence of SARS-CoV-2 infection at baseline, and analyses in participants 65 years of age or older. Severe Covid-19 occurred in 30 participants, with one fatality; all 30 were in the placebo group. Moderate, transient reactogenicity after vaccination occurred more frequently in the mRNA-1273 group. Serious adverse events were rare, and the incidence was similar in the two groups.

CONCLUSIONS

The mRNA-1273 vaccine showed 94.1% efficacy at preventing Covid-19 illness, including severe disease. Aside from transient local and systemic reactions, no safety concerns were identified. (Funded by the Biomedical Advanced Research and Development Authority and the National Institute of Allergy and Infectious Diseases; COVE ClinicalTrials.gov number, NCT04470427.)

The authors' full names, academic degrees, and affiliations are listed in the Appendix. Address reprint requests to Dr. El Sahly at the Departments of Molecular Virology and Microbiology and Medicine, 1 Baylor Plaza, BCM-MS280, Houston, TX 77030, or at hana.elsahly@bcm.edu; or to Dr. Baden at the Division of Infectious Diseases, Brigham and Women's Hospital, 15 Francis St., PBB-A4, Boston, MA 02115, or at lbaden@bwh.harvard.edu.

*A complete list of members of the COVE Study Group is provided in the Supplementary Appendix, available at NEJM.org.

Drs. Baden and El Sahly contributed equally to this article.

This article was published on December 30, 2020, at NEJM.org.

DOI: 10.1056/NEJMoa2035389

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A Quick Take is available at NEJM.org

The emergence in December 2019 of a novel coronavirus, the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has had devastating consequences globally. Control measures such as the use of masks, physical distancing, testing of exposed or symptomatic persons, contact tracing, and isolation have helped limit the transmission where they have been rigorously applied; however, these actions have been variably implemented and have proved insufficient in impeding the spread of coronavirus disease 2019 (Covid-19), the disease caused by SARS-CoV-2. Vaccines are needed to reduce the morbidity and mortality associated with Covid-19, and multiple vaccine platforms have been involved in the rapid development of vaccine candidates.[1-9]

The mRNA vaccine platform has advantages as a pandemic-response strategy, given its flexibility and efficiency in immunogen design and manufacturing. Earlier work had suggested that the spike protein of the coronavirus responsible for the 2002 SARS outbreak was a suitable target for protective immunity.[10] Numerous vaccine candidates in various stages of development are now being evaluated.[11-13] Shortly after the SARS-CoV-2 genetic sequence was determined in January 2020, mRNA-1273, a lipid-nanoparticle (LNP)–encapsulated mRNA vaccine expressing the prefusion-stabilized spike glycoprotein, was developed by Moderna and the Vaccine Research Center at the National Institute of Allergy and Infectious Diseases (NIAID), within the National Institutes of Health (NIH).[14] The mRNA-1273 vaccine demonstrated protection in animal-challenge experiments[15] and encouraging safety and immunogenicity in early-stage human testing.[1,4] The efficacy and safety of another mRNA vaccine, BNT162b2, was recently demonstrated.[16]

The Coronavirus Efficacy (COVE) phase 3 trial was launched in late July 2020 to assess the safety and efficacy of the mRNA-1273 vaccine in preventing SARS-CoV-2 infection. An independent data and safety monitoring board determined that the vaccine met the prespecified efficacy criteria at the first interim analysis. We report the primary analysis results of this ongoing pivotal phase 3 trial.

Methods

Trial Oversight

This phase 3 randomized, stratified, observer-blinded, placebo-controlled trial enrolled adults in medically stable condition at 99 U.S. sites. Participants received the first trial injection between July 27 and October 23, 2020. The trial is being conducted in accordance with the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use, Good Clinical Practice guidelines, and applicable government regulations. The central institutional review board approved the protocol and the consent forms. All participants provided written informed consent before enrollment. Safety is reviewed by a protocol safety review team weekly and by an independent data and safety monitoring board on a continual basis. The trial Investigational New Drug sponsor, Moderna, was responsible for the overall trial design (with input from the Biomedical Advanced Research and Development Authority, the NIAID, the Covid-19 Prevention Network, and the trial cochairs), site selection and monitoring, and data analysis. Investigators are responsible for data collection. A medical writer funded by Moderna assisted in drafting the manuscript for submission. The authors vouch for the accuracy and completeness of the data and for the fidelity of the trial to the protocol. The trial is ongoing, and the investigators remain unaware of participant-level data. Designated team members within Moderna have unblinded access to the data, to facilitate interface with the regulatory agencies and the data and safety monitoring board; all other trial staff and participants remain unaware of the treatment assignments.

Participants, Randomization, and Data Blinding

Eligible participants were persons 18 years of age or older with no known history of SARS-CoV-2 infection and with locations or circumstances that put them at an appreciable risk of SARS-CoV-2 infection, a high risk of severe Covid-19, or both. Inclusion and exclusion criteria are provided in the protocol (available with the full text of this article at NEJM.org). To enhance the diversity of the trial population in accordance with Food and Drug Administration Draft Guidance, site-selection and enrollment processes were adjusted to increase the number of persons from racial and ethnic minorities in the trial, in addition to the persons at risk for SARS-CoV-2 infection in the local population. The upper limit for stratification of enrolled participants considered

to be "at risk for severe illness" at screening was increased from 40% to 50%.[17]

Participants were randomly assigned in a 1:1 ratio, through the use of a centralized interactive response technology system, to receive vaccine or placebo. Assignment was stratified, on the basis of age and Covid-19 complications risk criteria, into the following risk groups: persons 65 years of age or older, persons younger than 65 years of age who were at heightened risk (at risk) for severe Covid-19, and persons younger than 65 years of age without heightened risk (not at risk). Participants younger than 65 years of age were categorized as having risk for severe Covid-19 if they had at least one of the following risk factors, based on the Centers for Disease Control and Prevention (CDC) criteria available at the time of trial design: chronic lung disease (e.g., emphysema, chronic bronchitis, idiopathic pulmonary fibrosis, cystic fibrosis, or moderate-to-severe asthma); cardiac disease (e.g., heart failure, congenital coronary artery disease, cardiomyopathies, or pulmonary hypertension); severe obesity (body mass index [the weight in kilograms divided by the square of the height in meters] ≥40); diabetes (type 1, type 2, or gestational); liver disease; or infection with the human immunodeficiency virus.[18]

Vaccine dose preparation and administration were performed by pharmacists and vaccine administrators who were aware of treatment assignments but had no other role in the conduct of the trial. Once the injection was completed, only trial staff who were unaware of treatment assignments performed assessments and interacted with the participants. Access to the randomization code was strictly controlled at the pharmacy. The data and safety monitoring board reviewed efficacy data at the group level and unblinded safety data at the participant level.

TRIAL VACCINE

The mRNA-1273 vaccine, provided as a sterile liquid at a concentration of 0.2 mg per milliliter, was administered by injection into the deltoid muscle according to a two-dose regimen. Injections were given 28 days apart, in the same arm, in a volume of 0.5 ml containing 100 μg of mRNA-1273 or saline placebo.[1] Vaccine mRNA-1273 was stored at 2° to 8°C (35.6° to 46.4°F) at clinical sites before preparation and vaccination. No dilution was required. Doses could be held in syringes for up to 8 hours at room temperature before administration.

SAFETY ASSESSMENTS

Safety assessments included monitoring of solicited local and systemic adverse events for 7 days after each injection; unsolicited adverse reactions for 28 days after each injection; adverse events leading to discontinuation from a dose, from participation in the trial, or both; and medically attended adverse events and serious adverse events from day 1 through day 759. Adverse event grading criteria and toxicity tables are described in the protocol. Cases of Covid-19 and severe Covid-19 were continuously monitored by the data and safety monitoring board from randomization onward.

EFFICACY ASSESSMENTS

The primary end point was the efficacy of the mRNA-1273 vaccine in preventing a first occurrence of symptomatic Covid-19 with onset at least 14 days after the second injection in the per-protocol population, among participants who were seronegative at baseline. End points were judged by an independent adjudication committee that was unaware of group assignment. Covid-19 cases were defined as occurring in participants who had at least two of the following symptoms: fever (temperature ≥38°C), chills, myalgia, headache, sore throat, or new olfactory or taste disorder, or as occurring in those who had at least one respiratory sign or symptom (including cough, shortness of breath, or clinical or radiographic evidence of pneumonia) and at least one nasopharyngeal swab, nasal swab, or saliva sample (or respiratory sample, if the participant was hospitalized) that was positive for SARS-CoV-2 by reverse-transcriptase–polymerase-chain-reaction (RT-PCR) test. Participants were assessed for the presence of SARS-CoV-2–binding antibodies specific to the SARS-CoV-2 nucleocapsid protein (Roche Elecsys, Roche Diagnostics International) and had a nasopharyngeal swab for SARS-CoV-2 RT-PCR testing (Viracor, Eurofins Clinical Diagnostics) before each injection. SARS-CoV-2–infected volunteers were followed daily, to assess symptom severity, for 14 days or until symptoms resolved, whichever was longer. A nasopharyngeal swab for RT-PCR testing and a blood sample for identifying serologic evidence of SARS-CoV-2 infection were collected from participants with symptoms of Covid-19.

The consistency of vaccine efficacy at the primary end point was evaluated across various subgroups, including age groups (18 to <65 years

of age and ≥65 years), age and health risk for severe disease (18 to <65 years and not at risk; 18 to <65 years and at risk; and ≥65 years), sex (female or male), race and ethnic group, and risk for severe Covid-19 illness. If the number of participants in a subgroup was too small, it was combined with other subgroups for the subgroup analyses.

A secondary end point was the efficacy of mRNA-1273 in the prevention of severe Covid-19 as defined by one of the following criteria: respiratory rate of 30 or more breaths per minute; heart rate at or exceeding 125 beats per minute; oxygen saturation at 93% or less while the participant was breathing ambient air at sea level or a ratio of the partial pressure of oxygen to the fraction of inspired oxygen below 300 mm Hg; respiratory failure; acute respiratory distress syndrome; evidence of shock (systolic blood pressure <90 mm Hg, diastolic blood pressure <60 mm Hg, or a need for vasopressors); clinically significant acute renal, hepatic, or neurologic dysfunction; admission to an intensive care unit; or death. Additional secondary end points included the efficacy of the vaccine at preventing Covid-19 after a single dose or at preventing Covid-19 according to a secondary (CDC), less restrictive case definition: having any symptom of Covid-19 and a positive SARS-CoV-2 test by RT-PCR (see Table S1 in the Supplementary Appendix, available at NEJM.org).

STATISTICAL ANALYSIS

For analysis of the primary end point, the trial was designed for the null hypothesis that the efficacy of the mRNA-1273 vaccine is 30% or less. A total of 151 cases of Covid-19 would provide 90% power to detect a 60% reduction in the hazard rate (i.e., 60% vaccine efficacy), with two planned interim analyses at approximately 35% and 70% of the target total number of cases (151) and with a one-sided O'Brien–Fleming boundary for efficacy and an overall one-sided error rate of 0.025. The efficacy of the mRNA-1273 vaccine could be demonstrated at either the interim or the primary analysis, performed when the target total number of cases had been observed. The Lan–DeMets alpha-spending function was used for calculating efficacy boundaries at each analysis. At the first interim analysis on November 15, 2020, vaccine efficacy had been demonstrated in accordance with the prespecified statistical criteria. The vaccine efficacy estimate, based on a total of 95 adjudicated cases (63% of the target total), was 94.5%, with a one-sided P value of less than 0.001 to reject the null hypothesis that vaccine efficacy would be 30% or less. The data and safety monitoring board recommendation to the oversight group and the trial sponsor was that the efficacy findings should be shared with the participants and the community (full details are available in the protocol and statistical analysis plan).

Vaccine efficacy was assessed in the full analysis population (randomized participants who received at least one dose of mRNA-1273 or placebo), the modified intention-to-treat population (participants in the full analysis population who had no immunologic or virologic evidence of Covid-19 on day 1, before the first dose), and the per-protocol population (participants in the modified intention-to-treat population who received two doses, with no major protocol deviations). The primary efficacy end point in the interim and primary analyses was assessed in the per-protocol population. Participants were evaluated in the treatment groups to which they were assigned. Vaccine efficacy was defined as the percentage reduction in the hazard ratio for the primary end point (mRNA-1273 vs. placebo). A stratified Cox proportional hazards model was used to assess the vaccine efficacy of mRNA-1273 as compared with placebo in terms of the percentage hazard reduction. (Details regarding the analysis of vaccine efficacy are provided in the Methods section of the Supplementary Appendix.)

Safety was assessed in all participants in the solicited safety population (i.e., those who received at least one injection and reported a solicited adverse event). Descriptive summary data (numbers and percentages) for participants with any solicited adverse events, unsolicited adverse events, unsolicited severe adverse events, serious adverse events, medically attended adverse events, and adverse events leading to discontinuation of the injections or withdrawal from the trial are provided by group. Two-sided 95% exact confidence intervals (Clopper–Pearson method) are provided for the percentages of participants with solicited adverse events. Unsolicited adverse events are presented according to the *Medical Dictionary for Regulatory Activities* (MedDRA), version 23.0, preferred terms and system organ class categories.

To meet the regulatory agencies' requirement of a median follow-up duration of at least 2 months

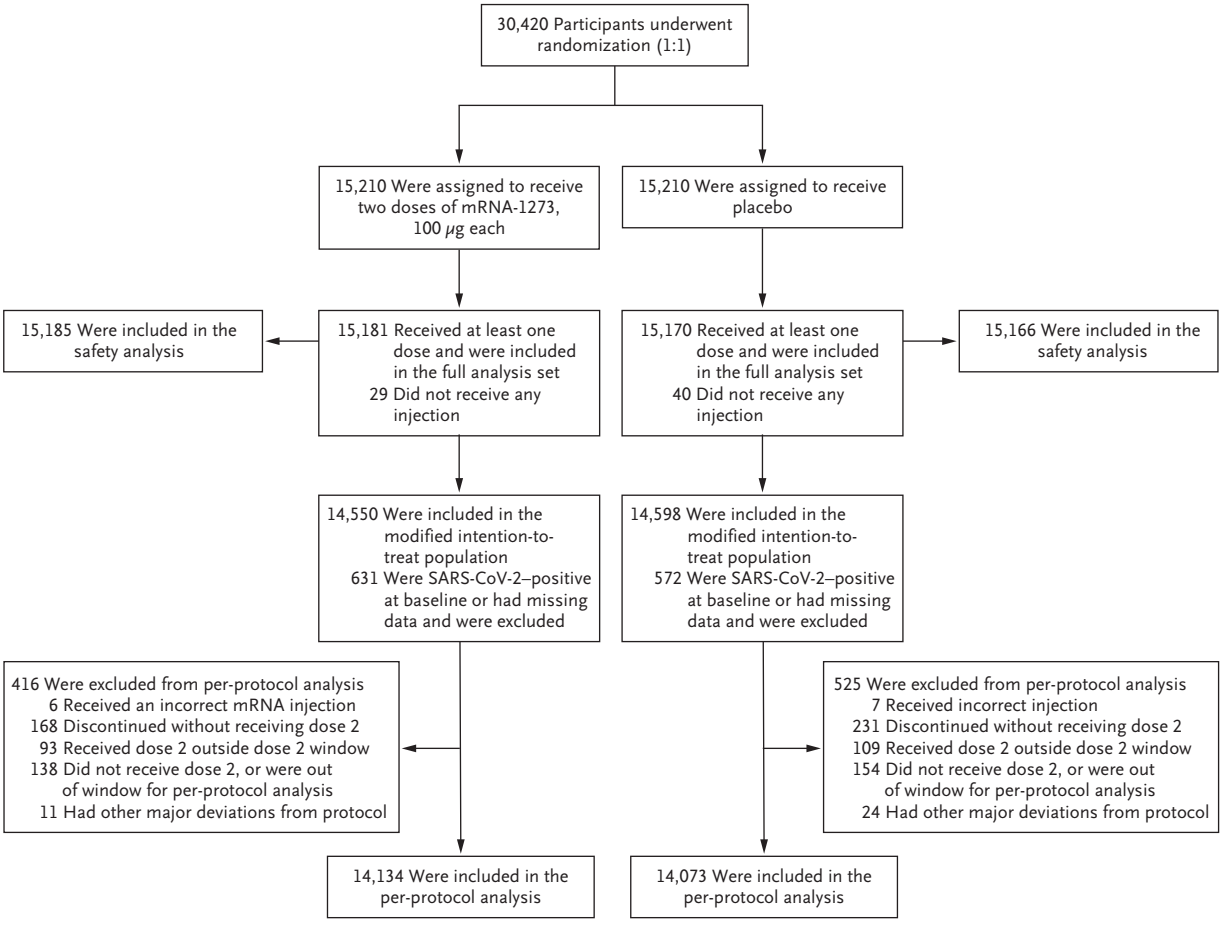


Figure 1. Randomization and Analysis Populations.

The data cutoff for the primary analysis occurred on November 25, 2020. The full analysis population consisted of participants who underwent randomization and received at least one dose of mRNA-1273 or placebo; the modified intention-to-treat population comprised participants in the full analysis population who had no immunologic or virologic evidence of Covid-19 on day 1, before the first dose; and the per-protocol analysis population included participants in the modified intention-to-treat population who received two doses, with no major protocol deviations. The safety population included all participants who received at least one injection. Among participants who received an incorrect injection, three participants in the mRNA-1273 group received at least one dose of placebo and no dose of mRNA-1273 and were included in the placebo safety population, and three received one dose of placebo and one dose of mRNA-1273 and were included in the mRNA-1273 safety population; in the placebo group all seven received mRNA-1273 and were included in the mRNA-1273 safety population. Participants who received dose 2 outside the window for the per-protocol analysis are those who did not receive the second dose between 7 days before and 14 days after day 29.

after completion of the two-dose regimen, a second analysis was performed, with an efficacy data cutoff date of November 21, 2020. This second analysis is considered the primary analysis of efficacy, with a total of 196 adjudicated Covid-19 cases in the per-protocol population, which exceeds the target total number of cases (151) specified in the protocol. This was an increase from the 95 cases observed at the first interim analysis data cutoff on November 11, 2020. Results from the primary analysis are presented in this report. Subsequent analyses are considered supplementary.

RESULTS

TRIAL POPULATION

Between July 27, 2020, and October 23, 2020, a total of 30,420 participants underwent randomization, and the 15,210 participants in each group were assigned to receive two doses of either placebo or mRNA-1273 (100 μg) (Fig. 1).

Table 1. Demographic and Clinical Characteristics at Baseline.*

Characteristics	Placebo (N=15,170)	mRNA-1273 (N=15,181)	Total (N=30,351)
Sex — no. of participants (%)			
Male	8,062 (53.1)	7,923 (52.2)	15,985 (52.7)
Female	7,108 (46.9)	7,258 (47.8)	14,366 (47.3)
Mean age (range) — yr	51.3 (18–95)	51.4 (18–95)	51.4 (18–95)
Age category and risk for severe Covid-19 — no. of participants (%)†			
18 to <65 yr, not at risk	8,886 (58.6)	8,888 (58.5)	17,774 (58.6)
18 to <65 yr, at risk	2,535 (16.7)	2,530 (16.7)	5,065 (16.7)
≥65 yr	3,749 (24.7)	3,763 (24.8)	7,512 (24.8)
Hispanic or Latino ethnicity — no. of participants (%)‡			
Hispanic or Latino	3,114 (20.5)	3,121 (20.6)	6,235 (20.5)
Not Hispanic or Latino	11,917 (78.6)	11,918 (78.5)	23,835 (78.5)
Not reported and unknown	139 (0.9)	142 (0.9)	281 (0.9)
Race or ethnic group — no. of participants (%)‡			
White	11,995 (79.1)	12,029 (79.2)	24,024 (79.2)
Black or African American	1,527 (10.1)	1,563 (10.3)	3,090 (10.2)
Asian	731 (4.8)	651 (4.3)	1,382 (4.6)
American Indian or Alaska Native	121 (0.8)	112 (0.7)	233 (0.8)
Native Hawaiian or Other Pacific Islander	32 (0.2)	35 (0.2)	67 (0.2)
Multiracial	321 (2.1)	315 (2.1)	636 (2.1)
Other	316 (2.1)	321 (2.1)	637 (2.1)
Not reported and unknown	127 (0.8)	155 (1.0)	282 (0.9)
Baseline SARS-CoV-2 status — no. of participants (%)§			
Negative	14,598 (96.2)	14,550 (95.8)	29,148 (96.0)
Positive	337 (2.2)	343 (2.3)	680 (2.2)
Missing data	235 (1.5)	288 (1.9)	523 (1.7)
Baseline RT-PCR test — no. of participants (%)			
Negative	14,923 (98.4)	14,917 (98.3)	29,840 (98.3)
Positive	95 (0.6)	87 (0.6)	182 (0.6)
Missing data	152 (1.0)	177 (1.2)	329 (1.1)
Baseline bAb anti–SARS-CoV-2 assay — no. of participants (%)			
Negative	14,726 (97.1)	14,690 (96.8)	29,416 (96.9)
Positive	303 (2.0)	305 (2.0)	608 (2.0)
Missing data	141 (0.9)	186 (1.2)	327 (1.1)
Risk factor for severe Covid-19 — no. of participants (%)			
Chronic lung disease	744 (4.9)	710 (4.7)	1,454 (4.8)
Significant cardiac disease	744 (4.9)	752 (5.0)	1,496 (4.9)
Severe obesity	1,021 (6.7)	1,025 (6.8)	2,046 (6.7)
Diabetes	1,440 (9.5)	1,435 (9.5)	2,875 (9.5)
Liver disease	96 (0.6)	100 (0.7)	196 (0.6)
Human immunodeficiency virus infection	87 (0.6)	92 (0.6)	179 (0.6)

Table 1. (Continued.)

Characteristics	Placebo (N=15,170)	mRNA-1273 (N=15,181)	Total (N=30,351)
Body-mass index¶			
No. of participants	15,007	14,985	29,992
Mean ±SD	29.3±6.7	29.3±6.9	29.3±6.8

* Internet-based randomization was used to assign participants to treatment groups on the basis of information entered by the investigator regarding the participant's age and coexisting conditions. Percentages are based on the full analysis population; baseline demographics and characteristics for the per-protocol population are provided in the Supplementary Appendix. Percentages may not total 100 because of rounding. The abbreviation bAb denotes binding antibody concentration, and RT-PCR reverse-transcriptase polymerase chain reaction.
† Risk was based on a stratification factor from the Internet-based interactive response system used for randomization; participants who were younger than 65 years of age were categorized as at risk for severe Covid-19 illness if they had at least one of the risk factors specified in the trial protocol at screening.
‡ Race or ethnic group was reported by the participant. Participants could be included in more than one category.
§ Baseline SARS-CoV-2 status was positive if there was immunologic or virologic evidence of previous illness with Covid-19, as defined by a positive RT-PCR test or a positive bAb against SARS-CoV-2 nucleocapsid assay result that was above the limit of detection or by a lower limit of quantification at day 1. Baseline SARS-CoV-2 status was negative if there was a negative RT-PCR test and negative bAb against SARS-CoV-2 assay result at day 1.
¶ The body-mass index is the weight in kilograms divided by the square of the height in meters.

More than 96% of participants received the second dose (Fig. S1). Common reasons for not receiving the second dose were withdrawal of consent (153 participants) and the detection of SARS-CoV-2 by PCR before the administration of the second dose on day 29 (114 participants: 69 in the placebo group and 45 in the mRNA-1273 group). The primary efficacy and safety analyses were performed in the per-protocol and safety populations, respectively. Of the participants who received a first injection, 14,073 of those in the placebo group and 14,134 in the mRNA-1273 group were included in the primary efficacy analysis; 525 participants in the placebo group and 416 in the mRNA-1273 group were excluded from the per-protocol population, including those who had not received a second dose by the day 29 data cutoff (Fig. 1). As of November 25, 2020, the participants had a median follow-up duration of 64 days (range, 0 to 97) after the second dose, with 61% of participants having more than 56 days of follow-up.

Baseline demographic characteristics were balanced between the placebo group and the mRNA-1273 vaccine group (Table 1 and Table S2). The mean age of the participants was 51.4 years, 47.3% of the participants were female, 24.8% were 65 years of age or older, and 16.7% were younger than 65 years of age and had predisposing medical conditions that put them at risk for severe Covid-19. The majority of participants were White (79.2%), and the racial and ethnic proportions were generally representative of U.S. demographics, including 10.2% Black or African American and 20.5% Hispanic or Latino. Evidence of SARS-CoV-2 infection at baseline was present in 2.3% of participants in the mRNA-1273 group and in 2.2% in the placebo group, as detected by serologic assay or RT-PCR testing.

SAFETY

Solicited adverse events at the injection site occurred more frequently in the mRNA-1273 group than in the placebo group after both the first dose (84.2%, vs. 19.8%) and the second dose (88.6%, vs. 18.8%) (Fig. 2 and Tables S3 and S4). In the mRNA-1273 group, injection-site events were mainly grade 1 or 2 in severity and lasted a mean of 2.6 and 3.2 days after the first and second doses, respectively (Table S5). The most common injection-site event was pain after injection (86.0%). Delayed injection-site reactions (those with onset on or after day 8) were noted in 244 participants (0.8%) after the first dose and in 68 participants (0.2%) after the second dose. Reactions were characterized by erythema, induration, and tenderness, and they resolved over the following 4 to 5 days. Solicited systemic adverse events occurred more often in the mRNA-1273 group than in the placebo group after both the first dose (54.9%, vs. 42.2%) and the second dose (79.4%, vs. 36.5%). The severity of the solicited systemic events increased after the second dose in the mRNA-1273 group, with

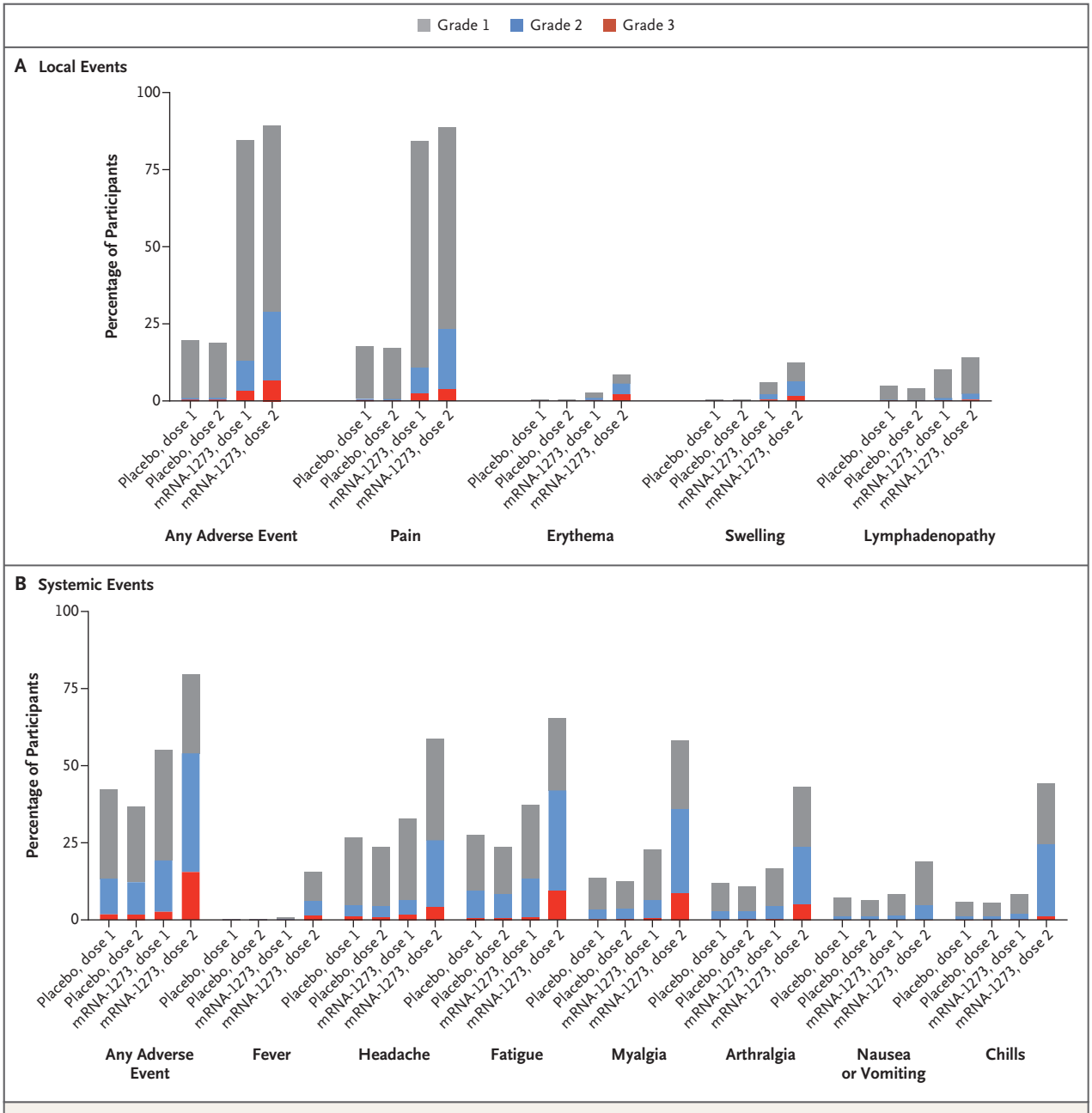


Figure 2. Solicited Local and Systemic Adverse Events.

Shown is the percentage of participants who had a solicited local or systemic adverse event within 7 days after injection 1 or injection 2 of either the placebo or the mRNA-1273 vaccine.

an increase in proportions of grade 2 events (from 16.5% after the first dose to 38.1% after the second dose) and grade 3 events (from 2.9% to 15.8%). Solicited systemic adverse events in the mRNA-1273 group lasted a mean of 2.6 days and 3.1 days after the first and second doses, respectively (Table S5). Both solicited injection-site and systemic adverse events were more common among younger participants (18 to <65 years of age) than among older participants (≥65 years of age). Solicited adverse events were less common in participants who were positive for SARS-

CoV-2 infection at baseline than in those who were negative at baseline (Tables S6 and S7).

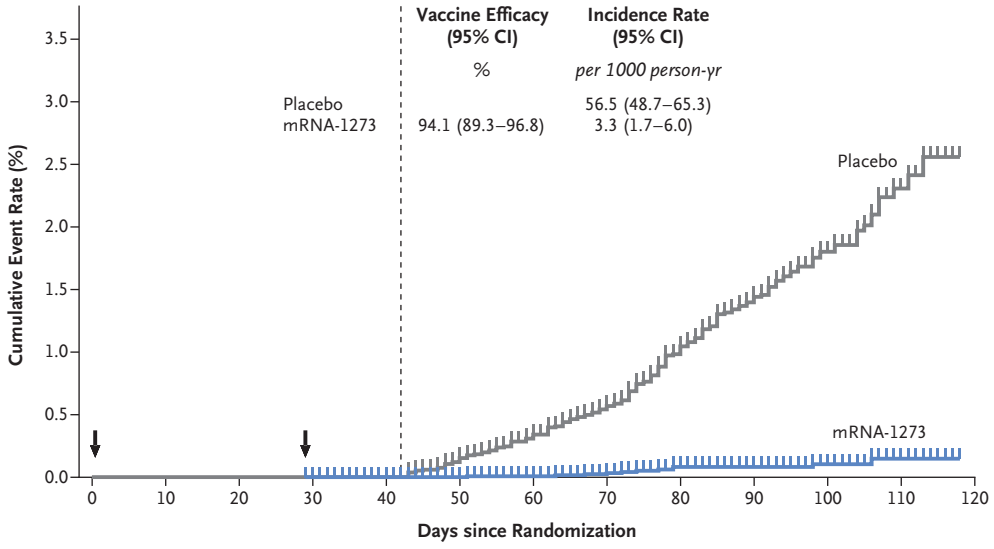
The frequency of unsolicited adverse events, unsolicited severe adverse events, and serious adverse events reported during the 28 days after injection was generally similar among participants in the two groups (Tables S8 through S11). Three deaths occurred in the placebo group (one from intraabdominal perforation, one from cardiopulmonary arrest, and one from severe systemic inflammatory syndrome in a participant with chronic lymphocytic leukemia and diffuse bullous rash) and two in the vaccine group (one from cardiopulmonary arrest and one by suicide). The frequency of grade 3 adverse events in the placebo group (1.3%) was similar to that in the vaccine group (1.5%), as were the frequencies of medically attended adverse events (9.7% vs. 9.0%) and serious adverse events (0.6% in both groups). Hypersensitivity reactions were reported in 1.5% and 1.1% of participants in the vaccine and placebo groups, respectively (Table S12). Bell's palsy occurred in the vaccine group (3 participants [<0.1%]) and the placebo group (1 participant [<0.1%]) during the observation period of the trial (more than 28 days after injection). Overall, 0.5% of participants in the placebo group and 0.3% in the mRNA-1273 group had adverse events that resulted in their not receiving the second dose, and less than 0.1% of participants in both groups discontinued participation in the trial because of adverse events after any dose (Table S8). No evidence of vaccine-associated enhanced respiratory disease was noted, and fewer cases of severe Covid-19 or any Covid-19 were observed among participants who received mRNA-1273 than among those who received placebo (Tables S13 and S14). Adverse events that were deemed by the trial team to be related to the vaccine or placebo were reported among 4.5% of participants in the placebo group and 8.2% in the mRNA-1273 group. The most common treatment-related adverse events (those reported in at least 1% of participants) in the placebo group and the mRNA-1273 group were fatigue (1.2% and 1.5%) and headache (0.9% and 1.4%). In the overall population, the incidence of treatment-related severe adverse events was higher in the mRNA-1273 group (71 participants [0.5%]) than in the placebo group (28 participants [0.2%]) (Tables S8 and S15). The relative incidence of these adverse events according to vaccine group was not affected by age.

EFFICACY

After day 1 and through November 25, 2020, a total of 269 Covid-19 cases were identified, with an incidence of 79.8 cases per 1000 person-years (95% confidence interval [CI], 70.5 to 89.9) among participants in the placebo group with no evidence of previous SARS-CoV-2 infection. For the primary analysis, 196 cases of Covid-19 were diagnosed: 11 cases in the vaccine group (3.3 per 1000 person-years; 95% CI, 1.7 to 6.0) and 185 cases in the placebo group (56.5 per 1000 person-years; 95% CI, 48.7 to 65.3), indicating 94.1% efficacy of the mRNA-1273 vaccine (95% CI, 89.3 to 96.8%; P<0.001) for the prevention of symptomatic SARS-CoV-2 infection as compared with placebo (Fig. 3A). Findings were similar across key secondary analyses (Table S16), including assessment starting 14 days after dose 1 (225 cases with placebo, vs. 11 with mRNA-1273, indicating a vaccine efficacy of 95.2% [95% CI, 91.2 to 97.4]), and assessment including participants who were SARS-CoV-2 seropositive at baseline in the per-protocol analysis (187 cases with placebo, vs. 12 with mRNA-1273; one volunteer assigned to receive mRNA-1273 was inadvertently given placebo], indicating a vaccine efficacy of 93.6% [95% CI, 88.6 to 96.5]). Between days 1 and 42, seven cases of Covid-19 were identified in the mRNA-1273 group, as compared with 65 cases in the placebo group (Fig. 3B).

A key secondary end point evaluated the efficacy of mRNA-1273 at preventing severe Covid-19. Thirty participants in the trial had severe Covid-19; all 30 were in the placebo group (indicating vaccine efficacy of 100% [95% CI, could not be estimated to 1.0]), and one death among these participants was attributed to Covid-19 (Table S16). The vaccine efficacy to prevent Covid-19 was consistent across subgroups stratified by demographic and baseline characteristics (Fig. 4): age groups (18 to <65 years of age and ≥65 years), presence of risk for severe Covid-19, sex, and race and ethnic group (non-Hispanic White and communities of color). Among participants who were positive for SARS-CoV-2, by serologic or virologic testing, at baseline (337 in the placebo group and 343 in the mRNA-1273

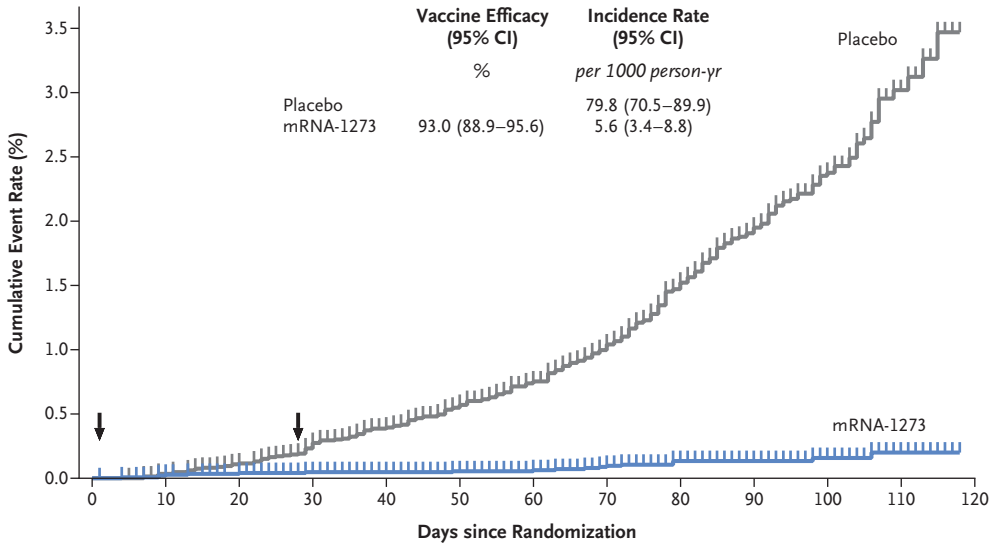
A Per-Protocol Analysis



No. at Risk

Placebo	14,073	14,073	14,073	14,072	13,416	12,992	12,361	11,147	9474	6563	3971	1172	0
mRNA-1273	14,134	14,134	14,134	14,133	13,483	13,073	12,508	11,315	9684	6721	4094	1209	0

B Modified Intention-to-Treat Analysis



No. at Risk

Placebo	14,598	14,590	14,567	14,515	13,806	12,352	12,694	11,450	9736	6729	4067	1200	0
mRNA-1273	14,550	14,543	14,532	14,504	13,825	13,398	12,791	11,573	9911	6871	4179	1238	0

Covid-19 Onset	Placebo (N=14,598)	mRNA-1273 (N=14,550)
Randomization to 14 days after dose 1	11	5
14 Days after dose 1 to dose 2	35	2
Dose 2 to 14 days after dose 2	19	0
Starting 14 days after dose 2	204	12
Total (any time after randomization)	269	19

Figure 3 (facing page). Vaccine Efficacy of mRNA-1273 to Prevent Covid-19.

Shown is the cumulative incidence of Covid-19 events in the primary analysis based on adjudicated assessment starting 14 days after the second vaccination in the per-protocol population (Panel A) and after randomization in the modified intention-to-treat population (Panel B) (see the Supplementary Appendix). The dotted line in Panel A indicates day 42 (14 days after vaccination 2), when the per-protocol follow-up began, and arrows in both panels indicate days 1 and 29, when injections were administered. Tick marks indicate censored data. Vaccine efficacy was defined as 1 minus the hazard ratio (mRNA vs. placebo), and the 95% confidence interval was estimated with the use of a stratified Cox proportional hazards model, with Efron's method of tie handling and with treatment group as a covariate, with adjustment for stratification factor. Incidence was defined as the number of events divided by number of participants at risk and was adjusted by person-years. Symptomatic Covid-19 case accrual for placebo and vaccine in the modified intention-to-treat population is displayed (does not include asymptomatic cases of SARS-CoV-2 detected at the day 29 by nasopharyngeal swab).

group), one case of Covid-19 was diagnosed by RT-PCR testing in a placebo recipient and no cases were diagnosed in mRNA-1273 recipients (Table S17). Among participants who were negative for SARS-CoV-2 at baseline (by RT-PCR or antibody testing), in addition to symptomatic Covid-19 cases 39 (0.3%) in the placebo group and 15 (0.1%) in the mRNA-1273 group had nasopharyngeal swabs that were positive for SARS-CoV-2 by RT-PCR at the second dose visit (surveillance swab) but had no evidence of Covid-19 symptoms (Table S18).

DISCUSSION

The COVE trial provides evidence of short-term efficacy of the mRNA-1273 vaccine in preventing symptomatic SARS-CoV-2 infection in a diverse adult trial population. Of note, the trial was designed for an infection attack rate of 0.75%, which would have necessitated a follow-up period of 6 months after the two vaccine doses to accrue 151 cases in 30,000 participants. The pandemic trajectory accelerated in many U.S. regions in the late summer and fall of 2020, resulting in rapid accrual of 196 cases after a median follow-up of 2 months. It is important to note that all the severe Covid-19 cases were in the placebo group, which suggests that mRNA-1273 is likely to have an effect on preventing severe illness, which is the major cause of health care utilization, complications, and death. The finding of fewer occurrences of symptomatic SARS-CoV-2 infection after a single dose of mRNA-1273 is encouraging; however, the trial was not designed to evaluate the efficacy of a single dose, and additional evaluation is warranted.

The magnitude of mRNA-1273 vaccine efficacy at preventing symptomatic SARS-CoV-2 infection is higher than the efficacy observed for vaccines for respiratory viruses, such as the inactivated influenza vaccine against symptomatic, virologically confirmed disease in adults, for which studies have shown a pooled efficacy of 59%.[19] This high apparent efficacy of mRNA-1273 is based on short-term data, and waning of efficacy over time has been demonstrated with other vaccines.[20] Also, the efficacy of the vaccine was tested in a setting of national recommendations for masking and social distancing, which may have translated into lower levels of infectious inoculum. The efficacy of mRNA-1273 is in line with that of the recently reported BNT162b2 mRNA vaccine.[16] The COVE trial is ongoing, and longitudinal follow-up will allow an assessment of efficacy changes over time and under evolving epidemiologic conditions.

Overall, the safety of the mRNA-1273 vaccine regimen and platform is reassuring; no unexpected patterns of concern were identified. The reactogenicity associated with immunization with mRNA-1273 in this trial is similar to that in the phase 1 data reported previously.[1,4] Overall, the local reactions to vaccination were mild; however, moderate-to-severe systemic side effects, such as fatigue, myalgia, arthralgia, and headache, were noted in about 50% of participants in the mRNA-1273 group after the second dose. These side effects were transient, starting about 15 hours after vaccination and resolving in most participants by day 2, without sequelae. The degree of reactogenicity after one dose of mRNA-1273 was less than that observed for the recently approved recombinant adjuvanted zoster vaccine and after the second mRNA-1273 dose was similar to that of the zoster vaccine.[21,22] Delayed injection-site reactions, with an onset

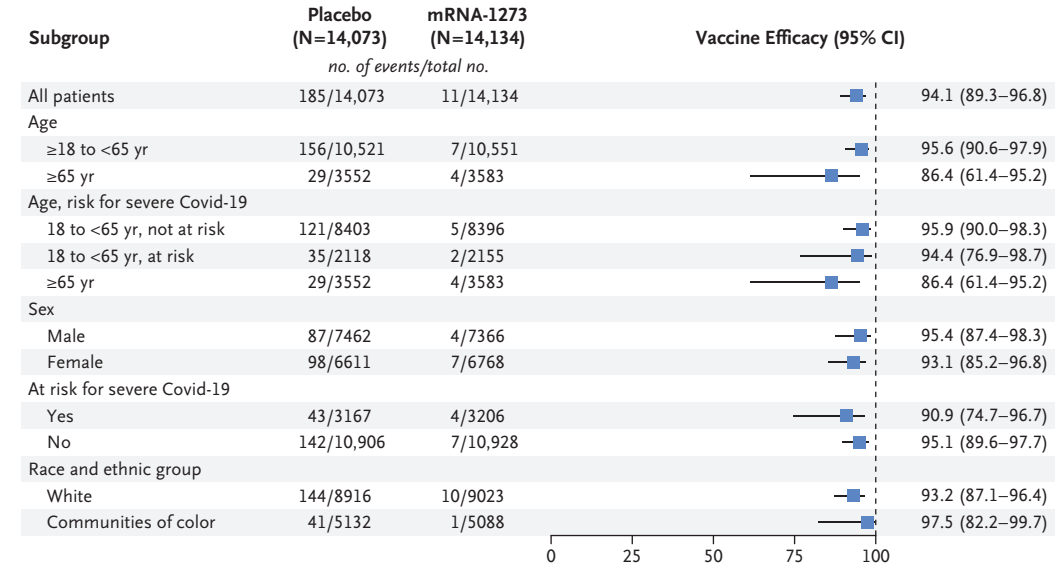


Figure 4. Vaccine Efficacy of mRNA-1273 to Prevent Covid-19 in Subgroups.

The efficacy of the RNA-1273 vaccine in preventing Covid-19 in various subgroups in the per-protocol population was based on adjudicated assessments starting 14 days after the second injection. Vaccine efficacy, defined as 1 minus the hazard ratio (mRNA-1273 vs. placebo), and 95% confidence intervals were estimated with the use of a stratified Cox proportional hazards model, with Efron's method of tie handling and with the treatment group as a covariate, adjusting for stratification factor if applicable. Race and ethnic group categories shown are White (non-Hispanic) and communities of color (all others, including those whose race and ethnicity were both reported as unknown, were not reported, or were both missing at screening). Data for communities of color were pooled owing to limited numbers of participants in each racial or ethnic group, to ensure that the subpopulations would be large enough for meaningful analyses.

8 days or more after injection, were uncommon. The overall incidence of unsolicited adverse events reported up to 28 days after vaccination and of serious adverse events reported throughout the entire trial was similar for mRNA-1273 and placebo. A risk of acute hypersensitivity is sometimes observed with vaccines; however, no such risk was evident in the COVE trial, although the ability to detect rare events is limited, given the trial sample size. The anecdotal finding of a slight excess of Bell's palsy in this trial and in the BNT162b2 vaccine trial arouses concern that it may be more than a chance event, and the possibility bears close monitoring.[16]

The mRNA-1273 vaccine did not show evidence in the short term of enhanced respiratory disease after infection, a concern that emerged from animal models used in evaluating some SARS and Middle East respiratory syndrome (MERS) vaccine constructs.[23-25] A hallmark of enhanced respiratory disease is a Th2-skewed immune response and eosinophilic pulmonary infiltration on histopathological examination. Of note, preclinical testing of mRNA-1273 and other SARS-CoV-2 vaccines in advanced clinical evaluation has shown a Th1-skewed vaccine response and no pathologic lung infiltrates.[15,26-28] Whether mRNA-1273 vaccination results in enhanced disease on exposure to the virus in the long term is unknown.

Key limitations of the data are the short duration of safety and efficacy follow-up. The trial is ongoing, and a follow-up duration of 2 years is planned, with possible changes to the trial design to allow participant retention and ongoing data collection. Another limitation is the lack of an identified correlate of protection, a critical tool for future bridging studies. As of the data cutoff, 11 cases of Covid-19 had occurred in the mRNA-1273 group, a finding that limits our ability to detect a correlate of protection. As cases accrue and immunity wanes, it may be-

come possible to determine such a correlate. In addition, although our trial showed that mRNA-1273 reduces the incidence of symptomatic SARS-CoV-2 infection, the data were not sufficient to assess asymptomatic infection, although our results from a preliminary exploratory analysis suggest that some degree of prevention may be afforded after the first dose. Evaluation of the incidence of asymptomatic or subclinical infection and viral shedding after infection are under way, to assess whether vaccination affects infectiousness. The relatively smaller numbers of cases that occurred in older adults and in participants from ethnic or racial minorities and the small number of previously infected persons who received the vaccine limit efficacy evaluations in these groups. Longer-term data from the ongoing trial may allow a more careful evaluation of the vaccine efficacy in these groups. Pregnant women and children were excluded from this trial, and additional evaluation of the vaccine in these groups is planned.

Within 1 year after the emergence of this novel infection that caused a pandemic, a pathogen was determined, vaccine targets were identified, vaccine constructs were created, manufacturing to scale was developed, phase 1 through phase 3 testing was conducted, and data have been reported. This process demonstrates what is possible in the context of motivated collaboration among key sectors of society, including academia, government, industry, regulators, and the larger community. Lessons learned from this endeavor should allow us to better prepare for the next pandemic pathogen.

Supported by the Office of the Assistant Secretary for Preparedness and Response, Biomedical Advanced Research and Development Authority (contract 75A50120C00034) and by the National Institute of Allergy and Infectious Diseases (NIAID). The NIAID provides grant funding to the HIV Vaccine Trials Network (HVTN) Leadership and Operations Center (UM1 AI 68614HVTN), the Statistics and Data Management Center (UM1 AI 68635), the HVTN Laboratory Center (UM1 AI 68618), the HIV Prevention Trials Network Leadership and Operations Center (UM1 AI 68619), the AIDS Clinical Trials Group Leadership and Operations Center (UM1 AI 68636), and the Infectious Diseases Clinical Research Consortium leadership group 5 (UM1 AI148684-03).

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

A data sharing statement provided by the authors is available with the full text of this article at NEJM.org.

We thank the participants in the trial and the members of the mRNA-1273 trial team (listed in the Supplementary Appendix) for their dedication and the contributions to the trial, and the members of the data and safety monitoring board (Richard J. Whitley [chair], University of Alabama School of Medicine; Abdel Babiker, MRC Clinical Trials Unit at University College, London; Lisa A. Cooper, Johns Hopkins University School of Medicine and Bloomberg School of Public Health; Susan S. Ellenberg, University of Pennsylvania; Alan Fix, Vaccine Development Global Program Center for Vaccine Innovation and Access PATH; Marie Griffin, Vanderbilt University Medical Center; Steven Joffe, Perelman School of Medicine, University of Pennsylvania; Jorge Kalil, Heart Institute, Hospital das Clínicas da Faculdade de Medicina da Universidade de São Paulo; Myron M. Levine, University of Maryland School of Medicine; Malegapuru W. Makgoba, University of KwaZulu-Natal; Anastasios A. Tsiatis, North Carolina State University; Renee H. Moore, Emory University); and Sally Hunsberger [Executive Secretary], NIAID) for their hard work, support, and guidance of the trial; and the adjudication committee (Richard J. Hamill [chair], Baylor College of Medicine; Lewis Lipsitz, Harvard Medical School; Eric S. Rosenberg, Massachusetts General Hospital; and Anthony Faugno, Tufts Medical Center) for their critical and timely review of the trial data. We also acknowledge the contribution from the mRNA-1273 Product Coordination Team from the Biomedical Advanced Research and Development Authority (BARDA) (Robert Bruno, Richard Gorman, Holli Hamilton, Gary Horwith, Chuong Huynh, Nutan Mytle, Corrina Pavetto, Xiaomi Tong, and John Treanor), and Joanne E. Tomassini (JET Scientific), for assistance in writing the manuscript for submission, and Frank J. Dutko, for editorial support (funded by Moderna).

APPENDIX

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Does the FDA think these data justify the first full approval of a covid-19 vaccine?
August 23, 2021
The FDA should demand adequate, controlled studies with long term follow up, and make data publicly available, before granting full approval to covid-19 vaccines, says Peter Doshi

On 28 July 2021, Pfizer and BioNTech posted updated results for their ongoing phase 3 covid-19 vaccine trial. The preprint came almost a year to the day after the historical trial commenced, and nearly four months since the companies announced vaccine efficacy estimates "up to six months."

But you won't find 10 month follow-up data here. While the preprint is new, the results it contains aren't particularly up to date. In fact, the paper is based on the same data cut-off date (13 March 2021) as the 1 April press release, and its topline efficacy result is identical: 91.3% (95% CI 89.0 to 93.2) vaccine efficacy against symptomatic covid-19 through "up to six months of follow-up."

The 20 page preprint matters because it represents the most detailed public account of the pivotal trial data Pfizer submitted in pursuit of the world's first "full approval" of a coronavirus vaccine from the Food and Drug Administration. It deserves careful scrutiny.

The elephant named "waning immunity"

Since late last year, we've heard that Pfizer and Moderna's vaccines are "95% effective" with even greater efficacy against severe disease ("100% effective," Moderna said).

Whatever one thinks about the "95% effective" claims (my thoughts are here), even the most enthusiastic commentators have acknowledged that measuring vaccine efficacy two months after dosing says little about just how long vaccine-induced immunity will last. "We're going to be looking very intently at the durability of protection," Pfizer senior vice president William Gruber, an author on the recent preprint, told the FDA's advisory committee last December.

The concern, of course, was decreased efficacy over time. "Waning immunity" is a known problem for influenza vaccines, with some studies showing near zero effectiveness after just three months, meaning a vaccine taken early may ultimately provide no protection by the time "flu season" arrives some months later. If vaccine efficacy wanes over time, the crucial question becomes what level of effectiveness will the vaccine provide when a person is actually exposed to the virus? Unlike covid vaccines, influenza vaccine performance has always been judged over a full season, not a couple months.

And so the recent reports from Israel's Ministry of Health caught my eye. In early July, they reported that efficacy against infection and symptomatic disease "fell to 64%." By late July it had fallen to 39% where Delta is the dominant strain. This is very low. For context, the FDA's expectation is of "at least 50%" efficacy for any approvable vaccine.

Now Israel, which almost exclusively used Pfizer vaccine, has begun administering a third "booster" dose to all adults over 40. And starting 20 September 2021, the US plans to follow suit for all "fully vaccinated" adults eight months past their second dose.

Delta may not be responsible

Enter Pfizer's preprint. As an RCT reporting "up to six months of follow-up," it is notable that evidence of waning immunity was already visible in the data by the 13 March 2021 data cut-off.

"From its peak post-dose 2," the study authors write, "observed VE [vaccine efficacy] declined." From 96% to 90% (from two months to <4 months), then to 84% (95% CI 75 to 90) "from four months to the data cut-off," which, by my calculation (see footnote at the end of the piece), was about one month later.

But although this additional information was available to Pfizer in April, it was not published until the end of July.

And it's hard to imagine how the Delta variant could play a real role here, for 77% of trial participants were from the United States, where Delta was not established until months after data cut-off.

Waning efficacy has the potential to be far more than a minor inconvenience; it can dramatically change the risk-benefit calculus. And whatever its cause—intrinsic properties of the vaccine, the circulation of new variants, some combination of the two, or something else—the bottom line is that vaccines need to be effective.

Until new clinical trials demonstrate that boosters increase efficacy above 50%, without increasing serious adverse events, it is unclear whether the 2-dose series would even meet the FDA's approval standard at six or nine months.

The "six month" preprint based on the 7% of trial participants who remained blinded at six months

The final efficacy timepoint reported in Pfizer's preprint is "from four months to the data cut-off." The confidence interval here is wider than earlier time points because only half of trial participants (53%) made it to the four month mark, and mean follow-up is around 4.4 months (see footnote).

This all happened because starting last December, Pfizer allowed all trial participants to be formally unblinded, and placebo recipients to get vaccinated. By 13 March 2021 (data cut-off), 93% of trial participants (41,128 of 44,060; Fig 1) were unblinded, officially entering "open-label followup." (Ditto for Moderna: by mid April, 98% of placebo recipients had been vaccinated.)

Despite the reference to "six month safety and efficacy" in the preprint's title, the paper only reports on vaccine efficacy "up to six months," but not from six months. This is not semantics, as it turns out only 7% of trial participants actually reached six months of blinded follow-up ("8% of BNT162b2 recipients and 6% of placebo recipients had ≥6 months follow-up post-dose 2.") So despite this preprint appearing a year after the trial began, it provides no data on vaccine efficacy past six months, which is the period Israel says vaccine efficacy has dropped to 39%.

It is hard to imagine that the <10% of trial participants who remained blinded at six months (which presumably further dwindled after 13 March 2021) could constitute a reliable or valid sample to produce further findings. And the preprint does not report any demographic comparisons to justify future analyses.

Severe disease

With the US awash in news about rising cases of the Delta variant, including among the "fully vaccinated," the vaccine's efficacy profile is in question. But some medical commentators are delivering an upbeat message. Former FDA commissioner Scott Gottlieb, who is on Pfizer's board, said: "Remember, the original premise behind these vaccines were [sic] that they would substantially reduce the risk of death and severe disease and hospitalization. And that was the data that came out of the initial clinical trials."

Yet, the trials were not designed to study severe disease. In the data that supported Pfizer's EUA, the company itself characterized the "severe covid-19" endpoint results as "preliminary evidence." Hospital admission numbers were not reported, and zero covid-19 deaths occurred.

In the preprint, high efficacy against "severe covid-19" is reported based on all follow-up time (one event in the vaccinated group vs 30 in placebo), but the number of hospital admissions is not reported so we don't know which, if any, of these patients were ill enough to require hospital treatment. (In Moderna's trial, data last year showed that 21 of 30 "severe covid-19" cases were not admitted to hospital; Table S14).

And on preventing death from covid-19, there are too few data to draw conclusions—a total of three covid-19 related deaths (one on vaccine, two on placebo). There were 29 total deaths during blinded follow-up (15 in the vaccine arm; 14 in placebo).

The crucial question, however, is whether the waning efficacy seen in the primary endpoint data also applies to the vaccine's efficacy against severe disease. Unfortunately, Pfizer's new preprint does not report the results in a way that allows for evaluating this question.

Approval imminent without data transparency, or even an advisory committee meeting?

Last December, with limited data, the FDA granted Pfizer's vaccine an EUA, enabling access to all Americans who wanted one. It sent a clear message that the FDA could both address the enormous demand for vaccines without compromising on the science. A "full approval" could remain a high bar.

But here we are, with FDA reportedly on the verge of granting a marketing license 13 months into the still ongoing, two year pivotal trial, with no reported data past 13 March 2021, unclear efficacy after six months due to unblinding, evidence of waning protection irrespective of the Delta variant, and limited reporting of safety data. (The preprint reports "decreased appetite, lethargy, asthenia, malaise, night sweats, and hyperhidrosis were new adverse events attributable to BNT162b2 not previously identified in earlier reports," but provides no data tables showing the frequency of these, or other, adverse events.)

It's not helping matters that FDA now says it won't convene its advisory committee to discuss the data ahead of approving Pfizer's vaccine. (Last August, to address vaccine hesitancy, the agency had "committed to use an advisory committee composed of independent experts to ensure deliberations about authorization or licensure are transparent for the public.")

Prior to the preprint, my view, along with a group of around 30 clinicians, scientists, and patient advocates, was that there were simply too many open questions about all covid-19 vaccines to support approving any this year. The preprint has, unfortunately, addressed very few of those open questions, and has raised some new ones.

I reiterate our call: "slow down and get the science right—there is no legitimate reason to hurry to grant a license to a coronavirus vaccine."

FDA should be demanding that the companies complete the two year follow-up, as originally planned (even without a placebo group, much can still be learned about safety). They should demand adequate, controlled studies using patient outcomes in the now substantial population of people who have recovered from covid. And regulators should bolster public trust by helping ensure that everyone can access the underlying data.

Peter Doshi, senior editor, The *BMJ*.

Competing interests: I helped organize the Coalition Advocating for Adequately Licensed Medicines (CAALM), which has formally petitioned the FDA to refrain from fully approving any covid-19 vaccine this year (docket FDA-2021-P-0786). A full list of competing interests is available here. The views and opinions expressed here are mine and do not necessarily reflect official policy or the position of the University of Maryland.

Provenance: commissioned; externally peer-reviewed.

Footnote: Calculations in this article are as follows. "About 1 month" past month 4 is based on the final row of Fig 2 in the preprint: 1030/12670*12 = 0.98 months (vaccine group) and 895/11802*12 = 0.91 months (placebo group). "53%" is based on Fig 2: (12670+11802)/(23040+23037). "4.4 months" is based on the average of 8412/22505*12 = 4.5 (vaccine) and 8124/22434*12 = 4.3 (placebo) in Fig 2.

https://blogs.bmj.com/bmj/2021/08/23/does-the-fda-think-these-data-justify-the-first-full-approval-of-a-covid-19-vaccine/

Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Elsevier hereby grants permission to make all its COVID-19-related research that is available on the COVID-19 resource centre - including this research content - immediately available in PubMed Central and other publicly funded repositories, such as the WHO COVID database with rights for unrestricted research re-use and analyses in any form or by any means with acknowledgement of the original source. These permissions are granted for free by Elsevier for as long as the COVID-19 resource centre remains active.

Safety and immunogenicity of the ChAdOx1 nCoV-19 vaccine against SARS-CoV-2: a preliminary report of a phase 1/2, single-blind, randomised controlled trial

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Summary

Background The pandemic of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) might be curtailed by vaccination. We assessed the safety, reactogenicity, and immunogenicity of a viral vectored coronavirus vaccine that expresses the spike protein of SARS-CoV-2.

Methods We did a phase 1/2, single-blind, randomised controlled trial in five trial sites in the UK of a chimpanzee adenovirus-vectored vaccine (ChAdOx1 nCoV-19) expressing the SARS-CoV-2 spike protein compared with a meningococcal conjugate vaccine (MenACWY) as control. Healthy adults aged 18–55 years with no history of laboratory confirmed SARS-CoV-2 infection or of COVID-19-like symptoms were randomly assigned (1:1) to receive ChAdOx1 nCoV-19 at a dose of 5×10^{10} viral particles or MenACWY as a single intramuscular injection. A protocol amendment in two of the five sites allowed prophylactic paracetamol to be administered before vaccination. Ten participants assigned to a non-randomised, unblinded ChAdOx1 nCoV-19 prime-boost group received a two-dose schedule, with the booster vaccine administered 28 days after the first dose. Humoral responses at baseline and following vaccination were assessed using a standardised total IgG ELISA against trimeric SARS-CoV-2 spike protein, a muliplexed immunoassay, three live SARS-CoV-2 neutralisation assays (a 50% plaque reduction neutralisation assay [$PRNT_{50}$]; a microneutralisation assay [MNA_{50}, MNA_{80}, and MNA_{90}]; and Marburg VN), and a pseudovirus neutralisation assay. Cellular responses were assessed using an ex-vivo interferon-γ enzyme-linked immunospot assay. The co-primary outcomes are to assess efficacy, as measured by cases of symptomatic virologically confirmed COVID-19, and safety, as measured by the occurrence of serious adverse events. Analyses were done by group allocation in participants who received the vaccine. Safety was assessed over 28 days after vaccination. Here, we report the preliminary findings on safety, reactogenicity, and cellular and humoral immune responses. The study is ongoing, and was registered at ISRCTN, 15281137, and ClinicalTrials.gov, NCT04324606.

Findings Between April 23 and May 21, 2020, 1077 participants were enrolled and assigned to receive either ChAdOx1 nCoV-19 (n=543) or MenACWY (n=534), ten of whom were enrolled in the non-randomised ChAdOx1 nCoV-19 prime-boost group. Local and systemic reactions were more common in the ChAdOx1 nCoV-19 group and many were reduced by use of prophylactic paracetamol, including pain, feeling feverish, chills, muscle ache, headache, and malaise (all $p<0\cdot05$). There were no serious adverse events related to ChAdOx1 nCoV-19. In the ChAdOx1 nCoV-19 group, spike-specific T-cell responses peaked on day 14 (median 856 spot-forming cells per million peripheral blood mononuclear cells, IQR 493–1802; n=43). Anti-spike IgG responses rose by day 28 (median 157 ELISA units [EU], 96–317; n=127), and were boosted following a second dose (639 EU, 360–792; n=10). Neutralising antibody responses against SARS-CoV-2 were detected in 32 (91%) of 35 participants after a single dose when measured in MNA_{80} and in 35 (100%) participants when measured in $PRNT_{50}$. After a booster dose, all participants had neutralising activity (nine of nine in MNA_{80} at day 42 and ten of ten in Marburg VN on day 56). Neutralising antibody responses correlated strongly with antibody levels measured by ELISA ($R^2=0\cdot67$ by Marburg VN; $p<0\cdot001$).

Interpretation ChAdOx1 nCoV-19 showed an acceptable safety profile, and homologous boosting increased antibody responses. These results, together with the induction of both humoral and cellular immune responses, support large-scale evaluation of this candidate vaccine in an ongoing phase 3 programme.

Funding UK Research and Innovation, Coalition for Epidemic Preparedness Innovations, National Institute for Health Research (NIHR), NIHR Oxford Biomedical Research Centre, Thames Valley and South Midland's NIHR Clinical Research Network, and the German Center for Infection Research (DZIF), Partner site Gießen-Marburg-Langen.

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Lancet 2020; 396: 467–78

Published **Online** July 20, 2020 https://doi.org/10.1016/S0140-6736(20)31604-4

This online publication has been corrected. The corrected version first appeared at thelancet.com on August 13, 2020, and further correction has been made on November 19, 2020

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See **Online** for appendix 1

See **Online** for appendix 2

Research in context

Evidence before this study

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was identified as the causative agent of COVID-19 in January, 2020. There are currently no licensed vaccines to prevent COVID-19. ChAdOx1 nCoV-19 has previously been reported to be immunogenic and protective against pneumonia in a rhesus macaque challenge model. We searched PubMed for research articles published between database inception and July 6, 2020, using the terms "SARS-CoV-2", "vaccine", "clinical trial", and "phase". No language restrictions were applied. We identified one published clinical trial, describing a trial done in China of an adenovirus-5-vectored vaccine against SARS-CoV-2, using a single dose at three different dose levels. The vaccine was tolerated, with reactogenicity increased at the highest dose. Antibodies, neutralising antibodies in a proportion of vaccinees, and cellular responses were induced. A further clinical trial, which was done in the USA, has been reported on *medRxiv*. The vaccine was a lipid nanoparticle-formulated, nucleoside-modified, mRNA vaccine that encodes trimerised SARS-CoV-2 spike glycoprotein receptor binding domain administered at one or two doses of three dose levels. The vaccine was tolerated, with reactogenicity increased at the highest dose. Antibodies and neutralising antibodies were induced in a dose-dependent manner and increased after a second dose.

Added value of this study

We report the results of the first clinical study of ChAdOx1 nCoV-19 (AZD1222). The vaccine was safe and tolerated, with reduced reactogenicity when paracetamol was used prophylactically for the first 24 h after vaccination. Reactogenicity was reduced after a second dose. Humoral responses to SARS-CoV-2 spike protein peaked by day 28 post prime and cellular responses were induced in all participants by day 14. Neutralising antibodies were induced in all participants after a second vaccine dose. After two doses, potent cellular and humoral immunogenicity was present in all participants studied.

Implications of all the available evidence

A vaccine against SARS-CoV-2 could be used to prevent infection, disease, and death in the global population, with high-risk populations such as hospital workers and older adults (eg, ≥65 years of age) prioritised to receive vaccination. The immune correlates of protection against SARS-CoV-2 have not yet been determined. Immunisation with ChAdOx1 nCoV-19 results in rapid induction of both humoral and cellular immune responses against SARS-CoV-2, with increased responses after a second dose. Further clinical studies, including in older adults, should be done with this vaccine.

Introduction

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) emerged as a zoonotic virus late in 2019 and is the causative agent of COVID-19. Exposure to SARS-CoV-2 can result in a range of clinical outcomes, varying from asymptomatic infection to severe acute respiratory distress and death. SARS-CoV-2 has spread globally and was declared a pandemic on March 11, 2020, by WHO. As of July 19, 2020, more than 14 million people globally have been infected with more than 597 000 deaths.[1] The pandemic has placed substantial pressures on health systems delivering care for patients with COVID-19 and caused disruption of non-COVID-19 health-care provision, in addition to negative effects on the global economy. Further health consequences are anticipated.

No vaccines have been approved for prevention of COVID-19. There are currently more than 137 candidates undergoing preclinical development and 23 in early clinical development, according to WHO.[2] An ideal vaccine against SARS-CoV-2 would be effective after one or two vaccinations; would protect target populations such as older adults and those with comorbidities, including immunocompromised individuals; would confer protection for a minimum of 6 months; and would reduce onward transmission of the virus to contacts. Replication-deficient viral vectored vaccines have been used in immunocompromised individuals with no safety concerns[3–5] and ChAdOx1 vaccines are immunogenic in older adults[6] and can be manufactured at large scale, making this platform technology a promising candidate to develop a vaccine for the prevention of COVID-19. Adenoviral vectors have previously been combined with DNA and poxviral vectors to attempt to improve immunogenicity, with adenovirus or modified vaccinia virus Ankara prime-boost regimens showing enhancement of both cellular and humoral immunity. Use of homologous adenoviral regimens has largely been avoided because of presumed induction of antivector immunity, inhibiting the potency of a second dose.

Coronaviruses are enveloped, positive sense single-stranded RNA viruses with a glycoprotein spike on the surface, which mediates receptor binding and cell entry during infection. The roles of the spike protein in receptor binding and membrane fusion make it an attractive vaccine antigen. We have previously shown that a single dose of ChAdOx1 MERS, a chimpanzee adenovirus-vectored vaccine that encodes the spike protein of Middle East respiratory syndrome coronavirus (MERS-CoV), protected non-human primates against MERS-CoV-induced disease,[7] and data from a phase 1 clinical trial showed that ChAdOx1 MERS was safe and well tolerated at all three doses tested (5×10^9 viral particles, $2{\cdot}5\times10^{10}$ viral particles, and 5×10^{10} viral particles).[8] In addition, the highest dose elicited both humoral and cellular responses

against MERS-CoV in all vaccinees within 1 month of vaccination.

The ChAdOx1 nCoV-19 vaccine (AZD1222) consists of the replication-deficient simian adenovirus vector ChAdOx1, containing the full-length structural surface glycoprotein (spike protein) of SARS-CoV-2, with a tissue plasminogen activator leader sequence. ChAdOx1 nCoV-19 expresses a codon-optimised coding sequence for the spike protein (GenBank accession number MN908947).

In rhesus macaques, a single vaccination with ChAdOx1 nCoV-19 induced humoral and cellular immune responses. Protection against lower respiratory tract infection was observed in vaccinated non-human primates after high-dose SARS-CoV-2 challenge.[9]

We did a phase 1/2 single-blind, randomised controlled trial of ChAdOx1 nCoV-19 compared with a licensed meningococcal group A, C, W-135, and Y conjugate vaccine (MenACWY; Nimenrix, Pfizer, UK), as control vaccine, in healthy adults in the UK. In this preliminary report, we describe the immunogenicity, reactogenicity, and safety of vaccination with 5×10^{10} viral particles of ChAdOx1 nCoV-19 in single-dose and two-dose regimens.

Methods

Study design and participants

This phase 1/2, participant-blinded, multicentre, randomised controlled trial is being done at five centres in the UK (Centre for Clinical Vaccinology and Tropical Medicine, University of Oxford; NIHR Southampton Clinical Research Facility, University Hospital Southampton NHS Foundation Trust, Southampton; Clinical Research Facility, Imperial College London; St Georges University of London and University Hospital NHS Foundation Trust; and University Hospitals Bristol and Weston NHS Foundation Trust). Healthy adult participants aged 18–55 years were recruited through local advertisements. All participants underwent a screening visit where a full medical history and examination was taken in addition to blood and urine tests (HIV; hepatitis B and C serology; full blood count; kidney and liver function tests; and urinary screen for blood, protein, and glucose and a pregnancy test done in women of childbearing potential). Volunteers with a history of laboratory confirmed SARS-CoV-2 infection; those at higher risk for SARS-CoV-2 exposure pre-enrolment (ie, front-line health-care workers working in emergency departments, intensive care units, and COVID-19 wards, and close contacts of confirmed COVID-19 cases; see appendix 1 p 82 for further details); and those with a new onset of fever, cough, shortness of breath, and anosmia or ageusia since Feb 1, 2020, were excluded from the study. An amendment to the study protocol (amendment date April 21, 2020) allowed for recruitment of health-care workers with a negative SARS-CoV-2 serology at screening, once an antibody test became available. As it was not possible to screen for negative SARS-CoV-2 serology in all participants, some enrolled participants had high-level anti-spike antibodies at baseline and their data are included in all analyses. Full details of the eligibility criteria are described in the trial protocol provided in the appendix 1 (pp 80–82).

Written informed consent was obtained from all participants, and the trial is being done in accordance with the principles of the Declaration of Helsinki and Good Clinical Practice. This study was approved in the UK by the Medicines and Healthcare products Regulatory Agency (reference 21584/0424/001-0001) and the South Central Berkshire Research Ethics Committee (reference 20/SC/0145). Vaccine use was authorised by Genetically Modified Organisms Safety Committees at each participating site.

Randomisation and masking

Participants were randomly assigned (1:1) to receive either the ChAdOx1 nCoV-19 vaccine or the MenACWY vaccine. MenACWY was used as a comparator vaccine to maintain blinding of participants who experienced local or systemic reactions, since these reactions are a known association with viral vector vaccinations. Use of saline as a placebo would risk unblinding participants as those who had notable reactions would know they were in the ChAdOx1 nCoV-19 vaccine group.

Randomisation lists, using block randomisation stratified by study group and study site, were generated by the study statistician (MV). Block sizes of two and four were chosen to align with the study group sizes and the sequence of enrolment, and varied across study groups. Computer randomisation was done with full allocation concealment within the secure web platform used for the study electronic case report form (REDCap version 9.5.22; Vanderbilt University, Nashville, TN, USA). The trial staff administering the vaccine prepared vaccines out of sight of the participants and syringes were covered with an opaque material until ready for administration to ensure blinding of participants. Clinical investigators and the laboratory team remained blinded to group allocation.

Procedures

The recombinant adenovirus for ChAdOx1 nCoV-19 was produced as previously described.[10] The vaccine was manufactured according to current Good Manufacturing Practice by the Clinical BioManufacturing Facility (University of Oxford, Oxford, UK) as previously described,[11] with only minor modifications, as described in the Investigational Medicinal Product Dossier and approved by the regulatory agency in the UK. ChAdOx1 nCoV-19 was administered at a dose of 5×10^{10} viral particles. The MenACWY vaccine was provided by the UK Department of Health and Social Care and administered as per summary of product characteristics at the standard dose of 0·5 mL. Vaccines were administered as a single intramuscular injection into the deltoid.

Participants were recruited and followed up according to groups. Participants were recruited first for groups 1

and 3, then group 2, and then group 4. Group 1 (the phase 1 component of the study) consisted of participants who had intensive early follow-up visits for safety and immunogenicity purposes at days 3, 7, 14, 28, and 56 after vaccination. Group 2 consisted of participants who had higher blood volumes drawn for humoral and cellular immunogenicity assessment than group 4, which consisted of participants who had a serum sample drawn for humoral immunology assessments only. Group 3 consisted of ten participants who were enrolled in a non-randomised prime-boost group and received a booster ChAdOx1 nCoV-19 administered 28 days after the first dose. These participants were not blinded and had extensive follow-up for safety and immunogenicity purposes, as per group 1, after each dose. A staggered-enrolment approach was used for the first two, six, and 90 participants recruited in groups 1 and 3 (appendix 1 p 89) and interim safety reviews with the independent Data and Safety Monitoring Board were done before proceeding with vaccinations in larger numbers of volunteers. Volunteers were considered enrolled into the trial at the point of vaccination.

Participants in all groups had blood samples drawn and clinical assessments for safety as well as immunology at days 0 and 28, and will also be followed up at days 184 and 364. A later amendment to the protocol (amendment date June 22, 2020) provided for additional testing of booster vaccinations in a subset of participants, the results of which are not yet available and are not included in this Article.

In two of the five trial sites (Oxford and Southampton), a protocol amendment (amendment date May 6, 2020) was implemented to allow prophylactic paracetamol to be administered before vaccination and participants were advised to continue with 1 g of paracetamol every 6 h for 24 h to reduce vaccine-associated reactions. All participants enrolled after the protocol amendment at these two sites were given prophylactic paracetamol and randomised equally to the vaccine or control arms of the study.

Participants were observed in the clinic for 30–60 min after the vaccination procedure and were asked to record any adverse events using electronic diaries during the 28-day follow-up period. Expected and protocol-defined local site reactions (injection site pain, tenderness, warmth, redness, swelling, induration, and itch) and systemic symptoms (malaise, muscle ache, joint pain, fatigue, nausea, headache, chills, feverishness [ie, a self-reported feeling of having a fever], and objective fever defined as an oral temperature of 38°C or higher) were recorded for 7 days. All other events were recorded for 28 days and serious adverse events are recorded throughout the follow-up period.

Severity of adverse events are graded with the following criteria: mild (transient or mild discomfort for <48 h, no interference with activity, and no medical intervention or therapy required), moderate (mild to moderate limitation in activity [some assistance might be needed] and no or minimal medical intervention or therapy required), severe (marked limitation in activity [some assistance usually required] and medical intervention or therapy required), and potentially life-threatening (requires assessment in emergency department or hospitalisation). Unsolicited adverse events are reviewed for causality by two clinicians blinded to group allocation, and events considered to be possibly, probably, or definitely related to the study vaccines were reported. Laboratory adverse events were graded by use of site-specific toxicity tables, which were adapted from the US Food and Drug Administration toxicity grading scale.

Cellular responses were assessed using an ex-vivo interferon-γ enzyme-linked immunospot (ELISpot) assay to enumerate antigen-specific T cells. Humoral responses at baseline and following vaccination were assessed using a standardised total IgG ELISA against trimeric SARS CoV-2 spike protein, a muliplexed immunoassay (Meso Scale Discovery multiplexed immunoassay [MIA] against spike and receptor binding domain), three live SARS-CoV-2 neutralisation assays (Public Health England [PHE] plaque reduction neutralisation test [PRNT IC_{50}], PHE microneutralisation assay [MNA IC_{50}, IC_{80}, IC_{90}], and Marburg virus neutralisation [VN IC_{100}]), and a pseudovirus neutralisation assay (PseudoNA IC_{50}). PHE PRNT is a live neutralisation assay and was done at PHE (Porton Down, UK). PHE MNA is a rapid microneutralisation assay, which was conducted in the same laboratory. The third assay, Marburg VN, was conducted at Marburg University (Marburg, Germany). Full details on the assays are provided in the appendix 1 (pp 31–34). Owing to the labour-intensive nature of some of these assays, we prioritised analysis of samples from the ChAdOx1 nCoV-19 group, randomly selecting more samples from ChAdOx1 nCoV-19 participants than control samples to be sent for analysis.

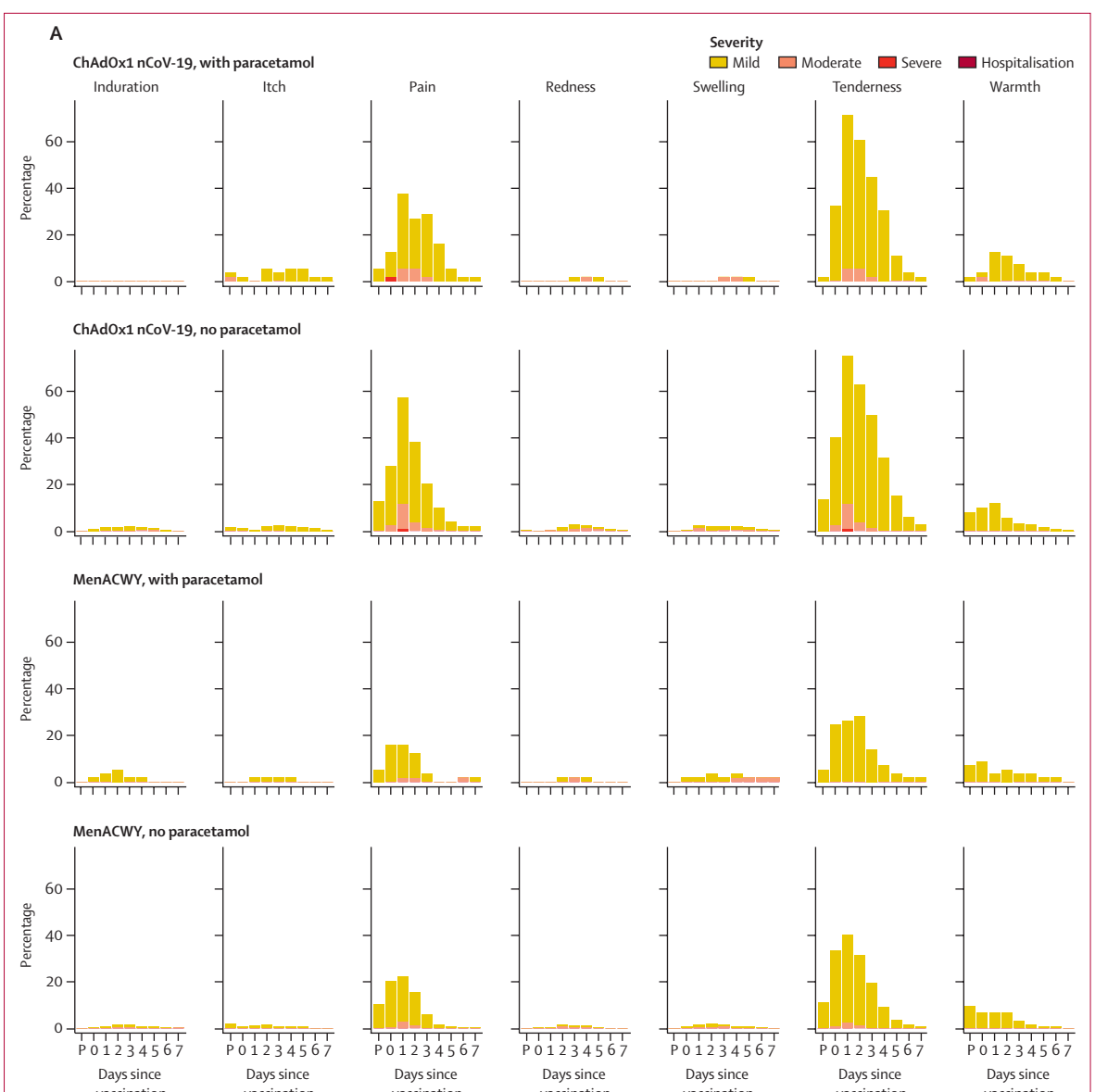
Convalescent plasma samples from adults (≥18 years) with PCR-positive SARS-CoV-2 infection were obtained from symptomatic patients admitted to hospital or from surveillance on health-care workers who did not have symptomatic infection. These samples were tested using standardised ELISA, MIA, PseudoNA, and Marburg VN. Different samples were analysed across the assays, dependent on sample availability, laboratory capacity, and assay-specific requirements. Where multiple longitudinal samples were available for the same participant, only one timepoint is included in the analyses in this Article and the earliest timepoint (at least 20 days after initial symptoms) was selected.

Outcomes

The co-primary outcomes are to assess efficacy as measured by cases of symptomatic virologically confirmed COVID-19 and safety of the vaccine as

measured by the occurrence of serious adverse events. Secondary outcomes include safety, reactogenicity, and immunogenicity profiles of ChAdOx1 nCoV-19, and efficacy against hospital-attended COVID-19, death, and seroconversion against non-spike proteins (appendix 1 pp 72–73). Preliminary results for secondary endpoints are reported here: occurrence of local and systemic reactogenicity signs and symptoms for 7 days after vaccination; occurrence of unsolicited adverse events for 28 days after vaccination; change from day 0 (baseline) to day 28 for safety laboratory measures; and cellular and humoral immunogenicity of ChAdOx1 nCoV-19. Neutralising antibodies and laboratory adverse events were tested on participants in groups 1 and 3 only. Unsolicited adverse events are reported for group 1 only.

The convalescent sample collection of PCR-positive hospitalised patients with COVID-19 or asymptomatic health-care workers was done to characterise the immunological properties of COVID-19 and not for the purposes of the clinical trial (Gastrointestinal Illness in Oxford: COVID substudy [Sheffield Research Ethics Committee reference: 16/YH/0247], ISARIC/WHO Clinical Characterisation Protocol for Severe Emerging Infections [Oxford Research Ethics Committee C reference 13/SC/0149], and Sepsis Immunomics project [Oxford Research Ethics Committee C, reference 19/SC/0296]).



(Figure 1 continues on next page)

Statistical analysis

Safety endpoints are described as frequencies (%) with 95% binomial exact CIs. Medians and IQRs are presented for immunological endpoints and analyses are considered descriptive only, as the full set of samples have not yet been analysed on all platforms and therefore results reported here are preliminary. Participants were analysed according to the group to which they were randomised. To assess the effect of prophylactic paracetamol use, the occurence of adverse reactions in the first 2 days after vaccination was analysed as a binary variable using adjusted logistic regression with results presented as adjusted odds ratios. The model adjusted for age, sex, occupation (health-care worker or not), smoking, alcohol consumption, and body-mass index. To assess the relationship between responses on different assays, linear regression was used to analyse log-transformed post-baseline values. Statistical analyses were done using SAS version 9.4 and R version 3.6.1 or later.

The sample size for the study was determined by the number of doses of vaccine that were available for use after the initial clinical manufacturing process. Sample sizes for efficacy are based on the number of primary outcome events that accrue and are presented in the protocol

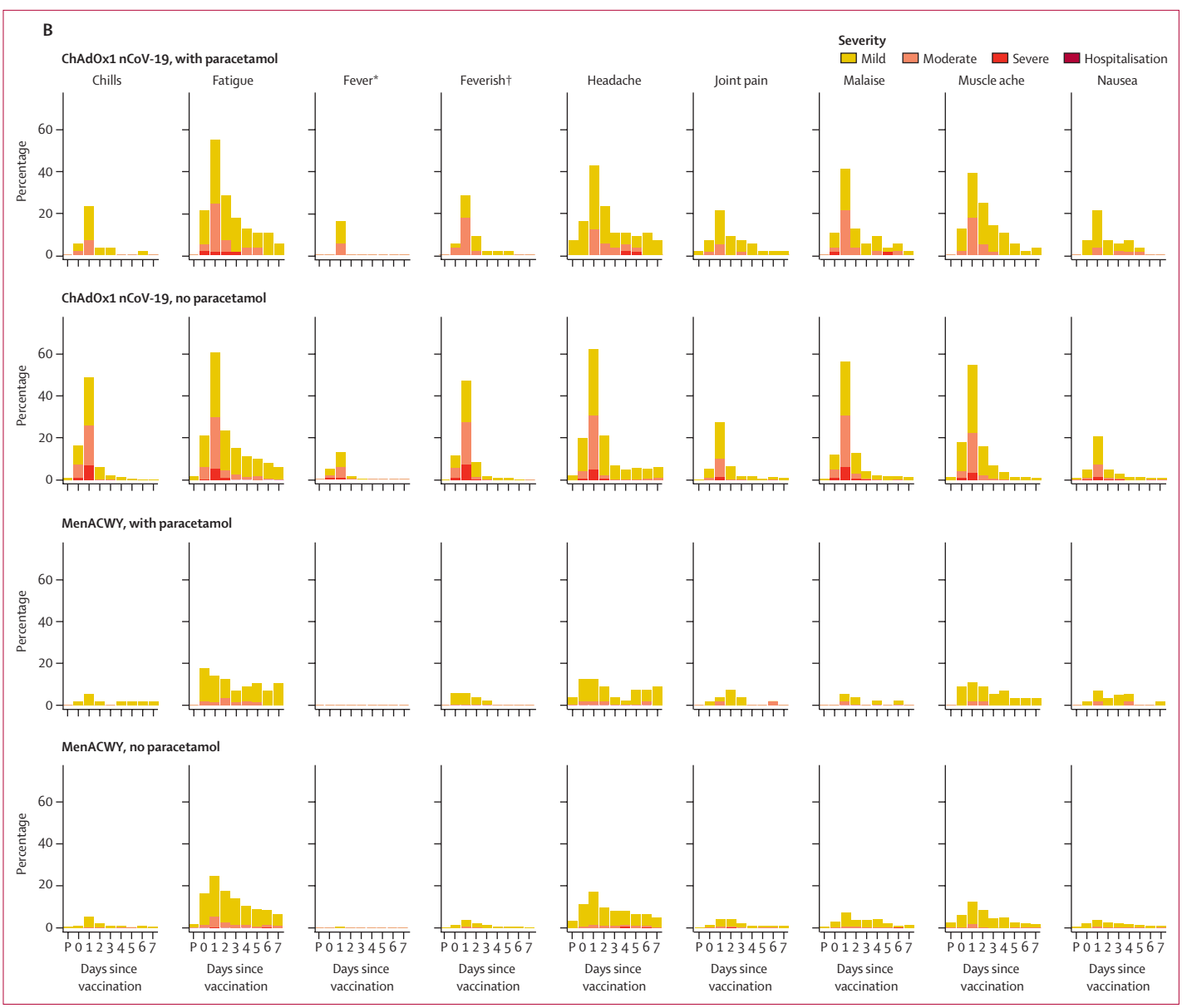


Figure 1: **Solicited local (A) and systemic (B) adverse reactions in first 7 days after vaccination as recorded in participant symptom electronic diaries**
Day 0 is the day of vaccination. P=60-min post-vaccination observation period in the clinic. MenACWY=meningococcal group A, C, W-135, and Y conjugate vaccine. *Mild: 38·0°C to <38·5°C; moderate: 38·5°C to <39·0°C; severe: ≥39·0°C. †Self-reported feeling of feverishness.

(appendix 1 pp 116–117). Efficacy analyses have not yet been done and are not included in this Article.

An independent data and safety monitoring board provided safety oversight (appendix 1 p 46). This study is registered with ClinicalTrials.gov, NCT04324606, and with ISRCTN, 15281137.

Role of the funding source

The funders of the study had no role in the study design, data collection, data analysis, data interpretation, or writing of the report. All authors had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

Between April 23 and May 21, 2020, 1077 participants were enrolled into the study and assigned to vaccination with either ChAdOx1 nCoV-19 (n=543) or MenACWY (n=534; appendix 1 p 3); ten of these participants were enrolled in group 3, the prime-boost group, and thus were not randomly assigned. 88 participants were included in group 1, 412 in group 2, and 567 in group 4 (appendix 1

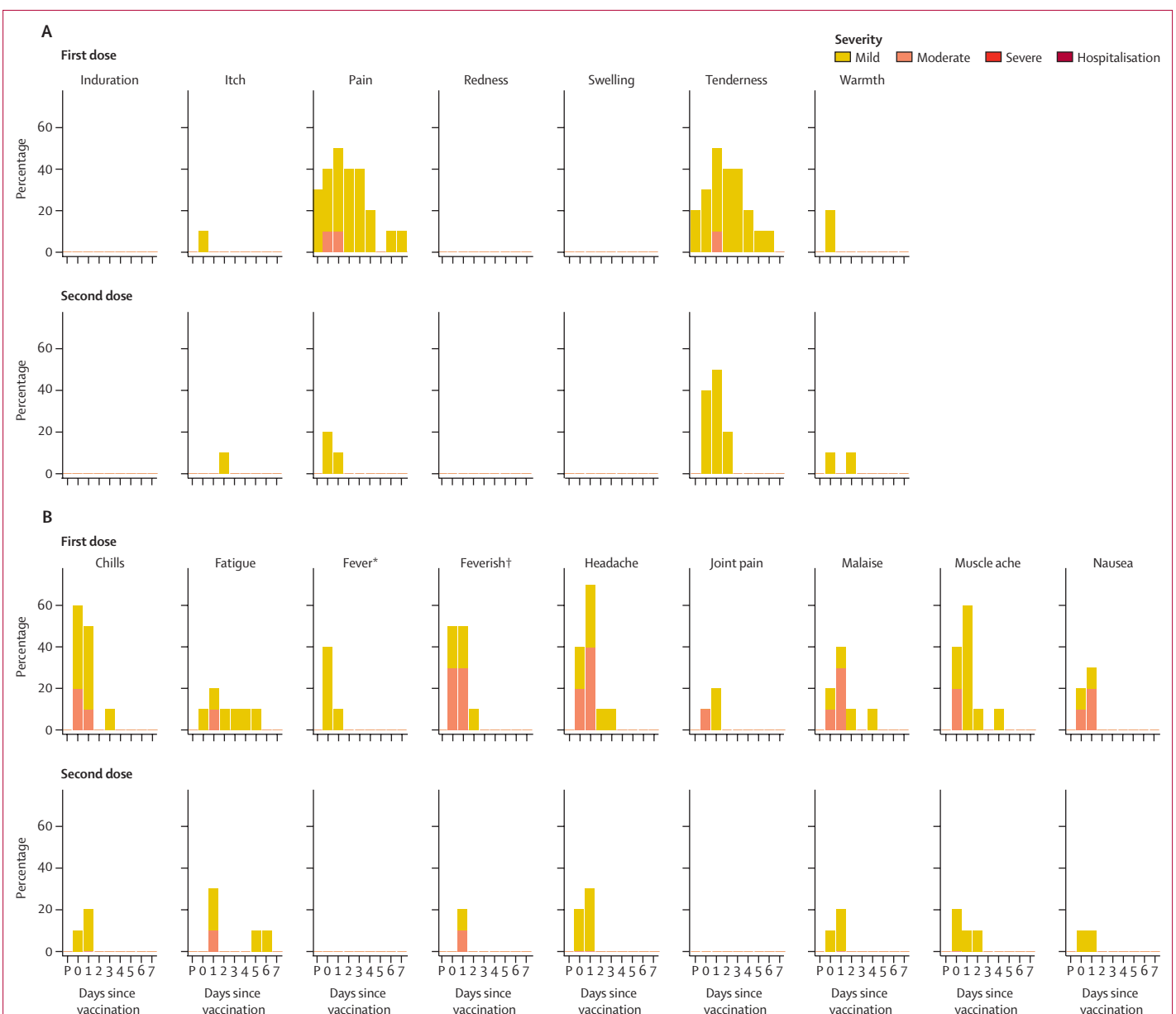


Figure 2: **Solicited local (A) and systemic (B) adverse reactions in first 7 days after priming and booster doses of ChAdOx1 nCoV-19 in the non-randomised subset of ten participants**
Day 0 is the day of vaccination. P=60-min post-vaccination observation period in the clinic. *Mild: 38·0°C to <38·5°C; moderate: 38·5°C to <39·0°C; severe: ≥39·0°C. †Self-reported feeling of feverishness.

p 3). All randomised participants were vaccinated; one participant in the MenACWY group received the ChAdOx1 nCoV-19 vaccine (appendix 1 p 3).

The median age of participants was 35 years (IQR 28–44 years), 536 (49·8%) participants were female and 541 (50·2%) were male, and the majority of participants (979 [90·9%]) were white (appendix 1 p 4). Baseline characteristics seemed similar between randomised groups (appendix 1 p 4).

56 participants in the ChAdOx1 nCoV-19 group and 57 in the MenACWY group received prophylactic paracetamol. In those who did not receive prophylactic paracetamol, 328 (67%) of 487 participants in the ChAdOx1 nCoV-19 group and 180 (38%) of 477 participants in the MenACWY group reported pain after vaccination, which was mostly mild to moderate in intensity (appendix 1 pp 5–7). With prophylactic paracetamol, pain was reported by fewer participants: 28 (50%) in the ChAdOx1 nCoV-19 group and 18 (32%) in the MenACWY group. Tenderness of mostly mild intensity was reported in the ChAdOx1 nCoV-19 group by 403 (83%) participants without paracetamol and 43 (77%) with paracetamol, and in the MenACWY group by 276 (58%) participants without paracetamol and 26 (46%) with paracetamol (figure 1; appendix 1 pp 5–7).

Fatigue and headache were the most commonly reported systemic reactions. Fatigue was reported in the ChAdOx1 nCoV-19 group by 340 (70%) participants without paracetamol and 40 (71%) with paracetamol and in the MenACWY group by 227 (48%) participants without paracetamol and 26 (46%) with paracetamol, whereas headaches were reported in the ChAdOx1 nCoV-19 group by 331 (68%) participants without paracetamol and 34 (61%) with paracetamol and in the MenACWY group by 195 (41%) participants without paracetamol and 21 (37%) participants with paracetamol.

Other systemic adverse reactions were common in the ChAdOx1 nCoV-19 group: muscle ache (294 [60%] participants without paracetamol and 27 [48%] with paracetamol), malaise (296 [61%] and 27 [48%]), chills (272 [56%] and 15 [27%]); and feeling feverish (250 [51%] and 20 [36%]). In the of ChAdOx1 nCoV-19 group, 87 (18%) participants without paracetamol and nine (16%) participants with paracetamol reported a temperature of at least 38°C, and eight (2%) patients without paracetamol had a temperature of at least 39°C. In comparison, two (<1%) of those receiving MenACWY reported a fever of at least 38°C, none of whom were receiving prophylactic paracetamol (figure 1; appendix 1 pp 5–7).

The severity and intensity of local and systemic reactions was highest on day 1 after vaccination (figure 1).

Adjusted analysis of the effect of prophylactic paracetamol on adverse reactions of any severity in the first 2 days after vaccination with ChAdOx1 nCoV-19 showed significant reductions in pain, feeling feverish, chills, muscle ache, headache, and malaise (appendix 1 pp 10–11).

All ten participants in the prime-boost group received their booster vaccine at day 28; solicited local and systemic reactions were measured in these participants for 7 days after both the prime and booster doses. The reactogenicity profile after the second dose appeared less severe in this subset, although the small number of participants in this group led to wide CIs (figure 2; appendix 1 pp 8–9).

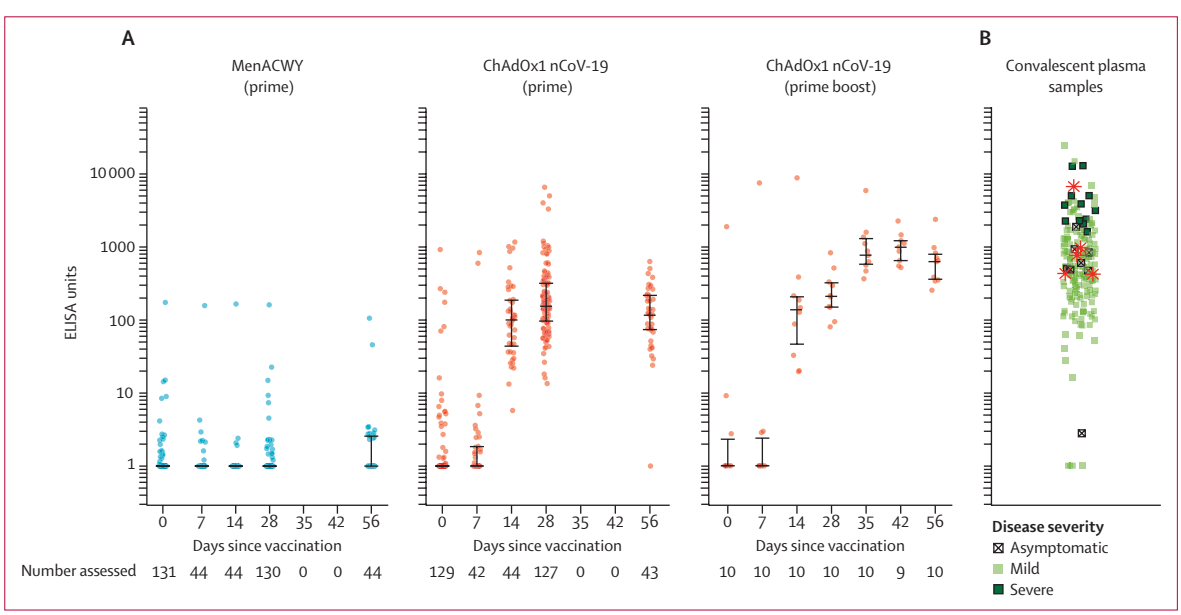


Figure 3: **SARS-CoV-2 IgG response by standardised ELISA to spike protein in trial participants (A) and in 180 convalescent plasma samples from 172 patients with PCR-confirmed COVID-19 and eight asymptomatic health-care workers (B)**

Error bars show median (IQR). Participants in the prime boost group received their second dose at day 28. Lower limit of quantification is 1 ELISA unit. Red stars in panel B show five samples also tested on the Marburg VN assay (see figure 4). MenACWY=meningococcal group A, C, W-135, and Y conjugate vaccine. SARS-CoV-2=severe acute respiratory syndrome coronavirus 2.

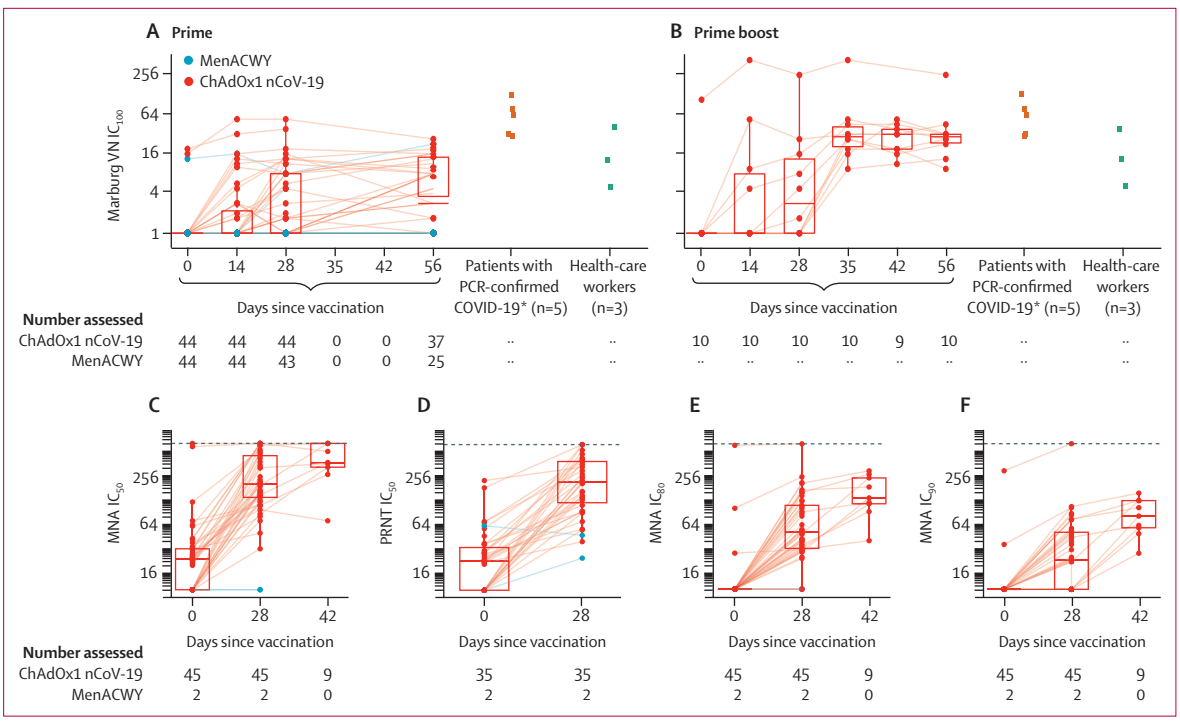


Figure 4: **Live SARS-CoV-2 neutralisation assays (Marburg VN and PHE PRNT$_{50}$) and microneutralisation assays (PHE MNA)**
Panels A and B show live SARS-CoV-2 neutralisation (Marburg VN) in prime (A) and prime boost (B) trial participants (boosted at day 28) and convalescent plasma from patients with PCR-confirmed COVID-19 and asymptomatic health-care workers. Panels C, E, and F show the PHE MNA (at IC$_{50}$, IC$_{80}$, and IC$_{90}$, respectively) and panel D the PHE PRNT$_{50}$. The day 42 timepoint was only measured in participants who received a booster dose at day 28. Solid lines connect samples from the same participant. Boxes show median (IQR). Dotted lines show upper limits of detection. MenACWY=meningococcal group A, C, W-135, and Y conjugate vaccine. PHE=Public Health England. MNA=microneutralisation assay. PRNT=plaque reduction neutralisation test. VN=virus neutralisation. IC=inhibitory concentration. SARS-CoV-2=severe acute respiratory syndrome coronavirus 2. *ELISA results for these five convalescent plasma samples are shown in figure 3 as red stars.

Unsolicited adverse events in the 28 days following vaccination considered to be possibly, probably, or definitely related to ChAdOx1 nCoV-19 were predominantly mild and moderate in nature and resolved within the follow-up period (appendix 1 pp 12–15). Laboratory adverse events considered to be at least possibly related to the study intervention were self-limiting and predominantly mild or moderate in severity (data not shown). Transient haematological changes from baseline (neutropenia) were observed in 25 (46%) of 54 participants in the ChAdOx1 nCoV-19 group compared with three (7%) of 44 participants in the MenACWY group. There was one serious adverse event in the MenACWY group consisting of a new diagnosis of haemolytic anaemia, occurring 9 days after vaccination. The participant was clinically well throughout the study. The event was reported as a suspected unexpected serious adverse reaction relating to the MenACWY vaccine.

In the ChAdOx1 nCoV-19 group, antibodies against SARS-CoV-2 spike protein peaked by day 28 (median 157 ELISA units [EU], IQR 96–317; n=127) and remained elevated to day 56 (119 EU, 70–203; n=43) in participants who received only one dose, and increased to a median of 639 EU (360–792) at day 56 in the ten participants who received a booster dose (figure 3).

Similar increases in serum antibody levels to both the spike protein and the receptor binding domain by day 28 and after a booster dose were observed when measured by MIA (appendix 1 p 16). Immunogenicity among those who were advised to take paracetamol prophylactically was

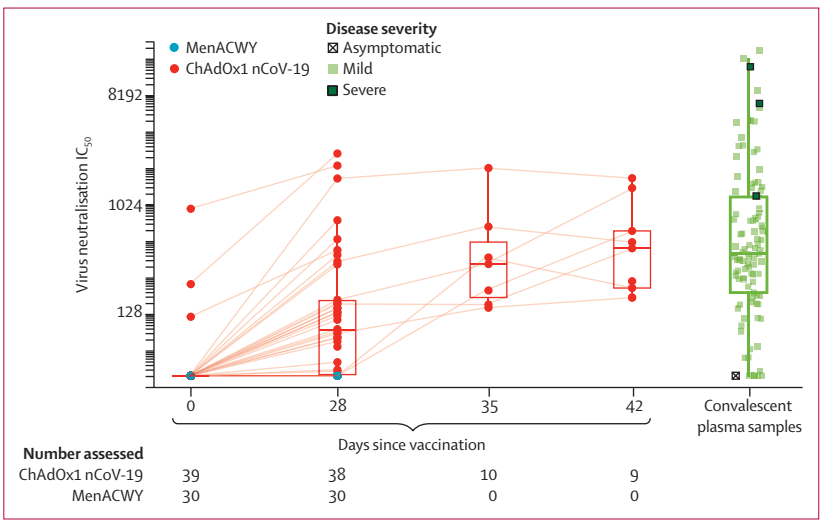


Figure 5: **PseudoNA results in trial participants and in convalescent plasma samples from 146 patients with PCR-confirmed COVID-19 and 24 asymptomatic health-care workers**
Solid lines connect samples from the same participant. Boxes show median (IQR). Results for days 35 and 42 are samples from participants who received a booster dose at day 28. IC=inhibitory concentration. MenACWY=meningococcal group A, C, W-135, and Y conjugate vaccine.

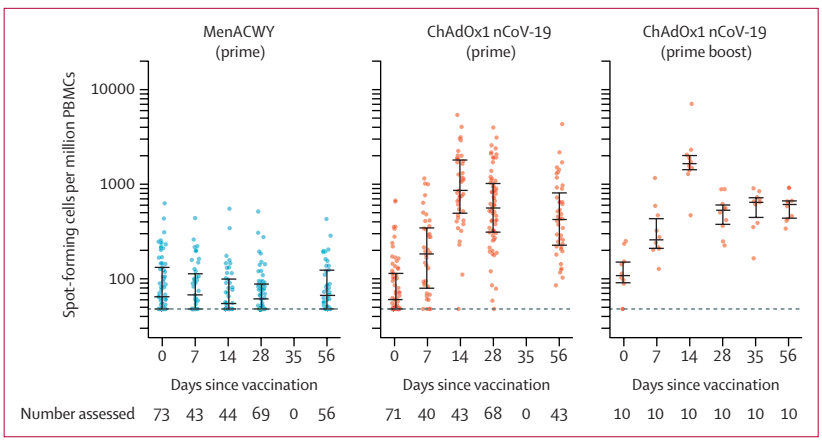


Figure 6: **Interferon-γ ELISpot response to peptides spanning the SARS-CoV-2 spike vaccine insert**
Error bars show median (IQR). The lower limit of detection, indicated with the dotted line, is 48 spot-forming cells per million PBMCs. PBMC=peripheral blood mononuclear cell. SARS-CoV-2=severe acute respiratory syndrome coronavirus 2. ELISpot=enzyme linked immunospot. MenACWY=meningococcal group A, C, W-135, and Y conjugate vaccine.

similar to that seen among those who were not advised to use it prophylactically (data not shown).

In the PHE $PRNT_{50}$ assay, which determined the extent to which serum can be diluted and still reduce SARS-CoV-2 plaque formation by 50%, 35 (100%) of 35 participants achieved neutralising titres with a median titre of 218 (IQR 122–395) at day 28 and similar results were obtained with the PHE MNA_{80} assay, with titres inducing 80% virus neutralisation achieved in 32 (91%) of 35 participants after one dose (median titre 51, 32–103), and in nine (100%) of nine participants after the booster dose (median titre 136, 115–241; figure 4; appendix 1 pp 17–19). In the Marburg VN assay, 23 (62%) of 37 recipients had neutralising antibodies that induced complete inhibition of the cytopathic effect caused by SARS-CoV-2 by day 56 after one dose, as did ten (100%) of ten participants after a booster dose, with a median titre of 29 (24–32; figure 4).

Titres from the PseudoNA assay and the Marburg VN assay correlated positively with other live virus neutralisation assay titres and with ELISA (PseudoNA R^2=0·53 and Marburg VN R^2=0·67; both p<0·001; figure 4, 5; appendix 1 pp 20–21). We included responses following natural exposure as a point of reference for vaccine response data, and found that vaccine-induced responses were in a similar range (figure 5). Interferon-γ ELISpot responses against SARS-CoV-2 spike peptides peaked at 856 spot-forming cells per million peripheral blood mononuclear cells (IQR 493–1802; n=43) at day 14, declining to 424 (221–799; n=43) by day 56 after vaccination (figure 6).

A small number (four [4%] of 98) participants had neutralising antibody titres greater than 8 against SARS-CoV-2 spike protein before vaccination (Marburg VN) and 11 (4%) of 270 participants had high ELISA titres at baseline, representing possible prior asymptomatic infection.

Before vaccination, only one (1%) of 98 participants who were tested had high titre (>200) neutralising antibodies against ChAdOx1. Antibodies were detectable at a lower level in a further 18 (18%) participants, and in 79 (81%) participants there were no detectable anti-ChAdOx1 antibodies. We found no relationship between presence of low-level antibodies to ChAdOx1 on the day of vaccination and the ELISA titre to SARS-CoV-2 spike protein in those randomly assigned to receive ChAdOx1 nCoV-19 (appendix 1 p 22).

Discussion

Our preliminary findings show that the candidate ChAdOx1 nCoV-19 vaccine given as a single dose was safe and tolerated, despite a higher reactogenicity profile than the control vaccine, MenACWY. No serious adverse reactions to ChAdOx1 nCoV-19 occurred. The majority of adverse events reported were mild or moderate in severity, and all were self-limiting. The profile of adverse events reported here is similar to that for other ChAdOx1-vectored vaccines and other closely related simian adenoviruses, such as ChAdOx2, ChAd3, and ChAd63, expressing multiple different antigens[8,12–14] at this dose level, as well as to some licensed vaccines.[15] A dose of 5×10^{10} viral particles was chosen on the basis of our previous experience with ChAdOx1 MERS, where despite increased reactogenicity, a dose–response relationship with neutralising antibodies was observed.[8] The protocol was written when the pandemic was accelerating in the UK and a single higher dose was chosen to provide the highest chance of rapid induction of neutralising antibody. In the context of a pandemic wave where a single higher, but more reactogenic, dose might be more likely to rapidly induce protective immunity, the use of prophylactic paracetamol appears to increase tolerability and would reduce confusion with COVID-19 symptoms that might be caused by short-lived vaccine-related symptoms without compromising immunogenicity.

We show that a single dose of ChAdOx1 nCoV-19 elicits an increase in spike-specific antibodies by day 28 and neutralising antibody in all participants after a booster dose. High levels of neutralising antibody at baseline seen in a small number of participants probably indicates prior asymptomatic infection, as potential participants with recent COVID-19-like symptoms or with a history of positive PCR test for SARS-CoV-2 were excluded from the study. Individuals with high titres on the day of vaccination who received ChAdOx1 nCoV-19 were boosted by vaccination.

Neutralising antibodies targeting different epitopes of the spike glycoprotein have been associated with protection from COVID-19 in early preclinical rhesus macaque studies.[16] Although a correlate of protection has not been defined for COVID-19, high levels of neutralising antibodies have been shown in convalescent individuals, with a wide range, as confirmed in our study.[17,18]

Antibodies capable of neutralising live SARS-CoV-2 were induced by day 28 with titres of 51 (PHE MNA_{80}) and 218 (PHE $PRNT_{50}$), and with titres of 29 (Marburg VN) or

136 (PHE MNA_{80}) after a booster dose, as measured using different assays. In a non-human primate study where primary SARS-CoV-2 infection elicited at least short-term protection against reinfection, neutralising antibody titres of the magnitude found in our study after boosting appeared sufficient to confer protection using the Marburg VN assay methodology.[19] Neutralising antibody titres were increased by a two-dose regimen, and further investigation of this approach is underway. The correlation of neutralisation assays with IgG quantitation indicates that, if confirmed, a standardised ELISA might be sufficient to predict protection, should neutralising antibody also be shown to be protective in humans. We have presented data from three different live neutralising antibody assays and a pseudo-neutralisation assay, which show tight correlation with each other but give very different neutralising antibody titres. This issue highlights the urgent need for centralised laboratory infrastructure to allow bridging between vaccine candidates and accelerate the availability of multiple products to provide the global capacity to end the pandemic. If any one candidate demonstrates efficacy, bridging this result to other candidate vaccines through rigorously conducted laboratory assays will become a crucial issue for global health.

Importantly, there are accumulating data to suggest T-cell responses play an important role in COVID-19 mitigation; individuals who were exposed but asymptomatic developed a robust memory T-cell response without symptomatic disease in the absence of a measurable humoral response.[20–22] Adenovirus-vectored vaccines are known to induce strong cellular immunity and ChAdOx1 nCoV-19 vaccination resulted in marked increases in SARS-CoV-2 spike-specific effector T-cell responses as early as day 7, peaking at day 14 and maintained up to day 56 as expected with adenoviral vectors. However, a boost in cellular responses was not observed following the second ChAdOx1 nCoV-19 dose. This is consistent with previous findings on viral vectored vaccines given as part of a homologous prime-boost regimen.[12]

Severe and fatal cases of COVID-19 disproportionally affect older individuals. Therefore, it is important that vaccines developed to reduce or prevent COVID-19 are suitable for administration in older age groups. Immunogenicity of a ChAdOx1-vectored vaccine against influenza has been shown in older adults (50–78 years of age).[6] As previously reported,[10] anti-vector immunity was low before vaccination in UK adults aged 18–55 years, with no relationship between the presence of antibodies to ChAdOx1 and immune response to the vaccine antigen. Future studies will address the potential effect of anti-vector antibodies on homologous boosting, although in the subgroup reported on here, who received two vaccinations 28 days apart, there was clear evidence of boosting of antibody response to SARS-CoV-2 spike protein.

Limitations of this study include the short follow-up reported to date, the small number of participants in the prime-boost group, and single-blinded design, although staff undertaking clinical evaluation and laboratory staff all remained blinded. Additionally, the study findings are not easily generalisable, as this is a first-in-human study of fairly young and healthy volunteers, the majority of whom were white. Further studies are required to assess the vaccine in various population groups including older age groups, those with comorbidities, and in ethnically and geographically diverse populations. The participants recruited in this study will be followed up for at least 1 year and further safety, tolerability, and immunogenicity (in addition to efficacy) results will be reported when data are available.[23–25]

In conclusion, ChAdOx1 nCoV-19 was safe, tolerated, and immunogenic, while reactogenicity was reduced with paracetamol. A single dose elicited both humoral and cellular responses against SARS-CoV-2, with a booster immunisation augmenting neutralising antibody titres. The preliminary results of this first-in-human clinical trial supported clinical development progression into ongoing phase 2 and 3 trials. Older age groups with comorbidities, health-care workers, and those with higher risk for SARS-CoV-2 exposure are being recruited and assessed for efficacy, safety, and immunogenicity of ChAdOx1 nCoV-19 given as a single-dose or two-dose administration regimen in further trials conducted in the UK and overseas. We will also evaluate the vaccine in children, once sufficient safety data have been accumulated in adult studies. Phase 3 trials are now underway in Brazil, South Africa, and the UK and will evaluate vaccine efficacy in diverse populations.

Contributors

SCG and AJP conceived and designed the trial and AJP is the chief investigator. AJP, PMF, DJ, HR, and MV contributed to the protocol and design of the study. AF, PH, RL, KMP, SNF, BA, and AVSH were the study site principal investigators. DB, MB, CD, SBi, SBe, EAC, TL, KJE, ALF, BH, RM, and SB-R were responsible for laboratory testing and assay development. PKA, DJ, HR, PMF, AMM, MR, and MS contributed to the implementation of the study. MV conducted the statistical analysis. CG, ADD, and RT were responsible for vaccine manufacturing. TL and SCG were responsible for vaccine development. AVSH and SCG developed the ChAdOx1 vector. TL, KJE, MV, SCG, AVSH, PMF, and AJP contributed to the preparation of the report. All other authors contributed to the implementation of the study and data collection. All authors critically reviewed and approved the final version.

Declaration of interests

SCG is co-founder and board member of Vaccitech (collaborators in the early development of this vaccine candidate) and named as an inventor on a patent covering use of ChAdOx1-vectored vaccines and a patent application covering this SARS-CoV-2 vaccine. TL is named as an inventor on a patent application covering this SARS-CoV-2 vaccine and consultant to Vaccitech. PMF is a consultant to Vaccitech. AJP is Chair of the UK Department of Health and Social Care's Joint Committee on Vaccination & Immunisation (JCVI), but does not participate in policy advice on coronavirus vaccines, and is a member of the WHO Strategic Advisory Group of Experts (SAGE). AVSH is a co-founder of and consultant to Vaccitech and is named as an inventor on a patent covering design and use of ChAdOx1-vectored vaccines. AF is a member of JCVI, Chair of the WHO European Technical Advisory Group of Experts on Immunisation, an ex-officio member of WHO SAGE working group on COVID-19 vaccines, and acting director of National Institute for Health Research West of England Local Clinical Research Network. KMP reports grants from the NIHR Imperial Biomedical Research Centre and Gilead Sciences, and personal fees from Sanofi Pasteur, outside of the submitted work. MS reports grants from Janssen, GlaxoSmithKline, Medimmune,

Novavax, and MCM and grants and non-financial support from Pfizer, outside of the submitted work. CG reports personal fees from the Duke Human Vaccine Institute, outside of the submitted work. ADD reports grants and personal fees from AstraZeneca, outside of the submitted work. In addition, ADD has a patent manufacturing process for ChAdOx vectors with royalties paid to AstraZeneca, and a patent ChAdOx2 vector with royalties paid to AstraZeneca. The other authors declare no competing interests.

Data sharing

The study protocol is provided in the appendix 1 (pp 49–130). Individual participant data will be made available when the trial is complete, upon requests directed to the corresponding author; after approval of a proposal, data can be shared through a secure online platform.

Acknowledgments

This work is funded by UK Research and Innovation (MC_PC_19055), Engineering and Physical Sciences Research Council (EP/R013756/1), Coalition for Epidemic Preparedness Innovations (CEPI), the National Institute for Health Research (NIHR), the NIHR Oxford Biomedical Research Centre, and the German Center for Infection Research (DZIF), Partner site Gießen-Marburg-Langen. Additional resources for study delivery were provided by NIHR Southampton Clinical Research Facility and NIHR Southampton Biomedical Research Centre, University Hospital Southampton NHS Foundation Trust; the NIHR Imperial Clinical Research Facility; and NIHR North West London, South London, Wessex, and West of England Local Clinical Research Networks and NIHR Oxford Health Biomedical Research Centre. PMF received funding from the Coordenacao de Aperfeicoamento de Pessoal de Nivel Superior, Brazil (finance code 001). Development of SARS-CoV-2 reagents was partially supported by the US National Institute of Allergy and Infectious Diseases Centers of Excellence for Influenza Research and Surveillance contract HHSN272201400008C. The research reagent for SARS-CoV-2 RNA (NIBSC 20/130) was obtained from the National Institute for Biological Standards and Control, UK. The control vaccine was provided free of charge by the UK Department of Health and Social Care. The views expressed in this publication are those of the author(s) and not necessarily those of the NIHR or the UK Department of Health and Social Care. The University of Oxford has entered into a partnership with AstraZeneca on vaccine development; the authors are grateful to the senior management at AstraZeneca for facilitating and funding the pseudovirus neutralisation assays and Meso Scale antibody assay included in this Article. AstraZeneca reviewed the data from the study and the final manuscript before submission, but the authors retained editorial control. The investigators express their gratitude for the contribution of all the trial participants, the invaluable advice of the international Data Safety Monitoring Board (appendix 1 p 46) and the independent members of the Trial Steering Committee. We additionally acknowledge the broader support from the various teams within the University of Oxford including Medical Sciences Division, Nuffield Department of Medicine and Department of Paediatrics, the Oxford Immunology Network COVID Consortium, Clinical Trials Research Governance, Research Contracts, Public Affairs Directorate and the Clinical Biomanufacturing Facility, as well as the Oxford University Hospitals NHS Foundation Trust and Oxford Health NHS Foundation Trust and the trial sites (appendix 1 pp 46–48). We are grateful for the input of the protein production team at the Jenner Institute and the team at the Pirbright Institute.

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ORIGINAL ARTICLE

Efficacy of the mRNA-1273 SARS-CoV-2 Vaccine at Completion of Blinded Phase

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ABSTRACT

BACKGROUND

At interim analysis in a phase 3, observer-blinded, placebo-controlled clinical trial, the mRNA-1273 vaccine showed 94.1% efficacy in preventing coronavirus disease 2019 (Covid-19). After emergency use of the vaccine was authorized, the protocol was amended to include an open-label phase. Final analyses of efficacy and safety data from the blinded phase of the trial are reported.

METHODS

We enrolled volunteers who were at high risk for Covid-19 or its complications; participants were randomly assigned in a 1:1 ratio to receive two intramuscular injections of mRNA-1273 (100 μg) or placebo, 28 days apart, at 99 centers across the United States. The primary end point was prevention of Covid-19 illness with onset at least 14 days after the second injection in participants who had not previously been infected with the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). The data cutoff date was March 26, 2021.

RESULTS

The trial enrolled 30,415 participants; 15,209 were assigned to receive the mRNA-1273 vaccine, and 15,206 to receive placebo. More than 96% of participants received both injections, 2.3% had evidence of SARS-CoV-2 infection at baseline, and the median follow-up was 5.3 months in the blinded phase. Vaccine efficacy in preventing Covid-19 illness was 93.2% (95% confidence interval [CI], 91.0 to 94.8), with 55 confirmed cases in the mRNA-1273 group (9.6 per 1000 person-years; 95% CI, 7.2 to 12.5) and 744 in the placebo group (136.6 per 1000 person-years; 95% CI, 127.0 to 146.8). The efficacy in preventing severe disease was 98.2% (95% CI, 92.8 to 99.6), with 2 cases in the mRNA-1273 group and 106 in the placebo group, and the efficacy in preventing asymptomatic infection starting 14 days after the second injection was 63.0% (95% CI, 56.6 to 68.5), with 214 cases in the mRNA-1273 group and 498 in the placebo group. Vaccine efficacy was consistent across ethnic and racial groups, age groups, and participants with coexisting conditions. No safety concerns were identified.

CONCLUSIONS

The mRNA-1273 vaccine continued to be efficacious in preventing Covid-19 illness and severe disease at more than 5 months, with an acceptable safety profile, and protection against asymptomatic infection was observed. (Funded by the Biomedical Advanced Research and Development Authority and the National Institute of Allergy and Infectious Diseases; COVE ClinicalTrials.gov number, NCT04470427.)

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*The members of the COVE Study Group are listed in the Supplementary Appendix, available at NEJM.org.

Drs. El Sahly and Baden contributed equally to this article.

This article was published on September 22, 2021, at NEJM.org.

DOI: 10.1056/NEJMoa2113017

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The global morbidity, mortality, and societal disruption caused by the coronavirus disease 2019 (Covid-19) pandemic prompted accelerated clinical vaccine development and regulatory interventions to mitigate some of its consequences. Between December 2020 and February 2021, three vaccines against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) received Emergency Use Authorization (EUA) from the Food and Drug Administration (FDA) on the basis of data from observer-blinded, randomized, controlled trials demonstrating safety and efficacy against Covid-19 after a median follow-up of 2 months after vaccination.[1-4] The short-term efficacy of the vaccines observed in the clinical trials was also observed after vaccine deployment in the general population.[5-10] Longer-term safety and efficacy of the vaccines have remained open questions of public health import.

The phase 3 trial of mRNA-1273, a lipid nanoparticle–encapsulated mRNA expressing the prefusion-stabilized spike glycoprotein of SARS-CoV-2,[11] showed a 94.1% vaccine efficacy against Covid-19, with an acceptable safety and side-effect profile after a median follow-up of 64 days.[1] These early findings supported the issuance of the EUA, after which the protocol was amended to offer participants the option of having the group assignments unblinded and, for those who had received placebo, the option to receive the mRNA-1273 vaccine. Here we report the vaccine efficacy and safety results of the final analysis of the blinded phase of the trial, ending 5.3 months after the second dose, and in additional analyses in important subgroups of interest, as well as findings on the effect of vaccination on asymptomatic infection and on efficacy at various time intervals since vaccination.

Methods

Trial Oversight

In this phase 3, observer-blinded, randomized, placebo-controlled trial, adults in medically stable condition were enrolled at 99 sites in the United States.[1] After the FDA issued an EUA for the use of mRNA-1273 in December 2020, the protocol was amended to include two parts (A and B; see Figs. S1 and S2 in the Supplementary Appendix, available together with the protocol with the full text of this article at NEJM.org). Part A, the observer-blinded phase of the trial, concluded when participants were informed of their group assignments; those in the placebo group were offered the opportunity to receive mRNA-1273 (the participant-decision visit). Part B, the open-label phase of the trial, is currently ongoing. Participants will continue to be followed for up to 2 years, as originally planned.

The trial is being conducted in accordance with the Good Clinical Practice guidelines of the International Council Harmonisation of Technical Requirements for Pharmaceuticals for Human Use, and applicable government regulations. The central institutional review board approved the protocol and the consent forms. All participants provided written informed consent.

Participants, Randomization, and Data Blinding

Part A of the trial was a stratified, observer-blinded, randomized, placebo-controlled evaluation of the efficacy, safety, and immunogenicity of the mRNA-1273 SARS-CoV-2 vaccine as compared with placebo in eligible participants who were at least 18 years old and had no known history of SARS-CoV-2 infection and whose locations or circumstances put them at appreciable risk of acquiring SARS-CoV-2 infection or who were at high risk for severe disease (or both).[1] Participants were randomly assigned in a 1:1 ratio to receive two doses of the mRNA-1273 vaccine (100 μg) or placebo and were stratified according to age and Covid-19 complications risk criteria (≥18 to <65 years and not at risk, ≥18 to <65 years and at risk, and ≥65 years). The trial design, efficacy assessments, and vaccine have been described previously.[1]

Safety Assessments

Safety measures included solicited local and systemic adverse events with onset during the 7 days after each injection; unsolicited adverse events with onset during the 28 days after each injection; adverse events leading to discontinuation from receiving injections, participating in the trial, or both; medically attended and serious adverse events occurring during the trial; and severity of the events, which were graded as described in the protocol. Safety data, all Covid-19 cases, and severe Covid-19 cases were continuously monitored by the data and safety monitoring board.

EFFICACY ASSESSMENTS

Participants provided nasopharyngeal swab and blood samples before the first and second injections of vaccine or placebo and before the unblinding of the group assignments at the participant-decision visit. Efficacy assessments included surveillance for Covid-19 symptoms from enrollment throughout the trial. Efficacy end points were adjudicated by an independent adjudication committee whose members were unaware of group assignments.

For the primary end point, mRNA-1273 vaccine efficacy in preventing a first occurrence of Covid-19 with onset at least 14 days after the second injection, Covid-19 cases were defined by at least two systemic symptoms (temperature ≥38°C, chills, myalgia, headache, sore throat, or new olfactory or taste disorders), or at least one respiratory sign or symptom (cough, shortness of breath, or clinical or radiologic evidence of pneumonia), and were confirmed by positive SARS-CoV-2 reverse-transcriptase–polymerase-chain-reaction (RT-PCR) assay of nasopharyngeal swab, nasal, or saliva samples. Participants were monitored daily for at least 14 days after diagnosis or until symptoms resolved. Severe Covid-19 was defined as confirmed Covid-19 plus one clinical sign of severe systemic illness (Tables S1 and S2). Secondary end points include the efficacy of the mRNA-1273 vaccine in preventing severe Covid-19, Covid-19 after the first dose, Covid-19 regardless of prior SARS-CoV-2 infection, Covid-19 according to a secondary definition (the Centers for Disease Control and Prevention definition, requiring only one symptom), serologically confirmed SARS-CoV-2 infection (positive binding antibody against SARS-CoV-2 nucleocapsid protein in participants who were SARS-CoV-2–negative at baseline), SARS-CoV-2 infection (positive RT-PCR assay) regardless of symptom status, and asymptomatic SARS-CoV-2 infection (absence of symptoms, with infections starting at least 14 days after the second injection, including seroconversion at day 57 or at the participant-decision visit, or a positive RT-PCR assay at the participant-decision visit).

STATISTICAL ANALYSIS

Determination of the sample size (30,000 participants) and aspects of the statistical analysis designed to demonstrate the efficacy of the mRNA-1273 vaccine as compared with placebo for the primary end point, prevention of Covid-19 starting at 14 days after the second dose, were described previously[1] and are also provided in the protocol. Analysis populations included the randomization population; the full analysis population, comprising participants who had undergone randomization and received at least one dose of mRNA-1273 or placebo; the modified intention-to-treat population, consisting of participants in the full analysis population who had no immunologic or virologic evidence of SARS-CoV-2 infection before the first dose; the per-protocol population, consisting of participants in the modified intention-to-treat population who received two doses, with no major protocol deviations; and the solicited safety and safety populations (described in Table S3).

The prespecified primary efficacy analysis was performed in the per-protocol data set, starting 14 days after the second dose of vaccine or placebo. The efficacy of the mRNA-1273 vaccine was estimated with a stratified Cox proportional-hazards model. Incidence rates and vaccine efficacy were estimated by 1 minus the hazard ratio (mRNA-1273 vs. placebo), and the corresponding 95% confidence interval was based on the total number of cases adjusted according to total person-time. Additional details of the primary and secondary efficacy analyses are provided in Table S4 and in Supplementary Methods. The final efficacy analysis presented herein is based on cleaned data through the completion of the blinded phase, Part A, with a data cutoff date of March 26, 2021, when 95.0% of the trial participants had completed the participant-decision visit or had discontinued participation in the trial.

RESULTS

TRIAL POPULATION

From July 27 to October 23, 2020, a total of 30,415 participants underwent randomization; 15,206 were assigned to the placebo group and 15,209 to the mRNA-1273 group (Fig. 1 and Fig. S2).[1] More than 96% of participants (14,727 in the placebo group and 14,635 in the mRNA-1273 group) received second injections. A total of 531 participants (3.5%) in the placebo group and 453 (3.0%) in the mRNA-1273 group did not receive the second injection, mainly owing to confirmed

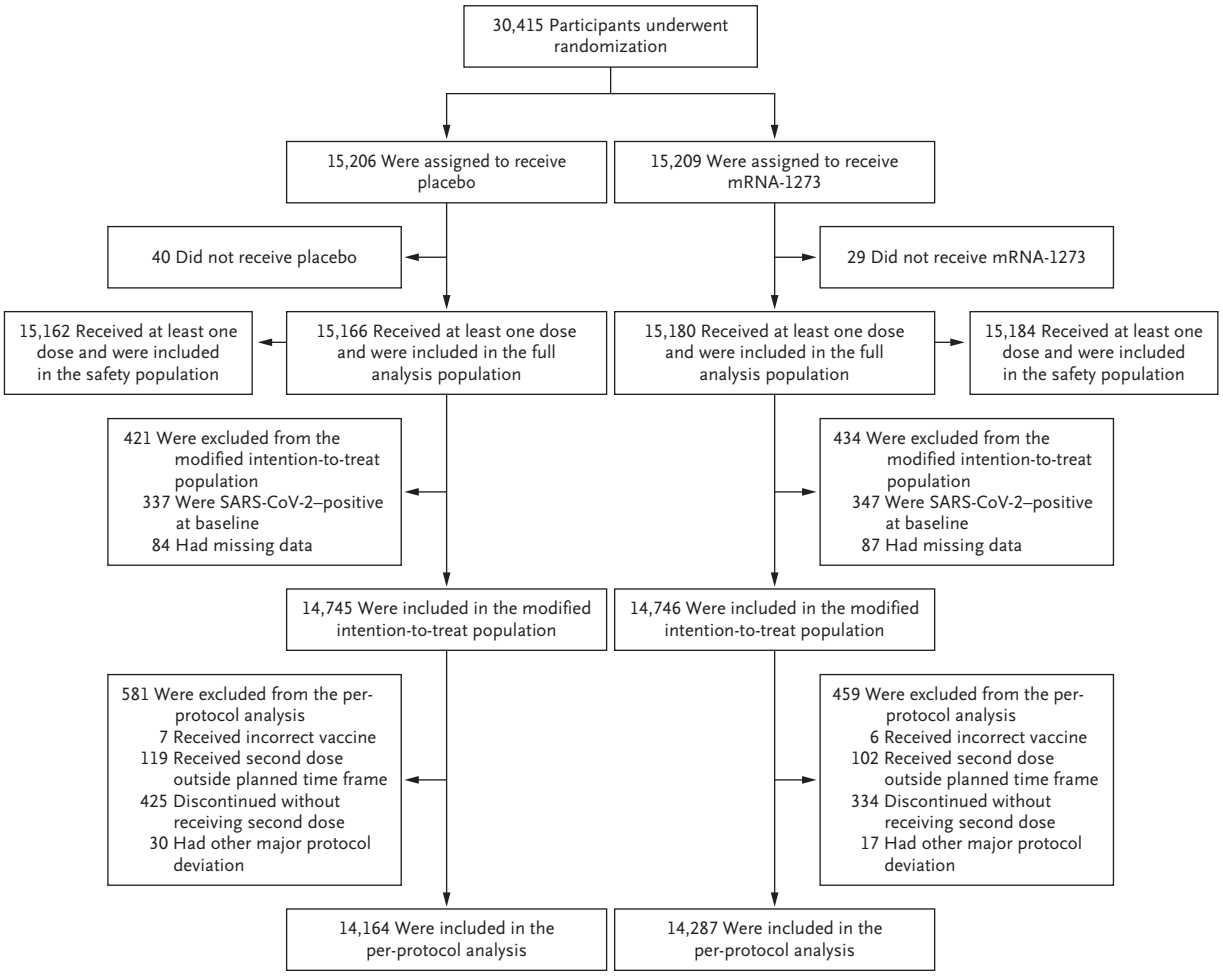


Figure 1. Randomization and Analysis Populations.

Eight participants, including six with major protocol deviations and two who erroneously underwent randomization twice, were excluded from the original randomization population (30,423 participants) and from all analysis sets. The full analysis population comprised all participants who had undergone randomization and received at least one injection; the modified intention-to-treat population included participants in the full analysis population who had no immunologic or virologic evidence of previous Covid-19 (i.e., had both a negative nasopharyngeal swab specimen and a negative anti-nucleocapsid antibody test result) at day 1 before the first injection; and the per-protocol population consisted of all participants in the modified intent-to-treat population who received planned injections according to the schedule and had no major protocol deviations that affected key trial data. The safety population included all participants who had undergone randomization and received at least one injection; this population was used for all safety analyses except the analysis for solicited adverse events. For safety analyses, participants were evaluated according to the injection received. Three participants assigned to the mRNA-1273 group received two doses of placebo and were included in the placebo safety population, and seven participants assigned to the placebo group received one or two doses of mRNA-1273 and were included in the mRNA-1273 safety population. The data cutoff date was March 26, 2021.

SARS-CoV-2 infection or withdrawal of consent. Trial discontinuations in the placebo group (691 participants [4.5%]) and the mRNA-1273 group (440 participants [2.9%]) were most commonly due to protocol deviations, withdrawal of consent, or loss to follow-up. The imbalance of discontinuations between the placebo and mRNA-1273 groups coincided with the FDA issuance of the EUAs for Covid-19 vaccines and reflected the intent of placebo recipients to receive a vaccine under EUA as it became available (Fig. S3). By the data cutoff date (March 26, 2021), 27,109 participants had been informed of their group assignments at a participant-decision visit, and

1855 had been informed before the participant-decision visit because they intended to receive a vaccine under EUA through their provider. A total of 28,964 participants entered the open-label phase of the trial.

Vaccine safety was assessed among 30,346 participants in the safety population (Fig. 1). The prespecified primary efficacy analysis was performed in the per-protocol population, which included 28,451 participants who were SARS-CoV-2–negative at baseline and had received two doses of vaccine by the final analysis in the blinded phase. The median duration of follow-up from randomization to data cutoff or trial discontinuation was 212 days (interquartile range, 193 to 225), the duration from the second dose to data cutoff or discontinuation was 183 days (interquartile range, 165 to 194), and the duration from randomization to unblinding was 148 days (interquartile range, 131 to 162). Baseline demographic and clinical characteristics were balanced between the placebo group and the mRNA-1273 group (Table S5).[1]

SAFETY

At the end of the blinded phase, the frequencies of solicited local and systemic adverse events were consistent with those reported previously,[1] with such events occurring less frequently in the placebo group (in 48% and 43% of participants after the first and second injections, respectively) than in the mRNA-1273 group (88% and 92%) (Fig. S4 and Tables S6 through S13). Women were slightly more likely than men to have grade 3 solicited adverse events after the first and second injections (Table S8). Occurrences of solicited adverse events were generally similar with the two injections, regardless of severe Covid-19 risk status (Table S9), and were less common after both doses among participants with previous SARS-CoV-2 infection than among those without previous SARS-CoV-2 infection, with the exception of systemic adverse events after the first dose of mRNA-1273, which occurred more often in participants previously infected with SARS-CoV-2 (62% vs. 55%, respectively) (Tables S11 and S12). The incidence of local adverse events with delayed onset starting on day 8 after an injection was higher after the first injection (80 participants [0.5%]) than after the second injection (10 participants [<0.1%]), and the most common local adverse event reported on or after day 8 was erythema in the mRNA-1273 group after the first (68 participants [0.4%]) and second (6 [<0.1%]) injections (Table S13).

The frequencies of unsolicited, severe, and serious adverse events reported during the 28 days after either injection were generally similar in the two groups in the overall safety population, regardless of age or risk factors for severe Covid-19 (Tables S14 through S18). The frequency of grade 3 and medically attended adverse events that were considered to be related to injection of placebo or vaccine was lower in the placebo group (0.2% and 0.6%, respectively) than in the mRNA-1273 group (0.5% and 1.3%) (Table S14). Overall, 0.6% of placebo recipients and 0.4% of vaccine recipients had adverse events that resulted in their not receiving the second dose, and less than 0.1% in both groups discontinued trial participation because of adverse events after either injection. Adverse events that were considered to be related to the injections were reported by 8.5% of placebo recipients and 13.9% of mRNA-1273 recipients during the observation period of the study and were generally similar to those reported previously regardless of age (Tables S19 through S21). Serious injection-related adverse events occurred in 4 placebo recipients (<0.1%) and in 12 mRNA-1273 recipients (<0.1%).

Hypersensitivity reactions were reported in 1.8% of placebo recipients and in 2.2% of vaccine recipients, with anaphylaxis occurring in 2 participants (<0.1%) in each group (Table S22). Dermal filler reactions were reported in 14 placebo recipients (<0.1%) and in 20 mRNA-1273 recipients (0.1%) with a history of dermal filler injections (Table S23). Three cases of Bell's palsy (<0.1%) were reported in the placebo group and 8 in the mRNA-1273 group (<0.1%); no case was considered to be related to the placebo or the vaccine (Table S24). Thromboembolic events were observed in 43 placebo recipients (0.3%) and in 47 mRNA-1273 recipients (0.3%) (Table S25). No cases of myocarditis were reported. Pericarditis events occurred in 2 participants each (<0.1%) in the placebo and mRNA-1273 groups (both events >28 days after the second dose) and were considered serious (Tables S20 and S21). A total of 32 deaths had occurred by completion of the blinded phase, with 16 deaths each (0.1%) in the placebo and mRNA-1273 groups; no deaths were considered to be related to injections of placebo or vaccine, and 4 were attributed to Covid-19

(3 in the placebo group and 1 in the mRNA-1273 group) (Tables S19 and S26). The Covid-19 death in the mRNA-1273 group occurred in a participant who had received only one dose; Covid-19 was diagnosed 119 days after the first dose, and the participant died of complications 56 days after diagnosis.

Figure 2 (facing page). Efficacy of the mRNA-1273 Vaccine in Preventing Covid-19.

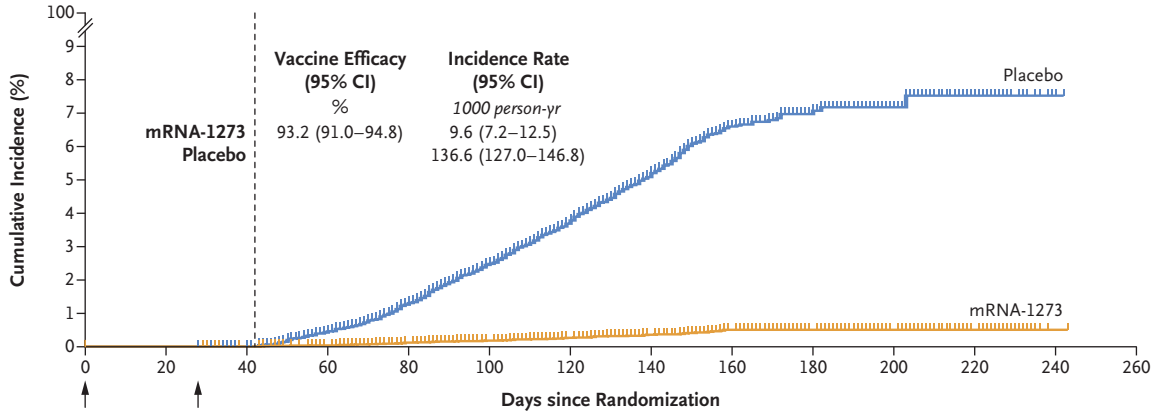
In Panels A and C, the dashed vertical line denotes the adjudicated assessment beginning at day 42 (14 days after the second injection of vaccine or placebo). Tick marks in all three panels indicate censored data. Vaccine efficacy was defined as 1 minus the hazard ratio (mRNA-1273 vs. placebo), and 95% confidence intervals were estimated with the use of a stratified Cox proportional-hazards model with Efron's method of tie handling and with treatment group as a covariate, adjusted for stratification factor. The data cutoff date was March 26, 2021.

EFFICACY ANALYSES

A total of 799 adjudicated cases of Covid-19 in the per-protocol population were included in the primary efficacy analysis; 744 cases (5.3%) were in the placebo group and 55 (0.4%) were in the mRNA-1273 group (Figs. 2 and 3 and Tables S27 and S28). The vaccine efficacy was 93.2% for the prevention of Covid-19 starting at least 14 days after the second dose, with incidences of 136.6 cases per 1000 person-years (95% confidence interval [CI], 127.0 to 146.8) in the placebo group and 9.6 cases per 1000 person-years (95% CI, 7.2 to 12.5) in the mRNA-1273 group. The vaccine efficacy for adjudicated cases in the modified intention-to-treat population was 92.3% (95% CI, 90.1 to 93.9). Vaccine efficacy in preventing severe Covid-19, a key secondary end point, was 98.2% (95% CI, 92.8 to 99.6) in the per-protocol population, with 106 severe cases in the placebo group and 2 in the mRNA-1273 group. Vaccine efficacy was consistently high in subgroups, including participants 65 years of age or older and 75 years of age or older, those with coexisting conditions, those belonging to various racial and ethnic groups, and those with various categories of occupational risk exposures (Fig. 4 and Table S29). When examined by specific time interval since completion of vaccination over the duration of follow-up, the efficacy of the mRNA-1273 vaccine in preventing Covid-19 remained consistent, with efficacy greater than 90% observed 4 months or more after the second injection (Fig. 5, Fig. S5, and Table S30). Symptoms most commonly reported in the adjudicated Covid-19 cases in both groups were cough, fatigue, headaches, and nasal congestion; severe obesity and diabetes were contributing risk factors for severe Covid-19 (Tables S31 and S32).

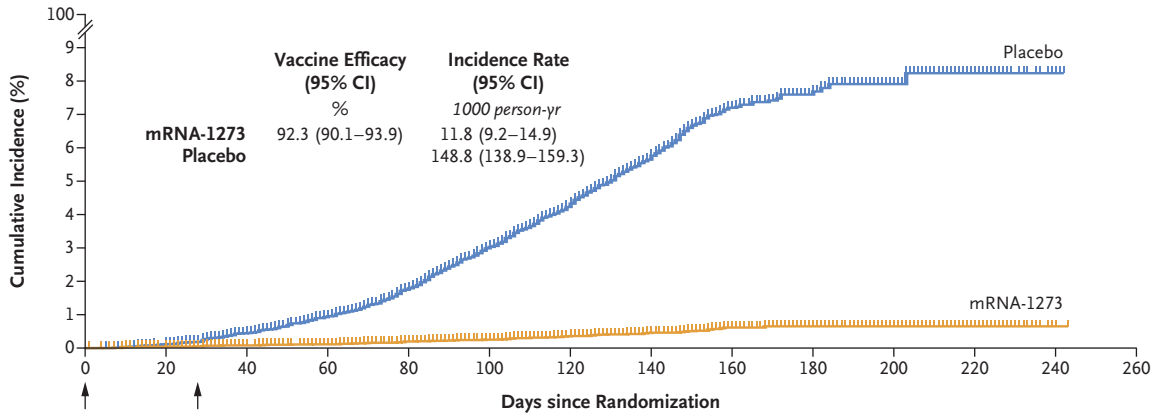
Secondary end points (Fig. 3 and Table S27) also included vaccine efficacy according to the secondary definition of Covid-19 (the Centers for Disease Control and Prevention definition, requiring only one symptom) starting 14 days after the second injection in the per-protocol population; according to the secondary definition, the vaccine efficacy was 93.4% (95% CI, 91.4 to 94.9). Among participants who were SARS-CoV-2–negative at baseline, a total of 712 participants (498 in the placebo group and 214 in the mRNA-1273 group) were found to be SARS-CoV-2–positive by RT-PCR assay or anti-nucleocapsid antibody test in the absence of symptoms starting 14 days after the second injection, through and including the participant-decision visit, and were considered to have asymptomatic infection (Fig. 3 and Tables S27 and S28). Vaccine efficacy in preventing asymptomatic SARS-CoV-2 infection, based on the hazard ratio using the competing risk method, was 63.0% (95% CI, 56.6 to 68.5). In an analysis of asymptomatic infections after randomization, with data accrued up to and including the participant-decision visit, 157 participants in the placebo group and 153 in the mRNA-1273 group were RT-PCR–positive only; 306 participants in the placebo group and 48 in the mRNA-1273 group showed seroconversion by anti-nucleocapsid antibodies, and 115 participants in the placebo group and 7 in the mRNA-1273 group tested positive in both anti-nucleocapsid antibody testing and RT-PCR assay in the absence of symptoms. Findings for asymptomatic infection were similar in the modified intention-to-treat population (Table S28). For the secondary end point of prevention of SARS-CoV-2 infection (regardless of symptom or severity), the vaccine efficacy was 82.0% (95% CI, 79.5 to 84.2) beginning 14 days after the second injection in the per-protocol population, with 1339 participants in the placebo group and 280 in the mRNA-1273 group who had documented infection, defined as a positive result on RT-PCR assay at 14 days or more after the second injection or seroconversion at day 57 or later, through the participant-decision visit.

A Covid-19 Events, Per-Protocol Analysis



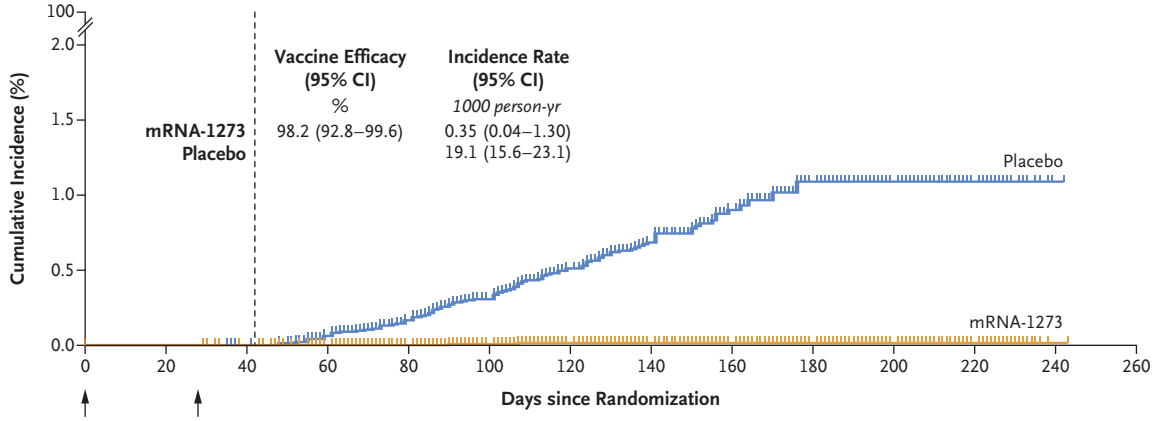
No. at Risk														
Placebo	14,164	14,164	14,134	13,030	13,733	12,970	11,199	7783	3323	953	336	64	5	0
mRNA-1273	14,287	14,287	14,281	14,246	14,096	13,584	12,196	9031	4252	1375	473	49	2	0

B Covid-19 Events, Modified Intention-to-Treat Analysis



No. at Risk														
Placebo	14,745	14,709	14,549	14,399	14,081	13,292	11,473	7989	3417	996	355	68	7	0
mRNA-1273	14,746	14,717	14,626	14,561	14,379	13,851	12,437	9223	4349	1415	486	54	2	0

C Severe Covid-19 Events, Per-Protocol Analysis



No. at Risk														
Placebo	14,164	14,164	14,154	14,105	13,909	13,279	11,587	8190	3627	1076	379	68	5	0
mRNA-1273	14,287	14,287	14,283	14,253	14,114	13,607	12,225	9063	4277	1385	478	49	2	0

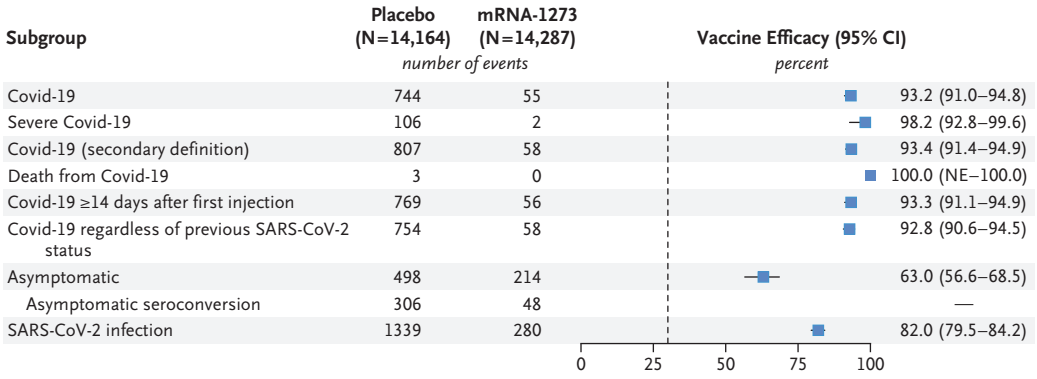


Figure 3. Vaccine Efficacy for Primary and Secondary End Points.

Vaccine efficacy was defined as 1 minus the hazard ratio (mRNA-1273 vs. placebo), and 95% confidence intervals were estimated using a stratified Cox proportional-hazards model with Efron's method of tie handling and with the treatment group as a covariate, adjusted for stratification factor. The P value for the vaccine efficacy against Covid-19 (upper right corner) is P<0.001. The dashed vertical line represents a vaccine efficacy of 30%, based on the null hypothesis that the primary efficacy of the mRNA-1273 vaccine is 30% or less. In the Covid-19 rows, censoring rules for efficacy analyses (Covid-19 cases based on eligible symptoms and positive reverse-transcriptase–polymerase-chain-reaction [RT-PCR] assay within 14 days before the second injection) were applied, except for deaths from Covid-19. If a participant had a positive RT-PCR assay at the visit before the second dose (day 29) without eligible symptoms within the previous 14 days, or a positive anti-nucleocapsid antibody test at a scheduled visit before Covid-19 was diagnosed, the participant's data were censored at the date of the positive RT-PCR assay or anti-nucleocapsid antibody test. Covid-19 diagnoses were based on adjudication committee assessments. The data for Covid-19 regardless of previous SARS-CoV-2 status were based on the number of participants in the full analysis population (15,166 participants in the placebo group and 15,180 participants in the mRNA-1273 group). Data for the asymptomatic subgroup include data from the participant-decision visit. Asymptomatic was defined as the absence of symptoms (according to either the primary efficacy end point of Covid-19 or the secondary definition of Covid-19 [the Centers for Disease Control and Prevention definition, requiring only one symptom]) and of infection as detected by RT-PCR assay (at scheduled visits) or seroconversion (anti-nucleocapsid antibody test). In the primary approach, documented asymptomatic infection was counted beginning 14 days after the second injection, which required seroconversion at month 2 (day 57 through the participant-decision visit). Asymptomatic seroconversion excludes infections confirmed by RT-PCR assay only and includes infections confirmed by seroconversion and those confirmed by both RT-PCR and seroconversion (Table S28). Vaccine efficacy and 95% confidence intervals for asymptomatic SARS-CoV-2 infection were estimated with Fine and Gray's subdistribution hazard model, with disease cases as competing events and with treatment group as a covariate, adjusted for stratification factor. Results for additional end points are summarized in Table S27. The data cutoff date was March 26, 2021. NE indicates that the lower bound of the 95% confidence interval could not be estimated.

For the secondary end point of Covid-19 with onset at least 14 days after the first injection, the vaccine efficacy, based on adjudicated cases of Covid-19 in the per-protocol population among participants who received both injections (769 in the placebo group and 56 in the mRNA-1273 group), was 93.3% (95% CI, 91.1 to 94.9). In an exploratory analysis performed in a modified intention-to-treat subpopulation of 425 participants in the placebo group and 334 in the mRNA-1273 group who had no evidence of SARS-CoV-2 infection at baseline and who received only one injection, adjudicated Covid-19 cases were observed in 45 participants (10.6%) in the placebo group and in 4 participants (1.2%) in the mRNA-1273 group (Table S33). Six severe Covid-19 cases occurred in recipients of a single injection of placebo (1.4%), and one severe case occurred in a recipient of a single injection of the mRNA-1273 vaccine (0.3%).

DISCUSSION

The data compiled through the completion of the blinded phase of the COVE trial provide further evidence of the safety and efficacy of mRNA-

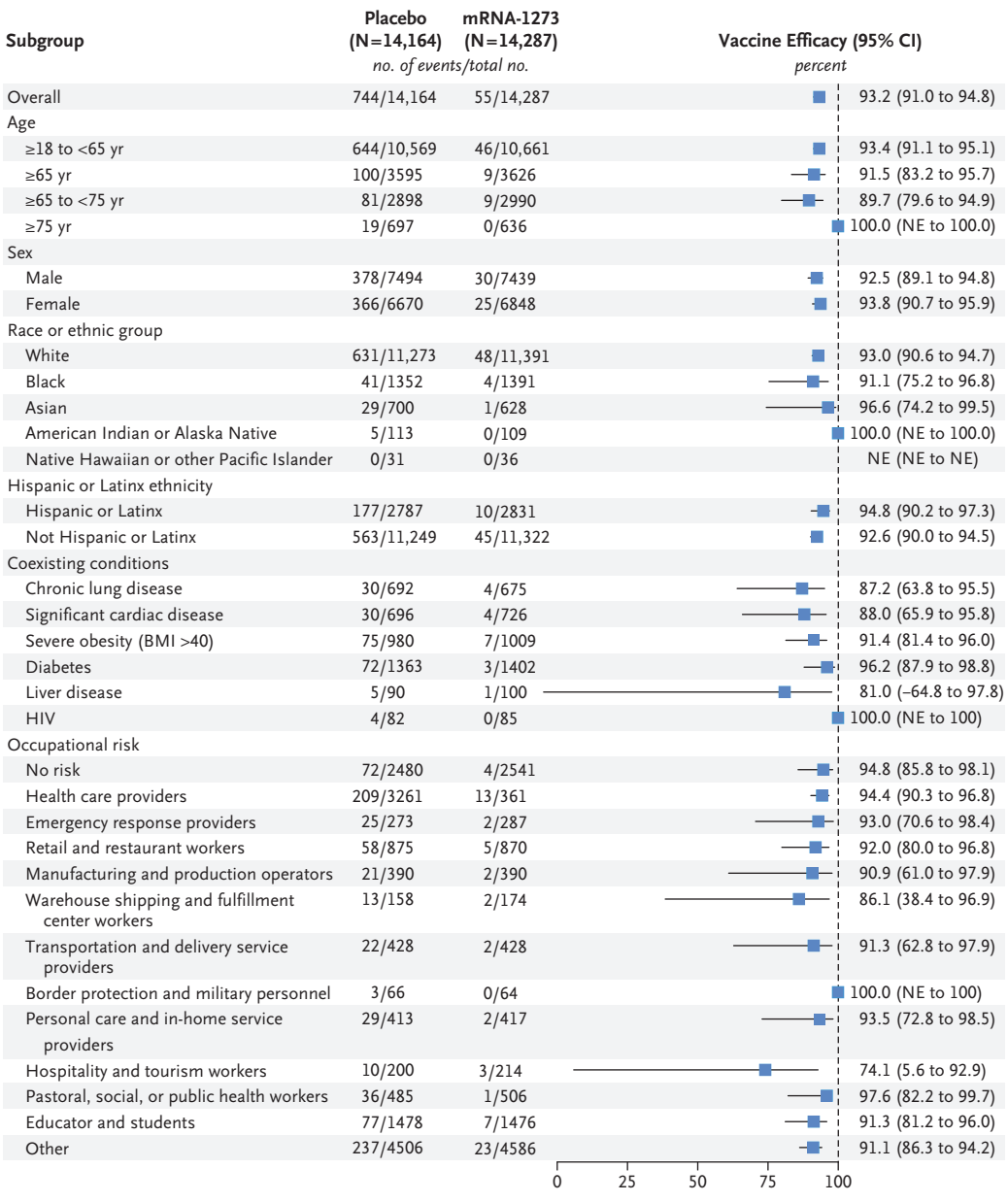


Figure 4. Efficacy of the mRNA-1273 Vaccine in Preventing Covid-19 in Subgroups.

Analysis of the vaccine efficacy of mRNA-1273 in the prevention of Covid-19 in various subgroups in the per-protocol population was based on adjudicated assessments starting 14 days after the second injection. Vaccine efficacy, defined as 1 minus the hazard ratio (mRNA-1273 vs. placebo), and 95% confidence intervals were estimated with the use of a stratified Cox proportional-hazards model with Efron's method of tie-handling and with the treatment group as a covariate, adjusted for stratification factor if applicable. The total number of events for race includes 38 placebo recipients and 3 mRNA-1273 recipients who were in "Multiple," "Other," or not reported or unknown categories, and the total number for ethnicity includes 4 placebo recipients and no mRNA-1273 recipients who were in not reported or unknown categories (not shown). Race and ethnic group were reported by the participant. The body-mass index (BMI) is the weight in kilograms divided by the square of the height in meters. Additional subgroup data are provided in Table S29. The data cutoff date was March 26, 2021. HIV denotes human immunodeficiency virus.

Onset of Covid-19	Placebo (N=14,164)	mRNA-1273 (N=14,287)	Placebo (N=14,164)	mRNA-1273 (N=14,287)	Vaccine Efficacy (95% CI)
	number of cases		*incidence rate per 1000 person-yr*		*percent*
After randomization	769	56	141.2	9.8	93.1 (90.9–94.8)
≥14 Days after first injection	769	56	141.2	9.8	93.1 (90.9–94.8)
After second injection	768	56	141.0	9.8	93.1 (90.9–94.8)
≥14 Days after second injection	744	55	136.7	9.6	93.0 (90.8–94.8)
After first injection	769	56	141.2	9.8	93.1 (90.9–94.8)
After first injection up to second injection	1	0	0.9	0	100.0
After first injection to <14 days after first injection	0	0	0	0	—
≥14 Days after first injection up to second injection	1	0	1.7	0	100.0
Second injection to <14 days after second injection	24	1	44.2	1.8	95.9 (74.7–99.9)
≥14 Days after second injection	744	55	197.4	13.6	93.1 (90.9–94.9)
≥14 Days after second injection to <2 mo after second injection	227	19	141.5	11.6	91.8 (86.9–95.1)
≥2 Mo after second injection to <4 mo after second injection	434	28	247.3	14.8	94.0 (91.2–96.1)
≥4 Mo after second injection	83	8	202.4	15.4	92.4 (84.3–96.8)

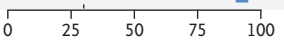


Figure 5. Incidence of Covid-19 According to Time Periods in the Per-Protocol Population.

The incidence rate based on adjudicated Covid-19 cases was defined as the number of participants with an event during the period divided by the number of participants at risk at the beginning of each period and adjusted by person-years (total time at risk) in each treatment group. The dashed vertical line represents a vaccine efficacy of 30% based on the null hypothesis that the primary efficacy of the mRNA-1273 vaccine is 30% or less. The number of person-years was calculated from randomization to the date of onset of Covid-19, the end of each time period, the last date of participation in the trial, or the efficacy data cutoff date, whichever date was the earliest. For the analysis of time intervals starting from 14 days after the first injection, starting from the second injection, and starting 14 days after the second injection, assessed every 2 months, person-years for each time period were defined starting from the beginning of each time interval and truncating at the end of the interval (if there was an ending time). Vaccine efficacy was defined as 1 minus the hazard ratio (mRNA-1273 vs. placebo). The 95% confidence interval for the ratio was calculated with the exact method, conditional on the total number of cases and adjusted for person-years for the time period. The data cutoff date was March 26, 2021.

1273 in preventing symptomatic Covid-19 as well as preventing SARS-CoV-2 infection regardless of symptom and severity in adults, including those 65 years of age or older and those with coexisting conditions, and across various ethnic and racial groups. These findings are based on a median follow-up of 148 days in the blinded phase and are similar to those observed previously at a median follow-up of 64 days, indicating that the high efficacy of the mRNA-1273 vaccine is maintained in the medium term. Of importance, the vaccine provided substantial protection against asymptomatic infection (63%; 95% CI, 56.6 to 68.5), though at a lower vaccine efficacy than that for symptomatic infection. The efficacy of the mRNA-1273 vaccine did not wane up to 4 months after the second injection and beyond. It is notable that the efficacies found in phase 3 trials of Covid-19 vaccines have thus far translated into high effectiveness in the general population, including effectiveness against variants of concern that are associated with reductions in neutralization, such as the B.1.351 (beta) and B.1.617.2 (delta) variants.[8,12-15] Additional data gathered from regions with current and potential surges in transmission of variants of concern are important toward informing strategies for administering additional doses of vaccine.

No safety concerns were identified in this trial. However, robust safety surveillance systems have identified rare events during the global distribution of Covid-19 vaccines that the phase 3 studies were not powered to detect; thus, continued vigilance is warranted, including monitoring for anaphylactic reactions, especially in persons with allergic phenotypes, and for other potential unexpected reactions, such as myocarditis in adolescents and young adults.[16] Given the high efficacies of the vaccines[1,3,17] and the burden of the pandemic, the risk–benefit ratio remains strongly in favor of broad deployment of the vaccines. Despite differences in the definitions of disease severity, the vaccine efficacy is supported by real-world data: vaccination has been shown to be highly effective in pre-

venting severe Covid-19, associated hospitalizations, and deaths, as well as mild or asymptomatic infection, regardless of race and age.[9,12,18-20]

Several important limitations of the trial should be considered. At the trial design stage in early 2020, the efficacy and safety of the mRNA-1273 vaccine were unknown; for that reason, certain key populations such as pregnant women, children, and immunocompromised persons were not included in the trial. Studies in these populations are currently ongoing, and the data that are emerging in adolescents and pregnant women are reassuring.[21-24] Although no safety concerns associated with the mRNA vaccines have been identified in immunocompromised persons, these vaccines appear to be less immunogenic in such persons.[25,26] Given the period during which the blinded phase of the trial was conducted, assessment of vaccine efficacy in preventing Covid-19 caused by SARS-CoV-2 variants of concern is limited, since circulation of the variants was low. Future exploratory analyses are needed to probe this question. It should also be noted that the sensitivity of detection of asymptomatic infection in this trial was somewhat limited by the assessment of seroconversion at fixed time points, the kinetics of seroconversion of anti-nucleocapsid antibodies (which may take weeks to emerge after an initial infection and then wane relatively quickly), as well as the possible diminished detection of SARS-CoV-2 by RT-PCR, owing to a reduced duration of infection in vaccine recipients and the infrequent collection of samples from asymptomatic participants in the trial.

We found that the efficacy of the mRNA-1273 vaccine against Covid-19 and severe Covid-19 was maintained for more than 5 months after the second dose among all subgroups in the trial, including those at risk for severe complications. Asymptomatic SARS-CoV-2 infections were also reduced. No safety concerns were identified in this trial. The interplay of viral evolution with vaccine distribution in the next months will determine the trajectory of the pandemic, which continues to evade predictions and shape much of the social and economic life in the United States and worldwide.

Supported by the Office of the Assistant Secretary for Preparedness and Response, Biomedical Advanced Research and Development Authority (contract 75A50120C00034), and by the National Institute of Allergy and Infectious Diseases (NIAID). The NIAID provides grant funding to the HIV Vaccine Trials Network (HVTN) Leadership and Operations Center (UM1 AI 68614HVTN), the Statistics and Data Management Center (UM1 AI 68635), the HVTN Laboratory Center (UM1 AI 68618), the HIV Prevention Trials Network Leadership and Operations Center (UM1 AI 68619), the AIDS Clinical Trials Group Leadership and Operations Center (UM1 AI 68636), and the Infectious Diseases Clinical Research Consortium leadership group 5 (UM1 AI148684-03).

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

A data sharing statement provided by the authors is available with the full text of this article at NEJM.org.

We thank the participants in the trial and the members of the data and safety monitoring board (Richard J. Whitley, chair, University of Alabama School of Medicine; Abdel Babiker, MRC Clinical Trials Unit at University College, London; Lisa Angeline Cooper, Johns Hopkins University School of Medicine and Bloomberg School of Public Health; Susan Smith Ellenberg, University of Pennsylvania; Alan Fix, Vaccine Development Global Program Center for Vaccine Innovation and Access PATH; Marie Griffin, Vanderbilt University Medical Center; Steven Joffe, Perelman School of Medicine, University of Pennsylvania; Jorge Kalil, Clinics Hospital (HC-FMUSP), Universidade de São Paulo, Brazil; Myron M. Levine, University of Maryland School of Medicine; Malegapuru William Makgoba, University of KwaZulu-Natal; Anastasios A. Tsiatis, North Carolina State University; and Renee H. Moore, Emory University) and the adjudication committee (Richard J. Hamill, chair, Baylor College of Medicine; Lewis Lipsitz, Harvard Medical School; Eric S. Rosenberg, Massachusetts General Hospital; and Anthony Faugno, Tufts Medical Center) for their critical and timely review of the trial data. We also acknowledge the contribution from the mRNA-1273 Product Coordination Team from the Biomedical Advanced Research and Development Authority (BARDA) (Robert Bruno, Richard Gorman, Holli Hamilton, Gary Horwith, Chuong Huynh, Nutan Mytle, Corrina Pavetto, Xiaomi Tong, and John Treanor), as well as Frank J. Dutko (Moderna consultant) for editorial support and Katherine Kacena for input on statistics.

APPENDIX

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of California, Los Angeles (J.C.), and Wake Research–Medical Center for Clinical Research, San Diego (L.H.-C.) — both in California; Kaiser Permanente Washington Health Research Institute (L.A.J.), and Fred Hutchinson Cancer Research Center (L.C., P.G., H.J.) — both in Seattle; University of Cincinnati, Cincinnati (C.J.F.); Henry Ford Health System, Detroit (M.Z.); Vitalink Research, Greenville, SC (G.F.); Clinical Research Center of Nevada, Wake Research, Las Vegas (M.L.); and the University of Maryland, College Park (K.M.N.), and the Vaccine Research Center (J.R.M., J.E.L., B.S.G.), National Institute of Allergy and Infectious Diseases (D.F., M.M., L.P.), National Institutes of Health, Bethesda — both in Maryland.

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Conflicts of interest and pandemic flu
Author(s): Fiona Godlee
Source: *BMJ: British Medical Journal*, Vol. 340, No. 7759 (12 June 2010), pp. 1256-1257
Published by: BMJ
Stable URL: https://www.jstor.org/stable/40700783
Accessed: 12-09-2019 17:24 UTC

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drugs prescribed will have prevented thousands of relapses, which the health economists might acknowledge. And as Professor Compston stresses, it leaves a platform for introducing new treatments and executing clinical research that is second to none in the world. Meanwhile, a treatment rate in the UK of around 10-15% of patients, compared with 55-70% in the United States and 40-50% in France and Germany, suggests that we may not have strayed excessively from a sound evidence base.

As for the financial reckoning, the expiry of patents beckons, and substantially cheaper interferon beta preparations are already available and being used (such as Extavia). To add a political point to this lively mix of medicine and economics, the workings of the market may ultimately achieve what central planners have not.

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Conflicts of interest and pandemic flu

WHO must act now to restore its credibility, and Europe should legislate

ROCHE

FEATURE, p 1274

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Competing interests: The author has completed the Unified Competing Interest form at www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declares: (1) No financial support for the submitted work from anyone other than her employer; (2) No financial relationships with commercial entities that might have an interest in the submitted work; (3) No spouse, partner, or children with relationships with commercial entities that might have an interest in the submitted work; (4) FG has written articles on the challenges faced by WHO, and on the influence of the drugs industry. She is in favour of a more assertive approach to conflict of interest and supports efforts to control the influence of the drugs industry on medical research, medical education, and health policy.

Provenance and peer review: Commissioned; not externally peer reviewed.

Cite this as: *BMJ* 2010;340:c2947
doi: 10.1136/bmj.c2947

The world should of course be thankful that the 2009 influenza A/H1N1 pandemic proved such a damp squib. With so many fewer lives lost than had been predicted, it almost seems ungrateful to carp about the cost. But carp we must because the cost has been huge. Some countries—notably Poland—declined to join the panic buying of vaccines and antivirals triggered when the World Health Organization declared the pandemic a year ago this week. However, countries like France and the United Kingdom who have stockpiled drugs and vaccines are now busy unpicking vaccine contracts, selling unused vaccine to other countries, and sitting on huge piles of unused oseltamivir. Meanwhile drug companies have banked vast profits—$7bn (£4.8bn; €5.7bn) to $10bn from vaccines alone according to investment bank JP Morgan.[1] Given the scale of public cost and private profit, it would seem important to know that WHO's key decisions were free from commercial influence.

An investigation by the *BMJ* and the Bureau of Investigative Journalism, published this week, finds that this was far from the case.[2] As reported by Deborah Cohen and Philip Carter, some of the experts advising WHO on the pandemic had declarable financial ties with drug companies that were producing antivirals and influenza vaccines. As an example, WHO's guidance on the use of antivirals in a pandemic was authored by an influenza expert who at the same time was receiving payments from Roche, the manufacturer of oseltamivir (Tamiflu), for consultancy work and lecturing. Although most of the experts consulted by WHO made no secret of their industry ties in other settings, WHO itself has so far declined to explain to what extent it knew about these conflicts of interest or how it managed them.

This lack of transparency is compounded by the existence of a secret "emergency committee," which advised the director general Margaret Chan on when to declare the pandemic—a decision that triggered costly pre-established vaccine contracts around the world. Curiously, the names of the 16 committee members are known only to people within WHO.

Cohen and Carter's findings resonate with those of other investigations, most notably an inquiry by the Council of Europe, which reports this week and is extremely critical of WHO.[1] It concludes that decision making around the influenza A/H1N1 crisis has been lacking in transparency.

One of its chief protagonists is Paul Flynn, a UK member of parliament and a member of the council's Parliamentary Assembly. He and others raised concerns last year about the lack of evidence to justify the scale of the international response to H1N1 (as also covered in the *BMJ* in December[3]), and the lack of transparency around the decision making process for declaring the pandemic.[1]

WHO's response to these concerns has been disappointing. Although Margaret Chan has ordered an inquiry and WHO has stressed its commitment to transparency, her office has turned down requests to clear up concerns about potential conflicts of interest.[2] And at a hearing of the Council of Europe's Parliamentary Assembly in January, WHO denied any industry influence on the scientific advice it received.[1] Such a knee jerk defence before the facts were known may come to haunt the organisation.

This response is also disappointing given WHO's track record of standing up to industry. In the late 1970s WHO sparked two iconic clashes with multinational companies over the marketing of breast milk substitutes in the developing world and the setting up of the Essential Drugs Programme.[4] Both issues set WHO at loggerheads with the United States where these industries had major holdings. Partly in response to WHO's position, America withdrew contributions to WHO's budget.

More recently, in 1999, when the forced disclosure of confidential tobacco industry documents alerted WHO to possible interference in its anti-tobacco activities, its then director general Gro Harlem Brundtland quickly set up an independent inquiry. She then published and press released its shocking findings—of an elaborate industry funded campaign to undermine WHO—without any attempt at interference or spin.[5] The report recommended that all staff, consultants, temporary advisers, and members of expert committees should be required to declare their conflicts of interest, with

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"Concerning the members of the Emergency Committee that advised WHO on the pandemic, including phase changes, the names will be released when the Committee finishes its work, as has always been intended."
Margaret Chan, director-general, World Health Organization
To submit a rapid response, go to any article on bmj.com and click "respond to this article."

well enforced penalties for those who failed to do so.[6]

As Cohen and Carter report, WHO subsequently published in 2003 new rules on managing conflicts of interest. These recommended that people with a conflict of interest should not be involved in the part of the discussion or the piece of work affected by that interest or, in certain circumstances, that they should not participate in the relevant discussion or work at all.[7] WHO seems not to have followed its own rules for the decision making around the pandemic.

WHO will not be the only body to come under scrutiny for its handling of the pandemic. The coming months will see a spate of reports, from the European Commission, the European Parliament, and from national bodies including the French Senate, and the UK's Cabinet Office. This soul searching takes place against a backdrop of hardening attitudes to conflicts of interest around the world. Last year's report from the Institute of Medicine[8] has been followed by new guidance from groups such as the World Association of Medical Editors[9] and the American College of Chest Physicians,[10] which stress that declaration alone is no longer enough. To quote the Institute of Medicine report, "Disclosure is the essential though limited first step in identifying and responding to conflicts of interest." The big question is what to do about the conflicts.

On the basis of our own investigation and those of others, the answer is now inescapable. As Barbara Mintzes says in Cohen and Carter's report, "No one should be on a committee developing guidelines if they have links to companies that either produce a product—vaccine or drug—or a medical device or test for a disease." The same, and more, must apply to committees making major decisions on public health. Where entirely independent experts are hard to find, experts who are involved with industry could be consulted but should be excluded from decision making. The United States has made important progress with its Sunshine Act and other legislation. European legislation on managing conflicts of interest is long overdue.

As for WHO, its credibility has been badly damaged. Recovery will be fastest if it publishes its own report without delay or defensive comment; makes public the membership and conflicts of interest of its emergency committee; and develops, commits to, and monitors stricter rules of engagement with industry that keep commercial influence away from its decision making.

In a briefing at the end of last year, a spokesperson for WHO said, "Given the discrepancy between what was expected [from the pandemic] and what has happened, a search for ulterior motives on the part of WHO and its scientific advisors is understandable, though without justification."[11] The implication is that, had there been a huge death toll, the process behind WHO's decision making would not have been subject to such scrutiny. This is almost certainly true. But it does not mean that we are wrong to ask hard questions. Neither does it make the answers we have found any less troubling. And nor does it remove from WHO the urgent need to restore its credibility and public trust before the next pandemic comes along.

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Improving immunisation coverage in rural India

Incentives help, but not nearly enough


WHO

RESEARCH, p 1291
Cite this as: *BMJ* 2010;340:c2553
doi: 10.1136/bmj.c2553

Despite decades of rhetoric about improving health and two decades of economic growth, vaccination rates in India remain low. As in Ethiopia, Burkina Faso, and Afghanistan, measles vaccination rates in India are around 70%, and only 44% of children aged 1-2 years are fully immunised.[1] Low vaccination rates have been alternately blamed on insufficient public funds, poor implementation of vaccination programmes, and a general apathy towards the health of the poor. Yet, we have remarkably little evidence to help us separate problems with implementation of vaccination programmes from design flaws that restrict take-up.

Banerjee and colleagues' linked cluster randomised trial brings together time tested methods from public health (randomised trials) with the latest thinking in economics on incentives and human behaviour to examine fundamental problems of design in the delivery of vaccinations.[2]

The authors compared two interventions in a region where vaccination rates are low. In the first intervention, vaccination camps were held in villages on a monthly basis. The second intervention also established camps, but the researchers provided households a small food incentive (lentils worth $1; £0.66; €0.78) for every vaccination and a slightly larger incentive for children who completed the full package (plates, worth just under $2). In the control villages with no interventions, 6% (95% confidence interval 3% to 9%) of children aged 1-3 years had received the basic package of vaccinations in the end point survey. This increased to 18% (11% to 23%) in villages that received the first intervention and to 39% (30% to 47%) in those that received the second intervention. The relative risk of being immunised was 3.09 (1.96 to 4.21) for the first intervention versus the control and 2.16 (1.54 to 2.78) for the second intervention versus the first intervention.

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Graña C, Ghosn L, Evrenoglou T, Jarde A, Minozzi S, Bergman H, Buckley BS, Probyn K, Villanueva G, Henschke N, Bonnet H, Assi R, Menon S, Marti M, Devane D, Mallon P, Lelievre JD, Askie LM, Kredo T, Ferrand G, Davidson M, Riveros C, Tovey D, Meerpohl JJ, Grasselli G, Rada G, Hróbjartsson A, Ravaud P, Chaimani A, Boutron I

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Efficacy and safety of COVID-19 vaccines.
Cochrane Database of Systematic Reviews 2022, Issue 12. Art. No.: CD015477.
DOI: 10.1002/14651858.CD015477.

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[Intervention Review]

Efficacy and safety of COVID-19 vaccines

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Editorial group: Cochrane Emergency and Critical Care Group.
Publication status and date: Edited (no change to conclusions), published in Issue 3, 2023.

Citation: Graña C, Ghosn L, Evrenoglou T, Jarde A, Minozzi S, Bergman H, Buckley BS, Probyn K, Villanueva G, Henschke N, Bonnet H, Assi R, Menon S, Marti M, Devane D, Mallon P, Lelievre J-D, Askie LM, Kredo T, Ferrand G, Davidson M, Riveros C, Tovey D, Meerpohl JJ, Grasselli G, Rada G, Hróbjartsson A, Ravaud P, Chaimani A, Boutron I. Efficacy and safety of COVID-19 vaccines. *Cochrane Database of Systematic Reviews* 2022, Issue 12. Art. No.: CD015477. DOI: 10.1002/14651858.CD015477.

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ABSTRACT

Background

Different forms of vaccines have been developed to prevent the SARS-CoV-2 virus and subsequent COVID-19 disease. Several are in widespread use globally.

Objectives

To assess the efficacy and safety of COVID-19 vaccines (as a full primary vaccination series or a booster dose) against SARS-CoV-2.

Search methods

We searched the Cochrane COVID-19 Study Register and the COVID-19 L·OVE platform (last search date 5 November 2021). We also searched the WHO International Clinical Trials Registry Platform, regulatory agency websites, and Retraction Watch.

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Selection criteria

We included randomized controlled trials (RCTs) comparing COVID-19 vaccines to placebo, no vaccine, other active vaccines, or other vaccine schedules.

Data collection and analysis

We used standard Cochrane methods. We used GRADE to assess the certainty of evidence for all except immunogenicity outcomes.

We synthesized data for each vaccine separately and presented summary effect estimates with 95% confidence intervals (CIs).

Main results

We included and analyzed 41 RCTs assessing 12 different vaccines, including homologous and heterologous vaccine schedules and the effect of booster doses. Thirty-two RCTs were multicentre and five were multinational. The sample sizes of RCTs were 60 to 44,325 participants. Participants were aged: 18 years or older in 36 RCTs; 12 years or older in one RCT; 12 to 17 years in two RCTs; and three to 17 years in two RCTs. Twenty-nine RCTs provided results for individuals aged over 60 years, and three RCTs included immunocompromized patients. No trials included pregnant women. Sixteen RCTs had two-month follow-up or less, 20 RCTs had two to six months, and five RCTs had greater than six to 12 months or less. Eighteen reports were based on preplanned interim analyses.

Overall risk of bias was low for all outcomes in eight RCTs, while 33 had concerns for at least one outcome.

We identified 343 registered RCTs with results not yet available.

This abstract reports results for the *critical outcomes* of confirmed symptomatic COVID-19, severe and critical COVID-19, and serious adverse events only for the 10 WHO-approved vaccines. For remaining outcomes and vaccines, see main text. The evidence for mortality was generally sparse and of low or very low certainty for all WHO-approved vaccines, except AD26.COV2.S (Janssen), which probably reduces the risk of all-cause mortality (risk ratio (RR) 0.25, 95% CI 0.09 to 0.67; 1 RCT, 43,783 participants; high-certainty evidence).

Confirmed symptomatic COVID-19

High-certainty evidence found that BNT162b2 (BioNtech/Fosun Pharma/Pfizer), mRNA-1273 (ModernaTx), ChAdOx1 (Oxford/AstraZeneca), Ad26.COV2.S, BBIBP-CorV (Sinopharm-Beijing), and BBV152 (Bharat Biotect) reduce the incidence of symptomatic COVID-19 compared to placebo (vaccine efficacy (VE): BNT162b2: 97.84%, 95% CI 44.25% to 99.92%; 2 RCTs, 44,077 participants; mRNA-1273: 93.20%, 95% CI 91.06% to 94.83%; 2 RCTs, 31,632 participants; ChAdOx1: 70.23%, 95% CI 62.10% to 76.62%; 2 RCTs, 43,390 participants; Ad26.COV2.S: 66.90%, 95% CI 59.10% to 73.40%; 1 RCT, 39,058 participants; BBIBP-CorV: 78.10%, 95% CI 64.80% to 86.30%; 1 RCT, 25,463 participants; BBV152: 77.80%, 95% CI 65.20% to 86.40%; 1 RCT, 16,973 participants).

Moderate-certainty evidence found that NVX-CoV2373 (Novavax) probably reduces the incidence of symptomatic COVID-19 compared to placebo (VE 82.91%, 95% CI 50.49% to 94.10%; 3 RCTs, 42,175 participants).

There is low-certainty evidence for CoronaVac (Sinovac) for this outcome (VE 69.81%, 95% CI 12.27% to 89.61%; 2 RCTs, 19,852 participants).

Severe or critical COVID-19

High-certainty evidence found that BNT162b2, mRNA-1273, Ad26.COV2.S, and BBV152 result in a large reduction in incidence of severe or critical disease due to COVID-19 compared to placebo (VE: BNT162b2: 95.70%, 95% CI 73.90% to 99.90%; 1 RCT, 46,077 participants; mRNA-1273: 98.20%, 95% CI 92.80% to 99.60%; 1 RCT, 28,451 participants; AD26.COV2.S: 76.30%, 95% CI 57.90% to 87.50%; 1 RCT, 39,058 participants; BBV152: 93.40%, 95% CI 57.10% to 99.80%; 1 RCT, 16,976 participants).

Moderate-certainty evidence found that NVX-CoV2373 probably reduces the incidence of severe or critical COVID-19 (VE 100.00%, 95% CI 86.99% to 100.00%; 1 RCT, 25,452 participants).

Two trials reported high efficacy of CoronaVac for severe or critical disease with wide CIs, but these results could not be pooled.

Serious adverse events (SAEs)

mRNA-1273, ChAdOx1 (Oxford-AstraZeneca)/SII-ChAdOx1 (Serum Institute of India), Ad26.COV2.S, and BBV152 probably result in little or no difference in SAEs compared to placebo (RR: mRNA-1273: 0.92, 95% CI 0.78 to 1.08; 2 RCTs, 34,072 participants; ChAdOx1/SII-ChAdOx1: 0.88, 95% CI 0.72 to 1.07; 7 RCTs, 58,182 participants; Ad26.COV2.S: 0.92, 95% CI 0.69 to 1.22; 1 RCT, 43,783 participants); BBV152: 0.65, 95% CI 0.43 to 0.97; 1 RCT, 25,928 participants). In each of these, the likely absolute difference in effects was fewer than 5/1000 participants.

Evidence for SAEs is uncertain for BNT162b2, CoronaVac, BBIBP-CorV, and NVX-CoV2373 compared to placebo (RR: BNT162b2: 1.30, 95% CI 0.55 to 3.07; 2 RCTs, 46,107 participants; CoronaVac: 0.97, 95% CI 0.62 to 1.51; 4 RCTs, 23,139 participants; BBIBP-CorV: 0.76, 95% CI 0.54 to 1.06; 1 RCT, 26,924 participants; NVX-CoV2373: 0.92, 95% CI 0.74 to 1.14; 4 RCTs, 38,802 participants).

For the evaluation of heterologous schedules, booster doses, and efficacy against variants of concern, see main text of review.

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Authors' conclusions

Compared to placebo, most vaccines reduce, or likely reduce, the proportion of participants with confirmed symptomatic COVID-19, and for some, there is high-certainty evidence that they reduce severe or critical disease. There is probably little or no difference between most vaccines and placebo for serious adverse events. Over 300 registered RCTs are evaluating the efficacy of COVID-19 vaccines, and this review is updated regularly on the COVID-NMA platform (covid-nma.com).

Implications for practice

Due to the trial exclusions, these results cannot be generalized to pregnant women, individuals with a history of SARS-CoV-2 infection, or immunocompromized people. Most trials had a short follow-up and were conducted before the emergence of variants of concern.

Implications for research

Future research should evaluate the long-term effect of vaccines, compare different vaccines and vaccine schedules, assess vaccine efficacy and safety in specific populations, and include outcomes such as preventing long COVID-19. Ongoing evaluation of vaccine efficacy and effectiveness against emerging variants of concern is also vital.

PLAIN LANGUAGE SUMMARY

What are the benefits and risks of vaccines for preventing COVID-19?

Key messages

– Most vaccines reduce, or probably reduce, the number of people who get COVID-19 disease and severe COVID-19 disease.

– Many vaccines likely increase number of people experiencing events such as fever or headache compared to placebo (sham vaccine that contains no medicine but looks identical to the vaccine being tested). This is expected because these events are mainly due to the body's response to the vaccine; they are usually mild and short-term.

– Many vaccines have little or no difference in the incidence of serious adverse events compared to placebo.

– There is insufficient evidence to determine whether there was a difference between the vaccine and placebo in terms of death because the numbers of deaths were low in the trials.

– Most trials assessed vaccine efficacy over a short time, and did not evaluate efficacy to the COVID variants of concern.

What is SARS-CoV-2 and COVID-19?

SARS-CoV-2 (severe acute respiratory syndrome coronavirus 2) is the virus that causes COVID-19 disease. Not everyone infected with SARS-CoV-2 will develop symptoms of COVID-19. Symptoms can be mild (e.g. fever and headaches) to life-threatening (e.g. difficulty breathing), or death.

How do vaccines prevent COVID-19?

While vaccines work slightly differently, they all prepare the body's immune system to prevent people from getting infected with SARS-CoV-2 or, if they do get infected, to prevent severe disease.

What did we want to find out?

We wanted to find out how well each vaccine works in reducing SARS-CoV-2 infection, COVID-19 disease with symptoms, severe COVID-19 disease, and total number of deaths (including any death, not only those related to COVID-19).

We wanted to find out about serious adverse events that might require hospitalization, be life-threatening, or both; systemic reactogenicity events (immediate short-term reactions to vaccines mainly due to immunological responses; e.g. fever, headache, body aches, fatigue); and any adverse events (which include non-serious adverse events).

What did we do?

We searched for studies that examined any COVID-19 vaccine compared to placebo, no vaccine, or another COVID-19 vaccine.

We selected only randomized trials (a study design that provides the most robust evidence because they evaluate interventions under ideal conditions among participants assigned by chance to one of two or more groups). We compared and summarized the results of the studies, and rated our confidence in the evidence based on factors such as how the study was conducted.

What did we find?

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We found 41 worldwide studies involving 433,838 people assessing 12 different vaccines. Thirty-five studies included only healthy people who had never had COVID-19. Thirty-six studies included only adults, two only adolescents, two children and adolescents, and one included adolescents and adults. Three studied people with weakened immune systems, and none studied pregnant women.

Most cases assessed results less than six months after the primary vaccination. Most received co-funding from academic institutions and pharmaceutical companies. Most studies compared a COVID-19 vaccine with placebo. Five evaluated the addition of a 'mix and match' booster dose.

Main results

We report below results for three main outcomes and for 10 World Health Organization (WHO)-approved vaccines (for the remaining outcomes and vaccines, see main text). There is insufficient evidence regarding deaths between vaccines and placebo (mainly because the number of deaths was low), except for the Janssen vaccine, which probably reduces the risk of all-cause deaths.

People with symptoms

The Pfizer, Moderna, AstraZeneca, Sinopharm-Beijing, and Bharat vaccines produce a large reduction in the number of people with symptomatic COVID-19.

The Janssen vaccine reduces the number of people with symptomatic COVID-19.

The Novavax vaccine probably has a large reduction in the number of people with symptomatic COVID-19.

There is insufficient evidence to determine whether CoronaVac vaccine affects the number of people with symptomatic COVID-19 because results differed between the two studies (one involved only healthcare workers with a higher risk of exposure).

Severe disease

The Pfizer, Moderna, Janssen, and Bharat vaccines produce a large reduction in the number of people with severe disease.

There is insufficient evidence about CoronaVac vaccine on severe disease because results differed between the two studies (one involved only healthcare workers with a higher risk of exposure).

Serious adverse events

For the Pfizer, CoronaVac, Sinopharm-Beijing, and Novavax vaccines, there is insufficient evidence to determine whether there was a difference between the vaccine and placebo mainly because the number of serious adverse events was low.

Moderna, AstraZeneca, Janssen, and Bharat vaccines probably result in no or little difference in the number of serious adverse events.

What are the limitations of the evidence?

Most studies assessed the vaccine for a short time after injection, and it is unclear if and how vaccine protection wanes over time. Due to the exclusion criteria of COVID-19 vaccine trials, results cannot be generalized to pregnant women, people with a history of SARS-CoV-2 infection, or people with weakened immune systems. More research is needed comparing vaccines and vaccine schedules, and effectiveness and safety in specific populations and outcomes (e.g. preventing long COVID-19). Further, most studies were conducted before the emergence of variants of concerns.

How up to date is this evidence?

The evidence is up to date to November 2021. This is a living systematic review. Our results are available and updated bi-weekly on the COVID-NMA platform at covid-nma.com.

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SUMMARY OF FINDINGS

Summary of findings 1. BNT162b2 – Pfizer/BioNTech + Fosun Pharma compared to placebo for vaccination against COVID-19[a]

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants	Certainty of the evidence (GRADE)	Comments
	Risk with placebo	Risk with BNT162b2				
Confirmed SARS-CoV-2 infection	Outcome not yet measured or reported					
Confirmed symptomatic COVID-19[b]	3923 per 100,000	**85 per 100,000** (3 to 2187)	**VE 97.84** (44.25 to 99.92)	44,077 (2 RCTs)[c]	⊕⊕⊕⊕ **High**[d]	—
Severe or critical COVID-19[e]	100 per 100,000	**4 per 100,000** (0 to 26)	**VE 95.70** (73.90 to 99.90)	46,077 (1 RCT)[f]	⊕⊕⊕⊕ **High**	—
All-cause mortality[g]	64 per 100,000	**68 per 100,000** (33 to 142)	**RR 1.07** (0.52 to 2.22)	43,847 (1 RCT)[f]	⊕⊕⊖⊖ **Low**[h]	2 additional studies (Frenck 2021 (adolescents aged 12–15 years); Walsh 2020 (adults aged 18–85 years)) reported this outcome in 2302 participants (1131 versus 1129 participants and 24 versus 18 participants in the BNT162b2 versus placebo groups, respectively). There were no events in either group and the trials did not contribute to the effect estimate.
Systemic reactogenicity events	Outcome not yet measured or reported					
Any adverse event[i]	Outcome not pooled due to considerable heterogeneity (I^2 = 90%) between included studies: Thomas 2021 (≥ 16 years): RR 2.17, 95% CI 2.09 to 2.26; n = 43,847; Frenck 2021 (12–15 years): RR 1.01, 95% CI 0.73 to 1.41; n = 2260; Walsh 2020 (≥ 18 years): RR 1.50, 95% CI 0.53 to 4.21; n = 42			46,149 (3 RCTs)[j]	⊕⊕⊖⊖ **Low**[k]	—
Serious adverse events[i]	508 per 100,000	**660 per 100,000** (279 to 1558)	**RR 1.30** (0.55 to 3.07)	46,107 (2 RCTs)[c]	⊕⊕⊖⊖ **Low**[l,m]	1 additional trial (Walsh 2020 (adults aged 18–85 years)) reported this outcome in 42 participants (24 BNT162b2 versus 18 placebo). There

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		were no events in either group and the trial did not contribute to the effect estimate.
Local reactogenicity events	Outcome not yet measured or reported	

*__The risk in the intervention group__ (and its 95% CI) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

COVID-19: coronavirus disease 2019;**CI:** confidence interval; **RR:** risk ratio; **SARS-CoV-2:** severe acute respiratory syndrome coronavirus 2; **VE:** vaccine efficacy.

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate; the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited; the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate; the true effect is likely to be substantially different from the estimate of effect.

[a]Last updated: 3 May 2022
[b]Follow-up: from 7 days following the second dose to 1.81 months and six months.
[c]BioNTech/Fosun Pharma/Pfizer: Thomas 2021 (adolescents and adults aged from 16 years); Frenck 2021 (adolescents aged 12–15 years)
[d]Despite some concerns with deviations from intervention, not downgraded for risk of bias.
[e]Follow-up: from seven days following the second dose to six months.
[f]BioNTech/Fosun Pharma/Pfizer: Thomas 2021 (adolescents and adults aged from 16 years)
[g]Follow-up: six months
[h]Imprecision: downgraded two levels due to small number of events observed and a wide CIs that encompasses a potential benefit and a potential harm with the intervention.
[i]Follow-up: 1.7 months
[j]BioNTech/Fosun Pharma/Pfizer: Thomas 2021 (adolescents and adults aged from 16 years); Frenck 2021 (adolescents aged 12–15 years); Walsh 2020 (adults aged 18–85 years)
[k]Inconsistency: downgraded two levels (I^2 = 90%)
[l]Inconsistency: downgraded one level (I^2 = 76%)
[m]Imprecision: downgraded one level due to wide CIs consistent with the possibility of benefit and the possibility of harm. This outcome was not downgraded an additional level for imprecision because it was downgraded one level for inconsistency, which is related to and would have contributed to the severity of the imprecision.

Summary of findings 2. mRNA-1273 – ModernaTX compared to placebo for vaccination against COVID-19[a]

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with placebo	Risk with mRNA-1273				
Confirmed SARS-CoV-2 infection[b]	8957 per 100,000	**2394 per 100,000** (997 to 5749)	**VE 73.27** (35.82 to 88.87)	31,632 (2 RCTs)[c]	⨁⨁⨁◯ Moderate[d,e]	Substantial heterogeneity (I^2 = 66%) between included studies: Ali 2021 (adolescents aged 12–17 years, median 2.3 months' follow-up):

						VE 55.7% (95% CI 16.8 to 76.4), n = 3181; El Sahly 2021 (adults aged 18–95 years, 5.3 months' follow-up): VE 82% (95% CI 79.5 to 84.2), n = 28,451
Confirmed symptomatic COVID-19 [b]	4939 per 100,000	**336 per 100,000** (255 to 442)	**VE 93.20** (91.06 to 94.83)	31,632 (2 RCTs)[c]	⊕⊕⊕⊕ High[d]	—
Severe or critical COVID-19[f]	748 per 100,000	**13 per 100,000** (3 to 54)	**VE 98.20** (92.80 to 99.60)	28,451 (1 RCT)[g]	⊕⊕⊕⊕ High[d]	—
All-cause mortality[f]	106 per 100,000	**112 per 100,000** (57 to 222)	**RR 1.06** (0.54 to 2.10)	30,346 (1 RCT)[g]	⊕⊕◯◯ Low[h]	1 additional trial: (Ali 2021 (adolescents aged 12–17 years)) reported on this outcome in 3726 participants (2486 mRNA-1273 and 1240 placebo). There were no events in either group and the trial did not contribute to the pooled effect estimate
Systemic reactogenicity events[i]	432 per 1000	**553 per 1000** (527 to 579)	**RR 1.28** (1.22 to 1.34)	34,037 (2 RCTs)[c]	⊕⊕⊕⊕ High[j]	—
Any adverse event[k]	Outcome not pooled due to considerable heterogeneity (I^2 = 100%) between included studies: Ali 2021 (all solicited adverse events, adolescents aged 12–17 years, median 2.8 months' follow-up): RR 1.47 (95% CI 1.41 to 1.54), n = 3726; El Sahly 2021 (all solicited adverse events, adults aged 18–95 years, 5.3 months' follow-up): RR 2.15 (95% CI 2.11 to 2.19), n = 29,269		—	32,995 (2 RCTs)[c]	⊕⊕◯◯ Low[l]	—
Serious adverse events[l]	1792 per 100,000	**1649 per 100,000** (1398 to 1936)	**RR 0.92** (0.78 to 1.08)	34,072 (2 RCTs)[c]	⊕⊕⊕◯ Moderate[m]	—
Local reactogenicity events[i]	211 per 1000	**697 per 1000** (427 to 1000)	**RR 3.30** (2.02 to 5.40)	34,037 (2 RCTs)[c]	⊕⊕⊕⊕ High[n]	—

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the __relative effect__ of the intervention (and its 95% CI).

COVID-19: coronavirus disease 2019;**CI:** confidence interval; **RCT:** randomized controlled trial; **RR:** risk ratio; **SARS-CoV-2:** severe acute respiratory syndrome coronavirus 2; **VE:** vaccine efficacy.

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GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

a. Last updated: 01 March 2023
b. Follow-up: from 14 days after dose 2 to 2.3 months (median) and 5.3 months
c. Moderna TX: Ali 2021 (adolescents aged 12–17 years); El Sahly 2021 (adults aged 18–95 years)
d. Despite some concerns with deviations from intervention, not downgraded for risk of bias
e. Inconsistency: downgraded one level: I^2 = 66.37%
f. Follow-up: 5.3 months
g. Moderna TX: El Sahly 2021 (adults aged 18–95 years)
h. Imprecision downgraded two levels due to small number of events observed and wide CIs that encompass a potential benefit and a potential harm with the intervention
i. Follow-up: seven days
j. Despite inconsistency (I^2 = 61%) not downgraded for inconsistency, as the same direction of effect in both effect estimates
k. Follow-up: 2.8 months (median) and 5.3 months
l. Inconsistency: downgraded two levels (I^2 = 100%)
m. Imprecision: downgraded one level due to wide CIs that encompass a potential benefit and a potential harm with the intervention.
n. Despite inconsistency (I^2 = 99%), not downgraded for inconsistency, as the same direction of effect in both effect estimates

Summary of findings 3. CVnCoV – CureVac AG compared to placebo for vaccination against COVID-19[a]

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with placebo	Risk with CVnCOV				
Confirmed SARS-CoV-2 infection	Outcome not yet measured or reported					
Confirmed symptomatic COVID-19[b]	1187 per 100,000	**615 per 100,000** (464 to 811)	**VE 48.20** (31.70 to 60.90)	25,062 (1 RCT)[c]	⊕⊕⊕⊖ **Moderate**[d,e]	—
Severe or critical COVID-19[f]	82 per 100,000	**30 per 100,000** (7 to 82)	**VE 63.80** (0.00 to 91.70)	25,062 (1 RCT)[c]	⊕⊖⊖⊖ **Very low**[d,e,g]	—
All-cause mortality[h]	30 per 100,000	**40 per 100,000** (14 to 116)	**RR 1.33** (0.46 to 3.83)	39,529 (1 RCT)[c]	⊕⊖⊖⊖ **Very low**[e,g]	—

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Systemic reactogenicity events[i]	635 per 1000	**940 per 1000** (908 to 971)	**RR 1.48** (1.43 to 1.53)	3982 (1 RCT)[c]	⊕⊕⊕⊕ **High**	—
Any adverse event[j]	679 per 1000	**965 per 1000** (937 to 999)	**RR 1.42** (1.38 to 1.47)	3982 (1 RCT)[c]	⊕⊕⊕⊖ **Moderate**[e]	—
Serious adverse events[k]	334 per 100,000	**414 per 100,000** (301 to 572)	**RR 1.24** (0.90 to 1.71)	39,529 (1 RCT)[c]	⊕⊕⊖⊖ **Low**[e,l]	—
Local reactogenicity events[i]	241 per 1000	**847 per 1000** (782 to 920)	**RR 3.51** (3.24 to 3.81)	3982 (1 RCT)[c]	⊕⊕⊕⊕ **High**	—

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

COVID-19: coronavirus disease 2019**CI:** confidence interval; **RCT:** randomized controlled trial; **RR:** risk ratio; **SARS-CoV-2:** severe acute respiratory syndrome coronavirus 2; **VE:** vaccine efficacy.

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate; the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited; the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate; the true effect is likely to be substantially different from the estimate of effect.

[a]Last updated: 10 May 2022
[b]Follow-up: from 14 days following the second dose to 6.23 months
[c]CureVac AG: Kremsner 2021 (adults aged 18–98 years)
[d]Despite some concerns with deviations from intervention, not downgraded for risk of bias.
[e]Indirectness: downgraded one level as data are from interim analyses of the trial and from the available information it is unclear whether these were preplanned.
[f]Follow-up: from seven days following the second dose to six months
[g]Imprecision: downgraded two levels due to small number of events observed and wide CIs that encompass a potential benefit and a potential harm with the intervention.
[h]Follow-up: 6.23 months
[i]Follow-up: seven days
[j]Follow-up: one month
[k]Follow-up: 1.7 months
[l]Imprecision: downgraded one level due to wide CIs consistent with the possibility of benefit and the possibility of harm.

Summary of findings 4. ChAdOx1 – AstraZeneca + University of Oxford compared to placebo for vaccination against COVID-19[a]

Outcomes	Anticipated absolute effects* (95% CI)	Relative effect (95% CI)	№ of participants	Certainty of the evidence	Comments

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	Risk with placebo	Risk with ChAdOx1		(studies)		
Confirmed SARS-CoV-2 infection[b]	3199 per 100,000	**1300 per 100,000** (1017 to 1663)	**VE 59.35** (48.00 to 68.22)	43,390 (5 RCTs)[c]	⊕⊕⊕⊖ **Moderate**[d,e]	Substantial heterogeneity (I^2 = 68%) between included studies: Falsey 2021 (VE 64.35%, 95% CI 56.10% to 71.00%; n = 26,212); Voysey 2021a (VE 54.10%, 95% CI 44.70% to 61.90%; n = 17,178)
Confirmed symptomatic COVID-19[b]	2207 per 100,000	**657 per 100,000** (516 to 836)	**VE 70.23** (62.10 to 76.62)	43,390 (5 RCTs)[c]	⊕⊕⊕⊕ **High**[d]	—
Severe or critical COVID-19	Outcome not yet measured or reported					
All-cause mortality[f]	52 per 100,000	**25 per 100,000** (10 to 59)	**RR 0.48** (0.20 to 1.14)	56,727 (5 RCTs)[g]	⊕⊕⊖⊖ **Low**[h]	2 additional trials (Asano 2022; Kulkarni 2021) reported this outcome in 1392 participants (192 ChAdOx1 versus 64 placebo and 900 SII-ChAdOx1 versus 300 placebo, respectively). There were no events in either group in either trial and they did not contribute to the pooled effect estimate.
Systemic reactogenicity events[i]	141 per 1000	**553 per 1000** (297 to 1000)	**RR 3.93** (2.11 to 7.29)	256 (1 RCT)[j]	⊕⊕⊕⊖ **Moderate**[k]	—
Any adverse event[l]	Outcome not pooled due to considerable heterogeneity (I^2 = 90%) between included studies: Asano 2022 (RR 2.54, 95% CI 1.73 to 3.74; n = 256); Falsey 2021 (RR 1.37, 95% CI 1.33 to 1.42; n = 32,379); Kulkarni 2021 (RR 1.39, 95% CI 1.12 to 1.74; n = 1200); Voysey 2021a (RR 0.74, 95% CI 0.56 to 0.96; n = 23,745)		—	57,580 (7 RCTs)[m]	⊕⊕⊖⊖ **Low**[n]	—
Serious adverse events[o]	794 per 100,000	**699 per 100,000** (572 to 850)	**RR 0.88** (0.72 to 1.07)	58,182 (7 RCTs)[p]	⊕⊕⊕⊖ **Moderate**[q]	—
Local reactogenicity events[i]	94 per 1000	**604 per 1000** (279 to 1000)	**RR 6.44** (2.98 to 13.92)	256 (1 RCT)[j]	⊕⊕⊕⊖ **Moderate**[k,r]	—

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

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COVID-19: coronavirus disease 2019**CI:** confidence interval; **RCT:** randomized controlled trial; **RR:** risk ratio; **SARS-CoV-2:** severe acute respiratory syndrome coronavirus 2; **VE:** vaccine efficacy.

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate; the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited; the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate; the true effect is likely to be substantially different from the estimate of effect.

[a]Last updated: 4 May 2022
[b]Follow-up: from 14 days after second dose up to 1.34 months (median) and 2 months (median)
[c]Falsey 2021; Voysey 2021a (data from four pooled RCTs)
[d]Despite some concerns with deviations from intervention, not downgraded for risk of bias.
[e]Inconsistency: downgraded one level (I^2 = 68%).
[f]Follow-up: 2 months, 4.2 months and 2 months (median)
[g]Falsey 2021; Voysey 2021a (data from four pooled RCTs); Madhi 2021a (participants with HIV, trial already counted in Voysey 2021a)
[h]Imprecision: downgraded two levels due to small number of events observed and wide CIs that encompass a potential benefit and a potential harm with the intervention.
[i]Follow-up: seven days
[j]Asano 2022
[k]Imprecision: downgraded one level due to low number of participants/few events observed.
[l]Follow-up: 1 month, 1.16 months, 1.9 months, and 3.4 months
[m]Asano 2022; Falsey 2021; Kulkarni 2021; Voysey 2021a (data from four pooled RCTs)
[n]Inconsistency: downgraded two levels (I^2 = 90%).
[o]Follow-up: 1 month, 1.9 months, 6 months, and 3.64 months (median)
[p]Asano 2022; Falsey 2021; Kulkarni 2021; Voysey 2021a (data from four pooled RCTs). Madhi 2021a (participants with HIV, trial already counted in Voysey 2021a)
[q]Imprecision: downgraded one level due to wide CIs consistent with the possibility of benefit and the possibility of no effect.
[r]Despite some concerns with selection of reported results, not downgraded for risk of bias.

Summary of findings 5. SII-ChAdOx1 – Serum Institute of India/AstraZeneca + University of Oxford compared to ChAdOx1 – University of Oxford for vaccination against COVID-19[a]

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with ChAdOx1	Risk with SII-ChAdOx1				
Confirmed SARS-CoV-2 infection	Outcome not yet measured or reported					
Confirmed symptomatic COVID-19	Outcome not yet measured or reported					

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Severe or critical COVID-19	Outcome not yet measured or reported					
All-cause mortality	—	—	—	—	—	1 study reported this outcome in 400 participants (Kulkarni 2021). There were no events in either group and no effect estimate could be calculated.
Systemic reactogenicity events[b]	390 per 1000	**285 per 1000** (211 to 382)	**RR 0.73** (0.54 to 0.98)	400 (1 RCT)[c]	⊕⊕⊕⊖ **Moderate**[d]	—
Any adverse event[e]	200 per 1000	**166 per 1000** (104 to 266)	**RR 0.83** (0.52 to 1.33)	400 (1 RCT)[c]	⊕⊕⊖⊖ **Low**[f]	—
Serious adverse events[g]	2000 per 100,000	**1000 per 100,000** (160 to 5900)	**RR 0.50** (0.08 to 2.95)	400 (1 RCT)[c]	⊕⊕⊖⊖ **Low**[f]	—
Local reactogenicity events[b]	360 per 1000	**274 per 1000** (198 to 378)	**RR 0.76** (0.55 to 1.05)	400 (1 RCT)[c]	⊕⊕⊖⊖ **Low**[h]	—

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

COVID-19: coronavirus disease 2019**CI:** confidence interval; **RCT:** randomized controlled trial; **RR:** risk ratio; **SARS-CoV-2:** severe acute respiratory syndrome coronavirus 2.

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate; the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited; the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate; the true effect is likely to be substantially different from the estimate of effect.

[a]Last updated: 10 May 2022
[b]Follow-up: seven days
[c]Kulkarni 2021
[d]Imprecision: downgraded one level due to low number of events/participants.
[e]Follow-up: 1.9 months
[f]Imprecision: downgraded two levels due to wide CIs consistent with the possibility of benefit and the possibility of harm and low number of events/participants.
[g]Follow-up: six months
[h]Imprecision: downgraded two levels due to wide CIs consistent with the possibility of no effect and the possibility of benefit and low number of events/participants.

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Summary of findings 6. AD26.COV2.S – Janssen Pharmaceutical Companies compared to placebo for vaccination against COVID-19[a]

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with placebo	Risk with AD26.COV2.S				
Confirmed SARS-CoV-2 infection	Outcome not yet measured or reported					
Confirmed symptomatic COVID-19[b]	1796 per 100,000	**594 per 100,000** (478 to 735)	**VE 66.90** (59.10 to 73.40)	39,058 (1 RCT)[c]	⊕⊕⊕⊕ **High**[d]	—
Severe or critical COVID-19[b]	409 per 100,000	**97 per 100,000** (51 to 172)	**VE 76.30** (57.90 to 87.50)	39,058 (1 RCT)[c]	⊕⊕⊕⊕ **High**[d]	—
All-cause mortality[b]	91 per 100,000	**23 per 100,000** (8 to 61)	**RR 0.25** (0.09 to 0.67)	43,783 (1 RCT)[c]	⊕⊕⊕⊕ **High**	—
Serious adverse events[b]	448 per 100,000	**412 per 100,000** (309 to 546)	**RR 0.92** (0.69 to 1.22)	43,783 (1 RCT)[c]	⊕⊕⊕⊖ **Moderate**[j]	—
Systemic reactogenicity events[e]	34,575 per 100,000	**63,273 per 100,000** (44,602 to 89,896)	**RR 1.83** (1.29 to 2.60)	7222 (2 RCTs)[f]	⊕⊕⊕⊕ **High**[d,g]	—
Any adverse event[h]	Outcome not pooled due to considerable heterogeneity (I^2 = 96%) between included studies: Sadoff 2021a (RR 1.09, 95% CI 0.96 to 1.24; n = 6736); Sadoff 2021b (RR 2.31, 95% CI 1.80 to 2.97; n = 486)		—	7222 (2 RCTs)[f]	⊕⊕⊖⊖ **Low**[d,i]	—

*__The risk in the intervention group__ (and its 95% CI) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

COVID-19: coronavirus disease 2019**CI:** confidence interval; **RCT:** randomized controlled trial; **RR:** risk ratio; **SARS-CoV-2:** severe acute respiratory syndrome coronavirus 2; **VE**: vaccine efficacy.

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate; the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited; the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate; the true effect is likely to be substantially different from the estimate of effect.

[a]Last updated: 4 May 2022

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[b]Follow-up: 1.9 months (median)
[c]Sadoff 2021b
[d]Despite some concerns with deviations from intervention, not downgraded for risk of bias.
[e]Follow-up: seven days and 14 days
[f]Sadoff 2021a; Sadoff 2021b
[g]Despite I^2 = 83%, not downgraded for inconsistency, as the same direction of effect in both effect estimates.
[h]Follow-up: 0.23 months and 0.92 months
[i]Inconsistency: downgraded two levels (I^2 = 96%).
[j]Imprecision: downgraded one level due to wide CIs consistent with the possibility of no effect and the possibility of benefit.
[k]Follow-up: seven days
[l]Despite I^2 = 84%, not downgraded for inconsistency, as the same direction of effect in both effect estimates.

Summary of findings 7. Gam-COVID-VAC – Sputnik V compared to placebo for vaccination against COVID-19[a]

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with placebo	Risk with Gam-COVID-VAC				
Confirmed SARS-CoV-2 infection	Outcome not yet measured or reported					
Confirmed symptomatic COVID-19[b]	1022 per 100,000	**92 per 100,000** (51 to 167)	**VE 91.10** (83.80 to 95.10)	18,695 (1 RCT)[c]	⊕⊕⊕⊖ **Moderate**[d,e]	—
Severe or critical COVID-19[b]	408 per 100,000	**0 per 100,000** (0 to 23)	**VE 100.00** (94.40 to 100.00)	19,866 (1 RCT)[c]	⊕⊕⊕⊖ **Moderate**[d,e]	—
All-cause mortality[f]	18 per 100,000	**18 per 100,000** (2 to 176)	**RR 0.99** (0.10 to 9.54)	21,862 (1 RCT)[c]	⊕⊖⊖⊖ **Very low**[d,e,g]	—
Systemic reactogenicity events	Outcome not yet measured or reported					
Any adverse event	Outcome not yet measured or reported					
Serious adverse events[f]	423 per 100,000	**275 per 100,000** (165 to 453)	**RR 0.65** (0.39 to 1.07)	21,862 (1 RCT)[c]	⊕⊕⊖⊖ **Low**[d,e,h]	—
Local reactogenicity events	Outcome not yet measured or reported					

*__The risk in the intervention group__ (and its 95% CI) is based on the assumed risk in the comparison group and the __relative effect__ of the intervention (and its 95% CI).

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COVID-19: coronavirus disease 2019;**CI:** confidence interval; **RCT:** randomized controlled trial; **RR:** risk ratio; **SARS-CoV-2:** severe acute respiratory syndrome coronavirus 2; **VE:** vaccine efficacy.

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate; the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited; the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate; the true effect is likely to be substantially different from the estimate of effect.

[a]Last updated: 27 May 2022
[b]Follow-up: from seven days after second dose
[c]Logunov 2021
[d]Indirectness: downgraded one level as data are from interim analyses of the trial and from the available information it is unclear whether these were preplanned.
[e]Concern regarding the internal validity of the trial.
[f]Follow-up: 1.6 months (median)
[g]Imprecision: downgraded two levels due to wide CIs consistent with the possibility of benefit and the possibility of harm and few events.
[h]Imprecision: downgraded one level due to wide CIs consistent with the possibility of no effect and the possibility of benefit.

Summary of findings 8. CoronaVac – Sinovac compared to placebo for vaccination against COVID-19[a]

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with placebo	Risk with CoronaVac				
Confirmed SARS-CoV-2 infection	Outcome not yet measured or reported					
Confirmed symptomatic COVID-19[b]	2398 per 100,000	**724 per 100,000** (249 to 2104)	**VE 69.81** (12.27 to 89.61)	19,852 (2 RCTs)[c]	⊕⊕⊖⊖ **Low**[d,e,f]	Considerable heterogeneity (I^2 = 92%) between included studies: Tanriover 2021 (VE 83.50%, 95% CI 65.40% to 92.10%; n = 10,029); Palacios 2020 (VE 50.70%, 95% CI 35.90 to 62.00%; n = 9823)
Severe or critical COVID-19[b]	2 studies report on severe or critical disease due to COVID-19: Tanriover 2021, with 0/6559 events in the CoronaVac group versus 1/3470 events in the placebo group and a VE of 100%, 95% CI (20.40% to 100.00%); and Palacios 2020, with 0/4953 events in the CoronaVac group and 6/4870 events in the placebo group and a VE of 100%, 95% CI (16.90% to 100.00%). (Note:		—	19,852 (2 RCTs)[c]	⊕⊕⊖⊖ **Low**[d,g]	—

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	estimates could not be pooled due to asymmetry in the CIs)					
All-cause mortality[h]	20 per 100,000	**10 per 100,000** (1 to 113)	**RR 0.50** (0.05 to 5.52)	22,610 (2 RCTs)[c]	⊕⊕⊖⊖ **Low**[i]	—
Systemic reactogenicity events[j]	409 per 1000	**487 per 1000** (409 to 581)	**RR 1.19** (1.00 to 1.42)	23,966 (6 RCTs)[k]	⊕⊕⊖⊖ **Low**[l,m,n]	—
Any adverse event[o]	531 per 1000	**579 per 1000** (568 to 590)	**RR 1.09** (1.07 to 1.11)	23,367 (6 RCTs)[p]	⊕⊕⊕⊕ **High**[q]	—
Serious adverse events[r]	372 per 100,000	**361 per 100,000** (231 to 562)	**RR 0.97** (0.62 to 1.51)	23,139 (4 RCTs)[s]	⊕⊕⊖⊖ **Low**[i,q]	2 additional trials (Bueno 2021; Zhang 2021) reported this outcome in 482 participants (270 versus 164 and 24 versus 24 respectively, receiving CoronaVac versus placebo). There were no events in either group and the trials did not contribute to the pooled effect estimate.
Local reactogenicity events[j]	227 per 1000	**400 per 1000** (384 to 414)	**RR 1.76** (1.69 to 1.82)	23,962 (6 RCTs)[k]	⊕⊕⊕⊕ **High**[l]	—

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

COVID-19: coronavirus disease 2019**CI:** confidence interval; **RCT:** randomized controlled trial; **RR:** risk ratio; **SARS-CoV-2:** severe acute respiratory syndrome coronavirus 2; **VE:** vaccine efficacy.

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate; the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited; the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate; the true effect is likely to be substantially different from the estimate of effect.

[a]Last updated: 4 May 2022
[b]Follow-up: from 14 days after the second dose up to two months (median)
[c]Palacios 2020; Tanriover 2021
[d]Despite some concerns with deviations from intervention, not downgraded for risk of bias.
[e]Inconsistency: downgraded one level (I^2 = 92%).

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[f]Imprecision: downgraded one level due to wide CIs consistent with the possibility of benefit and the possibility of harm.
[g]Imprecision: downgraded two levels due to low number of events and wide CIs.
[h]Follow-up: 1.4 and 2 months (median)
[i]Imprecision: downgraded two levels due to wide CIs consistent with the possibility of benefit and the possibility of harm and few events.
[j]Follow-up: 7–28 days
[k]Bueno 2021; Fadlyana 2021; Palacios 2020; Tanriover 2021; Wu 2021a; Zhang 2021
[l]Despite some concerns with adequate randomisation, deviation from intended intervention, missing data, and selection of reported results not downgraded for risk of bias.
[m]Inconsistency: downgraded one level (I^2 = 55%).
[n]Imprecision: downgraded one level due to wide CIs consistent with the possibility of no effect and the possibility of harm.
[o]Follow-up: one to three months (median)
[p]Bueno 2021; Han 2021; Palacios 2020; Tanriover 2021; Wu 2021a; Zhang 2021
[q]Despite some concerns with adequate randomisation, not downgraded for risk of bias.
[r]Follow-up: 4.1 months, 2 months (median), 3 months (median)
[s]Han 2021; Palacios 2020; Tanriover 2021; Wu 2021a

Summary of findings 9. WIBP-CorV – Sinopharm-Wuhan compared to placebo for vaccination against COVID-19[a]

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants	Certainty of the evidence (GRADE)	Comments
	Risk with placebo	Risk with WIBP-CorV				
Confirmed SARS-CoV-2 infection[b]	912 per 100,000	**328 per 100,000** (231 to 467)	**VE 64.00** (48.80 to 74.70)	25,449 (1 RCT)[c]	⊕⊕⊕⊕ **High**[d]	—
Confirmed symptomatic COVID-19[b]	746 per 100,000	**203 per 100,000** (131 to 313)	**VE 72.80** (58.10 to 82.40)	25,480 (1 RCT)[c]	⊕⊕⊕⊕ **High**[d]	—
Severe or critical COVID-19	Outcome not yet measured or reported					
All-cause mortality	—	—	—	—	—	1 trial reported on this outcome in 26,917 participants (13,464 WIBP-CorV versus 13,453 placebo) (Al Kaabi 2021). There were no events in either group and no effect estimate could be calculated for this outcome.
Systemic reactogenicity events[e]	278 per 1000	**275 per 1000** (264 to 286)	**RR 0.99** (0.95 to 1.03)	27,029 (2 RCTs)[f]	⊕⊕⊕⊕ **High**[g]	—

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Any adverse event[h]	504 per 1000	**484 per 1000** (469 to 494)	**RR 0.96** (0.93 to 0.98)	27,029 (2 RCTs)[f]	⊕⊕⊕⊕ **High**	—
Serious adverse events[i]	579 per 100,000	**480 per 100,000** (347 to 665)	**RR 0.83** (0.60 to 1.15)	27,029 (2 RCTs)[f]	⊕⊕⊖⊖ **Low**[g,j]	—
Local reactogenicity events[k]	290 per 1000	**255 per 1000** (247 to 267)	**RR 0.88** (0.85 to 0.92)	27,029 (2 RCTs)[f]	⊕⊕⊕⊕ **High**[g]	—

*__The risk in the intervention group__ (and its 95% CI) is based on the assumed risk in the comparison group and the __relative effect__ of the intervention (and its 95% CI).

COVID-19: coronavirus disease 2019**CI:** confidence interval; **RCT:** randomized controlled trial; **RR:** risk ratio; **SARS-CoV-2:** severe acute respiratory syndrome coronavirus 2; **VE:** vaccine efficacy.

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate; the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited; the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate; the true effect is likely to be substantially different from the estimate of effect.

[a]Last updated: 4 May 2022
[b]Follow-up: from 2 weeks after the second dose up to 2.6 months (median)
[c]Al Kaabi 2021
[d]Despite some concerns with deviations from intervention, not downgraded for risk of bias.
[e]Follow-up: seven days and 28 days
[f]Al Kaabi 2021; Guo 2021
[g]Despite some concerns with adequate randomisation, not downgraded for risk of bias.
[h]Follow-up: one month
[i]Follow-up: 1.6 and 2.6 months (median)
[j]Imprecision: downgraded two levels due to wide CIs consistent with the possibility of no effect and the possibility of benefit and few events.
[k]Follow-up: seven days

Summary of findings 10. BBIBP-CorV – Sinopharm-Beijing compared to placebo for vaccination against COVID-19[a]

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with placebo	Risk with BBIBP-CorV				

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Confirmed SARS-CoV-2 infection[b]	912 per 100,000	**242 per 100,000** (162 to 359)	**VE 73.50** (60.60 to 82.20)	25,435 (1 RCT)[c]	⊕⊕⊕⊕ **High**[d]	—
Confirmed symptomatic COVID-19[b]	746 per 100,000	**163 per 100,000** (102 to 263)	**VE 78.10** (64.80 to 86.30)	25,463 (1 RCT)[c]	⊕⊕⊕⊕ **High**[d]	—
Severe or critical COVID-19	Outcome not yet measured or reported					
All-cause mortality	—	—	—	—	—	1 study reported this outcome in 26,924 participants (13,471 BBIBP-CorV versus 13,453 placebo) (Al Kaabi 2021). There were no events in either group and no effect estimate could be calculated for this outcome.
Systemic reactogenicity events[e]	274 per 1000	**288 per 1000** (236 to 351)	**RR 1.05** (0.86 to 1.28)	27,540 (3 RCTs)[f]	⊕⊕⊕⊖ **Moderate**[g]	—
Any adverse event[h]	3 studies (n = 27,540) reported any adverse event with 1 month or 2.9 months' follow-up. 2 of the studies reported an effect estimate in favour of BBIBP-CorV: 1 with RR 0.91, 95% CI 0.89 to 0.94; n = 26,924; and 1 with CIs crossing the line of no effect (RR 0.83, 95% CI 0.36 to 1.95; n = 112). 1 study reported an effect estimate in favour of placebo with CIs not crossing the line of null effect (RR 2.05, 95% CI 1.47 to 2.87; n = 504)		—	26,924 (3 RCTs)[f]	⊕⊕⊖⊖ **Low**[i,j]	—
Serious adverse events[k]	580 per 100,000	**441 per 100,000** (313 to 615)	**RR 0.76** (0.54 to 1.06)	26,924 (1 RCT)[c]	⊕⊕⊖⊖ **Low**[l]	1 additional study reported this outcome in 112 participants (84 BBIBP-CorV versus 28 placebo) (Xia 2020). There were no events in either group and the trial did not contribute to the effect estimate.

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Local reactogenicity events[e]	3 studies (n = 27,540) reported local adverse events with 7 days' follow-up. 1 study reported an effect estimate in favour of BBIBP-CorV: RR 0.71, 95% CI 0.68 to 0.74; n = 26,924. 2 studies reported an effect estimate in favour of placebo with CIs not crossing the line of null effect (RR 10.00, 95% CI 2.36 to 42.34; n = 504 and RR 3.33, 95% CI 0.45 to 24.89; n = 112).	—	26,924 (3 RCTs)[f]	⊕⊕⊖⊖ **Low**[i,j]	—

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the __relative effect__ of the intervention (and its 95% CI).

COVID-19: coronavirus disease 2019**CI:** confidence interval; **RCT:** randomized controlled trial; **RR:** risk ratio; **SARS-CoV-2:** severe acute respiratory syndrome coronavirus 2; **VE:** vaccine efficacy.

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate; the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited; the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate; the true effect is likely to be substantially different from the estimate of effect.

[a]Last updated: 4 May 2022
[b]Follow-up: from 2 weeks after second dose up to 2.6 months (median)
[c]Al Kaabi 2021
[d]Despite some concerns with deviations from intervention, not downgraded for risk of bias.
[e]Follow-up: seven days
[f]Al Kaabi 2021; Xia 2021 (children); Xia 2020
[g]Imprecision: downgraded one level due to wide CIs consistent with the possibility of no effect and the possibility of harm.
[h]Follow-up: one month and 2.9 months
[i]Inconsistency: downgraded one level as studies are not pooled, effect estimates and direction of effect inconsistent between included studies.
[j]Imprecision: downgraded one level due to wide CIs consistent with the possibility of benefit and the possibility of harm.
[k]Follow-up: 2.6 months (median)
[l]Imprecision: downgraded two levels due to wide CIs consistent with the possibility of no effect and the possibility of benefit and few events.

Summary of findings 11. BBV152 – Bharat Biotech compared to placebo for vaccination against COVID-19[a]

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with placebo	Risk with BBV152				
Confirmed SARS-CoV-2 infection[b]	1841 per 100,000	**575 per 100,000** (322 to 982)	**VE 68.80**	6289 (1 RCT)[c]	⊕⊕⊕⊕ **High**[d]	—

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			(46.70 to 82.50)			
Confirmed symptomatic COVID-19[b]	1247 per 100,000	**277 per 100,000** (170 to 434)	**VE 77.80** (65.20 to 86.40)	16,973 (1 RCT)[c]	⊕⊕⊕⊕ **High**[d]	—
Severe or critical COVID-19[b]	176 per 100,000	**12 per 100,000** (0 to 76)	**VE 93.40** (57.10 to 99.80	16,976 (1 RCT)[c]	⊕⊕⊕⊕ **High**[d]	—
All-cause mortality[e]	78 per 100,000	**39 per 100,000** (13 to 113)	**RR 0.50** (0.17 to 1.46)	25,753 (1 RCT)[c]	⊕⊕⊖⊖ **Low**[f]	—
Systemic reactogenicity events[g]	20 per 1000	**26 per 1000** (23 to 31)	**RR 1.34** (1.15 to 1.58)	25,925 (2 RCTs)[h]	⊕⊕⊕⊕ **High**[d]	—
Any adverse event[i]	124 per 1000	**124 per 1000** (117 to 133)	**RR 1.00** (0.94 to 1.07)	25,753 (1 RCT)[j]	⊕⊕⊕⊕ **High**	—
Serious adverse events[i]	463 per 100,000	**301 per 100,000** (199 to 449)	**RR 0.65** (0.43 to 0.97)	25,928 (1 RCT)[j]	⊕⊕⊕⊕ **High**[d]	1 additional trial reported this outcome in 175 participants (100 BBV152 versus 75 placebo) (Ella 2021a). There were no events in either group and the trial did not contribute to the pooled effect estimate.
Local reactogenicity events[g]	31 per 1000	**34 per 1000** (30 to 39)	**RR 1.08** (0.95 to 1.24)	25,750 (2 RCTs)[h]	⊕⊕⊕⊕ **High**[d]	—

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

COVID-19: coronavirus disease 2019**CI:** confidence interval; **RCT:** randomized controlled trial; **RR:** risk ratio; **SARS-CoV-2:** severe acute respiratory syndrome coronavirus 2; **VE:** vaccine efficacy.

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate; the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited; the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate; the true effect is likely to be substantially different from the estimate of effect.

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[a]Last updated: 4 May 2022
[b]Follow-up: from two weeks after second dose to 3.3 months (median)
[c]Ella 2021a
[d]Despite some concerns with deviations from intervention, not downgraded for risk of bias.
[e]Follow-up: 3.3 months (median)
[f]Imprecision: downgraded two levels due to wide CIs consistent with the possibility of benefit and the possibility of harm and low number of events.
[g]Follow-up: seven days
[h]Ella 2021a; Ella 2021b
[i]Follow-up: 4.9 months (median)
[j]Ella 2021b

Summary of findings 12. NVX-CoV2373 – Novavax compared to placebo for vaccination against COVID-19[a]

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with placebo	Risk with NVX-CoV2373				
Confirmed SARS-CoV-2 infection	Outcome not yet measured or reported					
Confirmed symptomatic COVID-19[b]	1140 per 100,000	**195 per 100,000** (67 to 564)	**VE 82.91** (50.49 to 94.10)	42,175 (3 RCTs)[c]	⊕⊕⊕⊖ **Moderate**[d,e]	Substantial heterogeneity (I^2 = 65%) between included studies: Dunkle 2021 (VE 90.40%, 95% CI 82.88 to 94.62%; n = 25,452); Heath 2021 (VE 89.70%, 95% CI 80.20% to 94.60%; n = 14,039); Shinde 2021 (VE 49.40%, 95% CI 6.10% to 72.80%; n = 2684)
Severe or critical COVID-19	172 per 100,000	**0 per 100,000** (0 to 22)	**VE 100.00** (86.99 to 100.00)	25,452 (1 RCT)[f]	⊕⊕⊕⊖ **Moderate**[d,g]	—
All-cause mortality[h]	51 per 100,000	**46 per 100,000** (15 to 136)	**RR 0.90** (0.30 to 2.68)	29,582 (1 RCT)[f]	⊕⊕⊖⊖ **Low**[d,i]	1 additional study reported on this outcome in 14,039 participants (7020 NVX-CoV2373 versus 7019 placebo) (Heath 2021). There were no events in either group and the trial did not contribute to the pooled effect estimate.
Systemic reactogenicity events[j]	363 per 1000	**439 per 1000** (425 to 454)	**RR 1.21** (1.17 to 1.25)	31,063 (3 RCTs)[k]	⊕⊕⊕⊕ **High**[l]	—

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Any adverse event[m]	173 per 1000	**199 per 1000** (182 to 218)	**RR 1.15** (1.05 to 1.26)	46,231 (5 RCTs)[n]	⊕⊕⊕⊖ **Moderate**[l,o]	Substantial heterogeneity (I^2 = 57%) between the 5 included studies.
Serious adverse events[m]	777 per 100,000	**715 per 100,000** (575 to 886)	**RR 0.92** (0.74 to 1.14)	38,802 (4 RCTs)[p]	⊕⊕⊖⊖ **Low**[i,q]	1 additional trial reported on this outcome in 52 participants (29 NVX-CoV2373 versus 23 placebo) (Keech 2020). There were no events in either group and the trial did not contribute to the pooled effect estimate.
Local reactogenicity events[j]	191 per 1000	**532 per 1000** (381 to 742)	**RR 2.78** (1.99 to 3.88)	31,063 (3 RCTs)[k]	⊕⊕⊕⊕ **High**[l,r]	—

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

COVID-19: coronavirus disease 2019**CI:** confidence interval; **RCT:** randomized controlled trial; **RR:** risk ratio; **SARS-CoV-2:** severe acute respiratory syndrome coronavirus 2; **VE:** vaccine efficacy.

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate; the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited; the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate; the true effect is likely to be substantially different from the estimate of effect.

[a]Last updated: 2 June 2022
[b]Follow-up: from seven days after second dose up to three months (median)
[c]Dunkle 2021; Heath 2021; Shinde 2021
[d]Despite some concerns with deviations from intervention, not downgraded for risk of bias.
[e]Inconsistency: downgraded one level (I^2 = 65%).
[f]Dunkle 2021
[g]Indirectness: downgraded one level as outcome in this trial included participants with moderate severity.
[h]Follow-up: two months (median)
[i]Imprecision: downgraded two levels due to wide CIs consistent with the possibility of benefit and the possibility of harm and few events.
[j]Follow-up: seven days
[k]Dunkle 2021; Frenck 2021; Shinde 2021
[l]Despite some concerns with adequate randomisation and missing data, not downgraded for risk of bias.
[m]Unsolicited adverse events, follow-up to three months (median)
[n]Dunkle 2021; Formica 2021; Heath 2021; Keech 2020; Shinde 2021
[o]Inconsistency: downgraded one level (I^2 = 57%).
[p]Dunkle 2021; Formica 2021; Heath 2021; Shinde 2021
[q]Despite some concerns with adequate randomisation, deviation from intended intervention and missing data, not downgraded for risk of bias.
[r]Despite I^2 = 86%, not downgraded for inconsistency, as the same direction of effect in both effect estimates.

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Summary of findings 13. FINLAY-FR-2 – Instituto Finlay de Vacunas compared to placebo for vaccination against COVID-19[a]

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with placebo	Risk with FINLAY-FR-2				
Confirmed SARS-CoV-2 infection	Outcome not yet measured or reported					
Confirmed symptomatic COVID-19[b]	1084 per 100,000	**314 per 100,000** (226 to 445)	**VE 71.00** (58.90 to 79.10)	28,674 (1 RCT)[c]	⊕⊕⊕⊖ **Moderate**[d]	—
Severe or critical COVID-19	Outcome not yet measured or reported					
All-cause mortality[e]	168 per 100,000	**62 per 100,000** (29 to 134)	**RR 0.37** (0.17 to 0.80)	28,674 (1 RCT)[c]	⊕⊕⊕⊖ **Moderate**[d]	—
Systemic reactogenicity events	Outcome not yet measured or reported					
Any adverse event	Outcome not yet measured or reported					
Serious adverse events	Outcome not yet measured or reported					
Local reactogenicity events	Outcome not yet measured or reported					

*__The risk in the intervention group__ (and its 95% CI) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

COVID-19: coronavirus disease 2019**CI:** confidence interval; **RCT:** randomized controlled trial; **RR:** risk ratio; **SARS-CoV-2:** severe acute respiratory syndrome coronavirus 2; **VE:** vaccine efficacy.

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate; the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited; the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate; the true effect is likely to be substantially different from the estimate of effect.

[a]Last updated: 6 May 2022
[b]Follow-up: from seven days after second dose up to three months (median)
[c]Toledo-Romani 2021
[d]Risk of bias downgraded one level: some concerns regarding adequate randomisation and deviation from intended intervention.

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[e]Follow-up: 1.7 months (median)

Summary of findings 14. Heterologous vaccination scheme compared to homologous vaccination scheme for vaccination against COVID-19[a]

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants	Certainty of the evidence (GRADE)	Comments
	Risk with homologous vaccination scheme	Risk with heterologous vaccination scheme				
Confirmed SARS-CoV-2 infection	Outcome not yet measured or reported					
Confirmed symptomatic COVID-19	Outcome not yet measured or reported					
Severe or critical COVID-19	Outcome not yet measured or reported					
All-cause mortality	Outcome not yet measured or reported					
Systemic reactogenicity events[b]	60 per 1000	**118 per 1000** (31 to 445)	**RR 1.96** (0.52 to 7.41)	101 (1 RCT)[c]	⊕⊕⊖⊖ **Low**[d,e]	—
Any adverse event[f]	3 studies (n = 564) that compared heterologous versus homologous vaccination schemes reported any adverse event with 1 or 2 months' follow-up. 2 of the studies reported an effect estimate in favour of homologous scheme but with CIs crossing the line of no effect (RR 1.21, 95% CI 0.87 to 1.68; n = 234; and RR 1.03, 95% CI 0.75 to 1.43; n = 229). 1 study reported an effect estimate in favour of homologous scheme with CIs not crossing the line of null effect (RR 3.19, 95% CI 1.11 to 9.11; n = 101)		—	(3 RCTs)[g]	⊕⊖⊖⊖ **Very low**[h,i,j]	—
Serious adverse events[k]	1 study (Liu 2021: ChAdOx1/BNT162b2 versus ChAdOx1/ChAdOx1) that compared heterologous versus homologous vaccination schemes reported no serious adverse events in the heterologous scheme (0/114) versus 1 serious adverse event (1/115) in the homologous scheme (RR 0.34, 95% CI 0.01 to 8.17). 2 more studies reported the outcome, with 0 events in both groups: Li 2021a: CoronaVac/Ad5 versus CoronaVac/CoronaVac in n = 51 versus n = 50 and Liu 2021: BNT162b2/ChAdOx1 versus BNT162b2/BNT162b2 in n = 115 versus n = 119 respectively, in heterologous versus homologous scheme		—	229 (1 RCT)[l]	⊕⊖⊖⊖ **Very low**[h,m]	—

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Local reactogenicity events[b]	20 per 1000	**235 per 1000** (32 to 1000)	**RR 11.76** (1.59 to 87.14)	101 (1 RCT)[c]	⊕⊕⊖⊖ **Low**[d,n]	—

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

COVID-19: coronavirus disease 2019**CI:** confidence interval; **RCT:** randomized controlled trial; **RR:** risk ratio; **SARS-CoV-2:** severe acute respiratory syndrome coronavirus 2.

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate; the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited; the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate; the true effect is likely to be substantially different from the estimate of effect.

[a]Last updated: 4 May 2022
[b]Follow-up: 28 days
[c]Li 2021a: CoronaVac/Ad5 versus CoronaVac/CoronaVac
[d]Despite some concerns with deviation from intended intervention, not downgraded for risk of bias.
[e]Imprecision: downgraded two levels due to wide CIs consistent with the possibility of benefit for heterologous and benefit for homologous vaccination scheme and the low number of events/participants.
[f]Follow-up: one and two months
[g]Li 2021a: CoronaVac/Ad5 versus CoronaVac/CoronaVac; Liu 2021: BNT162b2/ChAdOx1 versus BNT162b2/BNT162b2; Liu 2021: ChAdOx1/BNT162b2 versus ChAdOx1/ChAdOx1
[h]Risk of bias downgraded one level: some concerns regarding outcome measurement.
[i]Inconsistency: downgraded one level as studies are not pooled, effect estimates and direction of effect inconsistent between included studies.
[j]Imprecision: downgraded one level due to wide CIs consistent with the possibility of no effect and benefit for homologous vaccination scheme and the low number of events/participants.
[k]Follow-up: one month
[l]Liu 2021: ChAdOx1/BNT162b2 versus ChAdOx1/ChAdOx1
[m]Imprecision: downgraded two levels due to wide CIs consistent with the possibility of benefit for the heterologous and benefit for homologous vaccination scheme and the low number of events/participants.
[n]Imprecision: downgraded two levels due to very few events or participants (or both).

Summary of findings 15. Booster compared to placebo/no booster for vaccination against COVID-19[a]

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants	Certainty of the evidence	Comments
	Risk with placebo/no booster	Risk with booster				
Confirmed SARS-CoV-2 infection	Outcome not yet measured or reported					

Efficacy and safety of COVID-19 vaccines (Review)
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Confirmed symptomatic COVID-19	Outcome not yet measured or reported					
Severe or critical COVID-19	Outcome not yet measured or reported					
All-cause mortality[b]	63 per 100,000	**80 per 100,000** (33 to 191)	**RR 1.27** (0.52 to 3.05)	28,254 (1 RCT)[c]	⊕⊖⊖⊖ **Very low**[d,e]	—
Systemic reactogenicity events[f]	102 per 1000	**183 per 1000** (72 to 464)	**RR 1.80** (0.71 to 4.56)	119 (1 RCT)[g]	⊕⊕⊖⊖ **Low**[d]	—
Any adverse event	Outcome not yet measured or reported					
Serious adverse events	Outcome not yet measured or reported					
Local reactogenicity events[f]	119 per 1000	**766 per 1000** (377 to 1000)	**RR 6.46** (3.18 to 13.13)	119 (1 RCT)[g]	⊕⊕⊕⊖ **Moderate**[h]	—

*__The risk in the intervention group__ (and its 95% CI) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

COVID-19: coronavirus disease 2019**CI:** confidence interval; **RCT:** randomized controlled trial; **RR:** risk ratio; **SARS-CoV-2:** severe acute respiratory syndrome coronavirus 2.

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate; the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited; the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate; the true effect is likely to be substantially different from the estimate of effect.

[a]Last updated: 4 May 2022
[b]Follow-up: 1.7 months (median)
[c]Toledo-Romani 2021: FINLAY-FR-2/booster FR-1 versus FINLAY-FR-2
[d]Imprecision: downgraded two levels due to wide CIs consistent with the possibility of benefit and the possibility of harm and few events.
[e]Risk of bias downgraded one level: some concerns regarding adequate randomization and deviation from intended intervention.
[f]Follow-up: seven days
[g]Hall 2021: mRNA-1273 booster versus placebo (solid organ transplant recipients).
[h]Imprecision: downgraded one level due to low number of participants.

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BACKGROUND

Description of the condition

In December 2019, a novel coronavirus, severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) outbreak began in Wuhan, Hubei Province, China. SARS-CoV-2 began to spread worldwide, and on 11 March 2020, the World Health Organization (WHO) declared coronavirus disease 2019 (COVID-19) a pandemic (WHO 2020a).

In many countries, the number of cases increased exponentially during the first and subsequent waves (Worldometer 2022). The clinical spectrum of COVID-19 ranges from mild to critical, and approximately 15% to 30% of patients infected with the wild-type variant of SARS-CoV-2 experienced acute respiratory distress syndrome (Attaway 2021). Persons with underlying conditions and weakened immune systems were at higher risk of becoming severely sick (Formica 2021).

Further, genetic variants of SARS-CoV-2 have been emerging and circulating at a global level: B.1.1.7 (Alpha), B.1.351 (Beta), P.1 (Gamma), and B.1.617.2 (Delta) variants, and more recently B.1.1.529 (Omicron) (WHO 2022a). Consequently, the WHO has developed a definition of variants of concern for molecular surveillance (WHO 2022a).

Intensive research and development of vaccines is currently underway to curtail the pandemic and prevent disease outbreaks that could overwhelm health systems worldwide (van Riel 2020; WHO 2022b).

Description of the intervention

Vaccines exploit the ability of the immune system to respond to and remember encounters with pathogenic antigens. COVID-19 vaccine development, aimed at conferring protection against infection, or symptomatic disease, or both, has been accelerated due to priority funding over other diseases.

Different vaccine platform technologies (i.e. technologies that have in common the use of a 'backbone' carrier or vector) are being, and have been tested: live attenuated virus vaccines or inactivated virus vaccines (either inactivated whole or altered pathogens); protein-based vaccines (protein subunits or virus-like particles); viral vector vaccines (non-replicating viral vector, replicating viral vector); and nucleic acid-based vaccines (DNA- and RNA-based vaccines)(Abbasi 2020).

Vaccines may be categorized as either live or non-live (CDC 2021), distinguishing those vaccines that contain an attenuated (live) form of the pathogen from those that harbour the killed (inactivated, non-live) version of the pathogen. Non-live vaccines predominantly induce humoral immunity, whereas live vaccines create a robust cellular and humoral response. The present review includes 12 vaccines within four different non-live vaccine platform technologies.

- Inactivated virus vaccines
  - CoronaVac
  - WIBP-CorV
  - BBIBP-CorV
  - BBV152
- Protein subunit vaccines
  - NVX-CoV2373
  - FINLAY-FR-2
- Viral vector (non-replicating) vaccines
  - ChAdOx1
  - Ad26.COV2.S
  - Gam-COVID-Vac
- Nucleic acid-based (RNA) vaccines
  - BNT162b2
  - mRNA-1273
  - CVnCoV

How the intervention might work

Vaccines aim to generate an immune response that prevents SARS-CoV-2 infection or reduces the risk of severe disease or death.

Live attenuated virus vaccines

Live attenuated virus vaccines use a weakened form of the virus and are developed so that in an immunocompetent host, they replicate sufficiently to generate a robust immune response (Pollard 2021). Live attenuated vaccines may potentially replicate in an uncontrolled manner in immunosuppressed individuals, thus rendering them less suitable for use within this population (Rubin 2013).

Inactivated virus vaccines

In contrast, inactivated vaccines contain either inactivated whole or altered pathogens, thus precluding their replication; however, inactivated vaccines do not always induce as strong or long-lasting an immune response as live attenuated vaccines.

Inactivated virus technologies present multiple viral proteins for immune recognition. They have a stable expression of conformation-dependent antigenic epitopes (Roper 2009). Pitfalls include their potential to alter viral epitopes, which may adversely affect immunogenicity if the native structure of the viral antigen is not maintained (DeZure 2016). As a result, the administration of multiple doses, booster injections, or adjuvant addition is often needed to elicit protective humoral immune responses(Pollard 2021).

Protein subunit vaccines are composed of fragments of the virus. Akin to inactivated whole-cell vaccines, protein subunit vaccines do not harbour live components of the pathogen. They are distinguished from inactivated whole-cell vaccines by containing only the necessary antigenic parts of the pathogen for mounting a protective immune response. As the subunit vaccine only relies on the antigen of interest made using recombinant technology, it is considered a more reliable and safer technique than inactivated vaccines(Dong 2020). Nevertheless, this advantage may be offset by its inability to display the virus's full antigenic complexity. This may cause an unbalanced immune response and lower its protective effect (Enjuanes 2016). Consequently, adjuvants may be required to boost immune responses and increase immunogenicity.

Several other platforms have developed over the past few decades. These include virus-like particles, viral vectors, nucleic acid-based RNA and DNA vaccines (Pollard 2021), all of which have been employed in COVID-19 vaccine development.

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Virus-like particle (VLP) vaccines contain virus-like particles which closely resemble viruses, but are non-infectious as they contain no viral genetic material (Oxford Vaccine Group 2020). This platform has been used against hepatitis B and human papillomavirus (HPV), and constitutes another protein-based vaccine composed of proteins from the viral capsid (Fuenmayor 2017). VLP vaccines consist of self-assembled viral structural proteins that mimic the conformation of native SARS-CoV virions (Mortola 2004), making them immunogenic and inducing highly neutralizing-antibody titres. In light of their non-replicating and non-infectious constructs, VLPs may have an enhanced safety profile.

Unlike previous vaccines, viral vectors and nucleic acid-based RNA and DNA vaccines do not contain antigens, but rather nucleic acid sequences (RNA or DNA) that code for the proteins of interest inside the organism (Pollard 2021).

Viral vector vaccines

They differ from most conventional vaccines because they do not contain antigens (Gavi 2020). They are generally constructed from a carrier virus, such as an adeno- or pox-virus, and are engineered to carry the key target for COVID-19 vaccines (Dong 2020). Whilst vector vaccines confer the key advantage of including the innate immune responses required for eliciting adaptive immune responses, a potential disadvantage is that the host may already possess immunity against the vector due to prior exposure, thus reducing its effect (Pollard 2021). However, this disadvantage does not exist for all vectors. If the anti-vector response is likely to interfere with the efficacy induced by adenovirus vectors widely used for SARS-CoV-2 vaccines, this is not the case with Pox virus vectors (Dong 2020).

Nucleic acid-based vaccine – mRNA vaccine

Whilst mRNA vaccines are considered a new type of vaccine (CDC 2021), this platform has garnered interest among researchers for decades. The mechanism of action of mRNA vaccines is to instruct cells how to make a protein that may trigger an immune response (CDC 2021). mRNA translation occurs in the host cell's cytosol, circumventing the risk of integration into the host genome (CDC 2021). Like viral vectors, mRNA vaccines induce dendritic cell sensing – mRNA can stimulate TLR7, thus avoiding the use of adjuvants. Like viral vectors, attenuated vaccines and DNA vaccines, these vaccines can induce a CD8 T cell response. Finally, RNAs rapidly destroy mRNAs in the extracellular medium; these vaccines must be encapsulated.

Nucleic acid-based vaccine – DNA vaccine

DNA vaccine candidates function by injecting a plasmid containing the DNA sequence encoding a SARS-CoV-2 antigen which will stimulate the immune response. Due to the biocompatibility of plasmid DNA, their cost-efficient production and long shelf life, DNA vaccine-based immunotherapeutic strategies have been developed for treatment of infections (Hobernik 2018). However, their disadvantage is that the DNA molecules must cross the nuclear membrane to be transcribed, and they generally have low immunogenicity (Dong 2020).

These vaccines are used systemically (usually intramuscular injection), but mucosal SARS-CoV-2 vaccines are under development. This type of vaccine is predicted to have a better efficacy against infection. Apart from COVID-19, only one vaccine used via the nasal route has been approved to date: an attenuated vaccine against the influenza virus.

Why it is important to do this review

Given the importance to global health and the increasing number of vaccine candidates now being tested in phase 2 and phase 3 trials, there is a need to produce and maintain a living synthesis of the efficacy and safety of COVID-19 vaccines.

This review is part of a larger project: the COVID-NMA initiative (Boutron 2020a). The COVID-NMA initiative provides decision-makers with a complete, high-quality, and up-to-date mapping and synthesis of evidence on interventions for preventing and treating COVID-19. We developed a master protocol on the effect of all interventions for preventing and treating COVID-19 (Boutron 2020b), followed by specific protocols for more specific questions. Our results are made available and updated bi-weekly on the COVID-NMA platform at covid-nma.com.

We followed the PRISMA guidelines (Page 2021). The protocol is available at doi.org/10.5281/zenodo.6458272 and registered on PROSPERO (www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42021271897). It was peer-reviewed and processed by Cochrane's Central Editorial Service.

This review will be updated as soon as new evidence changes the conclusions or certainty of the evidence of the review, or at least twice a year if no substantial changes occur.

OBJECTIVES

To assess the efficacy and safety of COVID-19 vaccines (as a full primary vaccination series or as a booster dose) against SARS-CoV-2.

METHODS

Criteria for considering studies for this review

Types of studies

We included parallel individually or cluster-randomized controlled trials (RCTs) evaluating COVID-19 vaccines in humans with no restrictions on language. Single-arm studies, non-randomized studies, and modelling studies of interventions for COVID-19 were not eligible to be included in the review.

Types of participants

We included individuals with no restriction on age and comorbidities, irrespective of their serological status at baseline.

Types of interventions

Eligible interventions included any COVID-19 vaccines, particularly:

- live attenuated virus vaccine;
- inactivated virus vaccine;
- protein subunit vaccine;
- virus-like particle (VLP) vaccine;
- non-replicating viral vector (e.g. recombinant adenovirus) vaccine;
- replicating viral vector vaccine;
- RNA-based vaccine.

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- DNA-based vaccine;
- Other vaccine types for COVID-19, if any.

In the analysis, we included only results for vaccine candidates with a selected dose evaluated in phases 2-3 or phase 3 trials and their corresponding early phases.

Comparators included placebo (placebo could consist of saline placebo, injecting only the vaccine adjuvant or injecting a vaccine protecting against other diseases, such as meningococcal conjugate vaccine), no vaccine, or another COVID-19 vaccine.

Types of outcome measures

Our outcomes were identified with content experts, considering the outcomes most frequently evaluated in the registered RCTs, and after consulting the main outcomes recommended by the US Food and Drug Administration (FDA) guidance for developing a vaccine (FDA 2020a).

Efficacy outcomes

- Incidence of confirmed SARS-CoV-2 infection after complete vaccination (all doses of the primary vaccination schedule)*
- Incidence of confirmed symptomatic COVID-19 after complete vaccination
- Severe or critical COVID-19 after complete vaccination, as reported by authors (a table summarising the definitions used in each study can be found in Appendix 1)
- All-cause mortality

**confirmed by reverse transcription polymerase chain reaction (RT-PCR), nucleic acid amplification testing (NAAT), or any other validated test.*

Safety outcomes

- Incidence of systemic reactogenicity events (i.e. the immediate short-term reactions of a system to vaccines mainly due to immunological responses, such as fever) reported at day 14 after first dose.

When the number of participants with at least one systemic reactogenicity event is not reported, we used proxy measures as follows.

- For adults: the number of participants with malaise as first choice, headache as second choice, and fever 37.5 °C or greater as third choice;
- For children: irritability as first choice, decreased activity/weakness as second choice, and fever 37.5 °C or greater as third choice.
- Incidence of any adverse event (including non-serious adverse events). We considered any adverse event reported by authors, prioritizing 'solicited' adverse events. However, when these were not available, we collected 'unsolicited' adverse events.
- Incidence of any serious adverse events (SAEs) as reported by authors (a table reporting the definitions used in each study can be found in Appendix 1).

Immunogenicity outcomes

- Geometric mean titre (GMT) of a specific antibody against SARS-CoV-2 (two weeks after the first dose or nearest follow-up, as mentioned in the manuscript)
- GMT of a neutralizing antibody against SARS-CoV-2 (two weeks after second dose or nearest follow-up, as mentioned in the manuscript)
- Cellular immune responses (i.e. interferon gamma (IFN-γ) enzyme-linked immunospot (ELISpot)) (any time point reported by authors)

Specific safety outcomes

- Incidence of local reactogenicity events (i.e. the immediate local short-term reactions of a system to vaccines mainly due to immunological responses, such as pain and swelling) reported at day seven after first dose.

When the number of participants with at least one local adverse event is not reported, we used as a proxy measure pain as the first choice, local swelling/induration as the second choice, and erythema (redness) as the third choice.

- Incidence of specific safety outcomes
- Cardioembolic events (i.e. pulmonary embolism, stroke, venous thrombosis, cavernous sinus thrombosis, pericarditis, myocardial infarction)
- Haematological events (i.e. thrombocytopenia, haemorrhage, neutropenia, anaemia, lymphadenopathy)
- Neurological events (i.e. nervous system diseases)
- Vaccine-enhanced disease

Note: as the start of follow-up (T0) varies (e.g. follow-up starts "14 days after the last dose" or "21 days after the first dose"), we systematically recorded the T0 considered in the study report. For safety outcomes, we considered T0 = time the first dose is injected when the comparison is vaccine versus placebo/no vaccine; T0 = time after the second dose when the comparison focuses on heterologous vaccination; and T0 = time after the booster or placebo when the comparison assessed the booster dose. We systematically recorded the follow-up duration for the outcomes considered. When the same outcome was recorded at several time points, we recorded the latest.

For specific antibodies against SARS-CoV-2, we considered T0 = 2 weeks after the first dose where available, or the nearest time point.

For neutralizing antibodies against SARS-CoV-2, we considered T0 = 2 weeks after the second dose where available, or the nearest time point.

Search methods for identification of studies

We used the search strategies defined in the protocol of the larger COVID-NMA initiative (covid-nma.com) (Boutron 2020b), and outlined in Appendix 2 to identify randomized trials evaluating vaccines for COVID-19. The search methods and strategies to identify records for this review are being revised approximately yearly, to ensure that they reflect any terminology changes in the topic area, or in the databases.

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Electronic searches

The Epistemonikos L·OVE COVID-19 platform was searched regularly from 4 September 2020 until 5 November 2021 (Epistemonikos) (app.iloveevidence.com/covid19). This platform is a digital repository built by systematic searches in multiple databases, trial registries and preprint servers. Complete data sources and search methods are available at: app.iloveevidence.com/covid19/methods.

The Cochrane COVID-19 Study Register has been searched on a regular basis (covid-19.cochrane.org/; last searched 5 November 2021). The Cochrane COVID-19 Study Register is a specialized register built within the Cochrane Register of Studies (CRS) and is maintained by Cochrane Information Specialists. The register contains study reports from several sources, including:

- daily searches of PubMed;
- daily searches of ClinicalTrials.gov;
- weekly searches of Embase.com;
- weekly searches of the WHO International Clinical Trials Registry Platform (ICTRP);
- weekly searches of medRxiv;
- monthly searches of the Cochrane Central Register of Controlled Trials (CENTRAL).

Complete data sources and search methods for the register are available at: community.cochrane.org/about-covid-19-study-register.

We also searched the Retraction Watch Database for retracted studies (retractionwatch.com/retracted-coronavirus-covid-19-papers/; last searched 5 November 2021).

We also systematically searched for updates or publications of preprints using a preprint tracker, developed in collaboration with a research team from the French National Centre for Scientific Research (CNRS) (Cabanac 2021).

Searching other resources

We searched the following trial registries for unpublished and ongoing studies.

- World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP) (trialsearch.who.int/), to identify ongoing and completed clinical trials on COVID-19 (last searched 3 November 2021). We used the *List by Health Topic*: 2019-nCoV / COVID-19 filter to retrieve all studies identified.
- European Medicines Agency (EMA) clinical data website (clinicaldata.ema.europa.eu/web/cdp/home) to identify trials submitted to the EMA and also for the clinical study report (CSR) of eligible studies (last searched 5 November 2021).
- FDA website (www.fda.gov) to identify FDA approval trials (last searched 5 November 2021).

Data collection and analysis

We search, screen and extract data weekly. The analysis is updated online every 2 weeks (covid-nma.com). The next update will be conducted soon after the publication of this review.

Selection of studies

We searched and screened the citations retrieved and used a spreadsheet to document search dates and citations identified. We identified duplicates in Rayyan (Ouzzani 2016), and then in a spreadsheet to enhance sensitivity. Two review authors (CR, HB) independently screened records and abstracts; a third review author (RA) resolved any disagreements.

We did not check the references of included reports as the living search process identifies COVID-19 trial records prospectively from the point of trial registration.

Whenever both preprints and subsequent peer-reviewed publications were available, we favoured the latter as they are the latest documents of trial findings (Boutron 2020b).

We retrieved CSRs for four vaccines (BNT162b2 – BioNtech/Fosun Pharma/Pfizer; mRNA-123 – ModernaTX; ChAdOx1 – Astra Zeneca +University of Oxford; and AD26.COV2.S – Janssen Pharmaceutical Companies) from the EMA website (www.ema.europa.eu/en). For three vaccines (BNT162b2, mRNA-123 – ModernaTX and Ad26.COV2.S), we found minor discrepancies when compared to the data reported in the peer-reviewed publication. Discrepancies were due to different cut-off dates and follow-up lengths. We were unable to compare data between the CSR and the peer-reviewed publication for one vaccine (ChAdOx1) since the publication reports pooled results for four trials (COV001, COV002, COV003, and COV005) and the CSR contains data for only two of them (COV002 and COV003).

Data extraction and management

All data were extracted in duplicate. Two review authors (HB, BB) independently read each preprint, publication, protocol, or other study reports, evaluated the completeness of the data, and assessed the risk of bias. Based on a pilot data extraction form, we designed, evaluated and modified a specific structured data extraction form whenever needed to ensure consistency in the extraction of information. The form was implemented on the COVID-NMA platform on the extraction module explicitly developed for this purpose (covid-nma.com). All discrepancies automatically identified by the platform data extraction module were discussed by the two review authors to reach a consensus.

Information extracted included study characteristics (such as first author, publication year and journal), number of participants randomized, patient characteristics (age, sex, pre-existing neutralizing or specific antibodies or participants seropositive, comorbidities), intervention details (type of vaccines, dosing, schedule and route of administration), outcome measures, and risk of bias assessment.

For dichotomous outcomes, we extracted the number of events and number of total participants in each study arm.

For *efficacy outcomes*, we extracted vaccine efficacy as reported by the authors and 95% confidence interval (CI) for each outcome, when available. Vaccine efficacy measures the percentage reduction in incidence of cases among vaccinated persons compared to unvaccinated persons. It is usually calculated as the incidence rate among unvaccinated – incidence rate among vaccinated / the incidence rate among unvaccinated.

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For *immunogenicity outcomes*, we recorded GMTs and 95% CIs for specific and neutralizing antibodies in the control and intervention. We extracted results related to cellular response as reported by authors.

For *safety outcomes,* we extracted the data as analyzed by the authors.

We extracted the data as analyzed by the trial authors.

To explore vaccine efficacy on variants of concern, such as Alpha (B.1.1.7), Beta (B.1.351), Gamma (P.1), Delta (B.1.617.2), and Omicron (B.1.1.529), we also took into account that:

- vaccine efficacy on variants of concern is determined by sequencing all available cases where available;
- study authors extrapolated vaccine efficacy on variants of concern
  - considering the prevalent variant during the study period
  - from other sources: the information was extrapolated from data on the prevalence of the variant in the population during the study period. This information was obtained from outbreak.info or other sources.

This was done only for critical outcomes of efficacy.

Assessment of risk of bias in included studies

We assessed each study with the Cochrane RoB 2 tool for randomized controlled trials (Sterne 2019). We assessed risk of bias for the critical outcomes of the review. We recorded judgements for each domain using the online data extraction tool we developed. Risk of bias was assessed independently, in duplicate with consensus by researchers with epidemiological training (currently 4 people) or Cochrane Response members (the number of people involved varies). All have been previously trained in clinical epidemiology and systematic reviews. All have participated in a training programme where they had to read the training material and perform data extraction and RoB assessments with a team of experienced researchers. The data quality was assessed by the Cochrane Bias Methods Group, who checked a random sample of 10% of the extracted reports.

The Cochrane RoB 2 tool is structured into five domains: 1) risk of bias arising from the randomisation process; 2) risk of bias due to deviations from intended interventions; 3) risk of bias due to missing outcome data; 4) risk of bias in the measurement of the outcome; and 5) risk of bias in the selection of the reported result. Within each domain, a series of 'signalling questions' elicit information relevant to the risk of bias assessment. The response options to the signalling questions are: "yes"; "probably yes"; "probably no"; "no"; and "no information." A risk of bias judgement for each domain is generated by an algorithm, based on answers to the signalling questions. Judgement can be 'low', 'some concerns' or 'high' risk of bias. Overall, risk of bias will be considered as "low risk of bias" if all domains are at 'low risk;' "some concerns" if at least one domain is of 'some concern' and no domains are 'high risk of bias;' and "high risk of bias" if there is at least one domain assessed as 'high risk,' or several domains with 'some concerns.' In the context of this review, we are interested in quantifying the effect of assignment to the interventions at baseline, regardless of whether the interventions are received as intended (i.e. the intention-to-treat effect).

For cluster-randomized trials, if any, we planned to rely on the extension of the RoB tool 2 for cluster-randomized trials. Particularly, we planned to add the domain 1b: risk of bias arising from the timing of identification or recruitment of participants in a cluster-randomized trial. There were no cluster-RCTs reported by the date of the last search.

While we relied on the signalling questions to assess each domain and justify our assessment, we did not record the answers of systematic reviewers or how consensus was obtained for the signalling questions; this was done only at the domain level.

The risk of bias assessment was considered part of an evaluation of the certainty of the evidence and sensitivity analysis.

Measures of treatment effect

For dichotomous outcomes, we used vaccine efficacy and risk ratio accompanied by the 95% CI as a measure of effect. For outcomes measured with GMTs, we calculated the geometric mean ratios (GMRs) by taking the anti-log of the mean difference of the log transformed data between arms.

To date, all trials reported vaccine efficacy. In the future if we identify trials reporting only rate ratio, we will calculate vaccine efficacy using the formula rate ratio = 1 − VE/100.

Unit of analysis issues

We analyzed separately different comparisons from multiple-arm trials for all pairwise meta-analyses.

Dealing with missing data

For missing outcome data, we extracted the number of participants who dropped out before the completion of the study, and how the study authors handled missing data. We assessed the appropriateness of any imputation methods used to account for early dropouts in our risk of bias assessments. We conducted sensitivity analysis to assess the potential impact of missing outcome data on the results.

Assessment of heterogeneity

We first generated descriptive statistics for study and population characteristics, and we examined the distribution of important clinical and methodological variables (such as age, immunocompromized status, location etc.). We have considered the variability in point estimates and the overlap in CIs in addition to the I^2 statistic to assess the level of statistical heterogeneity (Riley 2011).

Assessment of reporting biases

We assessed the selective non-reporting or under-reporting of results in the trials identified according to the framework proposed in Chapter 13 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2021).

Assessment of risk of bias due to missing results in the included studies

We checked whether the results of all our critical and important outcomes were reported as prespecified in the first version of the trial registry. When more than one version was available and the outcomes were modified, we checked the date of the modification

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using "history of changes." Of note, some platforms do not provide information about previous versions of the registers. In these cases, we could not know whether we were assessing the original. When registration was not prospective, we also checked the protocol or statistical analysis plan if available.

We used a matrix indicating the availability of study results as recommended in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2021; Kirkham 2018).

We evaluated whether results were unavailable because of the results' P value, magnitude, or direction. We considered the risk of bias due to missing results if an outcome specified in the registry was missing from the main report.

Due to the small number of trials, we could not assess the potential for reporting bias across studies graphically or statistically.

Data synthesis

We analyzed each type of vaccine separately. We combined trials with comparators as placebo or adjuvant or other control together under the same comparison at the specific vaccine level. We included all eligible RCTs in the primary analysis, whatever the risk of bias assessment. We included early-phase trials in the analysis only when the selected dose was clearly defined and efficacy outcomes (usually assessed in Phase 3 trials) were available.

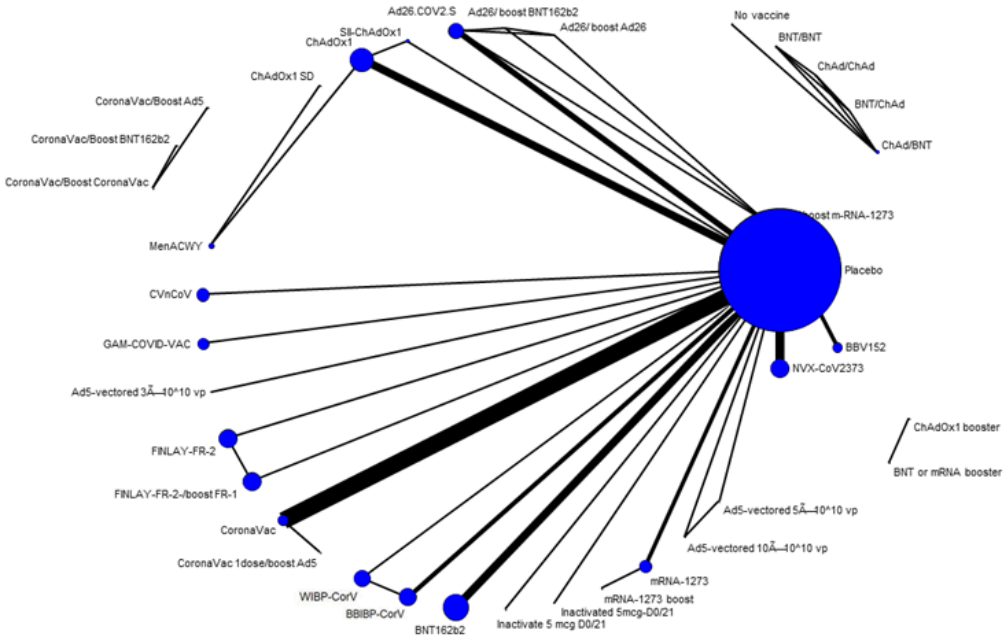
We performed a pairwise meta-analysis and presented summary effect estimates with 95% CIs for each direct comparison, with at least two studies providing data. We used the random-effects model to incorporate the anticipated clinical and methodological heterogeneity across studies. We presented trials reporting zero events in both arms in the forest plot but did not incorporate these in the analysis.

In the presence of excessive heterogeneity across studies (i.e. diverse forest plots or Tau^2 > 75% quartile of empirical distributions, or both) (Turner 2012), we did not synthesize the trial data quantitatively but qualitatively unless we could set up homogeneous subsets of the available trials.

All analyses were undertaken with the statistical software environment R (version 4.0.3) using the packages metafor and meta (Balduzzi 2019; Viechtbauer 2010).

We initially planned to conduct a network meta-analysis (NMA); however, the network of vaccines appeared very sparse, included mainly comparisons of vaccines against placebo, and only one or two studies informed most of the available comparisons (Figure 1). A network of such structure does not allow proper evaluation of the synthesis assumptions. Additionally, the NMA estimates from this network would not be substantially more precise (and could even be less precise for some comparisons) than the direct ones. We will reassess the feasibility of conducting an NMA regularly as part of the living systematic review process (details of the NMA methods considered for future update versions are available in Appendix 3).

Figure 1. Network graph. The size of the nodes is proportional to the number of participants randomized and the thickness of the lines to the number of studies in each comparison.



Subgroup analysis and investigation of heterogeneity

We had planned to perform subgroup analyses for critical outcomes only (Boutron 2020b). For future updates, we will pursue our prespecified subgroup analyses to explore whether the following population characteristics explain sources of heterogeneity.

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- Age:
  - children or adolescents (aged less than 18 years);
  - adults (aged 18 to 59 years);
  - older adults (aged greater than 60 years).
- Specific populations:
  - immunocompromized people;
  - pregnant women.

It should be noted that, as the evidence base on COVID-19/SARS-CoV-2 and its variants continues to evolve, we will reassess the feasibility of performing these subgroup analyses in future updates of the review when we could also evaluate the impact of the different SARS-CoV-2 variants in a meta-regression model.

For the current review, we assessed the level of heterogeneity by visual inspection of forest plots, the I^2 statistic, the between-study variance (Tau^2), and prediction intervals.

Sensitivity analysis

We performed sensitivity analyses for critical outcomes only. We performed sensitivity analyses by excluding RCTs reported in preprint only and early-phase trials (1 and 2). We also ran the analyses using the number of participants randomized instead of those analyzed for safety outcomes to assess the potential impact of missing outcome data on the results. For efficacy outcomes, it was not possible to calculate the effect estimate (vaccine efficacy) using the number of participants randomized. We did not perform the planned sensitivity analysis that excluded RCTs with an overall high risk of bias since no RCTs were considered at high risk of bias.

Summary of findings and assessment of the certainty of the evidence

To evaluate the certainty of the evidence in the results of the pairwise comparisons for all outcomes except immunogenetic outcomes, overall certainty of the evidence for each outcome was assessed by one review author (KP) and cross-checked by another review author (AJ) using the GRADE approach (Schünemann 2021). We used the five GRADE considerations (risk of bias, consistency of effect, imprecision, indirectness, and publication bias) to assess the certainty of the body of evidence. The assessment of imprecision was based on a non-contextualized approach i.e. rating the certainty that there is any effect (Hultcrantz 2017; Zeng 2021a), with the null effect as the threshold for the critical outcomes of mortality and SAEs (Guyatt 2011). In the description of the results for each outcome, we use different thresholds for the size of the effects.

For outcomes reported as vaccine efficacy, we used a threshold of 30%, based on the WHO guidance document which indicated that the primary efficacy endpoint estimate for a placebo-controlled trial should be at least 50%, with a statistical success criterion that the lower bound of the confidence interval be more than 30% (WHO 2020b; WHO 2020c). For additional adverse event outcomes (i.e. any adverse event, systemic reactogenicity events, and local reactogenicity events), we considered the thresholds for an effect to be RRs of 0.75 and 1.25 for downgrading imprecision.

For all-cause mortality and SAEs, we considered the effect was "large" when the absolute difference was greater than 5%; there was a "slight" effect when the absolute difference was from 1% to 5%, and there was "little or no effect" when the absolute difference was less than 1%.

For vaccine efficacy outcomes, when the effect estimate was 70% or greater we considered the vaccine to have a "large effect" (WHO 2020b; WHO 2020c).

For any adverse event, systemic reactogenicity events, and local reactogenicity events, we considered the effect as a "large effect" when the absolute difference was greater than 25%; a "slight effect" when the absolute difference was from 10% to 25%, and "little or no effect" when the absolute difference was less than 10%.

We prepared summary of findings tables to present estimated relative and absolute risks for critical and important outcomes, except for immunogenicity outcomes. We calculated absolute effects with GRADEpro GDT using the pooled baseline risks from the control groups of the included studies. Absolute effects are presented per 1000 for the outcomes 'any adverse event,' 'systemic adverse events,' and 'local adverse events,' and in remaining outcomes with low baseline risk (control group event rates less than 1%) per 100,000. We did not report absolute effect for results with low or very low certainty. For outcomes where vaccine efficacy is presented as the effect measure in the summary of findings tables, we used the corresponding RR to calculate the absolute effect. The rationale for using a footnote for the length of follow-up was to add the specific time per individual study for each outcome.

RESULTS

Description of studies

The full description of included studies is available at zenodo.org/record/6963352#.YuvhdhzP3RY. Characteristics of excluded studies and unpublished registered studies are summarized in the Characteristics of excluded studies section and in Appendix 4, respectively.

Results of the search

The results of the searches are detailed in Figure 2. On 5 November 2021, after excluding duplicates, we screened 48,047 records: 701 were eligible for full-text screening; we included 111 reports of 76 studies evaluating vaccine candidates against SARS-CoV-2. Thirty early-phase randomized trials (36 reports) are pending due to uncertainty regarding concentration of the vaccine candidate to be selected for the phase 3 trial or lack of results on efficacy for the selected dose reported in a phase 3 trial (Appendix 5). In seven reports of trials already included in the analysis and in five other reports of trials not included in the analysis, we did not find any outcomes of interest or we were unable to extract the data (i.e. results reported only as figures or in graphs) (Appendix 6). Overall, we included 41 studies in the analyses. These studies assessed four different types of vaccine platforms: RNA-based vaccines (six studies), non-replicating viral vector vaccines (10 studies), inactivated virus vaccines (13 studies), and protein subunit vaccines (six studies). They also assessed heterologous vaccine schedules and the effect of booster doses (six studies). Of note, we did not identify any trials reporting the efficacy outcome of interest for the vaccine Ad5-vectored (non-replicant viral vector) (Zhu 2021a); however, its efficacy as part of a heterologous scheme is assessed in a trial included in the analysis (Li 2021a).

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Figure 2. PRISMA flow diagram of included randomized controlled trials (RCTs) (last search date 5 November 2021). COVID-NMA is a living systematic review of all trials assessing treatment and preventive interventions for COVID-19

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(Boutron 2020a). This review is a subreview of the COVID-NMA. FDA: Food and Drug Administration; ICTRP: World Health Organization (WHO) International Clinical Trials Registry Platform.

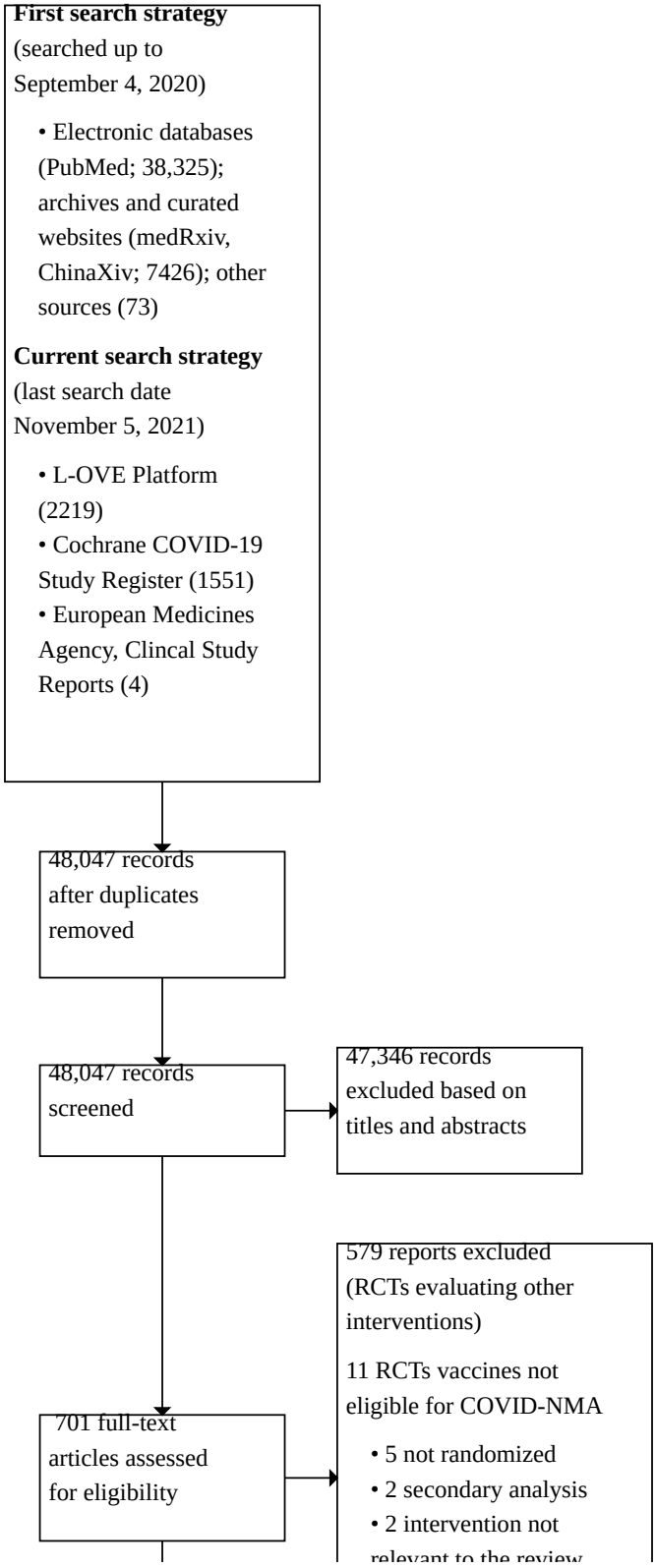

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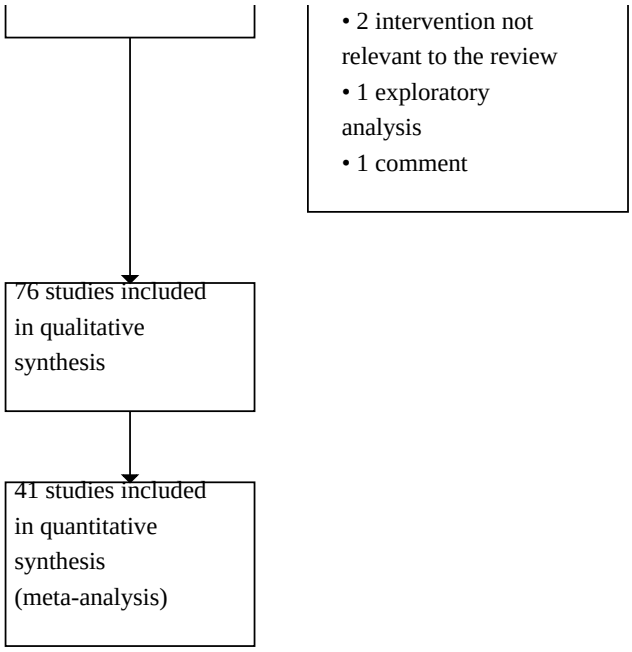
Figure 2. (Continued)



Included studies

Source of the data

We identified 41 trials overall. There were 37 primary analyses (Ali 2021; Al Kaabi 2021; Asano 2022; Bonelli 2021; Bueno 2021; Dunkle 2021; Ella 2021a; Ella 2021b; El Sahly 2021; Fadlyana 2021; Falsey 2021; Formica 2021; Frenck 2021; Guo 2021; Hall 2021; Han 2021; Heath 2021; Keech 2020; Kremsner 2021; Kulkarni 2021; Li 2021a; Liu 2021; Logunov 2021; Mok 2021; Palacios 2020; Sablerolles 2021; Sadoff 2021a; Sadoff 2021b; Shinde 2021; Tanriover 2021; Thomas 2021; Toledo-Romani 2021; Walsh 2020; Wu 2021a; Xia 2020; Xia 2021; Zhang 2021), and Voysey 2021a, which was a combined analysis of four trials ((COV001 (NCT04324606), COV002 (NCT04400838), COV003 (ISRCTN89951424), COV005 (NCT04444674)).

We also identified four articles reporting secondary analyses of the four trials included in Voysey 2021a. Emary 2021 reported results by variants for COV002 (NCT04400838); Clemens 2021 reported results by variants for COV003 (ISRCTN89951424); Madhi 2021b reported results by variants for COV005 (NCT04444674); and Madhi 2021a reported results for participants with HIV included in COV005 (NCT04444674).

The 41 included trials were reported in 63 reports (34 peer-reviewed publications, 22 reports of preprints, four clinical study reports, and three FDA briefings). Of the 34 peer-reviewed publications, 17 were published with earlier versions (Appendix 7). Data were initially extracted from these reports and then updated with subsequent publications. Only the latest versions of the reports are referenced. Most of the trials included were performed and results were retrieved before the detection of variants of concern. Overall, 10 trials reported results for a specific SARS-CoV-2 variant of concern; four trials presented results on the Alpha variant (B.1.1.7) (Dunkle 2021; Emary 2021; Heath 2021; Kremsner 2021), four on Beta variant (B.1.351) (Madhi 2021b; Sadoff 2021b; Shinde 2021; Thomas 2021), two on Gamma variant (P.1) (Clemens 2021; Kremsner 2021), and one on Delta (B.1.617.2) (Ella 2021b).

Study design

All trials used a parallel-group individually randomized design. Twenty-six of the RCTs included in the analysis had two arms (63.4%) and 15 (36.6%) were multiple-arm trials. There were 13 early-phase trials: three phase 1 (Ella 2021a; Keech 2020; Walsh 2020), seven phase 1-2 (Asano 2022; Guo 2021; Han 2021; Sadoff 2021a; Wu 2021a; Xia 2021; Zhang 2021), and three phase 2 (Formica 2021; Liu 2021; Xia 2020). In 40 trials (97.5%) the outcome assessor was blinded. All trials evaluating BNT162b2 (three), mRNA-1273 (two), CVnCoV RNA (one), Ad26.COV2.S (two), and NVX-CoV2373 (five) used placebo (normal saline) in the control arm. All trials assessing Gam-COVID-Vac (one), CoronaVac (six), WIBP-CorV (two), BBIBP-CorV (three), BBV152 (two), and FINLAY-FR-2 (one) used adjuvant in the control arm. In the case of ChAdOx1/SII-ChAdOx1, three trials used placebo (normal saline) in the control arm (Asano 2022; Falsey 2021; Madhi 2021b), three used a non-COVID-19 vaccine (MenACWY) (COV001, COV002 and COV003 included in Voysey 2021a), and one used adjuvant (Kulkarni 2021). Two trials assessing heterologous vaccine schedules used regular homologous vaccine schedules as control (Li 2021a; Liu 2021), and four trials compared the effect of different vaccine booster schedules (Bonelli 2021; Li 2021a; Mok 2021; Sablerolles 2021).

Recruitment was completed for 33 trials (80.4%), ongoing for seven trials that reported results of prespecified interim analyses (Frenck 2021; Sadoff 2021a; Sadoff 2021b; Voysey 2021a), and one trial was terminated due to an emergency use authorization for the

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vaccine candidate (Tanriover 2021). The mean sample size was 10,581 participants with median of 504 (interquartile range (IQR) 180 to 21,977; range: minimum 42 to maximum 44,325).

Study registration

All trial registration records were available; three trials were registered retrospectively (Asano 2022; Shinde 2021; Tanriover 2021).

Settings

Overall, 32 RCTs were multicentre and nine were single-centre trials (Bonelli 2021; Fadlyana 2021; Hall 2021; Han 2021; Li 2021a; Wu 2021a; Xia 2020; Xia 2021; Zhang 2021). The trials took place in Asia (14 trials, 34.1%), Europe (eight trials, 19.5%), North America (seven trials, 17.0%), worldwide (five trials, 12.1%), South America (four trials, 9.7%), Africa (two trials, 4.8%), and Oceania (one trial, 2.4%).

Characteristics of participants

There were 433,838 participants randomized; 250,200 (57.7%) were assigned to the intervention and 183,638 (42.3%) to the control arm. The number of participants analyzed varied by outcome, from 408 to 418,803 participants. The age range was between three and 100 years; 26 trials included participants 18 years of age or older, seven trials included adults between 18 and 65 years of age, two trials included participants 50 years or older (Liu 2021; Wu 2021a), two trials included participants 12 years old or older (Thomas 2021; Walsh 2020), two trials included only adolescents 12 to 17 years old (Ali 2021; Frenck 2021). Two trials included children and adolescents three to 17 years of age (Han 2021; Xia 2021). Overall, 54.0% of participants were male and the mean age ranged between 14 years (minimum) to 61 years (maximum).

Most trials (n = 35, 85.3%) enrolled healthy or clinically stable participants with no history of SARS-CoV-2 infection or COVID-19 diagnosis, four trials enrolled healthcare workers or individuals considered at substantial risk of exposure to and infection with SARS-CoV-2 (Bueno 2021; Dunkle 2021; Palacios 2020; Sablerolles 2021), and two trials included immunocompromized participants in trials assessing booster dose; transplant recipients (Hall 2021) and adults under current rituximab therapy (Bonelli 2021). Thirty-seven of 41 trials reported that pregnancy was an exclusion criterion. No trials reported data on vaccine efficacy and safety in pregnant women.

Details of the intervention

The included trials reported on four types of vaccine platforms and 12 vaccine candidates: three RNA-based vaccines (BNT162b2, mRNA-1273 and CVnCoV), three non-replicating viral vector vaccines (Ad26.COV2.S, ChAdOx1/SII-ChAdOx1 and Gam-COVID-Vac), four inactivated virus vaccines (CoronaVac, WIBP-CorV, BBIBP-CorV and BBV152), and two protein subunit vaccines (NVX-CoV2373 and FINLAY-FR-2). As SII-ChAdOx1, manufactured in India at Serum Institute of India, is the equivalent of ChAdOx1, we pooled the results for both vaccines in the analysis.

All COVID-19 vaccine candidates are to be administered through an intramuscular injection. Most of the vaccine candidates full vaccination schedules relied on two doses with a between-dose time interval varying from 14 to 28 days; however, four trials reported a time interval between doses of less than six weeks to 12 weeks or greater for ChAdOx1 (Voysey 2021a), and one trial one to three months for heterologous compared to a homologous scheme (CoronaVac/Ad5 versus CoronaVac/CoronaVac) (Li 2021a). One vaccine candidate had a two-dose schedule in adults and three-dose schedule in children and adolescents (BBIBP-CorV); one vaccine candidate necessitates a single dose (Ad26.COV2.S), and six studies evaluated the effect of a homologous compared to a heterologous booster dose; the time intervals between complete vaccination and boosters are 28 days (Toledo-Romani 2021), one month (Bonelli 2021), two months (Hall 2021), three months (Sablerolles 2021), four months (mean) (Mok 2021), and three to six months (Li 2021a). There were no studies on variant-adapted booster doses.

Outcome measurement

There was some heterogeneity in the way outcomes were assessed.

The definition of 'severe or critical disease' was most often based on the WHO clinical progression scale (Marshall 2020). 'Serious adverse events' were assessed using different grading scales such as ICH and EU Guidelines on Pharmacovigilance for Medicinal Products for Human Use (Sadoff 2021b), Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events (Kulkarni 2021), and toxicity grading scales adapted from Food and Drug Administration (FDA) grading guidance (Asano 2022). The list of definitions used for both outcomes is in Appendix 1.

Funding and conflict of interest

Trials received mixed (private and public) funding (20 trials, 48.78%), public/non-profit funding (14 trials, 34.14%), and private funding (seven trials, 17.07%). Overall, 37 trials declared competing interests and four trials declared no competing interests (Fadlyana 2021; Mok 2021; Sablerolles 2021; Tanriover 2021).

Excluded studies

We excluded 590 reports; 579 were RCTs evaluating other interventions and were consequently included in the COVID-NMA platform (covid-nma.com); 11 reports evaluated vaccines but were not eligible for the review (Baden 2021; Barrett 2021; Ewer 2021; Flaxman 2021; Hsieh 2021; Irfan 2021; Lazarus 2021; Patamatamkul 2021; Ward 2021a; Wu 2021b; Zdanowski 2021). Reasons for exclusion included: not randomized (five reports), secondary analysis (two reports), intervention not relevant to the review (two reports), exploratory analysis (one report), and comment (one report). See Characteristics of excluded studies table.

Ongoing studies

We identified 343 trials from registries; 10 were completed, two were terminated, 172 were not recruiting, 155 were ongoing and four were cancelled (Appendix 4).

RNA-based vaccine

We identified 73 unpublished trials; 34 were not recruiting (67,412 participants planned) and 39 were ongoing (192 participants planned).

Non-replicating viral vector

We identified 73 unpublished trials; there was one completed trial without results available (27 participants planned), 39 not recruiting (60,018 participants planned), 32 ongoing (157,387

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participants planned), and one cancelled (1210 participants planned).

Replicating viral vector

We identified 10 unpublished trials; one completed trial without results available (90 participants planned), four not recruiting (40,950 participants planned), three ongoing (6434 participants planned), and two terminated (495 participants planned).

Inactivated virus

We identified 61 unpublished trials; four completed trials without results available (19,512 participants planned), 25 not recruiting (146,312 participants planned), and 32 ongoing (122,182 participants planned).

Protein subunit

We identified 91 unpublished trials; two completed trials without results available (173 participants planned), 56 not recruiting (605,200 participants planned), 31 ongoing (260,273 participants planned), and two terminated (no participants).

Live attenuated virus

We identified two studies not recruiting (163 participants planned).

DNA-based vaccine

We identified 18 unpublished trials; two completed trials without results available (30 participants planned), nine not recruiting (16,238 participants planned), and seven ongoing (997 participants planned).

Virus-like particles

We identified 12 unpublished trials; two not recruiting (1818 participants planned), nine ongoing (2546 participants planned), and one terminated (997 participants planned).

Any SARS-CoV-2 vaccine

We identified three trials; two recruiting (2300 participants planned) and one not recruiting (1314 participants planned).

Risk of bias in included studies

For the overall risk of bias across trials, we judged 34 trials to have 'some concerns' for at least one outcome; eight trials were at low risk of bias for all outcomes (Asano 2022; Hall 2021; Han 2021; Kulkarni 2021; Sadoff 2021a; Walsh 2020; Xia 2020; Xia 2021). Further details of these assessments are available in the risk of bias assessment tables (Appendix 8).

Risk of bias arising from the randomisation process

We judged the risk of bias due to randomization to be appropriate and adequately done in 32 trials. In other trials, the allocation concealment was either unclear (Bueno 2021; Guo 2021; Zhang 2021), or not reported (Bonelli 2021; Formica 2021; Keech 2020; Mok 2021; Sablerolles 2021); we downgraded Toledo-Romani 2021 due to imbalances in baseline characteristics.

Risk of bias due to deviations from intended interventions

Thirty-four trials were blinded for participants, outcome assessors or healthcare providers, or both. Participants were blinded in six trials (Liu 2021; Sablerolles 2021; Voysey 2021a (which reported pooled results for four trials)), and blinding was unclear in one (Mok 2021). Nevertheless, no deviations from the intended intervention occurred due to awareness of the intervention received, and we did not downgrade the trials for this reason.

For efficacy outcomes, we judged the risk of bias due to deviation from intended interventions to be low in 13 trials and have 'some concerns' in 28 trials, mainly because analyses used to estimate the effect of assignment to intervention was inappropriate as most analyses were per protocol for efficacy outcomes. Participants were excluded for positive or unknown baseline SARS-CoV-2 status, not receiving a scheduled injection, not receiving the correct injection or major protocol deviation. We considered there would be no substantial impact of failure to analyse participants according to their randomized assignment due to the relatively small number of exclusions or a balanced number of exclusions between arms. In contrast, safety outcomes mainly were analyzed using intention-to-treat analysis. We considered this method appropriate to estimate the effect of assignment to intervention.

Risk of bias due to missing outcome data

We judged the risk of bias due to missing outcome data as low for all outcomes for 33 trials. There were no missing data or any missing outcome data were reasonably well-balanced across intervention groups, with similar reasons for missing data across the groups. Additionally, when missingness was related to deviations from the protocol, it was accounted for in the assessment of bias due to deviations from intended interventions and we did not downgrade the trial due to missing outcome data. For eight trials (Bonelli 2021; Bueno 2021; Ella 2021b; Frenck 2021; Hall 2021; Liu 2021; Sablerolles 2021; Shinde 2021), we judged the risk of bias as having 'some concerns' since trialists failed to report data for all or nearly all participants for at least one outcome, and missingness could depend on the true value of the outcome, for instance, unbalanced loss to follow-up due to adverse events or deceased participants not included in the analysis.

Risk of bias in the measurement of the outcome

We judged the risk of bias as low for all outcomes in 38 trials. We judged three trials as having 'some concerns' due to unclear or not blinded assessment of the safety outcomes whose evaluation can be influenced by knowledge of the intervention assignment (Bonelli 2021; Liu 2021; Mok 2021).

Risk of bias in the selection of the reported results

Thirty-three trials had prospective registrations or protocols (or both) available with no discrepancies between prespecified and reported outcomes; we judged these trials to be at low risk of bias. Six trials had risk of bias concerns due to reported outcomes that were not prespecified or had discrepancies in time points (Bonelli 2021; Ella 2021a; Fadlyana 2021; Formica 2021; Mok 2021; Wu 2021a).

Bias due to missing results in the synthesis

We present matrices indicating the availability of trial results for critical and important review outcomes in Appendix 9. There was evidence of bias due to missing results in four trials: El Sahly 2021, Dunkle 2021, Sadoff 2021b, and Shinde 2021 planned to assess 'GMTs of neutralizing and specific antibodies' but did not report on them. Toledo-Romani 2021 reported 'total adverse events', but only reported on 'local and systemic reactogenicity

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events', in addition to outcomes 'confirmed SARS-CoV-2 infection after complete vaccination' and 'GMTs of neutralizing and specific antibodies', which were not reported as well. Kulkarni 2021 did not report on the preplanned analysis for 'GMTs of neutralizing and specific antibodies' as well as 'systemic and local reactogenicity events' when compared to placebo. Tanriover 2021 planned to assess 'GMTs of neutralizing and specific antibodies' and 'confirmed SARS-CoV-2 infection after complete vaccination' but did not report on them. Zhang 2021 in phase 2 did not report on the results of 'serious adverse events'. Clemens 2021 did not report on the prespecified outcomes 'systemic and serious adverse events'. Liu 2021 did not report on the prespecified 'local and systemic reactogenicity events'. Hall 2021 and Kremsner 2021 did not report on the prespecified outcome 'confirmed SARS-CoV-2 infection after complete vaccination'. Finally, Voysey 2021a reporting on results of four trials did not report on results of 'local adverse events'. Ten registered trials are completed but not yet published (19,832 participants planned); the dates of completion range between 15 January 2021 and 13 October 2021. Publication delay since study completion ranged between 23 days and 295 days.

Overview of the risk of bias assessments by outcome

The outcome 'SARS-CoV-2 infection after complete vaccination' was reported in seven trials; in all trials we assessed the overall risk of bias to have 'some concerns'.

The outcome 'confirmed symptomatic COVID-19 after complete vaccination' was reported in 18 trials; in all trials we assessed the overall risk of bias to have 'some concerns'.

The outcome 'severe or critical COVID-19 after complete vaccination' was reported in 11 trials. In one of them, we assessed the overall risk of bias for this outcome to be 'low' (Thomas 2021). In 10 trials, we assessed the overall risk of bias for this outcome to have 'some concerns'.

The outcome 'all-cause mortality' was reported in 22 trials. In 17 trials, we assessed the overall risk of bias for this outcome to be 'low'. In five trials, we assessed the overall risk of bias for this outcome to have 'some concerns'.

The outcome 'serious adverse events' was reported in 32 trials. In 21 of them, we assessed the overall risk of bias for this outcome to be low. In 11 trials, we assessed the overall risk of bias for this outcome to have 'some concerns'.

The outcome 'any adverse event' was reported in 35 trials. In 24 of them, we assessed the overall risk of bias for this outcome to be 'low'. In 11 trials, we assessed the overall risk of bias for this outcome to have 'some concerns'.

The outcome 'systemic adverse events' was reported in 31 trials. In 15 of them, we assessed the overall risk of bias for this outcome to be 'low'. In 16 trials, we assessed the overall risk of bias for this outcome to have 'some concerns'.

Effects of interventions

See: **Summary of findings 1** BNT162b2 – Pfizer/BioNTech + Fosun Pharma compared to placebo for vaccination against COVID-19[a]; **Summary of findings 2** mRNA-1273 – ModernaTX compared to placebo for vaccination against COVID-19[a]; **Summary of findings 3** CVnCoV – CureVac AG compared to placebo for vaccination against COVID-19[a]; **Summary of findings 4** ChAdOx1 – AstraZeneca + University of Oxford compared to placebo for vaccination against COVID-19[a]; **Summary of findings 5** SII-ChAdOx1 – Serum Institute of India/AstraZeneca + University of Oxford compared to ChAdOx1 – University of Oxford for vaccination against COVID-19[a]; **Summary of findings 6** AD26.COV2.S – Janssen Pharmaceutical Companies compared to placebo for vaccination against COVID-19[a]; **Summary of findings 7** Gam-COVID-VAC – Sputnik V compared to placebo for vaccination against COVID-19[a]; **Summary of findings 8** CoronaVac – Sinovac compared to placebo for vaccination against COVID-19[a]; **Summary of findings 9** WIBP-CorV – Sinopharm-Wuhan compared to placebo for vaccination against COVID-19[a]; **Summary of findings 10** BBIBP-CorV – Sinopharm-Beijing compared to placebo for vaccination against COVID-19[a]; **Summary of findings 11** BBV152 – Bharat Biotech compared to placebo for vaccination against COVID-19[a]; **Summary of findings 12** NVX-CoV2373 – Novavax compared to placebo for vaccination against COVID-19[a]; **Summary of findings 13** FINLAY-FR-2 – Instituto Finlay de Vacunas compared to placebo for vaccination against COVID-19[a]; **Summary of findings 14** Heterologous vaccination scheme compared to homologous vaccination scheme for vaccination against COVID-19[a]; **Summary of findings 15** Booster compared to placebo/no booster for vaccination against COVID-19[a]

We report the network structure, irrespective of the outcomes in Figure 1 and the certainty of evidence for all critical outcomes in the summary of findings tables.

RNA-based vaccines

BNT162b2 – BioNtech/Fosun Pharma/Pfizer versus placebo (normal saline)

See Summary of findings 1 and table of results in Appendix 10.

We identified and included three trials in the analysis assessing BNT162b2. The outcomes 'confirmed SARS-CoV-2 infection after complete vaccination', 'systemic reactogenicity events', 'GMT of specific antibodies against SARS-CoV-2' and 'cellular immune response' were not reported for this comparison.

Critical outcomes

Confirmed symptomatic COVID-19 after complete vaccination

Two trials reported this outcome (Frenck 2021; Thomas 2021). BNT162b2 results in a large reduction in the incidence of symptomatic COVID-19 after complete vaccination compared to placebo measured at 1.8 months' and six months' follow-up (vaccine efficacy (VE) 97.84%, 95% confidence interval (CI) 44.25% to 99.92%; I^2 = 66%; 2 RCTs, 44,077 participants; high-certainty evidence; Figure 3).

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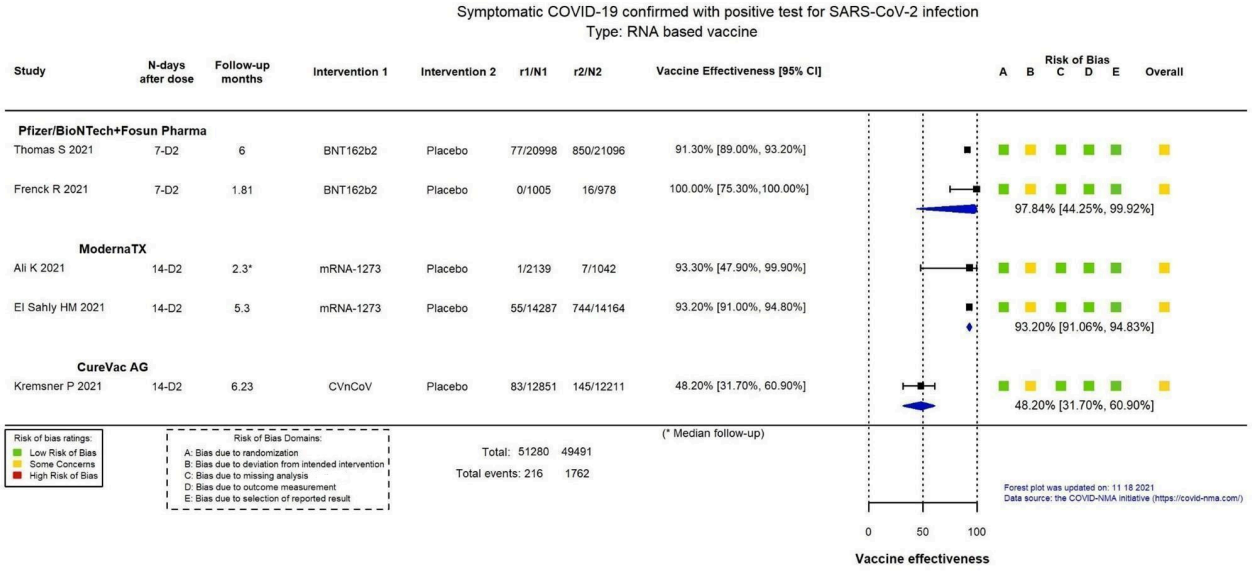
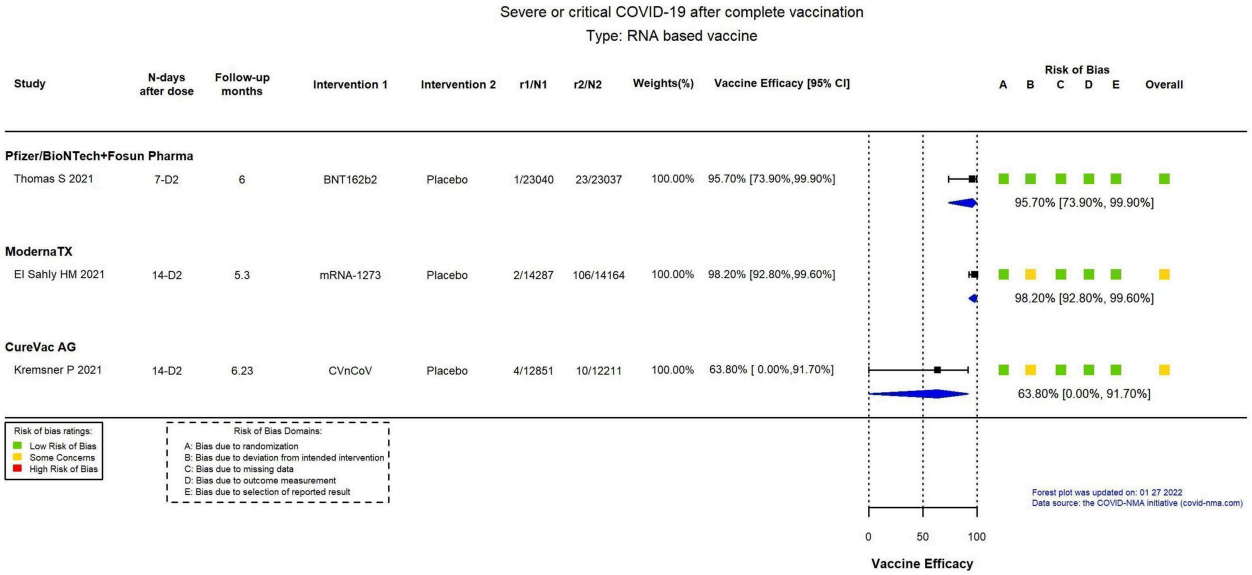
Figure 3. Analysis 1.1.2: RNA-based vaccine. Outcome: confirmed symptomatic COVID-19 after complete vaccination. Ali 2021 included only participants 3 to 17 years of age. Frenck 2021 included only participants 12 to 15 years of age.



Severe or critical COVID-19 after complete vaccination

One trial reported severe or critical COVID-19 (Thomas 2021). BNT162b2 results in a large reduction in the incidence of severe or critical disease due to COVID-19 compared to placebo measured at six months' follow-up (VE 95.70%, 95% CI 73.90% to 99.90%; 1 RCT, 46,077 participants; high-certainty evidence; Figure 4).

Figure 4. Analysis 1.1.3: RNA-based vaccine. Outcome: severe or critical COVID-19 after complete vaccination. *Thomas 2021 reports pooled results including adults' participants from Thomas 2021 and adolescent participants from Frenck 2021.



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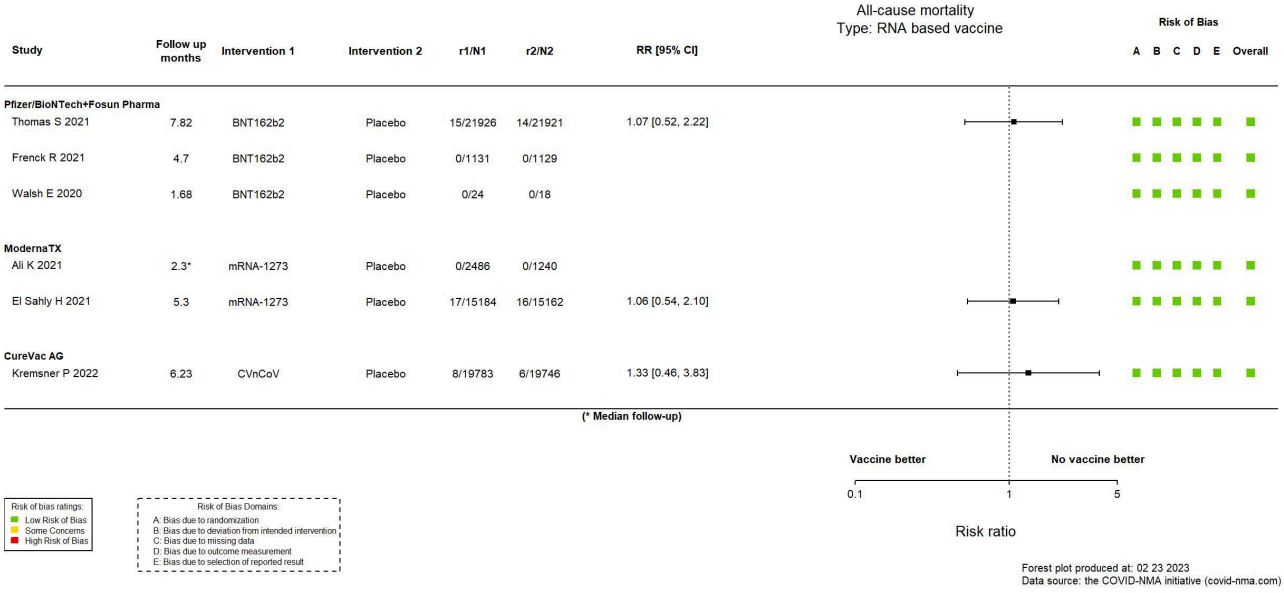
All-cause mortality

Two trials reported the outcome in 2302 participants at 1.7 months and 4.7 months' follow-up (Frenck 2021; Walsh 2020); there were no events and the trials did not contribute to the effect estimate.

Only one study contributed to the analysis (Thomas 2021), with a follow-up of six months. The evidence is uncertain for an effect of BNT162b2 on all-cause mortality compared to placebo due to very serious imprecision (risk ratio (RR) 1.07, 95% CI 0.52 to 2.22; 1 RCT, 43,847 participants; low-certainty evidence; Figure 5).

Figure 5. Analysis 1.1.4: RNA-based vaccine. Outcome: all-cause mortality. Ali 2021 included only participants 3 to 17 years of age. Frenck 2021 included only participants 12 to 15 years of age.



Serious adverse events

One trial reported the outcome in 42 participants at 1.7 months' follow-up (Walsh 2020); there were no events and the trial did not contribute to the effect estimate. Two trials contributed to the analysis at 1.7 months' follow-up (Frenck 2021; Thomas 2021). The evidence is uncertain for an effect of BNT162b2 on SAEs compared to placebo due to serious inconsistency and serious imprecision (RR 1.30, 95% CI 0.55 to 3.07; I^2 = 76%; 2 RCTs, 46,107 participants; low-certainty evidence; Figure 6).

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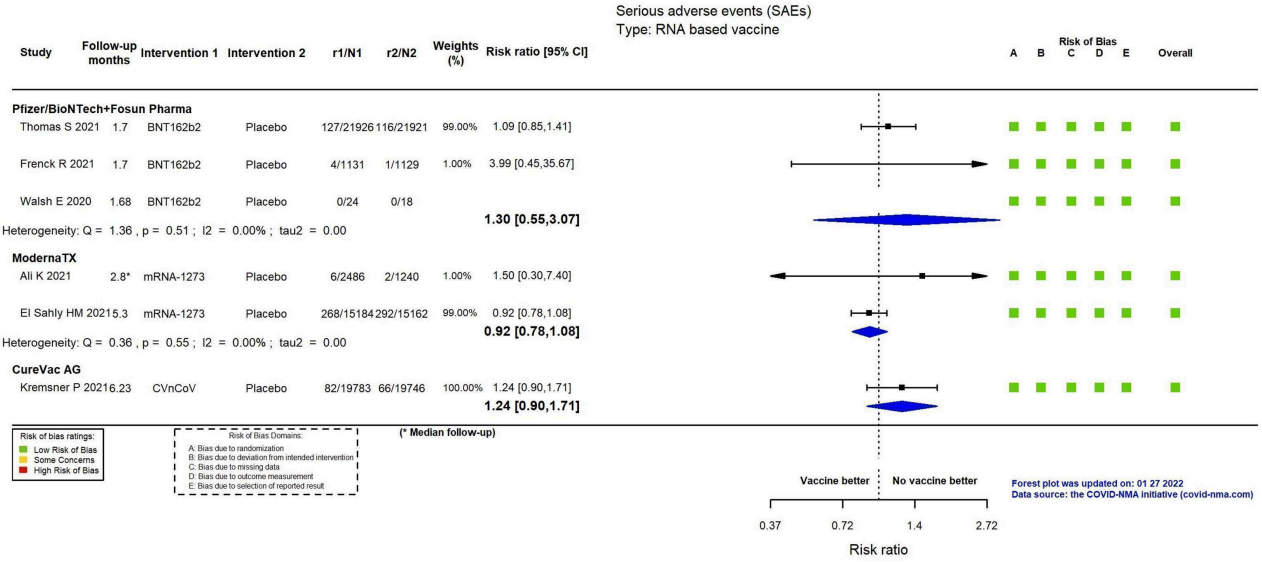
Figure 6. Analysis 1.1.5: RNA-based vaccine. Outcome: serious adverse events (SAEs). Ali 2021 included only participants 3 to 17 years of age. Frenck 2021 included only participants 12 to 15 years of age.

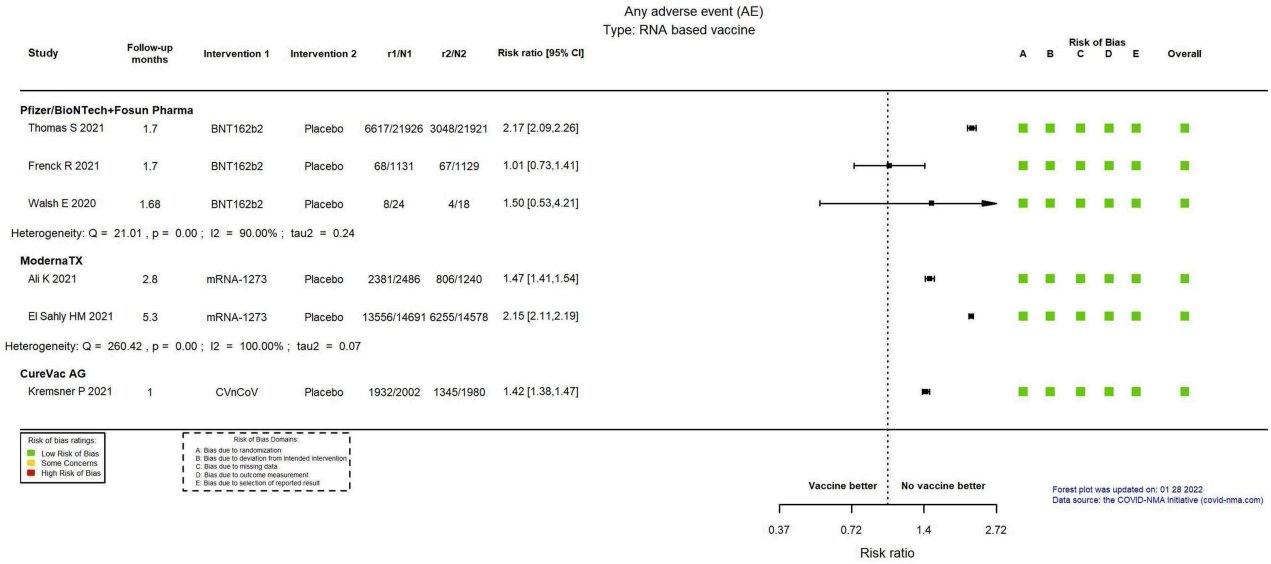


Any adverse event

Three RCTs reported the outcome at 1.7 months' follow-up (Frenck 2021; Thomas 2021; Walsh 2020). We decided not to pool the results due to considerable heterogeneity (I^2 = 90%) probably caused by studies assessing participants in different age groups; Thomas 2021 included adults while Frenck 2021 included adolescents.

One trial reported results for 43,847 participants 16 years and older (Thomas 2021), the RR for any adverse event was 2.17 (95% CI 2.09 to 2.26). Another trial reported results for 2260 participants between 12 and 15 years of age (Frenck 2021); the RR for any adverse event was 1.01 (95% CI 0.73 to 1.41). A third trial reported results for 42 participants 18 years or older (Walsh 2020); the RR for any adverse event in the study was 1.50 (95% CI 0.53 to 4.21) (Figure 7).

Figure 7. Analysis 1.1.7: RNA-based vaccine. Outcome: any adverse event (AE). Ali 2021 included only participants 3 to 17 years of age. Frenck 2021 included only participants 12 to 15 years of age.



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Important outcomes

GMTs of a neutralizing antibody against SARS-COV-2

Two trials reported GMTs of neutralizing antibodies against SARS-COV-2 (Frenck 2021; Walsh 2020). Results are detailed in Appendix 11.

Incidence of specific safety outcomes

Specific safety outcomes were not consistently reported throughout the included trials. Thomas 2021 reported the number of participants with stroke and myocardial infarction, Frenck 2021 reported the number of participants with cavernous sinus thrombosis, venous thrombosis and lymphadenopathy, and Walsh 2020 did not report any specific safety outcome of interest. These outcomes are summarized in detail in Appendix 12.

Vaccine-enhanced disease

This outcome was reported in a single trial which reported no vaccine-enhanced disease effect (Thomas 2021).

mRNA-1273 – ModernaTX versus placebo (normal saline)

See Summary of findings 2 and table of results in Appendix 13.

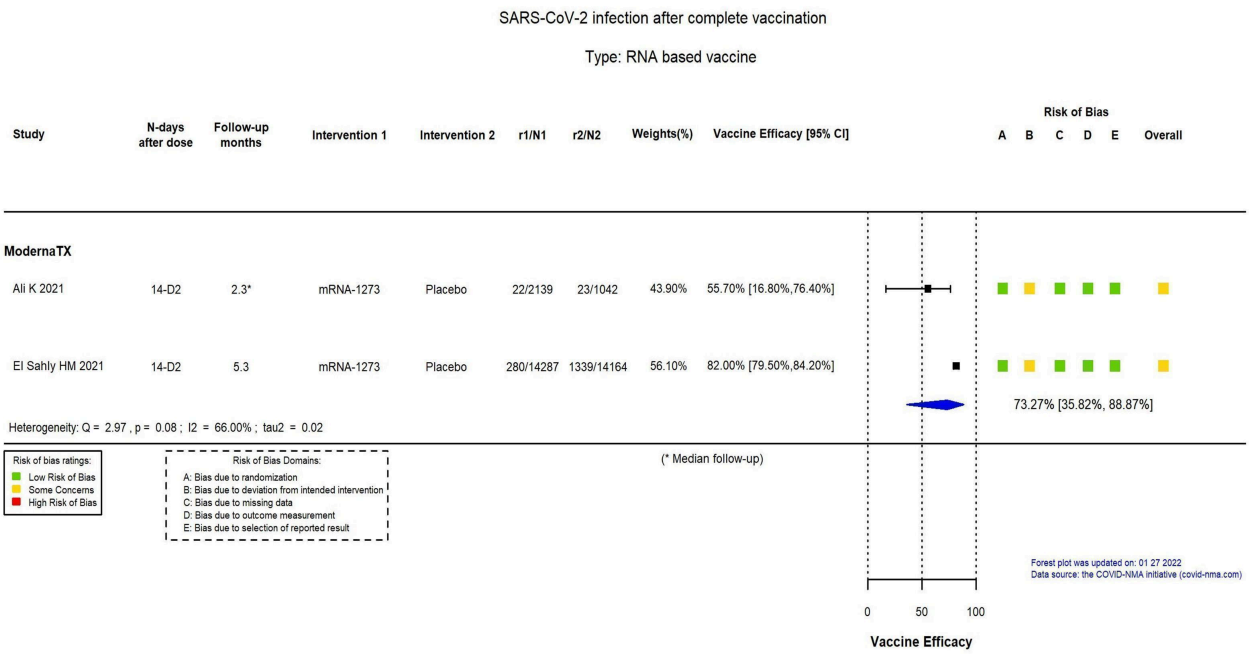
We identified and included two trials in the analysis assessing mRNA-1273. The outcomes 'GMT of specific antibodies against SARS-CoV-2', 'GMT of neutralizing antibodies against SARS-CoV-2' and 'cellular immune response' were not reported for this comparison.

Critical outcomes

Confirmed SARS-CoV-2 infection after complete vaccination

Two trials reported this outcome (Ali 2021; El Sahly 2021). mRNA-1273 probably results in a large reduction in the incidence of SARS-CoV-2 infection compared to placebo at 2.3 months (median) and 5.3 months' follow-up (VE 73.27%, 95% CI 35.82% to 88.87%; I^2 = 66%; 2 RCTs, 31,632 participants; moderate-certainty evidence; Figure 8).

Figure 8. Analysis 1.1.1: RNA-based vaccine. Outcome: confirmed SARS-CoV-2 infection after complete vaccination. Ali 2021 included only participants 3 to 17 years of age.



Confirmed symptomatic COVID-19 after complete vaccination

Two trials reported on this outcome (Ali 2021; El Sahly 2021). mRNA-1273 results in a large reduction in the incidence of confirmed symptomatic COVID-19 after complete vaccination compared to placebo at 2.3 months (median) and 5.3 months' follow-up (VE 93.20%, 95% CI 91.06% to 94.83%; I^2 = 0%; 2 RCTs, 31,632 participants; high-certainty evidence; Figure 3).

Severe or critical COVID-19 after complete vaccination

The outcome was reported in one trial (El Sahly 2021). mRNA-1273 results in a large reduction of the incidence of severe or critical disease due to COVID-19 compared to placebo at 5.3 months' follow-up (VE 98.20%, 95% CI 92.80% to 99.60%; 1 RCT, 28,451 participants; high-certainty evidence; Figure 4).

All-cause mortality

One study reported the outcome in 3726 participants at 2.3 months (median) follow-up (Ali 2021); there were no events and the trial did not contribute to the effect estimate. One trial contributed to the analysis with follow-up of 5.3 months (El Sahly 2021). The evidence is uncertain for an effect of mRNA-1273 on all-cause mortality compared to placebo due to very serious imprecision (RR 1.06, 95% CI 0.54 to 2.10; 1 RCT, 30,346 participants; low-certainty evidence; Figure 5).

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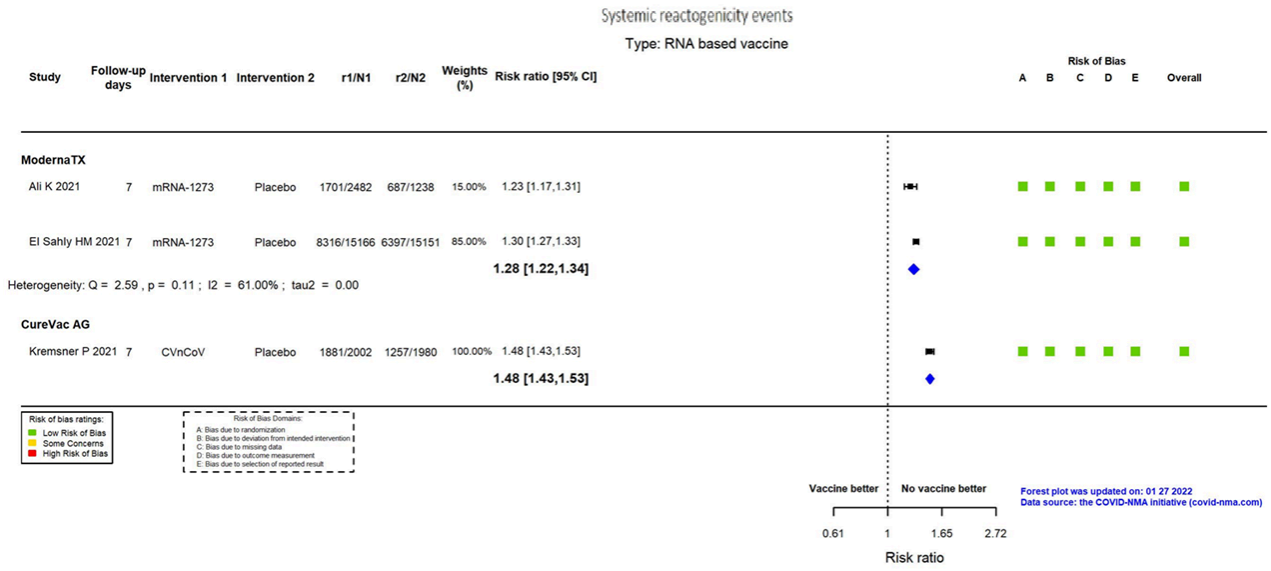
Serious adverse events

Two trials reported SAEs (Ali 2021; El Sahly 2021). mRNA-1273 probably results in no or little difference in the incidence of SAEs compared to placebo at 2.8 months (median) and 5.3 months' follow-up (RR 0.92, 95% CI 0.78 to 1.08; I^2 = 0%; 2 RCTs, 34,072 participants; absolute effect: 143 fewer per 100,000 (from 394 fewer to 143 more); moderate-certainty evidence; Figure 6).

Systemic reactogenicity events

Two trials reported the outcome (Ali 2021; El Sahly 2021). mRNA-1273 results in a slight increase in the occurrence of any systemic reactogenicity event compared to placebo (RR 1.28, 95% CI 1.22 to 1.34; I^2 = 61%; 2 RCTs, 34,037 participants; absolute effect: 121 more with systemic reactogenicity events per 1000 (from 95 fewer to 147 more); high-certainty evidence; Figure 9).

Figure 9. Analysis 1.1.6: RNA-based vaccine. Outcome: systemic reactogenicity events. Ali 2021 included only participants 3 to 17 years of age.



Any adverse event

Two RCTs reported the outcome at 2.8 months (median) and 5.3 months' follow-up (Ali 2021; El Sahly 2021). We decided not to pool the results due to considerable heterogeneity (I^2 = 100%) probably caused by studies assessing participants in different age groups; Ali 2021 included participants aged three years to 17 years while El Sahly 2021 included adults. One trial reported results for 3726 participants between 12 and 17 years of age (Ali 2021); the risk for any adverse event in the study was 1.47 (95% CI 1.41 to 1.54), the other study reported results for 29,269 participants 18 years and older (El Sahly 2021), the risk for any adverse event in this study was 2.15 (95% CI 2.11 to 2.19) (Figure 7).

Important outcomes

Local reactogenicity events

Two trials reported this outcome (Ali 2021; El Sahly 2021). mRNA-1273 results in a large increase of local reactogenicity events compared to placebo (RR 3.30, 95% CI 2.02 to 5.40; I^2 = 99%; 2 RCTs, 34,037 participants; absolute effect: 486 more with local reactogenicity events per 1000 (from 216 more to 930 more); high-certainty evidence; Figure 10).

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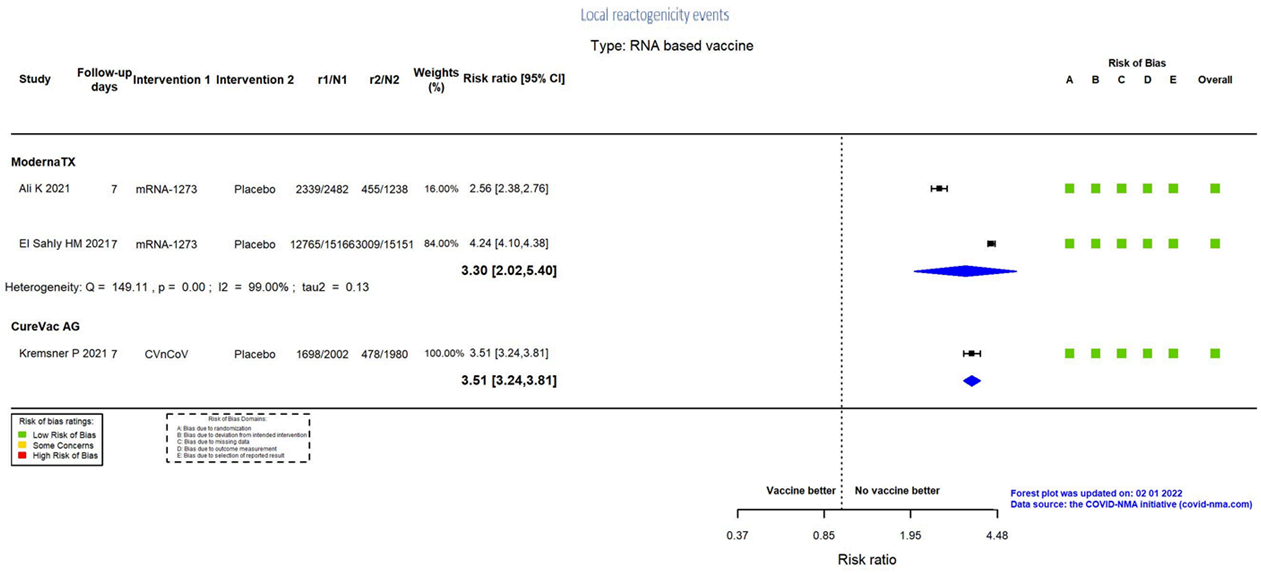
Figure 10. Analysis 1.1.8: RNA-based vaccine. Outcome: local reactogenicity events. Ali 2021 included only participants 3 to 17 years of age.



Incidence of specific safety outcomes

Specific safety outcomes were not consistently reported throughout the included trials. One trial reported number of participants with pulmonary embolism, pericarditis, venous thrombosis, myocardial infarction, thrombocytopaenia, anaemia and nervous system diseases (El Sahly 2021); the other trial reported number of participants with pericarditis myocardial infarction and lymphadenopathy (Ali 2021). Outcomes were summarized in detail in Appendix 12.

Vaccine-enhanced disease

One trial reported no vaccine-enhanced disease effect (El Sahly 2021).

CVnCoV – CureVac AG versus placebo (normal saline)

See Summary of findings 3 and table of results in Appendix 14.

We identified and included in the analysis one trial assessing CVnCoV. The outcomes 'SARS-CoV-2 infection after complete vaccination', 'GMT of specific antibodies against SARS-CoV-2', 'GMT of neutralizing antibodies against SARS-CoV-2', 'cellular immune response', 'incidence of specific safety outcomes' and 'vaccine-enhanced disease' were not reported for this comparison.

Critical outcomes

Confirmed symptomatic COVID-19 after complete vaccination

One trial reported this outcome at 6.2 months' follow-up (Kremsner 2021). CVnCoV probably results in a small reduction of confirmed symptomatic COVID-19 after complete vaccination compared to placebo (VE 48.20%, 95% CI 31.70% to 60.90%; 1 RCT, 25,062 participants; moderate-certainty evidence; Figure 3).

Severe or critical COVID-19 after complete vaccination

One trial reported the outcome at six months' follow-up (Kremsner 2021). The evidence is very uncertain for an effect of CVnCoV in reducing severe or critical COVID-19 compared to placebo due to serious indirectness and very serious imprecision (VE 63.80%, 95% CI 0.00% to 91.70%; 1 RCT, 25,062 participants; very low-certainty evidence; Figure 4).

All-cause mortality

One trial reported this outcome at six months' follow-up (Kremsner 2021). The evidence is very uncertain for an effect of CVnCoV on all-cause mortality compared to placebo due to serious indirectness and very serious imprecision (RR 1.33, 95% CI 0.46 to 3.83; 1 RCT, 39,529 participants; very low-certainty evidence; Figure 5).

Serious adverse events

One trial reported this outcome (Kremsner 2021). The evidence is very uncertain for an effect of CVnCoV on SAEs compared to placebo at 1.7 months' follow-up (RR 1.24, 95% CI 0.90 to 1.71; 1 RCT, 39,529 participants; low-certainty evidence; Figure 6).

Systemic reactogenicity events

One trial reported this outcome (Kremsner 2021). CVnCoV results in a large increase in the incidence of systemic reactogenicity events compared to placebo at 6.2 months' follow-up (RR 1.48, 95% CI 1.43 to 1.53; 1 RCT, 3982 participants; absolute effect: 305 more with systemic reactogenicity events per 1000 (from 273 more to 336 more); high-certainty evidence; Figure 9).

Any adverse event

One trial reported this outcome (Kremsner 2021). CVnCoV probably results in a large increase in the incidence of any adverse event compared to placebo at one-month follow-up (RR 1.42, 95% CI 1.38 to 1.47; 1 RCT, 3982 participants; absolute effect: 285 more with any

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adverse event per 1000 (from 258 more to 319 more); moderate-certainty evidence; Figure 7).

Important outcomes

Local reactogenicity events

One trial reported this outcome (Kremsner 2021). CVnCoV results in a large increase in the incidence of local reactogenicity events compared to placebo (RR 3.51, 95% CI 3.24 to 3.81; 1 RCT, 3982 participants; absolute effect: 606 more with local reactogenicity events per 1000 (from 541 more to 678 more); high-certainty evidence; Figure 10).

Non-replicant viral vector vaccines

ChAdOx1/SII-ChAdOx1 – AstraZeneca+University of Oxford/ Serum Institute of India versus placebo (normal saline/ adjuvant/MenACWY)

See Summary of findings 4 and table of results in Appendix 15.

We identified and included in the analysis seven trials assessing ChAdOx1 – AstraZeneca/University of Oxford and one trial assessing SII-ChAdOx1, the equivalent of ChAdOx1 manufactured in India at Serum Institute of India (Kulkarni 2021). The latter did not report efficacy outcomes.

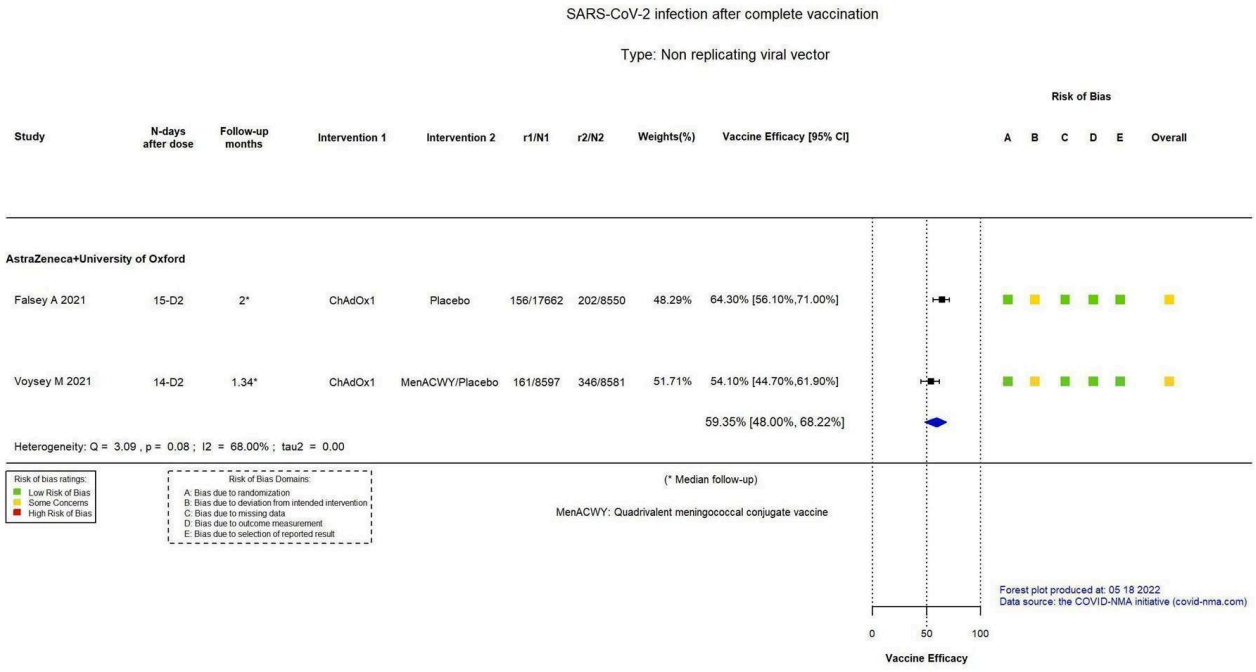
The outcomes 'severe or critical COVID-19 after complete vaccination', 'GMT of neutralizing antibodies against SARS-CoV-2' and 'cellular immune response' were not reported for this comparison.

Critical outcomes

Confirmed SARS-CoV-2 infection after complete vaccination

This outcome was reported in five RCTs (Falsey 2021; Voysey 2021a (which reported pooled results for four trials)). ChAdOx1 probably reduces SARS-CoV-2 infection compared to placebo and MenACWY vaccine at 1.3 months (median) and two months (median) follow-up (VE 59.35%, 95% CI 48.00% to 68.22%; I^2 = 68%; 5 RCTs, 43,390 participants; moderate-certainty evidence; Figure 11).

Figure 11. Analysis 2.1.1: Non-replicating viral vector vaccine. Outcome: confirmed SARS-CoV-2 infection after complete vaccination. Voysey 2021a: data pooled from four trials.



Confirmed symptomatic COVID-19 after complete vaccination

Five RCTs reported this outcome (Falsey 2021; Voysey 2021a) (Voysey 2021a (which reported pooled results for four trials)). ChAdOx1 results in a large reduction of the incidence of confirmed symptomatic COVID-19 after complete vaccination compared to placebo and MenACWY vaccine at 1.3 months (median) and two months (median) follow-up (VE 70.23%, 95% CI 62.10% to 76.62%; I^2 = 38%; 5 RCTs, 43,390 participants; high-certainty evidence; Figure 12).

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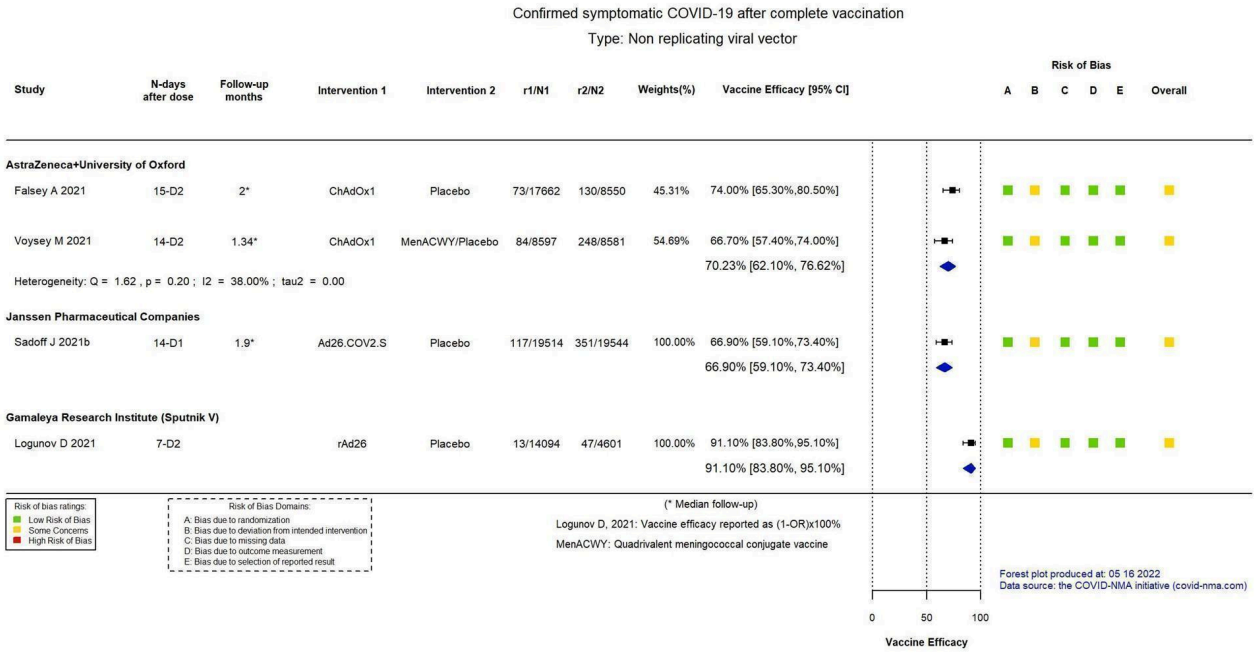
Figure 12. Analysis 2.1.2: non-replicating viral vector vaccine. Outcome: confirmed symptomatic COVID-19 after complete vaccination. Voysey 2021a: data pooled from four trials.



All-cause mortality

Two trials reported this outcome in 1456 participants at 2-month follow-up (Asano 2022; Kulkarni 2021); there were no events and the trials did not contribute to the effect estimate. Five trials contributed to the analysis with follow-up from 2.0 months to 4.2 months (Falsey 2021; Madhi 2021a (which reported on HIV-positive participants who were not included in this pooled analysis); Voysey 2021a (which reported pooled results for four trials)). The evidence is uncertain for an effect of ChAdOx1 on all-cause mortality compared to placebo and MenACWY vaccine due to very serious imprecision (RR 0.48, 95% CI 0.20 to 1.14; I^2 = 0%; 5 RCTs, 56,727 participants; low-certainty evidence; Figure 13).

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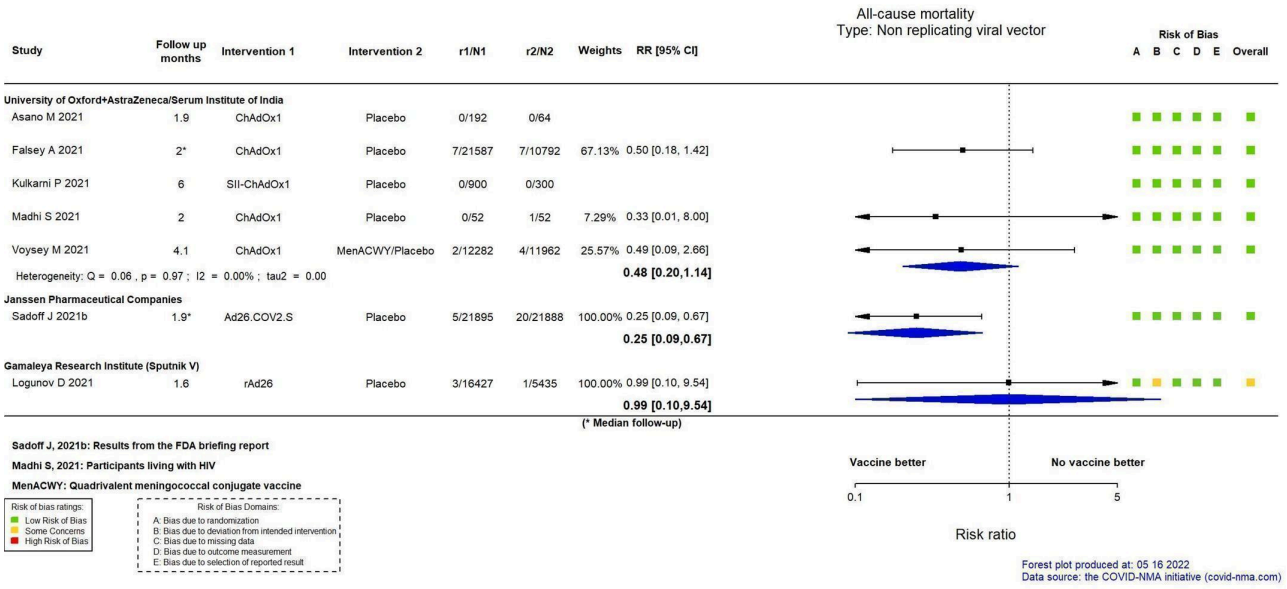
Figure 13. Analysis 2.1.4: non-replicating viral vector vaccine. Outcome: all-cause mortality. In Kulkarni 2021, the control arm received adjuvant. Voysey 2021a: data pooled from four trials.



Serious adverse events

Seven trials reported this outcome (Asano 2022; Falsey 2021; Kulkarni 2021; Madhi 2021a (which reported on HIV-positive participants who were not included in this pooled analysis); Voysey 2021a (which reported pooled results for four trials)). ChAdOx1 probably results in no or little increase in the incidence of SAEs compared to placebo and at one month' to 6 months' follow-up (RR 0.88, 95% CI 0.72 to 1.07; I^2 = 6%; 7 RCTs, 58,182 participants; absolute effect: 1 fewer with SAEs per 1000 (from 2 fewer to 1 more); moderate-certainty evidence; Figure 14).

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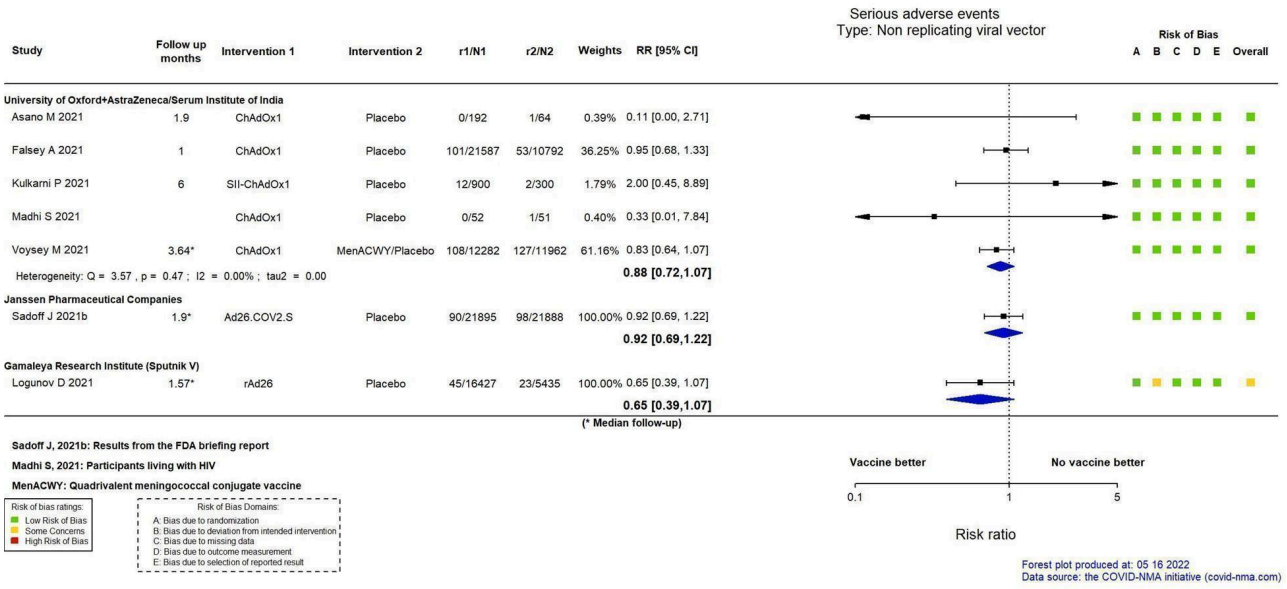
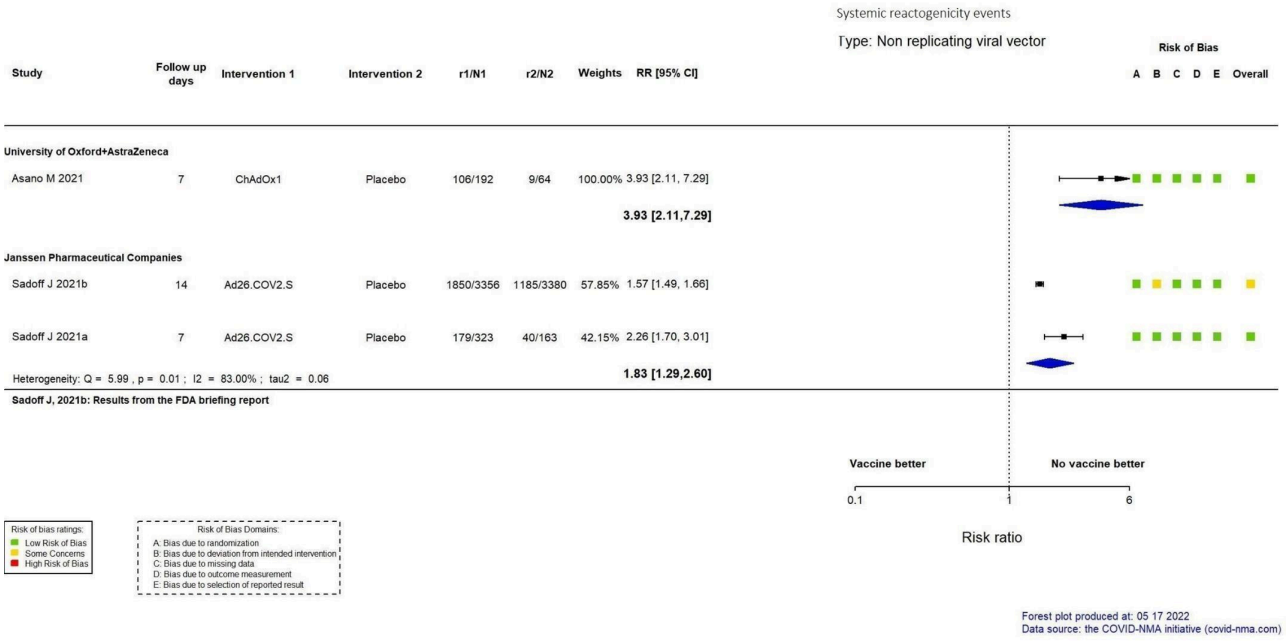
Figure 14. Analysis 2.1.5: non-replicating viral vector vaccine. Outcome: serious adverse events (SAEs). In Kulkarni 2021, the control arm received adjuvant. Voysey 2021a: data pooled from four trials.



Systemic reactogenicity events

This outcome was reported in one trial (Asano 2022). ChAdOx1 probably results in a large increase of systemic reactogenicity events compared to placebo (RR 3.93, 95% CI 2.11 to 7.29; 1 RCT, 256 participants; absolute effect: 412 more with systemic reactogenicity events per 1000 (from 156 more to 885 more); moderate-certainty evidence; Figure 15).

Figure 15. Analysis 2.1.6: non-replicating viral vector vaccine. Outcome: systemic reactogenicity events.



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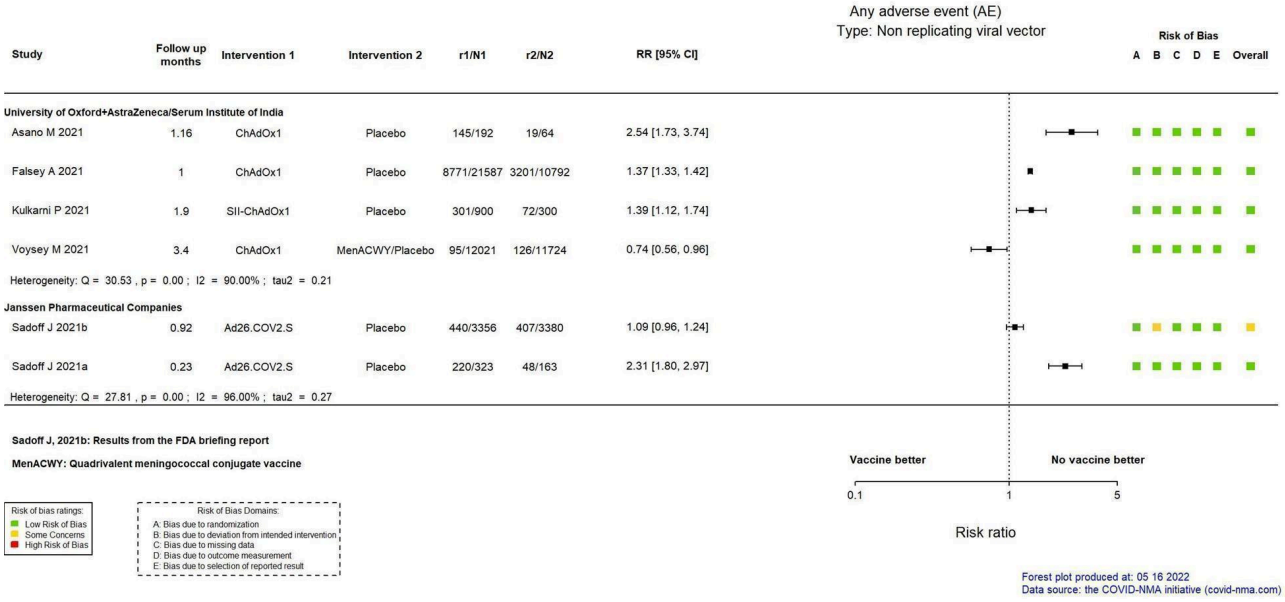
Any adverse event

Seven trials reported this outcome (Asano 2022; Falsey 2021; Kulkarni 2021; Voysey 2021a (which reported pooled results for four trials). Due to considerable heterogeneity, we decided not to pool the results (I^2 = 90%). Asano 2022 reported results for 256 participants at 1.2 months' follow-up; the risk of any adverse event in the study was 2.54 (95% CI 1.73 to 3.74). Falsey 2021 reported results for 32,379 participants at one-month follow-up; the risk for any adverse event was 1.37 (95% CI 1.33 to 1.42). Kulkarni 2021 reported results for 1200 participants at 1.9 months' follow-up; the risk for any adverse event was 1.39 (95% CI 1.12 to 1.74). Lastly, a report pooling four trials presented results for 23,745 participants, the risk for any adverse event was 0.74 (95% CI 0.56 to 0.96) at 3.4 months' follow-up (Voysey 2021a). Of note, participants in the control arm received different interventions across studies; three trials used normal saline as placebo (Asano 2022; COV005 included in Voysey 2021a; Falsey 2021) and three used MenACWY vaccine (COV001, COV002, COV003 included in Voysey 2021a) and one trial used adjuvant (Kulkarni 2021) (Figure 16).

Figure 16. Analysis 2.1.7: non-replicating viral vector vaccine. Outcome: any adverse event (AE). In Kulkarni 2021, the control arm received adjuvant. Voysey 2021a merged results from four different trials where three used quadrivalent meningococcal conjugate vaccine as placebo and one trial used normal saline.



Important outcomes

GMTs of a specific antibody against SARS-COV-2

Voysey 2021a reported GMTs of specific antibodies against SARS-COV-2. Results are detailed in Appendix 16.

Local reactogenicity events

The outcome was reported in one trial (Asano 2022). ChAdOx1 probably results in a large increase in the number of local reactogenicity events compared to placebo (RR 6.44, 95% CI 2.98 to 13.92; 1 RCT, 256 participants; absolute effect: 510 more with local reactogenicity events per 1000 (from 186 more to 1000 more); moderate-certainty evidence; Figure 17).

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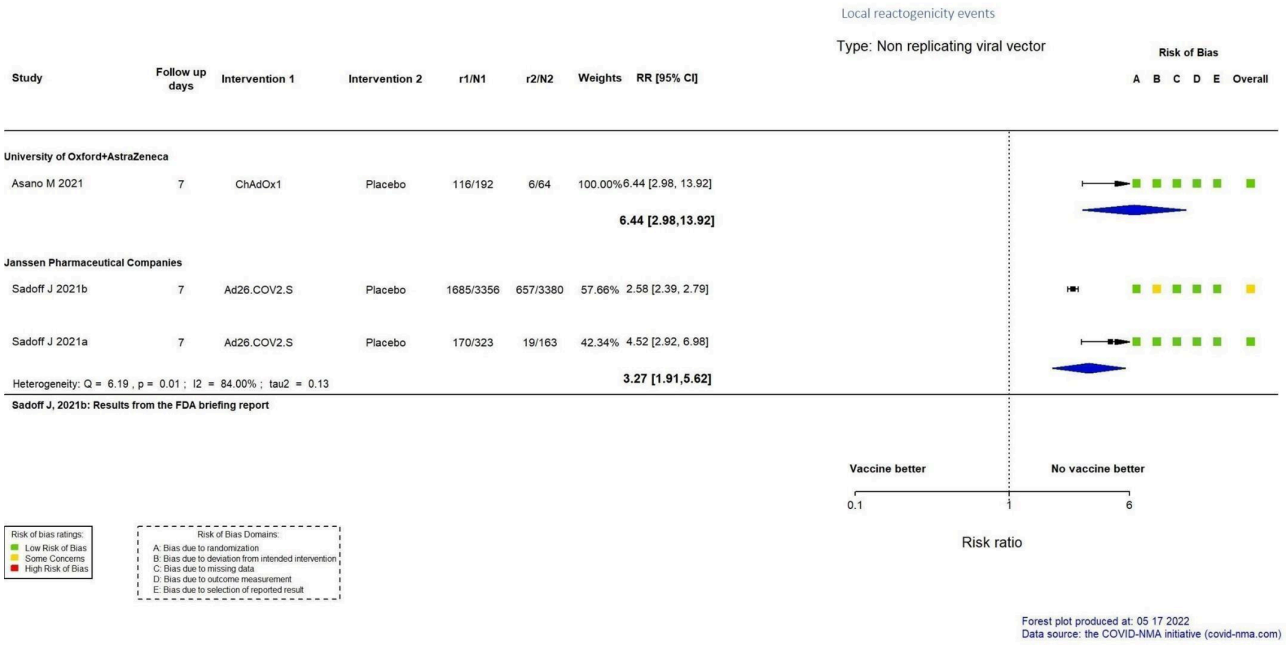
Figure 17. Analysis 2.1.8: non-replicating viral vector vaccine. Outcome: local reactogenicity events.



Incidence of specific safety outcomes

Specific safety outcomes were not consistently reported throughout the included trials. Madhi 2021a reported number of participants with subsequent nervous system diseases, Falsey 2021 reported number of participants with stroke, cavernous sinus thrombosis, venous thrombosis and nervous system disorders, Voysey 2021a presented results for the number of participants with pulmonary embolism, pericarditis, venous thrombosis, myocardial infarction, anaemia and nervous system diseases, and Asano 2022 and Kulkarni 2021 did not report any specific safety outcome of interest. Outcomes are summarized in detail in Appendix 12.

Vaccine-enhanced disease

Falsey 2021 reported no vaccine-enhanced disease effect.

ChAdOx1 – AstraZeneca+University of Oxford versus SII-ChAdOx1 – Serum Institute of India

See Summary of findings 5 and table of results in Appendix 17.

Kulkarni 2021 reported results on ChAdOx1 compared to SII-ChAdOx1 (the equivalent of ChAdOx1 manufactured in India at Serum Institute of India).

Critical outcomes

All-cause mortality

Kulkarni 2021 reported this outcome at six months' follow-up. The trial including 400 participants reported zero events for both groups for this outcome (Figure 18).

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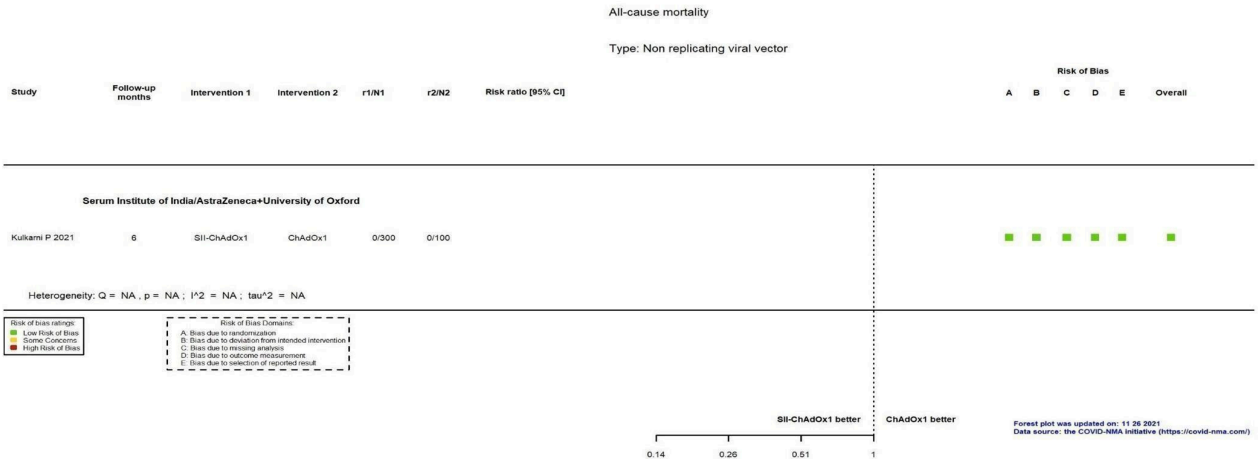
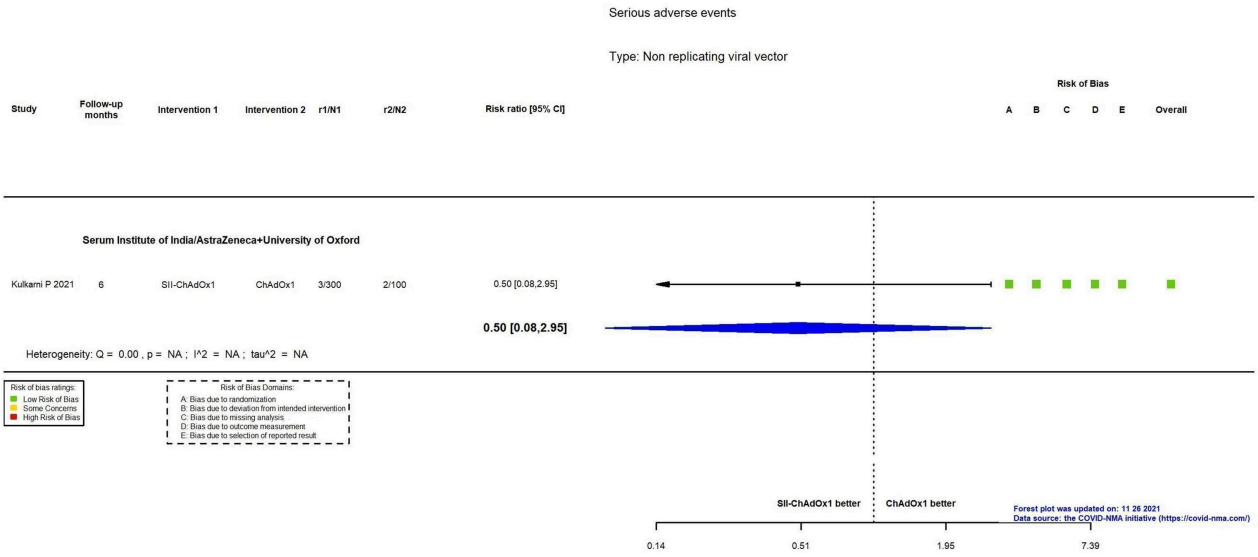
Figure 18. Analysis 2.2.1: serum Institute of India/Astra Zeneca+University of Oxford – SII-ChAdOx1 versus University of Oxford – ChAdOx1. Outcome: all-cause mortality.



Serious adverse events

Kulkarni 2021 reported this outcome at six months' follow-up. The evidence is uncertain for an effect of SII-ChAdOx1 on the incidence of SAEs compared to ChAdOx1 due to very serious imprecision (RR 0.50, 95% CI 0.08 to 2.95; 1 RCT, 400 participants; low-certainty evidence; Figure 19).

Figure 19. Analysis 2.2.2: SII-ChAdOx1 versus ChAdOx1. Outcome: serious adverse events (SAEs).



Systemic reactogenicity events

Kulkarni 2021 reported this outcome. SII-ChAdOx1 probably results in a slight decrease in the number of systemic reactogenicity events compared to ChAdOx1 (RR 0.73, 95% CI 0.54 to 0.98; 1 RCT, 400 participants; absolute effect: 105 fewer with systemic reactogenicity events per 1000 (from 179 fewer to 8 fewer); moderate-certainty evidence; Figure 20).

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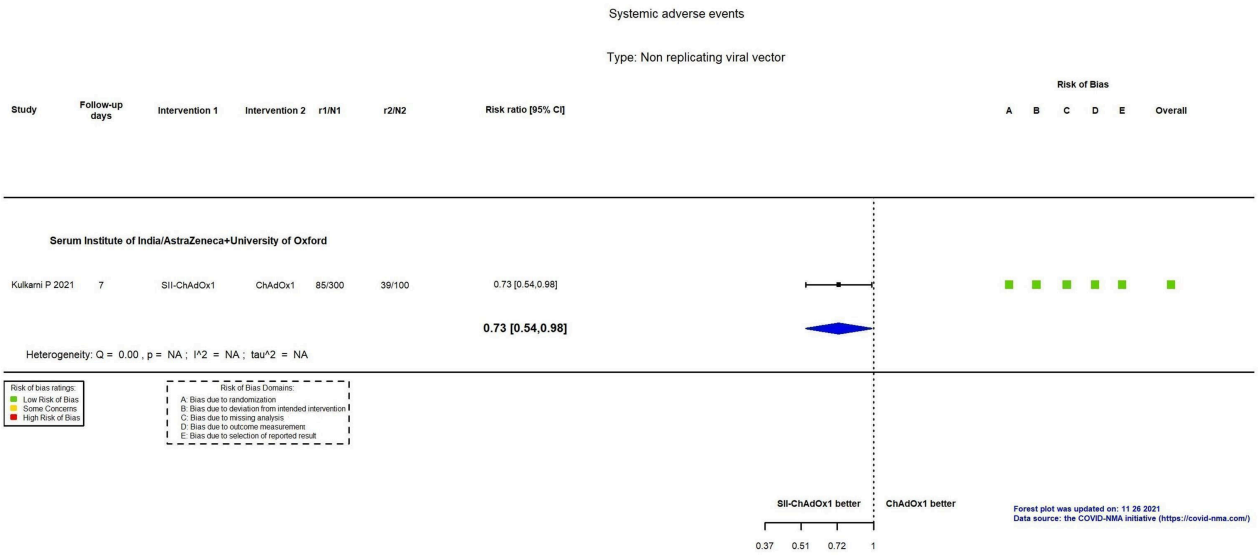
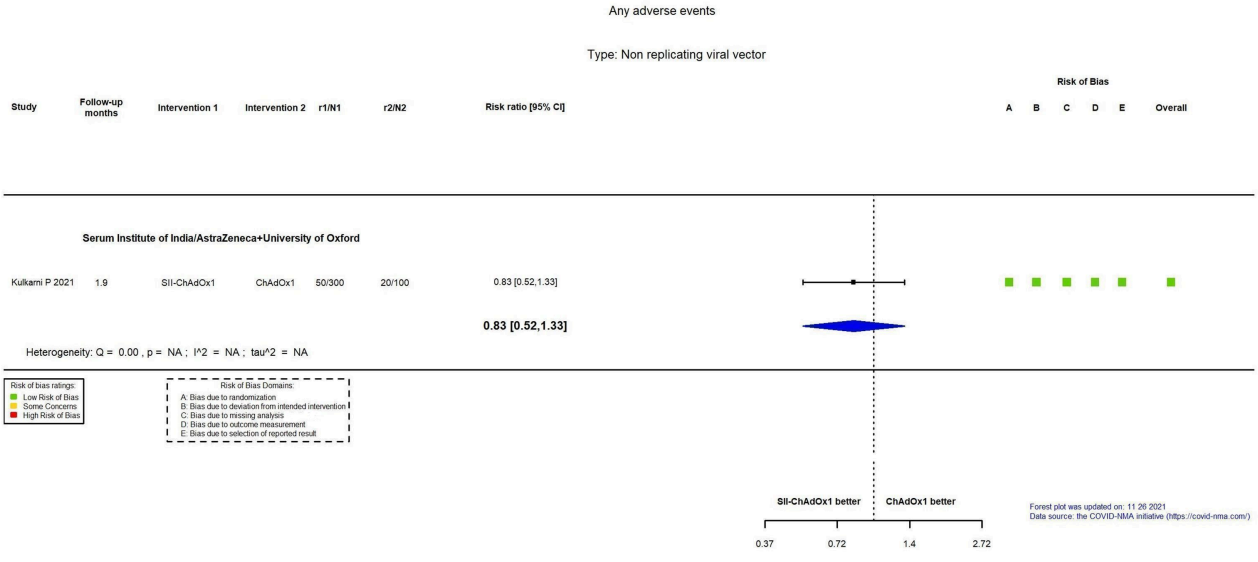
Figure 20. Analysis 2.2.3: SII-ChAdOx1 versus ChAdOx1. Outcome: systemic reactogenicity events.



Any adverse event

Kulkarni 2021 reported this outcome at 1.9 months' follow-up. The evidence is uncertain for an effect of SII-ChAdOx1 on the incidence of any adverse event compared to ChAdOx1 due to very serious imprecision (RR 0.83, 95% CI 0.52 to 1.33; 1 RCT, 400 participants; low-certainty evidence; Figure 21).

Figure 21. Analysis 2.2.4: SII-ChAdOx1 versus ChAdOx1. Outcome: any adverse event (AE).



Important outcomes

Immunogenicity outcomes

Kulkarni 2021 reported that SII-ChAdOx1 elicited slightly higher levels of specific antibodies against SARS-COV-2 (GMR 1.52, 95% CI 1.03 to 2.26) compared to ChAdOx1 (Appendix 16). Results for neutralizing antibodies against SARS-COV-2 were not conclusive because of imprecision (GMR 1.23, 95% CI 0.92 to 1.63).

Local reactogenicity events

Kulkarni 2021 reported this outcome. The evidence is uncertain for an effect of SII-ChAdOx1 on the incidence of local reactogenicity

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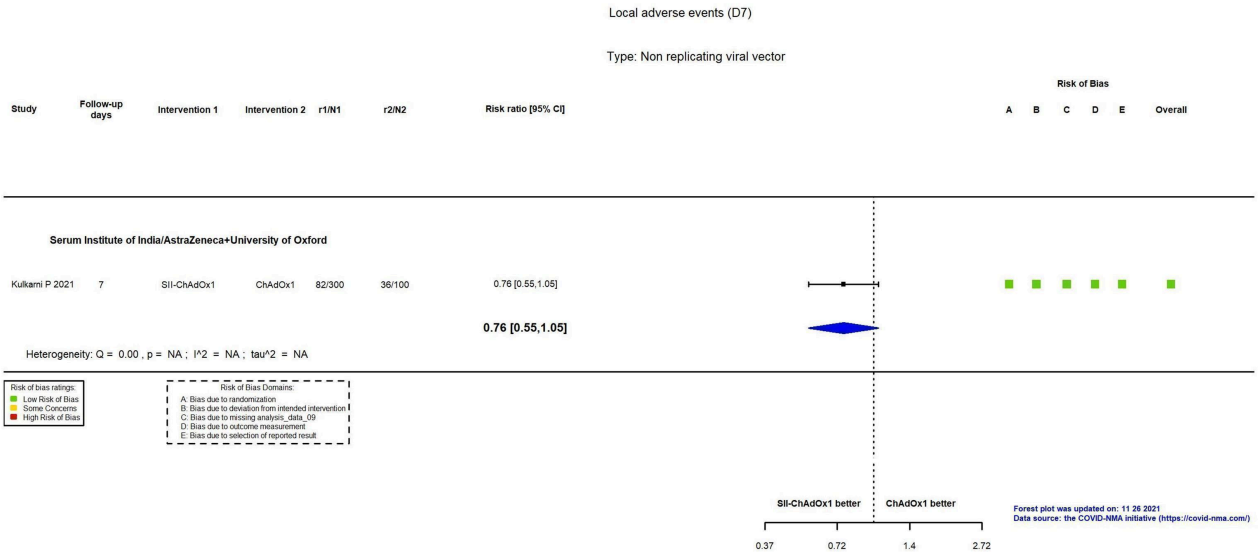
events compared to ChAdOx1 (RR 0.76, 95% CI 0.55 to 1.05; 1 RCT, 400 participants; low-certainty evidence; Figure 22).

Figure 22. Analysis 2.2.5: SII-ChAdOx1 versus ChAdOx1. Outcome: local reactogenicity events.



Ad26.COV2.S – Janssen Pharmaceutical Companies versus placebo (normal saline)

See Summary of findings 6 and table of results in Appendix 18.

We identified and included in the analysis two trials assessing Ad26.COV2.S. The outcomes 'SARS-CoV-2 infection after complete vaccination', 'GMT of specific antibodies against SARS-CoV-2', and 'cellular immune response' were not reported for this comparison.

Critical outcomes

Confirmed symptomatic COVID-19 after complete vaccination

This outcome was reported in Sadoff 2021b. Ad26.COV2.S reduces the incidence of confirmed symptomatic COVID-19 after complete vaccination compared to placebo at 1.9 months (median) follow-up (VE 66.90%, 95% CI 59.10% to 73.40%; 1 RCT, 39,058 participants; high-certainty evidence; Figure 12).

Severe or critical COVID-19 after complete vaccination

This outcome was reported in Sadoff 2021b. Ad26.COV2.S results in a large reduction of severe or critical COVID-19 compared to placebo at 1.9 months (median) follow-up (VE 76.30%, 95% CI 57.90% to 87.50%; 1 RCT, 39,058 participants; high-certainty evidence; Figure 23).

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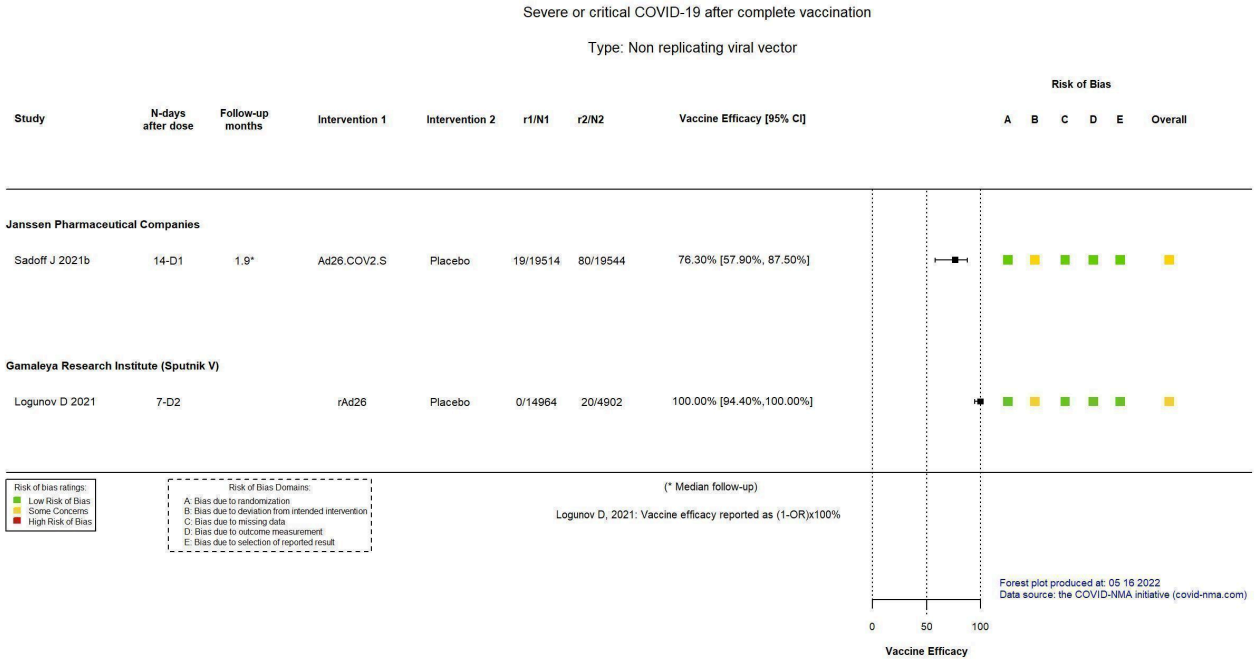
Figure 23. Analysis 2.1.3: non-replicating viral vector vaccine. Outcome: severe or critical COVID-19 after complete vaccination.



All-cause mortality

This outcome was reported in Sadoff 2021b. Ad26.COV2.S probably results in a reduction in all-cause mortality compared to placebo at 1.9 months (median) follow-up (RR 0.25, 95% CI 0.09 to 0.67; 1 RCT, 43,783 participants; absolute effect: 69 fewer per 100,000 (from 83 fewer to 30 fewer); high-certainty evidence; Figure 13).

Serious adverse events

This outcome was reported in Sadoff 2021b. Ad26.COV2.S probably results in little or no difference in the incidence of SAEs at 1.9 months (median) follow-up (RR 0.92, 95% CI 0.69 to 1.22; 1 RCT, 43,783 participants; absolute effect: 36 fewer per 100,000 (from 139 fewer to 99 more); moderate-certainty evidence; Figure 14).

Systemic reactogenicity events

Two trials reported this outcome (Sadoff 2021a; Sadoff 2021b). Ad26.COV2.S results in a large increase in systemic reactogenicity events compared to placebo (RR 1.83, 95% CI 1.29 to 2.60; I^2 = 83%; 2 RCTs, 7222 participants; absolute effect: 28,697 more per 100,000 (from 10,027 more to 55,320 more); high-certainty evidence; Figure 15).

Any adverse event

The outcome was reported in two trials (Sadoff 2021a; Sadoff 2021b). We decided not to pool the results due to considerable heterogeneity (I^2 = 96%). Sadoff 2021b reported results for 6736 participants at one-month follow-up; the risk for any adverse event was 1.09 (95% CI 0.96 to 1.24). Sadoff 2021a reported results for 486 participants; the risk for adverse events was 2.31 (95% CI 1.80 to 2.97; Figure 16).

Important outcomes

Immunogenicity outcomes

Sadoff 2021a reported GMTs of neutralizing antibodies against SARS-COV-2. Results are detailed in Appendix 11.

Local reactogenicity events

Two trials reported this outcome (Sadoff 2021a; Sadoff 2021b). Ad26.COV2.S results in a large increase in local reactogenicity events compared to placebo (RR 3.27, 95% CI 1.91 to 5.62; I^2 = 84%; 2 RCTs, 7222 participants; absolute effect: 433 more with local reactogenicity events per 1000 (from 174 more to 881 more); high-certainty evidence; Figure 17).

Incidence of specific safety outcomes

Specific safety outcomes were not consistently reported throughout the included trials: Sadoff 2021b reported the number of participants with pulmonary embolism, cavernous sinus thrombosis, pericarditis and venous thrombosis; Sadoff 2021a did not report any specific safety outcomes of interest. Outcomes are summarized in detail in Appendix 12.

Vaccine-enhanced disease

Sadoff 2021b reported no vaccine-enhanced disease effect.

Gam-COVID-Vac – Gamaleya Research Institute (Sputnik V) versus placebo (adjuvant)

See Summary of findings 7 and table of results in Appendix 19.

We identified and included one trial in the analysis assessing Gam-COVID-Vac (Logunov 2021).

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The outcomes 'SARS-CoV-2 infection after complete vaccination', 'incidence of any adverse event', 'systemic reactogenicity events' and 'vaccine-enhanced disease' were not reported for this comparison.

Some important concerns were raised concerning Logunov 2021: lack of clarity in the definition of the primary outcome; addition of interim analyses; change in outcomes; inadequate reporting with inconsistencies in numbers; and excess of homogeneity of vaccine efficacy across age groups (Bucci 2021). The authors responded to some of these concerns and the manuscript was corrected (Logunov 2021). Nevertheless, uncertainty persists related to the prespecification of the interim analysis and excess of homogeneity of vaccine efficacy across age groups. Consequently, we decided to downgrade the certainty of evidence for these reasons.

Critical outcomes

Confirmed symptomatic COVID-19 after complete vaccination

This outcome was reported in Logunov 2021. Gam-COVID-Vac probably results in a large reduction in the incidence of confirmed symptomatic COVID-19 after complete vaccination compared to placebo (follow-up time not reported) (VE 91.10%, 95% CI 83.80% to 95.10%; 1 RCT, 18,695 participants; moderate-certainty evidence). Of note, vaccine efficacy for this outcome was calculated using RR (Figure 12).

Severe or critical COVID-19 after complete vaccination

This outcome was reported in Logunov 2021. Gam-COVID-Vac probably results in a large reduction in the incidence of severe or critical COVID-19 compared to placebo (follow-up time not reported) (VE 100.00%, 95% CI 94.40% to 100.00%; 1 RCT, 19,866 participants; moderate-certainty evidence; Figure 23).

All-cause mortality

Logunov 2021 reported this outcome at 1.6 months' follow-up. The evidence is very uncertain for an effect of Gam-COVID-Vac in all-cause mortality compared to placebo due to serious imprecision (RR 0.99, 95% CI 0.10 to 9.54; 1 RCT, 21,862 participants; very low-certainty evidence; Figure 13).

Serious adverse events

Logunov 2021 reported this outcome. The evidence is uncertain for an effect of Gam-COVID-Vac in the incidence of SAEs compared to placebo at 1.6 months' follow-up (RR 0.65, 95% CI 0.39 to 1.07; 1 RCT, 21,862 participants; low-certainty evidence; Figure 14).

Important outcomes

Immunogenicity outcomes

Logunov 2021 reported GMTs of neutralizing and specific antibodies against SARS-CoV-2, and cellular immune response. Results are detailed in Appendix 11, Appendix 16, and Appendix 20, respectively.

Incidence of specific safety outcomes

Logunov 2021 reported number of participants with cavernous sinus thrombosis, venous thrombosis, myocardial infarction, lymphadenopathy and nervous system diseases. Details are in Appendix 12.

Inactivated virus vaccines

CoronaVac – Sinovac versus placebo (adjuvant)

See Summary of findings 8 and table of results in Appendix 21.

We identified and included in the analysis seven trials assessing CoronaVac – Sinovac. The outcome 'SARS-CoV-2 infection after complete vaccination' was not reported for this comparison.

Critical outcomes

Confirmed symptomatic COVID-19 after complete vaccination

This outcome was reported in two trials at 1.4 months (median) to 2 months (median) follow-up (Palacios 2020; Tanriover 2021). The evidence is uncertain for an effect of CoronaVac on the incidence of confirmed symptomatic COVID-19 after complete vaccination compared to adjuvant due to serious inconsistency and imprecision (VE 69.81%, 95% CI 12.27% to 89.61%; I^2 = 92%; 2 RCTs, 19,852 participants; low-certainty evidence). There was considerable heterogeneity between included studies which could be due to participant's different level of exposure to the virus across studies (all participants included in Palacios 2020 were healthcare workers compared to a third in Tanriover 2021) (Figure 24).

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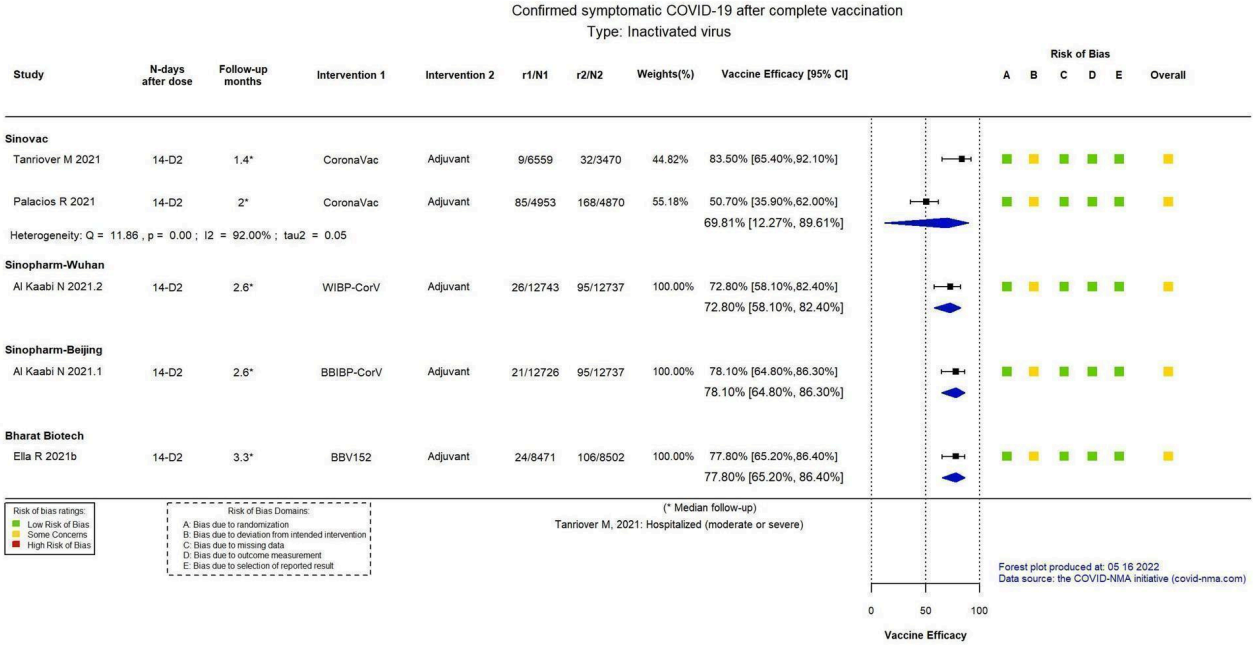
Figure 24. Analysis 3.1.2: inactivated virus vaccine. Outcome: confirmed symptomatic COVID-19 after complete vaccination. Al Kaabi 2021.1 and Al Kaabi N 2021.2 refers to two different comparisons from the same report (Al Kaabi 2021).



Severe or critical COVID-19 after complete vaccination

Two trials reported this outcome (Palacios 2020; Tanriover 2021). We did not conduct a meta-analysis for this outcome since the typical normality assumption of the meta-analysis model would be invalid due to the skewness of the data. This can be seen in the forest plots where the CI is not symmetric around the point estimate. Tanriover 2021, with 0/6559 events in the CoronaVac group versus 1/3470 events in the control group reported a vaccine efficacy of 100.00%, 95% CI 20.40% to 100.00% at 1.4 months (median) follow-up; and Palacios 2020, with 0/4953 events in the CoronaVac group and 6/4870 events in the control group reported a vaccine efficacy of 100.00%, 95% CI 16.90% to 100.00% at two months (median) follow-up (Figure 25).

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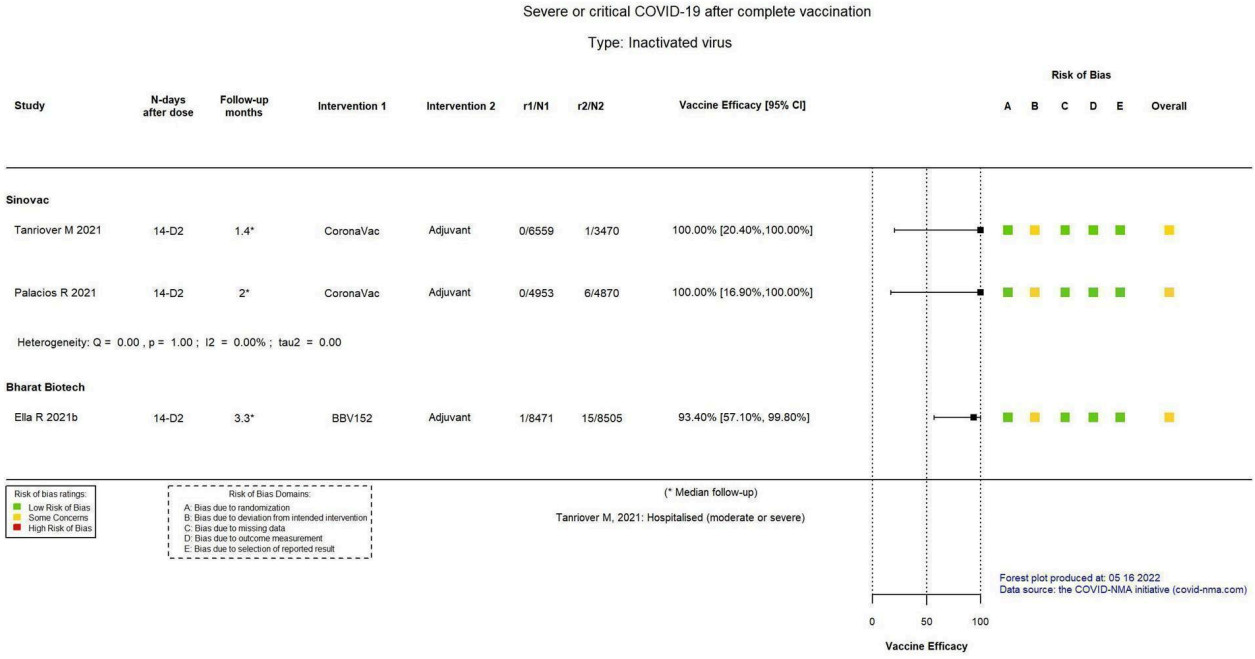
Figure 25. Analysis 3.1.3: inactivated virus vaccine. Outcome: severe or critical COVID-19 after complete vaccination.

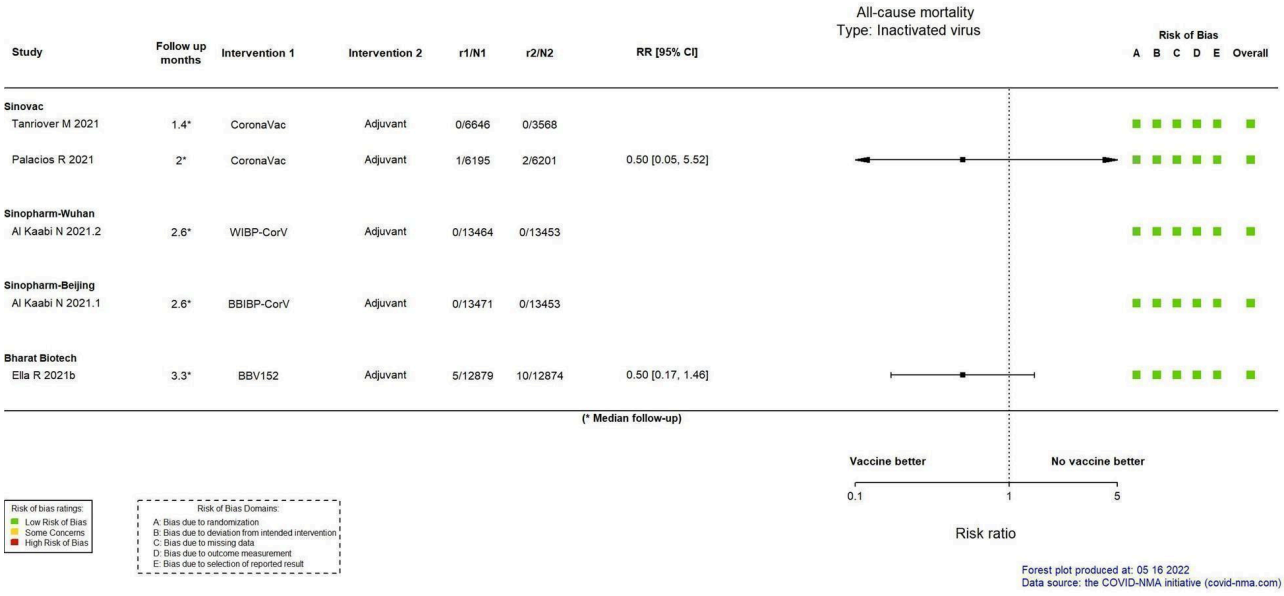


All-cause mortality

This outcome was reported in two trials at 1.4 months (median) to two months (median) follow-up (Palacios 2020; Tanriover 2021).

The evidence is uncertain for an effect of CoronaVac on all-cause mortality compared to adjuvant due to very serious imprecision (RR 0.50, 95% CI 0.05 to 5.52; 2 RCTs, 22,610 participants; I^2 = 32%; low-certainty evidence; Figure 26).

Figure 26. Analysis 3.1.4: inactivated virus vaccine. Outcome: all-cause mortality. Al Kaabi 2021.1 and Al Kaabi N 2021.2 refers to two different comparisons from the same report (Al Kaabi 2021).



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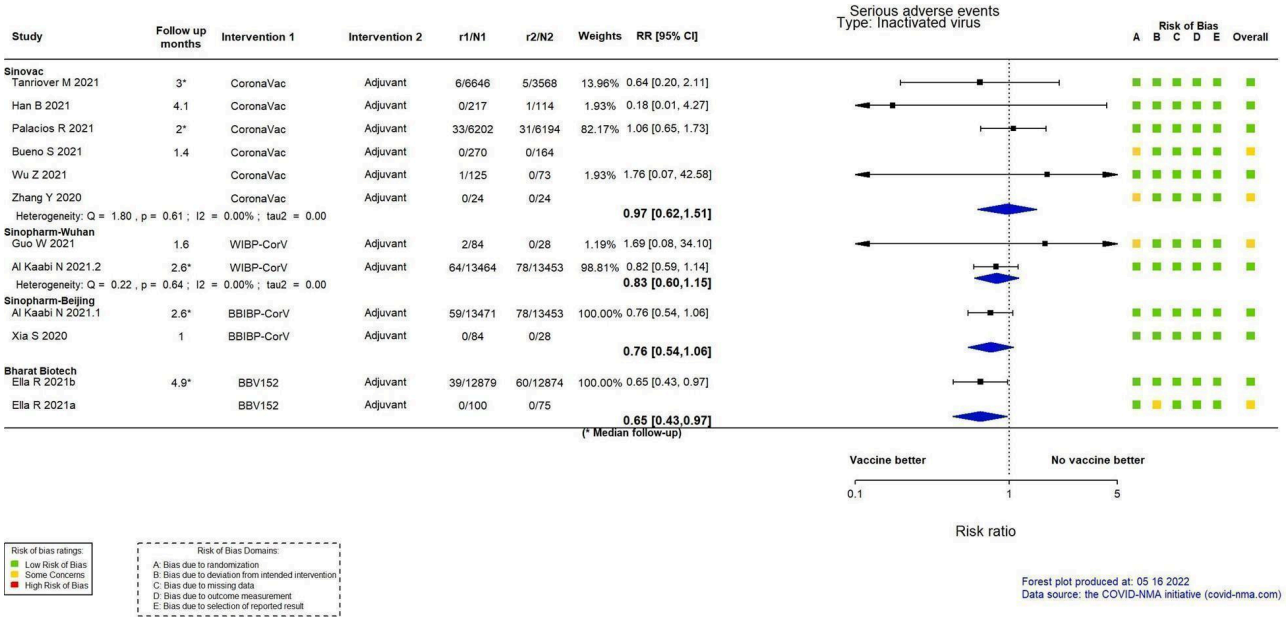
Serious adverse events

Two trials reported this outcome in 482 participants at 1.4 months' follow-up (Bueno 2021; Zhang 2021); there were no events and the trials did not contribute to the effect estimate. Four RCTs contributed to the analysis with follow-up of two months (median) to four months (Han 2021; Palacios 2020; Tanriover 2021; Wu 2021a). The evidence is uncertain for an effect of CoronaVac on SAEs compared to adjuvant due to very serious imprecision (RR 0.97, 95% CI 0.62 to 1.51; 4 RCTs, 23,139 participants; I^2 = 0%; low-certainty evidence; Figure 27).

Figure 27. Analysis 3.1.5: inactivated virus vaccine. Outcome: serious adverse events (SAEs). Han 2021 included only participants 3 to 17 years of age. Wu 2021a included only participants 60 years of age and older. Wu 2021a reports data for phase 1 and 2. Al Kaabi 2021.1 and Al Kaabi N 2021.2 refer to two different comparisons from the same report (Al Kaabi 2021).



Systemic reactogenicity events

Six trials reported this outcome (Bueno 2021; Fadlyana 2021; Palacios 2020; Tanriover 2021; Wu 2021a; Zhang 2021). The evidence is uncertain for an effect of CoronaVac on systemic reactogenicity events compared to adjuvant due to serious inconsistency and imprecision (RR 1.19, 95% CI 1.00 to 1.42; 6 RCTs, 23,966 participants; I^2 = 55%; low-certainty evidence; Figure 28).

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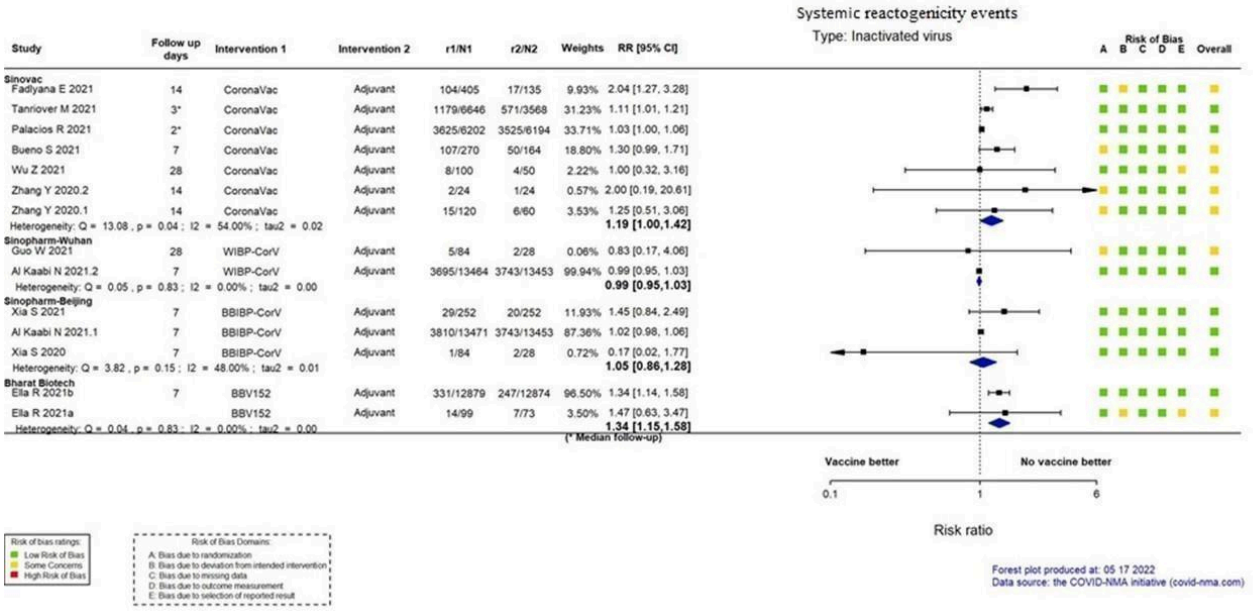
Figure 28. Analysis 3.1.6: inactivated virus vaccine. Outcome: systemic reactogenicity events. Xia S 2021 included only participants 3 to 17 years of age (Xia 2021). Wu Z 2021 included only participants 60 years of age and older (Wu 2021a). Wu Z 2021 reports data for phase 2 (Wu 2021a). Al Kaabi 2021.1 and Al Kaabi N 2021.2 refer to two different comparisons from the same report (Al Kaabi 2021). Zhang 2020.1 and Zhang 2020.2 refers to two different comparisons from the same report (Zhang 2021).



Any adverse event

This outcome was reported in five trials at one month' to three months' (median) follow-up (Han 2021; Palacios 2020; Tanriover 2021; Wu 2021a; Zhang 2021). CoronaVac results in a slight difference in the incidence of any adverse event compared to adjuvant (RR 1.09, 95% CI 1.07 to 1.11; 6 RCTs, 23,367 participants; absolute effect: 48 more with any adverse event per 1000 (from 37 more to 58 more); high-certainty evidence; Figure 29).

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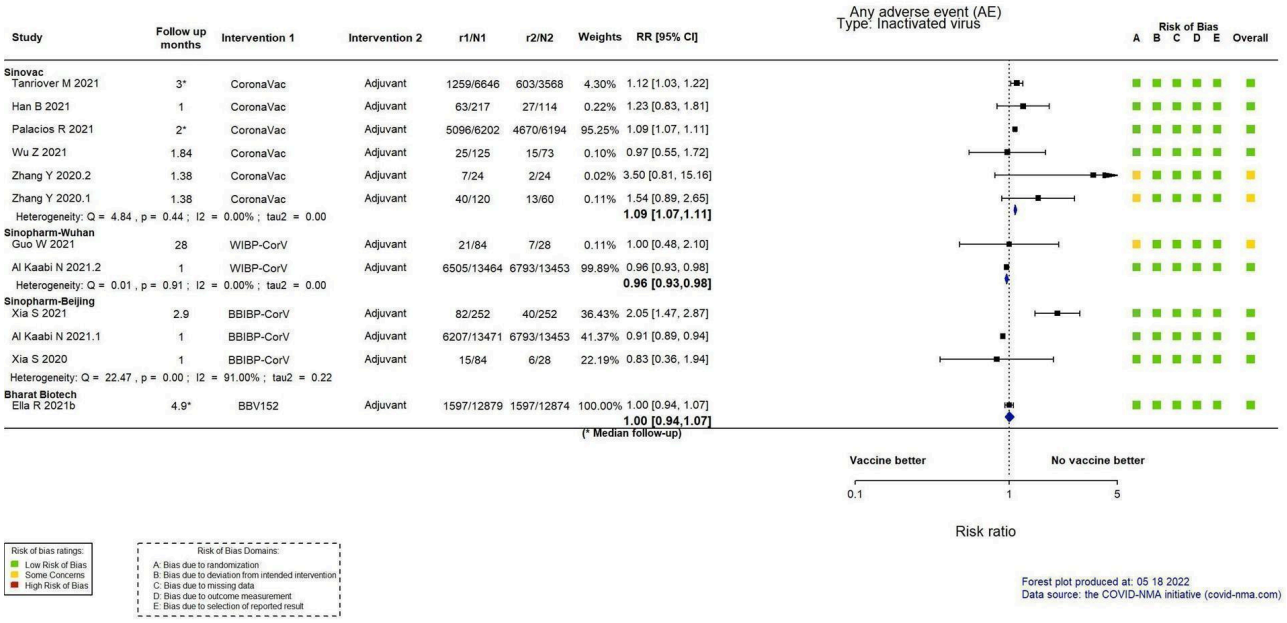
Figure 29. Analysis 3.1.7: inactivated virus vaccine. Outcome: any adverse event (AE). Han B 2021 and Xia 2021 included only participants 3 to 17 years of age (Han 2021; Xia 2021). Wu Z 2021 included only participants 60 years of age and older (Wu 2021a). Wu Z 2021 reports data for phase 1 and 2 (Wu 2021a), Al Kaabi 2021.1 and Al Kaabi N 2021.2 refer to two different comparisons from the same report (Al Kaabi 2021). Zhang 2020.1 and Zhang 2020.2 refers to two different comparisons from the same report (Zhang 2021).



Important outcomes

Immunogenicity outcomes

Five trials reported GMTs of neutralizing and specific antibodies against SARS-COV-2 (Bueno 2021; Fadlyana 2021; Han 2021; Wu 2021a; Zhang 2021), and one trial reported results for cellular immune response (Zhang 2021). Results are detailed in Appendix 11, Appendix 16, and Appendix 20.

Local reactogenicity events

Six trials reported this outcome (Bueno 2021; Fadlyana 2021; Palacios 2020; Tanriover 2021; Wu 2021a; Zhang 2021) CoronaVac results in a slight increase in the occurrence of local reactogenicity events compared to adjuvant (RR 1.76, 95% CI 1.69 to 1.82; 6 RCTs, 23,962 participants; I^2 = 0%; absolute effect: 173 more per 1000 (from 157 more to 187 more); high-certainty evidence; Figure 30).

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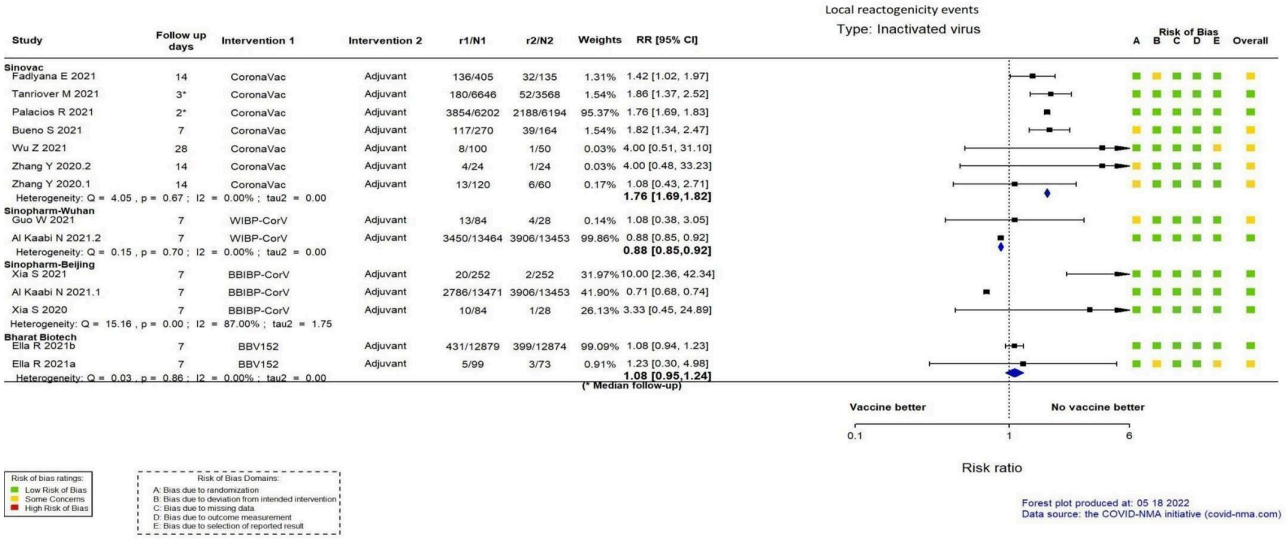
Figure 30. Analysis 3.1.8: inactivated virus vaccine. Outcome: local reactogenicity events. Xia S 2021 included only participants 3 to 17 years of age (Xia 2021). Wu Z 2021 included only participants 60 years of age and older (Wu 2021a). Wu Z 2021 reports data for phase 2 (Wu 2021a). Al Kaabi 2021.1 and Al Kaabi N 2021.2 refer to two different comparisons from the same report (Al Kaabi 2021). Zhang 2020.1 and Zhang 2020.2 refers to two different comparisons from the same report (Zhang 2021).



Incidence of specific safety outcomes

Specific safety outcomes were not consistently reported throughout the included trials: Tanriover 2021 reported number of participants with myocardial infarction and nervous system diseases; Fadlyana 2021 reported the number of participants with venous thrombosis and nervous system diseases; and five trials reported no specific safety outcome of interest (Bueno 2021; Han 2021; Palacios 2020; Wu 2021a; Zhang 2021). Outcomes of interest are summarized in Appendix 12.

Vaccine-enhanced disease

Palacios 2020 reported no vaccine-enhanced disease effect.

WIBP-CorV – Sinopharm-Wuhan versus placebo (adjuvant)

See Summary of findings 9 and table of results in Appendix 22.

We identified and included two trials in the analysis assessing WIBP-CorV. The outcomes 'severe or critical COVID-19 after complete vaccination', 'cellular immune response' and 'incidence of specific safety outcomes' were not reported for this comparison.

Critical outcomes

Confirmed SARS-CoV-2 infection after complete vaccination

This outcome was reported in Al Kaabi 2021. WIBP-CorV results in a reduction in the incidence of confirmed SARS-CoV-2 infection compared to adjuvant at 2.6 months (median) follow-up (VE 64.00%, 95% CI 48.80% to 74.70%; 1 RCT, 25,449 participants; high-certainty evidence; Figure 31).

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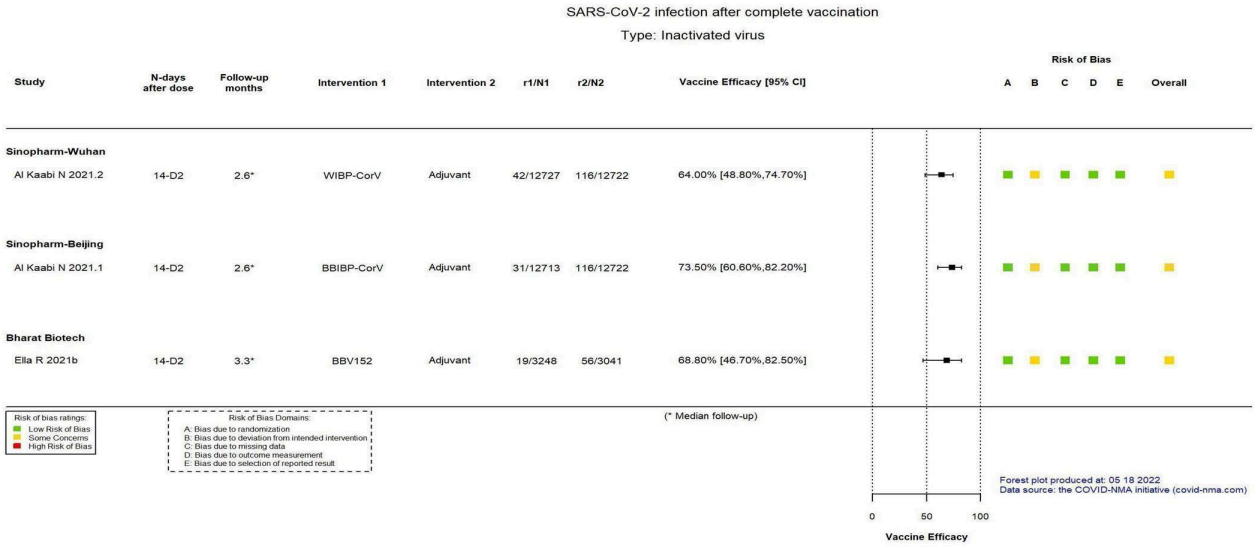
Figure 31. Analysis 3.1.1: inactivated virus vaccine. Outcome: confirmed SARS-CoV-2 infection after complete vaccination. Al Kaabi 2021.1 and Al Kaabi N 2021.2 refer to two different comparisons from the same report (Al Kaabi 2021).



Confirmed symptomatic COVID-19 after complete vaccination

This outcome was reported in Al Kaabi 2021. WIBP-CorV results in a large reduction in the incidence of confirmed symptomatic COVID-19 after complete vaccination compared to adjuvant at 2.6 months (median) follow-up (VE 72.80%, 95% CI 58.10% to 82.40%; 1 RCT, 25,480 participants; high-certainty evidence; Figure 24).

All-cause mortality

This outcome was assessed in one trial (26,917 participants) at 2.6 months (median) follow-up (Al Kaabi 2021). There were zero events in both groups, therefore no effect estimate could be calculated for this outcome (Figure 26).

Serious adverse events

Two trials assessed this outcome (Guo 2021; Al Kaabi 2021). The evidence is uncertain for an effect of WIBP-CorV on SAEs compared to adjuvant at 1.6 months (median) and 2.6 months (median) follow-up due to serious imprecision (RR 0.83, 95% CI 0.60 to 1.15; I^2 = 0%; 2 RCTs, 27,029 participants; low-certainty evidence; Figure 27).

Systemic reactogenicity events

Two trials reported this outcome (Guo 2021; Al Kaabi 2021). WIBP-CorV results in no or little difference in the occurrence of systemic reactogenicity events compared to adjuvant (RR 0.99, 95% CI 0.95 to 1.03; I^2 = 0%; 2 RCTs, 27,029 participants; absolute effect: 3 fewer with systemic reactogenicity events per 1000 (from 14 fewer to 8 more); high-certainty evidence; Figure 28).

Any adverse event

Two trials assessed the outcome (Guo 2021; Al Kaabi 2021). WIBP-CorV results in little difference in the incidence of any adverse event compared to adjuvant at one-month follow-up (RR 0.96, 95% CI 0.93 to 0.98; I^2 = 0%; 2 RCTs, 27,029 participants; absolute effect: 20 fewer with any adverse event per 1000 (from 35 fewer to 10 fewer); high-certainty evidence; Figure 29).

Important outcomes

Immunogenicity outcomes

Two trials reported GMTs of neutralizing and specific antibodies against SARS-COV-2 (Guo 2021; Al Kaabi 2021). Results are reported in Appendix 11 and Appendix 16.

Local reactogenicity events

Two trials reported this outcome (Guo 2021; Al Kaabi 2021). WIBP-CorV results in little difference in the occurrence of local reactogenicity events compared to adjuvant (RR 0.88, 95% CI 0.85 to 0.92; I^2 = 0%; 2 RCTs, 27,029 participants; absolute effect: 35 fewer with local reactogenicity events per 1000 (from 44 fewer to 23 fewer); high-certainty evidence; Figure 30).

Vaccine-enhanced disease

One trial reported no vaccine-enhanced disease effect (Al Kaabi 2021).

BBIBP-CorV – Sinopharm-Beijing versus placebo (adjuvant)

See Summary of findings 10 and table of results in Appendix 23.

We identified and included in the analysis three trials assessing BBIBP-CorV. The outcomes 'severe or critical COVID-19 after complete vaccination', 'cellular immune response' and 'incidence of specific safety outcomes' were not reported for this comparison.

Critical outcomes

Confirmed SARS-CoV-2 infection after complete vaccination

This outcome was reported in one trial (Al Kaabi 2021). BBIBP-CorV results in a large reduction in SARS-CoV-2 infection compared

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to adjuvant (VE 73.50%, 95% CI 60.60% to 82.20%; 1 RCT, 25,435 participants; high-certainty evidence; Figure 31).

Confirmed symptomatic COVID-19 after complete vaccination

This outcome was reported in one trial (Al Kaabi 2021). BBIBP-CorV results in a large reduction in the incidence of confirmed symptomatic COVID-19 after complete vaccination compared to placebo (adjuvant) (VE 78.10%, 95% CI 64.80% to 86.30%; 1 RCT, 25,463 participants; high-certainty evidence; Figure 24).

All-cause mortality

This outcome was assessed in one trial (26,924 participants) (Al Kaabi 2021). There were zero events in both groups, therefore no effect estimate could be calculated for this outcome (Figure 26).

Serious adverse events

One study assessed this outcome in 112 participants (Xia 2020). There were zero events in both groups and the trial did not contribute to the analysis. One trial contributed to the analysis (Al Kaabi 2021). The evidence is uncertain for an effect of BBIBP-CorV on SAEs compared to adjuvant at 2.6 months (median) follow-up (RR 0.76, 95% CI 0.54 to 1.06; 1 RCT, 26,924 participants; low-certainty evidence; Figure 27).

Systemic reactogenicity events

This outcome was reported in three trials (Al Kaabi 2021; Xia 2020; Xia 2021). BBIBP-CorV probably results in no or little difference in the occurrence of systemic reactogenicity events compared to adjuvant (RR 1.05, 95% CI 0.86 to 1.28; 3 RCTs, 27,540 participants; absolute effect: 14 more per 1000 (from 38 fewer to 77 more); moderate-certainty evidence; Figure 28).

Any adverse event

This outcome was reported in three trials (Al Kaabi 2021; Xia 2020; Xia 2021). We decided not to pool the results due to considerable heterogeneity (I^2 = 90%) probably caused by studies assessing participants in different age groups; reported data for participants aged three years to 17 years old. Xia 2021 reported results for 504 participants at 2.9 months' follow-up; the risk of any adverse event in the study was 2.05 (95% CI 1.47 to 2.87). Al Kaabi 2021 reported results for 26,941 participants at one-month follow-up; the risk for any adverse event was 0.91 (95% CI 0.89 to 0.94). Xia 2020 reported results for 112 participants at one-month follow-up; the risk for any adverse event was 0.83 (95% CI 0.36 to 1.94; Figure 29).

Important outcomes

Immunogenicity outcomes

Three trials reported GMTs of neutralizing and specific antibodies against SARS-COV-2 (Al Kaabi 2021; Xia 2020; Xia 2021). Results are reported in Appendix 11 and Appendix 16.

Local reactogenicity events

This outcome was reported in three trials (Al Kaabi 2021; Xia 2020; Xia 2021). We decided not to pool the results due to considerable heterogeneity (I^2 = 90%) probably caused by studies assessing participants in different age groups. Xia 2021 reported results for 504 participants at seven days' follow-up; the risk of local reactogenicity events in the study was 10.00 (95% CI 2.36 to 42.34). Al Kaabi 2021 reported results for 26,924 participants at seven days' follow-up; the risk for local reactogenicity events was 0.71 (95% CI 0.68 to 0.74). Xia 2020 reported results for 112 participants at seven days' follow-up; the risk for local reactogenicity events was 3.33 (95% CI 0.45 to 24.89; Figure 30).

Vaccine-enhanced disease

One trial reported no vaccine-enhanced disease effect (Al Kaabi 2021).

BBV152 – Bharat Biotech versus placebo (adjuvant)

See Summary of findings 11 and table of results in Appendix 24.

We identified and included two trials in the analysis assessing BBV152. The outcome 'vaccine-enhanced disease' was not reported for this comparison.

Critical outcomes

Confirmed SARS-CoV-2 infection after complete vaccination

One trial reported this outcome (Ella 2021b). BBV152 results in a reduction in the incidence of SARS-CoV-2 infections compared to adjuvant at 3.3 months (median) follow-up (VE 68.80%, 95% CI 46.70% to 82.50%; 1 RCT, 6289 participants; high-certainty evidence; Figure 31).

Confirmed symptomatic COVID-19 after complete vaccination

This outcome was reported in one trial (Ella 2021b). BBV152 results in a large reduction in the incidence of confirmed symptomatic COVID-19 after complete vaccination compared to adjuvant at 3.3 months (median) follow-up (VE 77.80%, 95% CI 65.20% to 86.40%; 1 RCT, 16,973 participants; high-certainty evidence; Figure 24).

Severe or critical COVID-19 after complete vaccination

This outcome was reported in one trial at 3.3 months (median) follow-up (Ella 2021b). BBV152 results in a large reduction of severe or critical COVID-19 after complete vaccination compared to adjuvant due to very serious imprecision (VE 93.40%, 95% CI 57.10% to 99.80%; 1 RCT, 16,976 participants; high-certainty evidence; Figure 25).

All-cause mortality

One trial reported this outcome at 3.3 months (median) follow-up (Ella 2021b). The evidence is uncertain for an effect of BBV152 on all-cause mortality compared to adjuvant due to very serious imprecision (RR 0.50, 95% CI 0.17 to 1.46; 1 RCT, 25,753 participants; low-certainty evidence; Figure 26).

Serious adverse events

This outcome was reported in two trials (Ella 2021a; Ella 2021b); Ella 2021b contributed to the analysis. BBV152 results in little or no difference in the incidence of SAEs compared to adjuvant at 4.9 months (median) follow-up (RR 0.65, 95% CI 0.43 to 0.97; 1 RCT, 25,928 participants; absolute effect: 162 fewer per 100,000 (from 264 fewer to 14 fewer); high-certainty evidence; Figure 27).

Systemic reactogenicity events

This outcome was reported in two trials (Ella 2021a; Ella 2021b). BBV152 results in little increase in the occurrence of systemic reactogenicity events compared to adjuvant (RR 1.34, 95% CI 1.15 to 1.58; I^2 = 0%; 2 RCTs, 25,925 participants; absolute effect: 7 more with systemic reactogenicity events per 1000 (from 3 more to 11 more); high-certainty evidence; Figure 28).

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Any adverse event

This outcome was reported in Ella 2021b. BBV152 results in no or little difference in the occurrence of any adverse event compared to adjuvant at 4.9 months (median) follow-up (RR 1.00, 95% CI 0.94 to 1.07; 1 RCT, 25,753 participants; absolute effect: 0 fewer with any adverse event per 1000 (from 7 fewer to 9 more); high-certainty evidence; Figure 29).

Important outcomes

Immunogenicity outcomes

Two trials reported GMTs of neutralizing and specific antibodies against SARS-COV-2 (Ella 2021a; Ella 2021b), and Ella 2021a reported results for cellular immune response. Results are detailed in Appendix 11, Appendix 16 and Appendix 20.

Local reactogenicity events

This outcome was reported in two trials (Ella 2021b; Ella 2021a). BBV152 results in no or little difference in the occurrence of local reactogenicity events compared to adjuvant (RR 1.08, 95% CI 0.95 to 1.24; I^2 = 0%; 2 RCTs, 25,750 participants; absolute effect: 2 more with local reactogenicity events per 1000 (from 2 fewer to 7 more); high-certainty evidence; Figure 30).

Incidence of specific safety outcomes

Specific safety outcomes were not consistently reported throughout the included trials and are summarized in detail in Appendix 12, rather than pooled in a meta-analysis.

Protein subunit vaccines

NVX-CoV2373 – Novavax versus placebo (normal saline)

See Summary of findings 12 and table of results in Appendix 25.

We identified and included five trials in the analysis assessing NVX-CoV2373. The outcomes 'SARS-CoV-2 infection after complete vaccination', 'severe or critical COVID-19 after complete vaccination' and 'cellular immune response' were not reported for this comparison.

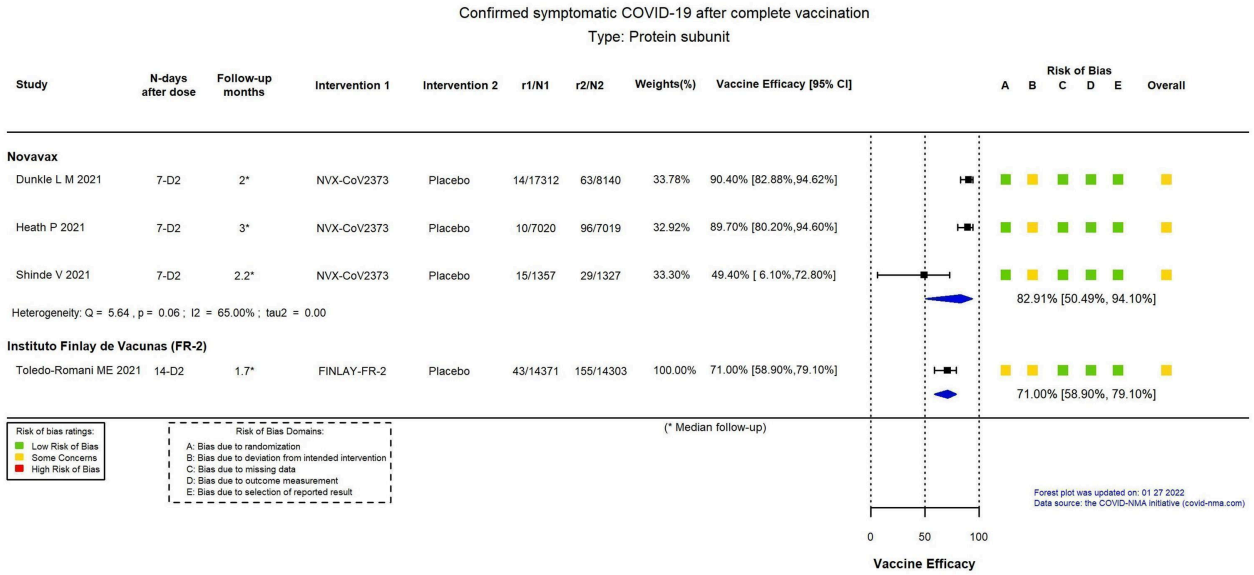
Low-certainty evidence for the efficacy outcomes might be explained by the inclusion of results from a trial conducted in South Africa during a period of high prevalence of the Beta variant (Shinde 2021). Vaccine efficacy against this variant was considerably lower than the efficacy reported in the primary analysis or against the Alpha variant.

Critical outcomes

Confirmed symptomatic COVID-19 after complete vaccination

This outcome was reported in three trials at two months (median) and three months (median) follow-up (Dunkle 2021; Heath 2021; Shinde 2021). NVX-CoV2373 probably results in a large reduction of the incidence of confirmed symptomatic COVID-19 after complete vaccination compared to placebo (VE 82.91%, 95% CI 50.49% to 94.10%; I^2 = 65%; 3 RCTs, 42,175 participants; moderate-certainty evidence; Figure 32).

Figure 32. Analysis 4.1.1: protein subunit vaccine. Outcome: confirmed symptomatic COVID-19 after complete vaccination.



Severe or critical COVID-19 after complete vaccination

This outcome was reported in one trial at two months (median) follow-up (Dunkle 2021). NVX-CoV2373 results in a large reduction of severe or critical COVID-19 after complete vaccination compared to adjuvant due to very serious imprecision (VE 100.00%, 95% CI 86.99% to 100.00%; 1 RCT, 25,452 participants; moderate-certainty evidence; Figure 33).

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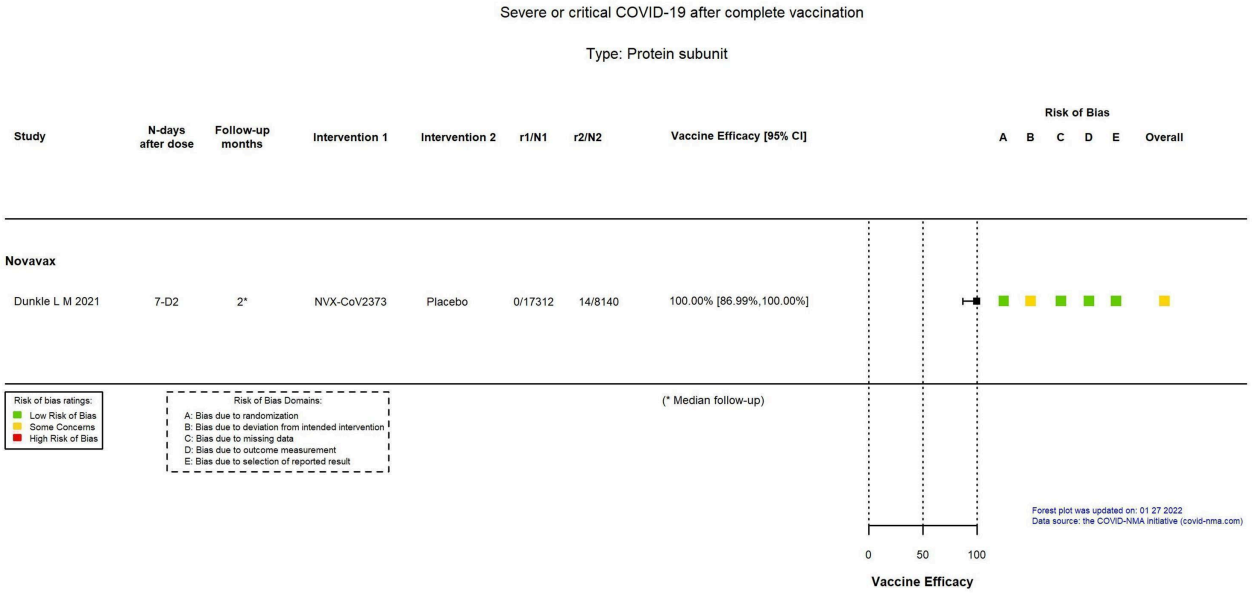
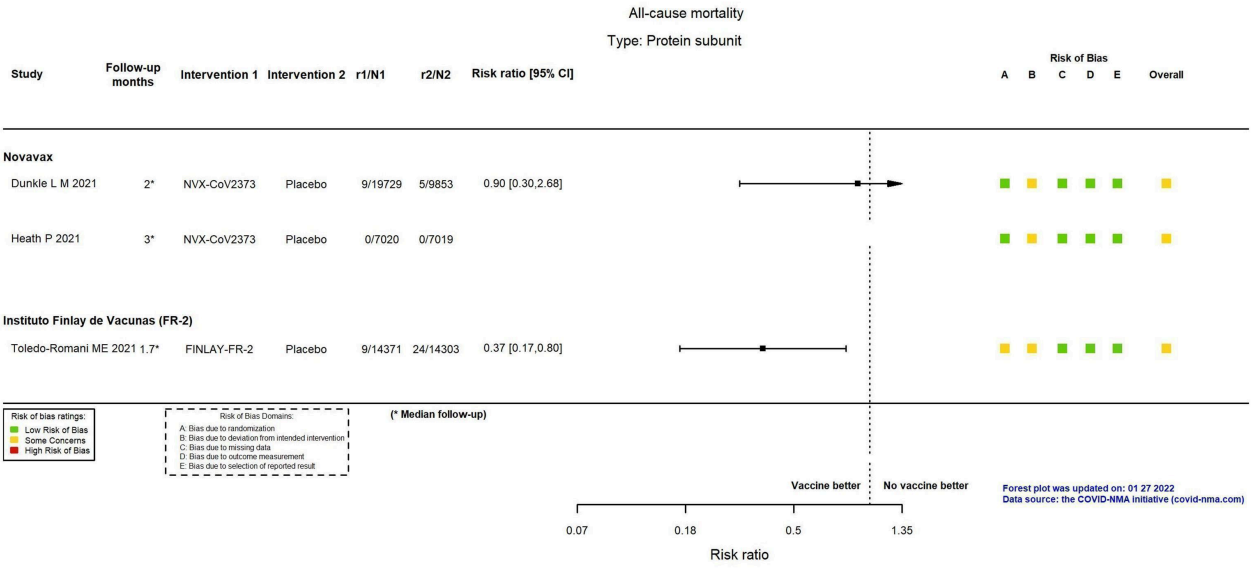
Figure 33. Analysis 4.1.2: protein subunit vaccine. Outcome: severe or critical COVID-19 after complete vaccination.



All-cause mortality

One trial reported this outcome in 14,039 participants at three months (median) follow-up (Heath 2021); there were no events and the trial did not contribute to the effect estimate. Dunkle 2021 contributed to the analysis with follow-up of two months (median); the evidence is uncertain for an effect of NVX-CoV2373 on all-cause mortality compared to placebo due to very serious imprecision (RR 0.90, 95% CI 0.30 to 2.68; 1 RCT, 29,582 participants; low-certainty evidence; Figure 34).

Figure 34. Analysis 4.1.3: protein subunit vaccine. Outcome: all-cause mortality.



Serious adverse events

One trial reported the outcome in 52 participants at 1.15 months' follow-up (Keech 2020); there were no events and the trial did not contribute to the effect estimate. Four trials contributed to the analysis with follow-up of 1.15 months, two months (median), and three months (Dunkle 2021; Formica 2021; Heath 2021; Shinde 2021). The evidence is uncertain for an effect of NVX-CoV2373 on SAEs compared to placebo due to very serious imprecision (RR 0.92, 95% CI 0.74 to 1.14, I^2 = 0%; 4 RCTs, 38,802 participants; low-certainty evidence; Figure 35).

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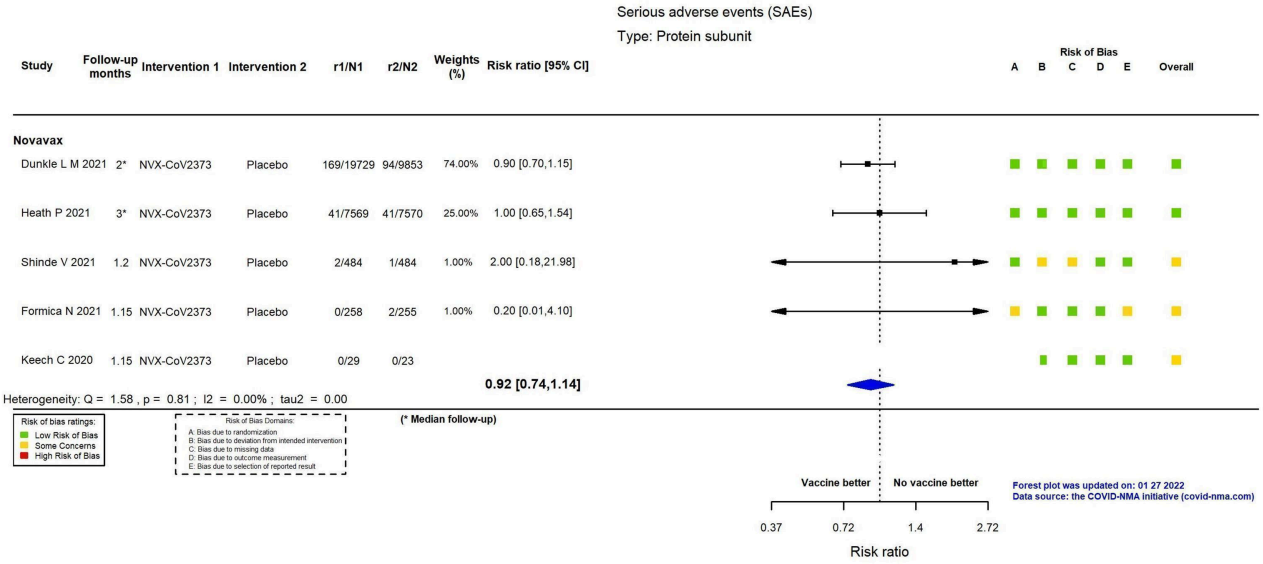
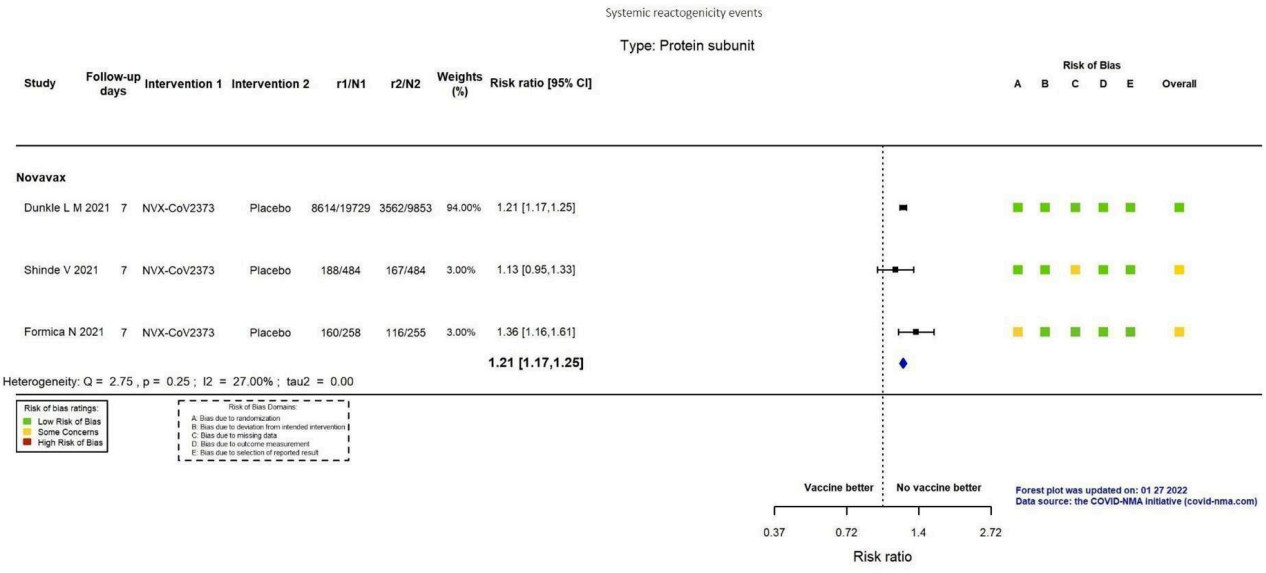
Figure 35. Analysis 4.1.4: protein subunit vaccine. Outcome: serious adverse events (SAEs).



Systemic reactogenicity events

This outcome was reported in three trials (Dunkle 2021; Formica 2021; Shinde 2021). NVX-CoV2373 increases slightly the occurrence of systemic reactogenicity events compared to placebo (RR 1.21, 95% CI 1.17 to 1.25, I^2 = 27%, 3 RCTs, 31,063 participants; absolute effect 76 more per 1000 (from 62 more to 91 more); high-certainty evidence; Figure 36).

Figure 36. Analysis 4.1.5: protein subunit vaccine. Outcome: systemic reactogenicity events.



Any adverse event

This outcome was reported in five trials (Dunkle 2021; Formica 2021; Heath 2021; Keech 2020; Shinde 2021). NVX-CoV2373 probably results in little increase in the incidence of any adverse event compared to placebo at 1.15 months (median) to three months (median) follow-up (RR 1.15, 95% CI 1.05 to 1.26; I^2 = 57%; 5 RCTs, 46,231 participants; absolute effect: 26 more with any adverse event per 1000 (from 9 more to 45 more); moderate-certainty evidence; Figure 37).

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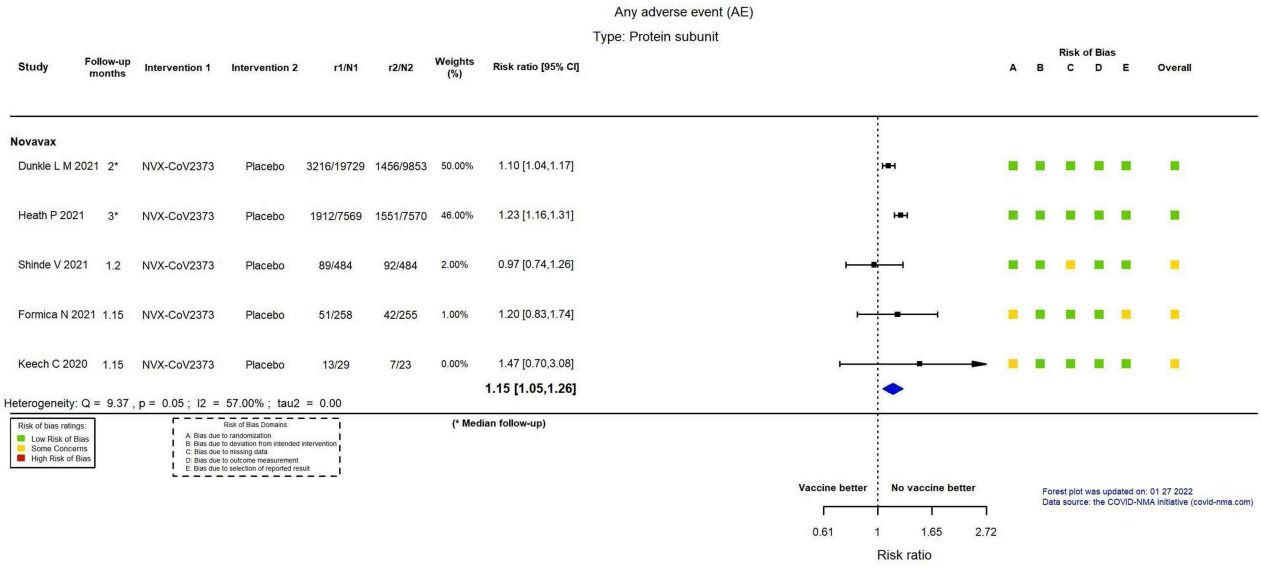
Figure 37. Analysis 4.1.6: protein subunit vaccine. Outcome: any adverse event (AE).



Important outcomes

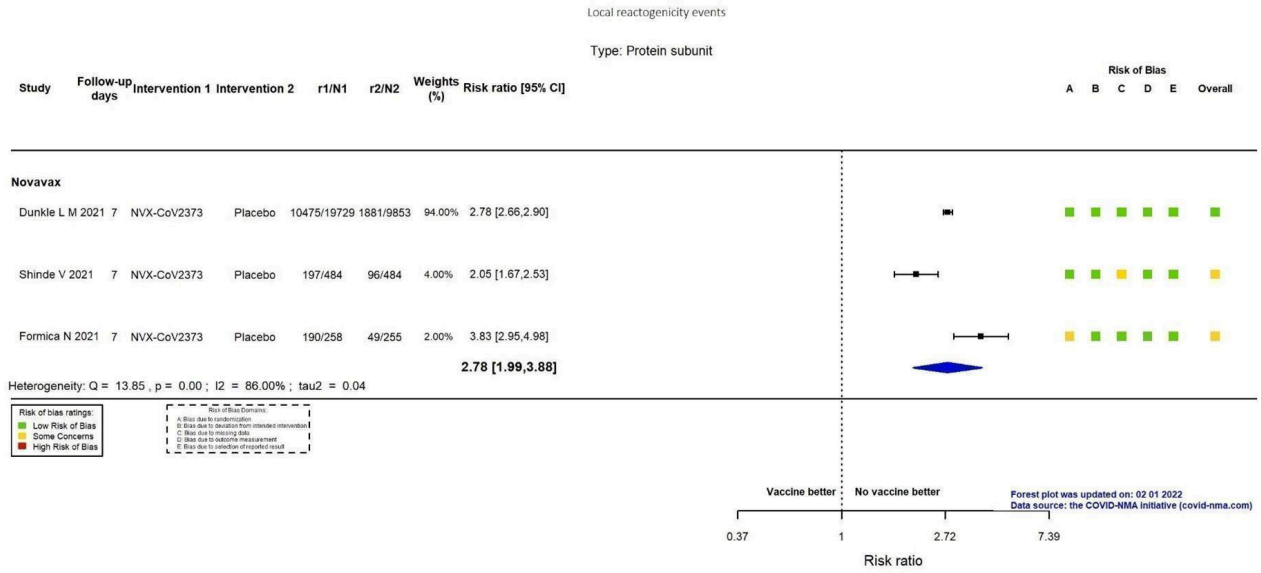
Immunogenetic outcomes

Two trials reported GMTs of specific antibodies against SARS-COV-2 (Formica 2021; Keech 2020), and Keech 2020 reported GMTs of neutralizing antibodies against SARS-COV-2. Results are detailed in Appendix 16 and Appendix 11.

Local reactogenicity events

Three trials reported the outcome (Dunkle 2021; Formica 2021; Shinde 2021). NVX-CoV2373 results in a large increase in local reactogenicity events compared to placebo (RR 2.78, 95% CI 1.99 to 3.88; I^2 = 86%; 3 RCTs, 31,063 participants; absolute effect: 340 more with local reactogenicity events per 1000 (from 189 more to 551 more); high-certainty evidence; Figure 38).

Figure 38. Analysis 4.1.7 Protein subunit vaccine. Outcome: local reactogenicity events



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Incidence of specific safety outcomes

Specific safety outcomes were not consistently reported throughout the included trials: Formica 2021 reported number of participants with venous thrombosis, lymphadenopathy and nervous system diseases; Shinde 2021 reported number of participants with anaemia and nervous system diseases; Heath 2021 reported number of participants with myocardial infarction, thrombocytopaenia and nervous system diseases; and Dunkle 2021 reported on the number of events for pulmonary embolism, stroke, venous thrombosis, thrombocytopenia, haemorrhage, neutropenia, anaemia, lymphadenopathy and nervous system diseases. Outcomes are summarized in detail in Appendix 12.

Vaccine-enhanced disease

One report mentioned this outcome without presenting results (Keech 2020), and two trials reported no vaccine-enhanced disease effect (Dunkle 2021; Heath 2021).

FINLAY-FR-2 – Instituto Finlay de Vacunas versus placebo (adjuvant)

See Summary of findings 13 and table of results in Appendix 26.

We identified and included in the analysis one trial assessing FINLAY-FR-2. The outcomes 'SARS-CoV-2 infection after complete vaccination', 'severe or critical COVID-19 after complete vaccination', 'systemic reactogenicity events', 'incidence of any adverse event', 'incidence of serious adverse events', 'GMT of specific antibodies against SARS-CoV-2', 'GMT of neutralizing antibodies against SARS-CoV-2', 'cellular immune response', 'incidence of specific safety outcomes' and 'vaccine-enhanced disease' were not reported for this comparison.

Critical outcomes

Confirmed symptomatic COVID-19 after complete vaccination

We found one trial reporting this outcome (Toledo-Romani 2021). FINLAY-FR-2 probably results in a large reduction in the incidence of confirmed symptomatic COVID-19 after complete vaccination compared to adjuvant (VE 71.00%, 95% CI 58.90% to 79.10%; 1 RCT, 28,674 participants; moderate-certainty evidence; Figure 32).

All-cause mortality

This outcome was reported in one trial (Toledo-Romani 2021). FINLAY-FR-2 probably results in a reduction of all-cause mortality compared to adjuvant due to serious risk of bias and imprecision (RR 0.37, 95% CI 0.17 to 0.80; 1 RCT, 28,674 participants; absolute effect: 106 fewer per 100,000 (from 139 fewer to 34 fewer) moderate-certainty evidence; Figure 34).

Primary series heterologous vaccination scheme versus homologous vaccination scheme

See Summary of findings 14 and table of results in Appendix 27.

Two publications reported results for three different comparisons involving an RNA-based vaccine (BNT162b2 – BioNtech/Fosun Pharma/Pfizer), non-replicating viral vector vaccine (ChAdOx1 – AstraZeneca/University of Oxford), and inactivated virus vaccine (CoronaVac – Sinovac). More specifically the following schemes were compared (vaccine first dose/vaccine second dose): BNT162b2/ChAdOx1 versus BNT162b2/BNT162b2 (Liu 2021), and ChAdOx1/BNT162b2 versus ChAdOx1/ChAdOx1 (Liu 2021), and CoronaVac/Ad5 versus CoronaVac/CoronaVac (Li 2021a).

The outcomes 'SARS-CoV-2 infection after complete vaccination', 'symptomatic COVID-19 after complete vaccination', 'severe or critical COVID-19', 'all-cause mortality', 'systemic reactogenicity events' and 'vaccine-enhanced disease' were not reported for these comparisons.

Critical outcomes

Serious adverse events

One trial reported this outcome in 101 participants at one-month follow-up for the comparison CoronaVac/Ad5 versus CoronaVac homologous (Li 2021a), and reported zero events in both groups. Liu 2021 reported the outcome in 234 participants for the comparison BNT162b2/ChAdOx1 versus BNT162b2 homologous and also reported zero events in both groups. The same trial reported the outcome for the comparison ChAdOx1/BNT162b2 versus ChAdOx1 homologous. The evidence is uncertain for an effect of ChAdOx1/BNT162b2 on SAEs compared to ChAdOx1/ChAdOx1 due to serious risk of bias, inconsistency and imprecision (RR 0.34, 95% CI 0.01 to 8.17; 1 RCT, 229 participants; very low-certainty evidence; Figure 39).

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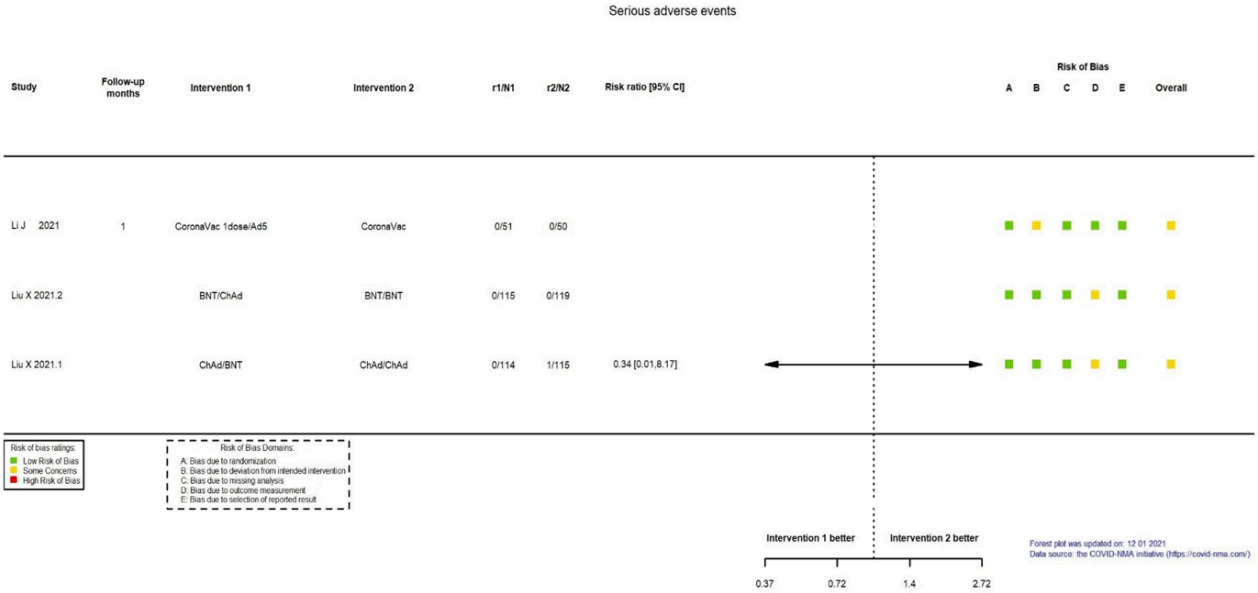
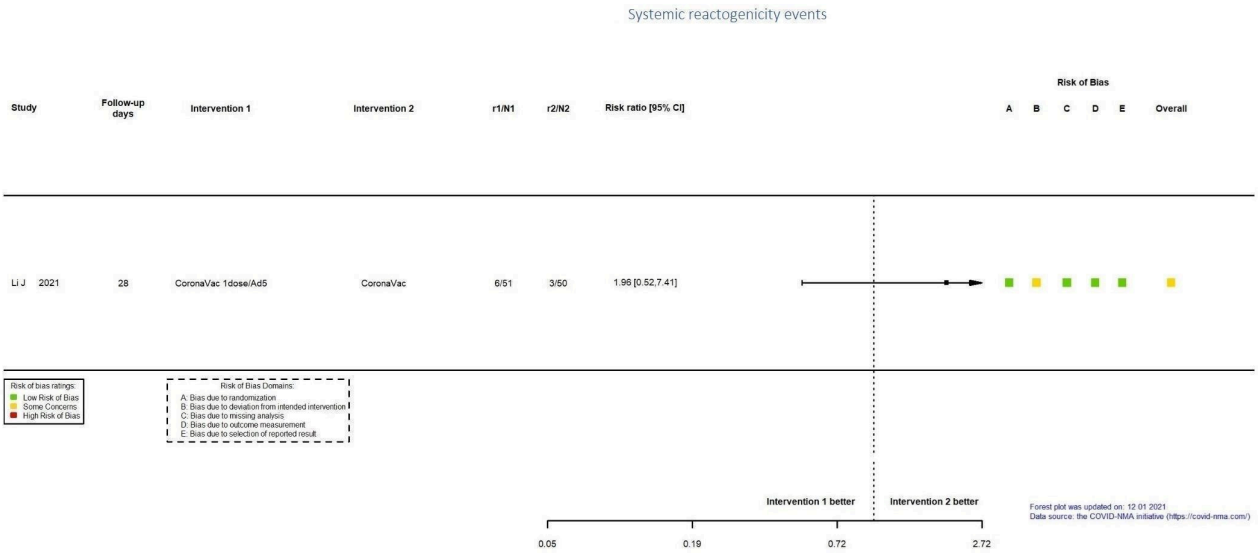
Figure 39. Analysis 5.1.1: heterologous vaccination scheme versus homologous vaccination scheme. Outcome: serious adverse events (SAEs). Liu X 2021.1 and Liu X 2021.2 are different comparisons for the same report (Liu 2021).



Systemic reactogenicity events

There was one comparison with results for this outcome (Li 2021a). The evidence is uncertain for an effect of CoronaVac/Ad5 on the incidence of systemic reactogenicity events compared to CoronaVac/CoronaVac due to very serious imprecision (RR 1.96, 95% CI 0.52 to 7.41; 1 RCT, 101 participants; low-certainty evidence; Figure 40).

Figure 40. Analysis 5.1.2: heterologous vaccination scheme versus homologous vaccination scheme. Outcome: systemic reactogenicity events.



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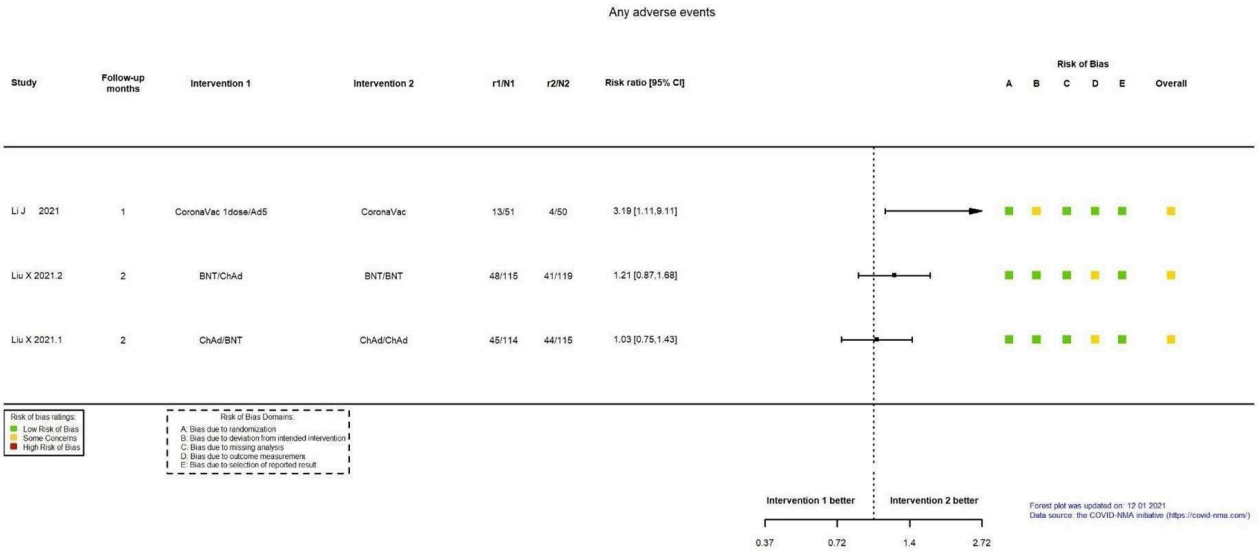
Any adverse event

Two trials reported any adverse event on three different comparisons (Li 2021a; Liu 2021). CoronaVac/Ad5 versus CoronaVac homologous at 1-month follow-up (RR 3.19, 95% CI 1.11 to 9.11), BNT162b2/ChAdOx1 versus BNT162b2 homologous at two months' follow-up (RR 1.21, 95% CI 0.87 to 1.68) and ChAdOx1/BNT162b2 versus ChAdOx1 homologous at 2 months' follow-up (RR 1.03, 95% CI 0.75 to 1.43). The evidence is very uncertain about the effect of heterologous schemes on the incidence of any adverse event compared to homologous schemes due to serious risk of bias, inconsistency and imprecision (Figure 41).

Figure 41. Analysis 5.1.3: heterologous vaccination scheme versus homologous vaccination scheme. Outcome: any adverse event (AE). Liu 2021 included only participants 50 years of age or older. Liu X 2021.1 and Liu X 2021.2 are different comparisons for the same report (Liu 2021).



Important outcomes

Immunogenicity outcomes

Li 2021a reported that the heterologous schedule CoronaVac/Ad5 elicited higher levels of specific antibodies against SARS-COV-2 (GMR 6.11, 95% CI 3.90 to 9.57) and neutralizing antibodies against SARS-COV-2 (GMR 4.25, 95% CI 2.63 to 6.86) compared to the homologous schedule CoronaVac/CoronaVac (Appendix 16 and Appendix 11).

Liu 2021 reported this outcome for two different comparisons. The outcome was measured using IFN-γ ELISpot 28 days after the administration of the second dose.

The heterologous schedule ChAdOx1/BNT162b2 elicited a larger immune cellular response compared to the homologous schedule ChAdOx1/ChAdOx1 (GMR of number of spot-forming cells (SFCs) per million peripheral blood mononuclear cell (PBMC)) 3.9 (95% CI 2.9 to 5.3)).

The GMR of SFCs per million PBMCs was 1.2 (95% CI 0.87 to 1.7) for the comparison of the heterologous schedule BNT162b2/ChAdOx to the homologous schedule BNT162b2/BNT162b2 (Appendix 20).

Local reactogenicity events

One trial reported this outcome (Li 2021a). The heterologous schedule (CoronaVac/Ad5) probably results in a large increase in the number of local reactogenicity events compared to the homologous schedule (CoronaVac/CoronaVac) (RR 11.76, 95% CI 1.59 to 87.14; 1 RCT, 101 participants; absolute effect: 215 more with local reactogenicity events per 1000 (from 12 more to 1000 more); low-certainty evidence; Figure 42).

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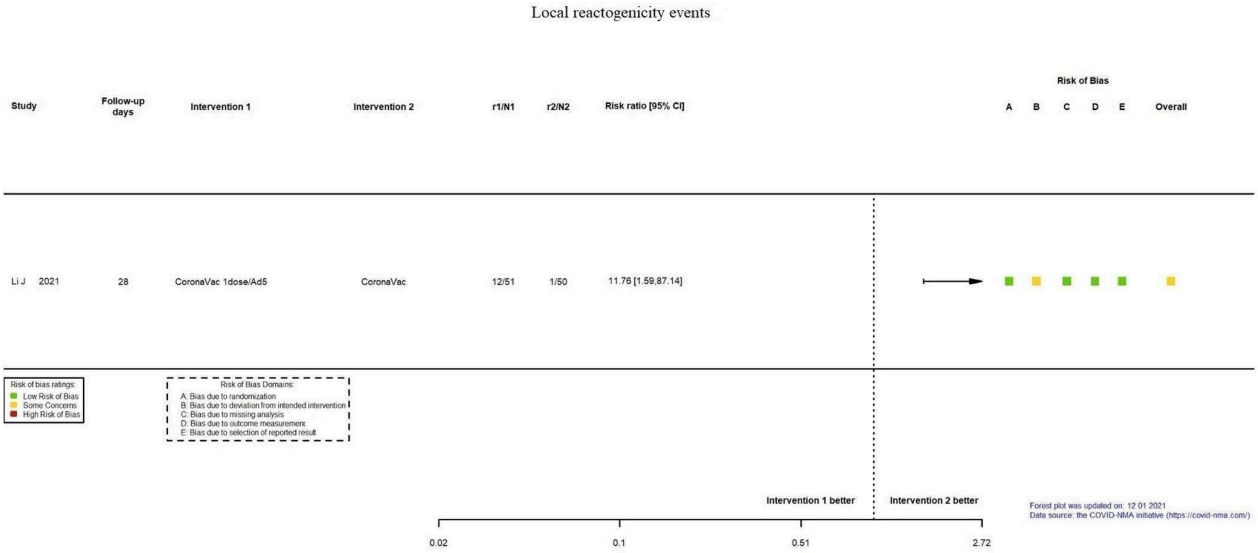
Figure 42. Analysis 5.1.4: heterologous vaccination scheme versus homologous vaccination scheme. Outcome: local reactogenicity events.



Incidence of specific safety outcomes

Specific safety outcomes were not consistently reported throughout the included trials. Two trials reported on the number of participants with venous thrombosis (Li 2021a; Liu 2021). Outcomes are summarized in detail in Appendix 12.

Boosters

Homologous or heterologous booster versus placebo/no booster

See Summary of findings 15 and table of results in Appendix 28.

We identified and included two trials in the analysis (Hall 2021; Toledo-Romani 2021). Hall 2021 included only kidney transplant recipient participants; in our judgement results from this trial are not generally applicable.

mRNA-1273 booster versus placebo (normal saline)

Hall 2021 compared a booster dose of mRNA-1273 to placebo after complete vaccination of mRNA-1273 in kidney transplant recipients. They reported three outcomes of interest.

Systemic reactogenicity events

Follow-up was seven days, starting after injection of the booster dose. There were 11 systemic reactogenicity events in the intervention arm (60 participants) compared to six in the control arm (59 participants). We assessed the overall risk of bias for the outcome to be low.

The evidence is uncertain for an effect of mRNA-1273 booster on the incidence of systemic reactogenicity events compared to placebo due to serious imprecision (RR 1.80, 95% CI 0.71 to 4.56; 1 RCT, 119 participants; low-certainty evidence; Figure 43).

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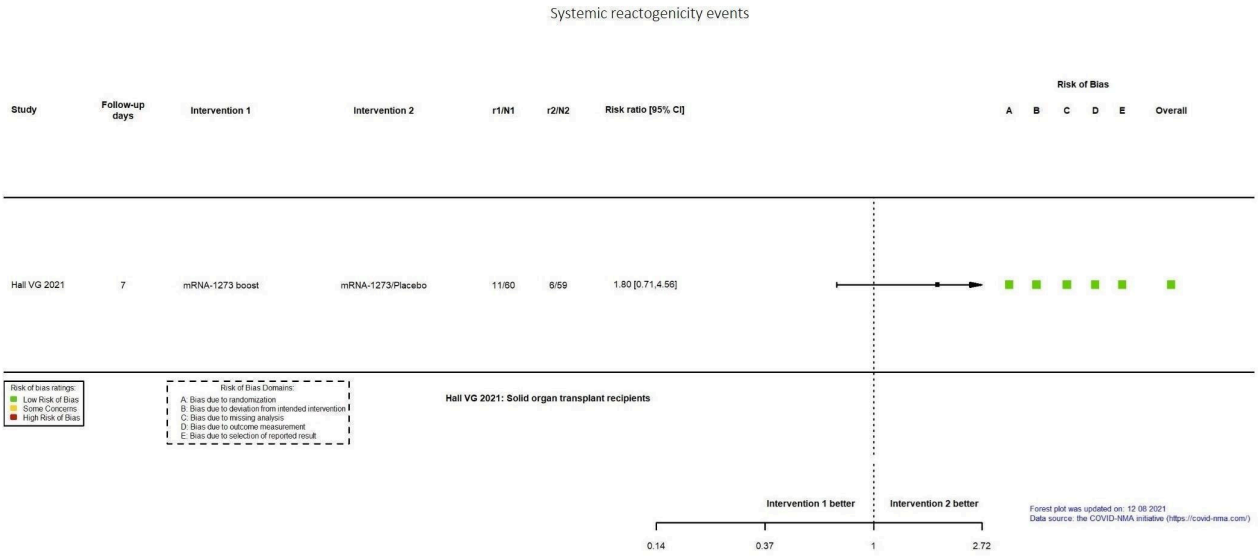
Figure 43. Analysis 6.1.2: booster versus placebo/no booster. Outcome: systemic reactogenicity events.



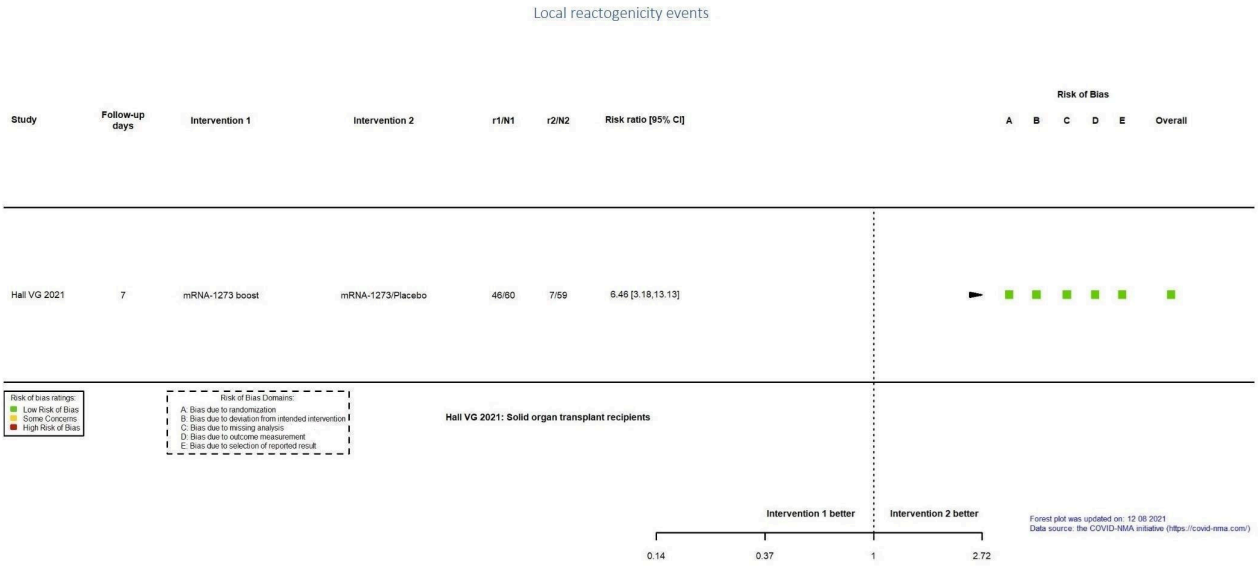
Immunogenicity outcomes

One trial reported results for cellular immune response (Hall 2021). The outcome was measured using intracellular cytokine staining 28 days after the administration of the booster or placebo. The median CD4+ T cells per million was higher in the booster arm than in the placebo arm (432 versus 67 cells per 100 CD4+ T cells; 95% CI for the between-group difference, 46 to 986; Appendix 20).

Local reactogenicity events

The follow-up period was seven days starting after the injection of the booster dose. There were 46 local reactogenicity events in the intervention arm (N = 60) compared to seven in the control arm (N = 59). We assessed the overall risk of bias for the outcome to be low. A-1273 booster probably results in a large increase in the number of local reactogenicity events compared to placebo (RR 6.46, 95% CI 3.18 to 13.13; 1 RCT, 119 participants; absolute effect: 648 more local adverse event per 1000 (from 259 more to 1000 more); moderate-certainty evidence; Figure 44).

Figure 44. Analysis 6.1.3: booster versus placebo/no booster. Outcome: local reactogenicity events.



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FINLAY-FR-1 booster versus no booster dose

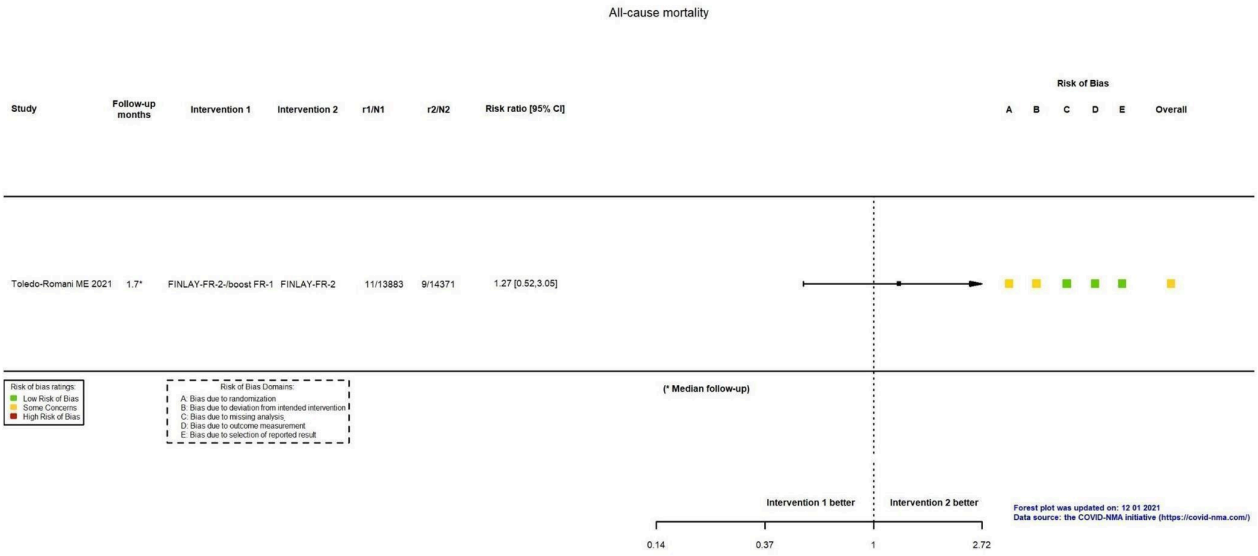
All-cause mortality

Toledo-Romani 2021 compared a booster dose of FINLAY-FR-1 to no booster dose after complete vaccination of FINLAY-FR-2 in adults; only all-cause mortality with a median follow-up of 1.7 months was reported.

There were 11 deaths in the intervention arm (of 13,883 participants) compared to nine in the control arm (of 14,371 participants). We assessed the overall risk of bias for the outcome to have some concerns due to lack of information about allocation concealment and the use of per-protocol analysis.

The evidence is very uncertain about the effect of the booster dose of FR-1 compared to adjuvant due to serious risk of bias and very serious imprecision (RR 1.27, 95% CI 0.52 to 3.05; 1 RCT, 28,254 participants; very low-certainty evidence; Figure 45).

Figure 45. Analysis 6.1.1: booster versus placebo/no booster. Outcome: all-cause mortality.



Homologous booster versus heterologous booster

We identified four trials for this comparison (Bonelli 2021; Li 2021a; Mok 2021; Sablerolles 2021). Of note, in all trials specific safety outcomes were not consistently reported; these are summarized in Appendix 9.

BNT162b2 or mRNA-1273 with homologous booster versus heterologous ChAdOx1 booster

One trial compared a homologous booster dose of BNT162b2 or mRNA-1273 to a booster dose of ChAdOx1 in immunocompromized adults under current rituximab therapy (Bonelli 2021). They only reported on two outcomes of interest.

Immunogenicity outcomes

Bonelli 2021 reported results for cellular immune response. The outcome was measured using IFN-γ ELISpot seven days after the administration of the booster dose. The median interquartile range (IQR) number of SFCs per million PBMCs was 459 (133 to 722) in the heterologous booster arm versus 305 (717 to 416) in the homologous booster arm (Appendix 20).

Local reactogenicity events

Follow-up was two days starting after the injection of the booster dose. There were fewer local reactogenicity events in the ChAdOx1 heterologous booster arm (8/27) compared to the homologous booster arm (16/28) (RR 0.52, 95% CI 0.27 to 1.01). We assessed the overall risk of bias for the outcome to have some concerns due to lack of information about allocation concealment, missingness of outcome data, unclear blinding which could have influenced the measurement of the outcome, and no information on whether the outcome was analyzed as prespecified (Figure 46).

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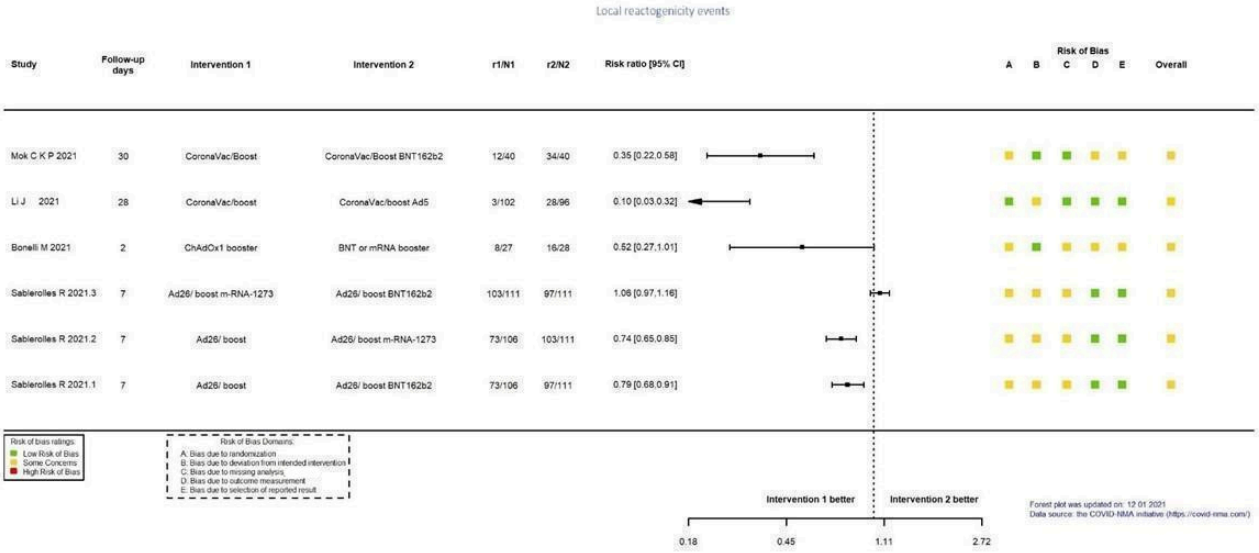
Figure 46. Analysis 6.2.4: homologous booster versus heterologous booster. Outcome: local reactogenicity events. Bonelli 2021 included only participants under current Rituximab therapy.



Incidence of specific safety outcomes

Bonelli 2021 reported on the number of participants with thrombocytopaenia and nervous system diseases; details are in Appendix 12.

Ad26.COV2.S with homologous booster versus heterologous mRNA-1273 booster

One trial compared a homologous booster dose of Ad26.COV2.S to a booster dose of mRNA-1273 in healthcare workers (Sablerolles 2021). They only reported on three outcomes of interest.

Systemic reactogenicity events

Follow-up was seven days starting after the injection of the booster dose. There were fewer systemic reactogenicity events in the homologous booster arm (62/106) compared to the mRNA-1273 booster arm (84/111) (RR 0.77, 95% CI 0.64 to 0.94). We assessed the overall risk of bias for the outcome to have some concerns due to lack of information on allocation concealment, use of per-protocol analysis and missing outcome data (Figure 47).

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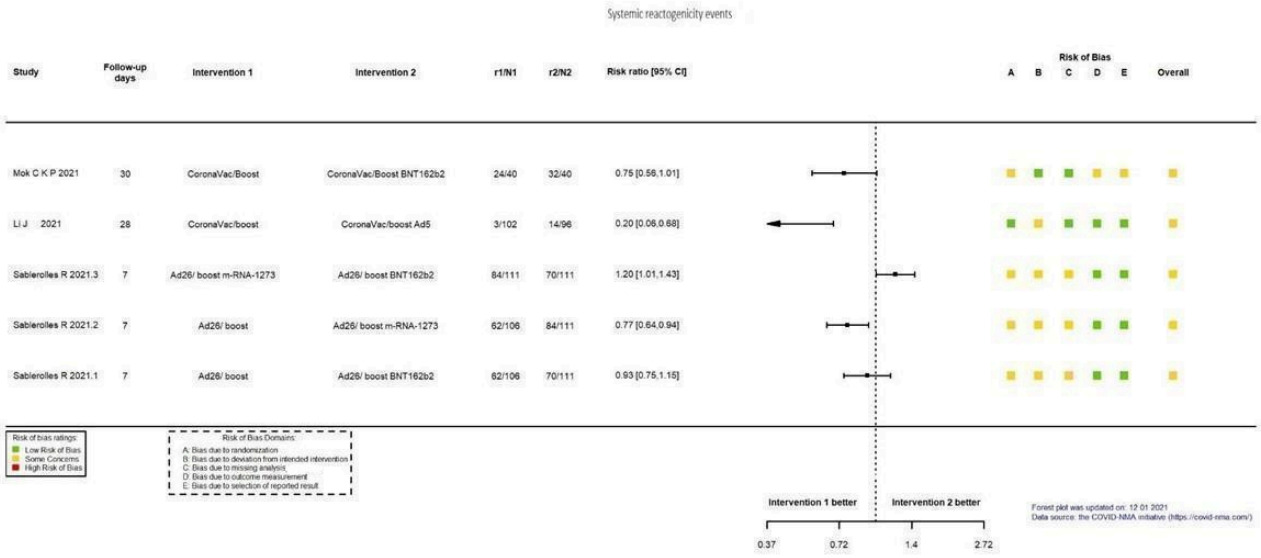
Figure 47. Analysis 6.2.2: homologous booster versus heterologous booster. Outcome: systemic reactogenicity events.



Immunogenicity outcomes

Sablerolles 2021 reported results for cellular immune response. The proportion of responders was measured using IFN-y release assay (cut-off is 0.15 IU/mL) 28 days after the administration of the booster dose. The proportion of responders was lower in the homologous booster arm (32/44; 72.7%) than in the heterologous booster arm (44/48; 91.7%) (RR 0.79, 95% CI 0.64 to 0.96; Appendix 20).

Local reactogenicity events

Follow-up was seven days starting after the injection of the booster dose. There were fewer local reactogenicity events in the homologous booster arm (73/106) compared to the mRNA-1273 booster arm (103/111) (RR 0.74, 95% CI 0.65 to 0.85). We assessed the overall risk of bias for the outcome to have some concerns due to lack of information on allocation concealment, use of per-protocol analysis and missing outcome data (Figure 46).

Ad26.COV2.S with homologous booster versus heterologous BNT162b2 booster

Sablerolles 2021 assessed complete vaccination of Ad26.COV2.S with a homologous booster dose of Ad26.COV2.S versus a heterologous booster dose of BNT162b2 in healthcare workers. They reported on three outcomes of interest.

Systemic reactogenicity events

Follow-up was seven days starting after the injection of the booster dose. There were 62/106 systemic reactogenicity events in the homologous booster arm compared to 70/111 in the BNT162b2 booster arm (RR 0.93, 95% CI 0.75 to 1.15). We assessed the overall risk of bias for the outcome to have some concerns due to lack of information on allocation concealment, use of per-protocol analysis and missing outcome data (Figure 47).

Immunogenicity outcomes

Sablerolles 2021 reported results for cellular immune response. The proportion of responders was measured using IFN-y release assay (cut-off is 0.15 IU/mL) 28 days after the administration of the booster dose. The response rate was lower in the homologous booster arm (32/44; 72.7%) than in the heterologous booster arm (43/47; 91.5%) (RR 0.79, 95% CI 0.65 to 0.97; Appendix 20).

Local reactogenicity events

Follow-up was seven days starting after the injection of the booster dose. There were fewer local reactogenicity events in the homologous booster arm (73/106) compared to the BNT162b2 booster arm (97/111) (RR 0.79, 95% CI 0.66 to 0.91). We assessed the overall risk of bias for the outcome to have some concerns due to lack of information on allocation concealment, use of per-protocol analysis and missing outcome data (Figure 46).

CoronaVac with homologous booster versus heterologous Ad5 booster

One trial compared a complete vaccination of CoronaVac with a homologous booster dose of CoronaVac to a heterologous booster dose of Ad5 in healthy adults (Li 2021a). They reported five outcomes of interest.

Serious adverse events

Zero SAEs were reported in both groups (Figure 48).

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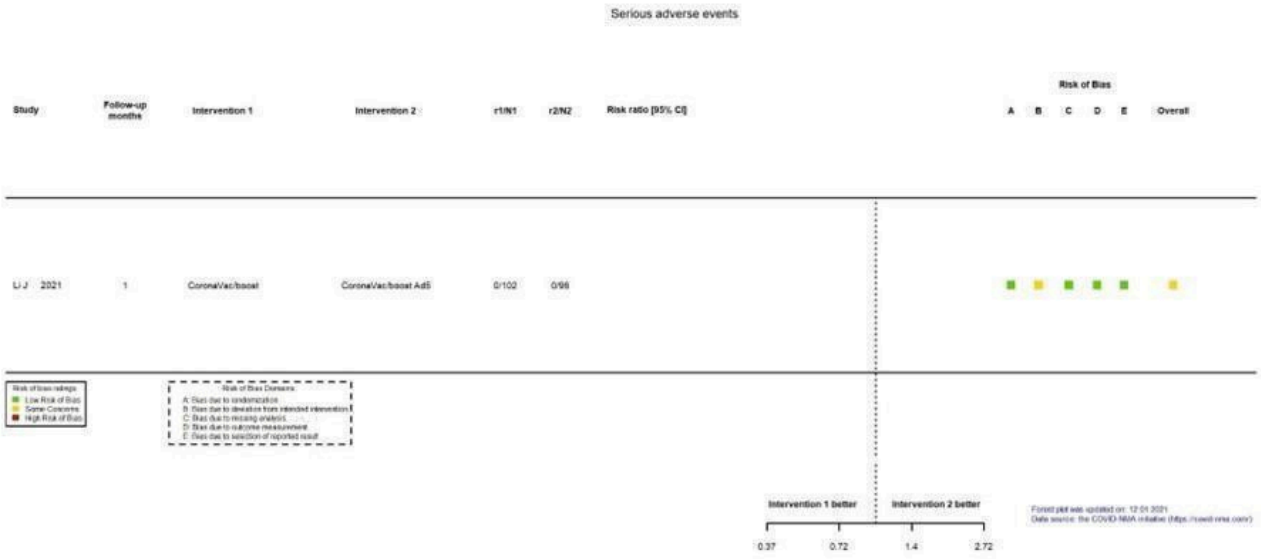
Figure 48. Analysis 6.2.1: homologous booster versus heterologous booster. Outcome: serious adverse events.



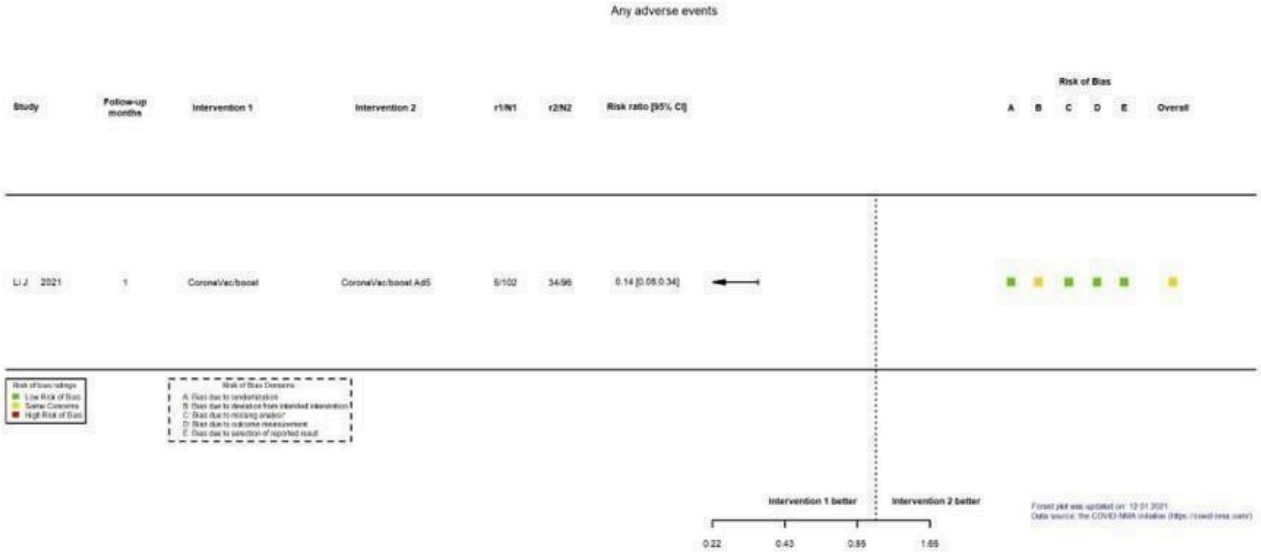
Systemic reactogenicity events

Follow-up was one month starting after the injection of the booster dose. There were fewer systemic reactogenicity events in the homologous booster arm (3/102) compared to the Ad5 booster arm (14/96) (RR 0.20, 95% CI 0.06 to 0.68). We assessed the overall risk of bias for the outcome to have some concerns due to the use of per-protocol analysis (Figure 47).

Any adverse event

Follow-up was one month starting after the injection of the booster dose. There were fewer adverse events in the homologous booster arm (5/102) compared to the Ad5 booster arm (34/96) (RR 0.14, 95% CI 0.06 to 0.34). We assessed the overall risk of bias for the outcome to have some concerns due to the use of per-protocol analysis (Figure 49).

Figure 49. Analysis 6.2.3: homologous booster versus heterologous booster. Outcome: any adverse event.



Immunogenicity outcomes

Li 2021a reported that the heterologous booster CoronaVac/Ad5 elicited higher levels of specific antibodies against SARS-COV-2 (GMR 8.37, 95% CI 6.52 to 10.75) and neutralizing antibodies against SARS-COV-2 (GMR 5.87, 95% CI 4.64 to 7.43) compared

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to the homologous booster CoronaVac/CoronaVac (Appendix 16; Appendix 11).

Local reactogenicity events

Follow-up was one month starting after the injection of the booster dose. There were fewer local reactogenicity events in the homologous booster arm (3/102) compared to the Ad5 booster arm (28/96) (RR 0.10, 95% CI 0.03 to 0.32). We assessed the overall risk of bias for the outcome to have some concerns due to the use of per-protocol analysis (Figure 46).

CoronaVac with a homologous booster versus heterologous BNT162b2 booster

One trial compared complete vaccination of CoronaVac with a homologous booster dose of CoronaVac to a heterologous booster dose of BNT162b2 in adults with low-immune response against SARS-CoV-2 after complete vaccination of CoronaVac (Mok 2021). They reported two outcomes of interest.

Systemic reactogenicity events

Follow-up was one month starting after the injection of the booster dose. There were fewer systemic reactogenicity events in the homologous booster arm (24/40) compared to the BNT162b2 booster arm (32/40) (RR 0.75, 95% CI 0.56 to 1.01). We assessed the overall risk of bias for the outcome to have some concerns due to lack of information on allocation concealment, unclear blinding which could have influenced the measurement of the outcome, and the outcome not being prespecified (Figure 47).

Local reactogenicity events

Follow-up was one month starting after the injection of the booster dose. There were fewer local reactogenicity events in the homologous booster arm (12/40) compared to the BNT162b2 booster arm (34/40) (RR 0.35, 95% CI 0.22 to 0.58). We assessed the overall risk of bias for the outcome to have some concerns due to lack of information on allocation concealment, unclear blinding which could have influenced the measurement of the outcome, and the outcome not being prespecified (Figure 46).

Heterologous booster versus heterologous booster

Ad26.COV2.S with mRNA-1273 booster versus Ad26.COV2.S with BNT162b2 booster

One trial compared mRNA-1273 booster to BNT162b2 booster in healthcare workers vaccinated with Ad26.COV2.S (Sablerolles 2021). They reported on three outcomes of interest.

Systemic reactogenicity events

Follow-up was seven days starting after the injection of the booster dose. There were more systemic reactogenicity events in the mRNA-1273 booster arm (84/111) compared to the BNT162b2 booster arm (70/111) (RR 1.20, 95% CI 1.01 to 1.43). We assessed the overall risk of bias for the outcome to have some concerns due to lack of information on allocation concealment, use of per-protocol analysis, and missing outcome data (Figure 47).

Immunogenicity outcomes

Sablerolles 2021 reported results for cellular immune response. The proportion of responders was measured using IFN-γ release assay (cut-off is 0.15 IU/mL) 28 days after the administration of the booster dose. The number of responders was similar in the mRNA-1273 booster arm (44/48; 91.7%) compared to the BNT162b2 booster arm (43/47; 91.5%) (RR 1.00, 95% CI 0.88 to 1.13; Appendix 20).

Local reactogenicity events

Follow-up was seven days starting after the injection of the booster dose. There were 103/111 participants with local reactogenicity events in the mRNA-1273 booster arm compared to 97/111 in the BNT162b2 booster arm (RR 1.06, 95% CI 0.97 to 1.16). We assessed the overall risk of bias for the outcome to have some concerns due to lack of information on allocation concealment, use of per-protocol analysis, and missing outcome data (Figure 46).

Effects of the intervention on variants of concern

Given that the prevalence of more than one variant in the same population changes and shifts over time, it is to be expected that most of the trials, which collect data over several months, reflect the heterogeneity of COVID-19 variants in their sample. However, among our included studies, 10 did report vaccine efficacy on confirmed symptomatic COVID-19 after complete vaccination against four variants of concern: Alpha (Dunkle 2021; Emary 2021; Heath 2021; Kremsner 2021), Beta (Madhi 2021b; Sadoff 2021b; Shinde 2021; Thomas 2021), Gamma (Clemens 2021; Kremsner 2021), and Delta (Ella 2021b). No study had yet reported data regarding the Omicron variant at the time of the data cut-off (5 November 2021).

We considered the direct evidence when study reports provided evidence on a sequenced sample. When sequencing was not performed, we extrapolated the exposure to variants from the prevalence in the study setting.

Alpha variant (B.1.1.7)

Vaccine efficacy against the Alpha variant was reported in three trials, assessing three different vaccines. All cases of the Alpha variant were detected with genome sequencing. Of note, Emary 2021 includes only participants of the COV002 trial (Voysey 2021a).

Reported vaccine efficacy on confirmed symptomatic COVID-19 after complete vaccination was 55.10%, 95% CI 23.50% to 73.60% for CVnCoV (Kremsner 2021); 70.40%, 95% CI 43.60% to 84.50% for ChAdOx1 (Emary 2021); and for NVX-CoV2373 was 86.30%, 95% CI 71.30% to 93.50% (Heath 2021) and 93.60%, 95% CI 81.70% to 97.80% (Dunkle 2021) (Figure 50).

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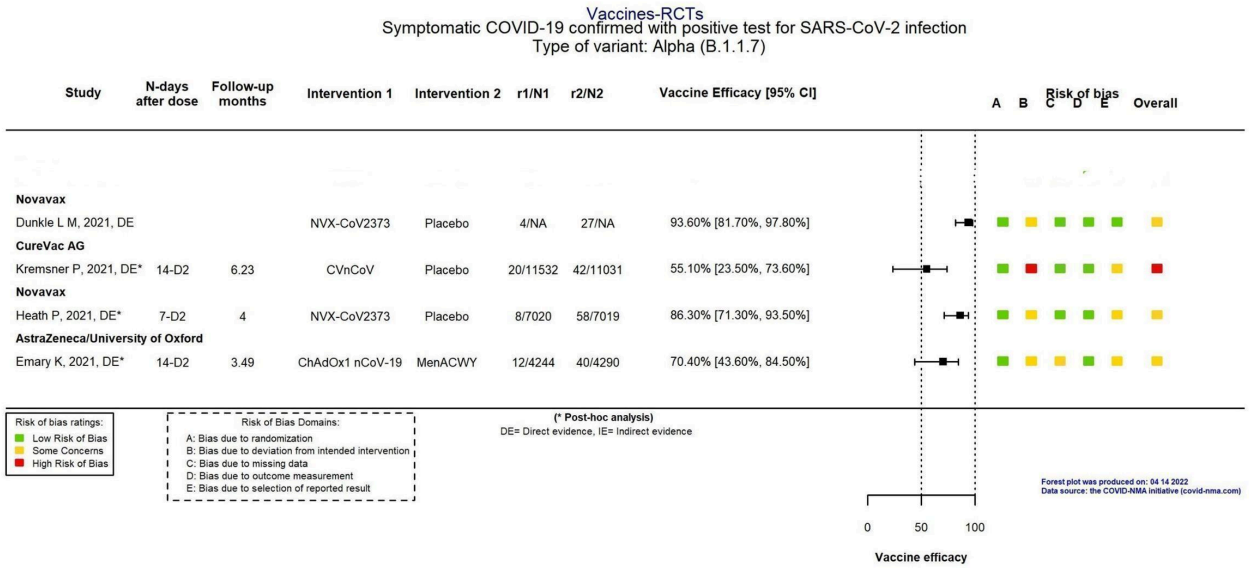
Figure 50. Analysis 7.1.1: variant-Alpha. Outcome: confirmed symptomatic COVID-19 after complete vaccination.

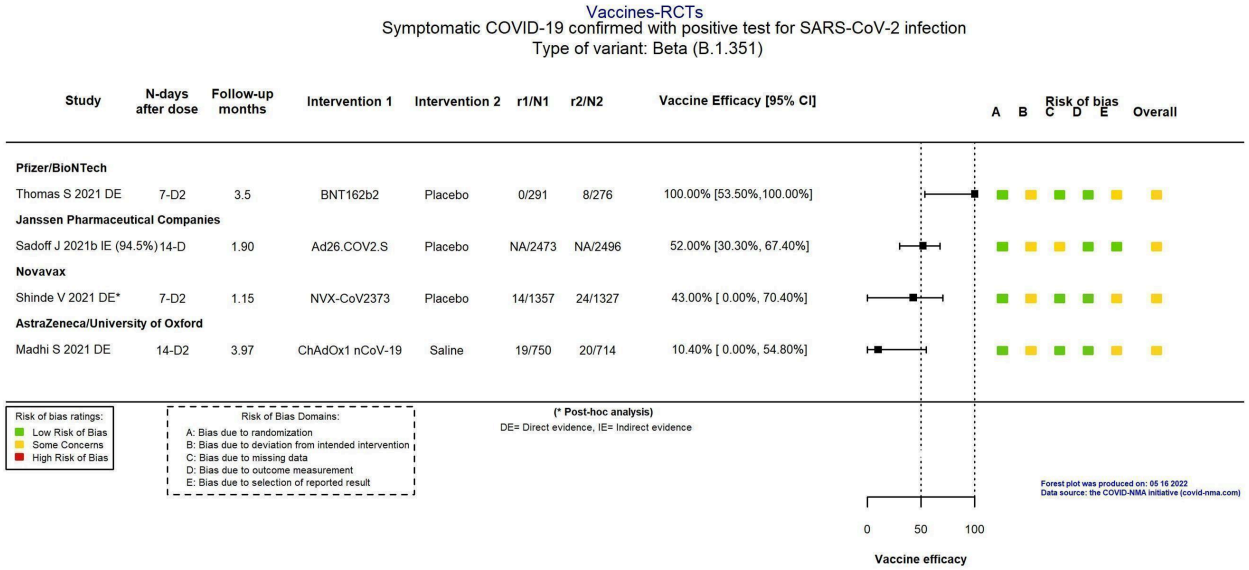


Beta variant (B.1.351)

Vaccine efficacy against the Beta variant was reported in four trials, assessing four different vaccines. Results from three trials are based only on genetically sequenced cases (direct evidence) (Madhi 2021b; Shinde 2021; Thomas 2021). In contrast, results in Sadoff 2021b include all cases identified and the prevalence of the Beta variant among participants (94.5%), obtained by sequencing a sample of RT-PCR positive cases, was extrapolated to the results (indirect evidence). Of note, Madhi 2021b includes only participants of the COV005 trial (Voysey 2021a).

Reported vaccine efficacy on confirmed symptomatic COVID-19 after complete vaccination was 100.00%, 95% CI 53.50% to 100.00% for BNT16b2 (Thomas 2021); 10.40%, 95% CI 0.00% to 54.80% for ChAdOx1 (Madhi 2021b); 52.00%, 95% CI 30.30% to 67.40% for Ad26.COV2.S (Sadoff 2021b), and 43.00%, 95% CI 0.00% to 70.40% for NVX-CoV2373 (Shinde 2021) (Figure 51).

Figure 51. Analysis 7.2.1: variant-Beta. Outcome: confirmed symptomatic COVID-19 after complete vaccination.



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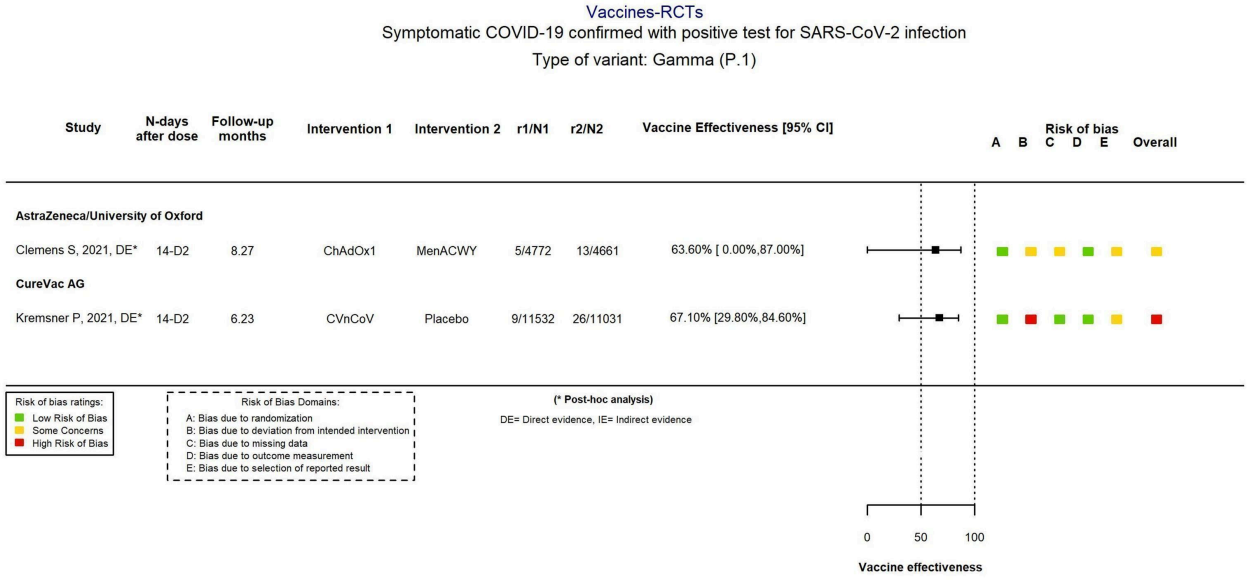
Gamma variant (P.1)

Vaccine efficacy against the Gamma variant was reported in two trials, assessing two different vaccines. All cases of the Gamma variant were detected with genome sequencing. Reported vaccine efficacy on confirmed symptomatic COVID-19 after complete vaccination was 67.10%, 95% CI 29.80% to 84.60% for CVnCoV (Kremsner 2021), and 63.60%, 95% CI 0.00% to 87.00% for ChAdOx1 (Clemens 2021) (Figure 52).

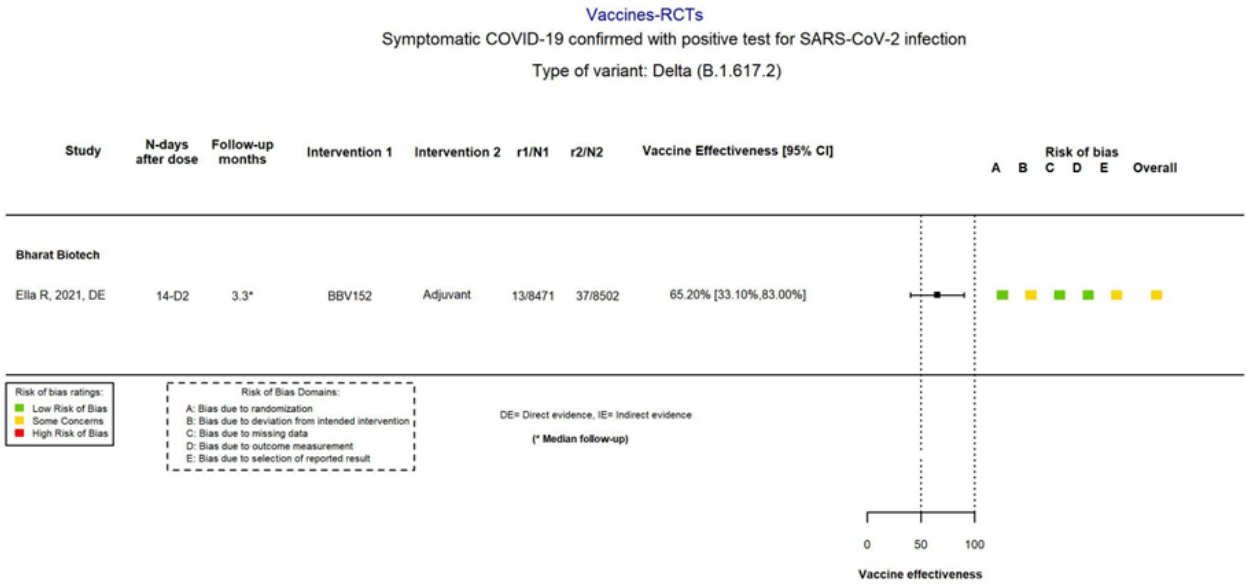
Figure 52. Analysis 7.3.1: variant-Gamma. Outcome: confirmed symptomatic COVID-19 after complete vaccination.



Delta (B.1.617.2)

Vaccine efficacy against the Delta variant was reported in one trial. All cases of the Delta variant were detected with genome sequencing. Reported vaccine efficacy on confirmed symptomatic COVID-19 after complete vaccination was 65.20%, 95% CI 33.10% to 83.00% for BBV152 (Ella 2021b) (Figure 53).

Figure 53. Analysis 7.4.1: variant-Delta. Outcome: confirmed symptomatic COVID-19 after complete vaccination.



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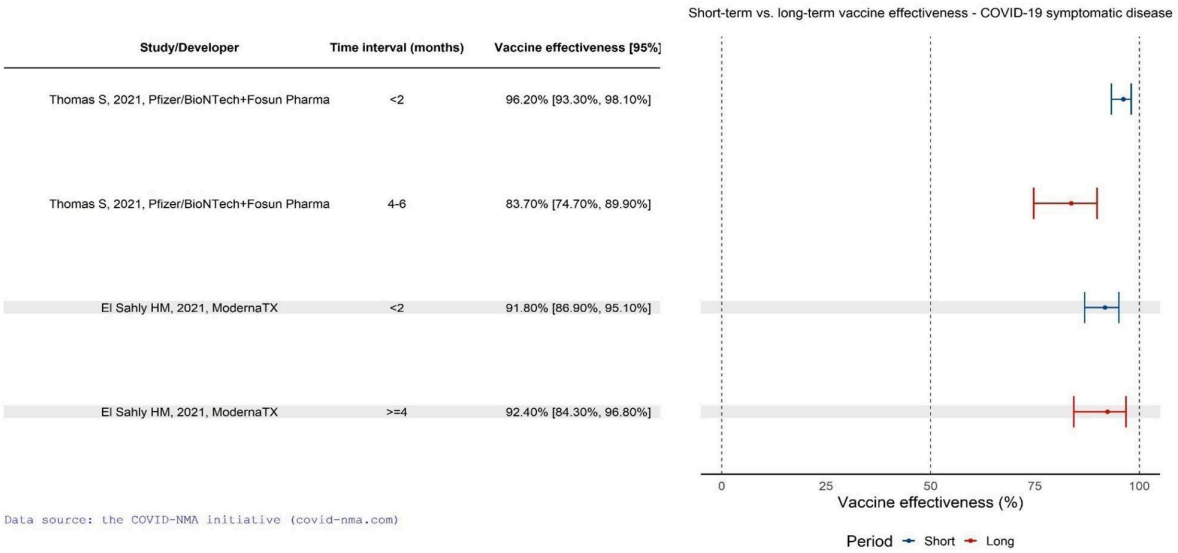
Assessment of vaccine efficacy over time

Out of the 41 included trials, only two studies reported on the change of vaccine efficacy over time for the outcome 'incidence of confirmed symptomatic COVID-19 after complete vaccination' for comparisons BNT162b2 versus placebo (BioNtech/Fosun Pharma/Pfizer) and mRNA-1273 versus placebo (ModernaTX) (El Sahly 2021; Thomas 2021).

For the comparison BNT162b2 versus placebo, vaccine efficacy seems to decrease slightly over time. However, the effect remains large: VE 96.20%, 95% CI 93.30% to 98.10% after a median follow-up less than 2 months and VE 83.70%, 95% CI 74.70% to 89.90% after a median follow-up of 4 months to 6 months (Figure 54).

Figure 54. Analysis 8.1: follow-up. RNA-based vaccine. Outcome: confirmed symptomatic COVID-19 after complete vaccination.



When comparing mRNA-1273 with placebo, vaccine efficacy was consistent over time (VE 91.80%, 95% CI 86.90% to 95.10%; median follow-up less than two months and VE 92.40%, 84.30% to 96.80%; median follow-up four months or greater) (Figure 54).

Exploration of heterogeneity

Subgroup analysis

We had planned to perform subgroup analysis for different age groups and immunocompromized patients; however due to the low number of studies we could not undertake formal subgroup analyses for each comparison.

Sensitivity analysis

Overall, all results for all outcomes were consistent in every sensitivity analysis as compared with the primary analysis. Small differences were mostly observed due to the increase of uncertainty in the summary estimate when excluding some trials.

RNA-based vaccines

Overall, results were consistent in all the analyses (Table 1).

Non-replicating viral vector vaccines

Overall, results were consistent in all the analyses (Table 2). An important but not statistically significant reduction in the RR for adverse event was observed, though, when excluding the early-phase trial.

Inactivated virus vaccines

Results were consistent, with the exception of an increase in vaccine efficacy against confirmed symptomatic COVID-19 after complete vaccination for CoronaVac compared to placebo when excluding results reported as preprints (VE 83.5%, 95% CI 65.4% to 92.1%) (Tanriover 2021) (Table 3). Using the participants randomized instead of those analyzed seemed to increase the heterogeneity, whereas excluding early-phase trials slightly decreased the heterogeneity and increased the precision of the summary estimate.

Protein subunit vaccines

Overall, results were consistent in all the analyses (Table 4).

DISCUSSION

Summary of main results

We identified and included 41 RCTs evaluating four different vaccine platforms and 12 vaccine candidates published in 65 reports in the analysis. Six RCTs reported results for three RNA-based vaccines (BNT162b2 from BioNtech/Fosun Pharma/Pfizer; mRNA-1273 from ModernaTX; CVnCoV by CureVac AG), and 10 RCTs evaluated three non-replicating viral vector vaccines (ChAdOx1 by AstraZeneca/University of Oxford and SII-ChAdOx1; Ad26.COV2.S by Janssen Pharmaceutical Companies; Gam-COVID-Vac by Gamaleya Research Institute), 13 RCTs evaluated four inactivated virus vaccines (CoronaVac by Sinovac; WIBP-CorV by Sinopharm-Wuhan;

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BBIBP-CorV by Sinopharm-Beijing; BBV152 by Bharat Biotech), and 6 RCTs evaluated two protein subunit vaccines (NVX-CoV2373 by Novavax; FINLAY-FR-2 by Instituto Finlay de Vacunas).

Our review also retrieved two trials comparing heterologous vaccination schemes with homologous vaccination schemes, two trials comparing booster versus placebo/no booster, and four trials comparing homologous and heterologous booster doses. Only 10 studies reported results on vaccine efficacy of six different vaccine candidates against any specific variant, which limits our ability to make any variant-specific claims.

Efficacy outcomes for vaccines versus placebo

There is moderate- to high-certainty evidence that several vaccine candidates are effective in preventing SARS-CoV-2 infection (i.e. mRNA-1273, ChAdOx1, WIBP-CorV, BBIBP-CorV, BBV152); symptomatic COVID-19 (i.e. BNT162b2, mRNA-1273, CVnCoV, ChAdOx1, Ad26.COV2.S, Gam-COVID-Vac, WIBP-CorV, BBIBP-CorV, BBV152, NVX-CoV2373, FINLAY-FR-2), and severe or critical disease compared to placebo (i.e. BNT162b2, mRNA-1273, Ad26.COV2.S, Gam-COVID-Vac, BBV152, NVX-CoV2373).

There is moderate-certainty evidence that Ad26.COV2.S and FINLAY-FR-2 result in a decrease in all-cause mortality compared to placebo. Evidence was uncertain and very uncertain for death for all other vaccines because of the low number of events.

Safety outcomes for vaccines versus placebo

Overall, we identified an increase in local reactogenicity events such as pain, redness, swelling, and systemic reactogenicities such as tiredness, headache, muscle pain, chills, fever, and nausea. There is moderate- to high-certainty evidence that most vaccine candidates have an increased risk of systemic reactogenicity events (e.g. fever) compared to placebo (mRNA-1273, CVnCoV, ChAdOx1, Ad26.COV2.S, WIBP-CorV, BBIBP-CorV, BBV152, NVX-CoV2373). These events were expected.

We did not find evidence of an increase in SAEs. There is moderate- to high-certainty evidence that there is probably little or no difference between mRNA-1273, ChAdOx1, Ad26.COV2.S and BBV152, and placebo in terms of SAEs. Evidence was uncertain and very uncertain for SAEs for other vaccines because of the low number of events.

We also extracted some specific adverse events, that is, cardioembolic events (pulmonary embolism, stroke, cavernous sinus thrombosis, pericarditis, venous thrombosis, myocardial infarction); haematological events (thrombocytopaenia, haemorrhage, neutropenia, anaemia, lymphadenopathy); and neurological events. The reporting of these events was very inconsistent and the number of events reported was very low.

The outcome 'any adverse event' was reported inconsistently. Some considered only the non-SAE including local and systemic reactogenicity events. Some also considered SAEs, and frequently it was unclear how these events were classified. Overall, we found moderate- to high-certainty evidence that vaccine increases any adverse event for three vaccines (i.e. CVnCoV, NVX-CoV2373, CoronaVac) and that vaccine results in no increase in any adverse event for two vaccines (i.e. WIBP-CorV, BBV152). Evidence was uncertain for other vaccines.

As trials' follow-up was short and the incidence of SAEs was very low, vaccine safety surveillance systems have been put in place to detect rare adverse events and concerns have been raised related to the occurrence of vaccine-induced immune thrombocytopaenia and thrombosis (Makris 2021; Ostrowski 2021; Rizk 2021; Sharifian-Dorche 2021).

Other evidence

We found little evidence regarding the differences between heterologous and homologous vaccination schemes, and the effect of booster vaccines (homologous or heterologous). Outcomes considered were mainly immunogenicity outcomes.

In the two studies (assessing mRNA-1273 and BNT162b2) for which we have data at different time points, vaccine efficacy at short term was consistent with longer-term results.

Effects of the interventions on specific subpopulations

Given the sparsity of data, we were unable to explore heterogeneity in the results by conducting subgroup analyses, and therefore decided to present results separately for specific subpopulations. We identified only four clinical trials including children and adolescents, and assessed BNT162b2, mRNA-1273, CoronaVac and BBIBP-CorV (Ali 2021; Frenck 2021; Han 2021; Xia 2020). We found more studies focused on, or reporting subgroup data for elderly participants, with single studies reporting different outcomes in elderly participants. However, data were still sparse and should be interpreted with caution. Finally, only three studies reported data for immunocompromized participants, each assessing a different vaccine candidate (ChAdOx1, NVX-CoV2373, and mRNA-1273 booster versus placebo). No studies were conducted on pregnant women, and pregnant women were very rarely included in trials although it has been reported that they are at greater risk of severe COVID-19 disease (Qiao 2020).

Impact of the results on future research

The high efficacy of several vaccine candidates, their marketing authorization and the rapid roll-out population-wide, raise the question of the feasibility and ethics of placebo RCTs assessing a new vaccine candidate.

For the ongoing placebo trials, the question is whether participants randomized to the placebo group should be unblinded and offered vaccine. Some argue the need to pursue follow-up to obtain strong data on long-term efficacy and safety (WHO Ad Hoc Expert Group 2021); others argue that given the clear evidence of a benefit for important outcomes, it would be unethical not to provide a vaccine to all participants (Dal-Ré 2021a; Dal-Ré 2021b).

Assessing vaccine efficacy and safety in randomized trials is also difficult considering the rapid evolution of the disease and the emergence of new variants that could impact vaccine efficacy. Large population-based observational data provide useful complementary information, although they need to be interpreted carefully because of the risk of bias.

Future research questions should focus on the efficacy and safety of vaccines on specific populations, such as pregnant women, immunosuppressed patients and other vulnerable populations, on variants of concerns, and on how we can overcome the waning of vaccine efficacy over time.

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An increasing number of trials consider only immunogenetic outcomes to allow a smaller sample size to generate a more rapid answer. However, there is considerable heterogeneity in assessing these outcomes and a consensus is needed on a core outcome set to enable effective comparison and synthesis of studies. Further, their results must be interpreted with caution.

Overall completeness and applicability of evidence

The evidence identified is incomplete. We identified 344 registered RCTs from registries evaluating the efficacy of COVID-19, of which 10 were completed but not published (non-replicating viral vector, replicating viral vector, inactivated virus, protein subunit and DNA-based platforms). The planned sample size of the completed trials for non-replicating viral vector vaccines is 27 participants, 90 participants for replicating viral vector vaccines, 19,512 for inactivated virus vaccines, 173 for protein subunit vaccines, and 30 for DNA-based vaccines, yielding a total planned sample size of 19,832.

The applicability of the results should be interpreted with caution. The trials spanned all geographical regions: seven trials were conducted in North America, 14 in Asia, four in South America, eight in Europe, two in Africa, and one in Oceania. Notwithstanding the worldwide geographical representation of trials, it is noteworthy that the representation is skewed. Inactivated vaccine and protein subunit vaccine trials were mostly limited to India, Cuba, and China. Furthermore, trials for mRNA-1273 were only conducted in the USA.

Our review also highlights the lack of evidence from RCTs regarding the efficacy of vaccines against specific variants. This is not surprising, given the relatively short period between the dominance of one variant and the next. Future studies might report more consistently on the specific variant predominating in their sample or report results stratified by variant, which would allow for more specific meta-analyses in the future. It is likely that data on efficacy by variant will mainly come from large population-based observational studies. The COVID-NMA initiative identified observational studies evaluating vaccine efficacy on the Delta variant, and provides some results on the platform (covid-nma.com). Given that Omicron has replaced all other variants in most countries, data may not be applicable to the current situation.

We found high- or moderate-certainty evidence for many of the main efficacy results of our review. However, the impact of effect modifiers, such as age or immunocompromized status, could not be explored adequately through subgroup analyses nor by meta-regression. Specific trials including these specific populations should be conducted. Vaccine efficacy on these subgroups could also be explored through large observational studies using routinely collected data.

Certainty of the evidence

Overall, evidence of the critical outcomes exhibited a certainty of evidence ranging from very low certainty to high certainty. The evidence for outcomes of efficacy against SARS-CoV-2 infection, symptomatic COVID-19, and severe or critical COVID-19 was most often of moderate or high certainty. In contrast, we frequently downgraded safety outcomes and all-cause mortality.

The reason for which we downgraded certainty of evidence most often, throughout the results for all vaccine types, was imprecision, referring to wide CIs in our results. This was often the result of a low number of events, and less often due to inconsistencies between the included studies or risk of bias. This explains why so few of the results related to mortality or severe adverse events, which are more rare events, achieved levels of moderate- or high-certainty evidence. We expect higher levels of certainty to be reached as more studies are published, and the body of evidence grows.

In one trial (Logunov 2021), we downgraded the certainty of evidence due to concerns about the trustfulness of the analyses (Bucci 2021). The authors responded to some of these concerns, and the manuscript was corrected (Logunov 2021). Nevertheless, uncertainty persists particularly related to the prespecification of the interim analysis and the excess of homogeneity of vaccine efficacy across age groups.

Potential biases in the review process

We followed the guidance of the *Cochrane Handbook for Systematic Reviews of Interventions* in order to minimize several potential biases in the review process (Higgins 2021). First, the search strategy was peer reviewed. We initially performed a thorough search in several electronic databases and then considered only high-quality sources, particularly the L·OVE platform and the Cochrane COVID-19 Study Register. Second, all data were extracted in duplicate with consensus. Third, to increase our review's informative value, we track all registered trials in a living mapping. Finally, the review is updated continually; each week, we search for new trials and collect data, and bi-weekly we update the syntheses. All updates of this review are available on the COVID-NMA platform (covid-nma.com).

Another consideration for this rapidly evolving field is the availability of preprint articles that have not yet undergone peer review. In this review, we also included preprints. However, we are aware of these publications' potentially differing quality and that results could change once the peer-reviewed journal publications are available (Oikonomidi 2020). To overcome this issue, we developed a preprint tracker to keep us informed of updates, so we can update data collection and data analysis when a preprint is modified or published (Cabanac 2021). We also conducted sensitivity analyses excluding preprints, and found consistent results.

Agreements and disagreements with other studies or reviews

We identified seven systematic reviews reporting on the efficacy of vaccines against COVID-19 and whose search strategy was run in the second half of 2021 or later. One included only RCTs (Rotshild 2021), three only observational studies (Harder 2021; Kow 2022; Liu 2021), and three a hybrid of RCTs and observational studies (Hayawi 2021; Higdon 2021; Zeng 2021b). We identified one systematic review focused on children and adolescents (Lv 2021). Overall, all the trials included in these reviews were identified in our search and our results are consistent.

There are other living systematic reviews of vaccines for COVID-19, such as Castagneto Gissey 2021, which includes only RCTs; Harder 2021, which includes, but is not limited to RCTs (the second interim results were published in October 2021). Finally, the Living Vaccine Project, a living systematic review with network meta-analysis that includes only RCTs recently published their results (Korang 2022). All studies included in their review were included in our

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review (either the same publication or another with more up-to-date data). For the most part, their results are consistent with ours. Concurrently, there are over a dozen protocols of systematic reviews assessing the safety or efficacy of vaccines registered in PROSPERO and listed as ongoing.

AUTHORS' CONCLUSIONS

Implications for practice

Several COVID-19 vaccines are highly effective or probably highly effective in preventing SARS-CoV-2 infection, symptomatic COVID-19 and severe or critical COVID-19.

There is moderate- to high-certainty evidence that most vaccine candidates increased the risk of systemic reactogenicity events (e.g. fever). Evidence related to any adverse event was mainly uncertain.

There is moderate- to high-certainty evidence that there is probably no difference between mRNA-1273, CVnCoV, ChAdOx1, Ad26.COV2.S, Gam-COVID-Vac, WIBP-CorV and BBIBP-CorV and placebo in terms of serious adverse events. Evidence was uncertain and very uncertain for serious adverse events for other vaccines and for all-cause mortality for most vaccines, mainly because of the low number of events.

In addition, as most RCTs only followed up participants for 2 months after full vaccination, all reports are related to short-term impacts of the vaccine.

Results cannot easily be generalized to pregnant women and immunocompromized individuals; more evidence is needed to elucidate the degree of additional protection conferred by COVID-19 vaccines in these populations.

Finally, the advent of variants of concern has highlighted the need for further research on each of the vaccine's capacity to limit infection, disease, and death in regard to specific variants of concern.

Implications for research

- Three hundred and forty-four RCTs are currently registered, of which 10 are completed. The findings from these trials will contribute to the body of evidence on efficacy and safety outcomes. The findings of this review will be updated as soon as new data are available on the COVID-NMA platform.
- Since the efficacy of vaccines is well established at this point, the ethics of RCT designs using a placebo as the comparison group should be questioned, and active comparators should be considered.
- With the notable impact of variants of concern on vaccine efficacy, it is crucial that variant type is assessed in clinical trials and reported for future meta-analyses to assess vaccine efficacy on considerably different variants.
- As a non-negligible global population has been infected by SARS-CoV-2, robust evidence-based vaccination schemes are also required.
- Finally, considering the rapidly changing situation (in terms of variants, policies, etc.) and the increasing and important heterogeneity in the population in terms of combinations of vaccines received, history of SARS-CoV-2 infection (and by which variant), type of booster vaccine received, and predominant variants at the time of data collection, RCTs might become increasingly difficult to conduct in such a rapidly-changing context and large population-based observational studies could provide relevant information.

ACKNOWLEDGEMENTS

We particularly thank Elise Diard for her help on the website and extraction tool development.

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Cochrane Emergency and Critical Care Group supported the authors in the development of this review. The following people conducted the editorial process for this review.

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- Managing Editor (selected peer reviewers, collated peer-reviewer comments, provided editorial guidance to authors, edited the article): Joey Kwong, Cochrane Central Editorial Service.
- Editorial Assistant (conducted editorial policy checks and supported editorial team): Leticia Rodrigues, Cochrane Central Editorial Service.
- Copy Editor (copy-editing and production): Clare Dooley, c/o Cochrane Production Service.
- Proofreader: Anne Lawson, Central Production Service, Cochrane.
- Peer-reviewers (provided comments and recommended an editorial decision): Ariel Izcovich, Internal Medicine Department, Hospital Alemán de Buenos Aires, Argentina (clinical/content review); Romina Brignardello-Petersen, Department of Health Research Methods, Evidence, and Impact, McMaster University (clinical/content review); Ana Katherine Gonçalves, Obstetric and Gynecology Department, Federal University of Rio Grande Do Norte, Brazil (clinical/content review); Stella O'Brien (consumer review); Robert Walton, Cochrane UK (summary versions review); Rachel Richardson, Cochrane Evidence Production and Methods Directorate (methods review); Kerry Dwan, Cochrane Methods Support Unit (statistical review); Robin Featherstone, Cochrane Central Editorial Service (search review). Two additional peer reviewers provided clinical/content peer review but chose not to be publicly acknowledged.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Ali 2021

Study characteristics
Methods
Participants
Interventions
Outcomes
Notes

Al Kaabi 2021

Study characteristics
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Al Kaabi 2021 *(Continued)*

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Asano 2022

Study characteristics
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Bonelli 2021

Study characteristics
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Bueno 2021

Study characteristics
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Clemens 2021

Study characteristics
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Dunkle 2021

Study characteristics
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Ella 2021a

Study characteristics
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Ella 2021b

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Ella 2021b *(Continued)*

Outcomes
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El Sahly 2021

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Emary 2021

Study characteristics
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Fadlyana 2021

Study characteristics
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Falsey 2021

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Formica 2021

Study characteristics
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Frenck 2021

Study characteristics
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Guo 2021

Study characteristics
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Guo 2021 *(Continued)*

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Hall 2021

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Han 2021

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Heath 2021

Study characteristics
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Keech 2020

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Kremsner 2021

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Kulkarni 2021

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Li 2021a

Study characteristics
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Li 2021a *(Continued)*

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Liu 2021

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Logunov 2021

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Madhi 2021a

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Madhi 2021b

Study characteristics
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Mok 2021

Study characteristics
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Palacios 2020

Study characteristics
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Sablerolles 2021

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Sablerolles 2021 *(Continued)*

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Sadoff 2021a

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Sadoff 2021b

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Shinde 2021

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Tanriover 2021

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Thomas 2021

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Toledo-Romani 2021

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Voysey 2021a

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Voysey 2021a *(Continued)*

Outcomes
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Walsh 2020

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Wu 2021a

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Xia 2020

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Xia 2021

Study characteristics
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Zhang 2021

Study characteristics
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Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Baden 2021	Exploratory analysis
Barrett 2021	Secondary analysis
Ewer 2021	Secondary analysis
Flaxman 2021	Not randomized
Hsieh 2021	Not randomized
Irfan 2021	Commentary
Lazarus 2021	Intervention not relevant to review
Patamatamkul 2021	Not randomized
Ward 2021a	Intervention not relevant to review
Wu 2021b	Not randomized
Zdanowski 2021	Not randomized

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ADDITIONAL TABLES

Table 1. Sensitivity analysis: RNA-based vaccines

Developer – comparison	Analyses[a]	Outcomes						
		SARS-CoV-2 infection	Symptomatic COVID-19	Severe COVID-19	All-cause mortality	SAEs	Systemic reactogenicity events	AEs
		VE (95% CI) No. of trials (No. of participants)			RR (95% CI) No. of trials (No. of participants)			
BNT162b2 – Pfizer/BioNTech+Fosun Pharma versus placebo	**Main analysis**	—	97.84% (44.25% to 99.92%) 2 RCTs (44,077)	95.70% (73.90% to 99.90%) 1 RCT (46,077)	1.07 (0.52 to 2.22) 1 RCT (43,846)	1.30 (0.55 to 3.07) 2 RCTs (46,107)	—	1.52 (0.88 to 2.63) 3 RCTs (46,419)
	Sensitivity 1	—	—	—	1.07 (0.52 to 2.22) 1 RCT (44,165)	1.30 (0.55 to 3.05) 2 RCTs (46,429)	—	1.52 (0.88 to 2.63) 3 RCTs (46,471)
	Sensitivity 2	—	—	—	—	—	—	—
	Sensitivity 3	—	—	—	—	—	—	—
mRNA-1273 – ModernaTX versus placebo	**Main analysis**	73.27% (35.82% to 88.87%) 2 RCTs (31,632)	93.20% (91.06% to 94.83%) 2 RCTs (31,632)	98.20% (92.80% to 99.60%) 1 RCT (28,451)	1.06 (0.54 to 2.10) 1 RCT (30,346)	0.92 (0.78 to 1.08) 2 RCTs (34,072)	1.28 (1.22 to 1.34) 2 RCTs (34,037)	1.19 (0.79 to 1.80) 2 RCTs (34,072)
	Sensitivity 1	—	—	—	1.06 (0.54 to 2.10) 1 RCT (30,415)	0.92 (0.78 to 1.09) 2 RCTs (34,147)	1.28 (1.22 to 1.34) 2 RCTs (34,147)	1.20 (0.79 to 1.80) 2 RCTs (34,147)
	Sensitivity 2	—	—	—	—	—	—	—
	Sensitivity 3	—	—	—	—	—	—	—

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Table 1. Sensitivity analysis: RNA-based vaccines *(Continued)*

CVnCoV – CureVac AG versus placebo	**Main analysis**	—	48.20% (31.70% to 60.90%) 1 RCT (25,062)	63.80% (0.00% to 91.70%) 1 RCT (25,062)	1.33 (0.46 to 3.83) 1 RCT (39,529)	1.24 (0.90 to 1.71) 1 RCT (39,529)	1.48 (1.43 to 1.53) 1 RCT (3982)	1.42 (1.38 to 1.47) 1 RCT (3982)
	Sensitivity 1	—	—	—	—	—	1.49 (1.39 to 1.60) 1 RCT (39,529)	1.43 (1.34 to 1.53) 1 RCT (39,529)
	Sensitivity 2	—	—	—	—	—	—	—
	Sensitivity 3	—	—	—	—	—	—	—

AE: adverse event; CI: confidence interval; COVID-19: coronavirus disease 2019; RCT: randomized controlled trial; RR: risk ratio; SAE: serious adverse event; SARS-CoV-2: severe acute respiratory syndrome coronavirus 2; VE: vaccine efficacy.

[a]**Sensitivity 1:** participants randomized; **Sensitivity 2:** early-phase studies excluded; **Sensitivity 3:** only published studies.

Table 2. Sensitivity analysis: non-replicating viral vector vaccine

Developer – comparison	Analyses[a]	**Outcomes**						
		SARS-CoV-2 infection	**Symptomatic COVID-19**	**Severe COVID-19**	**All-cause mortality**	**SAEs**	Systemic **reactogenicity events**	**AEs**
		VE (95% CI) **No. of trials (No. of participants)**			**RR (95% CI)** **No. of trials (No. of participants)**			
ChAdOx1 – AstraZeneca + University of Oxford- versus placebo	**Main analysis**	59.35% (48.00% to 68.22%) 5 RCTs (43,390)	70.23% (62.10% to 76.62%) 5 RCTs (43,390)	—	0.48 (0.20 to 1.14) 5 RCTs (56,726)	0.88 (0.72 to 1.07) 7 RCTs (58,182)	3.93 (2.11 to 7.29) 1 RCT (256)	Not pooled

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Table 2. Sensitivity analysis: non-replicating viral vector vaccine *(Continued)*

	Sensitivity 1	—	—	—	0.50 (0.20 to 1.21) 5 RCTs (56,873)	0.86 (0.70 to 1.06) 7 RCTs (58,329)	—	—
	Sensitivity 2	—	—	—	0.48 (0.20 to 1.14) 5 RCTs (56,623)	0.88 (0.72 to 1.08) 6 RCTs (57,823)	—	—
	Sensitivity 3	—	—	—	0.50 (0.20 to 1.21) 5 RCTs (56,623)	0.86 (0.70 to 1.05) 6 RCTs (56,879)	—	—
Ad26.COV2.S – Janssen Pharmaceutical Companies versus placebo	**Main analysis**	—	66.90% (59.10% to 73.40%) 1 RCT (39,058)	76.30% (57.90% to 87.50%) 1 RCT (39,058)	0.25 (0.09 to 0.67) 1 RCT (43,783)	0.92 (0.69 to 1.22) 1 RCT (43,783)	1.83 (1.29 to 2.60) 2 RCTs (7222)	1.57 (0.75 to 3.29) 2 RCTs (7222)
	Sensitivity 1	—	—	—	0.25 (0.09 to 0.67) 1 RCT (44,325)	0.92 (0.69 to 1.22) 1 RCT (44,325)	1.83 (1.27 to 2.63) 2 RCTs (44,813)	1.57 (0.74 to 3.32) 2 RCTs (44,813)
	Sensitivity 2	—	—	—	—	—	—	1.09 (0.96 to 1.24) 1 RCT (6736)
	Sensitivity 3	—	—	—	—	—	—	—
Gam-COVID-Vac – Gamaleya Research Institute (Sputnik V) Gam-COVID-Vac versus placebo	**Main analysis**	—	91.10% (83.80% to 95.10%) 1 RCT (18,695)	100.00% (94.40% to 100.00%) 1 RCT (19,866)	0.99 (0.10 to 9.54) 1 RCT (21,862)	0.65 (0.39 to 1.07) 1 RCT (21,862)	—	—
	Sensitivity 1	—	—	—	1.00 (0.10 to 9.57) 1 RCT (21,977)	0.65 (0.39 to 1.07) 1 RCT (21,977)	—	—

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Table 2. Sensitivity analysis: non-replicating viral vector vaccine *(Continued)*

Sensitivity 2	—	—	—	—	—	—	—
Sensitivity 3	—	—	—	—	—	—	—

AE: adverse event; CI: confidence interval; COVID-19: coronavirus disease 2019; RCT: randomized controlled trial; RR: risk ratio; SAE: serious adverse event; SARS-CoV-2: severe acute respiratory syndrome coronavirus 2; VE: vaccine efficacy.

[a]**Sensitivity 1:** participants randomized; **Sensitivity 2:** early-phase studies excluded; **Sensitivity 3:** only published studies.

Table 3. Sensitivity analysis: inactivated virus vaccine

Developer – comparison	Analyses[a]	**Outcomes**						
		SARS-CoV-2 infection	**Symptomatic COVID-19**	**Severe COVID-19**	**All-cause mortality**	**SAEs**	Systemic **reactogenicity events**	**AEs**
		VE (95% CI)			**RR (95% CI)**			
		No. of trials (No. of participants)			**No. of trials (No. of participants)**			
CoronaVac – Sinovac versus placebo	**Main analysis**	—	69.81% (12.27% to 89.61%) 2 RCTs (19,852)	—	0.50 (0.05 to 5.52) 1 RCT (12,396)	0.97 (0.62 to 1.51) 4 RCTs (23,139)	0.95 (0.55 to 1.62) 7 RCTs (23,956)	1.09 (1.07 to 1.11) 6 RCTs (23,367)
	Sensitivity 1	—	—	—	0.50 (0.05 to 5.52) 1 RCT (12,408)	0.99 (0.64 to 1.51) 4 RCTs (23,157)	1.56 (0.91 to 2.69) 7 RCTs (25,106)	1.09 (1.07 to 1.11) 6 RCTs (23,385)
	Sensitivity 2	—	—	—	—	0.99 (0.63 to 1.55) 2 RCTs (22,610)	1.21 (0.98 to 1.49) 4 RCTs (23,584)	1.09 (1.07 to 1.11) 2 RCTs (22,610)
	Sensitivity 3	—	83.50% (65.40% to 92.10%)	—	—	0.73 (0.24 to 2.21) 4 RCTs (10,894)	0.94 (0.49 to 1.81) 6 RCTs (11,617)	1.13 (1.04 to 1.23) 4 RCTs (10,640)

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Table 3. Sensitivity analysis: inactivated virus vaccine *(Continued)*

			1 RCT (10,029)					
WIBP-CorV – Sinopharm-Wuhan versus placebo	**Main analysis**	64.00% (48.80% to 74.70%) 1 RCT (25,449)	72.80% (58.10% to 82.40%) 1 RCT (25,480)	—	—	0.83 (0.60 to 1.15) 2 RCTs (27,029)	0.99 (0.95 to 1.03) 2 RCTs (27,029)	0.96 (0.93 to 0.98) 2 RCTs (27,029)
	Sensitivity 1	—	—	—	—	0.83 (0.60 to 1.15) 2 RCTs (27,053)	0.99 (0.95 to 1.03) 2 RCTs (27,053)	0.96 (0.93 to 0.98) 2 RCTs (27,053)
	Sensitivity 2	—	—	—	—	0.82 (0.59 to 1.14) 1 RCT (26,917)	0.99 (0.95 to 1.03) 1 RCT (26,917)	0.96 (0.93 to 0.98) 1 RCT (26,917)
	Sensitivity 3	—	—	—	—	—	—	—
BBIBP-CorV – Sinopharm-Beijing versus placebo	**Main analysis**	73.50% (60.60% to 82.20%) 1 RCT (25,463)	78.10% (64.80% to 86.30%) 1 RCT (25,463)	—	—	0.76 (0.54 to 1.06) 1 RCT (26,924)	1.05 (0.86 to 1.28) 3 RCTs (27,540)	Not pooled
	Sensitivity 1	—	—	—	—	—	1.05 (0.86 to 1.28) 3 RCTs (27,557)	Not pooled
	Sensitivity 2	—	—	—	—	—	1.02 (0.98 to 1.06) 1 RCT (26,924)	
	Sensitivity 3	—	—	—	—	—	—	—
BBV152 – Bharat Biotech versus placebo	**Main analysis**	68.80% (46.70% to 82.50%) 1 RCT (6289)	77.80% (65.20% to 86.40%) 1 RCT (16,973)	99.70% (96.79% to 99.79%) 1 RCT (16,976)	0.50 (0.17 to 1.46) 1 RCT (25,753)	0.65 (0.43 to 0.97) 1 RCT (25,753)	1.34 (1.15 to 1.58) 2 RCTs (25,925)	1.00 (0.94 to 1.07) 1 RCT (25,753)

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Table 3. Sensitivity analysis: inactivated virus vaccine *(Continued)*

Sensitivity 1	—	—	—	0.50 (0.17 to 1.46) 1 RCT (25,778)	0.65 (0.43 to 0.97) 2 RCTs (25,953)	1.35 (1.15 to 1.58) 2 RCTs (25,953)	1.00 (0.94 to 1.07) 1 RCT (25,778)
Sensitivity 2	—	—	—	—	0.65 (0.43 to 0.97) 1 RCT (25,753)	1.34 (1.14 to 1.58) 1 RCT (25,753)	—
Sensitivity 3	—	—	—	—	—	1.47 (0.63 to 3.47) 1 RCT (172)	—

AE: adverse event; CI: confidence interval; COVID-19: coronavirus disease 2019; RCT: randomized controlled trial; RR: risk ratio; SAE: serious adverse event; SARS-CoV-2: severe acute respiratory syndrome coronavirus 2; VE: vaccine efficacy.

[a]**Sensitivity 1:** participants randomized; **Sensitivity 2:** early-phase studies excluded; **Sensitivity 3:** only published studies.

Table 4. Sensitivity analysis: protein subunit vaccine

Developer-comparison	Analyses[a]	Outcomes						
		SARS-CoV-2 infection	**Symptomatic COVID-19**	**Severe COVID-19**	**All-cause mortality**	**SAEs**	**Systemic reactogenicity events**	**AEs**
		VE (95% CI) **No. of trials (No. of participants)**			**RR (95% CI)** **No. of trials (No. of participants)**			
NVX-CoV2373 – Novavax versus placebo	**Main analysis**	—	82.91% (50.49% to 94.10%) 3 RCTs (42,175)	100.00% (86.99% to 100.00%) 1 RCT (25,452)	0.90 (0.30 to 2.68) 1 RCT (29,582)	0.92 (0.74 to 1.14) 4 RCTs (46,202)	1.21 (1.17 to 1.25) 3 RCTs (31,063)	1.15 (1.05 to 1.26) 5 RCTs (46,231)
	Sensitivity 1	—	—	—	—	0.92 (0.74 to 1.14) 4 RCTs (50,111)	1.21 (1.17 to 1.26) 3 RCTs (34,870)	1.16 (1.05 to 1.27) 5 RCTs (50,111)

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Table 4. Sensitivity analysis: protein subunit vaccine *(Continued)*

	Sensitivity 2	—	—	—	—	0.93 (0.75 to 1.15) 3 RCTs (45,689)	1.20 (1.17 to 1.24) 2 RCTs (30,550)	1.14 (1.02 to 1.27) 3 RCTs (45,689)
	Sensitivity 3	—	77.10% (0.00% to 95.19%) 2 RCTs (16,723)	—	—	0.99 (0.65 to 1.51) 3 RCTs (16,620)	1.24 (1.03 to 1.49) 2 RCTs (1481)	1.18 (1.03 to 1.35) 4 RCTs (16,672)
FINLAY-FR-2 – Instituto Finlay de Vacunas versus placebo	**Main analysis**	—	71.00% (58.90% to 79.10%) 1 RCT (28,674)	—	0.37 (0.17 to 0.80) 1 RCT (28,674)	—	—	—
	Sensitivity 1	—	—	—	—	—	—	—
	Sensitivity 2	—	—	—	—	—	—	—
	Sensitivity 3	—	—	—	—	—	—	—

AE: adverse event; CI: confidence interval; COVID-19: coronavirus disease 2019; RCT: randomized controlled trial; RR: risk ratio; SAE: serious adverse event; SARS-CoV-2: severe acute respiratory syndrome coronavirus 2; VE: vaccine efficacy.

[a]**Sensitivity 1:** participants randomized; **Sensitivity 2:** early-phase studies excluded; **Sensitivity 3:** only published studies.

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APPENDICES

Appendix 1. List of definitions used for outcomes 'serious adverse events' and 'severe or critical disease'

	Definition: serious adverse events (SAEs)	Definition: severe or critical disease
RNA-based		
BNT162b2 – BioNTech/Fosun Pharma/Pfizer		
Walsh 2020	An SAE is defined as any untoward medical occurrence that, at any dose: results in death; is life-threatening; requires inpatient hospitalisation or prolongation of existing hospitalisation; results in persistent disability/incapacity; is a congenital anomaly/birth defect; other situations. Medical or scientific judgement should be exercised in deciding whether SAE reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalisation, but may jeopardize the participant or may require medical or surgical intervention to prevent 1 of the other outcomes listed in the above definition.	NR
Frenck 2021	An SAE is defined as any untoward medical occurrence that, at any dose: results in death; is life-threatening; requires inpatient hospitalisation or prolongation of existing hospitalisation; results in persistent disability/incapacity; is a congenital anomaly/birth defect.	Diagnosis of severe COVID-19 included confirmed COVID-19 and the presence of any of the following: (1) clinical signs at rest indicative of severe systemic illness (e.g. respiratory rate ≥ 30 breaths/min, heart rate ≥ 125 beats/min, $SpO_2 \leq 93\%$ on room air at sea level, or $PaO_2/FiO_2 < 300$ mmHg; (2) respiratory failure (i.e. needing high-flow oxygen, non-invasive ventilation, mechanical ventilation, or extracorporeal membrane oxygenation); (3) evidence of shock (i.e. systemic blood pressure < 90 mmHg, diastolic blood pressure < 60 mmHg, or requiring vasopressors); (4) significant acute renal, hepatic, or neurological dysfunction; (5) intensive care unit admission; or (6) death.
Thomas 2021	An SAE is defined as any untoward medical occurrence that, at any dose: results in death; is life-threatening; requires inpatient hospitalisation or prolongation of existing hospitalisation; results in persistent disability/incapacity; is a congenital anomaly/birth defect.	Confirmed severe COVID-19 required confirmation of COVID-19 and the presence of ≥ 1 of the following: clinical signs at rest indicative of severe systemic illness (respiratory rate ≥ 30 breaths/min, heart rate ≥ 125 beats/min, $SpO_2 \leq 93\%$ on room air at sea level, or $PaO_2/FiO_2 < 300$ mmHg); respiratory failure (defined as needing high-flow oxygen, non-invasive ventilation, mechanical ventilation, or extracorporeal membrane oxygenation); evidence of shock (systolic blood pressure < 90 mmHg, diastolic blood pressure < 60 mmHg, or requiring vasopressors); significant acute renal, hepatic, or neurological dysfunction; intensive care unit admission; death; or a combination of these.
mRNA-1273 – ModernaTX		

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Ali 2021	An SAE results in any of the following outcomes: death; is life-threatening; requires inpatient hospitalisation or prolongation of existing hospitalisation; persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions; is a congenital anomaly or birth defect; is a medically important event.	NR
El Sahly 2021	An adverse event (including an adverse reaction) is considered an SAE if, in the view of either the investigator or sponsor, it results in any of the following outcomes: death; is life-threatening; inpatient hospitalisation or prolongation of existing hospitalisation; persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions; congenital anomaly or birth defect; medically important event.	Confirmed severe COVID-19 requires any of the following criteria had to be met: clinical signs of severe systemic illness; respiratory rate ≥ 30 breaths/min; heart rate ≥ 125 beats/min; SpO_2 ≤ 93% on room air at sea level or PaO_2/FIO_2 < 300 mmHg, or respiratory failure or acute respiratory distress syndrome (defined as needing high-flow oxygen, non-invasive or mechanical ventilation, or extracorporeal membrane oxygenation); evidence of shock (systolic blood pressure < 90 mmHg, diastolic blood pressure < 60 mmHg or requiring vasopressors) or significant acute renal, hepatic or neurological dysfunction or admission to an intensive care unit or death.
CVnCoV – CureVac AG		
Kremsner 2021	NR	Severe COVID-19 was defined by clinical signs at rest that are indicative of severe systemic illness (respiratory rate ≥ 30 breaths/min, heart rate ≥ 125 beats/min, altitude-adjusted SpO_2 ≤ 93% or PaO_2/FIO_2 < 300 mmHg), respiratory failure, evidence of shock, significant renal, hepatic, or neurological dysfunction, admission to an intensive care unit, or death.
Non-replicating viral vector		
ChAdOx1/SII-ChAdOx1 nCoV-19 – AstraZeneca + University of Oxford		
Asano 2022	Severity of safety endpoints was assessed according to toxicity grading scales adapted from Food and Drug Administration (FDA) grading guidance	NR
Emary 2021	NR	NR
Falsey 2021	An adverse event that fulfils ≥ 1 of the following criteria: results in death; is immediately life-threatening; requires in-participant hospitalisation or prolongation of existing hospitalisation; results in persistent or significant disability or incapacity; is a congenital abnormality or birth defect; is an important medical event that may jeopardize the participant or may require medical treatment to prevent 1 of the outcomes listed above.	Laboratory-confirmed COVID-19 (SARS-CoV-2 RT-PCR-positive symptomatic illness) plus any of the following: clinical signs at rest indicative of severe systemic illness (respiratory rate ≥ 30 breaths/min, heart rate ≥ 125 beats/min, oxygen saturation ≤ 93% on room air at sea level, or PaO_2/FIO_2 < 300 mmHg); respiratory failure (defined as needing high-flow oxygen, non-invasive ventilation, mechanical ventilation or extracorporeal membrane oxygenation); evidence of shock (systolic blood pressure < 90 mmHg, diastolic blood pressure < 60 mmHg, or requiring vasopressors); significant acute

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		renal, hepatic, or neurological dysfunction; admission to an intensive care unit; death.
Kulkarni 2021	All adverse events were graded for severity using the Division of AIDS (DAIDS) table for Grading the Severity of Adult and Pediatric Adverse Events (corrected version 2.1, July 2017) from the US Department of Health and Human Services, National Institutes of Health, National Institute of Allergy and Infectious Diseases.	Severe cases as per the WHO clinical progression scale
Madhi 2021b	NR	As defined by WHO ordinal scale
Voysey 2021a	NR	Severe COVID-19 (WHO clinical progression score ≥ 6)
Gam-COVID-Vac (Sputnik V) – Gamaleya Research Institute		
Logunov 2021	SAEs were diagnosed on the basis of the event requiring hospital admission.	Moderate or severe COVID-19: fever > 38.5 °C; respiratory rate > 22 breaths/min; shortness of breath during physical exertion; pneumonia (confirmed by computed tomography of the lungs); oxygen saturation level < 95%.
Ad26.COV2.S – Janssen Pharmaceutical Companies		
Sadoff 2021a	NR	NR
Sadoff 2021b	An SAE based on ICH and EU guidelines on pharmacovigilance for medicinal products for human use is any untoward medical occurrence that at any dose: results in death; is life-threatening (the participant was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it were more severe); requires inpatient hospitalisation or prolongation of existing hospitalisation; results in persistent or significant disability/incapacity; is a congenital anomaly/birth defect; is a suspected transmission of any infectious agent via a medicinal product; is medically important.	A SARS-CoV-2 positive RT-PCR or molecular test result. Respiratory rate ≥ 30 breaths/min; heart rate ≥ 125 beats/min; oxygen saturation (SpO_2) ≤ 93% on room air at sea level, or PaO_2/FiO_2 < 300 mmHg; respiratory failure; evidence of shock; significant acute renal, hepatic, or neurological dysfunction; admission to the ICU; death
Inactivated virus		
BBV152 – Bharat Biotech		
Ella 2021a	NR	NR
Ella 2021b	NR	NR
CoronaVac – Sinovac		
Zhang 2021	NR	NR
Bueno 2021	Any untoward medical occurrence that: results in death; is life-threatening (i.e. the subject was, in the opinion of the investigator, at immediate risk	NR

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	of death from the event as it occurred; it does not refer to an event which hypothetically might have caused death if it were more severe); requires or prolongs subject's hospitalisation; results in persistent or significant disability/incapacity (i.e. the event causes a substantial disruption of a personal ability to conduct normal life functions); results in a congenital anomaly/birth defect; requires intervention to prevent permanent impairment or damage; is an important and significant medical event that may not be immediately life-threatening or resulting in death or hospitalisation but, based upon appropriate medical judgement, may jeopardize the subject or may require intervention to prevent 1 of the other outcomes listed above.	
Han 2021	NR	NR
Fadlyana 2021	NR	Severe or critical COVID-19 confirmed by RT-PCR
Palacios 2020	Any adverse event that results in any of the following outcomes: death; threat to life; there is a risk of death at the time of the event; hospitalisation or extension of hospitalisation; significant or persistent disability; congenital anomaly; any suspicion of transmission of an infectious agent by means of a medication; clinically significant event; any event resulting from the use of drugs that require medical intervention, in order to avoid death, risk to life, significant disability or hospitalisation.	Score ≥ 6 on WHO 10-point clinical progression scale (hospitalized with severe COVID-19 through to death)
Tanriover 2021	An SAE is an adverse event that results in any of the following outcomes, whether or not considered related to the study intervention: death; life-threatening event (i.e. the volunteer was, in the view of the investigator, at immediate risk of death from the event that occurred); persistent or significant disability or incapacity (i.e. substantial disruption of one's ability to carry out normal life functions); hospitalisation or prolongation of existing hospitalisation, regardless of length of stay, even if it is a precautionary measure for continued observation (hospitalisation (including inpatient or outpatient hospitalisation for an elective procedure) for a pre-existing condition that has not worsened unexpectedly does not constitute an SAE); an important medical event (that may not cause death, be life-threatening, or require hospitalisation) that may, based upon appropriate medical judgement, jeopardise the volunteer, require medical or surgical intervention to prevent 1 of the outcomes listed above, or a combination of these. Examples of such medical events include allergic reaction requiring intensive treatment in an emergency room or	WHO clinical progression scale ≥ 6: hospitalized, needing oxygen by non-invasive or high-flow ventilation or worse

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	clinic, blood dyscrasias, or convulsions that do not result in inpatient hospitalisation.	
Wu 2021a	Events during the clinical trial that need hospitalisation treatment, prolong hospitalisation time, disability, affect working ability, endanger life or death, cause congenital malformation, etc.	NR
WIBP-CorV – Sinopharm Wuhan		
Al Kaabi 2021	NR	Confirmed COVID-19 case, meeting any 1 of the following criteria: respiratory distress (respiratory rate ≥ 30 breaths/min); O_2 saturation ≤ 93% at rest; PaO_2/FiO_2 < 300 mmHg (1 mmHg = 0.133 kPa); clinical symptoms progressively worsened, and chest imaging showed > 50% obvious lesion progression within 24–48 hours.
Guo 2021	NR	
Protein subunit		
NVX-CoV2373 – Novavax		
Dunkle 2021	NR	Severe refers to ≥ 1 of the following: tachypnoea ≥ 30 breaths/min at rest; resting heart rate ≥ 125 beats/min; SpO_2 ≤ 93% on room air or PaO_2/FiO_2 < 300 mmHg; high-flow O_2 therapy or non-invasive ventilation/non-invasive positive pressure ventilation (e.g. continuous positive airway pressure or bilevel positive airway pressure; mechanical ventilation or extracorporeal membrane oxygenation; ≥ 1 major organ system dysfunction or failure to be defined by diagnostic testing/clinical syndrome/interventions, including any of the following – acute respiratory failure, including acute respiratory distress syndrome, acute renal failure, acute hepatic failure, acute right or left heart failure, septic or cardiogenic shock (with shock defined as systolic blood pressure < 90 mmHg or diastolic blood pressure < 60 mmHg), acute stroke (ischaemic or haemorrhagic), acute thrombotic event; acute myocardial infarction, deep vein thrombosis, pulmonary embolism, requirement for: vasopressors, systemic corticosteroids, or haemodialysis; admission to an intensive care unit; death.
Formica 2021	NR	NR
Heath 2021	An SAE is defined as any event that results in death, is immediately life-threatening, requires inpatient hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability/incapacity, or is a congenital anomaly/birth defect.	Tachypnoea ≥ 30 breaths/min at rest; resting heart rate ≥ 125 beats/min; SpO_2 ≤ 93% on room air or PaO_2/FiO_2 < 300 mmHg; high-flow O_2 therapy or non-invasive ventilation/non-invasive positive pressure ventilation (e.g. continuous positive airway pressure or bilevel positive airway pressure; mechanical ventilation or extracorporeal membrane oxygenation; ≥ 1 major organ system dysfunction or failure to be defined by diagnostic testing/clinical syndrome/interventions, including any of the following – acute respiratory failure, including acute respiratory distress syndrome, acute renal

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		failure, acute hepatic failure, acute right or left heart failure, septic or cardiogenic shock (with shock defined as systolic blood pressure < 90 mmHg or diastolic blood pressure < 60 mmHg), acute stroke (ischaemic or haemorrhagic), acute thrombotic event; acute myocardial infarction, deep vein thrombosis, pulmonary embolism, requirement for: vasopressors, systemic corticosteroids, or haemodialysis; admission to an intensive care unit; death.
Shinde 2021	NR	Severe refers to ≥ 1 of the following: tachypnoea ≥ 30 breaths/min at rest; resting heart rate ≥ 125 beats/min; SpO_2 ≤ 93% on room air or PaO_2/FiO_2 < 300 mmHg; high-flow O_2 therapy or non-invasive ventilation/non-invasive positive pressure ventilation (e.g. continuous positive airway pressure or bilevel positive airway pressure; mechanical ventilation or extracorporeal membrane oxygenation; ≥ 1 major organ system dysfunction or failure to be defined by diagnostic testing/clinical syndrome/interventions, including any of the following – acute respiratory failure, including acute respiratory distress syndrome, acute renal failure, acute hepatic failure, acute right or left heart failure, septic or cardiogenic shock (with shock defined as systolic blood pressure < 90 mmHg or diastolic blood pressure < 60 mmHg), acute stroke (ischaemic or haemorrhagic), acute thrombotic event; acute myocardial infarction, deep vein thrombosis, pulmonary embolism, requirement for: vasopressors, systemic corticosteroids, or haemodialysis; admission to an intensive care unit; death.
FINLAY-FR-2 – Instituto Finlay de Vacunas		
Toledo-Romani 2021	NR	Severe systemic confirmed COVID-19 disease (serious or critical), defined by 1 of the following criteria: polypnoea; x-ray infiltration/condensation, pulmonary echography; oxygen saturation ≤ 90% or assisted mechanical ventilation (serious disease), acute respiratory distress syndrome or evidence of septic shock (critical disease).
Heterologous vaccination		
Liu 2021	Any untoward medical occurrence that: results in death; is life-threatening; requires inpatient hospitalisation or prolongation of existing hospitalisation; results in persistent or significant disability/incapacity; consists of a congenital anomaly or birth defect.	NR

Appendix 2. Search strategies

Cochrane COVID-19 Study Register

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Source	Search strategy (last search date 5 November 2021)
PubMed	(2019 nCoV[tiab] OR 2019nCoV[tiab] OR corona virus[tiab] OR corona viruses[tiab] OR coronavirus[tiab] OR coronaviruses[tiab] OR COVID[tiab] OR COVID19[tiab] OR nCov 2019[tiab] OR SARS-CoV2[tiab] OR SARS CoV-2[tiab] OR SARSCoV2[tiab] OR SARSCoV-2[tiab] OR "COVID-19"[Mesh] OR "COVID-19 Testing"[Mesh] OR "COVID-19 Vaccines"[Mesh] OR "Coronavirus"[Mesh:NoExp] OR "Receptors, Coronavirus"[Mesh] OR "SARS-CoV-2"[Mesh] OR "Spike Glycoprotein, Coronavirus"[Mesh]) NOT ("animals"[mh] NOT "humans"[mh]) NOT (editorial[pt] OR newspaper article[pt])
Embase	((('anti-SARS-CoV-2 agent'/exp OR 'coronaviridae'/de OR 'coronavirinae'/de OR 'coronaviridae infection'/de OR 'coronavirus disease 2019'/exp OR 'coronavirus infection'/de OR 'COVID-19 testing'/exp OR 'sars coronavirus 2 test kit'/exp OR 'sars-related coronavirus'/de OR 'severe acute respiratory syndrome coronavirus 2'/exp OR '2019 ncov':ti,ab,kw OR 2019ncov:ti,ab,kw OR (((corona* OR corono*) NEAR/1 (virus* OR viral* OR virinae*)):ti,ab,kw) OR coronavir*:ti,ab,kw OR coronovir*:ti,ab,kw OR covid:ti,ab,kw OR covid19:ti,ab,kw OR hcov*:ti,ab,kw OR 'ncov 2019':ti,ab,kw OR 'sars cov2':ti,ab,kw OR 'sars cov 2':ti,ab,kw OR sarscov2:ti,ab,kw OR 'sarscov 2':ti,ab,kw) NOT (('animal experiment'/de OR 'animal'/exp) NOT ('human'/exp OR 'human experiment'/de))) NOT 'editorial'/it) NOT ([medline]/lim OR [pubmed-not-medline]/lim) AND [1-12-2019]/sd
CENTRAL	1 ("2019 nCoV" OR 2019nCoV OR "corona virus*" OR coronavirus* OR COVID OR COVID19 OR "nCov 2019" OR "SARS-CoV2" OR "SARS CoV-2" OR SARSCoV2 OR "SARSCoV-2"):TI,AB AND CENTRAL:TARGET 2 Coronavirus:MH AND CENTRAL:TARGET 3 Coronavirus:EH AND CENTRAL:TARGET 4 #1 OR #2 OR #3 5 2019 TO 2021:YR AND CENTRAL:TARGET 6 #5 AND #4 7 INSEGMENT 8 #6 NOT #7
ClinicalTrials.gov	COVID-19 OR 2019-nCoV OR SARS-CoV-2 OR coronavirus
WHO ICTRP	COVID OR 2019-nCoV OR SARS-CoV-2 OR coronavirus OR corona virus
medRxiv	All new medRxiv records are imported each week into the Cochrane Register of Studies. Records captured by this strategy are then evaluated: ("2019 nCoV" OR 2019nCoV OR "corona virus*" OR coronavirus* OR COVID OR COVID19 OR "nCov 2019" OR "SARS-CoV2" OR "SARS CoV-2" OR SARSCoV2 OR "SARSCoV-2"):TI,AB

Epistemonikos L·OVE COVID-19 platform

Search strategy
coronavir* OR coronovirus* OR betacoronavir* OR "beta-coronavirus" OR "beta-coronaviruses" OR "corona virus" OR "virus corona" OR "corono virus" OR "virus corono" OR hcov* OR covid* OR "2019-ncov" OR cv19* OR "cv-19" OR "cv 19" OR "n-cov" OR ncov* OR

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(Continued)
(wuhan* AND (virus OR viruses OR viral)) OR "2019-ncov-related" OR "cv-19-related" OR "n-cov-related" OR sars* OR sari OR "severe acute respiratory syndrome" OR antisars* OR "anti-sars-cov-2" OR "anti-sars-cov2" OR "anti-sarscov-2" OR "anti-sarscov-2" OR "post-COVID-19" OR "Not-of-COVID-19" OR "corona patients" OR "article-covid-19" OR "post-covid-19" OR "post-covid" OR "with-covid-19" OR "pre-covid" OR "pre-covid-19" OR "with-covid" OR "anti-covid-19" OR "n-covid" OR "no-covid"

For the Epistemonikos L*OVE COVID-19 platform we:

- select type of question “Prevention or treatment”
- select intervention “Public health”, “Vaccination” and “SARS-CoV-2 vaccines”
- select “Primary studies”
- filter results by “RCT”
- export the results in a.ris file
- upload the results into Rayyan ®
- export results in an excel file
- eliminate duplicates
- cross-check with the latest extraction to eliminate duplicates and obtain only new articles (L*OVE platform does not filter results by day)

For the Cochrane COVID-19 Study Register we:

- select new studies “Last week”
- select update new references “Last week”
- select results available “Report results”
- select study characteristics, study type “Interventional”
- select study characteristics, study aim “Treatment and management”
- select study characteristics, intervention assignment “Randomized”

For the Retraction Watch Website:

- click in « Retracted coronavirus (COVID-19) papers »
- check the list of news Retracted papers

For the ICTRP:

The records are automatically extracted in the platform https://ctr-dwh.limos.fr/

For the EMA Website we:

- select « Vaccines » in Covid-19 pandemic
- select « name of vaccine » in Authorized for use in the European Union
- search « Assessment report »
- export the results in a PDF file

For the FDA Website we:

- click in « FDA Covid-19 Response »
- select « name of vaccine » in COVID-19 Vaccines
- search reports of interest
- export the results in a PDF file
- in the home page, search in search Search Toolbar « Briefing Document » for each FDA-approved vaccine

Appendix 3. Additional methods for future network meta-analysis (NMA) updates

Below are additional methods to consider if a NMA and subgroup analyses are to be conducted in future updates.

Unit of analysis issues

If we perform a NMA, we will properly account for the correlation of effect sizes coming from multiple-arm trials.

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If we identify any eligible cluster-randomized trials, we will extract results that properly account for the cluster design (such as based on a multiple-level model or on generalized estimating equations). If such an analysis is not reported, we will contact study authors to try to obtain the parameters required to be able to calculate an estimate of the intraclass correlation coefficient for the meta-analyses to adjust for the design effect. Should these not be obtained, the trial will still be included, although it will be mentioned as a limitation of the analysis.

Assessment of transitivity

If a certain number of studies are available (e.g. at least 3 studies for 30% of the available direct comparisons), we will opt for conducting a NMA. Prior to this analysis, we will assess whether the assumption that the anchor treatments are transitive to allow valid indirect inference is likely to be plausible. Specifically, we will evaluate the similarity of the distribution of the potential effect modifiers (variants of the virus, baseline risk such as rate of transmission of COVID-19 at the time the trials were conducted, immune status) across the available comparisons. Throughout the living review, we will be consulting content experts and update, if necessary, the list of potential effect modifiers. We will use boxplots to depict the distributions of these variables across comparisons. In terms of node (i.e. vaccine) definition, we do not expect substantial heterogeneity that could threaten the transitivity assumption.

Assessment of reporting biases

We will use funnel plots (in the presence of at least 10 studies per meta-analysis) and statistical tests (such as the Egger's test) (Egger 1997) to assess the potential for small-study effects. If asymmetry is found, we will explore possible reasons for the apparent association between study size and study effect. If publication bias is suspected, we will apply selection models that make assumptions about the probability of publication based on the study results (Mavridis 2014). If NMA is deemed feasible, we will also draw comparison-adjusted funnel plots; these are modified funnel plots appropriate for putting together all studies from a NMA, irrespective of the comparison they evaluate(Chaimani 2013). This will be done only for critical outcomes.

If there are no major concerns about transitivity (see above), we will also perform a random-effects NMA for each outcome. The analysis will be performed at the vaccine level (not the type of vaccine), hence we will not combine different vaccines. We will assume a common heterogeneity parameter for each network. We will present the results in terms of effect sizes and 95% CIs in league tables and will use colours to represent the certainty of the evidence for every comparison. We will assess the impact of heterogeneity on the results by using prediction intervals. To rank the interventions, in the absence of excessive uncertainty in the relative effects, we will use the surface under the cumulative ranking curve (SUCRA) (Salanti 2011). This will be done for critical outcomes. We will run analyses and produce graphical displays using R (netmeta package)(Rucker 2013) and Stata network (White 2008), and network graphs packages (Chaimani 2015). If important concerns about transitivity are detected, we will only perform pairwise meta-analyses.

Assessment of incoherence

We will evaluate the assumption coherence, which refers to the agreement between direct and indirect evidence, using local and global tests. Local approaches assess coherence in parts of the network, while global approaches assess coherence in the entire network jointly. Specifically, we will use the side-splitting method (Dias 2010) and the design-by-treatment interaction model (Higgins 2021). We will consider P values < 0.10 as suspicious for incoherence. Tests for incoherence are known to have low power and may not be able to detect incoherence even when present, so we will interpret the results of the tests with caution.

Subgroup analysis and investigation of heterogeneity/incoherence

In the NMA, we will conduct the same subgroup analysis already prespecified for the for pairwise comparisons.

Sensitivity analysis

We will perform sensitivity analyses by excluding RCTs with an overall high risk of bias, RCTs reported in preprint only, and early-phase trials. For the NMA, we will also perform a sensitivity analysis assuming that the effects of the vaccines of the same type (e.g. RNA-based vaccine) are related, although not identical.

Summary of findings and assessment of the certainty of the evidence of the review findings

We will prepare separate summary of findings tables of the NMA for each critical outcome. These tables will report the different comparisons included in the network, relative and absolute effect estimates, and the certainty of the evidence (Chaimani 2022; Yepes-Nuñez 2019). We will calculate absolute effects using the baseline risks in the control groups of the included studies. Two review authors will independently rate the evidence's overall certainty for each outcome using the CINeMA tool and all decisions to downgrade or update the certainty of evidence will be made explicit.

To evaluate the certainty of the evidence in the NMA for the critical outcomes, we will use the CINeMA tool that considers the following domains: within-study-bias, across-studies bias, indirectness, imprecision, heterogeneity and incoherence (Nikolakopoulou 2020). For within-study bias and indirectness, CINeMA calculates the contribution of each study in the estimation and combines these contributions with the study-specific evaluations (low, moderate, high) to rate the relative effect for each comparison in the network. The domains of imprecision, heterogeneity and incoherence use a prespecified important size of effect to specify the margin of equivalence between two interventions. This will be defined by consulting the content experts.

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Appendix 4. Characteristics of unpublished registered studies

Characteristics of unpublished registered studies: RNA-based vaccine (73 studies)

Registration number	Registration date	Status	Design	Interventions	Estimated sample size	Phase
ChiCTR2000034112	24 June 2020	Not recruiting	Parallel	ARCoV	168	Phase 1
ChiCTR2100041855	8 January 2021	Not recruiting	Parallel	ARCoV	420	Phase 2
NCT04847102	15 April 2021	Not recruiting	Cross-over	ARCoV	28,000	Phase 3
NCT04668339	16 December	Not recruiting	Parallel	ARCT-021	600	Phase 2
ChiCTR2000040044	19 November 2020	Not recruiting	Parallel	BNT162b2	960	Phase 2
NCT04588480	19 October 2020	Not recruiting	Parallel	BNT162b2	160	Phase 1/ Phase 2
NCT04649021	2 December 2020	Not recruiting	Parallel	BNT162b2	950	Phase 2
NCT04816669	25 March 2021	Not recruiting	Parallel	BNT162b2	610	Phase 3
NCT04955626	9 July 2021	Not recruiting	Parallel	BNT162b2	10,000	Phase 3
NCT04961229	14 July 2021	Not recruiting	Parallel	BNT162b2	450	Phase 4
NCT04969250	20 July 2021	Not recruiting	Factorial	BNT162b2	640	Phase 4
NCT05057169	27 September 2021	Not recruiting	Parallel	BNT162b2	400	Phase 4
NCT05029245	31 August 2021	Not recruiting	Parallel	BNT162b2	1000	Phase 3
NCT05081271	18 October 2021	Not recruiting	Parallel	BNT162b2	60	Not reported
NCT05077254	14 October 2021	Not recruiting	Parallel	BNT162b2	400	Phase 2
TCTR20210923012	23 September 2021	Not recruiting	Parallel	BNT162b2 + Coro-naVac	80	Phase 2
AC-TRN12621001465842	26 October 2021	Not recruiting	Parallel	BNT162b2 + inulin	120	Not reported
AC-TRN12621001412820	20 October 2021	Not recruiting	Parallel	BNT162b2 + sirolimus	120	Not reported
NCT04566276	28 September 2020	Not recruiting	Sequential assignment	ChulaCov19 mRNA vaccine	96	Phase 1/ Phase 2
NCT04674189	19 December 2020	Not recruiting	Parallel	CVnCoV	2520	Phase 3
NCT04848467	19 April 2021	Not recruiting	Parallel	CVnCoV + influen-za vaccine	1000	Phase 3

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NCT04821674	29 March 2021	Not recruiting	Parallel	DS-5670a	152	Phase 1/ Phase 2
NCT04844268	14 April 2021	Not recruiting	Parallel	HDT 301 vaccine	78	Phase 1
ChiCTR2100049349	31 July 2021	Not recruiting	Parallel	LVRNA009	144	Phase 1
ChiCTR2100049104	21 July 2021	Not recruiting	Parallel	mRNA vaccine	2000	Phase 3
ChiCTR2100049521	2 August 2021	Not recruiting	Parallel	mRNA vaccine	320	Phase 1/ Phase 2
NCT04677660	21 December 2020	Not recruiting	Parallel	mRNA-1273	200	Phase 1/ Phase 2
NCT04805125	18 March 2021	Not recruiting	Parallel	mRNA-1273	380	Phase 3
PACTR202105817814362	20 May 2021	Not recruiting	Cross-over	mRNA-1273	14,000	Phase 3
NCT05000216	11 August 2021	Not recruiting	Parallel	mRNA-1273	600	Phase 2
NCT04978038	27 July 2021	Not recruiting	Parallel	mRNA-1273	414	Phase 4
NCT04785144	5 March 2021	Not recruiting	Parallel	mRNA-1273.351	210	Phase 1
NCT05069636	6 October 2021	Not recruiting	Parallel	mRNA-1273 + osteopathic manipulative medicine	100	Not reported
NCT04765436	21 February 2021	Not recruiting	Parallel	PTX-COVID19-B	60	Phase 1
EUCTR2021-005043-71-NL	9 October 2021	Ongoing	Parallel	BNT162b2	400	Phase 2
ChiCTR2000039212	22 October 2020	Ongoing	Parallel	ARCoV	120	Phase 1
ISRCTN15779782	8 October 2021	Ongoing	Adaptive	ARCT-021	100,000	Phase 3
NCT05012943	19 August 2021	Ongoing	Parallel	ARCT-154	21,000	Phase 2/ Phase 3
NCT05037097	8 September 2021	Ongoing	Parallel	ARCT-165	72	Phase 1/ Phase 2
ACTRN12621000661875	1 June 2021	Ongoing	Parallel	BNT162b2	100	Phase 4
NCT04713553	19 January 2021	Ongoing	Parallel	BNT162b2	1530	Phase 3
NCT04754594	15 February 2021	Ongoing	Parallel	BNT162b2	4000	Phase 3
NCT04907331	28 May 2021	Ongoing	Parallel	BNT162b2	3000	Phase 2
NCT04949490	2 July 2021	Ongoing	Sequential assignment	BNT162b2	549	Phase 2

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EUC-TR2021-003331-28-ES	21 June 2021	Ongoing	Parallel	BNT162b2	776	Phase 4
EUC-TR2020-005442-42-PL	11 August 2021	Ongoing	Parallel	BNT162b2	4644	Phase 1/ Phase 2/ Phase 3
NCT05022329	26 August 2021	Ongoing	Parallel	BNT162b2	300	Phase 2/ Phase 3
NCT05047640	17 September 2021	Ongoing	Parallel	BNT162b2	200	Phase 3
ISRCTN12348322	16 September 2021	Ongoing	Parallel	BNT162b2	360	Phase 2
TCTR20210917004	17 September 2021	Ongoing	Parallel	BNT162b2	120	Phase 2
NCT04977479	27 July 2021	Ongoing	Cross-over	BNT162b2	100	Phase 2
EUC-TR2021-004526-29-DE	6 September 2021	Ongoing	Adaptive	BNT162b2	85	Phase 2
EUC-TR2021-001993-52-BE	5 May 2021	Ongoing	Parallel	BNT162b2	840	Phase 4
NCT04887948	14 May 2021	Ongoing	Parallel	BNT162b2 + pneumococcal vaccine	600	Phase 3
NCT05060991	29 September 2021	Ongoing	Parallel	BNT162b2 + reduction in antimetabolite immunosuppression	50	Phase 4
ChiCTR2100045984	1 May 2021	Ongoing	Parallel	COVID-19 mRNA vaccine (nucleoside-modified)	240	Phase 1
NCT05028361	31 August 2021	Ongoing	Parallel	COVID-19 mRNA vaccine (nucleoside-modified) + influenza vaccine	450	Phase 4
NCT04863131	28 April 2021	Ongoing	Parallel	EXG-5003	60	Phase 1/ Phase 2
CTRI/2021/04/032688	28 April 2021	Ongoing	Parallel	HGCO19	620	Phase 1/ Phase 2
ISRCTN17072692	4 June 2020	Ongoing	Parallel	LNP-nCoVsaRNA	320	Phase 1
ISRCTN27841311	26 March 2021	Ongoing	Parallel	mRNA-1273	1050	Phase 2
NCT04761822	21 February 2021	Ongoing	Parallel	mRNA-1273	3400	Phase 2
NCT04796896	15 March 2021	Ongoing	Parallel	mRNA-1273	7050	Phase 2/ Phase 3
NCT04811664	23 March 2021	Ongoing	Cross-over	mRNA-1273	37,500	Phase 3

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NCT04894435	20 May 2021	Ongoing	Parallel	mRNA-1273	1300	Phase 1/ Phase 2
EUC-TR2021-004558-44-NL	13 September 2021	Ongoing	Parallel	mRNA-1273	460	Phase 4
NCT04900467	25 May 2021	Ongoing	Parallel	mRNA-1273	400	Not reported
NCT04852978	21 April 2021	Ongoing	Parallel	mRNA-1273 + casirivimab + imdevimab	180	Phase 2
NCT04969276	20 July 2021	Ongoing	Parallel	mRNA-1273 + quadrivalent influenza vaccine	300	Phase 2
NCT04813796	24 March 2021	Ongoing	Parallel	mRNA-1283	125	Phase 1
NCT04798027	15 March 2021	Ongoing	Parallel	MRT5500	333	Phase 1/ Phase 2
NCT05079633	15 October 2021	Ongoing	Parallel	MVC-COV1901 + mRNA-1273	220	Phase 4
JPRN-jRCT2071210067	28 September 2021	Ongoing	Parallel	VLPCOV-01	45	Phase 1

Characteristics of unpublished registered studies: non-replicating viral vector (73 studies)

Registration number	Registration date	Status	Design	Interventions	Estimated sample size	Phase
NCT04690387	30 December 2020	Completed	Adaptive	AV-COVID-19	27	Phase 1
ChiCTR2000031781	10 April 2020	Not recruiting	Parallel	Recombinant novel coronavirus (2019-ncov) vaccine (adenovirus vector)	500	Phase 2
CTRI/2021/02/031295	15 February 2021	Not recruiting	Parallel	BBV154	175	Phase 1
CTRI/2021/05/033665	18 May 2021	Not recruiting	Parallel	COVID-Vac Combined Vector Vaccine	228	Phase 3
NCT04398147	21 May 2020	Not recruiting	Adaptive	Ad5-nCoV	696	Phase 1/ Phase 2
NCT04509947	12 August 2020	Not recruiting	Parallel	Ad26.COV2.S	250	Phase 1
NCT04540419	7 September 2020	Not recruiting	Parallel	Ad5-nCoV	500	Phase 3

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NCT04564716	25 September 2020	Not recruiting	Parallel	Gam-COVID-Vac	100	Phase 3
NCT04614948	4 November 2020	Not recruiting	Parallel	Ad26.COV2.S	30,000	Phase 3
NCT04640233	23 November 2020	Not recruiting	Adaptive	Gam-COVID-Vac	1600	Phase 2/ Phase 3
NCT04642339	24 November 2020	Not recruiting	Parallel	Gam-COVID-Vac	2000	Phase 3
NCT04656613	7 December 2020	Not recruiting	Parallel	Gam-COVID-Vac	1000	Phase 3
NCT04679909	22 December 2020	Not recruiting	Parallel	AdCOVID	180	Phase 1
NCT04751682	12 February 2021	Not recruiting	Parallel	BBV154	175	Phase 1
NCT04760730	18 February 2021	Not recruiting	Parallel	ChAdOx1 nCoV-19 + rAd26-S	100	Phase 1/ Phase 2
NCT04791423	10 March 2021	Not recruiting	Parallel	GRAd-COV2	10,300	Phase 2/ Phase 3
NCT04840992	12 April 2021	Not recruiting	Parallel	Ad5-nCoV	840	Phase 1/ Phase 2
NCT04843722	13 April 2021	Not recruiting	Sequential assignment	hAd5-S-Fusion/N-ETSD vaccine	540	Phase 1/ Phase 2
NCT04845191	14 April 2021	Not recruiting	Sequential assignment	hAd5-S-Fusion/N-ETSD vaccine	540	Phase 1/ Phase 2
NCT04894305	20 May 2021	Not recruiting	Parallel	Ad26.COV2.S	380	Phase 1
NCT04895449	20 May 2021	Not recruiting	Parallel	MVA-SARS-2-S	240	Phase 1/ Phase 2
NCT04977024	26 July 2021	Not recruiting	Parallel	COH04S1	240	Phase 2
PACTR202104601572555	15 April 2021	Not recruiting	Parallel	Sputnik light vaccine	2200	Phase 3
NCT05011526	18 August 2021	Not recruiting	Parallel	ChAdOx1 nCoV-19	1020	Phase 3
NCT05027672	30 August 2021	Not recruiting	Parallel	Gam-COVID-Vac	348	Phase 2
NCT05030974	1 September 2021	Not recruiting	Parallel	Ad26.COV2.S vaccine	460	Phase 4
NCT04998240	10 August 2021	Not recruiting	Parallel	BBIBP-CorV + ChAdOx1 nCoV-19	360	Phase 2
TC-TR20210717002	17 July 2021	Not recruiting	Parallel	ChAdOx1 nCoV-19 + Coro-naVac	165	Phase 4
TC-TR20210903006	3 September 2021	Not recruiting	Sequential assignment	ChAdOx1 nCoV-19 + Coro-naVac	80	Phase 1/ Phase 2
TC-TR20210904004	4 September 2021	Not recruiting	Sequential assignment	ChAdOx1 nCoV-19 + inacti-vated COVID-19 vaccine	40	Phase 1/ Phase 2

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NCT05091307	25 October 2021	Not recruiting	Parallel	Ad26.COV2.S + influenza vaccine	1680	Phase 3
NCT04833101	6 April 2021	Not recruiting	Parallel	Ad5-nCoV + ZF2001	120	Phase 4
NCT05048940	17 September 2021	Not recruiting	Parallel	Ad26.COV2.S	386	Phase 3
NCT05049226	20 September 2021	Not recruiting	Parallel	ChAdOx1 nCoV-19	1320	Phase 2
ChiC-TR2100049530	2 August 2021	Not recruiting	Parallel	ChAdTS-S	360	Phase 2
TC-TR20210907003	7 September 2021	Not recruiting	Sequential assignment	ChAdOx1 nCoV-19	60	Phase 1/ Phase 2
TC-TR20211004005	4 October 2021	Not recruiting	Parallel	ChAdOx1 nCoV-19	300	Phase 2
NCT04730895	29 January 2021	Not recruiting	Parallel	ChAdOx1 nCoV-19	360	Phase 1/ Phase 2
NCT05094609	26 October 2021	Not recruiting	Parallel	Ad5-triCoV/Mac	30	Phase 1
NCT05007496	16 August 2021	Not recruiting	Parallel	AV-COVID-19	145	Phase 2
EUC-TR2020-005226-28-IT	23 November 2020	Ongoing	Parallel	ChAdOx1 nCoV-19	40,000	Phase 3
ChiC-TR2100044249	12 March 2021	Ongoing	Adaptive	Ad5-nCoV	40,000	Phase 3
EUC-TR2020-002584-63-DE	12 August 2020	Ongoing	Parallel	Ad26.COV2.S	225	Phase 2
EUC-TR2020-005801-14-PL	30 December 2020	Ongoing	Parallel	Ad26.COV2.S	570	Phase 3
EUC-TR2021-002693-10-AT	19 May 2021	Ongoing	Parallel	ChAdOx1 nCoV-19	150	Phase 2
ISRCTN73765130	13 May 2021	Ongoing	Adaptive	ChAdOx1 nCoV-19	2886	Phase 2
NCT04526990	26 August 2020	Ongoing	Adaptive	Ad5-nCoV	40,000	Phase 3
NCT04536051	2 September 2020	Ongoing	Sequential assignment	ChAdOx1 nCoV-19	10,300	Phase 3
NCT04639466	20 November 2020	Ongoing	Parallel	COH04S1	129	Phase 1
NCT04666012	14 December 2020	Ongoing	Sequential assignment	AdCLD-CoV19	150	Phase 1/ Phase 2
NCT04684446	24 December 2020	Ongoing	Parallel	ChAdOx1 nCoV-19 + rAd26-S	100	Phase 1/ Phase 2

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NCT04741061	5 February 2021	Ongoing	Parallel	Sputnik light vaccine	6000	Phase 3
NCT04776317	1 March 2021	Ongoing	Parallel	ChAdV68-S-TCE	140	Phase 1
NCT04816019	25 March 2021	Ongoing	Sequential assignment	ChAdOx1 nCoV-19	54	Phase 1
NCT04830800	5 April 2021	Ongoing	Parallel	COVIVAC	420	Phase 1/ Phase 2
NCT04916886	8 June 2021	Ongoing	Parallel	Ad5-nCoV	2016	Not report-ed
NCT04952727	7 July 2021	Ongoing	Parallel	Ad5-nCoV	300	Phase 4
NCT04954092	8 July 2021	Ongoing	Sequential assignment	Gam-COVID-Vac M	350	Phase 2/ Phase 3
NCT04962906	15 July 2021	Ongoing	Parallel	Gam-COVID-Vac + ChA-dOx1 nCov-19	150	Phase 2
NCT04973449	22 July 2021	Ongoing	Parallel	ChAdOx1 nCov-19	2475	Phase 2/ Phase 3
PACTR202006922165221	22 June 2020	Ongoing	Parallel	ChAdOx1 nCoV-19	2000	Phase 1/ Phase 2
NCT04983537	30 July 2021	Ongoing	Parallel	Gam-COVID-Vac	120	Phase 2
NCT04988048	3 August 2021	Ongoing	Parallel	Gam-COVID-Vac + ChA-dOx1 nCov-19	1760	Phase 2
NCT05007951	17 August 2021	Ongoing	Parallel	ChAdOx1 nCov-19	3990	Phase 3
NCT05005156	13 August 2021	Ongoing	Parallel	Ad5-nCoV	876	Phase 2
EUC-TR2019-003102-26-IT	7 June 2021	Ongoing	Parallel	ChAdOx1 nCov-19	33	Phase 1/ Phase 2
NCT05054621	23 September 2021	Ongoing	Parallel	ChAdOx1 nCoV-19 + MVC-COV1901	110	Phase 2
EUC-TR2021-001978-37-ES	6 May 2021	Ongoing	Adaptive	ChAdOx1 nCoV-19 + BN-T162b2	600	Phase 2
NCT05037188	8 September 2021	Ongoing	Sequential assignment	BCD-250	160	Phase 1/ Phase 2
NCT05067933	5 October 2021	Ongoing	Sequential assignment	VXA-CoV2-1.1-S	896	Phase 2
TC-TR20210722003	22 July 2021	Ongoing	Parallel	ChAdOx1 nCov-19	400	Phase 2
NCT04685603	25 December 2020	Ongoing	Adaptive	AV-COVID-19	27	Phase 1
NCT04535453	2 September 2020	Cancelled	Parallel	Ad26.COV2.S	1210	Phase 2

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Characteristics of unpublished registered studies: replicating viral vector (10 studies)

Registration number	Registration date	Status	Design	Interventions	Estimated sample size	Phase
NCT04497298	4 August 2020	Completed	Parallel	TMV-083/V-591	90	Phase 1
ChiCTR2000037782	1 September 2020	Not recruiting	Parallel	DelNS1-2019-nCoV-RBD-OPT1	60	Phase 1
ChiCTR2100048316	5 July 2021	Not recruiting	Parallel	DelNS1-2019-nCoV-RBD-OPT1	400	Not reported
NCT04990466	4 August 2021	Not recruiting	Parallel	rVSV-SARS-CoV-2-S vaccine	550	Phase 2/ Phase 3
ChiCTR2100051391	22 September 2021	Not recruiting	Parallel	DelNS1-2019-nCoV-RBD-OPT1	40,000	Phase 3
ChiCTR2000039715	6 November 2020	Ongoing	Parallel	DelNS1-2019-nCoV-RBD-OPT1	720	Phase 2
NCT04608305	29 October 2020	Ongoing	Sequential assignment	rVSV-SARS-CoV-2-S vaccine	1040	Phase 1/ Phase 2
NCT04993209	6 August 2021	Ongoing	Adaptive	NDV-HXP-S	5394	Phase 1/ Phase 2
NCT04498247	4 August 2020	Terminated	Sequential assignment	V591-001	263	Phase 1/ Phase 2
NCT04569786	30 September 2020	Terminated	Sequential assignment	V590-001	232	Phase 1

Characteristics of unpublished registered studies: inactivated virus vaccine (61 studies)

Registration number	Registration date	Status	Design	Interventions	Estimated sample size	Phase
ChiCTR2000034780	8 July 2020	Completed	Parallel	Inactivated SARS-CoV-2 vaccine (vero cell)	15,000	Phase 3
ChiCTR2100041704	1 January 2021	Completed	Parallel	SARS-CoV-2 vaccine	360	Not reported

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NCT04691908	31 December 2020	Completed	Parallel	QazCovid-in	3000	Phase 3
NCT04790851	10 March 2021	Completed	Parallel	Inactivated SARS-CoV-2 vaccine (vero cell) + IIV4 + Inactivated SARS-CoV-2 vaccine (vero cell) + pneumococcal vaccine	1152	Phase 4
ChiC-TR2100046174	8 May 2021	Not recruiting	Parallel	Inactivated SARS-CoV-2 vaccine (vero cell)	1152	Phase 4
ChiC-TR2000040146	22 November 2020	Not recruiting	Parallel	INO-4800 + CoronaVac	640	Phase 2
ChiC-TR2100046227	11 May 2021	Not recruiting	Parallel	Inactivated SARS-CoV-2 vaccine (vero cell)	1404	Phase 4
JPRN-jRCT2071200106	3 March 2021	Not recruiting	Parallel	KD-414	210	Phase 1/ Phase 2
NCT04560881	23 September 2020	Not recruiting	Parallel	BBIBP-CorV	3000	Phase 3
NCT04612972	3 November 2020	Not recruiting	Parallel	Inactivated SARS-CoV-2 vaccine (vero cell)	12,000	Phase 3
NCT04747821	10 February 2021	Not recruiting	Parallel	CoronaVac	27,711	Phase 4
NCT04852705	21 April 2021	Not recruiting	Parallel	Inactivated SARS-CoV-2 vaccine (vero cell)	28,000	Phase 3
NCT04884685	13 May 2021	Not recruiting	Parallel	CoronaVac	500	Phase 2
NCT04894227	20 May 2021	Not recruiting	Parallel	CoronaVac	1080	Phase 4
NCT04917523	8 June 2021	Not recruiting	Parallel	BBIBP-CorV	1800	Phase 3
NCT04953325	7 July 2021	Not recruiting	Parallel	CoronaVac	270	Phase 4
NCT04956224	9 July 2021	Not recruiting	Parallel	VLA2001	750	Phase 3
PER-051-20	18 August 2020	Not recruiting	Parallel	Inactivated SARS-CoV-2 vaccine (vero cell)	12,000	Phase 3
NCT04984408	30 July 2021	Not recruiting	Parallel	BBIBP-CorV	8825	Phase 3
NCT04992182	5 August 2021	Not recruiting	Parallel	CoronaVac	534	Phase 2

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NCT05003466	12 August 2021	Not recruiting	Parallel	Inactivated SARS-CoV-2 vaccine (vero cell)	480	Phase 2
NCT05003479	12 August 2021	Not recruiting	Parallel	Inactivated SARS-CoV-2 vaccine (vero cell)	84	Phase 1
IRCT20210206050259N3	29 August 2021	Not recruiting	Parallel	Inactivated SARS-CoV-2 vaccine FAKHRAVAC (MIVAC)	41,128	Phase 3
NCT05035238	3 September 2021	Not recruiting	Parallel	Turkovac	200	Phase 2
CTRI/2021/08/035648	13 August 2021	Not recruiting	Parallel	Covaxin	1100	Phase 4
NCT05046548	16 September 2021	Not recruiting	Parallel	Kovivac	400	Phase 1/ Phase 2
NCT05079217	15 October 2021	Not recruiting	Parallel	CoronaVac	1200	Phase 4
NCT04993365	6 August 2021	Not recruiting	Parallel	CoronaVac + influenza vaccine + pneumococcal vaccine	440	Phase 4
NCT05079152	15 October 2021	Not recruiting	Parallel	BBIBP-CorV + influenza vaccine + pneumococcal vaccine	1404	Phase 4
IRCT20201202049567N1	15 December 2020	Ongoing	Parallel	SARS-CoV-2 vaccine	56	Phase 1
IRCT20201202049567N2	13 March 2021	Ongoing	Parallel	Antigen protein	32	Phase 1
IRCT20201202049567N3	13 March 2021	Ongoing	Parallel	Antigen protein	20,000	Phase 2/ Phase 3
IRCT20210206050259N1	8 March 2021	Ongoing	Factorial	Inactivated SARS-CoV-2 vaccine FAKHRAVAC (MIVAC)	135	Phase 1
IRCT20210206050259N2	8 June 2021	Ongoing	Parallel	Inactivated SARS-CoV-2 vaccine FAKHRAVAC (MIVAC)	500	Phase 2
ChiCTR2000039000	13 October 2020	Ongoing	Parallel	Inactivated SARS-CoV-2 vaccine (vero cell)	600	Phase 3
ChiCTR2100043907	5 March 2021	Ongoing	Parallel	Inactivated SARS-CoV-2 vaccine (vero cell)	16	Phase 4
ChiCTR2100045109	7 April 2021	Ongoing	Parallel	Inactivated COVID-19 vaccine	472	Not reported
ChiCTR2100047917	27 June 2021	Ongoing	Sequential assignment	Inactivated SARS-CoV-2 vaccine (vero cell)	20	Phase 1
CTRI/2020/07/026302	26 August 2020	Ongoing	Parallel	Covaxin	1125	Phase 1/ Phase 2

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CTRI/2020/09/027674	8 September 2020	Ongoing	Adaptive	Covaxin	124	Phase 1/ Phase 2
NCT04470609	14 July 2020	Ongoing	Parallel	SARS-CoV-2 vaccine	471	Phase 1/ Phase 2
NCT04617483	5 November 2020	Ongoing	Parallel	SARS-CoV-2 vaccine (inactivated)	1040	Phase 3
NCT04659239	9 December 2020	Ongoing	Parallel	Inactivated SARS-CoV-2 vaccine (vero cell)	34,020	Phase 3
NCT04691947	31 December 2020	Ongoing	Parallel	ERUCOV-VAC	44	Phase 1
NCT04824391	1 April 2021	Ongoing	Parallel	ERUCOV-VAC	250	Phase 2
NCT04838080	8 April 2021	Ongoing	Parallel	Inactivated COVID-19 vaccine	38	Phase 1
NCT04863638	28 April 2021	Ongoing	Parallel	BBIBP-CorV	4400	Phase 4
NCT04864561	29 April 2021	Ongoing	Parallel	VLA2001	4000	Phase 3
NCT04866069	29 April 2021	Ongoing	Parallel	SARS-CoV-2 vaccine	50	Phase 1
NCT04942405	28 June 2021	Ongoing	Parallel	CoronaVac	40,800	Phase 3
NCT04962308	14 July 2021	Ongoing	Parallel	CoronaVac	1400	Phase 4
CTRI/2021/04/032941	19 April 2021	Ongoing	Parallel	Covaxin	190	Phase 2
NCT04979949	28 July 2021	Ongoing	Parallel	CoronaVac	111	Phase 2
NCT04992260	5 August 2021	Ongoing	Parallel	CoronaVac	7000	Phase 3
NCT05033847	3 September 2021	Ongoing	Parallel	Inactivated SARS-CoV-2 vaccine (vero cell)	1800	Phase 3
CTRI/2021/08/035993	27 August 2021	Ongoing	Parallel	Covaxin	608	Phase 2/ Phase 3
NCT05043259	14 September 2021	Ongoing	Parallel	Inactivated SARS-CoV-2 vaccine (vero cell)	420	Phase 1/ Phase 2
ChiC-TR2100050589	31 August 2021	Ongoing	Sequential assignment	Inactivated SARS-CoV-2 vaccine (vero cell)	500	Phase 4
TC-TR20210731003	31 July 2021	Ongoing	Parallel	BBIBP-CorV	960	Phase 2
ChiC-TR2100051645	29 September 2021	Ongoing	Parallel	Inactivated SARS-CoV-2 vaccine (vero cell)	600	Phase 2
NCT05095298	27 October 2021	Ongoing	Parallel	SARS-CoV-2 vaccine (inactivated)	400	Phase 4

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Characteristics of unpublished registered studies: protein subunit (91 studies)

Registration number	Registration date	Status	Design	Interventions	Estimated sample size	Phase
NCT04453852	1 July 2020	Completed	Parallel	COVAX-19	40	Phase 1
IRCT20201214049709N1	21 January 2021	Completed	Parallel	RAZI-COV PARS	133	Phase 1
RPCEC00000345	26 November 2020	Not recruiting	Parallel	CIGB-669 (RBD/AgnHB)	88	Phase 1/ Phase 2
RPCEC00000381	1 July 2021	Not recruiting	Parallel	CIGB-66 (RBD/aluminium hydroxide)	592	Phase 1/ Phase 2
RPCEC00000382	9 July 2021	Not recruiting	Parallel	CIGB-669 (RBD/HBcAg)	120	Phase 1/ Phase 2
NCT05084989	20 October 2021	Not recruiting	Cross-over	Recov – recombinant 2-component COVID-19 vaccine (cho cell)	20,301	Phase 2/ Phase 3
RPCEC00000346	26 November 2020	Not recruiting	Factorial	CIGB-66 (RBD/aluminium hydroxide)	132	Phase 1/ Phase 2
PACTR202107562437077	27 July 2021	Not recruiting	Factorial	Recombinant SARS-CoV-2 fusion protein vaccine (v-01)	22,500	Phase 3
PACTR202108616960696	6 August 2021	Not recruiting	Factorial	CpG 1018/alum adjuvant + scb-2019	600	Phase 3
ACTRN12620001308987	4 December 2020	Not recruiting	Parallel	RBD + alum adjuvant	255	Phase 1/ Phase 2
ACTRN12621000882820	8 July 2021	Not recruiting	Parallel	IVX-411	84	Phase 2
ChiCTR2000035691	16 August 2020	Not recruiting	Parallel	Recombinant SARS-CoV-2 vaccine (CHO Cell)	50	Phase 1
ChiCTR2000037518	28 August 2020	Not recruiting	Parallel	Recombinant SARS-CoV-2 vaccine (Sf9 Cell)	168	Phase 1
ChiCTR2000040153	22 November 2020	Not recruiting	Parallel	Recombinant SARS-CoV-2 vaccine (CHO Cell)	29,000	Phase 3
ChiCTR2100048439	7 July 2021	Not recruiting	Parallel	Recombinant SARS-CoV-2 vaccine (CHO cell)	75	Phase 1
CTRI/2020/11/029032	13 November 2020	Not recruiting	Parallel	BECOV2	360	Phase 1/ Phase 2

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CTRI/2021/02/031354	24 February 2021	Not recruiting	Parallel	SARS-CoV-2 rS/Matrix M1-adjuvant	1600	Phase 2/ Phase 3
JPRN-jRCT2051200092	9 December 2020	Not recruiting	Parallel	S-268019	300	Phase 1/ Phase 2
NCT04473690	16 July 2020	Not recruiting	Parallel	KBP-COVID-19	180	Phase 1/ Phase 2
NCT04672395	17 December 2020	Not recruiting	Parallel	SCB-2019 + CpG 1018/Alum-adjuvant	22,000	Phase 2/ Phase 3
NCT04683224	24 December 2020	Not recruiting	Parallel	UB-612	7320	Phase 2/ Phase 3
NCT04712110	15 January 2021	Not recruiting	Parallel	TAK-019	200	Phase 1/ Phase 2
NCT04742738	8 February 2021	Not recruiting	Parallel	GBP510 + aluminium hydroxide adjuvant	260	Phase 1/ Phase 2
NCT04750343	11 February 2021	Not recruiting	Parallel	GBP510 + AS03 adjuvant	320	Phase 1/ Phase 2
NCT04760743	18 February 2021	Not recruiting	Parallel	NBP2001	50	Phase 1
NCT04780035	3 March 2021	Not recruiting	Parallel	EpiVacCorona	3000	Phase 3
NCT04784767	5 March 2021	Not recruiting	Parallel	SpFN_1B-06-PL + ALFQ (QS21 adjuvant)	72	Phase 1
NCT04887207	14 May 2021	Not recruiting	Parallel	Recombinant SARS-CoV-2 vaccine (Sf9 Cell)	40,000	Phase 3
NCT04930003	18 June 2021	Not recruiting	Parallel	QazCoVac-P	244	Phase 1/ Phase 2
NCT04944368	29 June 2021	Not recruiting	Parallel	SARS-CoV-2 recombinant spike protein + Advax-SM adjuvant	400	Phase 2
NCT04950751	6 July 2021	Not recruiting	Parallel	SCB-2020S	150	Phase 2
NCT04951388	6 July 2021	Not recruiting	Parallel	COV1901	385	Phase 2
NCT04954131	8 July 2021	Not recruiting	Parallel	SCB-2019	800	Phase 2
PACTR202011523110603	10 December 2020	Not recruiting	Parallel	SARS-CoV-2 recombinant protein vaccine + AS03 adjuvant	34,520	Not reported
PACTR202103845381761	31 March 2021	Not recruiting	Parallel	Recombinant SARS-CoV-2 vaccine (Sf9 Cell)	40,000	Phase 3

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RPCEC00000347	17 December 2020	Not recruiting	Parallel	FINLAY-FR-2 anti-SARS-CoV-2 vaccine	910	Phase 2
RPCEC00000359	18 March 2021	Not recruiting	Parallel	CIGB-66 (RBD/aluminium hydroxide)	48,000	Phase 3
RPCEC00000366	9 April 2021	Not recruiting	Parallel	FINLAY-FR-1A anti-SARS-CoV-2 Vaccine	450	Phase 2
NCT05007509	16 August 2021	Not recruiting	Parallel	Hipra	30	Phase 1/ Phase 2
NCT05005559	13 August 2021	Not recruiting	Parallel	SARS-CoV-2 recombinant spike p + Advax-cpg adjuvant	16,876	Phase 3
NCT05012787	19 August 2021	Not recruiting	Parallel	SCB-2019 + CpG 1018 adjuvant	300	Phase 3
NCT05013983	20 August 2021	Not recruiting	Parallel	Recombinant SARS-CoV-2 vaccine (Sf9 Cell)	600	Phase 1/ Phase 2
NCT05016934	23 August 2021	Not recruiting	Parallel	Versamune-CoV-2FC	360	Phase 1/ Phase 2
JPRN-jRCT2051210057	29 July 2021	Not recruiting	Parallel	Recombinant SARS-CoV-2 vaccine (Sf9 Cell)	240	Phase 1/ Phase 2
NCT05029856	1 September 2021	Not recruiting	Parallel	Monovalent B.1.351 vaccine + Matrix-M1 Adjuvant	240	Phase 1/ Phase 2
CTRI/2021/08/036374	31 August 2021	Not recruiting	Parallel	Corbevax	2140	Phase 3
NCT05043285	14 September 2021	Not recruiting	Parallel	SCTV01C	8420	Phase 2/ Phase 3
NCT05043311	14 September 2021	Not recruiting	Parallel	SCTV01C	12,420	Phase 2/ Phase 3
NCT05067894	5 October 2021	Not recruiting	Parallel	SARS-CoV-2 recombinant protein vaccine	780	Phase 1/ Phase 2
JPRN-jRCT2031210269	23 August 2021	Not recruiting	Parallel	S-268019	60	Phase 1/ Phase 2
RPCEC00000385	23 July 2021	Not recruiting	Parallel	Finlay-fr-1a anti-SARS-CoV-2 vaccine + FINLAY-Fr-1 anti-SARS-CoV-2 vaccine	1166	Phase 2
NCT05096832	27 October 2021	Not recruiting	Parallel	Recombinant SARS-CoV-2 fusion protein vaccine (v-01)	10,722	Phase 3
NCT04961541	14 July 2021	Not recruiting	Parallel	ICC vaccine	720	Phase 1/ Phase 2
NCT05087368	21 October 2021	Not recruiting	Parallel	Alum adjuvant + SCB-2019	520	Phase 2

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NCT04522089	21 August 2020	Not recruiting	Sequential assignment	AdimrSC-2f	70	Phase 1
NCT04550351	16 September 2020	Not recruiting	Sequential assignment	Recombinant SARS-CoV-2 vaccine (CHO cell)	50	Phase 1/ Phase 2
RPCEC00000360	19 March 2021	Not recruiting	Single-group assignment	FINLAY-FR-2 anti-SARS-CoV-2 vaccine + FINLAY-FR-1A anti-SARS-CoV-2 vaccine	150,000	Not reported
RPCEC00000363	27 March 2021	Not recruiting	Single group assignment	CIGB-66 (RBD/aluminium hydroxide)	124,000	Not reported
IRCT20150303021315N23	24 May 2021	Ongoing	Parallel	SARS-CoV-2 spike (S) protein subunit vaccine + Advax-CpG adjuvant	400	Phase 2
IRCT20201214049709N2	13 April 2021	Ongoing	Parallel	RAZI-COV PARS	500	Phase 2
IRCT20150303021315N24	3 August 2021	Ongoing	Parallel	SARS-CoV-2 recombinant spike protein + Advax-SM adjuvant	16,876	Phase 3
IRCT20210303050558N1	24 April 2021	Ongoing	Parallel	FINLAY-FR-2 anti-SARS-CoV-2 vaccine	24,000	Phase 3
ACTRN12621000738820	11 June 2021	Ongoing	Parallel	IVX-411	84	Phase 1
ChiCTR2000039994	17 November 2020	Ongoing	Parallel	Recombinant SARS-CoV-2 vaccine (Sf9 Cell)	960	Phase 2
ChiCTR2100042374	21 January 2021	Ongoing	Parallel	Recombinant SARS-CoV-2 vaccine (Sf9 Cell)	4800	Phase 2
EUCTR2020-004272-17-DE	6 January 2021	Ongoing	Parallel	SCB-2019	800	Phase 2/ Phase 3
IRCT20210620051639N1	25 June 2021	Ongoing	Parallel	Noora	70	Phase 1
NCT04636333	19 November 2020	Ongoing	Parallel	Recombinant SARS-CoV-2 vaccine (CHO Cell)	216	Phase 1
NCT04646590	30 November 2020	Ongoing	Parallel	Recombinant SARS-CoV-2 vaccine (CHO Cell)	29,000	Phase 3
NCT04773067	26 February 2021	Ongoing	Parallel	UB-612	3850	Phase 2
NCT04783311	5 March 2021	Ongoing	Parallel	EuCorVac-19	280	Phase 1/ Phase 2
NCT04813562	24 March 2021	Ongoing	Parallel	Recombinant SARS-CoV-2 vaccine (CHO Cell)	480	Phase 2

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NCT04818801	26 March 2021	Ongoing	Parallel	ReCOV – recombinant 2-component COVID-19 vaccine (CHO cell)	160	Phase 1
NCT04822025	30 March 2021	Ongoing	Parallel	MVC-COV1901	400	Phase 2
NCT04869592	3 May 2021	Ongoing	Parallel	Recombinant SARS-CoV-2 vaccine (CHO Cell)	3580	Phase 1/ Phase 2
NCT04885361	13 May 2021	Ongoing	Parallel	CoVepiT (OSE13E)	48	Phase 1
NCT04904471	27 May 2021	Ongoing	Parallel	Recombinant SARS-CoV-2 vaccine (Sf9 Cell)	40,000	Phase 3
NCT04904549	27 May 2021	Ongoing	Parallel	SARS-CoV-2 adjuvanted recombinant protein vaccine (monovalent)	37,430	Phase 3
NCT04922788	11 June 2021	Ongoing	Parallel	Nanocovax	13,000	Phase 3
NCT04982068	29 July 2021	Ongoing	Parallel	202-CoV	144	Phase 1
NCT04990544	4 August 2021	Ongoing	Parallel	202-CoV	1056	Phase 2
IRC-T20201214049709202	29 August 2021	Ongoing	Parallel	RAZI-COV PARS	41,128	Phase 3
NCT05069129	6 October 2021	Ongoing	Parallel	Recombinant SARS-CoV-2 vaccine (CHO Cell)	1848	Phase 1/ Phase 2
NCT05091411	25 October 2021	Ongoing	Parallel	Recombinant SARS-CoV-2 vaccine (CHO Cell)	1680	Phase 3
NCT05096845	27 October 2021	Ongoing	Parallel	Recombinant SARS-CoV-2 fusion protein vaccine (v-01)	22,500	Phase 3
NCT05097053	27 October 2021	Ongoing	Parallel	Mvc-cov1901	200	Phase 4
ChiC-TR2100050849	5 September 2021	Ongoing	Parallel	Recombinant SARS-CoV-2 vaccine (CHO Cell)	14,600	Phase 3
NCT04702178	8 January 2021	Ongoing	Sequential assignment	COVAC-2	108	Phase 1/ Phase 2
NCT04961359	14 July 2021	Ongoing	Sequential assignment	Recombinant SARS-CoV-2 vaccine (CHO cell)	75	Phase 1
NCT04718467	22 January 2021	Cancelled	Parallel	Recombinant SARS-CoV-2 vaccine (Sf9 Cell)	0	Phase 2
NCT04806529	19 March 2021	Cancelled	Parallel	Adjuvanted SARS-CoV-2 subunit vaccine (aCoV2)	0	Phase 2/ Phase 3

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Characteristics of unpublished registered studies: live attenuated virus (2 studies)

Registration number	Registration date	Status	Design	Interventions	Estimated sample size	Phase
NCT04619628	6 November 2020	Not recruiting	Parallel	COVI-VAC	48	Phase 1
NCT04809389	22 March 2021	Not recruiting	Parallel	DelNS1-nCoV-RBD LAIV	115	Phase 1

Characteristics of unpublished registered studies: DNA-based vaccine (18 studies)

Registration number	Registration date	Status	Design	Interventions	Estimated sample size	Phase
ChiCTR2000038152	11 September 2020	Completed	Parallel	INO-4800 + electroporation	45	Phase 1
NCT04527081	26 August 2020	Completed	Parallel	AG0302-COVID19	30	Phase 1/Phase 2
CTRI/2020/07/026352	4 July 2020	Not recruiting	Adaptive	nCov vaccine	1048	Phase 1/Phase 2
CTRI/2021/03/032051	16 March 2021	Not recruiting	Parallel	ZyCov-D	150	Phase 1/Phase 2
NCT04655625	7 July 2020	Not recruiting	Parallel	AG0302-COVID19	500	Phase 2/Phase 3
NCT04742842	8 February 2021	Not recruiting	Sequential assignment	COVIGEN	150	Phase 1
NCT04993586	6 August 2021	Not recruiting	Parallel	AG0302-COVID19	80	Phase 1/Phase 2
JPRN-jRCT2051210052	16 July 2021	Not recruiting	Parallel	AG0302-COVID19	400	Phase 1/Phase 2
NCT05067946	5 October 2021	Not recruiting	Parallel	Gx-19n	14,000	Phase 2/Phase 3
NCT05085639	20 October 2021	Not recruiting	Parallel	GLS-5130	30	Phase 1
NCT05102643	1 November 2021	Not recruiting	Sequential assignment	SARS-CoV-2 DNA vaccine + electroporation	30	Phase 1
CTRI/2021/01/030416	12 January 2021	Ongoing	Parallel	ZyCov-D	28,216	Phase 3

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NCT04445389	24 June 2020	Ongoing	Parallel	GX-19	210	Phase 1/Phase 2
NCT04447781	25 June 2020	Ongoing	Sequential assignment	INO-4800 + electroporation	160	Phase 1/Phase 2
NCT04591184	19 October 2020	Ongoing	Parallel	Covigenix VAX-001	72	Phase 1/Phase 2
NCT04673149	17 December 2020	Ongoing	Parallel	GLS-5310	345	Phase 1/Phase 2
NCT05047445	17 September 2021	Ongoing	Parallel	Covidity	40	Phase 1
NCT04715997	20 January 2021	Ongoing	Sequential assignment	GX-19N	170	Phase 1/Phase 2

Characteristics of unpublished registered studies: virus-like particle (12 studies)

Registration number	Registration date	Status	Design	Interventions	Estimated sample size	Phase
NCT04662697	10 December 2020	Not recruiting	Parallel	Coronavirus-like particle COVID-19 + adjuvant	918	Phase 2
NCT05040789	10 September 2021	Not recruiting	Parallel	SARS-CoV-2 VLP vaccine	900	Phase 3
JPRN-jRCT2051210093	28 September 2021	Ongoing	Parallel	Adjuvant + coronavirus-like particle COVID-19	145	Phase 1/Phase 2
NCT05065619	4 October 2021	Ongoing	Parallel	Coronavirus-like particle COVID-19	145	Phase 1/Phase 2
ACTRN12620000817943	14 August 2020	Ongoing	Parallel	RBD SARS-CoV-2 HBsAg VLP vaccine	280	Phase 1/Phase 2
IRCT20210620051639N2	11 October 2021	Ongoing	Parallel	RBD SARS-CoV-2 HBsAg VLP vaccine	300	Phase 2
NCT04935528	23 June 2021	Ongoing	Single-group assignment	SARS-COV-2 vaccine	430	Not reported
NCT04844346	14 April 2021	Ongoing	Parallel	SARS-CoV-2 vaccine + plant stanol esters	100	Not reported
NCT04818281	26 March 2021	Ongoing	Parallel	SARS-CoV-2 VLP vaccine	36	Phase 1
NCT04962893	15 July 2021	Ongoing	Parallel	SARS-CoV-2 VLP vaccine-Wuhan	330	Phase 2

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NCT04773665	26 February 2021	Ongoing	Sequential assignment	VBI-2902a	780	Phase 1
NCT04854876	22 April 2021	Cancelled	Parallel	SARS-CoV-2 vaccine + 5-ALA/SFC	200	Not reported

Characteristics of unpublished registered studies: any COVID-19 vaccine (3 studies)

Registration number	Registration date	Status	Design	Interventions	Estimated sample size	Phase
ChiCTR2100049467	2 August 2021	Not recruiting	Parallel	COVID-19 vaccine	1314	Phase 3
ChiCTR2100051297	18 September 2021	Ongoing	Single-group assignment	COVID-19 vaccine	1500	Phase 0
ISRCTN15279830	14 October 2021	Ongoing	Parallel	COVID-19 vaccine	800	Phase 2

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Appendix 5. Baseline characteristics of early-phase studies not included in the analysis

Type of vaccine	Reference ID	Register	Phase	Vaccine	Comparator	Sample size	Participants/centre/location
RNA-based vaccine	Roozen 2021	NL9275	1-2	mRNA-1273 20 µg ID	mRNA-1273 20 µg IM	30	Healthy adults/single centre/the Netherlands
	Low 2021	NCT04480957	1-2	ARCT-021 (1 µg; 5 µg; 7.5 µg; 10 µg)	Placebo	106	Healthy adults/single centre/Singapore
	Li 2021b	ChiCTR2000034825 NCT04523571	1	BNT162b1 10 µg	BNT162b1 30 µg	144	Healthy young adults/single centre/China
	Mulligan 2020	NCT04368728	1-2	BNT162b1 (10 µg; 30 µg; 100 µg)	Placebo	45	Healthy adults/2 centres/USA
Non-replicating viral vector	Ramasamy 2020	NCT04400838; ISRCTN, 15281137	2/3	ChAdOx1 (2.2×10^{10} vp; 1 or 2 doses)	MenACWY	300	Healthy adults/2 centres/UK
Inactivated virus	Wu 2021c	NCT04552366	1	Ad5-nCoV 0.2 mL neb 2D	Ad5-nCoV (0.1 mL neb 2D; 0.5 mL IM + 0.2 mL neb; 0.5 mL IM; 1.0 mL IM)	130	Adults/single centre/China
	Zhu 2020	NCT04341389	2	Ad5-vectored (1×10^{11} vp; 5×10^{10} vp)	Placebo	508	Healthy young adults/single centre/China
	Zhu 2022	NCT04566770	2	Ad5-vectored (3×10^{10} vp)	Placebo	400	Healthy children and adolescents/single centre/China
	Che 2021	NCT04412538	2	KMS-1 (100 EU; 150 EU) D0/14; D0/28 KMS-1	Placebo	750	Healthy adults/2 centres/China
	Lazarus 2021	NCT04671017, ISRCTN 82411169	1-2	VL A2001 3 AU	VL A2001 35 AU; 7 AU	153	Healthy adults/4 centres/UK

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	Pan 2021a	NCT04758273	1	KCONVAC 5 µg	KCONVAC 10 µg	60	Healthy adults/single centre/China
	Pan 2021a	NCT04756323	2	KCONVAC (5 µg; 10 µg) (D0/14; D0/28)	Placebo	500	Healthy adults/single centre/China
	Pitisuttithum 2021	NCT04764422	1	NDV-HXP-S (1 µg; 1 µg + CpG1018; 3 µg; 3 µg + CpG1018; 10 µg)	Placebo	210	Healthy adults/single centre/Thailand
	Pu 2021	NCT04412538	1	KMS-1 100 EU D0/14; D0/28	Placebo	192	Healthy adults/single centre/China
	Zakarya 2021	NCT04530357	1	QazCovid-in	Placebo	44	Healthy adults/single centre/Kazakhstan
Protein subunit	Chappell 2021	NCT04495933	1	SARS-CoV-2 Sclamp (5 µg; 15 µg; 45 µg)	Placebo	120	Healthy adults/single centre/Australia
	Goepfert 2021	NCT04537208	1-2	CoV2 preS dTM LD + AFO3 CoV2 preS dTM LD + ASO3 CoV2 preS dTM HD + AFO3 CoV2 preS dTM HD + ASO3 CoV2 preS dTM HD	Placebo	271	Healthy adults/10 centres/USA
	Hsieh 2021	NCT04695652	2	MVC-COV1901	Placebo	3854	Healthy adults/11 centres/Taiwan
	Zhang 2021b	ChiCTR2100045108	1	V-01 (10 µg; 25 µg; 50 µg)	Placebo	180	Healthy adults/single centre/China
	Meng 2021b	NCT04530656	1	Sf9 cells vaccine (low dose in 2 doses; high dose in 2 or 3 doses)	Placebo	168	Healthy adults/single centre/China
	Meng 2021b	NCT04640402	2	Sf9 cells vaccine (low dose or high dose in 2 or 3 doses)	Placebo	960	Healthy adults/single centre/China
	Nguyen 2021	NCT04683484	2	Nanocovax (25 µg; 50 µg; 75 µg)	Placebo	560	Healthy adults/2 centres/Vietnam

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	Nguyen 2021	NCT04683484	1	Nanocovax (25 µg; 50 µg)	Nanocovax 75 µg	60	Healthy adults/2 centres/Vietnam
	Richmond 2021	NCT04405908	1	SCB-2019 (3 µg; 3 µg + AS03; 3 µg + CpG/Alum; 9 µg; 9 µg + AS03 9 µg + CpG/Alum; 30 µg; 30 µg + AS03; 30 µg + CpG/Alu)	Placebo	151	Healthy adults/single centre/Australia
	Ryzhikov 2021	NCT04527575	2	EpiVacCorona	Placebo	86	Healthy adults/single centre/Russia
	Shu 2021	ChiCTR2100045107	2	V-01 (10 µg; 25 µg; 50 µg)	Placebo	880	Healthy adults/single centre/China
	Sridhar 2021	NCT04762680	2	CoV2 preS dTM (15 µg; 10 µg)	CoV2 preS dTM 5 µg	722	Adults with and without prior SARS-CoV-2 infection and risk factors for severe disease/20 centres/USA and Honduras
	Yang 2021	NCT04466085	2	ZF2001 (25 µg 2 doses; 50 µg 2 doses; 25 µg 3 doses; 50 µg 3 doses)	Placebo	900	Healthy adults/single centre/China
	Yang 2021	NCT04445194	2	ZF2001 (25 µg 3 doses; 50 µg 3 dose)	Placebo	50	Healthy adults/single centre/China
DNA-based vaccine	Mammen 2021	NCT04642638		INO-4800 (1 mg; 2 mg) D0/28	Placebo	201	Healthy adults/19 centres/USA
Virus-like particle (VLP)	Gobeil 2021	NCT04636697		CoVLP 3.75 µg + AS03	Placebo	753	Healthy adults/multiple centres/Canada and USA
	Ward 2021b	NCT04450004		CoVLP (3.75 µg with CpG1018, AS03 or without adjuvant; 7.5 µg with CpG1018, AS03 or without adjuvant; 15 µg with CpG1018, AS03 or without adjuvant)	Placebo	180	Canada

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Appendix 6. Baseline characteristics of studies with no outcomes of interest or not extractable

Type of vaccine	Reference	Register	Phase	Vaccine	Comparator	Sample size	Population/centre/location
Reports of trials not included in the analysis (5 studies)							
RNA-based vaccine	Chu 2021	NCT04405076	2	mRNA-1273 (50 µg; 100 µg)	Placebo	600	Healthy adults/8 centres/USA
Inactivated virus	Feng 2021	ChiCTR2100041705; ChiCTR2100041706	*	BBIBP-CorV D0/14; D0/21	BBIBP-CorV D0/28	809	Healthy adults /single centre/China
Protein subunit	Pérez-Rodríguez 2021	RPCEC00000338-En	1	FINLAY-FR-1A (25 µg; 50 µg)	FINLAY-FR-1	60	Healthy adults/single centre/Cuba
Heterologous scheme	Borobia 2021	NCT04860739; EudraCT2021-001978	2	BNT162b2 after 1 dose ChAdOx1-S – 1 IM dose 30 µg/0.3 mL BNT162b2 8-12 weeks after 1 dose ChAdOx1-S	No second vaccine dose	676	Adults/multicentre/Spain
Non-replicating viral vector/inactivated virus	Angkasekwinai 2022	TCTR20210720002		CoronaVac 3 µg	ChAdOx1 (5×10^{10} vp)	360	Healthcare workers/single centre/Thailand
Reports of trials already included in the analysis (7 studies)							
RNA-based vaccine	Pajon 2021	NCT04470427	3	mRNA-1273	Placebo	791	Healthy adults/99 centres/USA
Non-replicating viral vector	Voysey 2021b	NCT04324606; ISRCTN89951424; NCT04400838; NCT04444674	1/2/3	ChAdOx1 (5×10^{10} vp or 2.2×10^{10} vp)	Placebo/MenACWY	17, 177	Adults/multicentre/Brazil, South Africa and UK
	Stephenson 2021	NCT04436276	1	Ad26.COV2.S	Placebo	10	Healthy adults/single centre/USA

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Inactivated virus	Pan 2021b	NCT04352608	2	CoronaVac (3 doses, 4 different schedules, 3 µg and 6 µg)	Placebo	600	Healthy adults/single centre/China
	Ella 2021a	NCT04471519	2	6 µg BBV152 + Algel-IMDG	3 µg BBV152 + Algel-IMDG	380	Healthy adults/9 centres/India
	Li 2021c	NCT04383574	1/2	CoronaVac (3 doses)	Placebo	350	Healthy adults aged ≥ 60 years/single centre/China
	Ella 2020b	NCT04471519	2	6 µg BBV152 + Algel-IMDG	3 µg BBV152 + Algel-IMDG	380	Healthy adults/9 centres/India

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Appendix 7. List of previous publications later updated

	Reference/study ID	Registry
RNA-based vaccine	FDA 2020b	NCT04470427
	Baden 2021	NCT04470427
	Walsh 2021	NCT04368728
	Thomas 2021	NCT04368728
	FDA 2020c	NCT04368728
	Polack 2020	NCT04368728
Non-replicating viral vector	Madhi 2021	NCT04444674
	Folegatti 2020	NCT04324606
	FDA 2021	NCT04505722
	Sadoff 2020c	NCT04436276
Inactivated virus	Bueno 2021	NCT04651790
	Xia 2020	ChiCTR2000031809
	Formica 2021	NCT04368988
Protein subunit	Shinde 2021	NCT04533399
	Heath 2021	NCT04583995
Heterologous schedule	Liu 2021	ISRCTN69254139

Appendix 8. Risk of bias assessments

RNA-based vaccines

BNT162b2 – BioNTech/Fosun Pharma/Pfizer versus placebo

Confirmed symptomatic COVID-19 after complete vaccination

Study	1. Randomization	2. Deviations from intervention	3. Missing outcome data	4. Measurement of the outcome	5. Selection of the reported results	Overall risk of bias
Frenck 2021	Low	**Some concerns**[a]	Low	Low	Low	**Some concerns**
Thomas 2021	Low	**Some concerns**[b]	Low	Low	Low	**Some concerns**

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[a]Frenck 2021**, RoB 2. Deviations from intervention:**
Quote: "observer-blinded" (report) “Masking: Triple (Participant, Care Provider, Investigator)” (registry)
Comment: blinded study (participants, personnel, investigators). Per-protocol analysis as planned in the trial protocol) was performed on the outcomes: 'confirmed symptomatic COVID'. As we are assessing the effect of assignment to intervention (intention-to-treat effect), we considered that the data were analyzed inappropriately.
Risk assessed as some concerns for this outcome.

[b]Thomas 2021**, RoB 2. Deviations from intervention:**
Quote: "observer blinded"
Comment: blinded study (participants and personnel/carers)
Per-protocol analysis was performed on the outcome: 'confirmed symptomatic COVID'.
Reasons for exclusion: positive at baseline (689 versus 716) not received 2 vaccinations as randomized (326 versus 430)
Reasons for exclusion in the 12–15-year group not reported
As we are assessing the effect of assignment to intervention (intention-to-treat effect), we considered that the data were analyzed inappropriately.
Risk assessed to have some concerns for this outcome.

Severe or critical COVID-19 after complete vaccination

Study	1. Randomization	2. Deviations from intervention	3. Missing outcome data	4. Measurement of the outcome	5. Selection of the reported results	Overall risk of bias
Thomas 2021	Low	Low	Low	Low	Low	Low

All-cause mortality

Study	1. Randomization	2. Deviations from intervention	3. Missing outcome data	4. Measurement of the outcome	5. Selection of the reported results	Overall risk of bias
Walsh 2020	Low	Low	Low	Low	Low	Low
Frenck 2021	Low	Low	Low	Low	Low	Low
Thomas 2021	Low	Low	Low	Low	Low	Low

Any adverse event

Study	1. Randomization	2. Deviations from intervention	3. Missing outcome data	4. Measurement of the outcome	5. Selection of the reported results	Overall risk of bias
Walsh 2020	Low	Low	Low	Low	Low	Low

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Frenck 2021	Low	Low	Low	Low	Low	Low
Thomas 2021	Low	Low	Low	Low	Low	Low

Serious adverse events

Study	1. Randomization	2. Deviations from intervention	3. Missing outcome data	4. Measurement of the outcome	5. Selection of the reported results	Overall risk of bias
Walsh 2020	Low	Low	Low	Low	Low	Low
Frenck 2021	Low	Low	Low	Low	Low	Low
Thomas 2021	Low	Low	Low	Low	Low	Low

mRNA-1273 – ModernaTX versus placebo

SARS-CoV-2 infection after complete vaccination

Study	1. Randomization	2. Deviations from intervention	3. Missing outcome data	4. Measurement of the outcome	5. Selection of the reported results	Overall risk of bias
Ali 2021	Low	**Some concerns**[a]	Low	Low	Low	**Some concerns**
El Sahly 2021	Low	**Some concerns**[b]	Low	Low	Low	**Some concerns**

[a]Ali 2021**, RoB 2. Deviations from intervention:**
Quote: "The investigators and trial staff, participants, site monitors, and sponsor personnel (or its designees) were unaware of the trial vaccine administered until unblinding of the trial data as specified in the protocol; however, pharmacists and vaccine administrators who were involved in injection preparation and administration and who had no other role in trial conduct were aware of these assignments."
Comment: blinded study (participants and personnel/carers).
Data for this outcome were analyzed using modified intention-to-treat or per protocol analysis. As we are assessing the effect of assignment to intervention (intention-to-treat effect), we considered that the data were analyzed inappropriately. There was probably no substantial impact of failure to analyse participants according to their randomized assignment.
Reasons for exclusion: mITT – did not receive at least one dose, had serological or virological evidence of previous SARS-CoV-2 infection before the first injection, received wrong injection; per protocol – did not receive planned injections of mRNA-1273 or placebo, did not comply with the timing of the second injection, had immunological or virological evidence of previous COVID-19 at baseline, and major protocol deviations.
Risk assessed to have some concerns for this outcome.

[b]El Sahly 2021**, RoB 2. Deviations from intervention:**
Quote: "The investigator, study staff, study participants, site monitors, and Sponsor personnel (or its designees) will be blinded to the IP administered until study end." (protocol) "Masking: quadruple (participant, care provider, investigator, outcomes assessor." (registry)

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Comment: blinded study (participants and personnel/carers).
Per-protocol analysis was performed on the efficacy outcomes (as planned in the trial protocol).
Reasons for exclusions were balanced between treatment groups (922 (6.1%) versus 1042 (6.9%)), with the majority of those excluded due to positive or unknown baseline SARS-CoV-2 status (434 versus 421). Other reasons: did not receive any injection (29 versus 40), received an incorrect injection (6 versus 7), discontinued without receiving second dose (334 versus 425), received dose 2 outside planned time frame (102 versus 119), other major protocol deviation (17 versus 30).
As we are assessing the effect of assignment to intervention (intention-to-treat effect), we considered that the data were analyzed inappropriately. There was no substantial impact of failure to analyse participants according to their randomized assignment due to the small number.
Risk assessed to have some concerns for this outcome.

Confirmed symptomatic COVID-19 after complete vaccination

Study	1. Randomization	2. Deviations from intervention	3. Missing outcome data	4. Measurement of the outcome	5. Selection of the reported results	Overall risk of bias
Ali 2021	Low	**Some concerns[a]**	Low	Low	Low	**Some concerns**
El Sahly 2021	Low	**Some concerns[b]**	Low	Low	Low	**Some concerns**

[a]Ali 2021**, RoB 2. Deviations from intervention:**
Quote: "The investigators and trial staff, participants, site monitors, and sponsor personnel (or its designees) were unaware of the trial vaccine administered until unblinding of the trial data as specified in the protocol; however, pharmacists and vaccine administrators who were involved in injection preparation and administration and who had no other role in trial conduct were aware of these assignments."
Comment: blinded study (participants and personnel/carers).
Data for this outcome were analyzed using modified intention-to-treat or per protocol analysis. As we are assessing the effect of assignment to intervention (intention-to-treat effect), we considered that the data were analyzed inappropriately. There was probably no substantial impact of failure to analyse participants according to their randomized assignment.
Reasons for exclusion: mITT – did not receive at least one dose, had serological or virological evidence of previous SARS-CoV-2 infection before the first injection, received wrong injection; per protocol – did not receive planned injections of mRNA-1273 or placebo, did not comply with the timing of the second injection, had immunological or virological evidence of previous COVID-19 at baseline, and major protocol deviations.
Risk assessed to have some concerns for this outcome.

[b]El Sahly 2021**, RoB 2. Deviations from intervention:**
Quote: "The investigator, study staff, study participants, site monitors, and Sponsor personnel (or its designees) will be blinded to the IP administered until study end." (protocol) "Masking: quadruple (participant, care provider, investigator, outcomes assessor." (registry)
Comment: blinded study (participants and personnel/carers).
Per-protocol analysis was performed on the efficacy outcomes (as planned in the trial protocol).
Reasons for exclusions were balanced between treatment groups (922 (6.1%) versus 1042 (6.9%)), with the majority of those excluded due to positive or unknown baseline SARS-CoV-2 status (434 versus 421). Other reasons: did not receive any injection (29 versus 40), received an incorrect injection (6 versus 7), discontinued without receiving second dose (334 versus 425), received dose 2 outside planned time frame (102 versus 119), other major protocol deviation (17 versus 30).
As we are assessing the effect of assignment to intervention (intention-to-treat effect), we considered that the data were analyzed inappropriately. There was no substantial impact of failure to analyse participants according to their randomized assignment due to the small number.
Risk assessed to have some concerns for this outcome.

Severe or critical COVID-19 after complete vaccination

Study	1. Randomization	2. Deviations from intervention	3. Missing outcome data	4. Measurement of the outcome	5. Selection of the reported results	Overall risk of bias

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El Sahly 2021	Low	**Some concerns[a]**	Low	Low	Low	**Some concerns**

[a]El Sahly 2021**, RoB 2. Deviations from intervention:**
Quote: "The investigator, study staff, study participants, site monitors, and Sponsor personnel (or its designees) will be blinded to the IP administered until study end." (protocol) "Masking: quadruple (participant, care provider, investigator, outcomes assessor." (registry)
Comment: blinded study (participants and personnel/carers).
Per-protocol analysis was performed on the efficacy outcomes (as planned in the trial protocol).
Reasons for exclusions were balanced between treatment groups (922 (6.1%) versus 1042 (6.9%)), with the majority of those excluded due to positive or unknown baseline SARS-CoV-2 status (434 versus 421). Other reasons: did not receive any injection (29 versus 40), received an incorrect injection (6 versus 7), discontinued without receiving second dose (334 versus 425), received dose 2 outside planned time frame (102 versus 119), other major protocol deviation (17 versus 30).
As we are assessing the effect of assignment to intervention (intention-to-treat effect), we considered that the data were analyzed inappropriately. There was no substantial impact of failure to analyse participants according to their randomized assignment due to the small number.
Risk assessed to have some concerns for this outcome.

All-cause mortality

Study	1. Randomization	2. Deviations from intervention	3. Missing outcome data	4. Measurement of the outcome	5. Selection of the reported results	Overall risk of bias
Ali 2021	Low	Low	Low	Low	Low	Low
El Sahly 2021	Low	Low	Low	Low	Low	Low

Systemic reactogenicity events

Study	1. Randomization	2. Deviations from intervention	3. Missing outcome data	4. Measurement of the outcome	5. Selection of the reported results	Overall risk of bias
Ali 2021	Low	Low	Low	Low	Low	Low
El Sahly 2021	Low	Low	Low	Low	Low	Low
Hall 2021	Low	Low	Low	Low	Low	Low

Any adverse event

Study	1. Randomization	2. Deviations from intervention	3. Missing outcome data	4. Measurement of the outcome	5. Selection of the reported results	Overall risk of bias

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Ali 2021	Low	Low	Low	Low	Low	Low
El Sahly 2021	Low	Low	Low	Low	Low	Low

Serious adverse events

Study	1. Randomization	2. Deviations from intervention	3. Missing outcome data	4. Measurement of the outcome	5. Selection of the reported results	Overall risk of bias
Ali 2021	Low	Low	Low	Low	Low	Low
El Sahly 2021	Low	Low	Low	Low	Low	Low

CVnCoV – CureVac AG versus placebo

Confirmed symptomatic COVID-19 after complete vaccination

Study	1. Randomization	2. Deviations from intervention	3. Missing outcome data	4. Measurement of the outcome	5. Selection of the reported results	Overall risk of bias
Kremsner 2021	**Low**	**Some concerns**[a]	Low	Low	Low	**Some concerns**

[a]Kremsner 2021**, RoB 2. Deviations from intervention:**
Quote: "Due to the difference in appearance and presentation between the CVnCoV vaccine candidate and placebo, site personnel involved in preparing and administering the vaccine were not involved in the further conduct of the trial, and investigators, site personnel, and others directly involved in the conduct of the trial were blinded to participant treatment for the duration of the trial."
Comment: blinded study (participants and personnel/carers).
Per-protocol analysis was performed on the outcome: confirmed symptomatic COVID-19.
Analyses were carried out on participants who received both doses of CVnCoV or placebo according to their treatment allocation, who had not developed virologically confirmed COVID-19 before day 43 (15 days after the second dose), and who were SARS-CoV-2 naïve at baseline and day 43.
As we are assessing the effect of assignment to intervention (intention-to-treat effect), we considered that the data were analyzed inappropriately.
There was probably no substantial impact of failure to analyse participants according to their randomized assignment due to these being standard reasons from exclusion from per-protocol analyses. Risk assessed to have some concerns for this outcome.

Severe or critical COVID-19 after complete vaccination

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Study	1. Randomization	2. Deviations from intervention	3. Missing outcome data	4. Measurement of the outcome	5. Selection of the reported results	Overall risk of bias
Kremsner 2021	Low	**Some concerns**[a]	Low	Low	Low	**Some concerns**

[a]Kremsner 2021**, RoB 2. Deviations from intervention:**
Quote: "Due to the difference in appearance and presentation between the CVnCoV vaccine candidate and placebo, site personnel involved in preparing and administering the vaccine were not involved in the further conduct of the trial, and investigators, site personnel, and others directly involved in the conduct of the trial were blinded to participant treatment for the duration of the trial."
Comment: blinded study (participants and personnel/carers).
Per-protocol analysis was performed on the outcome: severe confirmed COVID-19.
Analyses were carried out on participants who received both doses of CVnCoV or placebo according to their treatment allocation, who had not developed virologically confirmed COVID-19 before day 43 (15 days after the second dose), and who were SARS-CoV-2 naïve at baseline and day 43.
As we are assessing the effect of assignment to intervention (intention-to-treat effect), we considered that the data were analyzed inappropriately.
There was probably no substantial impact of failure to analyse participants according to their randomized assignment due to these being standard reasons from exclusion from per-protocol analyses. Risk assessed to have some concerns for this outcome.

All-cause mortality

Study	1. Randomization	2. Deviations from intervention	3. Missing outcome data	4. Measurement of the outcome	5. Selection of the reported results	Overall risk of bias
Kremsner 2021	Low	Low	Low	Low	Low	Low

Systemic reactogenicity events

Study	1. Randomization	2. Deviations from intervention	3. Missing outcome data	4. Measurement of the outcome	5. Selection of the reported results	Overall risk of bias
Kremsner 2021	Low	Low	Low	Low	Low	Low

Any adverse event

Study	1. Randomization	2. Deviations from intervention	3. Missing outcome data	4. Measurement of the outcome	5. Selection of the reported results	Overall risk of bias

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Kremsner 2021	Low	Low	Low	Low	Low	Low

Serious adverse events

Study	1. Randomization	2. Deviations from intervention	3. Missing outcome data	4. Measurement of the outcome	5. Selection of the reported results	Overall risk of bias
Kremsner 2021	Low	Low	Low	Low	Low	Low

Non-replicating viral vector

ChAdOx1/SII-ChAdOx1 nCoV-19 – AstraZeneca + University of Oxford versus placebo/MenACWY

SARS-CoV-2 infection after complete vaccination

Study	1. Randomization	2. Deviations from intervention	3. Missing outcome data	4. Measurement of the outcome	5. Selection of the reported results	Overall risk of bias
Falsey 2021	Low	**Some concerns[a]**	Low	Low	Low	**Some concerns**
Voysey 2021a	Low	**Some concerns[b]**	Low	Low	Low	**Some concerns**

[a]Falsey 2021**, RoB 2. Deviations from intervention:**
Quote: "double-blind"
Comment: blinded study (participants and personnel/carers).
Per-protocol analysis was performed for the outcome: confirmed COVID-19.
Reasons for exclusion: did not receive first dose: 52 (0.2%) versus 20 (0.2%), had a positive, missing, or indeterminate serostatus at baseline: 1046 (4.8%) versus 516 (4.8%); were followed for < 15 days after second dose: 2206 (10.2%) versus 920 (8.5%); had confirmed SARS-CoV-2 RT-PCR–positive COVID-19 infection < 15 days after second dose: 73 (0.3%) versus 69 (0.6%).
As we are assessing the effect of assignment to intervention (intention-to-treat effect), we considered that the data were analyzed inappropriately.
There was probably no substantial impact of failure to analyse participants according to their randomized assignment due to similar levels of and reasons for exclusion in either arm.
Risk assessed to have some concerns for this outcome.

[b]Voysey 2021a**, RoB 2. Deviations from intervention:**
Quote: "three single-blind randomized controlled trials in the UK (COV001/COV002), Brazil (COV003), and one double-blind study in South Africa (COV005)"
Comment: blinded studies (patients in 3 trials, patients and physicians in 1 trial).
No participant cross-over.
Per-protocol analysis (as planned in the trial protocol) was performed on the outcomes: confirmed COVID-19.
Reasons for exclusions: in non-randomized open-label group; in HIV cohorts; not enrolled in an efficacy cohort; not in SD/SD or LD/SD vaccine group; baseline seropositivity results unavailable; baseline seropositivity results positive; Vaccine administration errors; Less than 15 days of follow-up accrued post second dose; PCR+ test < 14 days post-second dose

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As we are assessing the effect of assignment to intervention (intention-to-treat effect), we considered that the data were analyzed inappropriately.
There was probably no substantial impact of failure to analyse participants according to their randomized assignment due to balance in the number of exclusions.
Risk assessed to have some concerns for this outcome.

Confirmed symptomatic COVID-19 after complete vaccination

Study	1. Randomization	2. Deviations from intervention	3. Missing outcome data	4. Measurement of the outcome	5. Selection of the reported results	Overall risk of bias
Falsey 2021	Low	**Some concerns[a]**	Low	Low	Low	**Some concerns**
Voysey 2021a	Low	**Some concerns[b]**	Low	Low	Low	**Some concerns**

[a]Falsey 2021**, RoB 2. Deviations from intervention:**
Quotes: "double-blind"
Comment: blinded study (participants and personnel/carers).
Per-protocol analysis was performed for the outcome: confirmed COVID-19.
Reasons for exclusion: did not receive first dose: 52 (0.2%) versus 20 (0.2%), had a positive, missing, or indeterminate serostatus at baseline: 1046 (4.8%) versus 516 (4.8%); were followed for < 15 days after second dose: 2206 (10.2%) versus 920 (8.5%); had confirmed SARS-CoV-2 RT-PCR–positive COVID-19 infection < 15 days after second dose: 73 (0.3%) versus 69 (0.6%).
As we are assessing the effect of assignment to intervention (intention-to-treat effect), we considered that the data were analyzed inappropriately.
There was probably no substantial impact of failure to analyse participants according to their randomized assignment due to similar levels of and reasons for exclusion in either arm.
Risk assessed to have some concerns for this outcome.

[b]Voysey 2021a**, RoB 2. Deviations from intervention:**
Quote: "three single-blind randomized controlled trials in the UK (COV001/COV002), Brazil (COV003), and one double-blind study in South Africa (COV005)"
Comment: blinded studies (patients in 3 trials, patients and physicians in 1 trial).
No participant cross-over.
Per-protocol analysis (as planned in the trial protocol) was performed on the outcomes: confirmed COVID-19.
Reasons for exclusions: in non-randomized open-label group; in HIV cohorts; not enrolled in an efficacy cohort; not in SD/SD or LD/SD vaccine group; baseline seropositivity results unavailable; baseline seropositivity results positive; Vaccine administration errors; Less than 15 days of follow-up accrued post second dose; PCR+ test < 14 days post-second dose
As we are assessing the effect of assignment to intervention (intention-to-treat effect), we considered that the data were analyzed inappropriately.
There was probably no substantial impact of failure to analyse participants according to their randomized assignment due to balance in the number of exclusions.
Risk assessed to have some concerns for this outcome.

Severe or critical COVID-19 after complete vaccination

Study	1. Randomization	2. Deviations from intervention	3. Missing outcome data	4. Measurement of the outcome	5. Selection of the reported results	Overall risk of bias
Kulkarni 2021	Low	Low	Low	Low	**Some concerns[a]**	**Some concerns**

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[a]Kulkarni 2021, **RoB 5. Selection of the reported results:**
Comment: the trial registry was available (registered prospectively on 15 August 2020).
No information on whether the result was selected from multiple outcome measurements or analyses of the data.
Trial probably not analyzed as prespecified.
Risk assessed as some concerns for this outcome. Outcome not prespecified.

All-cause mortality

Study	1. Randomization	2. Deviations from intervention	3. Missing outcome data	4. Measurement of the outcome	5. Selection of the reported results	Overall risk of bias
Asano 2022	Low	Low	Low	Low	Low	Low
Falsey 2021	Low	Low	Low	Low	Low	Low
Kulkarni 2021	Low	Low	Low	Low	Low	Low
Madhi 2021a	Low	Low	Low	Low	Low	Low
Voysey 2021a	Low	Low	Low	Low	Low	Low

Systemic reactogenicity events

Study	1. Randomization	2. Deviations from intervention	3. Missing outcome data	4. Measurement of the outcome	5. Selection of the reported results	Overall risk of bias
Asano 2022	Low	Low	Low	Low	Low	Low

Any adverse event

Study	1. Randomization	2. Deviations from intervention	3. Missing outcome data	4. Measurement of the outcome	5. Selection of the reported results	Overall risk of bias
Asano 2022	Low	Low	Low	Low	Low	Low
Falsey 2021	Low	Low	Low	Low	Low	Low
Kulkarni 2021	Low	Low	Low	Low	Low	Low
Voysey 2021a	Low	Low	Low	Low	Low	Low

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Serious adverse events

Study	1. Randomization	2. Deviations from intervention	3. Missing outcome data	4. Measurement of the outcome	5. Selection of the reported results	Overall risk of bias
Asano 2022	Low	Low	Low	Low	Low	Low
Falsey 2021	Low	Low	Low	Low	Low	Low
Kulkarni 2021	Low	Low	Low	Low	Low	Low
Madhi 2021a	Low	Low	Low	Low	Low	Low
Voysey 2021a	Low	Low	Low	Low	Low	Low

Ad26.COV2.S – Janssen Pharmaceutical Companies versus placebo

Confirmed symptomatic COVID-19 after complete vaccination

Study	1. Randomization	2. Deviations from intervention	3. Missing outcome data	4. Measurement of the outcome	5. Selection of the reported results	Overall risk of bias
Sadoff 2021b	Low	**Some concerns[a]**	Low	Low	Low	**Some concerns**

[a]Sadoff 2021b**, RoB 2. Deviations from intervention:**
Quote: "Quadruple (participant, care provider, investigator, outcomes assessor)."
Comment: blinded study (participants and personnel/carers)
Per-protocol analysis was performed on the efficacy outcomes (as planned in the trial protocol).
Reasons for exclusion: positive SARS-CoV-2 status at time of vaccination based on serology or PCR (or both); major protocol deviation evaluated to possibly impact efficacy (inclusion/exclusion criteria; received wrong treatment or incorrect dose; received a disallowed concomitant medication; other).
As we are assessing the effect of assignment to intervention (intention-to-treat effect), we considered that the data were analyzed inappropriately.
There was no substantial impact of failure to analyse participants according to their randomized assignment due to the small number.
Risk assessed to have some concerns for this outcome.

Severe or critical COVID-19 after complete vaccination

Study	1. Randomization	2. Deviations from intervention	3. Missing outcome data	4. Measurement of the outcome	5. Selection of the reported results	Overall risk of bias
Sadoff 2021b	Low	**Some concerns[a]**	Low	Low	Low	**Some concerns**

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[a]Sadoff 2021b, **RoB 2. Deviations from intervention:**
Quote: "Quadruple (participant, care provider, investigator, outcomes assessor)."
Comment: blinded study (participants and personnel/carers)
Per-protocol analysis was performed on the efficacy outcomes (as planned in the trial protocol).
Reasons for exclusion: positive SARS-CoV-2 status at time of vaccination based on serology or PCR (or both); major protocol deviation evaluated to possibly impact efficacy (in/exclusion criteria; received wrong treatment or incorrect dose; received a disallowed concomitant medication; other)
As we are assessing the effect of assignment to intervention (intention-to-treat effect), we considered that the data were analyzed inappropriately.
There was no substantial impact of failure to analyse participants according to their randomized assignment due to the small number.
Risk assessed to have some concerns for this outcome.

All-cause mortality

Study	1. Randomization	2. Deviations from intervention	3. Missing outcome data	4. Measurement of the outcome	5. Selection of the reported results	Overall risk of bias
Sadoff 2021b	Low	Low	Low	Low	Low	Low

Systemic reactogenicity events

Study	1. Randomization	2. Deviations from intervention	3. Missing outcome data	4. Measurement of the outcome	5. Selection of the reported results	Overall risk of bias
Sadoff 2021a	Low	Low	Low	Low	Low	Low
Sadoff 2021b	Low	**Some concerns[a]**	Low	Low	Low	**Some concerns**

[a]Sadoff 2021b, **RoB 2. Deviations from intervention:**
Quote: "Quadruple (participant, care provider, investigator, outcomes assessor)."
Comment: blinded study (participants and personnel/carers)
Adverse events (solicited and unsolicited) were monitored in a safety subset of volunteers in centres (as planned in the trial protocol).
Reasons: centres selected based on rapid start-up capacity and projected incidence rates for COVID-19 that would allow for rapid efficacy signal detection
As we are assessing the effect of assignment to intervention (intention-to-treat effect), we considered that the data were analyzed inappropriately.
There was probably no substantial impact of failure to analyse participants according to their randomized assignment due to:

- the safety subset was prespecified and the researchers are transparent about any differences between the safety subset and the overall population;
- furthermore, it was used as a way to gather detailed data on solicited local/systemic adverse events for the 7 days after each injection. All participants were trained in assessing and reporting events by study staff. All data was transferred automatically to the centres using e-diaries. As a result, the participants were all at a subset of centres that had sufficient research capacity, which we considered a reasonable logistical decision. Risk assessed to have some concerns for this outcome.

Any adverse event

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Study	1. Randomization	2. Deviations from intervention	3. Missing outcome data	4. Measurement of the outcome	5. Selection of the reported results	Overall risk of bias
Sadoff 2021a	Low	Low	Low	Low	Low	Low
Sadoff 2021b	Low	**Some concerns**[a]	Low	Low	Low	**Some concerns**

[a]Sadoff 2021b**, RoB 2. Deviations from intervention:**
Quote: "Quadruple (participant, care provider, investigator, outcomes assessor)."
Comment: blinded study (participants and personnel/carers)
Adverse events (solicited and unsolicited) were monitored in a safety subset of volunteers in centres (as planned in the trial protocol).
Reasons: centres selected based on rapid start-up capacity and projected incidence rates for COVID-19 that would allow for rapid efficacy signal detection
As we are assessing the effect of assignment to intervention (intention-to-treat effect), we considered that the data were analyzed inappropriately.
There was probably no substantial impact of failure to analyse participants according to their randomized assignment due to:

- the safety subset was prespecified and the researchers are transparent about any differences between the safety subset and the overall population;
- furthermore, it was used as a way to gather detailed data on solicited local/systemic adverse events for the 7 days after each injection. All participants were trained in assessing and reporting events by study staff. All data was transferred automatically to the centres using e-diaries. As a result, the participants were all at a subset of centres that had sufficient research capacity, which we considered a reasonable logistical decision. Risk assessed to have some concerns for this outcome.

Serious adverse events

Study	1. Randomization	2. Deviations from intervention	3. Missing outcome data	4. Measurement of the outcome	5. Selection of the reported results	Overall risk of bias
Sadoff 2021b	Low	Low	Low	Low	Low	Low

Gam-COVID-Vac (Sputnik V) – Gamaleya Research Institute versus placebo

Confirmed symptomatic COVID-19 after complete vaccination

Study	1. Randomization	2. Deviations from intervention	3. Missing outcome data	4. Measurement of the outcome	5. Selection of the reported results	Overall risk of bias
Logunov 2021	Low	**Some concerns**[a]	Low	Low	Low	**Some concerns**

[a]Logunov 2021**, RoB 2. Deviations from intervention:**
Quote: "Investigators, participants, and all study staff were masked to group assignment."

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Comment: blinded study (participants, personnel/carers).
Patients were excluded from analysis due to protocol violations such as vaccine administration error, not meeting eligibility criteria, receipt of other vaccines, error in date of second dose, skipped visits.
As we are assessing the effect of assignment to intervention (intention-to-treat effect), we considered that the data were analyzed inappropriately.
There was no substantial impact of failure to analyse participants according to their randomized assignment due to the small number.
Risk assessed to have some concerns for this outcome.

Severe or critical COVID-19 after complete vaccination

Study	1. Randomization	2. Deviations from intervention	3. Missing outcome data	4. Measurement of the outcome	5. Selection of the reported results	Overall risk of bias
Logunov 2021	Low	**Some concerns[a]**	Low	Low	Low	**Some concerns**

[a]Logunov 2021**, RoB 2. Deviations from intervention:**
Quote: "Investigators, participants, and all study staff were masked to group assignment."
Comment: blinded study (participants, personnel/carers).
Patients were excluded from analysis due to protocol violations such as vaccine administration error, not meeting eligibility criteria, receipt of other vaccines, error in date of second dose, skipped visits.
As we are assessing the effect of assignment to intervention (intention-to-treat effect), we considered that the data were analyzed inappropriately.
There was no substantial impact of failure to analyse participants according to their randomized assignment due to the small number.
Risk assessed to have some concerns for this outcome.

All-cause mortality

Study	1. Randomization	2. Deviations from intervention	3. Missing outcome data	4. Measurement of the outcome	5. Selection of the reported results	Overall risk of bias
Logunov 2021	Low	**Some concerns[a]**	Low	Low	Low	**Some concerns**

[a]Logunov 2021**, RoB 2. Deviations from intervention:**
Quote: "Investigators, participants, and all study staff were masked to group assignment."
Comment: blinded study (participants, personnel/carers).
Patients were excluded from analysis due to protocol violations such as vaccine administration error, not meeting eligibility criteria, receipt of other vaccines, error in date of second dose, skipped visits.
As we are assessing the effect of assignment to intervention (intention-to-treat effect), we considered that the data were analyzed inappropriately.
There was no substantial impact of failure to analyse participants according to their randomized assignment due to the small number.
Risk assessed to have some concerns for this outcome.

Serious adverse events

Study	1. Randomization	2. Deviations from intervention	3. Missing outcome data	4. Measurement of the outcome	5. Selection of the reported results	Overall risk of bias

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(Continued)

Logunov 2021	Low	**Some concerns[a]**	Low	Low	Low	**Some concerns**

[a]Logunov 2021**, RoB 2. Deviations from intervention:**
Quote: "Investigators, participants, and all study staff were masked to group assignment."
Comment: blinded study (participants, personnel/carers).
Patients were excluded from analysis due to protocol violations such as vaccine administration error, not meeting eligibility criteria, receipt of other vaccines, error in date of second dose, skipped visits.
As we are assessing the effect of assignment to intervention (intention-to-treat effect), we considered that the data were analyzed inappropriately.
There was no substantial impact of failure to analyse participants according to their randomized assignment due to the small number.
Risk assessed to have some concerns for this outcome.

Inactivated virus

CoronaVac – Sinovac versus adjuvant

Confirmed symptomatic COVID-19 after complete vaccination

Study	1. Randomization	2. Deviations from intervention	3. Missing outcome data	4. Measurement of the outcome	5. Selection of the reported results	Overall risk of bias
Palacios 2020	Low	**Some concerns[a]**	Low	Low	Low	**Some concerns**
Tanriover 2021	Low	**Some concerns[b]**	Low	Low	Low	**Some concerns**

[a]Palacios 2020**, RoB 2. Deviations from intervention:**
Quote: "Participants and all other study staff as well as monitors, lab technicians, and data management team remained unaware of the product allocation."
Comment: blinded study (participants, personnel, investigators).
Per-protocol analysis (as planned in the trial protocol was performed on the outcome: confirmed symptomatic COVID-19.
65 (1.0%) versus 74 (1.2%) participants were excluded due to protocol violations, reasons for exclusions: not eligible (0 versus 1), received 3rd dose or incorrect injection (11 versus 8), out of window for per-protocol analysis (54 versus 65).
As we are assessing the effect of assignment to intervention (intention-to-treat effect), we considered that the data were analyzed inappropriately.
There was probably no substantial impact of failure to analyse participants according to their randomized assignment due to balance of the exclusions between arms.
Risk assessed to have some concerns for this outcome.

[b]Tanriover 2021**, RoB 2. Deviations from intervention:**
Quote: "Participants and practitioners were masked to the group allocation. The masking was removed in the event of a medical emergency requiring acute intervention, upon the responsible investigator's approval and the data and safety monitoring board's knowledge." "the placebo and study vaccine looked exactly the same, they were administered by staff masked to group allocation."
Comment: blinded study (participants, staff, investigators).
Per-protocol analysis was performed on the efficacy outcomes (as planned in the trial protocol).
69 (1%) versus 86 (2.4%) participants were excluded from the efficacy analysis post-randomization because of protocol violations: positive for SARS-CoV-2 (60 (0.9%) versus 35 (1%)), unmasked before the second dose (due to emergency use authorization and commencement of community vaccination) (4 (0.06%) versus 45 (1.3%)), received incorrect injection (1 (0.02%) versus 4 (0.1%)), had protocol violations (2 (0.03%) versus 0), pregnant (2 (0.03%) versus 1 (0.03%)), withdrawn by study investigator (0 versus 1 (0.03%)).
As we are assessing the effect of assignment to intervention (intention-to-treat effect), this method was considered inappropriate to estimate the effect of assignment to intervention. Although reasons for exclusions were not balanced between treatment groups, there

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was probably no substantial impact of failure to analyse participants according to their randomized groups since the imbalance was due to unmasking and subsequent vaccination after emergency use authorization.
Risk assessed to have some concerns for this outcome.

Severe or critical COVID-19 after complete vaccination

Study	1. Randomization	2. Deviations from intervention	3. Missing outcome data	4. Measurement of the outcome	5. Selection of the reported results	Overall risk of bias
Palacios 2020	Low	**Some concerns**[a]	Low	Low	Low	**Some concerns**
Tanriover 2021	Low	**Some concerns**[b]	Low	Low	Low	**Some concerns**

[a]Palacios 2020**, RoB 2. Deviations from intervention:**
Quote: "Participants and all other study staff as well as monitors, lab technicians, and data management team remained unaware of the product allocation"
Comment: blinded study (participants, personnel, investigators).
Per-protocol analysis (as planned in the trial protocol was performed on the outcome: confirmed symptomatic COVID-19.
65 (1.0%) versus 74 (1.2%) participants were excluded due to protocol violations, reasons for exclusions: not eligible (0 versus 1), received 3rd dose or incorrect injection (11 versus 8), out of window for per-protocol analysis (54 versus 65).
As we are assessing the effect of assignment to intervention (intention-to-treat effect), we considered that the data were analyzed inappropriately.
There was probably no substantial impact of failure to analyse participants according to their randomized assignment due to balance of the exclusions between arms.
Risk assessed to have some concerns for this outcome.

[b]Tanriover 2021**, RoB 2. Deviations from intervention:**
Quote: "Participants and practitioners were masked to the group allocation. The masking was removed in the event of a medical emergency requiring acute intervention, upon the responsible investigator's approval and the data and safety monitoring board's knowledge." "the placebo and study vaccine looked exactly the same, they were administered by staff masked to group allocation."
Comment: blinded study (participants, staff, investigators).
Per-protocol analysis was performed on the efficacy outcomes (as planned in the trial protocol).
69 (1%) versus 86 (2.4%) participants were excluded from the efficacy analysis post-randomization because of protocol violations: positive for SARS-CoV-2 (60 (0.9%) versus 35 (1%)), unmasked before the second dose (due to emergency use authorization and commencement of community vaccination) (4 (0.06%) versus 45 (1.3%)), received incorrect injection (1 (0.02%) versus 4 (0.1%)), had protocol violations (2 (0.03%) versus 0), pregnant (2 (0.03%) versus 1 (0.03%)), withdrawn by study investigator (0 versus 1 (0.03%)).
As we are assessing the effect of assignment to intervention (intention-to-treat effect), this method was considered inappropriate to estimate the effect of assignment to intervention. Although reasons for exclusions were not balanced between treatment groups, there was probably no substantial impact of failure to analyse participants according to their randomized groups since the imbalance was due to unmasking and subsequent vaccination after emergency use authorization.
Risk assessed to have some concerns for this outcome.

All-cause mortality

Study	1. Randomization	2. Deviations from intervention	3. Missing outcome data	4. Measurement of the outcome	5. Selection of the reported results	Overall risk of bias
Palacios 2020	Low	Low	Low	Low	Low	Low
Tanriover 2021	Low	Low	Low	Low	Low	Low

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Systemic reactogenicity events

Study	1. Randomization	2. Deviations from intervention	3. Missing outcome data	4. Measurement of the outcome	5. Selection of the reported results	Overall risk of bias
Zhang 2021[a]	**Some concerns[b]**	Low	Low	Low	Low	**Some concerns**
Zhang 2021[a]	**Some concerns[c]**	Low	Low	Low	Low	**Some concerns**
Bueno 2021	**Some concerns[d]**	Low	Low	Low	Low	**Some concerns**
Fadlyana 2021	Low	**Some concerns[e]**	Low	Low	Low	**Some concerns**
Palacios 2020	Low	Low	Low	Low	Low	Low
Tanriover 2021	Low	Low	Low	Low	Low	Low
Wu 2021a	Low	Low	Low	Low	**Some concerns[f]**	**Some concerns**

[a]Zhang 2021 reported two different comparisons/sets of participants.

[b]Zhang 2021**, RoB 1. Randomization:**
Quote: "no specific randomization was used when allocating participants to the vaccinations schedule cohorts." "The randomization codes for each vaccination schedule cohort were generated individually, using block randomization with a block size of six in phase 1 and a block size of five in phase 2, using SAS software (version 9.4). The randomization code was assigned to each participant in sequence in the order of enrolment, and then the participants received the investigational products labelled with the same code."
Comment: no specific randomization between schedule cohorts. The allocation sequence between vaccine groups and placebo was generated adequately. Unclear allocation concealment.
Risk assessed as some concerns

[c]Zhang 2021**, RoB 1. Randomization:**
Quote: "no specific randomization was used when allocating participants to the vaccinations schedule cohorts." "In phase 1, participants in blocks 1 and 2 in each schedule cohort were randomly assigned (2:1) to either CoronaVac or placebo." "The randomization codes for each vaccination schedule cohort were generated individually, using block randomization with a block size of six in phase 1 and a block size of five in phase 2, using SAS software (version 9.4). The randomization code was assigned to each participant in sequence in the order of enrolment, and then the participants received the investigational products labelled with the same code."
Comment: no specific randomization between schedule cohorts or between low-dose and high-dose arms. The allocation sequence between vaccine groups and placebo was generated adequately. Unclear allocation concealment. Imbalances in baseline characteristics appear to be compatible with chance.
Risk assessed as some concerns.

[d]Bueno 2021**, RoB 1. Randomization:**
Quote: "Volunteers were randomly assigned to immunization with CoronaVac or injection with placebo in a 1:1 ratio. A subgroup of volunteers was assigned to the immunogenicity arm and randomly received CoronaVac or placebo (3:1 ratio). Randomization was done using a sealed enveloped system integrated into the electronic Case Report Forms (eCRF) in the OpenClinica platform."
Comment: authors report 1:1 allocation ratio for intervention/control group. However, in the flow chart and result tables there are 290 participants in the vaccine group and 164 in the control group.

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Comment: allocation sequence concealed. Allocation sequence unclear. Baseline characteristics not reported by arm. Risk assessed as some concerns.

[e]Fadlyana 2021**, RoB 2. Deviations from intervention:**
Quote: "Double-blind."
Comment: blinded study (participants and outcome assessors)
Safety outcomes were monitored in a safety subset (first 540 participants randomized).
As we are assessing the effect of assignment to intervention (intention-to-treat effect), we considered that the data were analyzed inappropriately.
There was probably no substantial impact of failure to analyse participants all participants according to their randomized assignment
Risk assessed to have some concerns for this outcome.

[f]Wu 2021a**, RoB 5. Selection of the reported results:**
Comment: the prospective registry was available (12 May 2020). The outcome: systemic adverse events was not prespecified.
No information on whether the result was selected from multiple outcome measurements or analyses of the data. Trial not analyzed as prespecified. Risk assessed to have some concerns for this outcome.

Any adverse event

Study	1. Randomization	2. Deviations from intervention	3. Missing outcome data	4. Measurement of the outcome	5. Selection of the reported results	Overall risk of bias
Zhang 2021	**Some concerns[a]**	Low	Low	Low	Low	**Some concerns**
Zhang 2021	**Some concerns[b]**	Low	Low	Low	Low	**Some concerns**
Han 2021	Low	Low	Low	Low	Low	Low
Palacios 2020	Low	Low	Low	Low	Low	Low
Tanriover 2021	Low	Low	Low	Low	Low	Low
Wu 2021a	Low	Low	Low	Low	Low	Low

[a]Zhang 2021**, RoB 1. Randomization:**
Quote: "no specific randomization was used when allocating participants to the vaccinations schedule cohorts." "The randomization codes for each vaccination schedule cohort were generated individually, using block randomization with a block size of six in phase 1 and a block size of five in phase 2, using SAS software (version 9.4). The randomization code was assigned to each participant in sequence in the order of enrolment, and then the participants received the investigational products labelled with the same code."
Comment: no specific randomization between schedule cohorts. The allocation sequence between vaccine groups and placebo was generated adequately. Unclear allocation concealment.
Risk assessed as some concerns

[b]Zhang 2021**, RoB 1. Randomization:**
Quote: "no specific randomization was used when allocating participants to the vaccinations schedule cohorts." "In phase 1, participants in blocks 1 and 2 in each schedule cohort were randomly assigned (2:1) to either CoronaVac or placebo." "The randomization codes for each vaccination schedule cohort were generated individually, using block randomization with a block size of six in phase 1 and a block size of five in phase 2, using SAS software (version 9.4). The randomization code was assigned to each participant in sequence in the order of enrolment, and then the participants received the investigational products labelled with the same code."
Comment: no specific randomization between schedule cohorts or between low-dose and high-dose arms. The allocation sequence between vaccine groups and placebo was generated adequately. Unclear allocation concealment. Imbalances in baseline characteristics appear to be compatible with chance. Risk assessed as some concerns.

Serious adverse events

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Study	1. Randomization	2. Deviations from intervention	3. Missing outcome data	4. Measurement of the outcome	5. Selection of the reported results	Overall risk of bias
Bueno 2021	**Some concerns[a]**	Low	Low	Low	Low	**Some concerns**
Han 2021	Low	Low	Low	Low	Low	Low
Palacios 2020	Low	Low	Low	Low	Low	Low
Tanriover 2021	Low	Low	Low	Low	Low	Low
Wu 2021a	Low	Low	Low	Low	Low	Low

[a]Bueno 2021**, RoB 1. Randomization:**
Quote: "Volunteers were randomly assigned to immunization with CoronaVac or injection with placebo in a 1:1 ratio. A subgroup of volunteers was assigned to the immunogenicity arm and randomly received CoronaVac or placebo (3:1 ratio). Randomization was done using a sealed enveloped system integrated into the electronic Case Report Forms (eCRF) in the OpenClinica platform."
Comment: authors report 1:1 allocation ratio for intervention/control group. However, in the flow chart and result tables there are 290 participants in the vaccine group and 164 in the control group.
Comment: allocation sequence concealed. Allocation sequence unclear. Baseline characteristics not reported by arm.
Risk assessed as some concerns.

WIBP-CorV – Sinopharm – Wuhan versus adjuvant

SARS-CoV-2 infection after complete vaccination

Study	1. Randomization	2. Deviations from intervention	3. Missing outcome data	4. Measurement of the outcome	5. Selection of the reported results	Overall risk of bias
Al Kaabi 2021	Low	**Some concerns[a]**	Low	Low	Low	**Some concerns**

[a]Al Kaabi 2021**, RoB 2. Deviations from intervention:**
Quote: "The concealed random grouping allocation and blind codes were kept in signed and sealed envelopes and were blinded to the investigators, participants, and statisticians." "The vaccines and controls were approved by the National Institutes for Food and Drug Control of China, and were supplied in coded, identical-appearing, single-dose vials." (report) "Masking: quadruple (participant, care provider, investigator, outcomes assessor)." (registry)
Comment: blinded study (participants and personnel/carers).
Per-protocol analysis was performed on the efficacy outcomes (as planned in the trial protocol).
Reasons for exclusions were balanced between treatment groups: due to positive or unknown baseline SARS-CoV-2 RT-PCR status (118 versus 134 versus 98), did not receive any injection (11 versus 5 versus 13), did not receive second dose (393 versus 379 versus 387).
As we are assessing the effect of assignment to intervention (intention-to-treat effect), we considered that the data were analyzed inappropriately.
There was no substantial impact of failure to analyse participants according to their randomized assignment.
Risk assessed to have some concerns for this outcome.

Confirmed symptomatic COVID-19 after complete vaccination

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Study	1. Randomization	2. Deviations from intervention	3. Missing outcome data	4. Measurement of the outcome	5. Selection of the reported results	Overall risk of bias
Al Kaabi 2021	Low	**Some concerns[a]**	Low	Low	Low	**Some concerns**

[a]Al Kaabi 2021, RoB 2. Deviations from intervention:
Quote: "The concealed random grouping allocation and blind codes were kept in signed and sealed envelopes and were blinded to the investigators, participants, and statisticians." "The vaccines and controls were approved by the National Institutes for Food and Drug Control of China, and were supplied in coded, identical-appearing, single-dose vials." (report) "Masking: quadruple (participant, care provider, investigator, outcomes assessor)." (registry)
Comment: blinded study (participants and personnel/carers).
Per-protocol analysis was performed on the efficacy outcomes (as planned in the trial protocol).
Reasons for exclusions were balanced between treatment groups: due to positive or unknown baseline SARS-CoV-2 RT-PCR status (118 versus 134 versus 98), did not receive any injection (11 versus 5 versus 13), did not receive second dose (393 versus 379 versus 387).
As we are assessing the effect of assignment to intervention (intention-to-treat effect), we considered that the data were analyzed inappropriately.
There was no substantial impact of failure to analyse participants according to their randomized assignment.
Risk assessed to have some concerns for this outcome.

Severe or critical COVID-19 after complete vaccination

Study	1. Randomization	2. Deviations from intervention	3. Missing outcome data	4. Measurement of the outcome	5. Selection of the reported results	Overall risk of bias
Al Kaabi 2021	Low	**Some concerns[a]**	Low	Low	Low	**Some concerns**

[a]Al Kaabi 2021, RoB 2. Deviations from intervention:
Quote: "The concealed random grouping allocation and blind codes were kept in signed and sealed envelopes and were blinded to the investigators, participants, and statisticians." "The vaccines and controls were approved by the National Institutes for Food and Drug Control of China, and were supplied in coded, identical-appearing, single-dose vials." (report) "Masking: quadruple (participant, care provider, investigator, outcomes assessor)." (registry)
Comment: blinded study (participants and personnel/carers).
Per-protocol analysis was performed on the efficacy outcomes (as planned in the trial protocol).
Reasons for exclusions were balanced between treatment groups: due to positive or unknown baseline SARS-CoV-2 RT-PCR status (118 versus 134 versus 98), did not receive any injection (11 versus 5 versus 13), did not receive second dose (393 versus 379 versus 387).
As we are assessing the effect of assignment to intervention (intention-to-treat effect), we considered that the data were analyzed inappropriately.
There was no substantial impact of failure to analyse participants according to their randomized assignment.
Risk assessed to have some concerns for this outcome.

All-cause mortality

Study	1. Randomization	2. Deviations from intervention	3. Missing outcome data	4. Measurement of the outcome	5. Selection of the reported results	Overall risk of bias

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(Continued)

Al Kaabi 2021	Low	Low	Low	Low	Low	Low

Systemic reactogenicity events

Study	1. Randomization	2. Deviations from intervention	3. Missing outcome data	4. Measurement of the outcome	5. Selection of the reported results	Overall risk of bias
Al Kaabi 2021	Low	Low	Low	Low	Low	Low
Guo 2021	**Some concerns**[a]	Low	Low	Low	Low	**Some concerns**

[a]Guo 2021**, RoB 1. Randomization:**
Quote: "Sequential computer-generated randomization numbers were assigned to participants, and stratified block randomization by age and doses was adopted (block size 8)."
Comment: allocation sequence random. Unclear allocation concealment.
Imbalances in baseline characteristics appear to be compatible with chance.
Risk assessed as some concerns

Any adverse event

Study	1. Randomization	2. Deviations from intervention	3. Missing outcome data	4. Measurement of the outcome	5. Selection of the reported results	Overall risk of bias
Al Kaabi 2021	Low	Low	Low	Low	Low	Low
Guo 2021	**Some concerns**[a]	Low	Low	Low	Low	**Some concerns**

[a]Guo 2021**, RoB 1. Randomization:**
Quote: "Sequential computer-generated randomization numbers were assigned to participants, and stratified block randomization by age and doses was adopted (block size 8)."
Comment: allocation sequence random. Unclear allocation concealment.
Imbalances in baseline characteristics appear to be compatible with chance.
Risk assessed as some concerns.

Serious adverse events

Study	1. Randomization	2. Deviations from intervention	3. Missing outcome data	4. Measurement of the outcome	5. Selection of the reported results	Overall risk of bias

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(Continued)

Al Kaabi 2021	Low	Low	Low	Low	Low	Low
Guo 2021	**Some concerns[a]**	Low	Low	Low	Low	**Some concerns**

[a]Guo 2021, **RoB 1. Randomization:**
Quote: "Sequential computer-generated randomization numbers were assigned to participants, and stratified block randomization by age and doses was adopted (block size 8)."
Comment: allocation sequence random. Unclear allocation concealment.
Imbalances in baseline characteristics appear to be compatible with chance.
Risk assessed as some concerns

BBIBP-CorV – Sinopharm-Beijing versus adjuvant

SARS-CoV-2 infection after complete vaccination

Study	1. Randomization	2. Deviations from intervention	3. Missing outcome data	4. Measurement of the outcome	5. Selection of the reported results	Overall risk of bias
Al Kaabi 2021	Low	**Some concerns[a]**	Low	Low	Low	**Some concerns**

[a]Al Kaabi 2021, **RoB 2. Deviations from intervention:**
Quote: "The concealed random grouping allocation and blind codes were kept in signed and sealed envelopes and were blinded to the investigators, participants, and statisticians." "The vaccines and controls were approved by the National Institutes for Food and Drug Control of China, and were supplied in coded, identical-appearing, single-dose vials." (report) "Masking: quadruple (participant, care provider, investigator, outcomes assessor)." (registry)
Comment: blinded study (participants and personnel/carers).
Per-protocol analysis was performed on the efficacy outcomes (as planned in the trial protocol).
Reasons for exclusions were balanced between treatment groups: due to positive or unknown baseline SARS-CoV-2 RT-PCR status (118 versus 134 versus 98), did not receive any injection (11 versus 5 versus 13), did not receive second dose (393 versus 379 versus 387).
As we are assessing the effect of assignment to intervention (intention-to-treat effect), we considered that the data were analyzed inappropriately.
There was no substantial impact of failure to analyse participants according to their randomized assignment.
Risk assessed to have some concerns for this outcome.

Confirmed symptomatic COVID-19 after complete vaccination

Study	1. Randomization	2. Deviations from intervention	3. Missing outcome data	4. Measurement of the outcome	5. Selection of the reported results	Overall risk of bias
Al Kaabi 2021	Low	**Some concerns[a]**	Low	Low	Low	**Some concerns**

[a]Al Kaabi 2021, **RoB 2. Deviations from intervention:**

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Quote: "The concealed random grouping allocation and blind codes were kept in signed and sealed envelopes and were blinded to the investigators, participants, and statisticians." "The vaccines and controls were approved by the National Institutes for Food and Drug Control of China, and were supplied in coded, identical-appearing, single-dose vials." (report) "Masking: quadruple (participant, care provider, investigator, outcomes assessor)." (registry)
Comment: blinded study (participants and personnel/carers).
Per-protocol analysis was performed on the efficacy outcomes (as planned in the trial protocol).
Reasons for exclusions were balanced between treatment groups: due to positive or unknown baseline SARS-CoV-2 RT-PCR status (118 versus 134 versus 98), did not receive any injection (11 versus 5 versus 13), did not receive second dose (393 versus 379 versus 387).
As we are assessing the effect of assignment to intervention (intention-to-treat effect), we considered that the data were analyzed inappropriately.
There was no substantial impact of failure to analyse participants according to their randomized assignment.
Risk assessed to have some concerns for this outcome.

All-cause mortality

Study	1. Randomization	2. Deviations from intervention	3. Missing outcome data	4. Measurement of the outcome	5. Selection of the reported results	Overall risk of bias
Al Kaabi 2021	Low	Low	Low	Low	Low	Low

Systemic reactogenicity events

Study	1. Randomization	2. Deviations from intervention	3. Missing outcome data	4. Measurement of the outcome	5. Selection of the reported results	Overall risk of bias
Al Kaabi 2021	Low	Low	Low	Low	Low	Low
Xia 2020	Low	Low	Low	Low	Low	Low
Xia 2021	Low	Low	Low	Low	Low	Low

Any adverse event

Study	1. Randomization	2. Deviations from intervention	3. Missing outcome data	4. Measurement of the outcome	5. Selection of the reported results	Overall risk of bias
Al Kaabi 2021	Low	Low	Low	Low	Low	Low
Xia 2020	Low	Low	Low	Low	Low	Low
Xia 2021	Low	Low	Low	Low	Low	Low

Serious adverse events

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Study	1. Randomization	2. Deviations from intervention	3. Missing outcome data	4. Measurement of the outcome	5. Selection of the reported results	Overall risk of bias
Al Kaabi 2021	Low	Low	Low	Low	Low	Low
Xia 2020	Low	Low	Low	Low	Low	Low

BBV152 – Bharat Biotech versus adjuvant

SARS-CoV-2 infection after complete vaccination

Study	1. Randomization	2. Deviations from intervention	3. Missing outcome data	4. Measurement of the outcome	5. Selection of the reported results	Overall risk of bias
Ella 2021b	Low	**Some concerns**[a]	Low	Low	Low	**Some concerns**

[a]Ella 2021b**, RoB 2. Deviations from intervention:**
Quote: "Participants, investigators, study coordinators, study-related personnel, and the sponsor were masked to the treatment group allocation, and masked study nurses at each site were responsible for vaccine preparation and administration."
Comment: blinded study (participants, personnel, investigators).
Per-protocol analysis was performed on the outcome: Confirmed COVID (as planned in the trial protocol).
As we are assessing the effect of assignment to intervention (intention-to-treat effect), we considered that the data were analyzed inappropriately.
Reasons for exclusions were balanced: did not received dose 1 (20 versus 25), did not received dose 2 (658 versus 676), positive for anti-SARS-CoV-2 IgG (3932 versus 3886), positive for SARS-CoV-2 by PCR (108 versus 105).
There was probably no substantial impact of failure to analyse participants according to their randomized assignment
Risk assessed to have some concerns for this outcome.

Confirmed symptomatic COVID-19 after complete vaccination

Study	1. Randomization	2. Deviations from intervention	3. Missing outcome data	4. Measurement of the outcome	5. Selection of the reported results	Overall risk of bias
Ella 2021b	Low	**Some concerns**[a]	Low	Low	Low	**Some concerns**

[a]Ella 2021b**, RoB 2. Deviations from intervention:**
Quote: "Participants, investigators, study coordinators, study-related personnel, and the sponsor were masked to the treatment group allocation, and masked study nurses at each site were responsible for vaccine preparation and administration."
Comment: blinded study (participants, personnel, investigators).
Per-protocol analysis was performed on the outcomes: Confirmed symptomatic COVID (as planned in the trial protocol).
As we are assessing the effect of assignment to intervention (intention-to-treat effect), we considered that the data were analyzed inappropriately.
Reasons for exclusions were balanced: did not received dose 1 (20 versus 25), did not received dose 2 (658 versus 676), positive for anti-SARS-CoV-2 IgG (3932 versus 3886), positive for SARS-CoV-2 by PCR (108 versus 105).

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There was probably no substantial impact of failure to analyse participants according to their randomized assignment
Risk assessed to have some concerns for this outcome.

Severe or critical COVID-19 after complete vaccination

Study	1. Randomization	2. Deviations from intervention	3. Missing outcome data	4. Measurement of the outcome	5. Selection of the reported results	Overall risk of bias
Ella 2021b	Low	**Some concerns[a]**	Low	Low	Low	**Some concerns**

[a]Ella 2021b**, RoB 2. Deviations from intervention:**
Quote: "Participants, investigators, study coordinators, study-related personnel, and the sponsor were masked to the treatment group allocation, and masked study nurses at each site were responsible for vaccine preparation and administration."
Comment: blinded study (participants, personnel, investigators).
Per-protocol analysis was performed on the outcomes: Confirmed severe COVID (as planned in the trial protocol).
As we are assessing the effect of assignment to intervention (intention-to-treat effect), we considered that the data were analyzed inappropriately.
Reasons for exclusions were balanced: did not received dose 1 (20 versus 25), did not received dose 2 (658 versus 676), positive for anti-SARS-CoV-2 IgG (3932 versus 3886), positive for SARS-CoV-2 by PCR (108 versus 105).
There was probably no substantial impact of failure to analyse participants according to their randomized assignment
Risk assessed to have some concerns for this outcome.

All-cause mortality

Study	1. Randomization	2. Deviations from intervention	3. Missing outcome data	4. Measurement of the outcome	5. Selection of the reported results	Overall risk of bias
Ella 2021b	Low	Low	Low	Low	Low	Low

Systemic reactogenicity events

Study	1. Randomization	2. Deviations from intervention	3. Missing outcome data	4. Measurement of the outcome	5. Selection of the reported results	Overall risk of bias
Ella 2021b	Low	Low	Low	Low	Low	Low
Ella 2021a	Low	**Some concerns[a]**	Low	Low	**Some concerns[b]**	**Some concerns**

[a]Ella 2021a**, RoB 2. Deviations from intervention:**
Quote: "The appearance, color, and viscosity were identical across all treatment and control formulations. Participants, investigators, study coordinators, study-related personnel, and the sponsor were blinded to the treatment group allocation (excluding an unblinded CRO, who was tasked with the dispatch and labeling of vaccine vials and the generation of the master randomization code). Blinding was maintained using the randomization code."
Comment: blinded study (patients, personnel, and investigators).
No participant cross-over.

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Per-protocol analysis was performed on the outcomes.
Reasons for exclusion: protocol deviation (1), positive for SARS-CoV-2 (1)
As we are assessing the effect of assignment to intervention (intention-to-treat effect), we considered that the data were analyzed inappropriately.
There was probably no substantial impact of failure to analyse participants according to their randomized assignment due to the small number of exclusions
Risk assessed to have some concerns for this outcome.

[b]Ella 2021a**, RoB 5. Selection of the reported results:**
Comment: the prospective registry was available (July 15, 2020). Outcome not prespecified
No information on whether the results were selected from multiple outcome measurements or analyses of the data. Trial not analyzed as prespecified.
Risk assessed to have some concerns for this outcome.

Any adverse event

Study	1. Randomization	2. Deviations from intervention	3. Missing outcome data	4. Measurement of the outcome	5. Selection of the reported results	Overall risk of bias
Ella 2021b	Low	Low	Low	Low	Low	Low

Serious adverse events

Study	1. Randomization	2. Deviations from intervention	3. Missing outcome data	4. Measurement of the outcome	5. Selection of the reported results	Overall risk of bias
Ella 2021b	Low	Low	Low	Low	Low	Low
Ella 2021a	Low	**Some concerns[a]**	Low	Low	Low	**Some concerns**

[a]Ella 2021a**, RoB 2. Deviations from intervention:**
Quote: "The appearance, color, and viscosity were identical across all treatment and control formulations. Participants, investigators, study coordinators, study-related personnel, and the sponsor were blinded to the treatment group allocation (excluding an unblinded CRO, who was tasked with the dispatch and labeling of vaccine vials and the generation of the master randomization code). Blinding was maintained using the randomization code."
Comment: blinded study (patients, personnel, and investigators).
No participant cross-over.
Per-protocol analysis was performed on the outcomes.
Reasons for exclusion: protocol deviation (1), positive for SARS-CoV-2 (1)
As we are assessing the effect of assignment to intervention (intention-to-treat effect), we considered that the data were analyzed inappropriately.
There was probably no substantial impact of failure to analyse participants according to their randomized assignment due to the small number of exclusions
Risk assessed to have some concerns for this outcome.

Protein subunit

NVX-CoV2373 – Novavax versus placebo

Confirmed symptomatic COVID-19 after complete vaccination

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Study	1. Randomization	2. Deviations from intervention	3. Missing outcome data	4. Measurement of the outcome	5. Selection of the reported results	Overall risk of bias
Dunkle 2021	Low	**Some concerns[a]**	Low	Low	Low	**Some concerns**
Heath 2021	Low	**Some concerns[b]**	Low	Low	Low	**Some concerns**
Shinde 2021	Low	**Some concerns[c]**	Low	Low	Low	**Some concerns**

[a]Dunkle 2021, RoB 2. Deviations from intervention:
Quote: "Masking: quadruple (participant, care provider, investigator, outcomes assessor)." "Only unblinded site personnel managed study vaccine logistics/preparation and had no other role in trial conduct." "The trial is ongoing, and investigators and Novavax clinical team remain blinded to participant-level treatment assignments."
Comment: blinded study (participants and personnel/carers)
Per-protocol analysis was performed on the efficacy outcomes.
Reasons for exclusion: were anti-NP or PCR positive at baseline (vaccine 6.2%, placebo 6.8%), did not receive two Nv-CXoV2373 doses or were dosed out of window (vaccine 3.2%, placebo 4.6%), had major protocol deviation, were unblinded, or had a censoring event (vaccine 3.3%, placebo 6.9%).
As we are assessing the effect of assignment to intervention (intention-to-treat effect), we considered that the data were analyzed inappropriately.
There was probably no substantial impact of failure to analyse participants according to their randomized assignment due to relatively equal attrition in both arms.
Risk assessed to have some concerns for this outcome.

[b]Heath 2021, RoB 2. Deviations from intervention:
Quote: "This was an observer-blinded study. Only unblinded site personnel managed study vaccine logistics and preparation and they were not involved in study-related assessments or had participant contact for data collection following vaccine administration" (report) "Masking: Quadruple (Participant, Care Provider, Investigator, Outcomes Assessor" (NCT04583995 registry) "Double blind" (EudraCT 2020-004123-16 registry)
Comment: blinded study (participants, personnel, investigators).
Per-protocol analysis was performed on the efficacy outcomes (as planned in the trial protocol).
Reasons for exclusions were balanced between treatment groups (549 (7.2%) versus 551 (7.3%)), with the majority of those excluded due to seropositivity before 7 days after dose 2 (399 versus 402). Other reasons: received only one dose (102 versus 107); had major protocol deviation, missed dose, or censoring event (48 versus 42).
As we are assessing the effect of assignment to intervention (intention-to-treat effect), we considered that the data were analyzed inappropriately.
Risk assessed to have some concerns for this outcome.

[c]Shinde 2021, RoB 2. Deviations from intervention:
Quote: "To maintain the blind, placebo vaccination via the intramuscular route was included, and unblinded site personnel managed vaccine logistics, preparation, and administration (if necessary) to maintain the blind from the remainder of the site personnel and participants."
Comment: not fully blinded study (participants and some personnel were blinded).
Two participants crossed over from placebo to vaccine group.
This deviation was considered negligible among 2684 participants analyzed for efficacy outcomes.
Per-protocol analysis was performed on the efficacy outcomes evaluated in this cohort (as planned in the trial protocol).
Reasons for exclusion: seropositivity at baseline (849 versus 873), SARS-CoV-2 positivity before day 28 (97 versus 78), did not receive both doses (24 versus 31), had important protocol deviations (4 versus 7), lost to follow-up (6 versus 9), was withdrawn by physicians (1 versus 0), became pregnant (2 versus 3), withdrew with no reason reported (10 versus 15), had adverse event, not related to vaccine (1 versus 0).
Risk assessed to have some concerns for this outcome.

Severe or critical COVID-19 after complete vaccination

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Study	1. Randomization	2. Deviations from intervention	3. Missing outcome data	4. Measurement of the outcome	5. Selection of the reported results	Overall risk of bias
Dunkle 2021	Low	**Some concerns[a]**	Low	Low	Low	**Some concerns**

[a]Dunkle 2021, RoB 2. Deviations from intervention:
Quote: "masking: quadruple (participant, care provider, investigator, outcomes assessor)." "Only unblinded site personnel managed study vaccine logistics/preparation and had no other role in trial conduct." "The trial is ongoing, and investigators and Novavax clinical team remain blinded to participant-level treatment assignments."
Comment: blinded study (participants and personnel/carers)
Per-protocol analysis was performed on the efficacy outcomes.
Reasons for exclusion: Were Anti-NP or PCR positive at baseline (vaccine 6.2%, placebo 6.8%), did not receive two Nv-CXoV2373 doses or were dosed out of window (vaccine 3.2%, placebo 4.6%), had major protocol deviation, were unblinded, or had a censoring event (vaccine 3.3%, placebo 6.9%).
As we are assessing the effect of assignment to intervention (intention-to-treat effect), we considered that the data were analyzed inappropriately.
There was probably no substantial impact of failure to analyse participants according to their randomized assignment due to relatively equal attrition in both arms.
Risk assessed to have some concerns for this outcome.

All-cause mortality

Study	1. Randomization	2. Deviations from intervention	3. Missing outcome data	4. Measurement of the outcome	5. Selection of the reported results	Overall risk of bias
Dunkle 2021	Low	**Some concerns[a]**	Low	Low	Low	**Some concerns**
Heath 2021	Low	**Some concerns[b]**	Low	Low	Low	**Some concerns**

[a]Dunkle 2021, RoB 2. Deviations from intervention:
Quote: "Masking: quadruple (participant, care provider, investigator, outcomes assessor)." "Only unblinded site personnel managed study vaccine logistics/preparation and had no other role in trial conduct." "The trial is ongoing, and investigators and Novavax clinical team remain blinded to participant-level treatment assignments."
Comment: blinded study (participants and personnel/carers)
Per-protocol analysis was performed on the efficacy outcomes.
Reasons for exclusion: were anti-NP or PCR positive at baseline (vaccine 6.2%, placebo 6.8%), did not receive two Nv-CXoV2373 doses or were dosed out of window (vaccine 3.2%, placebo 4.6%), had major protocol deviation, were unblinded, or had a censoring event (vaccine 3.3%, placebo 6.9%).
As we are assessing the effect of assignment to intervention (intention-to-treat effect), we considered that the data were analyzed inappropriately.
There was probably no substantial impact of failure to analyse participants according to their randomized assignment due to relatively equal attrition in both arms.
Risk assessed to have some concerns for this outcome.

[b]Heath 2021, RoB 2. Deviations from intervention:
Quote: "This was an observer-blinded study. Only unblinded site personnel managed study vaccine logistics and preparation and they were not involved in study-related assessments or had participant contact for data collection following vaccine administration." (report) "Masking: quadruple (participant, care provider, investigator, outcomes assessor." (NCT04583995 registry) "Double blind" (EudraCT 2020-004123-16 registry)
Comment: blinded study (participants, personnel, investigators).

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Per-protocol analysis was performed on the efficacy outcomes (as planned in the trial protocol).
Reasons for exclusions were balanced between treatment groups (549 (7.2%) versus 551 (7.3%)), with the majority of those excluded due to seropositivity before 7 days after dose 2 (399 versus 402). Other reasons: received only 1 dose (102 versus 107); had major protocol deviation, missed dose, or censoring event (48 versus 42).
As we are assessing the effect of assignment to intervention (intention-to-treat effect), we considered that the data were analyzed inappropriately.
Risk assessed to have some concerns for this outcome.

Systemic reactogenicity events

Study	1. Randomization	2. Deviations from intervention	3. Missing outcome data	4. Measurement of the outcome	5. Selection of the reported results	Overall risk of bias
Dunkle 2021	Low	Low	Low	Low	Low	Low
Formica 2021	**Some concerns**[a]	Low	Low	Low	Low	**Some concerns**
Shinde 2021	Low	Low	**Some concerns**[b]	Low	Low	**Some concerns**

[a]Formica 2021**, RoB 1. Randomization:**
Quote: "participants were randomly assigned in a blinded manner to one of five vaccine groups … according to pre-generated randomization schedules with two-factor, two-level stratification employed."
Comment: allocation sequence probably random
No information on allocation concealment
Imbalances in baseline characteristics appear to be compatible with chance.
Risk assessed to have some concerns

[b]Shinde 2021**, RoB 3. Missing outcome data:**
Comment: data from interim analysis
4406 participants randomized; 968 participants analyzed for safety.
Data available for 22% of population for safety.
For safety, only participants who were enrolled in the first stage were analyzed for the interim analysis. A large proportion (participants enrolled in the second stage of the trial) was missing, but it is unlikely that missingness depended on the true value of the outcome.
Risk assessed to have some concerns for this outcome

Any adverse event

Study	1. Randomization	2. Deviations from intervention	3. Missing outcome data	4. Measurement of the outcome	5. Selection of the reported results	Overall risk of bias
Keech 2020	**Some concerns**[a]	Low	Low	Low	Low	**Some concerns**
Dunkle 2021	Low	Low	Low	Low	Low	Low
Formica 2021	**Some concerns**[b]	Low	Low	Low	**Some concerns**[c]	**Some concerns**
Heath 2021	Low	Low	Low	Low	Low	Low

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(Continued)

Shinde 2021	Low	Low	**Some concerns[d]**	Low	Low	**Some concerns**

[a]Keech 2020, **RoB 1. Randomization:**
Quote: "As a safety measure, 6 participants were initially randomly assigned in a 1:1 ratio to the 5-µg and 25-µg rSARS-CoV-2 plus Matrix-M1 groups (groups C and D), vaccinated in an open-label manner, and observed for reactogenicity for 48 hours. Thereafter, the remaining 125 participants were randomly assigned, in a 1:1:1:1:1 ratio and in a blinded manner to one of five vaccine groups according to pregenerated randomization schedules, without stratification."
Comment: allocation sequence probably random
No information on allocation concealment
Risk assessed to have some concerns

[b]Formica 2021, **RoB 1. Randomization:**
Quote: "participants were randomly assigned in a blinded manner to one of five vaccine groups … according to pre-generated randomization schedules with two-factor, two-level stratification employed."
Comment: allocation sequence probably random
No information on allocation concealment
Imbalances in baseline characteristics appear to be compatible with chance.
Risk assessed to have some concerns

[c]Formica 2021, **RoB 5. Selection of the reported results:**
Comment: the prospective trial registry was available (30 April).
Different time point in the registry (prespecified at 28 days and reported at 35 days after first dose)
No information on whether the result was selected from multiple outcome measurements or analyses of the data.
Trial not analyzed as prespecified.
Risk assessed to have some concerns for this outcome

[d]Shinde 2021, **RoB 3. Missing outcome data:**
Comment: data from interim analysis
4406 participants randomized; 968 participants analyzed for safety.
For safety, only participants who were enrolled in the first stage were analyzed for the interim analysis. A large proportion (participants enrolled in the second stage of the trial) was missing, but it is unlikely that missingness depended on the true value of the outcome.
Risk assessed to have some concerns for this outcome. Data available for 22% of population for safety.

Serious adverse events

Study	1. Randomization	2. Deviations from intervention	3. Missing outcome data	4. Measurement of the outcome	5. Selection of the reported results	Overall risk of bias
Keech 2020	**Some concerns[a]**	Low	Low	Low	Low	**Some concerns**
Dunkle 2021	Low	Low	Low	Low	Low	Low
Formica 2021	**Some concerns[b]**	Low	Low	Low	**Some concerns[c]**	**Some concerns**
Heath 2021	Low	Low	Low	Low	Low	Low
Shinde 2021	Low	**Some concerns[d]**	**Some concerns[e]**	Low	Low	**Some concerns**

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[a]Keech 2020, **RoB 1. Randomization:**
Quote: "As a safety measure, 6 participants were initially randomly assigned in a 1:1 ratio to the 5-µg and 25-µg rSARS-CoV-2 plus Matrix-M1 groups (groups C and D), vaccinated in an open-label manner, and observed for reactogenicity for 48 hours. Thereafter, the remaining 125 participants were randomly assigned, in a 1:1:1:1:1 ratio and in a blinded manner to one of five vaccine groups according to pregenerated randomization schedules, without stratification".
Comment: allocation sequence probably random
No information on allocation concealment
Risk assessed to have some concerns

[b]Formica 2021, **RoB 1. Randomization:**
Quote: "participants were randomly assigned in a blinded manner to one of five vaccine groups … according to pre-generated randomization schedules with two-factor, two-level stratification employed."
Comment: allocation sequence probably random
No information on allocation concealment
Imbalances in baseline characteristics appear to be compatible with chance.
Risk assessed to have some concerns

[c]Formica 2021, **RoB 5. Selection of the reported results:**
Comment: the prospective trial registry was available (April 30th).
No information on whether the result was selected from multiple outcome measurements or analyses of the data.
Trial not analyzed as prespecified.
Risk assessed to have some concerns for this outcome. Outcome not prespecified

[d]Shinde 2021, **RoB 2. Deviations from intervention:**
Quote: "To maintain the blind, placebo vaccination via the intramuscular route was included, and unblinded site personnel managed vaccine logistics, preparation, and administration (if necessary) so as to maintain the blind from the remainder of the site personnel and participants."
Comment: not fully blinded study (participants and some personnel were blinded).
Two participants crossed over from placebo to vaccine group.
This deviation was considered negligible among 968 participants analyzed for safety outcomes.
The two participants randomized to the placebo group that crossed over were analyzed "as-treated" in the intervention group. Nevertheless, due to the small proportion crossing over, we considered the safety analyses to be probably appropriate to estimate the effect of assignment to intervention.
Risk assessed to have some concerns for this outcome.

[e]Shinde 2021, **RoB 3. Missing outcome data:**
Comment: data from interim analysis. 4406 participants randomized; 968 participants analyzed for safety.
For safety, only participants who were enrolled in the first stage were analyzed for the interim analysis. A large proportion (participants enrolled in the second stage of the trial) was missing, but it is unlikely that missingness depended on the true value of the outcome.
Risk assessed to have some concerns for this outcome. Data available for 22% of population for safety.

FINLAY-FR-2 – Instituto Finlay de Vacunas versus placebo

Confirmed symptomatic COVID-19 after complete vaccination

Study	1. Randomization	2. Deviations from intervention	3. Missing outcome data	4. Measurement of the outcome	5. Selection of the reported results	Overall risk of bias
Toledo-Romani 2021	**Some concerns[a]**	**Some concerns[b]**	Low	Low	Low	**Some concerns**

[a]Toledo-Romani 2021, **RoB 1. Randomization:**
Quote: "Randomization into study arms (A and B) and placebo was done on day 0 at a 1:1:1 ratio using a site stratified random and previously defined risk strata (19–64 years without risk comorbidities, 19–64 years with risk comorbidities and ≥65 years)."
Comment: allocation sequence random. No information on allocation concealment.

[b]Toledo-Romani 2021, **RoB 2. Deviations from intervention:**
Comment: blinded study (participants and personnel/carers).

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Per-protocol analysis was performed on the outcomes.
Reasons for exclusion: did not receive or discontinued the intervention.
As we are assessing the effect of assignment to intervention (intention-to-treat effect), we considered that the data were analyzed inappropriately.
There was probably no substantial impact of failure to analyse participants according to their randomized assignment due to balance between groups. Imbalances in baseline characteristics appear to be compatible with chance.

All-cause mortality

Study	1. Randomization	2. Deviations from intervention	3. Missing outcome data	4. Measurement of the outcome	5. Selection of the reported results	Overall risk of bias
Toledo-Romani 2021	**Some concerns[a]**	**Some concerns[b]**	Low	Low	Low	**Some concerns**

[a]Toledo-Romani 2021, **RoB 1. Randomization:**
Quote: "Randomization into study arms (A and B) and placebo was done on day 0 at a 1:1:1 ratio using a site stratified random and previously defined risk strata (19–64 years without risk comorbidities, 19–64 years with risk comorbidities and ≥65 years)."
Comment: allocation sequence random. No information on allocation concealment.
Imbalances in baseline characteristics appear to be compatible with chance.

[b]Toledo-Romani 2021, **RoB 2. Deviations from intervention:**
Comment: blinded study (participants and personnel/carers).
Per-protocol analysis was performed on the outcomes.
Reasons for exclusion: did not receive or discontinued the intervention.
As we are assessing the effect of assignment to intervention (intention-to-treat effect), we considered that the data were analyzed inappropriately.
There was probably no substantial impact of failure to analyse participants according to their randomized assignment due to balance between groups.

Heterologous vaccine

Comparison: heterologous vaccination scheme versus homologous vaccination scheme

Systemic reactogenicity events

Study	1. Randomization	2. Deviations from intervention	3. Missing outcome data	4. Measurement of the outcome	5. Selection of the reported results	Overall risk of bias
Li 2021a	Low	**Some concerns[a]**	Low	Low	Low	**Some concerns**

[a]Li 2021a, **RoB 2. Deviations from intervention:**
Quote "We masked participants, investigators, laboratory staff, and outcome assessors to the allocation of treatment groups … Designated unblinded personnel were responsible for the preparation and administration of the vaccination and were forbidden to reveal the identity of the study vaccines to the participants or other investigators"
Comment: blinded study (participants and personnel/carers).
Per-protocol analysis was performed on the outcomes.
One participant randomized to the Convidecia boost group (additional arm in the study extracted separately) crossed over to the CoronaVac/Convidecia group because the participant had in fact only received one primary dose.
As we are assessing the effect of assignment to intervention (intention-to-treat effect), we considered that the data were analyzed inappropriately.

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There was probably no substantial impact of failure to analyse participants according to their randomized assignment due to the single participant that crossed over.
Risk assessed to have some concerns for this outcome.

Any adverse event

Study	1. Randomization	2. Deviations from intervention	3. Missing outcome data	4. Measurement of the outcome	5. Selection of the reported results	Overall risk of bias
Li 2021a	Low	**Some concerns[a]**	Low	Low	Low	**Some concerns**
Liu 2021	Low	Low	Low	**Some concerns[b]**	Low	**Some concerns**
Liu 2021	Low	Low	Low	**Some concerns[c]**	Low	**Some concerns**

[a]Li 2021a, **RoB 2. Deviations from intervention:**
Quote "We masked participants, investigators, laboratory staff, and outcome assessors to the allocation of treatment groups … Designated unblinded personnel were responsible for the preparation and administration of the vaccination and were forbidden to reveal the identity of the study vaccines to the participants or other investigators"
Comment: blinded study (participants and personnel/carers).
Per-protocol analysis was performed on the outcomes.
One participant randomized to the Convidecia boost group (additional arm in the study extracted separately) crossed over to the CoronaVac/Convidecia group because the participant had in fact only received one primary dose.
As we are assessing the effect of assignment to intervention (intention-to-treat effect), we considered that the data were analyzed inappropriately.
There was probably no substantial impact of failure to analyse participants according to their randomized assignment due to the single participant that crossed over.
Risk assessed to have some concerns for this outcome.

[b]Liu 2021, **RoB 4. Measurement of the outcome:**
Comment: method of measuring the outcome probably appropriate.
Measurement or ascertainment of outcome probably does not differ between groups.
Quote: "Laboratory staff will also be blinded to the vaccine schedule received." (protocol) "The clinical team assessing the safety endpoints were not blinded" (report)
Comment: outcome assessment was unblinded for safety outcomes;
Adverse events may contain both clinically and laboratory-detected events, which can be influenced by knowledge of the intervention assignment but is not likely in the context of the pandemic. Risk assessed to have some concerns for this outcome.

[c]Liu 2021, **RoB 4. Measurement of the outcome:**
Comment: method of measuring the outcome probably appropriate.
Measurement or ascertainment of outcome probably does not differ between groups.
Quote: "Laboratory staff will also be blinded to the vaccine schedule received." (protocol) "The clinical team assessing the safety endpoints were not blinded" (report)
Comment: outcome assessment was unblinded for safety outcomes;
Adverse events may contain both clinically and laboratory-detected events, which can be influenced by knowledge of the intervention assignment but is not likely in the context of the pandemic. Risk assessed to have some concerns for this outcome.

Serious adverse events

Study	1. Randomization	2. Deviations from intervention	3. Missing outcome data	4. Measurement of the outcome	5. Selection of the reported results	Overall risk of bias
Li 2021a	Low	**Some concerns[a]**	Low	Low	Low	**Some concerns**

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(Continued)

Liu 2021	Low	Low	Low	**Some concerns[b]**	Low	**Some concerns**
Liu 2021	Low	Low	Low	**Some concerns[c]**	Low	**Some concerns**

[a]Li 2021a, **RoB 2. Deviations from intervention:**
Quote "We masked participants, investigators, laboratory staff, and outcome assessors to the allocation of treatment groups … Designated unblinded personnel were responsible for the preparation and administration of the vaccination and were forbidden to reveal the identity of the study vaccines to the participants or other investigators"
Comment: blinded study (participants and personnel/carers).
Per-protocol analysis was performed on the outcomes.
One participant randomized to the Convidecia boost group (additional arm in the study extracted separately) crossed over to the CoronaVac/Convidecia group because the participant had in fact only received one primary dose.
As we are assessing the effect of assignment to intervention (intention-to-treat effect), we considered that the data were analyzed inappropriately.
There was probably no substantial impact of failure to analyse participants according to their randomized assignment due to the single participant that crossed over.
Risk assessed to have some concerns for this outcome.

[b]Liu 2021, **RoB 4. Measurement of the outcome:**
Comment: method of measuring the outcome probably appropriate.
Measurement or ascertainment of outcome probably does not differ between groups.
Quote: "Laboratory staff will also be blinded to the vaccine schedule received." (protocol) "The clinical team assessing the safety endpoints were not blinded" (report)
Serious adverse events may contain both clinically and laboratory-detected events, which can be influenced by knowledge of the intervention assignment but is not likely in the context of the pandemic.
Risk assessed to have some concerns for this outcome. Outcome assessment was unblinded for safety outcomes

[c]Liu 2021, **RoB 4. Measurement of the outcome:**
Comment: method of measuring the outcome probably appropriate.
Measurement or ascertainment of outcome probably does not differ between groups.
Quote: "Laboratory staff will also be blinded to the vaccine schedule received." (protocol) "The clinical team assessing the safety endpoints were not blinded" (report)
Comment: outcome assessment was unblinded for safety outcomes;
Serious adverse events may contain both clinically and laboratory-detected events, which can be influenced by knowledge of the intervention assignment but is not likely in the context of the pandemic.
Risk assessed to have some concerns for this outcome.

Boosters

Comparison: booster versus placebo/no booster

Systemic reactogenicity events

Study	1. Randomization	2. Deviations from intervention	3. Missing outcome data	4. Measurement of the outcome	5. Selection of the reported results	Overall risk of bias
Li 2021a	Low	**Some concerns[a]**	Low	Low	Low	**Some concerns**
Mok 2021	**Some concerns[b]**	Low	Low	**Some concerns[c]**	**Some concerns[d]**	**Some concerns**
Sablerolles 2021	**Some concerns[e]**	**Some concerns[f]**	**Some concerns[g]**	Low	Low	**Some concerns**

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(Continued)

Sablerolles 2021	**Some concerns[h]**	**Some concerns[i]**	**Some concerns[j]**	Low	Low	**Some concerns**
Sablerolles 2021	**Some concerns[k]**	**Some concerns[l]**	**Some concerns[m]**	Low	Low	**Some concerns**

[a]Li 2021a**, RoB 2. Deviations from intervention:**
Quote "We masked participants, investigators, laboratory staff, and outcome assessors to the allocation of treatment groups … Designated unblinded personnel were responsible for the preparation and administration of the vaccination and were forbidden to reveal the identity of the study vaccines to the participants or other investigators"
Comment: blinded study (participants and personnel/carers). Per-protocol analysis was performed. Reasons for exclusion: three participants randomized to the Convidecia boost group crossed over to other groups. Two participants were wrongly administrated with a homogeneous boost dose of CoronaVac and were re-classified into the CoronaVac boost group. One participant had in fact only received one primary dose and was re-classified into the CoronaVac/Convidecia 2 dose group (additional arm in the study extracted separately). As we are assessing the effect of assignment to intervention (intention-to-treat effect), we considered that the data were analyzed inappropriately. There was probably no substantial impact of failure to analyse participants according to their randomized assignment due to the small number of participants who crossed over. Risk assessed to have some concerns for this outcome.

[b]Mok 2021**, RoB 1. Randomization:**
Quote: "participants were randomized to receive either BNT162b2 (n = 40) or CoronaVac (n = 40) as the third dose."
Comment: allocation sequence probably random. No information on allocation concealment.

[c]Mok 2021**, RoB 4. Measurement of the outcome:**
Comment: method of measuring the outcome probably appropriate. Measurement or ascertainment of outcome probably does not differ between groups. Unclear blinding (outcome assessor).
The authors reported on adverse events that may contain both clinically and laboratory-detected events, which can be influenced by knowledge of the intervention assignment but is not likely in the context of the pandemic.

[d]Mok 2021**, RoB 5. Selection of the reported results:**
Comment: the protocol, statistical analysis plan, registry were available (revision dated August 17, 2021). Outcome not prespecified. No information on whether the result was selected from multiple outcome measurements or analyses of the data. Trial not analyzed as prespecified.

[e]Sablerolles 2021**, RoB 1. Randomization:**
Quote: "Participants were assigned to study groups in a 1:1:1:1 fashion; randomization was stratified by study site after obtaining written informed consent."
Comment: allocation sequence probably random. No information on allocation concealment. Imbalances in baseline characteristics appear to be compatible with chance. Risk assessed as some concerns

[f]Sablerolles 2021**, RoB 2. Deviations from intervention:**
Quote: "single-(participant)-blinded Participants were unblinded for the booster vaccination by e-mail eight days after injection, after completing the reactogenicity questionnaires."
Comment: blinded study (participants). Deviations from intended intervention arising because of the study context: No participant cross-over. Per-protocol analysis was performed on the outcomes. Reasons for exclusion: baseline positive (2.6%, 1.7%, 0.9%, 1.7%), positive between baseline and follow-up (1.8%, 0.9%, 0.0%, 0.0%). As we are assessing the effect of assignment to intervention (intention-to-treat effect), we considered that the data were analyzed inappropriately. There was probably no substantial impact of failure to analyse participants according to their randomized assignment due to balance between groups. Risk assessed to have some concerns for this outcome.

[g]Sablerolles 2021**, RoB 3. Missing outcome data:**
Comment: 461 participants randomized; 433 participants analyzed for reactogenicity. No evidence that the result is not biased. Reasons (reactogenicity): baseline positive (2.6%, 1.7%, 0.9%, 1.7%), positive between baseline and follow-up (1.8%, 0.9%, 0.0%, 0.0%), failed bleed at baseline or follow-up (1.8%, 0.9%, 0.9%, 0.0%) or withdrew from the study (3.5%, 5.2%, 1.7%, 1.7%).
Not likely that missingness depended on the true value of the outcome because there is no major imbalance between groups.
Risk assessed to have some concerns for this outcome. Data not available for all or nearly all participants randomized. Missingness could depend on the true value of the outcome.

[h]Sablerolles 2021**, RoB 1. Randomization:**

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Quote: "Participants were assigned to study groups in a 1:1:1:1 fashion; randomization was stratified by study site after obtaining written informed consent."
Comment: allocation sequence probably random. No information on allocation concealment.
Imbalances in baseline characteristics appear to be compatible with chance.
Risk assessed as some concerns

[i]Sablerolles 2021**, RoB 2. Deviations from intervention:**
Quote: "single-(participant)-blinded Participants were unblinded for the booster vaccination by e-mail eight days after injection, after completing the reactogenicity questionnaires."
Comment: blinded study (participants). Deviations from intended intervention arising because of the study context: no participant cross-over.
Per-protocol analysis was performed on the outcomes.
Reasons for exclusion: baseline positive (2.6%, 1.7%, 0.9%, 1.7%), positive between baseline and follow-up (1.8%, 0.9%, 0.0%, 0.0%).
As we are assessing the effect of assignment to intervention (intention-to-treat effect), we considered that the data were analyzed inappropriately.
There was probably no substantial impact of failure to analyse participants according to their randomized assignment due to balance between groups.
Risk assessed to have some concerns for this outcome.

[j]Sablerolles 2021**, RoB 3. Missing outcome data:**
Comment: 461 participants randomized; 433 participants analyzed for reactogenicity.
Data not available for all or nearly all participants randomized.
No evidence that the result is not biased. Reasons (reactogenicity): baseline positive (2.6%, 1.7%, 0.9%, 1.7%), positive between baseline and follow-up (1.8%, 0.9%, 0.0%, 0.0%), failed bleed at baseline or follow-up (1.8%, 0.9%, 0.9%, 0.0%) or withdrew from the study (3.5%, 5.2%, 1.7%, 1.7%).
Missingness could depend on the true value of the outcome.
Not likely that missingness depended on the true value of the outcome because there is no major imbalance between groups.
Risk assessed to have some concerns for this outcome.

[k]Sablerolles 2021**, RoB 1. Randomization:**
Quote: "Participants were assigned to study groups in a 1:1:1:1 fashion; randomization was stratified by study site after obtaining written informed consent."
Comment: allocation sequence probably random. No information on allocation concealment. Imbalances in baseline characteristics appear to be compatible with chance. Risk assessed as some concerns

[l]Sablerolles 2021**, RoB 2. Deviations from intervention:**
Quote: "single-(participant)-blinded. Participants were unblinded for the booster vaccination by e-mail eight days after injection, after completing the reactogenicity questionnaires."
Comment: blinded study (participants) Deviations from intended intervention arising because of the study context: no participant cross-over. Per-protocol analysis was performed on the outcomes. Reasons for exclusion: baseline positive (2.6%, 1.7%, 0.9%, 1.7%), positive between baseline and follow-up (1.8%, 0.9%, 0.0%, 0.0%).
As we are assessing the effect of assignment to intervention (intention-to-treat effect), we considered that the data were analyzed inappropriately.
There was probably no substantial impact of failure to analyse participants according to their randomized assignment due to balance between groups. Risk assessed to have some concerns for this outcome.

[m]Sablerolles 2021**, RoB 3. Missing outcome data:**
Comment: 461 participants randomized; 433 participants analyzed for reactogenicity. Data not available for all or nearly all participants randomized. No evidence that the result is not biased.
Reasons (reactogenicity): baseline positive (2.6%, 1.7%, 0.9%, 1.7%), positive between baseline and follow-up (1.8%, 0.9%, 0.0%, 0.0%), failed bleed at baseline or follow-up (1.8%, 0.9%, 0.9%, 0.0%) or withdrew from the study (3.5%, 5.2%, 1.7%, 1.7%).
Missingness could depend on the true value of the outcome. Not likely that missingness depended on the true value of the outcome because there is no major imbalance between groups.
Risk assessed to have some concerns for this outcome.

Any adverse event

Study	1. Randomization	2. Deviations from intervention	3. Missing outcome data	4. Measurement of the outcome	5. Selection of the reported results	Overall risk of bias

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Li 2021a	Low	**Some concerns[a]**	Low	Low	Low	**Some concerns**

[a]Li 2021a, RoB 2. Deviations from intervention:
Quote "We masked participants, investigators, laboratory staff, and outcome assessors to the allocation of treatment groups … Designated unblinded personnel were responsible for the preparation and administration of the vaccination and were forbidden to reveal the identity of the study vaccines to the participants or other investigators"
Comment: blinded study (participants and personnel/carers).
Per-protocol analysis was performed.
Reasons for exclusion: three participants randomized to the Convidecia boost group crossed over to other groups. Two participants were wrongly administrated with a homogeneous boost dose of CoronaVac and were reclassified into the CoronaVac boost group. One participant had in fact only received one primary dose and was re-classified into the CoronaVac/Convidecia 2 dose group (additional arm in the study extracted separately).
As we are assessing the effect of assignment to intervention (intention-to-treat effect), we considered that the data were analyzed inappropriately.
There was probably no substantial impact of failure to analyse participants according to their randomized assignment due to the small number of participants who crossed over.
Risk assessed to have some concerns for this outcome.

Serious adverse events

Study	1. Randomization	2. Deviations from intervention	3. Missing outcome data	4. Measurement of the outcome	5. Selection of the reported results	Overall risk of bias
Li 2021a	Low	**Some concerns[a]**	Low	Low	Low	**Some concerns**

[a]Li 2021a, RoB 2. Deviations from intervention:
Quote "We masked participants, investigators, laboratory staff, and outcome assessors to the allocation of treatment groups … Designated unblinded personnel were responsible for the preparation and administration of the vaccination and were forbidden to reveal the identity of the study vaccines to the participants or other investigators"
Comment: blinded study (participants and personnel/carers).
Per-protocol analysis was performed.
Reasons for exclusion: three participants randomized to the Convidecia boost group crossed over to other groups. Two participants were wrongly administrated with a homogeneous boost dose of CoronaVac and were reclassified into the CoronaVac boost group. One participant had in fact only received one primary dose and was re-classified into the CoronaVac/Convidecia 2 dose group (additional arm in the study extracted separately).
As we are assessing the effect of assignment to intervention (intention-to-treat effect), we considered that the data were analyzed inappropriately.
There was probably no substantial impact of failure to analyse participants according to their randomized assignment due to the small number of participants who crossed over.
Risk assessed to have some concerns for this outcome.

Comparison: booster versus booster

All-cause mortality

Study	1. Randomization	2. Deviations from intervention	3. Missing outcome data	4. Measurement of the outcome	5. Selection of the reported results	Overall risk of bias

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Toledo-Romani 2021	**Some concerns[a]**	**Some concerns[b]**	Low	Low	Low	**Some concerns**

[a]Toledo-Romani 2021, **RoB 1. Randomization:**
Quote: "Randomization into study arms (A and B) and placebo was done on day 0 at a 1:1:1 ratio using a site stratified random and previously defined risk strata (19–64 years without risk comorbidities, 19–64 years with risk comorbidities and ≥65 years)."
Comment: allocation sequence random. No information on allocation concealment.
Imbalances in baseline characteristics appear to be compatible with chance.

[b]Toledo-Romani 2021, **RoB 2. Deviations from intervention:**
Comment: blinded study (participants and personnel/carers).
Per-protocol analysis was performed on the outcomes.
Reasons for exclusion: did not receive or discontinued the intervention.
As we are assessing the effect of assignment to intervention (intention-to-treat effect), we considered that the data were analyzed inappropriately.
There was probably no substantial impact of failure to analyse participants according to their randomized assignment due to balance between groups.

Systemic reactogenicity events

Study	1. Randomization	2. Deviations from intervention	3. Missing outcome data	4. Measurement of the outcome	5. Selection of the reported results	Overall risk of bias
Hall 2021[a]	Low	Low	Low	Low	Low	Low

[a]Trial in immunocompromized participants.

Appendix 9. Matrix indicating availability of trial results for the critical and important outcomes of the review

Key to tables:
✓ A study result is available for inclusion in the synthesis.
X No study result is available for inclusion, (probably) because the P value, magnitude or direction of the results generated were considered unfavourable by the study investigators.
* No study result is available for inclusion, (probably) because the outcome was not assessed, or for a reason unrelated to the P value, magnitude or direction of the results.
? No study result is available for inclusion, and it is unclear if the outcome was assessed in the study.

Abbreviations: AE: adverse event; GMR: geometric mean ratio; n: number of participants; SAE: serious adverse event.

RNA-based vaccines

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BNT162b2 – BioNTech/Fosun Pharma/Pfizer versus placebo

Study ID	Study follow-up (months)	BNT162b2 (n)	Placebo (n)	Critical outcomes						
				Confirmed SARS-CoV-2 infection after complete vaccination	Confirmed symptomatic COVID-19 after complete vaccination	Severe or critical COVID-19	All-cause mortality	Systemic reactogenicity events	Any AE	SAE
Walsh 2020 (NCT04368728)	1.68	24	18	*	*	*	✓	✓	✓	✓
Frenck 2021 (NCT04368728)	4.7	1134	1130	*	✓	✓	✓	✓	✓	✓
Thomas 2021 (NCT04368728)	6	22,085	22,080	*	✓	✓	✓	✓	✓	✓

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Study ID	Study follow-up (months)	BNT162b2 (n)	Placebo (n)	Important outcomes		
				GMT of specific antibody against 2019 novel coronavirus	GMT of neutralizing antibody against 2019 novel coronavirus	Local reactogenicity events
Walsh 2020 (NCT04368728)	1.68	24	18	*	✓	✓
Frenck 2021 (NCT04368728)	4.7	1134	1130	*	✓	✓
Thomas 2021 (NCT04368728)	6	22,085	22,080	*	*	✓

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mRNA-1273 – ModernaTX versus placebo

Study ID	Study follow-up (months)	mRNA-1273 (n)	Placebo (n)	Critical outcomes						
				Confirmed SARS-CoV-2 infection after complete vaccination	Confirmed symptomatic COVID-19 after complete vaccination	Severe or critical COVID-19	All-cause mortality	Systemic reactogenicity events	Any AE	SAE
Ali 2021 (NCT04649151)	2.8	2489	1243	✓	✓	*	✓	✓	✓	✓
El Sahly 2021 (NCT04470427)	5.3	15,209	15,206	✓	✓	✓	✓	✓	✓	✓

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Results reported in Pajon 2021 are already reported in El Sahly 2021; consequently, Pajon 2021 is not included in the forest plots.

Study ID	Study follow-up (months)	mRNA-1273 (n)	Placebo (n)	Important outcomes		
				GMT of specific antibody against 2019 novel coronavirus	GMT of neutralizing antibody against 2019 novel coronavirus	Local reactogenicity events
Ali 2021 (NCT04649151)	2.8	2489	1243	*	*	✓
El Sahly 2021 (NCT04470427)	5.3	15,209	15,206	X	X	✓

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CVnCoV – CureVac AG versus placebo

Study ID	Study follow-up (months)	CVnCoV (n)	Placebo (n)	Critical outcomes						
				Confirmed SARS-CoV-2 infection after complete vaccination	Confirmed symptomatic COVID-19 after complete vaccination	Severe or critical COVID-19	All-cause mortality	Systemic reactogenicity events	Any AE	SAE
Kremsner 2021 (NCT04652102; EudraCT 2020-003998-22)	6.23	19,783	19,746	X	✓	✓	✓	✓	✓	✓

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Study ID	Study follow-up (months)	CVnCoV (n)	Placebo (n)	Important outcomes		
				GMT of specific antibody against 2019 novel coronavirus	GMT of neutralizing antibody against 2019 novel coronavirus	Local reactogenicity events
Kremsner 2021 (NCT04652102; EudraCT 2020-003998-22)	6.23	19,783	19,746	*	*	✓

Non-replicating viral vector

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ChAdOx1/SII-ChAdOx1 – AstraZeneca/University of Oxford versus placebo/MenACWY

Study ID	Study follow-up (months)	ChAdOx1 (n)	Placebo (n)	Critical outcomes						
				Confirmed SARS-CoV-2 infection after complete vaccination	Confirmed symptomatic COVID-19 after complete vaccination	Severe or critical COVID-19	All-cause mortality	Systemic reactogenicity events	Any AE	SAE
Asano 2022 (NCT04568031)	1.9	192	64	*	*	*	✓	✓	✓	✓
Falsey 2021 (NCT04516746)	6.27	21,635	10,816	✓	✓	✓	✓	*	✓	✓
Clemens 2021[a] (ISRCTN89951424)	8.27	5207	5209	*	✓	✓	✓	X	*	X
Emary 2021 (NCT04400838)	4.93	5600	5211	*	✓	*	*	*	*	*
Madhi 2021b (NCT04444674; PACTR202006922165132)	2	52	52	*	*	*	✓	*	*	✓
Madhi 2021a (NCT04444674; PACTR202006922165132)	6.73	1013	1013	*	✓	*	*	*	*	*
Kulkarni 2021 (CTRI/2020/08/027170)	6	900	300	*	*	*	✓	X	✓	✓
Voysey 2021a (NCT04324606; ISRCTN89951424; NCT04400838; NCT04444674)	3.94	12,408	12,014	✓	✓	✓	✓	*	✓	✓
Voysey 2021a[b] (ISRCTN89951424;	3.94	12,048	12,014	✓	✓	✓	✓	*	✓	✓

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NCT04324606; NCT04400838; NCT04444674)

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[a]Results reported in Clemens 2021 are included in Voysey 2021a. Only results for "Confirmed SARS-CoV-2 infection after complete vaccination" against Gamma variant were extracted and analyzed.
[b]Results reported in Voysey 2021b are already reported in Voysey 2021a, consequently Voysey 2021b is not included in the forest plots.

Study ID	Study follow-up (months)	ChAdOx1 (n)	Placebo (n)	Important outcomes		
				GMT of specific antibody against 2019 novel coronavirus	GMT of neutralizing antibody against 2019 novel coronavirus	Local reactogenicity events
Asano 2022 (NCT04568031)	1.9	192	64	*	✓	✓
Falsey 2021 (NCT04516746)	6.27	21,635	10,816	*	*	*
Clemens 2021 (ISRCTN89951424)	8.27	5207	5209	*	*	X
Emary 2021 (NCT04400838)	4.93	5600	5211	*	*	*
Madhi 2021b (NCT04444674; PACTR202006922165132)	2	52	52	*	*	*
Madhi 2021a (NCT04444674; PACTR202006922165132)	6.73	1013	1013	*	*	*
Kulkarni 2021 (CTRI/2020/08/027170)	6	900	300	X	X	X
Voysey 2021a (NCT04324606; ISRCTN89951424; NCT04400838; NCT04444674)	3.94	12,408	12,014	✓	✓	X
Voysey 2021a (ISRCTN89951424; NCT04324606; NCT04400838; NCT04444674)	3.94	12,048	12,014	*	*	*

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ChAdOx1 – AstraZeneca/University of Oxford versus SII-ChAdOx1

Study ID	Study follow-up (months)	ChAdOx1 (n)	SII-ChAdOx (n)	Critical outcomes						
				Confirmed SARS-CoV-2 infection after complete vaccination	Confirmed symptomatic COVID-19 after complete vaccination	Severe or critical COVID-19	All-cause mortality	Systemic reactogenicity events	Any AE	AE
Kulkarni 2021 (CTRI/2020/08/027170)	6	300	100	*	*	*	✓	✓	✓	✓

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Study ID	Study follow-up (months)	ChAdOx1 (n)	SII-ChAdOx (n)	Important outcomes		
				GMT of specific antibody against 2019 novel coronavirus	GMT of neutralizing antibody against 2019 novel coronavirus	Local reactogenicity events
Kulkarni 2021 (CTRI/2020/08/027170)	6	300	100	✓	✓	✓

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Ad26.COV2.S – Janssen Pharmaceutical Companies versus placebo

Study ID	Study follow-up (months)	Ad26.COV2.S (n)	Placebo (n)	Critical outcomes						
				Confirmed SARS-CoV-2 infection after complete vaccination	Confirmed symptomatic COVID-19 after complete vaccination	Severe or critical COVID-19	All-cause mortality	Systemic reactogenicity events	Any AE	SAE
Sadoff 2021a (NCT04436276)	2.33	324	164	*	*	*	*	✓	✓	*
Sadoff 2021b (NCT04505722)	1.84 (median)	22,174	22,151	*	✓	✓	✓	✓	✓	✓

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Stephenson 2021 reported on a subset of participants included in Sadoff 2021a. We could not retrieve data from Stephenson 2021 and it was not included in the analysis.

Study ID	Study follow-up (months)	Ad26.COV2.S (n)	Placebo (n)	Important outcomes		
				GMT of specific antibody against 2019 novel coronavirus	GMT of neutralizing antibody against 2019 novel coronavirus	Local reactogenicity events
Sadoff 2021a (NCT04436276)	2.33	324	164	*	✓	*
Sadoff 2021b (NCT04505722)	1.84 (median)	22,174	22,151	X	X	✓

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Gam-COVID-Vac (Sputnik V) – Gamaleya Research Institute versus placebo

				Critical outcomes						
Study ID	**Study follow-up (months)**	**Gam-COVID-Vac (n)**	**Placebo (n)**	**Confirmed SARS-CoV-2 infection after complete vaccination**	**Confirmed symptomatic COVID-19 after complete vaccination**	**Severe or critical COVID-19**	**All-cause mortality**	**Systemic reactogenicity events**	**Any AE**	**SAE**
Logunov 2021 (NCT04530396)	2.56	16,501	5476	*	✓	✓	✓	*	*	✓

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Study ID	Study follow-up (months)	Gam-COV-ID-Vac (n)	Placebo (n)	Important outcomes		
				GMT of specific antibody against 2019 novel coronavirus	GMT of neutralizing antibody against 2019 novel coronavirus	Local reactogenicity events
Logunov 2021 (NCT04530396)	2.56	16,501	5476	✓	✓	*

Inactivated virus vaccine

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CoronaVac – Sinovac versus adjuvant

Study ID	Study follow-up (months)	CoronaVac (n)	Placebo (n)	Critical outcomes						
				Confirmed SARS-CoV-2 infection after complete vaccination	Confirmed symptomatic COVID-19 after complete vaccination	Severe or critical COVID-19	All-cause mortality	Systemic reactogenicity events	Any AE	SAE
Zhang 2021 (NCT04352608) Phase 2	1.41	120	60	*	*	*	*	✓	✓	X
Zhang 2021 (NCT04352608) Phase 1	1.41	24	24	*	*	*	*	✓	✓	✓
Bueno 2021a (NCT04651790)	1.4	270	164	*	*	*	*	✓	*	✓
Han 2021 (NCT04551547)	4.1	219	114	*	*	*	*	*	✓	✓
Palacios 2020 (NCT04456595)	12	6201	6207	*	✓	✓	✓	✓	✓	✓
Tanriover 2021 (NCT04582344)	6	6650	3568	X	✓	✓	✓	✓	✓	✓
Wu 2021a (NCT04383574)	1.84	124	74	*	*	*	*	✓	✓	✓
Li 2021a[a] (NCT04383574)	10.46	100	50	*	*	*	*	✓	✓	✓
Pan 2021a[b] (NCT04352608)		60	30	*	*	*	*	✓	✓	✓

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[a]Results reported in Li 2021a are already reported in Wu 2021a; consequently, Li 2021a is not included in the forest plots.
[b]We could not retrieve data from Pan 2021c; not included in the forest plots.

Study ID	Study follow-up (months)	CoronaVac (n)	Placebo (n)	Important outcomes		
				GMT of specific antibody against 2019 novel coronavirus	GMT of neutralizing antibody against 2019 novel coronavirus	Local reactogenicity events
Zhang 2021 (NCT04352608)	1.41	120	60	✓	✓	✓
Zhang 2021 (NCT04352608)	1.41	24	24	*	✓	✓
Bueno 2021a (NCT04651790)	1.4	270	164	*	*	✓
Han 2021 (NCT04551547)	4.1	219	114	*	✓	*
Palacios 2020 (NCT04456595)	12	6201	6207	*	*	✓
Tanriover 2021 (NCT04582344)	6	6650	3568	X	X	✓
Wu 2021a (NCT04383574)	1.84	100	74	*	✓	✓
Li 2021a (NCT04383574)	10.46	100	50	*	✓	✓
Pan 2021a (NCT04352608)		60	30	*	✓	✓

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WIBP-CorV – Sinopharm-Wuhan versus adjuvant

Study ID	Study follow-up (months)	WIV04 (n)	Placebo (n)	Critical outcomes						
				Confirmed SARS-CoV-2 infection after complete vaccination	Confirmed symptomatic COVID-19 after complete vaccination	Severe or critical COVID-19	All-cause mortality	Systemic reactogenicity events	Any AE	SAE
Al Kaabi 2021 (NCT04510207; ChiCTR2000034780)	5	13,470	13,471	✓	✓	✓	✓	✓	✓	✓
Guo 2021 (ChiCTR2000031809)	4.77	168	168	*	*	*	*	✓	✓	✓

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Study ID	Study follow-up (months)	WIV04 (n)	Placebo (n)	Important outcomes		
				GMT of specific antibody against 2019 novel coronavirus	GMT of neutralizing antibody against 2019 novel coronavirus	Local reactogenicity events
Al Kaabi 2021 (NCT04510207; ChiCTR2000034780)	5	13,470	13,471	*	✓	✓
Guo 2021 (ChiCTR2000031809)	4.77	168	168	*	✓	✓

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BBIBP-CorV – Sinopharm- Beijing versus adjuvant

Study ID	Study follow-up (months)	BBIBP-CorV (n)	Adjuvant (n)	Critical outcomes						
				Confirmed SARS-CoV-2 infection after complete vaccination	Confirmed symptomatic COVID-19 after complete vaccination	Severe or critical COVID-19	All-cause mortality	Systemic reactogenicity events	Any AE	SAE
Xia 2020 (ChiCTR2000032459)	0.92	84	28	*	*	*	*	✓	✓	✓
Al Kaabi 2021 (NCT04510207; ChiCTR2000034780)	5	13,470	13,471	✓	✓	✓	✓	✓	✓	✓
Xia 2021 (ChiCTR2000032459)	2.9	252	252	*	*	*	*	✓	✓	*

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Study ID	Study follow-up (months)	BBIBP-CorV (n)	Adjuvant (n)	Important outcomes		
				GMT of specific antibody against 2019 novel coronavirus	GMT of neutralizing antibody against 2019 novel coronavirus	Local reactogenicity events
Xia 2020 (ChiCTR2000032459)	0.92	84	28	*	✓	✓
Al Kaabi 2021(NCT04510207; ChiCTR2000034780)	5	13,470	13,471	*	✓	✓
Xia 2021 (ChiCTR2000032459)	2.9	252	252	*	✓	✓

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BBV152 – Bharat Biotech versus adjuvant

Study ID	Study follow-up (months)	BBV152 (n)	Placebo (n)	Critical outcomes						
				Confirmed SARS-CoV-2 infection after complete vaccination	Confirmed symptomatic COVID-19 after complete vaccination	Severe or critical COVID-19	All-cause mortality	Systemic reactogenicity events	Any AE	SAE
Ella 2021a (NCT04471519)	6.38	100	75	*	*	*	*	✓	*	✓
Ella 2021b (NCT04641481)	12	12,889	12,889	✓	✓	✓	✓	✓	✓	✓
Ella 2021a[a] (NCT04471519)	3.87	190	190	*	*	*	*	✓	*	✓

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[a]We could not retrieve data from Ella 2021c and the trial is not included in the analysis.

Study ID	Study follow-up (months)	BBV152 (n)	Placebo (n)	Important outcomes		
				GMT of specific antibody against 2019 novel coronavirus	GMT of neutralizing antibody against 2019 novel coronavirus	Local reactogenicity events
Ella 2021a (NCT04471519)	6.38	100	75	*	*	✓
Ella 2021b (NCT04641481)	12	12,889	12,889	*	*	✓
Ella 2021a (NCT04471519)	3.87	190	190	*	*	✓

Protein subunit

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NVX-CoV2373 – Novavax versus placebo

Study ID	Study follow-up (months)	NVX-CoV2373 (n)	Placebo (n)	Critical outcomes						
				Confirmed SARS-CoV-2 infection after complete vaccination	Confirmed symptomatic COVID-19 after complete vaccination	Severe or critical COVID-19	All-cause mortality	Systemic reactogenicity events	Any AE	SAE
Keech 2020 (NCT04368988)	1.15	29	25	*	*	*	*	*	✓	✓
Dunkle 2021 (NCT04611802)	2	19,965	9984	*	✓	✓	✓	✓	✓	✓
Formica 2021 (NCT04368988)	1.15	258	257	*	*	*	*	✓	✓	✓
Heath 2021 (NCT04583995; EudraCT 2020-004123-16)	13	7593	7594	*	✓	✓	✓	*	✓	✓
Shinde 2021 (NCT04533399; PACTR202009726132275)	1.15	2206	2200	*	✓	✓	*	✓	✓	✓

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Study ID	Study follow-up (months)	NVX-CoV2373 (n)	Placebo (n)	Important outcomes		
				GMT of specific antibody against 2019 novel coronavirus	GMT of neutralizing antibody against 2019 novel coronavirus	Local reactogenicity events
Keech 2020 (NCT04368988)	1.15	29	25	✓	✓	*
Dunkle 2021 (NCT04611802)	2	19,965	9984	X	X	✓
Formica 2021 (NCT04368988)	1.15	258	257	✓	*	✓
Heath 2021 (NCT04583995; EudraCT 2020-004123-16)	13	7593	7594	*	*	*
Shinde 2021 (NCT04533399; PACTR202009726132275)	1.15	2206	2200	X	X	✓

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FINLAY-FR-2 – FINLAY versus placebo

Study ID	Study follow-up (months)	FINLAY-FR-2 (n)	Placebo (n)	Critical outcomes						
				Confirmed SARS-CoV-2 infection after complete vaccination	Confirmed symptomatic COVID-19 after complete vaccination	Severe or critical COVID-19	All-cause mortality	Systemic reactogenicity events	Any AE	SAE
Toledo-Romani 2021 (RPCEC00000354)	5.2	14,679	14,675	X	✓	✓	✓	*	X	*

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Study ID	Study follow-up (months)	FINLAY-FR-2 (n)	Placebo (n)	Important outcomes		
				GMT of specific antibody against 2019 novel coronavirus	GMT of neutralizing antibody against 2019 novel coronavirus	Local reactogenicity events
Toledo-Romani 2021 (RPCEC00000354)	5.2	14,679	14,675	X	X	*

Heterologous vaccine

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Comparison: CoronaVac/Ad5-vectored versus homologous CoronaVac

Study ID	Study follow-up (months)	CoronaVac/ Ad5-vectored (n)	CoronaVac (n)	Critical outcomes						
				Confirmed SARS-CoV-2 infection after complete vaccination	Confirmed symptomatic COVID-19 after complete vaccination	Severe or critical COVID-19	All-cause mortality	Systemic reactogenicity events	Any AE	SAE
Li 2021a (NCT04892459)	1	50	50	*	*	*	*	✓	✓	✓
				Important outcomes						
				GMT of specific antibody against SARS-COV-2		GMT of neutralizing antibody against SARSCOV-2		Local reactogenicity events		
				✓		✓		✓		

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Comparison: ChAdOx1-S/BNT162b2 versus ChAdOx1-S

Study ID	Study follow-up (months)	ChAdOx1-S/BNT162b2 (n)	ChAdOx1-S (n)	Critical outcomes						
				Confirmed SARS-CoV-2 infection after complete vaccination	Confirmed symptomatic COVID-19 after complete vaccination	Severe or critical COVID-19	All-cause mortality	Systemic reactogenicity events	Any AE	SAE
Liu 2021 (ISRCTN69254139; EudraCT 2020-005085-33)	2	115	115	*	*	*	*	X	✓	✓
				Important outcomes						
				GMT of specific antibody against SARS-COV-2		**GMT of neutralizing antibody against SARSCOV-2**		**Local reactogenicity events**		
				*		*		X		

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Comparison: BNT162b2/ChAdOx1-S versus BNT162b2

Study ID	Study follow-up (months)	BNT162b2/ ChAdOx1-S (n)	BNT162b2 (n)	Critical outcomes						
				Confirmed SARS-CoV-2 infection after complete vaccination	Confirmed symptomatic COVID-19 after complete vaccination	Severe or critical COVID-19	All-cause mortality	Systemic reactogenicity events	Any AE	SAE
Liu 2021 (ISRCTN69254139; EudraCT 2020-005085-33)	2	114	119	*	*	*	*	*	✓	✓
				Important outcomes						
				GMT of specific antibody against SARS-COV-2		GMT of neutralizing antibody against SARSCOV-2		Local reactogenicity events		
				✓		✓		*		

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Boosters

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Comparison: BNT162b2 versus placebo

Study ID	Study follow-up (months)	BNT162b2 (n)	Placebo (n)	Critical outcomes						
				Confirmed SARS-CoV-2 infection after complete vaccination	Confirmed symptomatic COVID-19 after complete vaccination	Severe or critical COVID-19	All-cause mortality	Systemic reactogenicity events	Any AE	SAE
Hall 2021 (NCT04885907)[a]	1	60	60	X	✓	*	*	✓	*	*
				Important outcomes						
				GMT of specific antibody against SARS-COV-2		**GMT of neutralizing antibody against SARSCOV-2**		**Local reactogenicity events**		
				*		*		✓		

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[a]Trial in immunocompromized participants.

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Comparison: FINLAY-FR-2 (25 µg) + FR-1 (50 µg) versus no booster

Study ID	Study follow-up (months)	FINLAY-FR-2 (25 µg) + FR-1 (50 µg) (n)	Placebo (n)	Critical outcomes						
				Confirmed SARS-CoV-2 infection after complete vaccination	Confirmed symptomatic COVID-19 after complete vaccination	Severe or critical COVID-19	All-cause mortality	Systemic reactogenicity events	Any AE	SAE
Toledo-Romani 2021 (RPCEC00000354)	5.2	14,679	14,675	X	✓	✓	✓	*	X	*
				Important outcomes						
				GMT of specific antibody against SARS-COV-2		**GMT of neutralizing antibody against SARSCOV-2**		**Local reactogenicity events**		
				*		*		*		

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Booster versus booster

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Comparison: BNT162b2 or mRNA-1273/boost ChAdOx1 versus BNT162b2 or mRNA-1273/boost BNT162b2 or mRNA-1273

Study ID	Study follow-up (months)	BNT162b2 or mRNA-1273/Boost ChAdOx1 (n)	BNT162b2 or mRNA-1273/Boost BNT162b2 or mRNA-1273 (n)	Critical outcomes						
				Confirmed SARS-CoV-2 infection after complete vaccination	Confirmed symptomatic COVID-19 after complete vaccination	Severe or critical COVID-19	All-cause mortality	Systemic reactogenicity events	Any AE	SAE
Bonelli 2021[a] (EudraCT 2021-002348-57)	1	30	30	*	*	*	*	*	*	*
				Important outcomes						
				GMT of specific antibody against SARS-COV-2		GMT of neutralizing antibody against SARSCOV-2		Local reactogenicity events		
				*		*		✓		

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[a]Trial in immunocompromized participants.

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Comparison: CoronaVac/boost Ad5-vectored versus CoronaVac/boost

Study ID	Study follow-up (months)	CoronaVac/boost Ad5-vectored (n)	CoronaVac/boost (n)	Critical outcomes						
				Confirmed SARS-CoV-2 infection after complete vaccination	Confirmed symptomatic COVID-19 after complete vaccination	Severe or critical COVID-19	All-cause mortality	Systemic reactogenicity events	Any AE	SAE
Li 2021a (NCT04892459)	1	100	100	*	*	*	*	✓	✓	✓
				Important outcomes						
				GMT of specific antibody against SARS-COV-2		**GMT of neutralizing antibody against SARSCOV-2**		**Local reactogenicity events**		
				✓	✓			✓		

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Comparison: CoronaVac/boost BNT162b2 versus CoronaVac/boost

Study ID	Study follow-up (months)	CoronaVac/boost BNT162b2 (n)	CoronaVac/boost (n)	Critical outcomes						
				Confirmed SARS-CoV-2 infection after complete vaccination	Confirmed symptomatic COVID-19 after complete vaccination	Severe or critical COVID-19	All-cause mortality	Systemic reactogenicity events	Any AE	SAE
Mok 2021 (NCT04611243)	5.8	40	40	*	*	*	*	✓	*	*
				Important outcomes						
				GMT of specific antibody against SARS-COV-2		GMT of neutralizing antibody against SARSCOV-2		Local reactogenicity events		
				*		*		✓		

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Comparison: Ad26/Boost mRNA-1273 versus Ad26/boost

Study ID	Study follow-up (months	Ad26/Boost mRNA-1273 (n)	Ad26/boost (n)	Critical outcomes						
				Confirmed SARS-CoV-2 infection after complete vaccination	Confirmed symptomatic COVID-19 after complete vaccination	Severe or critical COVID-19	All-cause mortality	Systemic reactogenicity events	Any AE	SAE
Sablerolles 2021 (NCT04927936)	1	106	111	*	*	*	*	✓	*	*
				Important outcomes						
				GMT of specific antibody against SARS-COV-2		GMT of neutralizing antibody against SARSCOV-2		Local reactogenicity events		
				*		*		✓		

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Comparison: Ad26/Boost BNT162b2 versus Ad26/boost

Study ID	Study follow-up (months)	Ad26/Boost BNT162b2 (n)	Ad26 /boost (n)	Critical outcomes						
				Confirmed SARS-CoV-2 infection after complete vaccination	Confirmed symptomatic COVID-19 after complete vaccination	Severe or critical COVID-19	All-cause mortality	Systemic reactogenicity events	Any AE	SAE
Sablerolles 2021 (NCT04927936)	1	106	111	*	*	*	*	✓	*	*
				Important outcomes						
				GMT of specific antibody against SARS-COV-2		**GMT of neutralizing antibody against SARSCOV-2**		**Local reactogenicity events**		
				*		*		✓		

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Comparison: Ad26/Boost BNT162b2 versus Ad26/Boost mRNA-1273

Study ID	Study follow-up (months	Ad26/Boost mRNA-1273 (n)	Ad26/boost BNT162b2 (n)	Critical outcomes						
				Confirmed SARS-CoV-2 infection after complete vaccination	Confirmed symptomatic COVID-19 after complete vaccination	Severe or critical COVID-19	All-cause mortality	Systemic reactogenicity events	Any AE	SAE
Sablerolles 2021 (NCT04927936)	1	111	111	*	*	*	*	✓	*	*
				Important outcomes						
				GMT of specific antibody against SARS-COV-2		GMT of neutralizing antibody against SARSCOV-2		Local reactogenicity events		
				*		*		✓		

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Key:
✓ A study result is available for inclusion in the synthesis.
X No study result is available for inclusion, (probably) because the P value, magnitude or direction of the results generated were considered unfavourable by the study investigators.
* No study result is available for inclusion, (probably) because the outcome was not assessed, or for a reason unrelated to the P value, magnitude or direction of the results.
? No study result is available for inclusion, and it is unclear if the outcome was assessed in the study.

Abbreviations: AE: adverse event; GMR: geometric mean ratio; n: number of participants; SAE: serious adverse event.

Appendix 10. BNT162b2 – BioNtech/Fosun Pharma/Pfizer versus placebo

Outcome	No. of studies	No. of participants	Statistical method	Effect size	Vaccine efficacy (95% CI)
Confirmed SARS-CoV-2 infection after complete vaccination	N/A	N/A	N/A	N/A	N/A
Confirmed symptomatic COVID-19 after complete vaccination	2	44,077	N/A	N/A	97.84% (44.25% to 99.92%)
Severe or critical COVID-19 after complete vaccination	1	46,077	N/A	N/A	95.70% (73.90% to 99.90%)
All-cause mortality	1	43,847	Risk Ratio (M-H, Random, 95% CI)	1.07 (0.52 to 2.22)	N/A
Serious adverse events	2	46,107	Risk Ratio (M-H, Random, 95% CI)	1.30 (0.55 to 3.07)	N/A
Systemic reactogenicity events	N/A	N/A	N/A	N/A	N/A
Any adverse event	3	46,149	Risk Ratio (M-H, Random, 95% CI)	1.52 (0.88 to 2.63)	N/A
Local reactogenicity events	N/A	N/A	N/A	N/A	N/A
CI: confidence interval; N/A: not applicable.					

Appendix 11. Neutralizing antibody geometric mean titre

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RNA-based vaccines

Study	Intervention name	Results		Unit of analysis	Time point	Type of assay	Population
		GMT (95% CI)	GMR (95% CI)				
COVID-19**vaccine versus placebo**							
Frenck 2021	BNT162b2	1283.00 (1139.60 to 1444.50)	84.96 (58.90 to 122.55)	Not specified	1 month after 2nd dose	SARS-CoV-2 50% neutralizing assay	12–15 years
	Placebo	15.10 (10.70 to 21.40)					
	BNT162b2	730.80 (646.70 to 825.80)	68.29 (56.55 to 82.48)	Not specified	1 month after 2nd dose	SARS-CoV-2 50% neutralizing assay	16–25 years
	Placebo	10.70 (9.30 to 12.40)					
Walsh 2020	BNT162b2	163 (no CIs)	16.30	Not specified	14 days after 2nd dose (time point not specified for placebo)	SARS-CoV-2 serum 50% neutralizing assay	18–55 years
	Placebo						
	BNT162b2	206 (no CIs)	20.60	Not specified	14 days after 2nd dose (time point not specified for placebo)	SARS-CoV-2 serum 50% neutralizing assay	65–85 years
	Placebo						

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CI: confidence interval; GMR: geometric mean ratio; GMT: geometric mean titre.

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Non-replicant viral vector vaccines

Study	Intervention name	Results		Unit of analysis	Time point	Type of assay	Population
		GMT (95% CI)	GMR (95% CI)				
COVID-19**vaccine versus placebo**							
Sadoff 2021a	Ad26.COV2.S	224 (158 to 318)	3.86 (2.72 to 5.47)	Not reported	29 days after vaccination	Wild-type virus microneutralization assay using the Victoria/1/2020 SARSCoV-2 strain	18 and 55 years
	Placebo	58 (58 to 58)					
Sadoff 2021a	Ad26.COV2.S	212 (137 to 284)	3.65 (2.53 to 5.26)	Not reported	15 days after vaccination	Wild-type virus microneutralization assay using the Victoria/1/2020 SARS-CoV-2 strain	≥ 65 years
	Placebo	58 (58 to 58)					
Logunov 2021	Gam-COV-ID-Vac rAd26-S	44.50 (31.80 to 62.20)	28.46 (17.71 to 45.75)	Not reported	21 days after second dose	Microneutralization assay using SARS-CoV-2 (hCoV-19/Russia/Moscow_PMVL-1/2020) in a 96-well plate and a 50% tissue culture infective dose (TCID50) of 100	≥ 18 years
	Placebo	1.60 (1.12 to 2.19)					
COVID-19**vaccine versus** COVID-19**vaccine**							
Kulkarni 2021	SII-ChAdOx1	69.90 (60.80 to 80.40)	1.23 (0.92 to 1.63)	Not reported	28 days after dose 2	Pseudo virus-based microneutralization assay	≥ 18 years
	ChAdOx1	56.80 (44.40 to 72.50)					

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Inactivated virus vaccines

Study	Intervention name	Results		Units of analysis	Timepoint	Type of assay	Population
		GMT (95% CI)	GMR (95% CI)				
COVID-19**vaccine versus adjuvant/placebo**							
Bueno 2021	CoronaVac	10.10 (7.28 to 14.01)	1.84 (1.32 to 2.55)	Not reported	2 weeks after 2nd dose	A SINOVAC standardized microtitre methodology, conventional virus neutralization	≥ 18 years
	Adjuvant	5.48 (1.84 to 16.29)					
Zhang 2021	CoronaVac	5.60 (3.60 to 8.70)	2.80 (1.80 to 4.25)	Not reported	2 weeks after 2nd dose	Microcytopathogenic effect assay	Phase 1: 18–59 years, healthy
	Placebo	2 (2 to 2)					
Zhang 2021	CoronaVac	27.60 (22.70 to 33.50)	11.90 (10.23 to 13.83)	Not reported	2 weeks after 2nd dose	Microcytopathogenic effect assay	Phase 2: 18–59 years, healthy
	Placebo	2 (2 to 2)					
Han 2021	CoronaVac	142.20 (124.70 to 162.10)	67.71 (59.25 to 77.37)	Not reported	28 days after 2nd dose	Microcytopathogenic effect assay	Phase 2: 3–17 years
	Placebo	2.10 (2 to 2.1)					
Wu 2021a	CoronaVac	42.20 (35.20 to 50.60)	20.09 (16.73 to 24.13)	Not reported	28 days after 2nd dose	Microcytopathogenic effect assay	Phase 2: ≥ 60 years
	Adjuvant	2.10 (2 to 2.10)					
Fadlyana 2021	CoronaVac	15.76 (14.57 to 17.04)	7.80 (7.20 to 8.45)	Not reported	14 days after 2nd dose	Not clear	18–59 years
	Placebo	2.02 (1.98 to 2.05)					
Al Kaabi 2021	WIBP-CorV	94.50 (89.70 to 99.50)	35 (32.83 to 37.30)	Not reported	14 days after 2nd dose	Not reported	≥ 18 years
	Placebo	2.70 (2.60 to 2.80)					
Al Kaabi 2021	BBIBP-CorV	156 (149.60 to 162.70)	57.77 (54.63 to 61.10)	Not reported	14 days after 2nd-dose	Not reported	≥ 18 years

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	Placebo	2.70 (2.60 to 2.80)					
Guo 2021	WIBP-CorV	134 (104 to 174)	26.80 (20.71 to 34.66)	Not reported	28 days after whole course vaccination	Plaque reduction neutralization test (PRNT)	18–59 years
	Adjuvant	5 (5 to 5)					
Xia 2020	BBIBP-CorV	218.90 (165.60 to 289.50)	109.45 (82.77 to 144.73)	Not reported	14 days after 1st inoculation	Not reported	Phase 2: ≥ 18 years
	Placebo	2 (2 to 2)					
Xia 2021	BBIBP-CorV	180.20 (163.60 to 198.40)	90.10 (81.81 to 99.22)	Not reported	28 days after 2nd inoculation	Not reported	3–5 years
	Adjuvant	2 (2 to 2)					
Xia 2021	BBIBP-CorV	168.60 (151.90 to 187)	84.30 (75.97 to 93.53)	Not reported	28 days after 2nd inoculation	Not reported	6–12 years
	Adjuvant	2 (2 to 2)					
Xia 2021	BBIBP-CorV	155.7 (137.7 to 176.5)	77.87 (68.71 to 88.24)	Not reported	28 days after 2nd inoculation	Not reported	13–17 years
	Adjuvant	2 (2 to 2)					
Ella 2021b	BBV152	125.60 (111.20 to 141.80)	9.16 (2.28 to 36 to 78)	Not reported	28 days after 2nd vaccination	MNT50 assay	≥ 18 years
	Adjuvant	13.70 (10.70 to 170.40)					

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Ella 2021a	BBV152	66.40 (53.40 to 82.40)	9.22 (7.25 to 11.80)	Not reported	Day 28	MNT50 assay	18–55 years
	Adjuvant	7.20 (6.40 to 8.10)					

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Protein subunit vaccines

Study	Intervention name	Results		Unit of analysis	Time point	Type of assay	Population
		GMT (95% CI)	GMR (95% CI)				
COVID-19**vaccine versus placebo**							
Keech 2020	NVX-CoV2373	3906.30 (2555.90 to 5970)	195.315 (127.79 to 298.50)	Not reported	Day 35 (14 days after 2nddose)	Wild-type SARS-CoV-2 microneutralization	18–59 years
	Placebo	20 (20 to 20)					

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Primary series heterologous vaccination scheme versus homologous vaccination scheme

Study	Intervention name	Result		Unit of analysis	Time point	Type of assay	Population
		GMT (95% CI)	GMR (95% CI)				
Heterologous schedule versus homologous schedule							
Li 2021a	CoronaVac/Ad5	54.40 (37.90 to 78)	4.25 (2.63 to 6.86)	Not reported	14 days after 2nd dose	Cytopathic effect-based microneutralization assay with a wild-type SARS-CoV-2 virus strain	18–59 years
	CoronaVac	12.80 (9.30 to 17.50)					

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Boosters

Study	Intervention name	Estimate effect		Unit of analysis	Time point	Type of assay	Population
		GMT (95% CI)	GMR (95% CI)				
Heterologous boost versus homologous boost							
Li 2021a	CoronaVac/Ad5 boost	197.40 (167.70 to 232.40)	5.87 (4.64 to 7.43)	BAU/mL	14 days after boost	ELISA RBD-binding IgG	18–59 years
	CoronaVac/CoronaVac boost	33.60 (28.30 to 39.80)					

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BAU: binding antibody units; CI: confidence interval; ELISA: enzyme-linked immunosorbent assay; GMR: geometric mean ratio; GMT: geometric mean titre; IgG: immunoglobulin G; RBD: receptor-binding domain.

Appendix 12. Specific adverse events

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Cardioembolic events

Type of vaccine	Study ID	Arms (number analyzed)	Intervention	Pulmonary embolism	Stroke	Cavernous sinus thrombosis	Pericarditis	Venous thrombosis	Myocardial infarction
RNA-based vaccine	Thomas 2021	Intervention (21,926)	BNT162b2	NR	0	NR	NR	NR	0
		Control (21,921)	Placebo	NR	1	NR	NR	NR	2
	Frenck 2021	Intervention (1131)	BNT162b2	NR	NR	0	NR	0	NR
		Control (1129)	Placebo	NR	NR	0	NR	0	NR
	Walsh 2020	Intervention (24)	BNT162b2	NR	NR	NR	NR	NR	NR
		Control (18)	Placebo	NR	NR	NR	NR	NR	NR
	El Sahly 2021	Intervention (15,166)	mRNA-1273	6	NR	NR	2	47; 8 deep venous thrombosis	7
		Control (15,151)	Placebo	7	NR	NR	2	43; 6 deep venous thrombosis	9
	Ali 2021	Intervention	mRNA-1273	NR	NR	NR	0	NR	0

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		(2482)							
		Control (1238)	Placebo	NR	NR	NR	0	NR	0
	Kremsner 2021	Intervention (2002)	CVnCoV	NR	NR	NR	NR	NR	NR
		Control (1980)	Placebo	NR	NR	NR	NR	NR	NR
	Hall 2021	Intervention (60)	mRNA-1273 booster	NR	NR	NR	NR	NR	NR
		Control (59)	mRNA-1273/placebo	NR	NR	NR	NR	NR	NR
Non-replicating viral vector	Madhi 2021b	Intervention (52)	ChAdOx1	NR	NR	NR	NR	NR	NR
		Control (52)	Placebo	NR	NR	NR	NR	NR	NR
	Falsey 2021	Intervention (21,587)	ChAdOx1	NR	0	0	NR	0	NR
		Control (10,792)	Placebo	NR	2	0	NR	0	NR
	Voysey 2021a	Intervention (12,021)	ChAdOx1	0	NR	NR	1	0 deep venous thrombosis	0
		Control (11,724)	Placebo	1	NR	NR	2	0 deep venous thrombosis	2
	Asano 2022	Intervention	ChAdOx1	NR	NR	NR	NR	NR	NR

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(Continued)

		(192)						
		Control (64)	Placebo	NR	NR	NR	NR	NR	NR
	Kulkarni 2021	Intervention (300)	SII-ChAdOx1	NR	NR	NR	NR	NR	NR
		Control (100)	ChAdOx1	NR	NR	NR	NR	NR	NR
	Sadoff 2021a	Intervention (323)	Ad26.COV2.S	NR	NR	NR	NR	NR	NR
		Control (163)	Placebo	NR	NR	NR	NR	NR	NR
	Sadoff 2021b	Intervention (21,895)	Ad26.COV2.S	4	NR	1	1	6 deep venous thrombosis	NR
		Control (21,888)	Placebo	1	NR	0	0	2 deep venous thrombosis	NR
	Logunov 2021	Intervention (16,427)	Gam-COVID-Vac	NR	NR	0	NR	1 deep venous thrombosis	2
		Control (5435)	Placebo	NR	NR	1	NR	0 deep venous thrombosis	1
Inactivated virus	Ella 2021a	Intervention (99)	BBV152	NR	2	NR	NR	NR	NR
		Control (73)	Adjuvant	NR	NR	NR	NR	NR	NR

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Ella 2021b	Intervention (12,879)	BBV152	NR	NR	NR	NR	NR	0
	Control (12,874)	Adjuvant	NR	NR	NR	NR	NR	1
Zhang 2021	Intervention (24)	CoronaVac	NR	NR	NR	NR	NR	NR
	Control (24)	Adjuvant	NR	NR	NR	NR	NR	NR
Zhang 2021	Intervention	CoronaVac	NR	NR	NR	NR	NR	NR
	Control	Adjuvant	NR	NR	NR	NR	NR	NR
Bueno 2021	Intervention (270)	CoronaVac	NR	NR	NR	NR	NR	NR
	Control (164)	Adjuvant	NR	NR	NR	NR	NR	NR
Han 2021	Intervention (217)	CoronaVac	NR	NR	NR	NR	NR	NR
	Control (114)	Adjuvant	NR	NR	NR	NR	NR	NR
Palacios 2020	Intervention (6202)	CoronaVac	NR	NR	NR	NR	NR	NR
	Control (6194)	Adjuvant	NR	NR	NR	NR	NR	NR
Wu 2021a	Intervention (124)	CoronaVac	NR	NR	NR	NR	NR	NR

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	Control (74)	Adjuvant	NR	NR	NR	NR	NR	NR
Al Kaabi 2021	Intervention (13,464)	WIV04	NR	NR	NR	NR	NR	NR
	Intervention (13,471)	HBO2	NR	NR	NR	NR	NR	NR
	Control (13,453)	Adjuvant	NR	NR	NR	NR	NR	NR
Tanriover 2021	Intervention (6646)	CoronaVac	NR	NR	NR	NR	NR	0
	Control (3568)	Adjuvant	NR	NR	NR	NR	NR	1
Fadlyana 2021	Intervention (405)	CoronaVac	NR	NR	NR	NR	0 vascular disorders	NR
	Control (135)	Adjuvant	NR	NR	NR	NR	1 vascular disorder	NR
Xia 2020 Phase 1 and 2	Intervention (84)	WIBP-CorV	NR	NR	NR	NR	NR	NR
	Control (28)	Adjuvant	NR	NR	NR	NR	NR	NR
Xia 2021	Intervention (252)	BBIBP-CorV	NR	NR	NR	NR	NR	NR
	Control (252)	Adjuvant	NR	NR	NR	NR	NR	NR
Guo 2021	Intervention	WIBP-CorV	NR	NR	NR	NR	NR	NR

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		(84)							
		Control (28)	Adjuvant	NR	NR	NR	NR	NR	NR
Protein subunit	Formica 2021	Intervention (258)	NVX-CoV2373	NR	NR	NR	NR	2 vascular disorders	NR
		Control (255)	Placebo	NR	NR	NR	NR	2 vascular disorders	NR
	Keech 2020	Intervention (29)	NVX-CoV2373	NR	NR	NR	NR	NR	NR
		Control (23)	Placebo	NR	NR	NR	NR	NR	NR
	Shinde 2021	Intervention (484)	NVX-CoV2373	NR	NR	NR	NR	NR	NR
		Control (484)	Placebo	NR	NR	NR	NR	NR	NR
	Heath 2021	Intervention (7569)	NVX-CoV2373	NR	NR	NR	NR	NR	1 myocarditis
		Control (7570)	Placebo	NR	NR	NR	NR	NR	0 myocarditis
	Dunkle 2021	Intervention (19,965)	NVX-CoV2373	3	2	NR	NR	2 deep venous thrombosis	NR
		Control (9984)	Placebo	2	0	NR	NR	0 deep venous thrombosis	NR

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	Toledo-Romani 2021	Intervention (14,675)	FINLAY-FR-2	NR	NR	NR	NR	NR	NR
		Intervention (14,679)	FINLAY-FR-2/booster FR-1	NR	NR	NR	NR	NR	NR
		Control (14,677)	Placebo	NR	NR	NR	NR	NR	NR
Homologous versus heterologous scheme	Li 2021a	Intervention (51)	CoronaVac/Ad5	NR	NR	NR	NR	0	NR
		Control (50)	CoronaVac	NR	NR	NR	NR	0	NR
	Liu 2021	Intervention (115)	ChAd/BNT	NR	NR	NR	NR	1 deep venous thrombosis	NR
		Control (114)	ChAd/ChAd	NR	NR	NR	NR	NR	NR
		Intervention (119)	BNT162b2/ChAdOx1	NR	NR	NR	NR	NR	NR
		Control (115)	BNT162b2/BNT162b2	NR	NR	NR	NR	NR	NR
Homologous or heterologous booster versus	Bonelli 2021	Intervention (27)	ChAdOx1 booster	NR	NR	NR	NR	NR	NR
		Control (28)	BNT162b2 or mRNA-1273 booster	NR	NR	NR	NR	NR	NR
	Sablerolles 2021	Control	Ad26.COV2.S/no booster	NR	NR	NR	NR	NR	NR

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heterologous booster		(105)						
		Intervention (106)	Ad26/booster	NR	NR	NR	NR	NR	NR
		Intervention (112)	Ad26/booster mRNA-1273	NR	NR	NR	NR	NR	NR
		Intervention (111)	Ad26/booster BNT162b2	NR	NR	NR	NR	NR	NR
	Mok 2021	Intervention (30)	CoronaVac/booster	NR	NR	NR	NR	NR	NR
		Control (30)	CoronaVac/booster BNT162b2	NR	NR	NR	NR	NR	NR
	Li 2021a	Intervention (96)	CoronaVac/booster Ad5	NR	NR	NR	NR	NR	NR
		Control (102)	CoronaVac/booster	NR	NR	NR	NR	NR	NR

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NR: not reported; RNA: ribonucleic acid.

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Haematological events

Type of vaccine	Study ID	Arms (number analyzed)	Intervention	Thrombocytopaenia	Haemorrhage	Neutropenia	Anaemia	Lymphadenopathy
RNA-based vaccine	Thomas 2021	Intervention (21,926)	BNT162b2	NR	NR	NR	NR	NR
		Control (21,921)	Placebo	NR	NR	NR	NR	NR
	Frenck 2021	Intervention (1131)	BNT162b2	NR	NR	NR	NR	10
		Control (1129)	Placebo	NR	NR	NR	NR	2
	Walsh 2020a	Intervention (24)	BNT162b2	NR	NR	NR	NR	NR
		Control (18)	Placebo	NR	NR	NR	NR	NR
	El Sahly 2021	Intervention (15,166)	mRNA-1273	1	NR	NR	2	NR
		Control (15,151)	Placebo	1	NR	NR	2	NR
	Ali 2021	Intervention (2482)	mRNA-1273	NR	NR	NR	NR	108
		Control (1238)	Placebo	NR	NR	NR	NR	5

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	Kremsner 2021	Intervention (2002)	CVnCoV	NR	NR	NR	NR	NR
		Control (1980)	Placebo	NR	NR	NR	NR	NR
	Hall 2021	Intervention (60)	mRNA-1273 booster	NR	NR	NR	NR	NR
		Control (59)	mRNA-1273/placebo	NR	NR	NR	NR	NR
Non-replicating viral vector	Madhi 2021b	Intervention (52)	ChAdOx1	NR	NR	NR	NR	NR
		Control (52)	Placebo	NR	NR	NR	NR	NR
	Falsey 2021	Intervention (21,587)	ChAdOx1	NR	NR	NR	NR	NR
		Control (10,792)	Placebo	NR	NR	NR	NR	NR
	Voysey 2021a	Intervention (12,021)	ChAdOx1	NR	NR	NR	0	NR
		Control (11,724)	Placebo	NR	NR	NR	1	NR
	Asano 2022	Intervention (192)	ChAdOx1	NR	NR	NR	NR	NR
		Control (64)	Placebo	NR	NR	NR	NR	NR

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	Kulkarni 2021	Intervention (300)	SII-ChAdOx1	NR	NR	NR	NR	NR
		Control (100)	ChAdOx1	NR	NR	NR	NR	NR
	Sadoff 2021a	Intervention (323)	Ad26.COV2.S	NR	NR	NR	NR	NR
		Control (163)	Placebo	NR	NR	NR	NR	NR
	Sadoff 2021b	Intervention (21,895)	Ad26.COV2.S	NR	NR	NR	NR	NR
		Control (21,888)	Placebo	NR	NR	NR	NR	NR
	Logunov 2021	Intervention (16,427)	Gam-COVID-Vac	NR	NR	NR	NR	6
		Control (5435)	Placebo	NR	NR	NR	NR	1
Inactivated virus	Ella 2021a	Intervention (99)	BBV152	NR	NR	NR	NR	NR
		Control (73)	Adjuvant	NR	NR	NR	NR	NR
	Ella 2021b	Intervention (12,879)	BBV152	NR	1 death due to cerebellar haemorrhage; 1 death due to haem-	NR	NR	NR

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				orrhagic stroke			
	Control (12,874)	Adjuvant	NR	NR	NR	NR	NR
Zhang 2021	Intervention (24)	CoronaVac	NR	NR	NR	NR	NR
	Control (24)	Adjuvant	NR	NR	NR	NR	NR
Zhang 2021	Intervention	CoronaVac	NR	NR	NR	NR	NR
	Control	Adjuvant	NR	NR	NR	NR	NR
Bueno 2021a	Intervention (270)	CoronaVac	NR	NR	NR	NR	NR
	Control (164)	Adjuvant	NR	NR	NR	NR	NR
Han 2021	Intervention (217)	CoronaVac	NR	NR	NR	NR	NR
	Control (114)	Adjuvant	NR	NR	NR	NR	NR
Palacios 2020	Intervention (6202)	CoronaVac	NR	NR	NR	NR	NR
	Control (6194)	Adjuvant	NR	NR	NR	NR	NR
Wu 2021a	Intervention (124)	CoronaVac	NR	NR	NR	NR	NR
	Control	Adjuvant	NR	NR	NR	NR	NR

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	(74)						
Al Kaabi 2021	Intervention (13,464)	WIV04	NR	NR	NR	NR	NR
	Intervention (13,471)	HBO2	NR	NR	NR	NR	NR
	Control (13,453)	Adjuvant	NR	NR	NR	NR	NR
Tanriover 2021	Intervention (6646)	CoronaVac	NR	NR	NR	NR	NR
	Control (3568)	Adjuvant	NR	NR	NR	NR	NR
Fadlyana 2021	Intervention (405)	CoronaVac	NR	NR	NR	NR	NR
	Control (135)	Adjuvant	NR	NR	NR	NR	NR
Xia 2020	Intervention (84)	WIBP-CorV	NR	NR	NR	NR	NR
	Control (28)	Adjuvant	NR	NR	NR	NR	NR
Xia 2021	Intervention (252)	BBIBP-CorV	NR	NR	NR	NR	NR
	Control (252)	Adjuvant	NR	NR	NR	NR	NR
Guo 2021	Intervention (84)	WIBP-CorV	NR	NR	NR	NR	NR
	Control	Adjuvant	NR	NR	NR	NR	NR

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		(28)						
Protein subunit	Formica 2021	Intervention (258)	NVX-CoV2373	NR	NR	NR	NR	3
		Control (255)	Placebo	NR	NR	NR	NR	1
	Keech 2020	Intervention (29)	NVX-CoV2373	NR	NR	NR	NR	NR
		Control (23)	Placebo	NR	NR	NR	NR	NR
	Shinde 2021	Intervention (484)	NVX-CoV2373	NR	NR	NR	1	NR
		Control (484)	Placebo	NR	NR	NR	0	NR
	Heath 2021	Intervention (7569)	NVX-CoV2373	72 blood and lymphatic system disorders	NR	NR	NR	NR
		Control (7570)	Placebo	61 blood and lymphatic system disorders	NR	NR	NR	NR
	Dunkle 2021	Intervention (19,965)	NVX-CoV2373	1	2	1	3	53
		Control (9984)	Placebo	0	1	0	0	13

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	Toledo-Romani 2021	Intervention (14,675)	FINLAY-FR-2	NR	NR	NR	NR	NR
		Intervention (14,679)	FINLAY-FR-2/boost FR-1	NR	NR	NR	NR	NR
		Control (14,677)	Placebo	NR	NR	NR	NR	NR
Homologous versus heterologous scheme	Li 2021a	Intervention (51)	CoronaVac/Ad5	NR	NR	NR	NR	NR
		Control (50)	CoronaVac	NR	NR	NR	NR	NR
	Liu 2021	Intervention (115)	ChAdOx1/BNT162b2	NR	NR	NR	NR	NR
		Control (114)	ChAdOx1/ChAdOx1	NR	NR	NR	NR	NR
		Intervention (119)	BNT162b2/ChAdOx1	NR	NR	NR	NR	NR
		Control (115)	BNT162b2/BNT162b2	NR	NR	NR	NR	NR
Homologous or heterologous booster versus heterologous booster	Bonelli 2021	Intervention (27)	ChAdOx1 booster	0	NR	NR	NR	NR
		Control (28)	BNT162b2 or mRNA-1273 booster	0	NR	NR	NR	NR
	Sablerolles 2021	Control	Ad26.COV2.S/no boost	NR	NR	NR	NR	NR

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	(105)						
	Intervention (106)	Ad26/booster	NR	NR	NR	NR	NR
	Intervention (112)	Ad26/booster mRNA-1273	NR	NR	NR	NR	NR
	Intervention (111)	Ad26/booster BNT162b2	NR	NR	NR	NR	NR
Mok 2021	Intervention (30)	CoronaVac/booster	NR	NR	NR	NR	NR
	Control (30)	CoronaVac/booster BNT162b2	NR	NR	NR	NR	NR
Li 2021a	Intervention (96)	CoronaVac/booster Ad5	NR	NR	NR	NR	NR
	Control (102)	CoronaVac/booster	NR	NR	NR	NR	NR

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NR: not reported; RNA: ribonucleic acid.

Neurological events

Type of vaccine	Study ID	Arms (number analyzed)	Intervention	Nervous system diseases
RNA-based vaccine	Thomas 2021	Intervention (21,926)	BNT162b2	NR
		Control (21,921)	Placebo	NR
	Frenck 2021	Intervention (1131)	BNT162b2	NR
		Control (1129)	Placebo	NR
	Walsh 2020	Intervention (24)	BNT162b2	NR
		Control (18)	Placebo	NR
	El Sahly 2021	Intervention (15,166)	mRNA-1273	2 embolic stroke; 0 ischaemic stroke
		Control (15,151)	Placebo	0 embolic stroke; 1 ischaemic stroke
	Ali 2021	Intervention (2482)	mRNA-1273	NR
		Control (1238)	Placebo	NR
	Kremsner 2021	Intervention (2002)	CVnCoV	NR
		Control (1980)	Placebo	NR
	Hall 2021	Intervention (60)	mRNA-1273 boost	NR
		Control	mRNA-1273/placebo	NR

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(Continued)

		(59)		
Non-replicating viral vector	Madhi 2021b	Intervention (52)	ChAdOx1	16
		Control (52)	Placebo	10
	Falsey 2021	Intervention (21,587)	ChAdOx1	34 paresthesia
		Control (10,792)	Placebo	16 paresthesia
	Voysey 2021a	Intervention (12,021)	ChAdOx1	1 ischaemic stroke
		Control (11,724)	Placebo	0 ischaemic stroke
	Asano 2022	Intervention (192)	ChAdOx1	NR
		Control (64)	Placebo	NR
	Kulkarni 2021	Intervention (300)	SII-ChAdOx1	NR
		Control (100)	ChAdOx1	NR
	Sadoff 2021a	Intervention (323)	Ad26.COV2.S	NR
		Control (163)	Placebo	NR
	Sadoff 2021b	Intervention (21,895)	Ad26.COV2.S	NR
		Control (21,888)	Placebo	NR
	Logunov 2021	Intervention (16,427)	Gam-COVID-Vac	0 haemorrhagic stroke; 1 paraesthesia

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(Continued)

		Control (5435)	Placebo	1 haemorrhagic stroke; 1 paraesthesia
Inactivated virus	Ella 2021a	Intervention (99)	BBV152	NR
		Control (73)	Adjuvant	NR
	Ella 2021b	Intervention (12,879)	BBV152	NR
		Control (12,874)	Adjuvant	NR
	Zhang 2021	Intervention (24)	CoronaVac	NR
		Control (24)	Adjuvant	NR
	Zhang 2021	Intervention	CoronaVac	NR
		Control	Adjuvant	NR
	Bueno 2021	Intervention (270)	CoronaVac	NR
		Control (164)	Adjuvant	NR
	Han 2021	Intervention (217)	CoronaVac	NR
		Control (114)	Adjuvant	NR
	Palacios 2020	Intervention (6202)	CoronaVac	NR
		Control (6194)	Adjuvant	NR
	Wu 2021a	Intervention (124)	CoronaVac	NR
		Control	Adjuvant	NR

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(Continued)

		(74)		
	Al Kaabi 2021	Intervention (13,464)	WIV04 Al Kaabi	NR
		Intervention (13,471)	HBO2	NR
		Control (13,453)	Adjuvant	NR
	Tanriover 2021	Intervention (6646)	CoronaVac	NR
		Control (3568)	Adjuvant	1 acute cerebellar infarction
	Fadlyana 2021	Intervention (405)	CoronaVac	51
		Control (135)	Adjuvant	20
	Xia 2020	Intervention (84)	WIBP-CorV	NR
		Control (28)	Adjuvant	NR
	Xia 2021	Intervention (252)	BBIBP-CorV	NR
		Control (252)	Adjuvant	NR
	Guo 2021	Intervention (84)	WIBP-CorV	NR
		Control (28)	Adjuvant	NR
Protein subunit	Formica 2021	Intervention (258)	NVX-CoV2373	5
		Control (255)	Placebo	4
	Keech 2020	Intervention (29)	NVX-CoV2373	NR
		Control	Placebo	NR

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(Continued)

		(23)		
	Shinde 2021	Intervention (484)	NVX-CoV2373	0
		Control (484)	Placebo	1
	Heath 2021	Intervention (7569)	NVX-CoV2373	32
		Control (7570)	Placebo	31
	Dunkle 2021	Intervention (19,965)	NVX-CoV2373	2 stroke
		Control (9984)	Placebo	0 stroke
	Toledo-Romani 2021	Intervention (14,675)	FINLAY-FR-2	NR
		Intervention (14,679)	FINLAY-FR-2/boostwe FR-1	NR
		Control (14,677)	Placebo	NR
Homologous versus heterologous scheme	Li 2021a	Intervention (51)	CoronaVac/Ad5	NR
		Control (50)	CoronaVac	NR
	Liu 2021	Intervention (115)	ChAdOx1/BNT162b2	NR
		Control (114)	ChAdOx1/ ChAdOx1NR	NR
		Intervention (119)	BNT162b2/ChAdOx1	NR
		Control (115)	BNT162b2/BNT162b2	NR

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Homologous or heterologous booster versus heterologous booster	Bonelli 2021	Intervention (27)	ChAdOx1 booster	0 neurological complications
		Control (28)	BNT162b2 or mRNA-1273 booster	0 neurological complications
	Sablerolles 2021	Control (105)	Ad26.COV2.S/no booster	NR
		Intervention (106)	Ad26/booster	NR
		Intervention (112)	Ad26/booster mRNA-1273	NR
		Intervention (111)	Ad26/booster BNT162b2	NR
	Mok 2021	Intervention (30)	CoronaVac/booster	NR
		Control (30)	CoronaVac/booster BNT162b2	NR
	Li 2021a	Intervention (96)	CoronaVac/boost Ad5	NR
		Control (102)	CoronaVac/booster	NR

NR: not reported; RNA: ribonucleic acid.

Appendix 13. mRNA-1273 – ModernaTX versus placebo

Outcome	No. of studies	No. of participants	Statistical method	Effect size	Vaccine efficacy (95% CI)
Confirmed SARS-CoV-2 infection after complete vaccination	2	31,632	N/A	N/A	73.27% (35.82% to 88.87%)
Confirmed symptomatic COVID-19 after complete vaccination	2	31,632	N/A	N/A	93.20% (91.06% to 94.83%)
Severe or critical COVID-19 after complete vaccination	1	28,451	N/A	N/A	98.20% (92.80% to 99.60%)

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All-cause mortality	1	30,346	Risk Ratio (M-H, Random, 95% CI)	1.06 (0.54 to 2.10)	N/A
Serious adverse events	2	34,072	Risk Ratio (M-H, Random, 95% CI)	0.92 (0.78 to 1.08)	N/A
Systemic reactogenicity events	2	34,037	Risk Ratio (M-H, Random, 95% CI)	1.28 (1.22 to 1.34)	N/A
Any adverse event	2	34,072	N/A	Outcome not pooled due to considerable heterogeneity	N/A
Local reactogenicity events	2	34,037	Risk Ratio (M-H, Random, 95% CI)	3.30 (2.02 to 5.40)	N/A

CI: confidence interval; N/A: not applicable.

Appendix 14. CVnCoV – CureVac AG versus placebo

Outcome	No. of studies	No. of participants	Statistical method	Effect size	Vaccine efficacy (95% CI)
Confirmed SARS-CoV-2 infection after complete vaccination	N/A	N/A	N/A	N/A	N/A
Confirmed symptomatic COVID-19 after complete vaccination	1	25,062	N/A	N/A	48.20% (31.70% to 60.90%)
Severe or critical COVID-19 after complete vaccination	1	25,062	N/A	N/A	63.80% (0.00% to 91.70%)
All-cause mortality	1	39,529	Risk Ratio (M-H, Random, 95% CI)	1.33 (0.46 to 3.83)	N/A
Serious adverse events	1	39,529	Risk Ratio (M-H, Random, 95% CI)	1.24 (0.90 to 1.71)	N/A
Systemic reactogenicity events	1	3982	Risk Ratio (M-H, Random, 95% CI)	1.48 (1.43 to 1.53)	N/A
Any adverse event	1	3982	Risk Ratio (M-H, Random, 95% CI)	1.42 (1.38 to 1.47)	N/A
Local reactogenicity events	1	3982	Risk Ratio (M-H, Random, 95% CI)	3.51 (3.24 to 3.81)	N/A

CI: confidence interval; N/A: not applicable

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Appendix 15. ChAdOx1/SII-ChAdOx1 – AstraZeneca + University of Oxford/Serum Institute of India versus placebo

Outcome	No. of studies	No. of participants	Statistical method	Effect size	Vaccine efficacy (95% CI)
Confirmed SARS-CoV-2 infection after complete vaccination	5	43,390	N/A	N/A	59.35% (48.00% to 68.22%)
Confirmed symptomatic COVID-19 after complete vaccination	5	43,390	N/A	N/A	70.23% (62.10% to 76.62%)
Severe or critical COVID-19 after complete vaccination	N/A	N/A	N/A	N/A	N/A
All-cause mortality	5	56,727	Risk Ratio (M-H, Random, 95% CI)	0.48 (0.20 to 1.14)	N/A
Serious adverse events	7	58,182	Risk Ratio (M-H, Random, 95% CI)	0.88 (0.72 to 1.07)	N/A
Systemic reactogenicity events	1	256	Risk Ratio (M-H, Random, 95% CI)	3.93 (2.11 to 7.29)	N/A
Any adverse event	7	57,580		Not pooled	N/A
Local reactogenicity events	1	256	Risk Ratio (M-H, Random, 95% CI)	6.44 (2.98 to 13.92)	N/A

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Appendix 16. Specific antibody geometric mean titre

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Non-replicant viral vector vaccines

Study	Intervention name	Results		Unit of analysis	Time point	Type of assay	Population
		GMT (95% CI)	GMR (95% CI)				
COVID-19 vaccine versus placebo/other no COVID-19 vaccine							
Voysey 2021a	ChAdOx1 at < 6 weeks interval	219.66 (197.53 to 244.27)	296.83 (245.86 to 358.37)	ELISA units	28 days after second dose	Multiplexed immunoassay/RBD-binding IgG	18–55 years
	MenACWY vaccine/placebo	74 (63 to 86)					
Voysey 2021a	ChAdOx1 at < 6 weeks interval	188.59 (169.00 to 210.46)	471.47 (395.69 to 561.77)	ELISA units	28 days after second dose	Multiplexed immunoassay/RBD-binding IgG	≥ 56 years
	MenACWY vaccine/placebo	40 (35 to 46)					
Logunov 2021	Gam-COVID-Vac rAd26-S	8996 (7610 to 10 635)	294.46 (188.27 to 460.56)	Not reported	21 days after second dose	ELISA RBD-binding IgG	≥ 18
	Placebo	30.55 (20.18 to 46.26)					
COVID-19 vaccine versus COVID-19 vaccine							
Kulkarni 2021	SII-ChAdOx1	9636.70 (7983.70 to 11,631.90)	1.52 (1.03 to 2.26)	Arbitrary units (AU)/mL	28 days after dose 1	ELISpot assay RBD-binding IgG	≥ 18
	ChAdOx1	6311.20 (4470.10 to 8910.60)					

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CI: confidence interval; ELISA: enzyme-linked immunosorbent assay; GMR: geometric mean rate; GMT: geometric mean titre; IgG: immunoglobulin G; RBD: receptor-binding domain.

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Inactivated virus vaccines

Study	Intervention name	Results		Units of analysis	Time point	Type of assay	Population
		GMT (95% CI)	GMR (95% CI)				
COVID-19**vaccine versus adjuvant/placebo**							
Bueno 2021	CoronaVac	10.10 (7.28 to 14.01)	1.84 (1.32 to 2.55)	Not reported	2 weeks after 2nd dose	A SINOVAC standardized microtitre methodology, conventional virus neutralization	≥ 18 years
	Adjuvant	5.48 (1.84 to 16.29)					
Zhang 2021	CoronaVac	5.60 (3.60 to 8.70)	2.80 (1.80 to 4.25)	Not reported	2 weeks after 2nd dose	Micro-cytopathogenic effect assay	Phase 1: healthy and aged 18–59 years
	Placebo	2 (2 to 2)					
Zhang 2021	CoronaVac	27.60 (22.70 to 33.5)	11.90 (10.23 to 13.83)	Not reported	2 weeks after 2nd dose	Micro-cytopathogenic effect assay	Phase 2: healthy and aged 18–59 years
	Placebo	2 (2 to 2)					
Han 2021	CoronaVac	142.20 (124.70 to 162.10)	67.71 (59.25 to 77.37)	Not reported	28 days after 2nd dose	Micro-cytopathogenic effect assay	Phase 2: 3–17 years
	Placebo	2.10 (2 to 2.10)					
Wu 2021a	CoronaVac	42.20 (35.20 to 50.60)	20.09 (16.73 to 24.13)	Not reported	28 days after 2nd dose	Micro-cytopathogenic effect assay	Phase 2: aged ≥ 60 years
	Adjuvant	2.10 (2 to 2.10)					
Fadlyana 2021	CoronaVac	15.76 (14.57 to 17.04)	7.80 (7.20 to 8.45)	Not reported	14 days after 2nd dose	Not clear	18–59 years
	Placebo	2.02 (1.98 to 2.05)					
Al Kaabi 2021	WIBP-CorV	94.50 (89.70 to 99.50)	35 (32.83 to 37.30)	Not reported	14 days after 2nd dose	Not reported	≥ 18 years
	Placebo	2.70 (2.60 to 2.80)					

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Al Kaabi 2021	BBIBP-CorV	156 (149.60 to 162.70)	57.77 (54.63 to 61.10)	Not reported	14 days after 2nd dose	Not reported	≥ 80 years
	Placebo	2.70 (2.60 to 2.80)					
Guo 2021	WIBP-CorV	134 (104 to 174)	26.80 (20.71 to 34.66)	Not reported	28 days after whole course vaccination	Plaque reduction neutralization test (PRNT)	18–59 years
	Adjuvant	5 (5 to 5)					
Xia 2020	BBIBP-CorV	218.90 (165.60 to 289.50)	109.45 (82.77 to 144.73)	Not reported	14 days after lst in-oculation	Not reported	Phase 2 ≥ 18 years
	Placebo	2 (2 to 2)					
Xia 2021	BBIBP-CorV	180.20 (163.60 to 198.40)	90.10 (81.81 to 99.22)	Not reported	28 days after 2nd inoculation	Not reported	3–5 years
	Adjuvant	20 (20 to 20)					
	BBIBP-CorV	168.60 (151.90 to 187)	84.30 (75.97 to 93.53)	Not reported	28 days after 2nd inoculation	Not reported	6–12 years
	Adjuvant	2 (2 to 2)					
	BBIBP-CorV	155.70 (137.70 to 176.50)	77.87 (68.71 to 88.24)	Not reported	28 days after 2nd inoculation	Not reported	13–17 years
	Adjuvant	2 (2 to 2)					
Ella 2021b	BBV152	125.60	9.16 (2.28 to 36.78)	Not reported	28 days after 2nd vaccination	MNT50 assay	≥ 18 years

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		(111.20 to 141.80)					
	Adjuvant	13.70 (10.70 to 170.40)					
Ella 2021a	BBV152	66.40 (53.40 to 82.40)	9.22 (7.25 to 11.80)	Not reported	Day 28	MNT50 assay	18–55 years
	Adjuvant	7.20 (6.40 to 8.10)					

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Protein subunit vaccines

Study	Intervention name	Results		Unit of analysis	Time point	Type of assay	Population
		GMT (95% CI)	GMR (95% CI)				
COVID-19 vaccine versus placebo							
Keech 2020	NVX-CoV2373	1984.20 (1405.80 to 2800.70)	18.08 (12.18 to 26.85)	EU/mL	Day 21 after 1st dose	ELISA RBD-binding IgG	18–59 years
	Placebo	109.70 (90.40 to 133.20)					
Formica 2021	NVX-CoV2373	44,420.90 (37,929.10 to 52,023.80)	352.26 (290 to 427.89)	EU/mL	Day 35 (14 days after the 2nd dose)	ELISA	18–84 years
	Placebo	126.10 (114 to 139.40)					

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CI: confidence interval; ELISA: enzyme-linked immunosorbent assay; GMR: geometric mean rate; GMT: geometric mean titre; IgG: immunoglobulin G; RBD: receptor-binding domain.

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Primary series heterologous vaccination scheme versus homologous vaccination scheme

Study	Intervention name	Results		Unit of analysis	Time point	Type of assay	Population
		GMT (95% CI)	GMR (95% CI)				
Heterologous schedule versus homologous schedule							
Li 2021a	CoronaVac/Ad5	941.80 (663.90 to 1336.10)	6.11 (3.90 to 9.57)	Not reported	14 days after 2nd dose	ELISA	18–59 years
	CoronaVac	154.10 (116.30 to 204.30)					

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Boosters

Study	Intervention name	Results		Unit of analysis	Time point	Type of assay	Population
		GMT (95% CI)	GMR (95% CI)				
Heterologous booster versus homologous booster							
Li 2021a	CoronaVac/Ad5 booster	3090.10 (2636.10 to 3622.30)	8.37 (6.52 to 10.75)	Not reported	14 days after boost	ELISA	18–59 years
	CoronaVac/CoronaVac boost	369 (304.20 to 447.50)					

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CI: confidence interval; GMR: geometric mean rate; GMT: geometric mean titre.

Appendix 17. ChAdOx1 – AstraZeneca + University of Oxford versus SII-ChAdOx1 – Serum Institute of India

Outcome	No. of studies	No. of participants	Statistical method	Effect size	Vaccine efficacy (95% CI)
Confirmed SARS-CoV-2 infection after complete vaccination	N/A	N/A	N/A	N/A	N/A
Confirmed symptomatic COVID-19 after complete vaccination	N/A	N/A	N/A	N/A	N/A
Severe or critical COVID-19 after complete vaccination	N/A	N/A	N/A	N/A	N/A
All-cause mortality	N/A	N/A	N/A	N/A	N/A
Serious adverse events	1	400	Risk Ratio (M-H, Random, 95% CI)	0.50 (0.08 to 2.95)	N/A
Systemic reactogenicity events	1	400	Risk Ratio (M-H, Random, 95% CI)	0.73 (0.54 to 0.98)	N/A
Any adverse event	1	400	Risk Ratio (M-H, Random, 95% CI)	0.83 (0.52 to 1.33)	N/A
Local reactogenicity events	1	400	Risk Ratio (M-H, Random, 95% CI)	0.76 (0.55 to 1.05)	N/A

CI: confidence interval; N/A: not applicable.

Appendix 18. Ad26.COV2.S – Janssen Pharmaceutical Companies versus placebo

Outcome	No. of studies	No. of participants	Statistical method	Effect size	Vaccine efficacy (95% CI)
Confirmed SARS-CoV-2 infection after complete vaccination	N/A	N/A	N/A	N/A	N/A
Confirmed symptomatic COVID-19 after complete vaccination	1	39,058	N/A	N/A	66.90% (59.10% to 73.40%)
Severe or critical COVID-19 after complete vaccination	1	39,058	N/A	N/A	76.30% (57.90% to 87.50%)
All-cause mortality	1	43,783	Risk Ratio (M-H, Random, 95% CI)	0.25 (0.09 to 0.67)	N/A
Serious adverse events	1	43,783	Risk Ratio (M-H, Random, 95% CI)	0.92 (0.69 to 1.22)	N/A

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Systemic reactogenicity events	2	7222	Risk Ratio (M-H, Random, 95% CI)	1.83 (1.29 to 2.60)	N/A
Any adverse event	2	7222	Risk Ratio (M-H, Random, 95% CI)	1.57 (0.75 to 3.29)	N/A
Local reactogenicity events	2	7222	Risk Ratio (M-H, Random, 95% CI)	3.27 (1.91 to 5.62)	N/A

CI: confidence interval; N/A: not applicable.

Appendix 19. Gam-COVID-Vac (Sputnik V) – Gamaleya Research Institute versus placebo

Outcome	No. of studies	No. of participants	Statistical method	Effect size	Vaccine efficacy (95% CI)
Confirmed SARS-CoV-2 infection after complete vaccination	N/A	N/A	N/A	N/A	N/A
Confirmed symptomatic COVID-19 after complete vaccination	1	18,695	N/A	N/A	91.10% (83.80% to 95.10%)
Severe or critical COVID-19 after complete vaccination	1	19,866	N/A	N/A	100.00% (94.40% to 100.00%)
All-cause mortality	1	21,862	Risk Ratio (M-H, Random, 95% CI)	0.99 (0.10 to 9.54)	N/A
Serious adverse events	1	21,862	Risk Ratio (M-H, Random, 95% CI)	0.65 (0.39 to 1.07)	N/A
Systemic reactogenicity events	N/A	N/A	N/A	N/A	N/A
Any adverse event	N/A	N/A	N/A	N/A	N/A
Local reactogenicity events	N/A	N/A	N/A	N/A	N/A

CI: confidence interval; N/A: not applicable.

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Appendix 20. Cellular immune response

Study	Intervention name	Estimate effect		Unit of analysis	Time point	Type of assay	Population
Ella 2021a	Intervention: BBV152	Median (IQR)	55N (22 to 173.80)	Number of SFCs per million PBMCs	28-D1	IFN-γ ELISpot	18–55 years
	Control: placebo	Median (IQR)	3 (1 to 23)				
Logunov 2021	Intervention: Gam-COVID-Vac	Median (IQR)	32.77 (13.94 to 50.76)	IFN-γ concentration pg/mL	28-D1	IFN-γ measured by ELISA	≥ 18 years
	Control: placebo	Median (IQR)	0.41 (0.11 to 0.85)				
Liu 2021	Intervention: ChAdOx1/ BNT162b2	Geometric mean ratio (95% CI)	3.90 (95% CI 2.90 to 5.30)	Number of spot-forming cells (SFCs) per million PBMCs	28-D2	IFN-γ ELISpot	≥ 50 years
	Control: ChAdOx1/ChAdOx1						
	Intervention: BNT162b2/ChAdOx1		1.20 (95% CI 0.87 to 1.70)				
	Control: BNT162b2/ BNT162b2						
Hall 2021	Intervention: mRNA-1273/mRNA-1273 boost	Median	432 versus 67; 95% CI for the between-group difference, 46 to 986	T-cell counts – cells per million CD4+ T cells	28-D3	Intracellular cytokine staining	Transplant recipients only
	Control: mRNA-1273/placebo boost	Median					
Bonelli 2021	Intervention: BNT162b2 or mRNA-1273/ChAdOx1 boost	Median (IQR)	459 (133 to 722)	Number of SFCs per million PBMCs	7-D3	IFN-γ ELISpot	People currently receiving rituximab
	Control: BNT162b2 or mRNA-1273/BNT162b2 or mRNA-1273 boost	Median (IQR)	305 (171 to 416)				
Zhang 2021	Intervention: CoronaVac	Median (Min, Max)	5.50 (0 to 35.70)	Number of SFCs per million PBMCs	14-D2	IFN-γ ELISpot	18–59 years
	Control: placebo	Median (Min, Max)	0 (0 to 11.70)				
Sablerolles 2021	Intervention: Ad26.COV2.S/mRNA-1273 boost	Percentage of responders	44/48 (91.66%) versus 32/44 (72.72%) (RR 0.79, 95% CI 0.64 to 0.96, P = 0.01726)	Number of responders (responder cut-off is 0.15 IU/mL)	28-D2	IFN-γ release assay	18–65 years

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Control: Ad26.COV2.S/Ad26.COV2.S boost		
Intervention: Ad26.COV2.S/BN-T162b2 boost	Percentage of responders	43/47 (91.48%) versus 32/44 (72.72%) (RR 0.79, 95% CI 0.65 to 0.97, P = 0.01946)
Control: Ad26.COV2.S/Ad26.COV2.S boost		
Intervention: Ad26.COV2.S/BN-T162b2 boost	Percentage of responders	43/47 (91.48%) versus 44/48 (91.66%) (RR 1.00, 95% CI 0.88 to 1.13, P = 0.9753)
Control: Ad26.COV2.S/mRNA-1273 boost		

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IFN: interferon; IQR: interquartile range; min: minimum; max: maximum; PBMC: peripheral blood mononuclear cell; RR: risk ratio; SFC: spot-forming cell

Appendix 21. CoronaVac – Sinovac versus placebo

Outcome	No. of studies	No. of participants	Statistical method	Effect size	Vaccine efficacy (95% CI)
Confirmed SARS-CoV-2 infection after complete vaccination	N/A	N/A	N/A	N/A	N/A
Confirmed symptomatic COVID-19 after complete vaccination	2	19,852	N/A	N/A	69.81% (12.27% to 89.61%)
Severe or critical COVID-19 after complete vaccination	2	19,852	N/A	N/A	N/A
All-cause mortality	1	12,396	Risk Ratio (M-H, Random, 95% CI)	0.50 (0.05 to 5.52)	N/A
Serious adverse events	4	23,139	Risk Ratio (M-H, Random, 95% CI)	0.97 (0.62 to 1.51)	N/A
Systemic reactogenicity events	6	23,956	Risk Ratio (M-H, Random, 95% CI)	0.95 (0.55 to 1.62)	N/A
Any adverse event	6	23,367	Risk Ratio (M-H, Random, 95% CI)	1.09 (1.07 to 1.11)	N/A
Local reactogenicity events	6	23,962	Risk Ratio (M-H, Random, 95% CI)	1.76 (1.69 to 1.82)	N/A

CI: confidence interval; N/A: not applicable.

Appendix 22. WIBP-CorV – Sinopharm-Wuhan versus placebo

Outcome	No. of studies	No. of participants	Statistical method	Effect size	Vaccine efficacy (95% CI)
Confirmed SARS-CoV-2 infection after complete vaccination	1	25,449	N/A	N/A	64.00% (48.80% to 74.70%)
Confirmed symptomatic COVID-19 after complete vaccination	1	25,480	N/A	N/A	72.80% (58.10% to 82.40%)
Severe or critical COVID-19 after complete vaccination	N/A	N/A	N/A	N/A	N/A
All-cause mortality	N/A	N/A	N/A	N/A	N/A

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(Continued)

Serious adverse events	2	27,029	Risk Ratio (M-H, Random, 95% CI)	0.83 (0.60 to 1.15)	N/A
Systemic reactogenicity events	2	27,029	Risk Ratio (M-H, Random, 95% CI)	0.99 (0.95 to 1.03)	N/A
Any adverse event	2	27,029	Risk Ratio (M-H, Random, 95% CI)	0.96 (0.93 to 0.98)	N/A
Local reactogenicity events	2	27,029	Risk Ratio (M-H, Random, 95% CI)	0.88 (0.85 to 0.92)	N/A

CI: confidence interval; N/A: not applicable.

Appendix 23. BBIBP-CorV – Sinopharm-Beijing versus placebo

Outcome	No. of studies	No. of participants	Statistical method	Effect size	Vaccine efficacy (95% CI)
Confirmed SARS-CoV-2 infection after complete vaccination	1	25,435	N/A	N/A	73.50% (60.60% to 82.20%)
Confirmed symptomatic COVID-19 after complete vaccination	1	25,463	N/A	N/A	78.10% (64.80% to 86.30%)
Severe or critical COVID-19 after complete vaccination	N/A	N/A	N/A	N/A	N/A
All-cause mortality	N/A	N/A	N/A	N/A	N/A
Serious adverse events	1	26,924	Risk Ratio (M-H, Random, 95% CI)	0.76 (0.54 to 1.06)	N/A
Systemic reactogenicity events	3	27,540	Risk Ratio (M-H, Random, 95% CI)	1.05 (0.86 to 1.28)	N/A
Any adverse event	3	27,540	–	Not pooled due to high heterogeneity	N/A
Local reactogenicity events	3	27,540	–	Not pooled due to high heterogeneity	N/A

CI: confidence interval; N/A: not applicable.

Appendix 24. BBV152 – Bharat Biotech versus placebo

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Outcome	No. of studies	No. of participants	Statistical method	Effect size	Vaccine efficacy (95% CI)
Confirmed SARS-CoV-2 infection after complete vaccination	1	6289	N/A	N/A	68.80% (46.70% to 82.50%)
Confirmed symptomatic COVID-19 after complete vaccination	1	16,973	N/A	N/A	77.80% (65.20% to 86.40%)
Severe or critical COVID-19 after complete vaccination	1	16,976	N/A	N/A	93.40% (57.10% to 99.80%)
All-cause mortality	1	25,753	Risk Ratio (M-H, Random, 95% CI)	0.50 (0.17 to 1.46)	N/A
Serious adverse events	1	25,753	Risk Ratio (M-H, Random, 95% CI)	0.65 (0.43 to 0.97)	N/A
Systemic reactogenicity events	2	25,925	Risk Ratio (M-H, Random, 95% CI)	1.34 (1.15 to 1.58)	N/A
Any adverse event	1	25,753	Risk Ratio (M-H, Random, 95% CI)	1.00 (0.94 to 1.07)	N/A
Local reactogenicity events	2	25,750	Risk Ratio (M-H, Random, 95% CI)	1.08 (0.95 to 1.24)	N/A

CI: confidence interval; N/A: not applicable.

Appendix 25. NVX-CoV2373 – Novavax versus placebo

Outcome	No. of studies	No. of participants	Statistical method	Effect size	Vaccine efficacy (95% CI)
Confirmed SARS-CoV-2 infection after complete vaccination	N/A	N/A	N/A	N/A	N/A
Confirmed symptomatic COVID-19 after complete vaccination	3	42,175	N/A	N/A	82.91% (50.49% to 94.10%)
Severe or critical COVID-19 after complete vaccination	1	25,452	N/A	N/A	100.00% (86.99% to 100.00%)
All-cause mortality	1	29,582	Risk Ratio (M-H, Random, 95% CI)	0.90 (0.30 to 2.68)	N/A
Serious adverse events	4	46,202	Risk Ratio (M-H, Random, 95% CI)	0.92 (0.74 to 1.14)	N/A
Systemic reactogenicity events	3	31,063	Risk Ratio (M-H, Random, 95% CI)	1.21 (1.17 to 1.25)	N/A

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(Continued)

Any adverse event	5	46,231	Risk Ratio (M-H, Random, 95% CI)	1.15 (1.05 to 1.26)	N/A
Local reactogenicity events	3	31,063	Risk Ratio (M-H, Random, 95% CI)	2.78 (1.99 to 3.88)	N/A

CI: confidence interval; N/A: not applicable.

Appendix 26. FINLAY-FR-2 – Instituto Finlay de Vacunas versus placebo

Outcome	No. of studies	No. of participants	Statistical method	Effect size	Vaccine efficacy (95% CI)
Confirmed SARS-CoV-2 infection after complete vaccination	N/A	N/A	N/A	N/A	N/A
Confirmed symptomatic COVID-19 after complete vaccination	1	28,674	N/A	N/A	71.00% (58.90% to 79.10%)
Severe or critical COVID-19 after complete vaccination	N/A	N/A	N/A	N/A	N/A
All-cause mortality	1	28,674	Risk Ratio (M-H, Random, 95% CI)	0.37 (0.17 to 0.80)	N/A
Serious adverse events	N/A	N/A	N/A	N/A	N/A
Systemic reactogenicity events	N/A	N/A	N/A	N/A	N/A
Any adverse event	N/A	N/A	N/A	N/A	N/A
Local reactogenicity events	N/A	N/A	N/A	N/A	N/A

CI: confidence interval; N/A: not applicable.

Appendix 27. Heterologous vaccination scheme versus homologous vaccination scheme

Outcome	No. of studies	No. of participants	Statistical method	Effect size	Vaccine efficacy (95% CI)
Confirmed SARS-CoV-2 infection after complete vaccination	N/A	N/A	N/A	N/A	N/A
Confirmed symptomatic COVID-19 after complete vaccination	N/A	N/A	N/A	N/A	N/A
Severe or critical COVID-19 after complete vaccination	N/A	N/A	N/A	N/A	N/A

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(Continued)

All-cause mortality	N/A	N/A	N/A	N/A	N/A
Serious adverse events	3	229	Risk Ratio (M-H, Random, 95% CI)	0.34 (0.01 to 8.17)	N/A
Systemic reactogenicity events	1	101	Risk Ratio (M-H, Random, 95% CI)	1.96 (0.52 to 7.41)	N/A
Any adverse event	3	N/A	Risk Ratio (M-H, Random, 95% CI) Not pooled	1.03 (0.75 to 1.43) 1.21 (0.87 to 1.68) 3.19 (1.11 to 9.11)	N/A
Local reactogenicity events	1	101	Risk Ratio (M-H, Random, 95% CI)	11.76 (1.59 to 87.14)	N/A

CI: confidence interval; N/A: not applicable.

Appendix 28. Booster versus placebo/no booster

Outcome	No. of studies	No. of participants	Statistical method	Effect size	Vaccine efficacy (95% CI)
Confirmed SARS-CoV-2 infection after complete vaccination	N/A	N/A	N/A	N/A	N/A
Confirmed symptomatic COVID-19 after complete vaccination	N/A	N/A	N/A	N/A	N/A
Severe or critical COVID-19 after complete vaccination	N/A	N/A	N/A	N/A	N/A
All-cause mortality	1	28,254	Risk Ratio (M-H, Random, 95% CI)	1.27 (0.52 to 3.05)	N/A
Serious adverse events	N/A	N/A	N/A	N/A	N/A
Systemic reactogenicity events	1	119	Risk Ratio (M-H, Random, 95% CI)	1.80 (0.71 to 4.56)	N/A
Any adverse event	N/A	N/A	N/A	N/A	N/A
Local reactogenicity events	1	119	Risk Ratio (M-H, Random, 95% CI)	6.46 (3.18 to 13.13)	N/A

CI: confidence interval; N/A: not applicable.

WHAT'S NEW

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Date	Event	Description
13 March 2023	Amended	Minor edits made to correct error in the number of events for the outcome 'All-cause mortality' for the Moderna TX-mRNA-1273 vaccine. We previously entered 16 deaths in the intervention arm and 17 deaths in the control arm. The correct data should be 17 deaths in the intervention arm and 16 deaths in the control arm (RR 1.06, 95% CI 0.54 to 2.10). Corresponding edits have been made throughout the review.

HISTORY

Review first published: Issue 12, 2022

Date	Event	Description
3 January 2023	Amended	URL correction in the abstract.
12 December 2022	Amended	'Acknowledgements' updated.

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Conception and design of the review: CG, LG, AC, MM, PA, JDL, LA DD, JJM, GR, AH, GG, DT, PR, IB

Co-ordination of the review: AC, LG, IB

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Collection of data for the review: BB, HB, KP, NH, EG, GV, CG, HB, MD, LG, SM

Assessment of the risk of bias in the included studies: BB, HB, KP, NH, EG, GV, CG, HB, MD, LG, IB

Analysis of data: AC, TE

Assessment of the certainty in the body of evidence: KP, HB, NH, GV

Interpretation of data: CG, LG, TE, AJ, SM, HB, BB, KP, GV, NH, HB, RA, SM, MM, DD, PM, JDL, LA, TK, GF, MD, CR, DT, JJM, GG, GR, AH, PR, AC, IB

Writing of and commenting on the review: CG, LG, AJ, AC, TE, BB, KP, NH, GF, CR, PK, HB, JDL, DD, JJM, GR, AH, GG, DT, PR, IB

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Theodoros Evrenoglou: none known.

Alexander Jarde: none known.

Silvia Minozzi: no relevant interests; Joint Co-ordinating Editor and Method editor of the Drugs and Alcohol Group.

Hanna Bergman: Cochrane Response – consultant; WHO – grant/contract (Cochrane Response was commissioned by the WHO to perform review tasks that contribute to this publication).

Brian Buckley: none known.

Katrin Probyn: Cochrane Response – consultant; WHO – consultant (Cochrane Response was commissioned to perform review tasks that contribute to this publication).

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Gemma Villanueva: Cochrane Response – employment (Cochrane Response has been commissioned by WHO to perform parts of this systematic review).

Nicholas Henschke: Cochrane Response – consultant; WHO – consultant (Cochrane Response was commissioned by the WHO to perform review tasks that contributed to this publication).

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Patrick Mallon: AstraZeneca – Advisory Board; spoken of vaccine effectiveness to media (print, online, and live); works as a consultant in a hospital that provides vaccinations; employed by St Vincent's University Hospital.

Jean-Daniel Lelievre: no relevant interests; published numerous interviews in the national press on the subject of COVID vaccination; Head of the Department of Infectious Diseases and Clinical Immunology CHU Henri Mondor APHP, Créteil; WHO (IVRI-AC): expert Vaccelarate (European project on COVID19 Vaccine): head of WP; involved with COVICOMPARE P et M Studies (APHP, INSERM) (public fundings).

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Giacomo Grasselli: Pfizer – speaking engagement.

Gabriel Rada: none known.

Asbjørn Hróbjartsson: no relevant interests; Cochrane Methodology Review Group Editor.

Philippe Ravaud: no relevant interests; involved with Mariette CORIMUNO-19 Collaborative 2021, the Ministry of Health, Programme Hospitalier de Recherche Clinique, Foundation for Medical Research, and AP-HP Foundation.

Anna Chaimani: none known.

Isabelle Boutron: no relevant interests; member of Cochrane Editorial Board.

SOURCES OF SUPPORT

Internal sources

- Cochrane France, France
- Center of Research in Epidemiology and Statistics (CRESS), France
- Centre d'Epidémiologie Clinique (GHU Cochin, Hôtel Dieu), France
- Université de Paris, France
- National Institute of Health and Medical Research (Inserm), France
- Assistance Publique Hôpitaux de Paris (APHP), France
- Centre National de la Recherche Scientifique (CNRS), France

External sources

- French Ministry of Health, France

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- French Ministry of Higher Education, Research and Innovation, France
- Agence Nationale de la Recherche (ANR), France
- World Health Organization (WHO), Switzerland
- European Union's Horizon 2020 Research and Innovation programme under the grant agreement N°101037867, Other

The research funding leading to these results was conducted as part of the VACCELERATE consortium. For further information please refer to https://www.vaccelerate.eu/.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

The protocol was developed early during the pandemic and is evolving.

We are no longer considering the following less relevant outcomes.

- Incidence of confirmed symptomatic COVID-19 after first dose (confirmed with positive test for SARS-CoV-2 infection by RT-PCR or NAAT or any other validated test)
- Incidence of participants with confirmed SARS-CoV-2 infection after first dose (confirmed by RT-PCR or NAAT or any other validated test (symptomatic or asymptomatic))
- Incidence of withdrawals due to adverse events

We clarified some outcomes. For the outcome 'specific adverse events' we collected data for 'nervous system diseases' (instead of stroke, headache, delirium, and paraesthesia) since we found this was reported more often. We did not collect data on 'bruising.'

As research and data on COVID-19 vaccines evolved, we noticed that authors started using the term 'reactogenicity' to define the immediate, short-in-duration, and usually expected effects of the vaccine, and to differentiate them from any other medium-term, long-term, or unexpected adverse event (related or unrelated to the vaccine). Therefore, we adopted the term to describe local and systemic effects of the vaccine in the immediate days after the injection.

Post-hoc analysis due to concern related to the waning of efficacy over time (Feikin 2022), we added a post-hoc analysis of vaccine efficacy according to the delay since vaccination.

We initially planned to conduct an NMA; however, the network of vaccines appeared very sparse, included mainly comparisons of vaccines against placebo, and only one or two studies informed most of the available comparisons (Figure 1). A network of such structure does not allow proper evaluation of the synthesis assumptions. Additionally, the NMA estimates from this network would not be substantially more precise (and could even be less precise for some comparisons) than the direct ones. We decided not to perform a NMA and will revisit its feasibility throughout the living systematic review process.

We obtained clinical study reports (CSRs) after the corresponding publication was available and data were already extracted. When CSRs were available, we cross-checked whether these provided data on the critical outcomes already extracted or critical outcome not available in the publication. In all cases, we did not obtain new data. The follow-up of outcome assessment in the CSR was frequently lower than the one reported in the publication. We have not contacted study authors yet for missing results or to request additional information.

INDEX TERMS

Medical Subject Headings (MeSH)

*2019-nCoV Vaccine mRNA-1273; *COVID-19 [prevention & control]; SARS-CoV-2

MeSH check words

Adolescent; Aged; Humans; Middle Aged

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Physical interventions to interrupt or reduce the spread of respiratory viruses (Review)

Jefferson T, Del Mar CB, Dooley L, Ferroni E, Al-Ansary LA, Bawazeer GA, van Driel ML, Nair NS, Jones MA, Thorning S, Conly JM

Jefferson T, Del Mar CB, Dooley L, Ferroni E, Al-Ansary LA, Bawazeer GA, van Driel ML, Nair NS, Jones MA, Thorning S, Conly JM. Physical interventions to interrupt or reduce the spread of respiratory viruses.
Cochrane Database of Systematic Reviews 2011, Issue 7. Art. No.: CD006207.
DOI: 10.1002/14651858.CD006207.pub4.

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[Intervention Review]

Physical interventions to interrupt or reduce the spread of respiratory viruses

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Editorial group: Cochrane Acute Respiratory Infections Group.
Publication status and date: Edited (no change to conclusions), published in Issue 4, 2020.

Citation: Jefferson T, Del Mar CB, Dooley L, Ferroni E, Al-Ansary LA, Bawazeer GA, van Driel ML, Nair NS, Jones MA, Thorning S, Conly JM. Physical interventions to interrupt or reduce the spread of respiratory viruses. *Cochrane Database of Systematic Reviews* 2011, Issue 7. Art. No.: CD006207. DOI: 10.1002/14651858.CD006207.pub4.

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ABSTRACT

Background

Viral epidemics or pandemics of acute respiratory infections like influenza or severe acute respiratory syndrome pose a global threat. Antiviral drugs and vaccinations may be insufficient to prevent their spread.

Objectives

To review the effectiveness of physical interventions to interrupt or reduce the spread of respiratory viruses.

Search methods

We searched *The Cochrane Library*, the Cochrane Central Register of Controlled Trials (CENTRAL 2010, Issue 3), which includes the Acute Respiratory Infections Group's Specialised Register, MEDLINE (1966 to October 2010), OLDMEDLINE (1950 to 1965), EMBASE (1990 to October 2010), CINAHL (1982 to October 2010), LILACS (2008 to October 2010), Indian MEDLARS (2008 to October 2010) and IMSEAR (2008 to October 2010).

Selection criteria

In this update, two review authors independently applied the inclusion criteria to all identified and retrieved articles and extracted data. We scanned 3775 titles, excluded 3560 and retrieved full papers of 215 studies, to include 66 papers of 67 studies. We included physical interventions (screening at entry ports, isolation, quarantine, social distancing, barriers, personal protection, hand hygiene) to prevent respiratory virus transmission. We included randomised controlled trials (RCTs), cohorts, case-controls, before-after and time series studies.

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Data collection and analysis

We used a standardised form to assess trial eligibility. We assessed RCTs by randomisation method, allocation generation, concealment, blinding and follow up. We assessed non-RCTs for potential confounders and classified them as low, medium and high risk of bias.

Main results

We included 67 studies including randomised controlled trials and observational studies with a mixed risk of bias. A total number of participants is not included as the total would be made up of a heterogenous set of observations (participant people, observations on participants and countries (object of some studies)). The risk of bias for five RCTs and most cluster-RCTs was high. Observational studies were of mixed quality. Only case-control data were sufficiently homogeneous to allow meta-analysis. The highest quality cluster-RCTs suggest respiratory virus spread can be prevented by hygienic measures, such as handwashing, especially around younger children. Benefit from reduced transmission from children to household members is broadly supported also in other study designs where the potential for confounding is greater. Nine case-control studies suggested implementing transmission barriers, isolation and hygienic measures are effective at containing respiratory virus epidemics. Surgical masks or N95 respirators were the most consistent and comprehensive supportive measures. N95 respirators were non-inferior to simple surgical masks but more expensive, uncomfortable and irritating to skin. Adding virucidals or antiseptics to normal handwashing to decrease respiratory disease transmission remains uncertain. Global measures, such as screening at entry ports, led to a non-significant marginal delay in spread. There was limited evidence that social distancing was effective, especially if related to the risk of exposure.

Authors' conclusions

Simple and low-cost interventions would be useful for reducing transmission of epidemic respiratory viruses. Routine long-term implementation of some measures assessed might be difficult without the threat of an epidemic.

PLAIN LANGUAGE SUMMARY

Physical interventions to interrupt or reduce the spread of respiratory viruses

Although respiratory viruses usually only cause minor disease, they can cause epidemics. Approximately 10% to 15% of people worldwide contract influenza annually, with attack rates as high as 50% during major epidemics. Global pandemic viral infections have been devastating. In 2003 the severe acute respiratory syndrome (SARS) epidemic affected around 8000 people, killed 780 and caused an enormous social and economic crisis. In 2006 a new avian H5N1, and in 2009 a new H1N1 'swine' influenza pandemic threat, caused global anxiety. Single and potentially expensive measures (particularly the use of vaccines or antiviral drugs) may be insufficient to interrupt the spread. Therefore, we searched for evidence for the effectiveness of simple physical barriers (such as handwashing or wearing masks) in reducing the spread of respiratory viruses, including influenza viruses.

We included 67 studies including randomised controlled trials and observational studies with a mixed risk of bias. A total number of participants is not included as the total would be made up of a varied set of observations: participant people and observations on participants and countries (the object of some studies). Any total figure would therefore be misleading. Respiratory virus spread can be reduced by hygienic measures (such as handwashing), especially around younger children. Frequent handwashing can also reduce transmission from children to other household members. Implementing barriers to transmission, such as isolation, and hygienic measures (wearing masks, gloves and gowns) can be effective in containing respiratory virus epidemics or in hospital wards. We found no evidence that the more expensive, irritating and uncomfortable N95 respirators were superior to simple surgical masks. It is unclear if adding virucidals or antiseptics to normal handwashing with soap is more effective. There is insufficient evidence to support screening at entry ports and social distancing (spatial separation of at least one metre between those infected and those non-infected) as a method to reduce spread during epidemics.

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BACKGROUND

Description of the condition

Pandemic viral infections pose a serious threat to all nations. There have been several recently, including pandemic influenza (one of which has just occurred) (Jefferson 2009; WHO 2009) and a novel coronavirus causing severe acute respiratory syndrome (SARS) (Shute 2003).

Even non-epidemic acute respiratory infections (ARIs) place a serious burden on the health of nations. In total these cause much of the 7% of total deaths in the world that are attributed to lower respiratory tract infections (representing four million deaths worldwide, mostly occurring in low-income countries). In addition there is a huge burden from ARIs on morbidity and nations' healthcare systems (www.who.int/healthinfo/global_burden_disease/estimates_regional/en/index.html).

High viral load and infectiousness probably increase the spread of acute respiratory infection outbreaks (Jefferson 2006a). Stopping the spread of virus from person to person may be effective at preventing these outbreaks. This can be achieved in a number of ways. However, single interventions (such as vaccination or antiviral drugs) may be inadequate (Jefferson 2005a; Jefferson 2005b; Jefferson 2005c; Jefferson 2006a).

Description of the intervention

There is increasing evidence (Jefferson 2005a; Jefferson 2005b; Jefferson 2005c; Jefferson 2006a; Thomas 2010) that single measures (such as the use of vaccines or antivirals) may be insufficient to interrupt the spread of influenza. However, a recent trial showed that handwashing may be effective in diminishing mortality due to respiratory disease (Luby 2005). The possible effectiveness of public health measures during the 'Spanish Flu' pandemic of 1918 to 1919 (Bootsma 2007) in US cities led us to wonder what evidence exists on the effectiveness of combined public health measures such as isolation, distancing and barriers. We also considered the major social implications for any community adopting them (CDC 2005a; CDC 2005b; WHO 2006). Given the potential global importance of interrupting viral transmission, up-to-date, concise estimates of effectiveness are necessary to inform planning and decision-making. We could find no previous systematic review of such evidence.

How the intervention might work

Epidemics and pandemics are more likely during antigenic shift in the virus (especially influenza), when the viral genes sufficiently alter to create a new subtype against which there is little circulating natural immunity (Smith 2006). This may happen when viruses cross from animal species such as ducks or pigs to infect humans (Bonn 1997). Minor changes in viral antigenic configurations, known as 'drift', cause local or more circumscribed epidemics (Smith 2006).

High viral load and high viral infectiousness are likely to be the drivers of such epidemics and pandemics (Jefferson 2006a).

Physical means might prevent the spread of virus by **aerosols or large droplets** from infected to susceptible people (such as by using masks and distancing measures) and by **contact** (such as by using handwashing, gloves and protective gowns). Such public health measures were widely adopted during the 'Spanish Flu' pandemic of 1918 to 1919 (Bootsma 2007).

Why it is important to do this review

Although the benefits of physical methods seem self-evident, they require establishing and quantifying. Physical methods have several possible advantages over other methods of suppressing acute respiratory infection outbreaks: they can be instituted rapidly and may be independent of any specific type of infective agent including novel viruses.

OBJECTIVES

To systematically review the evidence of effectiveness of physical interventions to interrupt or reduce the spread of acute respiratory viruses.

METHODS

Criteria for considering studies for this review

Types of studies

We considered trials (individual-level or cluster-randomised, or quasi-randomised), observational studies (cohort and case-control designs) and any other comparative design, provided some attempt had been made to control for confounding, carried out in people of all ages.

Types of participants

People of all ages.

Types of interventions

We included any intervention to prevent viral animal-to-human or human-to-human transmission of respiratory viruses (screening at entry ports, isolation, quarantine, social distancing, barriers, personal protection and hand hygiene) compared with doing nothing or with another intervention. We excluded vaccines and antivirals.

Types of outcome measures

1. Deaths.
2. Numbers of cases of viral illness.
3. Severity of viral illness in the compared populations. In children and healthy adults we measured burden by consequences of influenza, for example, losses in productivity due to absenteeism by parents. For the elderly in the community, we measured the burden by repeated primary healthcare contacts, hospital admissions and the risk of complications.
4. Any proxies for these (for example, clinical symptoms as a proxy for viral illness and confirmed viral polymerase chain reaction (PCR) testing or viral serological tests).

Search methods for identification of studies

Electronic searches

In this 2010 update we searched, as we have done previously, the Cochrane Central Register of Controlled Trials (CENTRAL) 2010, Issue 3, which includes the Acute Respiratory Infections Group's Specialised Register, MEDLINE (April 2009 to October week 2, 2010), EMBASE (April 2009 to October 2010) and CINAHL (January 2009

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to October 2010). Details of previous searches are in Appendix 1. In addition, to include more of the literature of low-income countries in this update, we ran searches in LILACS (2008 to October 2010), Indian MEDLARS (2008 to October 2010) and IMSEAR (2008 to October 2010).

We used the following search strategy (updated to include new and emerging respiratory viruses) to search MEDLINE and CENTRAL. We combined the MEDLINE search strategy with the Cochrane Highly Sensitive Search Strategy for identifying randomised trials in MEDLINE: sensitivity- and precision-maximising version (2008 revision) (Ovid format) (Lefebvre 2009). We also included an additional search strategy based on the work of Fraser, Murray and Burr (Fraser 2006) to identify observational studies. The search strategies were adapted for Embase.com (Appendix 2), CINAHL (Appendix 3), LILACS (Appendix 4), Indian MEDLARS (Appendix 5) and IMSEAR (Appendix 6).

MEDLINE (Ovid)

1 Influenza, Human/
2 exp Influenzavirus A/
3 exp Influenzavirus B/
4 Influenzavirus C/
5 (influenza* or flu).tw.
6 Common Cold/
7 common cold*.tw.
8 Rhinovirus/
9 rhinovir*.tw.
10 adenoviridae/ or mastadenovirus/ or adenoviruses, human/
11 adenoviridae infections/ or adenovirus infections, human/
12 adenovir*.tw.
13 coronavirus/ or coronavirus 229e, human/ or coronavirus oc43, human/ or infectious bronchitis virus/ or sars virus/
14 coronavir*.tw.
15 coronavirus infections/ or severe acute respiratory syndrome/
16 (severe acute respiratory syndrome* or sars).tw.
17 respiratory syncytial viruses/ or respiratory syncytial virus, human/
18 Respiratory Syncytial Virus Infections/
19 (respiratory syncytial virus* or rsv).tw.
20 Pneumovirus Infections/
21 parainfluenza virus 1, human/ or parainfluenza virus 3, human/
22 parainfluenza virus 2, human/ or parainfluenza virus 4, human/
23 (parainfluenza* or para-influenza* or para influenza).tw.
24 enterovirus a, human/ or exp enterovirus b, human/ or enterovirus c, human/ or enterovirus d, human/
25 Enterovirus Infections/
26 enterovir*.tw.
27 Human bocavirus/
28 bocavirus*.tw.
29 Metapneumovirus/
30 metapneumovir*.tw.
31 Parvovirus B19, Human/
32 parvoviridae infections/ or erythema infectiosum/
33 parvovirus*.tw.
34 Parechovirus/
35 parechovirus*.tw.
36 acute respiratory tract infection*.tw.
37 acute respiratory infection*.tw.
38 or/1-37
39 Handwashing/
40 (handwashing or hand washing or hand-washing).tw.
41 hand hygiene.tw.
42 (sanitiser* or sanitizer*).tw.
43 (cleanser* or disinfectant*).tw.
44 gloves, protective/ or gloves, surgical/
45 glov*.tw.
46 masks/ or respiratory protective devices/
47 (mask or masks or respirator or respirators).tw.
48 Protective Clothing/
49 Protective Devices/
50 Patient Isolators/
51 Patient Isolation/
52 patient isolat*.tw.
53 (barrier* or curtain* or partition*).tw.
54 negative pressure room*.tw.
55 ((reverse barrier or reverse-barrier) adj3 (nurs* or unit or isolation)).tw.
56 Cross Infection/pc [Prevention & Control]
57 (cross infection* adj2 prevent*).tw.
58 Communicable Disease Control/
59 Infection Control/
60 (school* adj3 (clos* or dismissal*)).tw.
61 temporary closur*.tw.
62 mass gathering*.tw.
63 (public adj2 (gathering* or event*)).tw.
64 (bans or banning or banned or ban).tw.
65 (outbreak adj3 control*).tw.
66 distancing*.tw.
67 Quarantine/
68 quarantine*.tw.
69 (protective adj2 (cloth* or garment* or device* or equipment)).tw.
70 ((protective or preventive) adj2 (procedure* or behaviour* or behavior*)).tw.
71 personal protect*.tw.
72 (isolation room* or isolation strateg*).tw.
73 (distance adj2 patient*).tw.
74 ((spatial or patient) adj separation).tw.
75 cohorting.tw.
76 or/39-75
77 38 and 76
78 (animals not (animals and humans)).sh.
79 77 not 78

Searching other resources

There were no language restrictions. Study design filters designed to retrieve RCTs, cohort case-control and cross-over studies, and before-after and time series trials were used in the original searches but we applied no filters to the searches carried out for this update. We scanned the references of all included studies to identify other potentially relevant studies. We also accessed the archives of the former MRC Common Cold Unit (Jefferson 2005d) as a possible source for interruption of transmission evidence.

Data collection and analysis

Selection of studies

We scanned the titles and abstracts after conducting the searches. We obtained full-text articles if a study appeared to meet our eligibility criteria (or when there was insufficient information to exclude it). We then used a standardised form to assess the eligibility of each study, based on the full article.

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Data extraction and management

For this 2010 update, two review authors (TOJ, JMC) independently applied inclusion criteria to all identified and retrieved articles and extracted data. CDM checked the procedure and arbitrated. MJ carried out data analysis.

Assessment of risk of bias in included studies

For the 2009 update (Jefferson 2009) we contacted one trial author (Dr Michael Broderick) to better understand the risk of bias in his study (Broderick 2008). For this 2010 update Drs Aiello and Larson were contacted and provided additional information.

A common problem in these studies was a lack of reporting of viral circulation in the reference population, making interpretation and generalisability of their conclusions questionable.

Randomised studies

Three RCTs were poorly reported with no description of randomisation sequence, concealment or allocation in three studies (Gwaltney 1980; Turner 2004a; Turner 2004b). Satomura 2005 reported the generation of randomisation but the very nature of the intervention (gargling with water with or without povidone iodine versus standard gargling with no attempt at masking the taste of iodine) made blinding impossible. The design of two trials was so artificial that their results cannot be generalised to everyday situations (Turner 2004a; Turner 2004b). One trial (Satomura 2005) is linked to a subsequent brief report which provides contradictory information which is difficult to reconcile (Kitamura 2007).

The quality of the cluster-randomised trials varied. Only the best reported cluster coefficients and conducted analysis of data by unit of (cluster) allocation instead of by individuals (Luby 2005; Roberts 2000; Sandora 2005). Analysing cluster-randomised trials at the individual level leads to spuriously narrow confidence intervals around the estimates of effect (Grimshaw 2004). Other frequent problems were a lack of description of randomisation procedure, partial reporting of outcomes, unclear numerators or denominators and unexplained attrition (Carabin 1999; Kotch 1994; Morton 2004; White 2001), and either complete failure of double-blinding (Farr 1988a; Farr 1988b) or inappropriate choice of placebo (Longini 1988). Three cluster-randomised trials involving the use of face masks (Cowling 2008; Cowling 2009; MacIntyre 2009) by influenza-like illness (ILI) contacts had poor compliance. This shows the difficulty of conducting clinical trials using bulky equipment in the absence of the perception of a real threat. One trial (Cowling 2008) was also conducted in a period of low viral circulation and randomisation was carried out on the basis of two different sequences. The other study (MacIntyre 2009) was underpowered to detect differences in effect between different types of masks.

The cluster-randomised trial by Sandora and colleagues (Sandora 2008) is at low risk of bias with careful evaluation of compliance in the intervention arm (hand sanitiser wipes and disinfection of surfaces).

Of the four RCTs in the 2010 update, one was classified at low risk of bias (Loeb 2009), one at medium risk of bias (Aiello 2010a) and two (Jacobs 2009; Larson 2010) at high risk of bias.

Non-randomised studies

These were assessed for the presence of potential confounders using the appropriate Newcastle-Ottawa Scales (NOS) (Wells 2005) for case-control and cohort studies and a three-point checklist for controlled before and after and ecological studies (Khan 2000).

Case-control studies

We classified five of the nine case-control studies as having medium risk of bias (Lau 2004a; Seto 2003; Wu 2004; Yin 2004; Yu 2007) and two as at low risk of bias (Nishiura 2005; Teleman 2004), mostly because of inconsistencies in the text and lack of adequate description of controls. Two were at high risk of bias (Chen 2009; Liu 2009).

Prospective cohort studies

Six of the 16 prospective cohort studies were classified as at low risk of bias (Agah 1987; Dick 1986; Falsey 1999; Leung 2004; Madge 1992; Somogyi 2004), six as of medium risk (Broderick 2008; Dyer 2000; Kimel 1996; Murphy 1981; White 2003, Yen 2006), and four as of high risk of bias (Makris 2000; Master 1997; Niffenegger 1997; Wang 2007). One was a very brief report of a small study with insufficient details to allow assessment (Derrick 2005).

Retrospective cohort studies

All six retrospective cohort studies had high risk of bias (Cowling 2010, Doherty 1998; Foo 2006; Isaacs 1991; Ou 2003; Yen 2006). In general, retrospective designs are prone to recall bias.

Time series studies

Six of the 13 controlled before-after studies were at low risk of bias (Hall 1981a; Leclair 1987; Macartney 2000; Pang 2003; Ryan 2001; Simon 2006), two of medium risk (Krasinski 1990; Pelke 1994) and five at high risk (Gala 1986; Hall 1981b; Heymann 2004; Krilov 1996; Snydman 1988).

Measures of treatment effect

When possible, we performed a quantitative analysis and summarised effectiveness as odds ratio (OR) using 95% confidence intervals (CI). We expressed absolute intervention effectiveness as a percentage using the formula intervention effectiveness = 1 - OR, whenever significant. In studies which could not be pooled, we used the effect measures reported by the trial authors (such as risk ratio (RR) or incidence rate ratio (IRR) with 95% CI or, when these where not available, relevant P values).

Unit of analysis issues

Outcome measures varied from incidence of experimentally-induced rhinovirus infections, to the incidence of naturally occurring undifferentiated acute respiratory infections (ARIs). This was measured in a variety of ways, including numbers of ARIs per time period, or number of ARIs per household per time period. In some studies the ARIs were replaced by influenza-like illness (ILI). Other included studies focused on SARS specifically, or respiratory syncytial virus (RSV).

Proxy measures of illness included absenteeism.

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Dealing with missing data

Whenever details of studies were unclear or studies were only known to us by abstracts or communications at meetings we corresponded with first or corresponding authors.

Assessment of heterogeneity

Aggregation of data was dependent on study design, types of comparisons, sensitivity and homogeneity of definitions of exposure, populations and outcomes used. We calculated the I^2 statistic for each pooled estimate to assess the presence of statistical heterogeneity (Higgins 2002; Higgins 2003).

Assessment of reporting biases

Given the limited nature of our quantitative synthesis and the widely disparate nature of our evidence base, we limited our assessment of possible reporting biases to funnel plot visual inspection.

Data synthesis

We systematically described and reviewed included studies separately by study design. In other words randomised studies were described and reviewed separately from case-control studies which were described and reviewed separately from prospective cohort studies, and so on. If possible and appropriate, we combined studies within a particular study design in a meta-analysis. We used fixed-effect meta-analysis providing there was no evidence of heterogeneity, otherwise we used random-effects meta-analysis.

Subgroup analysis and investigation of heterogeneity

An a priori subgroup analysis was planned for:

1. pandemic influenza outbreaks;
2. seasonal influenza; and
3. other epidemics (for example, SARS).

We had sufficient data to carry out only the last.

Sensitivity analysis

We aimed to perform a sensitivity analysis on the results of our meta-analysis. We assessed the robustness of the conclusions from the evidence of the effects of each intervention by comparing the results across the original multivariable analysis, looking for consistency of findings.

Summary of findings and assessment of the certainty of the evidence

RESULTS

Description of studies

Results of the search

We scanned 3775 titles, excluded 3560 and retrieved full papers of 215 studies, to include 66 papers of 67 studies.

Included studies

See Summary of main results section for a summary table of interventions and types of evidence.

In 2010 we included seven new studies and listed three trials as awaiting assessment. The seven newly included studies are four RCTs (Aiello 2010a; Jacobs 2009; Larson 2010; Loeb 2009), one retrospective cohort (Cowling 2010) and two case-control studies (Chen 2009; Liu 2009).

Excluded studies

We excluded 36 additional studies. The most frequent reasons for exclusion were no reporting of original data/non-comparative design, confounding by use of antivirals or other medication and in vitro studies (carried out without live patients).

Risk of bias in included studies

Three RCTs were poorly reported with no description of randomisation sequence, concealment or allocation (Gwaltney 1980; Turner 2004a; Turner 2004b). The design of two trials by one author means their results may not be generalised to everyday situations. This is due to the artefactual delivery of the interventions tested (see Quality of the evidence in the Discussion section) (Turner 2004a; Turner 2004b).

The quality of the cluster-randomised trials varied. Only the highest quality trials (Cowling 2009; Luby 2005; Roberts 2000; Sandora 2005) reported cluster coefficients and conducted analysis of data by unit of (cluster) allocation instead of by individuals. Analysing cluster-randomised trials at the individual level leads to spuriously narrow CIs around the estimates of effect (Grimshaw 2004). Other common problems were a lack of description of randomisation procedure, partial reporting of outcomes, unclear numerators or denominators and unexplained attrition (Carabin 1999; Kotch 1994; Morton 2004; White 2001) and either complete failure of double-blinding (Farr 1988a; Farr 1988b) or inappropriate choice of placebo (Longini 1988). Jacobs 2009 is an underpowered individual randomised trial carried out in Japan. Its open design means that due to lack of accounting for drop outs and definitions of outcomes the trial is at high risk of bias. In addition, no guidance as to the generalisability of its results to other settings and countries is provided to readers.

Aiello 2010a is at medium risk of bias. Despite logistical and design problems the trial appears to show an effectiveness gradient of mask-wearing and hand sanitation combined versus instruction on hand sanitation and mask-wearing in student halls. The last cluster-randomised trial (Larson 2010) compared the effects of education alone versus education plus the use of an alcohol-based hand sanitiser versus education plus the use of an alcohol-based hand sanitiser plus the use of medical face masks on the interruption of self-reported upper respiratory tract infection (URTI), ILI and laboratory-confirmed influenza or other viral pathogen by culture or polymerase chain reaction (PCR) in US immigrant Latino households. Due to design issues, difficulty interpreting whether there was an intention-to-treat (ITT) analysis and lack of sufficient details of dropouts and other reporting problems, we classified it at high risk of bias.

Loeb 2009 is a low risk of bias non-inferiority trial directly comparing the effects of surgical mask wearing versus N95 fit-tested respirators in nurses in acute units in Ontario Canada. The outcomes measured range from symptomatic and asymptomatic influenza to physician visits and ILI caused by non-influenza agents. This is possibly the most reliable piece of evidence available for this 2010 update.

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We classified five of the nine case-control studies as having medium risk of bias (Lau 2004a; Seto 2003; Wu 2004; Yin 2004; Yu 2007) and two as at low risk of bias (Nishiura 2005; Teleman 2004), mostly because of inconsistencies in the text and lack of adequate description of controls. Two case-control studies (Chen 2009; Liu 2009) were at high risk of bias. Their interpretation is not straightforward. Both studies assess the effects of multiple factors as risk and protective measures for SARS during the epidemic in China. They appeared to be searching for associations and lacked precision with respect to conducting true matched blinded assessments.

Only live cases were considered when we know that between 10% to 20% of infected healthcare workers died in the first weeks of the epidemic (Liu 2009 mentions the high mortality rate in the Introduction). However, the studies did ascertain the cases and controls of SARS by performing confirmatory laboratory testing rather than relying on a clinical diagnosis.

Six of the 16 prospective cohort studies were classified as at low risk of bias (Agah 1987; Dick 1986; Falsey 1999; Leung 2004; Madge 1992; Somogyi 2004), four as of medium risk (Dyer 2000; Kimel 1996; Murphy 1981; White 2003) and three as of high risk of bias (Makris 2000; Master 1997; Niffenegger 1997). One was a very brief report of a small study (Derrick 2005) and two recent studies (Broderick 2008; Wang 2007) report insufficient details to allow assessment.

Four retrospective cohort studies exploring the effect of barrier interventions (Doherty 1998; Isaacs 1991; Ou 2003; Yen 2006) and one study reporting on adverse effects of barrier interventions (Foo 2006) had a high risk of bias. The other high risk of bias retrospective cohort study is Cowling 2010, mainly due to the nature of its design, heavily dependent on web availability of information.

Six of the 13 controlled before-after studies were at low risk of bias (Hall 1981a; Leclair 1987; Macartney 2000; Pang 2003; Ryan 2001; Simon 2006), two of medium risk (Krasinski 1990; Pelke 1994) and five at high risk (Gala 1986; Hall 1981b; Heymann 2004; Krilov 1996; Snydman 1988).

The most common problem in all of these studies was a lack of reporting of viral circulation in the reference population, making interpretation and generalisability of their conclusions questionable.

The results of a GRADE evaluation (the GRADE Working Group available from http://www.gradeworkinggroup.org/index.htm) of the case-control studies categorised them as providing low to very low quality evidence and categorised the updated RCTs as very low quality with the exception of two studies which were considered of moderate quality.

The overall risk of bias is presented graphically in Figure 1 and summarised in Figure 2.

Figure 1. 'Risk of bias' graph: review authors' judgements about each risk of bias item presented as percentages across all included RCTs.

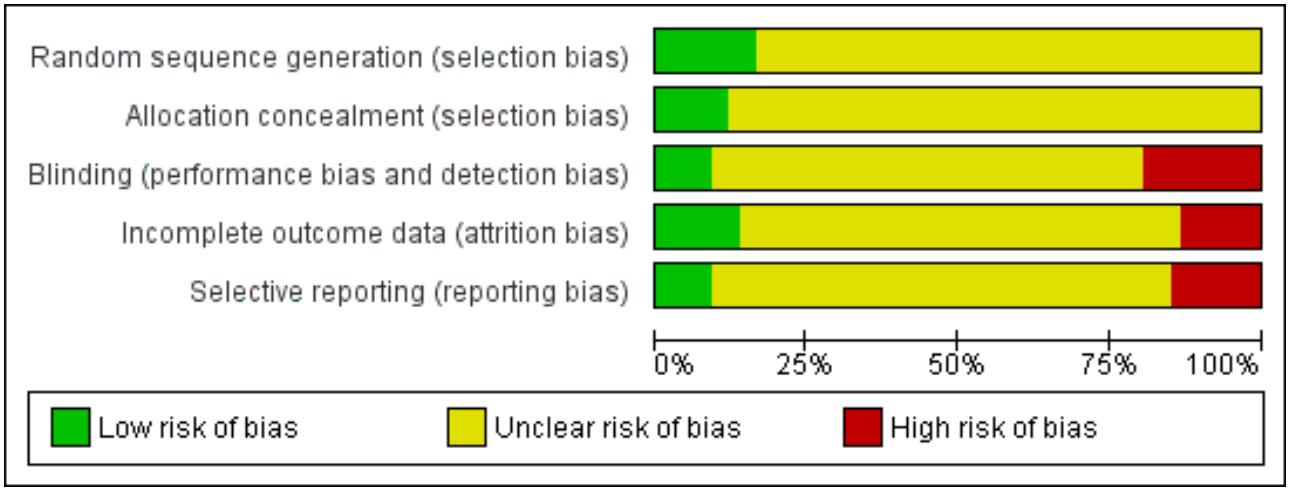

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Figure 2. 'Risk of bias' summary: review authors' judgements about each risk of bias item for each included RCT.

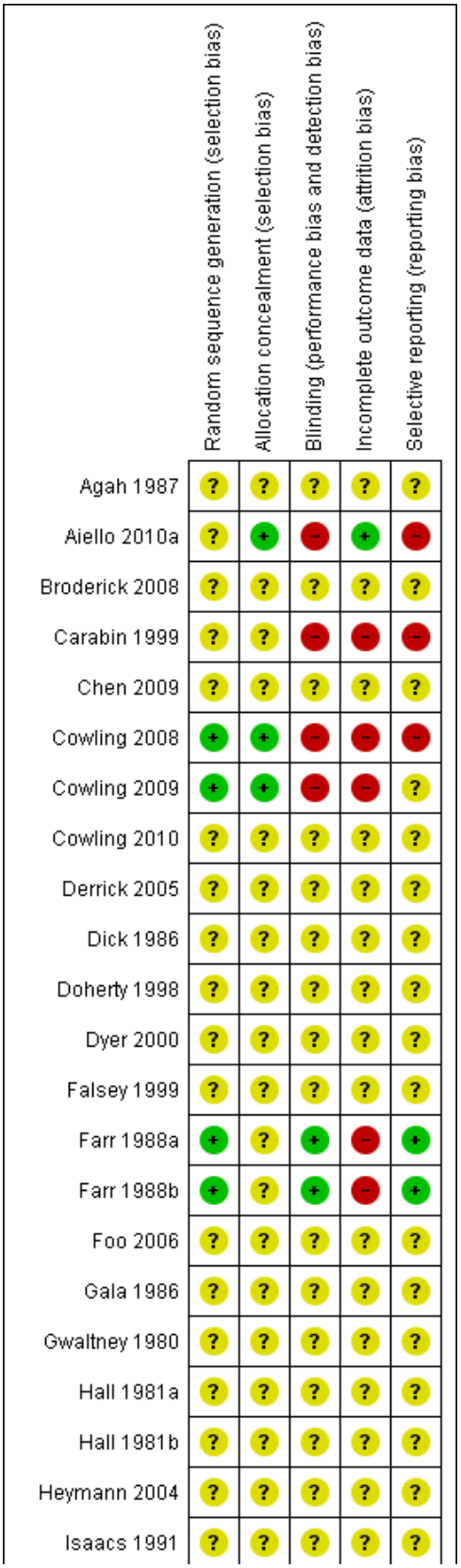

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Figure 2. (Continued)

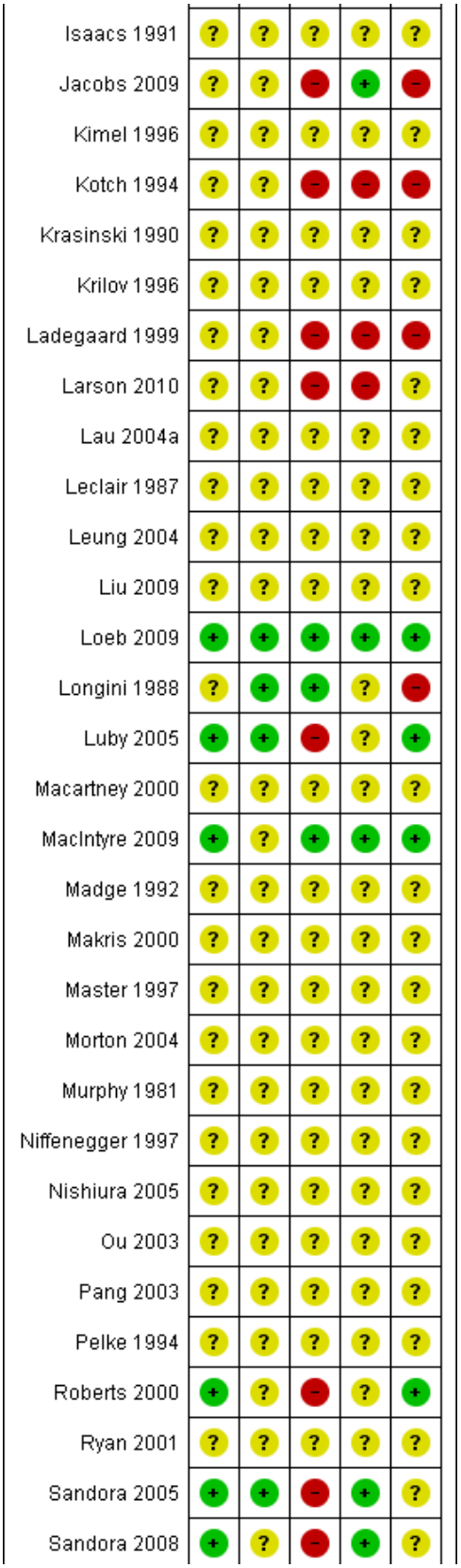

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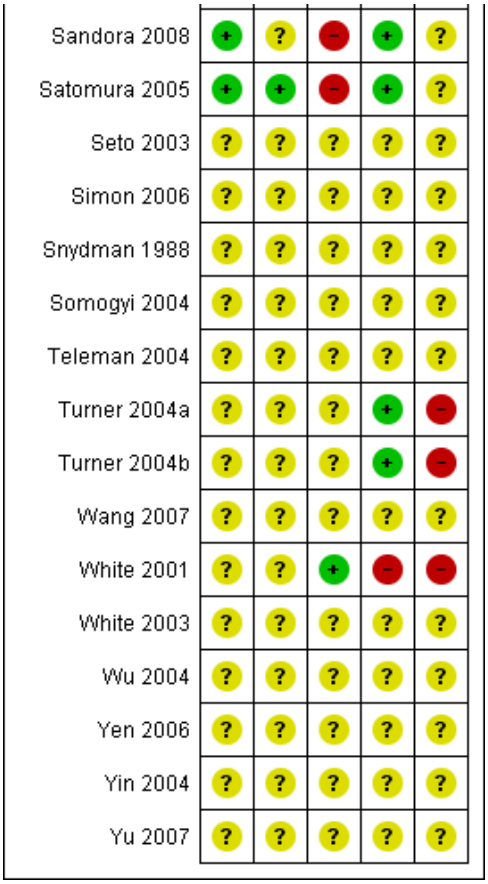
Figure 2. (Continued)



Effects of interventions

We scanned 3775 titles, excluded 3560 and retrieved the full papers of 215 studies, to include 66 papers of 67 studies. Four trials were listed in the Studies awaiting classification section. For one trial currently being submitted for publication we had insufficient information for assessment (Aiello 2010b). Two studies (Hubner 2009; Savolainen-Kopra 2010) assessed the effects of handwashing practices which were of less interest at this time than the use of the physical interventions featured in this update. Another study was identified after our searches had been conducted (Raboud 2010).

Reported results from randomised studies

Three studies tested the effects of hand-cleaning on inactivating the virus and preventing experimental rhinovirus colds. These resulted in either a reduction in the incidence of rhinovirus infection among volunteers treated using different combinations of the acids used for cleaning (P = 0.025) (Turner 2004a) or did not reach statistical significance (13% versus 30% with combined denominator of only 60) (Turner 2004b). Using iodine treatment of fingers, one out of 10 volunteers were infected compared to six out of 10 in the placebo preparation arm (P = 0.06 with Fisher's exact test) (Gwaltney 1980). One study found that gargling with water or povidone-iodine solution in addition to handwashing is effective in preventing URTIs, but not influenza-like illnesses (Satomura 2005).

Three cluster-randomised studies tested the effects of virucidal cleaning disposable handkerchief wipes on the incidence and spread of ARIs. One reported a reduced incidence of ARIs in the household over 26 weeks, from 14% to 5% (Farr 1988a). A similar study reported a small non-significant (5%) drop across families (Farr 1988b). However, since the drop in incidence was confined to primary illness, unaffected by tissue use, we might assume they were ineffective. A community trial also reported a non-significant reduction in ARI secondary attack rates (18.7% versus 11.8%) during a time of high circulation of influenza H3N2 and rhinoviruses in the community (Longini 1988). This result is likely to be an underestimate because of any barrier effect of the inert tissue wipes used in controls.

Eight cluster-randomised studies tested educational programmes to promote handwashing, with or without the adjunct of antiseptic agents, on the incidence of ARIs either in schools or in households. Because of different definitions, comparisons, lack of reporting of cluster coefficients and (in two cases) missing participant data (Carabin 1999; Kotch 1994), we judged it improper to meta-analyse the data. Two of these trials reported a lack of effect: RR for the prevention of acute respiratory illness of 0.94 (95% CI -2.43 to 0.66) (Kotch 1994); and 0.97 (95% CI 0.72 to 1.30) (Sandora 2005). Nevertheless, the highest quality trials reported a significant decrease in respiratory illness in children up to 24 months (RR 0.90, 95% CI 0.83 to 0.97), although the decrease was not significant in older children (RR 0.95, 95% CI 0.89 to 1.01) (Roberts 2000); and a 50% (95% CI -65% to -34%) lower incidence of pneumonia in children aged less than five years of age in a low-income country (Luby 2005). Another study reported a decrease of 30% to 38% in respiratory infections with additional hand-rubbing (RR for illness absence incidence 0.69, RR for absence duration 0.71) (White 2001).

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One study reported decreased school absenteeism of 43% with the additional use of alcohol gel as well as handwashing (Morton 2004). Two trials reported that repeated handwashing significantly reduced the incidence of colds by as much as 20% (Carabin 1999; Ladegaard 1999). One study found that in households in which interventions (handwashing with or without wearing a facemask) were implemented within 36 hours of symptom onset in the index patient, transmission of reverse transcription polymerase chain reaction (RT-PCR)-confirmed infection was reduced, an effect attributable to reductions in infection among participants using face masks plus hand hygiene (adjusted OR 0.33 (95% CI 0.13 to 0.87)) (Cowling 2009).

The findings of the cluster-randomised trial by Aiello et al (Aiello 2010a) suggest that face masks and hand hygiene may reduce respiratory illnesses in shared living settings and mitigate the impact of the influenza A (H1N1) pandemic compared to no intervention or hand sanitiser and education. This conclusion is based on a significantly lower level of ILI incidence in the mask and hand sanitiser arm compared to the other two arms after adjustment for covariates (30% to 50% less in arm one compared to controls in the last two weeks of the study). However, influenza virus circulation was very low during the study period.

The authors of Jacobs 2009 were unable to detect a difference in incidence of ILI of surgical mask wearing compared to no mask in healthcare workers in a Japanese hospital, possibly because of the study's lack of power.

The cluster-randomised trial by Larson et al (Larson 2010) tested the addition of mask and hand sanitiser use to hand sanitiser use alone to nothing other than education which was common to all three arms. Given the many biases in the design and reporting the results are difficult to interpret: the hand sanitiser group was significantly more likely to report that no household member had symptoms (P = 0.01) but there were no significant differences in rates of infection by intervention group in multivariate analyses. Knowledge improved significantly more in the hand sanitiser group (P = 0.0001).

The credible results of the individual trial by Loeb et al (Loeb 2009) report that the use of surgical masks was not inferior to the use of N95 respirators against influenza.

Reported results from case-control studies

Nine case-control studies assessed the impact of public health measures to curb the spread of the SARS epidemic during February to June 2003 in China, Singapore and Vietnam. Homogeneity of case definition, agent, settings and outcomes allowed meta-analysis. We pooled binary data; one of the comparisons showed significant heterogeneity (handwashing), however we used a fixed-effect model. A random-effects model made no appreciable difference to the handwashing comparison. Although continuous data were often available, the variables were different and measured in different units with standard deviations usually missing, which prevented their meta-analysis.

Studies reported that disinfection of living quarters was highly effective in preventing the spread of SARS (OR 0.30, 95% CI 0.23 to 0.39) (Lau 2004a); handwashing for a minimum of 11 times daily prevented many cases (OR 0.54, 95% CI 0.44 to 0.67) (Analysis 1.2), based on seven studies (Chen 2009; Lau 2004a; Nishiura 2005; Seto 2003; Teleman 2004; Wu 2004; Yin 2004); simple mask-wearing was highly effective (OR 0.32, 95% CI 0.26 to 0.39) (Analysis 1.3), based on seven studies (Chen 2009; Lau 2004a; Liu 2009; Nishiura 2005; Seto 2003; Wu 2004; Yin 2004); three studies found N95 respirator-wearing even more effective (OR 0.17, 95% CI 0.07 to 0.43) (Analysis 1.4), (Seto 2003; Teleman 2004; Liu 2009); glove-wearing was effective (OR 0.32, 95% CI 0.23 to 0.45) (Analysis 1.5) (Chen 2009; Liu 2009; Nishiura 2005; Seto 2003; Teleman 2004; Yin 2004); gown-wearing was also effective (OR 0.33, 95% CI 0.24 to 0.45) (Analysis 1.6) (Chen 2009; Nishiura 2005; Seto 2003; Teleman 2004; Yin 2004); all means combined (handwashing, masks, gloves and gowns) achieved very high effectiveness (OR 0.09, 95% CI 0.02 to 0.35) (Analysis 1.7) (Nishiura 2005; Seto 2003); use of eye protection such as goggles or masks with goggles is protective (OR 0.10, 95% CI 0.05 to 0.17) (Analysis 1.8) (Chen 2009; Liu 2009; Yin 2004) and nose-washing was also protective (OR 0.30, 95% CI 0.16 to 0.57) (Analysis 1.9) (Chen 2009; Liu 2009). As the data are all based on univariable analyses, they may be subject to confounding. We have separately tested how many of these measures were statistically significant in multivariable analyses (Table 1).

These data suggest that wearing a surgical mask or a N95 mask is the measure with the most consistent and comprehensive supportive evidence. Seven out of eight studies included masks as a measure in their study and six out of seven of these studies found masks to be statistically significant in multivariable analysis. Handwashing was also included in seven of the studies with four studies showing handwashing to be statistically significant in multivariable analysis. All other measures were shown to be statistically significant in multivariable analysis on only one or two occasions.

Another case-control study from Hong Kong and Guangzhou hospital wards reported that a minimum distance between beds of less than one metre was a risk factor for transmission (Yu 2007). Disaggregated data were not reported and therefore we did not pool this study in the meta-analysis. All studies selected cases from hospitals, except for one (Lau 2004a) in which cases were people with probable SARS reported to the Department of Health in Hong Kong.

The detailed results of Chen 2009 report that avoiding face-to-face contact while caring for SARS patient (OR 0.30, 95% 0.15 to 0.60) and wearing gloves coupled with methods of ventilation are highly protective practices (various ORs for the various combinations intensity of wearing and ventilation methods, all significant). Liu 2009 reports that personal protective measures against droplet spread, such as wearing multiple layers of mask, are effective against the nosocomial spread of SARS.

Reported results from prospective cohort studies

Using an alcohol rub in students' communal residences resulted in significantly fewer symptoms (reductions of 14.8% to 39.9 %) and lower absenteeism (40% reduction) (White 2003). In a much-cited small experimental study, virucidal paper handkerchiefs containing citric acid interrupted the transmission of rhinovirus colds transmitted through playing cards: 42% of re-usable cotton handkerchief users developed colds compared with none using disposable virucidal tissues (Dick 1986).

Few identified studies reported interventions in the daycare setting, either in staff or patients. One staff educational programme

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on handwashing in a daycare centre for adults was effective over a four-year period in reducing rates of respiratory infection in daycare patients from 14.5 to 10.4 per 100 person-months to 5.7 (P < 0.001), with an accompanying decline in viral isolates. This seems to be more effective than the use of additional portable virucidal hand foam as an adjunct to handwashing (Falsey 1999). This confirmed an earlier report of the effectiveness of a handwashing programme in reducing absenteeism for ILI in a primary school (Kimel 1996).

Two high risk of bias studies reported that education, a handwashing routine and encouragement for kindergarten children, parents and staff in correct sneezing and coughing procedure were effective, although there were considerable fluctuations in incidence of infections in the control and test centres (Niffenegger 1997); but the intervention was not effective in reducing absenteeism caused by ARIs (RR 0.79, P = 0.756) (Master 1997).

Dyer and colleagues reported a prospective, cluster, open-label, cross-over cohort study. The study assessed the effectiveness of a hand sanitiser in conjunction with at will soap-and-water handwashing in a private elementary school in California. Use of the sanitiser reduced illness absenteeism by 41.9% (reduction in respiratory illnesses of 49.7% over the 10-week period of the study) (Dyer 2000).

Curiously, an infection-control education programme reinforcing handwashing and other hygienic measures in a nosocomial setting reported reducing the number of organisms present on hands and surfaces, and ARIs, although the data tabled suggested the opposite (an incidence rate of 4.15/1000 patient-days in the test homes versus 3.15/1000 in the control homes) (Makris 2000).

A study found wearing a goggle-mask apparatus in healthcare workers visiting and caring for children aged up to five with respiratory syncytial virus (RSV) and symptoms of respiratory disease was effective (5% illness rate in goggle wearers against 61% in no-goggle controls) (Agah 1987).

Rapid laboratory diagnosis, cohort nursing and the wearing of gowns and gloves for all contacts with RSV-infected children significantly reduced the risk of nosocomial RSV infection (OR 0.013 to 0.76) (Madge 1992), although another similar study reported no effect of adding the use of both gown and mask to the usual handwashing routine on the development of illness in personnel caring for infants with respiratory disease (4 out of 30 in the handwashing group alone compared to 5 out of 28 in the handwashing, gown and masking group, P > 0.20); although the authors described poor compliance with the barrier protocol (Murphy 1981).

Strict procedures of triage and infection control to stop transmission of SARS from infected children to carers and visitors of a large hospital at the height of the epidemic in 2003 in Hong Kong was reported effective at interrupting the transmission of SARS, as no healthcare worker became ill, in contrast to experiences in other institutions (Leung 2004).

A tiny study comparing the N95 respirator with paper surgical masks in volunteers found that surgical masks, even when worn in multiple layers (up to five), filtered ambient particles poorly (Derrick 2005); this principle was confirmed in another small study of air filtration to prevent droplet spread (Somogyi 2004).

Reported results from retrospective cohort studies

Two studies investigated isolating together children less than three years of age with suspected RSV. In one, transmission was diminished by "up to 60%" (Isaacs 1991), while the statement that nosocomial transmission "was minimised" was not supported by data in the other study (Doherty 1998).

Isolation of cases during the 2003 epidemic of SARS in China was reported to limit transmission only to those contacts who actually had home or hospital contact with a symptomatic SARS patient (attack rate 31.1%, 95% CI 20.2 to 44.4 for carers; 8.9%, 95% CI 2.9 to 22.1 for visitors; 4.6%, 95% CI 2.3 to 8.9 for those living with a SARS case) but not to contacts living in the same building, working with cases, or without contact with SARS cases during the incubation period. This suggests extending quarantine only for contacts of symptomatic SARS cases (Ou 2003).

Another brief report carried out in 2003 during the SARS epidemic, in a military hospital in Taiwan, China and 86 control hospitals, compared an integrated infection-control policy to protect healthcare workers against infection; only two from the military hospital were infected with SARS compared to 43 suspected and 50 probable cases in the control hospitals (Yen 2006).

Cowling 2010 reports a marginal (one to two weeks) non-significant benefit in delaying spread of novel A/H1N1 autochthonous pandemic influenza by various means of entry screening. The high risk of bias is mainly due to the nature of its design, heavily dependent on web availability of information. However, it is difficult to see how else a similar study could have been conducted.

Reported results from controlled before and after studies

Two small studies by the same first author assessed means of nosocomial transmission of RSV in small children and the effects of introducing distancing and barriers: one with low risk of bias reported effective physical distancing and room separation (0 infected out of 14 who sat away from RSV-infected infants compared with five out of seven who cuddled and four out of 10 who touched infected infants) (Hall 1981a). The second with high risk of bias reported no incremental benefits of gowns and masks (32% infection versus 41%) (Hall 1981b). Adding disposable plastic eye-nose goggles to other respiratory infection-control procedures (isolating infected from uninfected people, handwashing) also reduced transmission of RSV (6% versus 42% of controls) (Gala 1986). Screening and subsequent isolation of infected from uninfected people ('cohorting') also reduced nosocomial RSV transmission in older children (from 5.33 infections per 1000/patient days of care to 1.23 infections per 1000/patient days after introduction of screening) (Krasinski 1990). A similar study reported that increased compliance with a policy of glove and gown isolation precautions reduced the high rate of nosocomial RSV transmission on an infant and toddler ward (RR for pre- and post-intervention periods infection rates 2.9, 95% CI 1.5 to 5.7) (Leclair 1987).

A study of protective gowning did not protect neonatal intensive care unit infants from RSV or any other type of infection, or affect mortality (1.21 per 100 patient-days of gowning compared to 1.38 of none), although selection bias was likely with 17% of participating children lost to follow up (Pelke 1994).

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A German study conducted over three seasons reported a decrease of nosocomial RSV infections, from 1.67/1000 patient-days in the first season to 0.18/1000 patient-days in the last season, after instituting enhanced surveillance and feedback, rapid diagnosis, barriers and isolation, and disinfection of surfaces (Simon 2006). A similar study but with high risk of bias reported a decrease from eight confirmed RSV cases per 1000 patient-days to none (Snydman 1988). A better conducted study over eight years implemented a combination of education with high index of suspicion for case-finding (contact precautions), with barriers (but no goggles or masks) and handwashing for patients and staff reduced RSV infections in a hospital in Philadelphia, USA: RR 0.61, 95% CI 0.53 to 0.69 (Macartney 2000).

One small study with serious potential biases assessed training and a sanitary programme (handwashing, disinfection of school buses, appliances and toys) in a special-needs daycare facility for children with Downs Syndrome, a pupil to staff ratio of five or six to one, and reported reductions in: respiratory illnesses from a mean of 0.67 to 0.42 per child per month ($P < 0.07$); physician visits from 0.50 to 0.33 ($P < 0.05$); mean courses of antibiotics prescribed from 0.33 to 0.28 ($P < 0.05$); and days of school missed because of respiratory infections from 0.75 to 0.40 ($P < 0.05$) (Krilov 1996).

A very large study of military recruits reported that a structured top-down programme of handwashing at least five times daily nearly halved the incidence of ARIs. Recruits who handwashed less frequently reported more episodes of ARIs (OR 1.5, 95% CI 1.2 to 1.8), which represents a difference of 4.7 versus 3.2 mean infections per recruit per year, and more hospitalisations (OR 10.9, 95% CI 2.7 to 46.2). However, implementation was difficult (Ryan 2001).

An ecological study analysed the effects of quarantine and port of entry screening on the SARS epidemic in early 2003 in Beijing, China, from data collected centrally. Hospitals were the initial sources of transmission of the SARS virus. The shape of the epidemic suggests these measures may have reduced SARS transmission although only 12 cases identified out of over 13 million people screened puts in doubt the direct effectiveness of entry port checks at airports and railway stations, and screening was probably more important (Pang 2003).

An Israeli study of 186,094 children aged six to 12 years reported that school closure was temporally associated with a 42% decreased morbidity from respiratory tract infections, a consequent 28% decrease in visits to physicians and to emergency departments, and a 35% reduction in purchase of medications (Heymann 2004).

DISCUSSION

Quality issues

Several features need consideration before drawing generalisations from these studies.

The settings of the studies, conducted over four decades, were heterogeneous and ranged from suburban schools (Carabin 1999; Dyer 2000; Heymann 2004; Niffenegger 1997) to military barracks (Ryan 2001), emergency departments, intensive care units and paediatric wards (Gala 1986; Leclair 1987; Loeb 2009) in high-income countries; slums in low-income countries (Luby 2005); an upper Manhattan immigrant Latino neighbourhood (Larson 2010) and special-needs daycare centres with a very high teacher to pupil ratio (Krilov 1996). Few attempts were made to obtain socio-economic diversity by (for example) involving more schools in the evaluations of the same programme (Dyer 2000). We were able to identify few studies from low-income countries where the vast majority of the burden lies, and where cheap interventions are so critical. Even in high-income countries, such as Israel, the dramatic fall in ARIs subsequent to school closure may have been related to that country's high child population (34%). Additionally, limited availability of over-the-counter medications and national universal comprehensive health insurance provided with consequent physician prescription of symptomatic treatment may further limit generalisability of findings (Heymann 2004).

The variable quality of the methods of these studies is striking. Hasty design of interventions for public health crises, particularly the SARS case-control studies, is understandable but less so when no randomisation - not even of clusters - was carried out in several unhurried cohort and before and after studies. Randomisation could often have involved minimal disruption to service delivery. Inadequate reporting especially made interpretation difficult of before-after studies. Incomplete or no reporting of randomisation (Turner 2004a), blinding (Farr 1988a; Farr 1988b), numerators and denominators (Carabin 1999; Kotch 1994), interventions, outcomes (White 2003), participant attrition (Makris 2000), confidence intervals (CIs) (Madge 1992) and cluster coefficients in the relevant trials (Carabin 1999) led to a considerable loss of information. Potential biases (such as cash incentives given to participants (White 2003)) were not discussed. Some trial authors even confused cohort with before-after designs to elaborate conclusions unsupported by their data (Makris 2000). Methodological quality was sometimes eroded by the need to deliver behavioural interventions in the midst of service delivery (Niffenegger 1997).

Nonetheless, even when suboptimal designs were selected, trial authors rarely attempted to articulate potential confounders. A commonly ignored confounder, specific to this area, is the huge variability in viral incidence (Heymann 2004; Isaacs 1991). Sometimes this was addressed in the study design (Falsey 1999), even in controlled before and after studies (one attempted correlation between respiratory syncytial virus (RSV) admissions and RSV circulating in the community) (Krasinski 1990). Another attempted linking exposure (measured as nasal excretion) and infection rate in the pre- and post-intervention periods (Leclair 1987).

Inappropriate placebos caused design problems. In some studies the placebo probably carried sufficient intervention effect apparently to dilute the intervention effects (Longini 1988). Two valiant attempts probably failed because placebo handkerchiefs were impregnated with a dummy compound which stung the users' nostrils (Farr 1988a; Farr 1988b).

Some studies used impractical interventions. Volunteers subjected to the intervention hand cleaner (organic acids) were not allowed to use their hands between cleaning and virus challenge, so the effect of normal use of the hands on the intervention remains unknown (Turner 2004a; Turner 2004b). Two per cent aqueous iodine painted on the hands, although a successful antiviral intervention, causes unacceptable cosmetic staining, impractical for all but those at the highest risk of epidemic contagion (Gwaltney 1980).

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Compliance with interventions, especially educational programmes, was a problem for several studies despite the importance of many such low-cost interventions. Overall the logistics of carrying out trials in immigrant neighbourhoods or students' halls of residence are demanding and recognition should be given to all those who planned and carried out studies in very difficult circumstances (as in the middle of an epidemic).

The evidence

The highest quality cluster-randomised trials indicate most effect on preventing respiratory virus spread from hygienic measures in younger children. Perhaps this is because younger children are least capable of hygienic behaviour themselves (Roberts 2000), and have longer-lived infections and greater social contact, thereby acting as portals of infection into the household (Monto 1969). Additional benefit from reduced transmission from them to other members of the household is broadly supported by the results of other study designs where the potential for confounding is greater.

The pooled case-control studies, which focused on the SARS coronavirus (SARS CoV), suggest that implementing barriers to transmission, isolation and hygienic measures are effective with the use of relatively cheap interventions to contain respiratory virus epidemics. We found limited evidence of the superior effectiveness of devices such as the N95 respirator over simple surgical masks. This evidence is supported by a high quality hospital-based trial (Loeb 2009) which reports non-inferiority between face barriers. Overall masks were the best performing intervention across populations, settings and threats. More expensive and uncomfortable (especially if worn for long periods) than simple surgical masks, N95 respirators may be useful in very high-risk situations but additional studies are required to define these situations.

It is uncertain whether the incremental effect of adding virucidals or antiseptics to normal handwashing actually decreased the respiratory disease burden outside the confines of the rather atypical studies, upon which we reported. The extra benefit may have been, at least in part, accrued by confounding additional routines.

Studies preventing transmission of RSV and similar viruses appeared to be closer to real life and suggest good effectiveness. However, methodological quality concerns of the controlled before and after studies, mentioned previously, suggest benefits may have been due to population differences, especially virus infection rates. These were poorly reported in most studies.

Routine long-term implementation of some of the measures assessed in this review would be problematic, particularly maintaining strict hygiene and barrier routines for long periods of time. This would probably only be feasible in highly motivated environments, such as hospitals, without a real threat of a looming epidemic. Most of the trial authors commented on the major logistic burden that barrier routines imposed at the community level. However, the threat of a looming epidemic may provide stimulus for their inception.

A disappointing finding was the lack of proper evaluation of global and highly resource-intensive measures such as screening at entry ports and social distancing. The handful of studies (mostly conducted during the SARS epidemic) do not allow us to reach any firm conclusions. It is remarkable that despite a long lead time to the declaration of a pandemic, an international, prospective study to evaluate entry screening practices was not set up. The study by Cowling et al is a good contribution to our evidence base but no substitute for a well designed and conducted trial (Cowling 2010). Finally, few studies reported harms from the interventions studied. Harms affect compliance, which may decrease even if the intervention is merely cumbersome (such as a mask) and the threat is unclear.

Summary of main results

See Table 2.

Overall completeness and applicability of evidence

See Discussion.

Quality of the evidence

See Discussion.

Potential biases in the review process

Through the World Health Organization (WHO), we made inquiries to identify a list of manufacturers of the interventions assessed in this review. However, no such list appears to exist. The low-tech (i.e. locally manufacturable) nature of some of the interventions, the lack of effective regulation in some settings and the possible endless number of manufacturers make the compilation and updating of such a list in a satisfactory manner very difficult. As a consequence it is impossible to gauge the existence of unpublished data. Low-tech device marketing is poorly regulated and incompletely understood.

Agreements and disagreements with other studies or reviews

We are not aware of systematic reviews of the same evidence.

AUTHORS' CONCLUSIONS

Implications for practice

The following effective interventions should be implemented, preferably in a combined fashion, to reduce transmission of viral respiratory disease:

1. frequent handwashing with or without adjunct antiseptics;
2. barrier measures such as gloves, gowns and masks with filtration apparatus; and
3. suspicion diagnosis with isolation of likely cases.

Special efforts should be focused on implementing the three above interventions in order to reduce transmission from young children, who are generally the most fecund sources of respiratory viruses.

Implications for research

Public health measures can be highly effective, especially when they are part of a structured programme that includes instruction and education and when they are delivered together. There is a clear requirement to carry out further large, pragmatic trials to evaluate the best combinations in the community and in healthcare settings and with other respiratory viruses. RCTs with a pragmatic design, similar to the Luby et al trial, should be

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carried out whenever possible (Luby 2005). Nevertheless, this systematic review of the available research does provide some important insights. Perhaps the impressive effect of the hygienic measures aimed at younger children derives from the children's poor capability with their own hygiene. The variable quality and small scale of some studies is known from descriptive studies (Aiello 2002; Fung 2006; WHO 2006) and systematic reviews of selected interventions (Meadows 2004). More research is needed to evaluate the most effective strategies to implement successful physical interventions in practice, both on a small scale and at a population level. More attention should be paid to describing and quantifying the harms of the interventions assessed in this review and their relationship with compliance.

ACKNOWLEDGEMENTS

Thanks to the following people for commenting on the draft protocol and review: Anne Lyddiatt, Stephanie Kondos, Tom Sandora, Kathryn Glass, Max Bulsara, Rick Shoemaker and Allen Cheng. Thanks also to the following people for translating non-English language trials for the draft review: Jørgen Lous for translating a Danish paper and extracting data, Ryuki Kassai who translated a Japanese paper, and Taixiang Wu who translated several Chinese papers. We thank the following people for commenting on the 2009, 2010 and 2011 updated reviews, respectively, for 2009: Anne Lyddiatt, Thomas Sandora, Michael Broderick, Sree Nair and Allen Cheng; for 2010: Carmem Pessoa da Sailva, Sergey Eremin; and for 2011: Amy Zelmer, Tom Sandora, Sree Nair and Allen Cheng. Drs Aiello and Larson provided additional information on their trials for the 2010 update. Dr V Shukla, Dr J Conly and K Lee prepared the GRADE tables using the GRADE Profiler software. Drs Carmem Pessoa da Silva and Thomas Haustein provided linguistic assistance for the 2010 update.

We gratefully acknowledge funding for this 2009 update from the UK National Institute for Health Research (NIHR) and the National Health and Research Council (NHMRC) of Australia and from WHO for the 2010 update. We also thank Ruth Foxlee and Alex Rivetti for constructing the search strategies for the previous review versions and Bill Hewak and Adi Prabhala for extracting data in the original review.

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CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

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* Indicates the major publication for the study

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Agah 1987

Methods	Prospective cohort study carried out in California hospital during the autumn 1984 to spring 1985 season. The study assessed the efficacy of healthcare workers (HCW) wearing goggle-mask apparatus while visiting and caring for children aged up to 5 with RSV and symptoms of respiratory disease compared to do nothing. Children admitted with a RSV diagnosis were assigned to the 2 arms balanced for age and sex
Participants	168 HCW caring for children < 5 years with differential diagnosis of RSV
Interventions	Mask and goggles (sometimes gowns too) versus normal care
Outcomes	RSV illness reduced from 61% (controls) to 5% (intervention) Laboratory: swabs for RSV diagnosis Effectiveness: RSV illness Safety: n/a
Notes	Risk of bias: low Notes: the authors conclude that wearing mask and goggles significantly reduced transmission to HCWs and other children of RSV (61% versus 5% illness rate). Analysis is also given by number of contacts (data not extracted). A reasonably reported if difficult to conduct study. Standard procedures such as handwashing should not have acted as a confounder given 100% coverage among HCWs

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	N/A
Allocation concealment (selection bias)	Unclear risk	N/A
Blinding (performance bias and detection bias) All outcomes	Unclear risk	N/A
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	N/A
Selective reporting (reporting bias)	Unclear risk	N/A

Aiello 2010a

Methods	Cluster-randomised trial assessing the effects of hand sanitiser and masks with masks or no intervention on ILI symptoms. The trial was conducted in University halls of residence with more than 100 student residents in a US university during the 2006 to 2007 influenza “season”. It lasted 6 weeks The units of randomisation were 7 of the 15 halls. One hall was very large (1240 residents) and the 6 remaining ones which had between 110 and 830 residents were combined into 2 clusters roughly equivalent in size. The 3 clusters were then randomised by random extraction of the clustered halls’ names out of a container. The largest hall (single-cluster) was randomised to the mask and hand sanitiser arm, the 4 halls cluster received masks and the remaining 2 halls were assigned as controls
Participants	Willing, consenting residents aged 18 or more. Recruitment of students began in November 26 but the trial did not go “live” with distribution of intervention materials until 22 January 2007 when the first

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Aiello 2010a *(Continued)*

	case of influenza was confirmed on campus by laboratory tests. Enrolment continued until 16 February 2007 and the study was completed on 16 March 2007. During the study period there was a 1-week break when the majority of residents left campus. There were 1327 eligible participants, of which 1297 had a complete baseline survey and at least 1 weekly survey result (367, 378 and 552 in the mask and hand sanitiser, mask only and control groups respectively, giving a total of 1297). It is unclear what the ineligibility criteria were for the 30 missing (1327 minus 1297) but the explanation may be in the appendix.
Interventions	Alcohol-based hand sanitiser (62% ethyl alcohol in a gel base) in a squeeze bottle and TECNOL procedure masks with ear loops (KC Ltd) and educational material or masks and educational material or no intervention. Compliance was encouraged within halls and outside. Sleep wearing was optional All participants received basic video-linked instruction on cough etiquette and hand sanitation. At baseline and weekly during the study participants were asked to fill in a web-based survey collecting demographic and ILI symptom data. This was supplemented by direct observation of compliance by staff Compliance with "optimal handwashing" (at least 20 seconds 5 or more times a day) was significantly higher in the sanitiser and mask arm
Outcomes	Laboratory details are described in appendix Effectiveness: ILI, defined as cough and at least 1 constitutional symptom (fever/feverishness, chills, headache, myalgia). ILI cases were given contact nurses phone numbers to record the illness and paid USD 25 to provide a throat swab. 368 participants had ILI and 94 of these had a throat swab analysed by PCR. 10 of these were positive for influenza (7 for A and 3 for B), respectively by arm 2, 5 and 3 using PCR, 7 using cell culture Safety: n/a
Notes	The authors conclude that "These findings suggest that face masks and hand hygiene may reduce respiratory illnesses in shared living settings and mitigate the impact of the influenza A (H1N1) pandemic". This conclusion is based on a significantly lower level of ILI incidence in the mask and hand sanitiser arm compared to the other 2 arms after adjustment for covariates (30% to 50% less in arm 1 compared to controls in the last 2 weeks of the study) Comparison with the ILI rate of the control arm may not be a reflection of the underlying rate of ILI because the intervention arm received instruction on hand sanitation and hand etiquette The play of adjustments is unclear. The intra cluster correlation coefficient is reported in the footer of Table 4. Its very small size suggests lack of clustering within halls The role of the spring break is mentioned in the Discussion as are the results of this study compared to other studies included in our review (Cowling 2008 and MacIntyre 2009) The authors report that 147 of 1297 participants (11.3%) "at baseline" had ILI symptoms and were excluded from analysis. During the 6 weeks of the study 368 of 1150 participants (32%) had ILI. This averages out at about 5% per week. It is unclear what the term "at baseline" means. Presumably this means during the 2 to 3 weeks of participant enrolment. If this is so, the reason for the triggering of the interventions (tied to influenza isolation) are obscure as the trial is supposedly about ILI and an ILI outbreak was already underway "at baseline"

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Described as randomised but sequence generation not reported
Allocation concealment (selection bias)	Low risk	The residence hall units were randomised by blindly selecting a uniform ticket with the name of each hall out of a container (A.S.M. and A.A.) for randomisation assignment to each study arm

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Aiello 2010a *(Continued)*

Blinding (performance bias and detection bias) All outcomes	High risk	Blinding not possible
Incomplete outcome data (attrition bias) All outcomes	Low risk	Attrition is reported as follows: 9, 11 and 19 ineligible and 26, 52 and 21 lost to follow up (respectively by arm). This makes a total of 39 and 99 for each cause of attrition. In total, 1297 (97%) of 1331 participants completed a baseline and at least 1 weekly survey The text reports an ITT analysis with only one ILI episode included by participant No reasons for the attrition of participants and swab volunteers are reported (were the swabs taken from a random sample or not?)
Selective reporting (reporting bias)	High risk	There is no information on the causes of ILI other than the reporting on the 10 influenza PCR-positive swabs of 94 out of 368 students with ILI. This is a very low rate (and the Discussion confirms that the influenza season was mild) but investigation of the other known causes of ILI is not even mentioned in the text. This is especially important because stress, alcohol intake levels and influenza vaccination were a significant predictor of ILI symptoms (Table 1). The reason for selective testing and/or reporting of influenza viruses tests over the other causes of ILI are unclear especially as the study objective was focused on ILI. The text also is difficult to follow, weaving the reporting of ILI and influenza without a clear rationale

Broderick 2008

Methods	Prospective, cohort study carried out in a military recruit training centre during the first 4 weeks of recruit training. Data were collected between February 2004 and March 2005 (duration of recruit training is not reported) It is not clear how the recruits were assigned to 'experimental' (closed) or control (open). Recruits were assigned to units on the basis of arrival order with no particular allocation scheme The study assessed if social distancing would reduce the incidence of febrile respiratory illness (FRI). Data were collected over 4 weeks for each new group of recruits Housing units (n = 196 units) were divided into closed units (n = 30) (experiment/intervention) or open units (n = 166) (control). For description of how the closed units were selected and geographical position in the training centre see notes Microbiological samples from physical structures (tables, surfaces, angles of surfaces, handles) of some units were done. However, it is not mentioned if these units were selected from among the closed or open units
Participants	Male military recruits (n = 13,114), distributed among 196 housing units (166 open units and 30 closed units) took part in the study. Unit size ranged from 44 to 88 recruits per unit. Reported denominators add up to 13488 recruits not 13114 (closed: 329/2099 versus open: 1586/11389). No exclusions were reported. Dimensions of the units are not described (space/subject or space/unit). The average number of subjects/unit in the closed units was not reported 10% of medical convalescent unit (MCU) subjects (762) and 6% of physical conditioning unit (PCU) subjects (395) were positive for adenovirus 4 by PCR
Interventions	To test the effect of social distancing: participants were either assigned (allocation process not clear) to closed or open units. The closed units did not introduce any new participants once their personnel had been assigned (socially-distant); sick recruits were removed but if their symptoms did not require

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Broderick 2008 *(Continued)*

	placement in the MCU, the recruits returned to their units. The open units accepted recovering subjects after being discharged from MCU and PCU To test an environmental aetiology: some of the units, which were vacant after 4 weeks of occupation, were swabbed. The MCU was also swabbed. The samples were tested by PCR and were cultured
Outcomes	Laboratory: (MicroTest M4 Transport; Remel) polymerase chain reaction (PCR) culture for Ad-4 virus Not used to confirm FRI in all index cases. Adenovirus was the only microorganism tested for and isolated Effectiveness: cases of FRI were defined either by a body temperature of > 38°C and 1 respiratory symptom or by the presence of non-febrile pneumonia Cases were reported as number of cases of FRI per 100 persons per week, averaged over the 4 weeks Safety: n/a
Notes	The institutional review board of the Naval Health Research Centre classified the protocol of this study as a non-research public health endeavour. Given the flaws of the study design (the disparity between the number of closed and open units, testing 2 different 'aetiological' hypothesis using different methodologies and lack of information on how the units were selected), one gets the impression that this study was probably carried out at least retrospectively instead of being carried out as a prospective study as claimed by the authors. The authors conclude that social distancing did not reduce FRI and that environmental contamination rather than person to person transmission is the culprit in the spread of FRI. The method used for social distancing, however, did not exclude those that were little bit sick but did not require placement in the MCU. In other words, sick people were allowed to remain in the closed unit (? as well as in the open units); only apparently healthy recruits were allowed to rejoin the open units after being placed in the MCU and PCU The study put emphasis on the importance of environmental cleaning. In addition to that crowded areas increase the risk of transmission of viruses. In the study, however, it was not clear if open and closed units are similar or different as pathogen reservoir. Also, analysis of closed units according to the population size was not done and information about the location of the closed units (all over the centre or localised in certain (isolated) area) is lacking. Despite these clear limitations this pragmatic study's findings may be interpreted in a variety of different ways. Perhaps the most interesting interpretation is that environmental conditions are determinants of adenoviral infectivity but not entry and exit from a community. In other words virological and presumably bacterial agents persist in the environment, they are not "brought" in and do not "arrive" and do not directly and invariably cause one-on-one disease. This hypothesis challenges the current simplistic interpretation of the postulates of Henle-Koch (one agent = one disease and suggests that the presence of microorganism may only be one of the many variables which determine infectious disease. This interpretation is comforted by the relatively small number of isolates found in studies of ILI causes (so called pie studies) The corresponding author provided the following additional information: each week a new cohort of about 500 recruits arrives at the camp, all of whom arrive by Wednesday. On Thursday the recruits are assigned to 6 platoons (each platoon housed in its own large room - called "housing units" in the article). Each cohort's 6 housing units are numbered from 1 to 6, with no particular distinction between them. Each house is given approximately the same number of recruits. The placement of the recruits into the housing units is based somewhat on the order of their arrival to the camp, but otherwise there are no criteria for placement, although relatives and friends are allowed to be in the same platoon. The recruits at MCRD San Diego tend to be from west of the Mississippi. There is no particular order of arrival at the camp from different regions. The number of the closed housing unit assigned in each cohort varied. In the majority of cases it was 1 or 2 Each building contains 4 wings of 3 floors each. From the sky, the buildings form an H shape. The line in the middle of the H connects the sides of the H, and on each side the half above the middle line is one wing and below the middle line is the other wing. If you go on maps.google.com and type in 'san diego ca mcrd' and zoom in on C you can see how big the buildings are. The housing units for each cohort typically occupy 2 wings one building, but occasionally one housing unit will be in a different building. E.g. if there are 6 housing units in a cohort, the cohort will occupy 3 floors of wing A and 3 floors of wing C. The map gives you an idea of the geography of horizontal distance between each wing, and each floor is about 10 feet high. Although the housing units are relatively close to each other, the platoons do

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Broderick 2008 *(Continued)*

	not typically interact with each other. They are large permanent buildings each consisting of 12 large rooms and a hallway

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	N/A
Allocation concealment (selection bias)	Unclear risk	N/A
Blinding (performance bias and detection bias) All outcomes	Unclear risk	N/A
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	N/A
Selective reporting (reporting bias)	Unclear risk	N/A

Carabin 1999

Methods	Cluster-randomised controlled trial carried out in daycare centres (DCC) in the Canadian province of Quebec between 1 Sept 1996 and 30 November 1997 (15 months). The aim was to test the effects of a hygiene programme on the incidence of diarrhoea and fecal contamination (data not extracted) and on colds and URTIs. The design included before and after periods analysed to assess the Hawthorne effect of study participation on control DCCs. Unit of randomisation was DCC but analysis was also carried out at classroom and single child level. This is a common mistake in C-RCT analysis. DCCS were stratified by URTI incidence preceding the trial and randomised by location. Cluster coefficients are not reported
Participants	1729 children aged 18 to 36 months in 47 DCCs (83 toddler classrooms)
Interventions	Training session (1 day) with washing of hands, toy cleaning, window opening, sand pit cleaning and repeated exhortations to handwash
Outcomes	Laboratory: n/a Effectiveness: diarrhoea and coliform contamination (data not extracted) Colds (nasal discharge with at least one of the following: fever, sneezing, cough, sore throat, earache, malaise, irritability) URTI (cold of at least 2 days' duration) Surveillance was carried out by educators, annotating absences or illness on calendars. Researchers also filled in a phone questionnaire with answers by DCC directors Safety: n/a
Notes	Risk of bias: high (no description of randomisation; partial reporting of outcomes, numerators and denominators) Notes: the authors conclude that the intervention reduced the incidence of colds (IRR 0.80, 95% CI 0.68 to 0.93). Confusingly written study with unclear interweaving of 2 study designs. For unclear reasons analysis was only carried out for the first autumn. Unclear why colds are not reported in the results. Cluster-coefficients and randomisation process not described

Risk of bias

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Carabin 1999 *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Block randomisation of DCC according to region, but sequence generation not reported
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding (performance bias and detection bias) All outcomes	High risk	Blinding not possible (hygiene session plus educational material versus none)
Incomplete outcome data (attrition bias) All outcomes	High risk	Originally 52 eligible DCCs with 89 classrooms agreed to take part but 5 dropped out (2 closed, 1 was sold, 2 either did not provide data or the data were "unreliable" and 6 classrooms had insufficient data). Forty-three children failing to attend DCC for at least 5 days in the autumn were also excluded. ITT analysis was carried out including an additional DCC whose director refused to let staff attend the training session No correction for clustering made
Selective reporting (reporting bias)	High risk	Denominators unclear and not explained

Chen 2009

Methods	Case-control study to test the association between SARS onset and a range of causative and protective variables in Sun Yan Tzen University hospitals in Guanzhou, Southern China The study collected information on cases and controls retrospectively during the first phase of the SARS epidemic in China (March to May 2003) but there is also a prospective element with antibody confirmation of SARS infection. Analysis plan was similar to that of Liu 2009 with a univariate and multivariate analysis conducted to assess risk factors
Participants	Description of cases. Probable SARS cases were defined using the criteria by the China Health Ministry. Criteria for probable and suspected SARS cases included travel to a SARS epidemic area in the 2 weeks before the onset of symptoms or close contact with a probable SARS patient; fever of ≥ 38°C; chest X-ray abnormalities; normal or decreased leukocyte count; and no response to treatment by antimicrobial drugs. In this study what appears to have happened is that available Sun Yan Tzen University hospitals HCWs who were willing to be interviewed were bled and those with raised IgG against SARS-CoV were included as cases. Cases enrolled were 90 out of the possible 112 who had SARS (80%) and 758/846 controls (89%). The choice criterion for interview of cases and controls was availability i.e. being “off duty” during the survey. It is unclear what this means and why such bias was knowingly introduced Description of controls. Controls were SARS-CoV negative HCW who had worked in the 2 hospitals attending SARS cases
Interventions	An extensive number of exposure and interventions variables were elicited and quantified with discrete scores. Definitions are absent in most cases *Use of personal protective and control measures* Number of gowns worn 0 = single, 1 = double Number of multilayered cotton mask worn 0 = single, 1 = double Number of pairs of gloves worn 0 = single, 1 = double Frequency of wearing shoe cover 0 = never, 1 = sometimes, 2 = often, 3 = every time Frequency of wearing cap 0 = never, 1 = sometimes, 2 = often, 3 = every time Frequency of face shield in SARS ward 0 = never, 1 = sometimes, 2 = often, 3 = every time

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Chen 2009 *(Continued)*

	Frequency of wearing goggles while performing operation for SARS patients 0 = never, 1 = sometimes, 2 = often, 3 = every time *Health-related behaviours* Frequency of washing uncovered skin after caring for SARS patients 0 = never, 1 = sometimes, 2 = often, 3 = every time Frequency of washing hands after caring for SARS patients 0 = never, 1 = sometimes, 2 = often, 3 = every time Frequency of washing nasal cavity after caring for SARS patients 0 = never, 1 = sometimes, 2 = often, 3 = every time Frequency of washing oral cavity after caring for SARS patients 0 = never, 1 = sometimes, 2 = often, 3 = every time *SARS patient care* Special training for SARS 0 = no, 1 = yes Performing tracheotomy 0 = no, 1 = yes Performing tracheal intubations 0 = no, 1 = yes Caring for "Super Spreading Patient" 0 = no, 1 = Yes Avoiding face to face while caring for patient 0 = never, 1 = sometimes, 2 = often, 3 = every time *Other relevant control measures* Method of air ventilation in offices and SARS wards 1 = artificial central ventilation (windows were closed in wards), 2 = natural ventilation (windows were opened in wards), 3 = natural ventilation and additional electronic exhaust fan (windows were opened in wards, at the same time, electronic exhaust fans were used for improving air circulation in wards) Type of equipment for washing hands 1 = automatic tap, 2 = non-automatic tap, 3 = other
Outcomes	N/A
Notes	The authors conclude that “Some measures, particularly good air ventilation in SARS wards, may be effective in minimising or preventing SARS transmission among HCWs in hospitals”. The study is biased by the selection of cases and controls (enrolment only of available personnel) and the non-eligibility (and lack of mention) of HCW who died of SARS (which may be up to 20% of people who were ill during the first wave of SARS). The design and analysis are very similar to those of Ma 2004/Liu 2009 and the design also lacks focus. i.e. it does not test a defined hypothesis, but trawls through large numbers of variables looking for associations. There is no attempt at matching cases with controls and part of the design is prospective (IgG estimation). As a consequence the design distinction between a case-control and a cohort study is blurred. There is no mention of whether interviewers were blinded to case or control status of interviewees Data extracted are from the univariate analysis table 3 which is the table reporting both numerators and denominators for cases and controls. Table 4 (multivariate logistic analysis) reports the significant multiple protective associations: caring for super spreading patient and avoiding face to face contact while caring for SARS patient (OR 0.30, 0.15 to 0.60) and wearing gloves coupled with methods of ventilation (various ORs for the various combinations intensity of wearing and ventilation methods, all significant). In the light of so many biases it is difficult to interpret the data but there does seem to be a gradient favouring multiple interventions

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	N/A
Allocation concealment (selection bias)	Unclear risk	N/A
Blinding (performance bias and detection bias)	Unclear risk	N/A

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Chen 2009 *(Continued)*
All outcomes

Incomplete outcome data (attrition bias) All outcomes	Unclear risk	N/A
Selective reporting (reporting bias)	Unclear risk	N/A

Cowling 2008

Methods	Cluster-randomised controlled trial carried out in Hong Kong SARS between February and September 2007. The study assessed the effects of non-pharmaceutical interventions on the household transmission of influenza over a 9-day period. ILI cases whose family contacts had been symptom-free for at least 2 weeks rapid tested for influenza A and B were used and randomised to 3 interventions carried out. Randomisation was carried out in 2 different schedules (2:1:1 for the first 100 households and subsequently 8:1:1) but it is unclear why and how
Participants	946 index subjects aged 2 years or more in 122 clusters (households). 116 households were included in the analysis, 6 were excluded because subsequent laboratory testing (culture) were negative. There were 350 household contacts in the analysis but there 370 household contacts at randomisation. Attrition is not explained. Index cases were defined as subjects presented with at least 2 influenza-like symptoms of at least 48 hour duration (such as fever more or equal to 38 degrees, cough, headache, coryza , sore throat, muscle aches and pains) and positive influenza A+B rapid test
Interventions	Households were randomised to either wearing face masks with education (as the control group plus education about face mask use) or handwashing with special medicated soap (with alcohol sanitiser) with education (as the control group plus education about handwashing) or education about general healthy lifestyle and diet (control group). The soap was distributed in special containers which were weighed at the start and the end of the study. Interventions visits to the households were done on average 1 day after randomisation of index case household
Outcomes	Laboratory: QuickVue RTI MDCK culture Samples were harvested using NTS, but the text refers to a second procedure from June 2007 onwards testing for non-influenza viruses but no data were reported Effectiveness: secondary attack ratios (SAR): SAR is the proportion of household contacts of an index case who subsequently were ill with influenza (symptomatic contact individuals with at least 1 NTS positive for influenza by viral culture or PCR) Three clinical definitions were used for secondary analysis: 1. Fever more or equal to 38 degrees or at least 2 of following symptoms, headache, coryza , sore throat, muscle aches and pains 2. At least 2 of the following S/S: fever more or equal to 37.8 degrees, cough, headache, sore throat and muscle aches and pains 3. Fever of more or equal to 37.8 degrees plus cough or sore throat Safety: no harms were reported in any of the arms
Notes	The authors conclude that “The secondary attack ratios were lower than anticipated, and lower than reported in other countries, perhaps due to differing patterns of susceptibility, lack of significant antigenic drift in circulating influenza virus strains recently, and/or issues related to the symptomatic recruitment design. Lessons learnt from this pilot have informed changes for the main study in 2008” Although billed as a pilot study the text is highly confusing and at times contradictory. The intervention was delivered at a home visit up to 36 hours after the index case was seen in the outpatients. This is a

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Cowling 2008 *(Continued)*

	long time and perhaps the reason for the failure of the intervention. Practically, the intervention will have to be organised before even seeking medical care – i.e. people know to do it when the kid gets sick at home

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation was computer-generated by a biostatistician "A pre-specified table of random numbers will be used to assign one of the three interventions to the household of the index case."
Allocation concealment (selection bias)	Low risk	The households of eligible study index patients were allocated to 3 groups in a 1:1:1 ratio under a block randomisation structure with randomly permuted block sizes of 18, 24 and 30 by using a random-number generator. Allocation was concealed from treating physicians and clinics and implemented by study nurses at the time of the initial household visit
Blinding (performance bias and detection bias) All outcomes	High risk	Participants and people who administered the interventions were not blinded to the interventions, but participants were not informed of the specific nature of the interventions applied to other participating households
Incomplete outcome data (attrition bias) All outcomes	High risk	Dropout was accounted for. Dropout from randomised population was high: 32% in control group, 37.5% in hand hygiene group and 39.4% in the face masks and hand hygiene group. Reasons for dropout distributed evenly over the 3 groups Authors report follow up as proportion of patients remaining in the study after initial dropout
Selective reporting (reporting bias)	High risk	The choice of season, change in randomisation schedules and unexplained dropouts among contacts, the use of QuickVue which proved unreliable, reporting bias on non-influenza isolates make this study at high risk of bias

Cowling 2009

Methods	Cluster-randomised controlled trial
Participants	Households in Hong Kong From 45 outpatient clinics in both the private and public sectors across Hong Kong, they enrolled persons who reported at least 2 symptoms of acute respiratory illness (temperature 37.8 °C, cough, headache, sore throat, or myalgia); had symptom onset within 48 hours; and lived in a household with at least 2 other people, none of whom had reported acute respiratory illness in the preceding 14 days. After participants gave informed consent, they provided nasal and throat swab specimens. 2750 patients were eligible and tested between 2 January through 30 September 2008. Included were 407 people with influenza-like illness who were positive for influenza A or B virus by rapid testing (index patients) and 794 household members (contacts) in 331 households
Interventions	Participants with a positive rapid test result and their household contacts were randomly assigned to 1 of 3 study groups: control (lifestyle measures - 134 households), control plus enhanced hand hygiene only (136 households) and control plus face masks and enhanced hand hygiene (137 households) for all household members. No detailed description of the instructions given to participants
Outcomes	Influenza virus infection in household contacts, as confirmed by reverse transcription polymerase chain reaction (RT-PCR) or diagnosed clinically after 7 days

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Cowling 2009 *(Continued)*

	"The primary outcome measure was the secondary attack ratio at the individual level: that is, the proportion of household contacts infected with influenza virus. We evaluated the secondary attack ratio using a laboratory definition (a household contact with a nose and throat swab specimen positive for influenza by RT-PCR) as the primary analysis and 2 secondary clinical definitions of influenza based on self-reported data from the symptom diaries as secondary analyses." Statistical analysis: adjusted for clustering Results: no significant difference in secondary attack ratio between groups in total population. Statistically significant reduction in RT-PCR confirmed influenza virus infections in the household contacts in 154 households in which the intervention was applied within 36 hours of symptom onset in the index patient. Adherence to hand hygiene between 44% and 62%. Adherence of index patient to wearing a face mask between 15% and 49%
Notes	"In an unintentional deviation from that protocol, 49 of the 407 randomly allocated persons had a household contact with influenza symptoms at recruitment (a potential co-index patient). We also randomly assigned 6 of 407 persons who had symptoms for slightly more than 48 hours." The authors conclude that "Hand hygiene and face masks seemed to prevent household transmission of influenza virus when implemented within 36 hours of index patient symptom onset. These findings suggest that non-pharmaceutical interventions are important for mitigation of pandemic and interpandemic influenza. "

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation was computer-generated by a biostatistician "A pre-specified table of random numbers will be used to assign one of the three interventions to the household of the index case."
Allocation concealment (selection bias)	Low risk	The households of eligible study index patients were allocated to 3 groups in a 1:1:1 ratio under a block randomisation structure with randomly permuted block sizes of 18, 24 and 30 by using a random-number generator. Allocation was concealed from treating physicians and clinics and implemented by study nurses at the time of the initial household visit
Blinding (performance bias and detection bias) All outcomes	High risk	Participants and people who administered the interventions were not blinded to the interventions, but participants were not informed of the specific nature of the interventions applied to other participating households
Incomplete outcome data (attrition bias) All outcomes	High risk	Dropout was accounted for. Dropout from randomised population was high: 32% in control group, 37.5% in hand hygiene group and 39.4% in the face masks and hand hygiene group. Reasons for dropout distributed evenly over the 3 groups Authors report follow up as proportion of patients remaining in the study after initial dropout
Selective reporting (reporting bias)	Unclear risk	In general good reporting

Cowling 2010

Methods	Retrospective cohort study carried out to test whether entry screening practices delayed the onset of endogenous (i.e. not linked with travel of travel contacts) cases of nH1N1 during the recent influenza pandemic in countries which had introduced them compared to countries which had not

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Cowling 2010 *(Continued)*

Participants	35 countries which reported more than 100 cases of nH1N1 influenza to WHO by 6 July 2009 and for which entry policies could be ascertained or date of first untraceable local case (n = 26 countries). Participants excluded Mexico and US where transmission seemingly occurred earlier
Interventions	Dates and types of entry screening: temp check prior to disembarkation, health questionnaires from traveller with H1N1 cases, observation of arrivals for symptoms and thermal body imaging. There was wide variation in implementation with China and Japan implemented all 4, and 5 other nations none (Table 1)
Outcomes	Laboratory: n/a Effectiveness: dates of first imported pandemic influenza case and confirmation of first untraceable case (identified by Google and sundry searches) Safety: n/a
Notes	The authors conclude that entry screening provided an additional 1 to 2 weeks' delay with distributions delay ranging from 0 to 30 days (the CIs of median days of delay overlap). The authors question the cost-effectiveness of entry screening given the uncertainty of its effects and the enormous amounts of resources required to implement it This an interesting broad-brush study, heavily dependent on web-based searches but with a wide-ranging scope reflected in the multilingual capabilities of the study group. Its many weaknesses are known to the authors and are discussed.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	N/A
Allocation concealment (selection bias)	Unclear risk	N/A
Blinding (performance bias and detection bias) All outcomes	Unclear risk	N/A
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	N/A
Selective reporting (reporting bias)	Unclear risk	N/A

Derrick 2005

Methods	Prospective cohort study testing the performance of 1, 2, 3, 4 and 5 surgical masks worn in layers against the droplet filtration capacity of a N95 respirator. The study is described as cross-over trial when all volunteers wore the combinations of layers, but this is not further described
Participants	6 volunteers who wore the masks and had their droplet count taken
Interventions	Pleated rectangular 3-ply surgical mask

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Derrick 2005 *(Continued)*

Outcomes	Laboratory
Notes	Risk of bias: high (report too brief to allow assessment) Notes: the authors conclude that the best combination of 5 surgical masks scored a fit factor of 13.7, well below the minimum level of 100 required for a half face respirator. The reduction in particle count went from 2.7 for a singe mask to 5.5 for 5 masks worn at the same time. Multiple surgical masks filter ambient particles poorly. They should not be used as a substitute for N95 respirator unless there is no alternative. Cautiously the authors state that they cannot comment on the capacity of 5 layers of masks to stop infections such as SARS as the infective count of the SARS-CoV is unknown Fascinating small study with no details of assignment so it was classified as a cohort study. Unfortunately there is no indication of how comfortable 5 masks are to wear in a layer and no description of the volunteers

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	N/A
Allocation concealment (selection bias)	Unclear risk	N/A
Blinding (performance bias and detection bias) All outcomes	Unclear risk	N/A
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	N/A
Selective reporting (reporting bias)	Unclear risk	N/A

Dick 1986

Methods	Prospective cohort study involving men ˜ 18 years of age. The objective of the study was to determine whether rhinovirus 16 colds could be stopped from spreading with the use of an highly virucidal paper handkerchief (CMF tissues) containing citric acid and other virucidal ingredients. 20 to 25 men ˜ 18 years of age were inoculated intranasally with a safety tested R16. The laboratory-induced cold was in all aspects comparable to natural colds. 8 of them with the most severe colds (donors) played cards with 12 antibody-free men (recipients) in a experiment room. Four experiments were conducted, in experiments B and C volunteers used CMF tissues to prevent spreading of R16 colds. In the 2 control experiments (A and D) volunteers were permitted to use cotton handkerchiefs
Participants	Males ˜ 18 years of age with a laboratory-induced R 16 cold (donors) and 12 antibody-free men (recipients)
Interventions	Use of virucidal paper handkerchief (CMF tissues), containing citric acid and other virucidal ingredients to stop the spreading of R16 colds versus normal cotton handkerchiefs
Outcomes	Laboratory: serological evidence (serum samples or viral isolation) Effectiveness: rhinovirus colds Safety: n/a
Notes	Risk of bias: low

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Dick 1986 *(Continued)*

	Notes: the authors concluded that the use of CMS tissues has been successful, because it determined a complete interruption of transmission of R16 among participants, stopping the spreading in an environment in which possibilities for transfer of virus were constant, and in which the rate of transmission was predictably high under standard conditions (42% of cotton handkerchief users developed colds, but no user of virucidal tissues did so)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	N/A
Allocation concealment (selection bias)	Unclear risk	N/A
Blinding (performance bias and detection bias) All outcomes	Unclear risk	N/A
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	N/A
Selective reporting (reporting bias)	Unclear risk	N/A

Doherty 1998

Methods	Retrospective cohort study carried out in North Staffordshire hospital (UK) during 2 periods: from 1 November 1994 to 31 January 1995 and from 1 November 1995 to 31 January 1996. The study assessed the use at admission of assigning children to a cohort once a rapid enzyme immunoassay or immunofluorescence testing had identified RSV-positive patients. The incidence of RSV illness was compared in cohorted and uncohorted children. The authors believed that this procedure would aid clinical management and minimise cross-infection from affected to susceptible patients. Nasopharyngeal aspirates were obtained from infants and young children with an acute respiratory illness. Aspirates were sent for rapid diagnostic testing. RSV-positive patients were cohorted into 6-bedded bays on the paediatric ward. All carers observed standard routines (handwashing and gown wearing)
Participants	Children less than 3 years of age with an acute respiratory illness on admission. During the study periods a total of 222 patients in 1994 to 1995 and 291 patients in 1995 to 1996 had positive rapid tests
Interventions	RSV diagnosis and cohorting versus normal care
Outcomes	Laboratory: aspirates for RSV diagnosis Effectiveness: RSV illness (developed at least 5 days since admission) Safety: n/a "RSV infection reduced" (but data tabled do not support this conclusion)
Notes	Risk of bias: high (poor descriptions) Notes: the authors conclude that cohorting has been shown to reduce nosocomial transmission of RSV infections (no OR or other measures of strength are reported: "nosocomial transmission was minimised"). The study presents many inconsistencies between text and table and data were not extracted. The objective of the study is not well-defined. Part of the results is in the discussion. Most of all it is unclear who the intervention and control arms were (i.e. cohorting of RSV-infected children to prevent infection in whom?)

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Doherty 1998 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	N/A
Allocation concealment (selection bias)	Unclear risk	N/A
Blinding (performance bias and detection bias) All outcomes	Unclear risk	N/A
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	N/A
Selective reporting (reporting bias)	Unclear risk	N/A

Dyer 2000

Methods	Prospective, cluster open-label cross-over cohort study of programmed use of a hand sanitiser in conjunction with at-will soap-and-water handwashing conducted in a private elementary school in California. The aim of the study was to assess the effectiveness of the SAB sanitiser at reducing illness absenteeism in a school setting. Subjects were grouped by classroom without formal randomisation. 7 classes received the instant sanitiser, while the remaining 7 classes were assigned to the control group. Male-to-female ratios and age distributions of the 2 groups did not differ significantly Prior to study commencement all students participated in an educational programme about germs and the importance of handwashing to prevent illnesses. Children in the hand sanitiser group received a spray to use under teacher supervision to supplement normal, at-will handwashing with soap and water. The control group was instructed to wash hands with water and soap, and it was not supervised. Data were collected for 10 weeks. After this period, there was a 2-week wash-out period, during which neither group of students used SAB sanitiser. Then SAB sanitiser was distributed to the student group that had previously served as the control and the study proceeded for another 4 weeks
Participants	420 children in a private elementary school in California aged 5 to 12 years; cluster, open-label, cross-over cohort study over 10 weeks
Interventions	Educational programme plus the SAB (surfactant, allantoin and benzalkonium chloride) spray hand sanitiser in 1 oz bottles fitted with a pump spray top and with at-will soap-and-water handwashing versus nothing
Outcomes	Laboratory: serological evidence: n/a Effectiveness: days of absences from school for respiratory illness (and gastrointestinal illness - data not extracted) Safety: n/a Respiratory illness and gastrointestinal illness: reduced absenteeism by 41.9%; respiratory illnesses by 49.7%
Notes	Risk of bias: medium Notes: the authors conclude that daily use of the SAB instant hand sanitiser with at-will handwashing using soap and water significantly decreased absences due to acute communicable illness. Use of the sanitiser reduced illness absenteeism by 41.9% (reduction in respiratory illnesses of 49.7% over the 10-week period of the study). The authors also described some limitations of the study, as limited so-

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Dyer 2000 *(Continued)*

	cio-economic diversity in the study population, limitation to a single study site and lack of blinding. Further soap-and-water washing was not monitored. Generalisability of the results is questionable as all participants underwent the educational programme

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	N/A
Allocation concealment (selection bias)	Unclear risk	N/A
Blinding (performance bias and detection bias) All outcomes	Unclear risk	N/A
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	N/A
Selective reporting (reporting bias)	Unclear risk	N/A

Falsey 1999

Methods	Prospective cohort study conducted at 3 adult daycare centres in Rochester, New York. The study assessed the value of a staff educational programme combined with the use of a portable virucidal hand foam for the reduction of respiratory infections in daycare participants. The authors report in the same paper an ecological study of the incidence of ILI in 3 previous seasons (1992 to 1996) which does not report numerators and denominators and was not extracted
Participants	In December 1995 when the study started there were centre 1: 69 elderly and 36 staff members; centre 2: 67 elderly and 45 staff members; centre 3: 68 elderly and 16 staff members
Interventions	Addition of virucidal hand foam as a supplement versus normal handwashing and educational programme
Outcomes	Laboratory: serological evidence and virology cultures (Table 1 reports a series of isolated pathogens, with no tie in with actual cases) Effectiveness: viral pathogens: influenza A/B, RSV, coronavirus, parainfluenza, rhinovirus Safety: n/a
Notes	Risk of bias: low Notes: the authors conclude that the educational programme for staff was associated with an almost 50% decrease in the infection rate in daycare attendees. The programme was effective only in the last of the 4 years of the programme (rates of infection in daycare patients fell from 14.5 to 10.4 per 100 person-months to 5.7 per 100 person months, $P < 0.001$). This is a conclusion based on an ecological study of the incidence of ILI in 3 previous seasons which the authors report in the same paper, but which does not report numerators and denominators and was not extracted. The lower infection rate is likely to reflect the combination of interventions and education, which increased staff awareness and more broadly changed behaviour. There was no apparent additional benefit from the virucidal foam. This is one of the few identified studies reporting circulating viruses in the daycare setting, both in staff and patients. The decline in influenza-like illness episodes across the 4 study years is reflected in the de-

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Falsey 1999 *(Continued)*

	cline in viral isolates, suggesting that aspecific measures such as handwashing are effective against the main respiratory viruses

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	N/A
Allocation concealment (selection bias)	Unclear risk	N/A
Blinding (performance bias and detection bias) All outcomes	Unclear risk	N/A
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	N/A
Selective reporting (reporting bias)	Unclear risk	N/A

Farr 1988a

Methods	The study was a 6-month cluster-randomised, controlled, double-blind trial of the efficacy of virucidal nasal tissues in the prevention of natural cold, and it was conducted in Charlottesville, Virginia, USA. Many of the families were enrolled, because one or more members worked at the State Farm Insurance Company; the remaining families were recruited from the Charlottesville community by advertisement in a local newspaper. Families were randomly assigned by the sponsoring company to receive boxes of treated tissues, placebo tissues or no tissues. The randomisation was performed by computer. Study participants and investigators were unaware of the type of tissues which each family was randomised to receive. Blinding efficacy was tested using a questionnaire: the mothers in each family were asked twice if she believed her family was using virucidal or placebo tissues Participants in the treated and placebo groups were instructed to use only tissues received through the study, while families in the additional control group without tissues were allowed to continue their usual practice of personal hygiene. Each family member kept a daily listing of respiratory symptoms on a record card. A nurse epidemiologist visited each family monthly to encourage recording
Participants	186 families, 58 in the active group, 59 in the placebo group and 69 in the no tissues group. A total of 302 families were originally recruited, 116 families who did not comply with the study protocol, lost their surveillance cards, could not complete the protocol were excluded from the analysis
Interventions	Use of virucidal tissues versus placebo tissues versus no tissues. The treated tissues were impregnated with malic and citric acids and sodium lauryl sulphate, while placebo tissues contained saccharin
Outcomes	Laboratory: serological evidence: no Effectiveness: respiratory illness Safety: n/a
Notes	Notes: the authors conclude that virucidal tissues have only a small impact upon the overall rate of natural acute respiratory illnesses. The total illness rate was lower in families using virucidal tissues than in both of the other 2 study groups, but only the difference between active and placebo groups was statistically significant (3.4 illness per person versus 3.9 for placebo group, P = 0.04 and 3.6 for no tissues control group P = 0.2, and overall 14% to 5% reduction). The questionnaire results suggest that some bias may have been present since a majority of mothers in the virucide group believed they were re-

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Farr 1988a *(Continued)*

	ceiving the "active" tissues. Another possible explanation of the low effectiveness of virucidal tissues is poor compliance by children in the use of virucidal tissues. A well-designed and honestly reported study

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"The randomisation was performed by computer in each trial."
Allocation concealment (selection bias)	Unclear risk	"In trial I, families were randomly assigned by the sponsoring company to receive boxes of treated tissues, placebo tissues or no tissues." "Families with one or two children were randomised in one stratum, and families with three or more children were randomised in a second stratum in trial I." Concealment of allocation not described
Blinding (performance bias and detection bias) All outcomes	Low risk	"Study participants and investigators were unaware of the type of tissues which each family was randomised to receive in both trials. In trial I, the mother in each family was asked twice if she believed her family was using active or placebo tissues, first after three months and then at the end of the study."
Incomplete outcome data (attrition bias) All outcomes	High risk	"A total of 116 of the 302 families were excluded from the analysis. Families were excluded if they lost their surveillance cards or did not conscientiously record data, did not comply with the study protocol, or simply could not complete the protocol for family reasons. It was discovered that families with five or more members had so many colds that it was not possible to distinguish primary and secondary illnesses. These large families were therefore excluded from the analysis in trial I and were excluded from enrolment in trial II."
Selective reporting (reporting bias)	Low risk	All indicated outcomes are reported

Farr 1988b

Methods	The study was a 6-month randomised, controlled, double-blind trial of the efficacy of virucidal nasal tissues in the prevention of natural cold and it was conducted in Charlottesville, Virginia. Families were recruited from the Charlottesville community by advertisement in a local newspaper. Families were randomly assigned by the sponsoring company to receive either virucidal tissues, or placebo-treated tissues. Stratified randomisation was performed by computer and the strata were defined by total number in the family. Study participants and investigators were unaware of the type of tissues which each family was randomised to receive. Each family member kept a daily listing of respiratory symptoms on a record card. A nurse epidemiologist visited each family monthly to encourage recording. In addition a study monitor visited each family bimonthly to further encourage compliance and reporting of symptoms
Participants	98 families, 58 in the active group and 40 in the placebo group. 231 families were initially recruited, 222 completed the trial, data of 98 families were analysed. The others were excluded from the analysis since they complained of side effects (sneezing, etc.) or reported not using the tissues regularly
Interventions	Use of virucidal tissues versus placebo tissues. The treated tissues were impregnated with malic and citric acids and sodium lauryl sulphate, while placebo tissues contained succinic acid. Participants in the treated and placebo groups were instructed to use only tissues received through the study

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Farr 1988b *(Continued)*

Outcomes	Laboratory: serological evidence: no Effectiveness: respiratory illness Safety: n/a
Notes	Notes: the study suggests that virucidal tissues have only a small impact upon the overall rate of natural acute respiratory illnesses. The total illness rate was lower in families using virucidal tissues than in the other study group, but the difference between active and placebo groups was not statistically significant. There was a small non-significant drop in illness rates across families (5%). The tissues appeared ineffective as the drop was confined to primary illness unaffected by tissue use. Placebo (succinic acid) was not inert, and it was associated with cough and nasal burning. This impacted on allocation concealment. A well-designed and honestly reported study marred by transparent allocation

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"The randomisation was performed by computer in each trial."
Allocation concealment (selection bias)	Unclear risk	"In trial II, families were randomly assigned by the sponsor to receive either virucidal tissues or placebo treated tissues." "In trial II, stratified randomisation was again used, but this time the strata were defined by total number in the family (i.e., one stratum for two-member families, another stratum for three-member families, and a final one for four-member families)." Concealment of allocation not described
Blinding (performance bias and detection bias) All outcomes	Low risk	"Study participants and investigators were unaware of the type of tissues which each family was randomised to receive in both trials."
Incomplete outcome data (attrition bias) All outcomes	High risk	"A total of 222 (of 231) families completed trial II; 9 families were terminated early (table 1). In 124 families, one or more family members reported not using the tissues regularly and/or reported having significant side effects. The data from these families were not analysed, leaving 58 families (177 persons) and 40 families (114 persons) for analysis in the virucide and placebo groups, respectively."
Selective reporting (reporting bias)	Low risk	All indicated outcomes are reported

Foo 2006

Methods	Retrospective cohort survey carried out in Singapore to assess the harm associated with the use of the personal protective equipment in healthcare staff working in a “SARS-designated hospital” from March 2003 to middle 2004. Three departments from the hospital were surveyed the National Skin Centre (NSC), Department of Emergency (A&E) and the intensive care unit (ICU) Control group: unclear Control group: none
Participants	340 healthcare staff were surveyed, 322 responded (60 from the NSC, 77 from the TTSH A&E, and 185 from the TTSH ICU)

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Foo 2006 *(Continued)*

Interventions	Use of personal protective equipment (PPE), namely, masks, gloves and gowns. Adverse skin reactions to PPE
Outcomes	Laboratory: none Effectiveness: not applicable Safety: adverse skin reactions (ASR) from the use of 3 types of PPE (masks (respirator, surgical or paper masks), plastic gloves and disposable gowns) developed with prolonged use (8.4, 9.4 and 8.8 months, respectively)
Notes	The authors conclude that prolonged use of PPEs (N95 respirators, rubber gloves) is associated with high frequency of ASR. The authors reported that there were no significant differences in adverse skin reactions to masks and gloves due to sex, race or profession. Some differences were reported by age as follows: • Those who developed acne with masks were younger (mean of 29.5 years) compared with those who did not (mean of 33.2; P < 0.001) • Those who developed dry skin with gloves were younger (mean of 28.7 years) compared with those who did not (mean of 33.2; P < 0.002) • Those who developed itch with gloves were younger (mean of 29.5 years) compared with those who did not (mean of 33.2; P < 0.001) Survey results show that acne, itch and rash are the most common harms reported after wearing a N95 respirator (59.6%, 51.4% and 35.8%) and that dry skin, itch and rash were reported by (73.4%, 56.3% and 37.5%, respectively) glove users. Other harms were reported by very small numbers of users (4 or below). This study, although a retrospective survey is important as it suggests that barrier intervention-using carries harms and such harms may affect compliance with the intervention

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	N/A
Allocation concealment (selection bias)	Unclear risk	N/A
Blinding (performance bias and detection bias) All outcomes	Unclear risk	N/A
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	N/A
Selective reporting (reporting bias)	Unclear risk	N/A

Gala 1986

Methods	The purpose of this study was to evaluate whether the use of a disposable plastic goggle designed to cover the eyes and nose could help reduce the rate of nosocomial infections during an outbreak of RSV infection. The rates of RSV infection in staff members and infants were determined on an infant and toddler ward during a seven-week study. Two 3-week study periods were compared: period 1, during which all staff members used the goggles, and period 2, were no goggles were worn. The respiratory infection control procedures were the same during both periods of study: handwashing, isolation and cohorting. In reality although on report, Gala and colleagues are conducting 2 studies. The first is a non-concurrent cohort study, in which 2 different population of children are assessed separated by a

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Gala 1986 *(Continued)*

	1-week 'wash-out' period and the intervention (goggles) on staff. The play of confounders here is too heavy and uncontrolled to include the data in the study. The second is a controlled before and after on the 40-odd members of staff (32 of whom took part in both periods). Here the play of confounders should be partly reduced. We extracted data relating to the second study only
Participants	74 children and 40 staff members in period 1; 77 children and 41 staff members in period 2. During the study 151 children were admitted to the ward; their mean age was 12.9 months, 59% were boys. During period 174 infants were examined, 15 were admitted with RSV infections, the remaining 59 constituted the group potentially susceptible to a nosocomial RSV infection. Seventeen infants were hospitalised for sufficient time for a nosocomial infection and in 1 nosocomial RSV infection was detected. During period 277 babies were studied, 17 of whom were admitted with RSV infection. Of the remaining 60, 39 children were excluded, 21 were considered susceptible, and in 9 of them nosocomial RSV infection was detected. Forty staff members were examined in period 1 and 41 during period 2. During period 2, 2 of the ward staff acquired RSV infection and were not considered susceptible
Interventions	Use of a disposable plastic eye-nose goggle and respiratory infection control procedures versus only respiratory infection control procedures (cohorting, isolation and handwashing)
Outcomes	Laboratory: serological evidence Effectiveness: RSV infection (symptoms and laboratory confirmation) Safety: n/a
Notes	Risk of bias: high Notes: the use of the disposable eye-nose goggles appeared to be associated with a significant decrease in nosocomial RSV infections (6% versus 42% of contacts when the goggles were used compared to when they were not). The expense of such goggles will have to be determined and compared with the cost of nosocomial infections. The study has an orgy of confounders, is it difficult to see how such studies can be carried out without disrupting patient care? Why not randomise staff to goggles or standard care?

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	N/A
Allocation concealment (selection bias)	Unclear risk	N/A
Blinding (performance bias and detection bias) All outcomes	Unclear risk	N/A
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	N/A
Selective reporting (reporting bias)	Unclear risk	N/A

Gwaltney 1980

Methods	The study assessed the effectiveness of aqueous iodine applied to the fingers in blocking hand transmission of experimental infection with rhinovirus from one volunteer to another. Healthy, young adult volunteers were recruited from the general population at the University of Virginia, Charlottesville. Volunteers were not informed about the contents of the hand preparation until after the study. Two exper-

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Gwaltney 1980 *(Continued)*

	iments were conducted to evaluate the virucidal activity of aqueous iodine applied to the fingers immediately before viral contamination. Another 2 experiments were conducted to determine whether there was sufficient residual activity of aqueous iodine after 2 hours to interrupt viral spread by the hand route. Volunteers who were donors of virus for the hand exposures were challenged intranasally on 3 consecutive days with strain HH rhinovirus. Recipients were randomly assigned to receive iodine or placebo. The donors contaminated their hands with nasal secretions by finger to nose contact before the exposure. Hand contact was made between a donor and a recipient by stroking of the fingers for 10 seconds. Donors and recipients wore masks during the exposure period
Participants	15 and 20 volunteers in 2 experiments
Interventions	Treatment of fingers with iodine versus placebo. The virucidal preparation used was aqueous iodine(2% iodine and 4% potassium iodide). The placebo was an aqueous solution of food colours
Outcomes	Experimental rhinovirus infection reduced (P = 0.06) Laboratory: serological evidence Effectiveness: rhinovirus infection (based on serology, isolation and clinical symptoms) with high score clinical illness. Score was published elsewhere Safety: N/A
Notes	Risk of bias: high (poor description of randomisation process, concealment, or allocation) Notes: the study suggests that aqueous iodine applied to the fingers was effective in blocking transmission by hand contact of experimental infection with rhinovirus for up to 2 hours after application (1 out 10 volunteers were infected compared to 6 out of 10 in the placebo preparation arm, P = 0.06 with Fisher's exact test). The effectiveness of iodine treatment of the fingers in interrupting viral transmission in volunteers recommends its use for attempting to block transmission of rhinovirus under natural conditions. Although the cosmetic properties of 2% aqueous iodine make it impractical for routine use, it can be used as an epidemiologic tool to study the importance of the hand transmission route and to develop an effective cosmetically acceptable hand preparation. A summarily reported study

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	N/A
Allocation concealment (selection bias)	Unclear risk	N/A
Blinding (performance bias and detection bias) All outcomes	Unclear risk	N/A
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	N/A
Selective reporting (reporting bias)	Unclear risk	N/A

Hall 1981a

Methods	Cohort study to determine the possible modes of spread a RSV to young adult volunteers working on a paediatric ward who were exposed in different manners to infants with RSV. Volunteers were divided into 3 groups: "cuddlers", exposed to an infected infant over 2 to 4 hours by caring for the baby in the usual manner, wearing gowns, but no mask or gloves; "touchers", exposed with the infant out of the

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Hall 1981a *(Continued)*

	room by touching surfaces contaminated with the baby's secretions; "sitters", exposed to an infected baby by sitting at a distance of more than 6 feet from an infant's bed, and they wore gowns and gloves, but no masks. In order to control for possible differences in infectivity among infants, a volunteer from each of the 3 groups was exposed to each infant, or to this environment in the case of touchers. In addition, volunteers from each group were exposed to more than one infant. After exposure volunteers were followed for 12 days
Participants	31 volunteers: 7 in the cuddler group, 10 in toucher group and 14 in the sitter group
Interventions	Exposure to infants admitted with bronchiolitis or pneumonia during a community outbreak of RSV isolation
Outcomes	Laboratory: serological evidence Effectiveness: RSV infection demonstrated by viral isolation and serology. Clinical symptom diary collected with questionnaires. Symptomatic, asymptomatic and febrile symptomatic data reported separately Safety: n/a
Notes	Risk of bias: low Notes: the authors concluded that the spread of RSV may occur by close contact with direct inoculation of large droplets or by self-inoculation after touching contaminated surfaces. Infection does not appear to occur after more distant contact requiring small particle aerosols (0 infected out of 14 "sitters", those that sat away from RSV infected infants, compared with 5 out of 7 who cuddled and 4 out of 10 who touched the infected infants). Ancillary procedures that may be helpful include the care of contaminated surfaces and gowns, cohorting of staff and infants, and limiting the traffic in and out of the infants' room. With limited facilities, isolation rooms might best be reserved for uninfected infants with underlying disease who, should they acquire nosocomial RSV infection, are at risk for severe disease

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	N/A
Allocation concealment (selection bias)	Unclear risk	N/A
Blinding (performance bias and detection bias) All outcomes	Unclear risk	N/A
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	N/A
Selective reporting (reporting bias)	Unclear risk	N/A

Hall 1981b

Methods	Controlled before and after study designed to evaluate the efficacy of infection-control procedures with the use of masks and gowns compared with procedures not using mask and gowns on the rate of nosocomial RSV infection in both infants and staff. The study, conducted at Strong Memorial Hospital in Rochester, NY, USA, in 1979, was begun 12 days after the hospital admission of the first infant infected by RSV, and was continued for the next 2 months. All patients and staff on the ward for children less than 3 years of age were included. During the first 4 weeks (period 1) of the study the infection-control

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Hall 1981b *(Continued)*

	procedures for infants with respiratory illness included handwashing and the use of mask and gowns by the staff on entering the room, with a change of gowns between contacts with each infant. After 4 weeks the wearing of gowns and masks was discontinued and handwashing alone was used for the final 5 weeks of the study. Throughout the study handwashing, cohorting and isolation were employed and emphasised. The number of nosocomial infections in patients and staff for period 1 were compared with the period 2 (last 4 weeks of the study). Infections that occurred in the interval week were not counted
Participants	162 patients suspected with RSV infections from infected infants; 78 admitted in the period 1 and 84 in period 2. The age range was 2 weeks to 3 years. 55% were male. Of 78 (period 1), 24 were admitted for RSV infections and the remaining 24 became the contacts. (Due to lack of comparability of children and an unclear text children data were not extracted) 39 ward personnel were included, 30 in the period 1 and 27 of these were also studied during period 2 along with 9 other personnel. Thus a total of 36 staff members were studied during period 2
Interventions	Use of gowns and masks and standard infection-control procedures (handwashing, cohorting, isolation) versus standard infection-control procedures only to prevent transmission of RSV infections from infected infants
Outcomes	Laboratory: serological evidence Effectiveness: RSV infection demonstrated by symptoms, viral isolation and serology Safety: n/a
Notes	Risk of bias: high Notes: the authors concluded that the use of masks and gowns as additional infection-control procedures for RSV infection shows no appreciable benefit in preventing nosocomial spread of RSV to infants or to the ward personnel. The nosocomial infection rate in the 2 periods was not significantly different in either the infants or staff (32% infection versus 41%). Both of the study periods appeared to be equal in terms of potential for transmission or exposure to RSV. The number of infants admitted during both periods was similar. Furthermore these 2 groups of contacts were alike in age and types of underlying diseases. The routine use of masks and gowns does not seem warranted in view of the considerable cost. A very poorly reported study with an unclear eligibility procedure and a lack of description of denominators. Why not use randomisation?

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	N/A
Allocation concealment (selection bias)	Unclear risk	N/A
Blinding (performance bias and detection bias) All outcomes	Unclear risk	N/A
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	N/A
Selective reporting (reporting bias)	Unclear risk	N/A

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Heymann 2004

Methods	Controlled before and after study to evaluate the effect of school closure on the occurrence of respiratory infection among children ages 6 to 12 years and its impact on healthcare services. The study was conducted in Maccabi healthcare services, which has a nationwide network of > 3000 independent physicians connected by a unified computer system. The authors assembled a retrospective cohort of all 6 to 12 year old children comprising 186,094 children. The computerised data were examined for three 2-week periods: before school closure, during closure and after closure. The occurrence of respiratory tract infections was determined according to recorded diagnoses, including cough, upper respiratory tract infection, common cold, sore throat and viral infection
Participants	186,094 children aged 6 to 12 years
Interventions	Effect of a school closure on the occurrence of respiratory infection during an "influenza" outbreak
Outcomes	Laboratory: no Effectiveness: respiratory tract infections Safety: n/a
Notes	Risk of bias: high Notes: the authors concluded that school closure was temporally associated with 42% decreased morbidity from respiratory tract infections, a consequent 28% decrease in visits to physicians and to emergency departments and a 35% reduction in purchase of medications. Limits of this study are: the fact that in Israel 33.8% of the population are children, hence these results may not be applicable to high-income countries with lower percentage of children. In addition there may be a difference in parental attitudes toward respiratory illness symptoms in other cultures that affect health care utilisation. Another reason for such a difference may be the basic structure of the health system in Israel, where comprehensive health insurance is universal and provided by the law. Finally there is limited availability of over-the-counter medications, and to obtain symptomatic therapeutic agents children are generally seen by a physician. The biggest limit to this study is not mentioned by the authors: the assumption that the circulation of respiratory viruses is constant throughout the study period. Although in the Discussion the authors mention some surveillance data on national diffusion of an H3N2 epidemic but this took place in December 1999 Observed effects may be due to school closure or they may be due to lower circulation of the viruses

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	N/A
Allocation concealment (selection bias)	Unclear risk	N/A
Blinding (performance bias and detection bias) All outcomes	Unclear risk	N/A
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	N/A
Selective reporting (reporting bias)	Unclear risk	N/A

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Isaacs 1991

Methods	Retrospective and prospective cohort study was conducted to evaluate the effectiveness of cohorting and educational programme (handwashing) in reducing the incidence of nosocomial respiratory syncytial virus infections Data on all children with RSV infection on any of the paediatric wards in winter of 1986 to 1987 were retrospectively collected. In order to define the population at risk of developing RSV infection it was determined the number of children under 2 years of age hospitalised on the 2 paediatric wards and the paediatric intensive care unit and the number they spent in hospital. For the next 2 winters (1987 to 1988 and 1988 to 1989) the same data were prospectively collected. In addition some interventions were made to try to reduce the incidence of hospital-acquired RSV infection. Children admitted with suspected RSV infection were nursed in a specific area until the result of an indirect immunofluorescent test. It was not possible to cohort babies on the paediatric intensive care unit. Staff were instructed on the importance of handwashing and this was reinforced on ward rounds. An educational leaflet was prepared and given to the parents of every child admitted with the infection
Participants	Children < 2 years of age: 425 in period 1; 840 in period 2; 552 in period 3
Interventions	Isolation and handwashing versus normal care
Outcomes	Laboratory: indirect immunofluorescence on nasopharyngeal secretions or by culture of secretions Effectiveness: RSV infection Safety: n/a
Notes	Risk of bias: high (poor descriptions) Notes: the authors concluded that handwashing and cohorting reduced at least 66% in the number of hospital acquired infections due to RSV in the 2 intervention winters. One minor problem with cohorting was that babies could not remain in the accident and emergency department until a diagnosis of RSV was virologically confirmed. Hence they were cohorted on the basis of a clinical diagnosis of bronchiolitis. The authors also underline the importance of a more rapid antigen test for RSV. It is doubtful whether the non-exposed cohort is similar to its hospital peers, especially because there are several cardiac children in the exposed cohort. The biggest limit to this study is mentioned by the authors in the Discussion: the assumption that the circulation of RSV is constant throughout the study period. Exposure however is not the same in the 3 seasons and observed effect may be due to cohorting or to the different viral circulation

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	N/A
Allocation concealment (selection bias)	Unclear risk	N/A
Blinding (performance bias and detection bias) All outcomes	Unclear risk	N/A
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	N/A
Selective reporting (reporting bias)	Unclear risk	N/A

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Jacobs 2009

Methods	Open randomised controlled trial lasting 77 days from January 2008 to test "superiority" of face masks in preventing URTI. This term appears as an acronym in the introduction and is not explained. It is assumed it stands for "upper respiratory infections" but it is preceded in the text by the term "common cold" which is also lacking a definition. Randomisation was carried out in blocks within each of 3 professional figures (physicians, nurses and "co-medical" personnel)
Participants	33 HCWs mainly females aged around 34 to 37 in a tertiary healthcare hospital in Tokyo, Japan. HCW with "predisposing conditions" (undefined) to "URTI" and those taking antibiotics were excluded A baseline descriptive survey was carried out including "quality of life" 1 participant dropped out at end of week 1 but no reason is reported nor the allocation arm
Interventions	Surgical mask MA-3 (Osu Sangyo, Japan) during all phases of hospital work (n = 17) or no mask (n = 15) (except when specifically required by hospital SOPs)
Outcomes	Laboratory; n/a Effectiveness: URTI is defined on the basis of a symptoms score with a score >14 being a URTI according to Jackson's 1958 criteria ("Jackson score"). These are not explained in text although the symptoms are listed in Table 3 (any, sore throat, runny nose, stuffy nose, sneeze, cough, headache, ear ache, feel bad) together with their mean and scores SD by intervention arm Safety: the text does not mention or report harms. These appear to be indistinguishable from URTI symptoms (e.g. headache which is reported as of significantly longer duration in the intervention arm). Compliance is self-reported as high (84.3% of participants)
Notes	The authors conclude that "Face mask use in healthcare workers has not been demonstrated to provide benefit in terms of cold symptoms or getting colds. A larger study is needed to definitively establish non-inferiority of no mask use" This is a small, badly reported trial. The purpose of trials is to test hypotheses not to prove or disprove "superiority" of interventions. There is no power calculation and CIs are not reported (although there is a mention in Discussion). No accurate definitions of a series of important variables (e.g. URTI, runny nose etc.) are reported and the Jackson scores are not explained, nor their use in Japanese personnel or language validated Intervention arm data not extracted because of the uncertainty of its meaning

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Open randomised controlled trial, but sequence generation not reported
Allocation concealment (selection bias)	Unclear risk	"Mask and no mask groups were formed using block randomisation of subjects within their respective job categories: nurses, doctors, and co-medical personnel." Concealment of allocation not described
Blinding (performance bias and detection bias) All outcomes	High risk	Not possible (mask wearing or not)
Incomplete outcome data (attrition bias) All outcomes	Low risk	One dropout in each group accounted for. "Analyses were performed following the principles of intention-to-treat."

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Jacobs 2009 *(Continued)*

Selective reporting (reporting bias)	High risk	NB: influenza vaccine coverage in mask group was 100% and only 81% in the non-mask wearing group

Kimel 1996

Methods	Prospective cohort study conducted in a school of Chicago, USA, to evaluate the effectiveness of a handwashing programme in reducing the absenteeism caused by flu-like illness. The school was located in a predominantly white, middle to upper middle class suburb. All 4 kindergarten and 5 first-grade classes were included in the study. No significant differences were found between participating classes for size, male-female ratio, percentage of low-income students, or students with chronic health problems. Teachers were surveyed to determine classroom handwashing activities. The influenza season usually occurs during December and January. The handwashing programme was planned for presentation just prior to this time. The effectiveness of the programme was determined by comparing absentee rates among participants and non-participating classes (the control group). Absentee rates were determined by reviewing the computerised daily school absence logs. Entries that listed flu-like symptoms were counted. A take-home handwashing chart was also given to each student to encourage follow-through with handwashing at home
Participants	199 children of kindergarten and first grade schools
Interventions	Handwashing and educational programme versus no intervention
Outcomes	Laboratory: no Effectiveness: flu-like illness Safety: n/a Absenteeism from influenza-like illness was approximately double in the control arm (P = 0.01)
Notes	Risk of bias: medium Notes: the authors concluded that handwashing education can decrease absenteeism even among kindergarten and first grade students. This study did not control for health and hygiene practices at home or exposure to ILI outside of school. Furthermore the student population at the school was generally healthy, probably because families were able to provide adequate health and hygiene resources. Another problem of the study is that the flu season was later than usual (February), and this represented a confounding variable. The teacher surveys indicated problems with handwashing facilities

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	N/A
Allocation concealment (selection bias)	Unclear risk	N/A
Blinding (performance bias and detection bias) All outcomes	Unclear risk	N/A
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	N/A
Selective reporting (reporting bias)	Unclear risk	N/A

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Kotch 1994

Methods	Pair-matched cluster-randomised, controlled trial conducted in the period 19 October 1988 to 23 May 1989 in 24 childcare centres in North Carolina, USA. The trial tested the effects of a handwashing and environment sterilising programme on diarrhoea (data not extracted) and ARIs. Child daycare centres had to care for 30 children or less, at least 5 of whom had to be in nappies and intending to stay open for at least another 2 years. Randomisation is not described, nor are cluster coefficients reported
Participants	389 children aged 3 years or less in daycare for at least 20 hours a week. There were some withdrawals but the attrition on participants is not stated, only that in the end data for 31 intervention classrooms and 36 control classrooms were available. There were 291 children aged up to 24 months and 80 over 24 months that took part. The text is very confusing as 371 seem to be the total of the number of families that took part. No denominator breakdown by arm is reported and numerators are only reported as new episodes per child-year
Interventions	Structured handwashing and environment (including surfaces, sinks, toilets and toys) disinfecting programme with waterless disinfectant scrub
Outcomes	Laboratory: N/A Effectiveness: ARI (coughing, runny nose, wheezing, sore throat or earache) Safety: N/A
Notes	Risk of bias: high (poor reporting of randomisation; outcomes; numerators and denominators) Notes: the authors conclude that the fully adjusted RR for prevention of ARIs was 0.94 (-2.43 to 0.66). A poorly reported study

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"Pair-matched cluster-randomised, controlled trial', but sequence generation not reported
Allocation concealment (selection bias)	Unclear risk	Centres were matched in pairs and then randomly allocated to either intervention or control programmes. Allocation concealment not reported.
Blinding (performance bias and detection bias) All outcomes	High risk	Not possible (intervention was training session)
Incomplete outcome data (attrition bias) All outcomes	High risk	18 families were dropped, denominator not clear
Selective reporting (reporting bias)	High risk	Denominators not clearly reported

Krasinski 1990

Methods	Controlled before and after study conducted in Bellevue Hospital Center, New York, USA, to determine the effectiveness of screening for RSV and assignment to a cohort at admission to reduce nosocomial transmission of RSV infections. Children who were 3 years of age and older were admitted to a paediatric ward that is equipped with private rooms for the control of communicable diseases. Children younger than 3 years of age were admitted to a separate ward without private rooms, where as many as 4 children shared a room. All paediatric patients hospitalised on or before 31 December 1986 were

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Krasinski 1990 *(Continued)*

	regarded as potentially infected with RSV and were constituted as an RSV-infected cohort. A second cohort, free of infection with RSV, was established on the toddlers' ward to segregate high-risk patients from RSV-infected patients. Patients requiring hospital admission and assignment to the high-risk cohort were screened for evidence of RSV infection by means of a rapid ELISA method. No gloves or masks were used in the RSV cohort
Participants	All hospitalised paediatric patients regarded as potentially infected with RSV
Interventions	RSV screening cohorting and service education programme versus do nothing
Outcomes	The authors concluded that screening and subsequent cohorting reduced RSV infections (from 5.33 infections per 1000/patient days of care to 1.23 infections per 1000/patient days after introduction of screening). There was an attempt at correlation between RSV admissions and RSV community circulation
Notes	Risk of bias: medium Notes: the authors concluded that screening and subsequent cohorting reduced RSV infections (from 5.33 infections per 1000/patient days of care to 1.23 infections per 1000/patient days after introduction of screening). There was an attempt at correlation between RSV admissions and RSV community circulation

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	N/A
Allocation concealment (selection bias)	Unclear risk	N/A
Blinding (performance bias and detection bias) All outcomes	Unclear risk	N/A
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	N/A
Selective reporting (reporting bias)	Unclear risk	N/A

Krilov 1996

Methods	Controlled before and after study carried out in a 16 classrooms of special needs school for Down Syndrome children in New York State. The study took place between November 1991 and November 1993. The 'before' period between November 1991 and October 1992, followed by a 1-month washout period during which the intervention was introduced, followed by 12 months of 'after' period (December 1992 to November 1993)
Participants	33 children aged 6 weeks to 5 years took part in the 'before' and 38 in year 2 ('after' period). During the study period there were about 110 children in the school but the parents of the majority did not agree to replying to 2-weekly questionnaires, so their children were not entered in the study. In addition 5 sets of questionnaires in the 'before' and 2 in the 'after' periods did not contain sufficient data (6 months' worth) and were excluded. Despite this there were no significant differences between 'before' and 'after' children. The authors also describe viral circulation during the study periods from isolates in

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Krilov 1996 *(Continued)*

	the local hospital. All community isolates were constant with the exception of adenovirus which doubled in the 'after' period of the study
Interventions	Training and sanitary programme with handwashing, disinfection of school buses, appliances and toys. In addition a person designated a study monitor carried out intensive monitoring of classroom behaviour and reinforced messages. Disinfection took place with Reckitt & Colman products (sponsors of the study)
Outcomes	Laboratory: viral isolates from surrounding community (non-random samples) Effectiveness: ARI (cough, runny nose, sore throat, wheezing or rattling in the chest, ear ache). Vomiting and diarrhoea (data not extracted). Follow up was carried out on the basis of parents' questionnaire Safety: N/A
Notes	Risk of bias: high (disinfectants provided and study sponsored by manufacturer) Notes: the authors concluded that respiratory illnesses decreased from a median of 0.67 to 0.42 per child per month (P < 0.07), physician visits, 0.50 versus 0.33 (P < 0.05), mean course of antibiotics prescribed 0.33 versus 0.28 (P < 0.05) and days of school missed because of respiratory infections 0.75 versus 0.40 (P < 0.05). Respiratory illnesses decreased from a median of 0.67 to 0.42 per child per month. Small study with a serious selection bias and generalisability problems

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	N/A
Allocation concealment (selection bias)	Unclear risk	N/A
Blinding (performance bias and detection bias) All outcomes	Unclear risk	N/A
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	N/A
Selective reporting (reporting bias)	Unclear risk	N/A

Ladegaard 1999

Methods	RCT with cluster-randomisation to intervention or control. Out of 10 institutions they excluded 2 because they wanted institutions to be comparable in uptake area (that means housing and income). Interventions were given to children, parents and teachers at the institutions
Participants	Children 0 to 6 years old
Interventions	Multifaceted: information, t-shirts to the children with: "Clean hands - yes, thank you", performance of a fairytale "The princess who did not want to wash her hands", exercise in handwashing, importance of clean and fresh air. The aims of the intervention were: - to increase the hygiene education of the daycare teachers - to motivate the children by practical learning to have a better hand hygiene - to inform the parents about better hand hygiene

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Ladegaard 1999 *(Continued)*

Outcomes	34% decrease in 'sickness' (probably mostly gastroenteritis)
Notes	Risk of bias: limited data only available Notes: the authors conclude that there was a 34% decrease in sickness in the intervention arm, this is probably overall sickness as gastroenteritis is part of the outcomes (data no extracted). Limited data only available from translation by Jørgen Lous

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Unclear risk	Randomisation by "lottery", the same as "flip the coin" Concealment not reported
Blinding (performance bias and detection bias) All outcomes	High risk	Not possible
Incomplete outcome data (attrition bias) All outcomes	High risk	No total numbers of children included in each arm reported
Selective reporting (reporting bias)	High risk	Limited data reported, especially denominators missing

Larson 2010

Methods	Cluster block-randomised, controlled trial carried out between 20 November 2006 and 20 June 2008 in an upper Manhattan immigrant Latino neighbourhood ("19 month data collection period"). The study aimed at assessing the effects of eduction versus education and hand sanitiser use versus education and hand sanitiser use and common mask use against upper respiratory infections over a period of under 2 years. Follow up was though an automated telephone system with a small financial incentive (USD 20) for those with 75% or more compliance. Those reporting an ILI received a visit within 48 hours for swabbing An index case was someone who at the "onset day of illness nobody else in the household had been symptomatic within the previous five days" A secondary case for each episode "was any member of the household who developed symptoms within five days following the index case", "The secondary attack rate was defined as the number of secondary cases recorded within 5 days of the onset of symptoms in the index case divided by the number of household members minus one" The text implies that the unit of observation was the episode ("study subjects contributed more than one episode in which they were considered to be the index case")
Participants	Recruitment and allocation were carried out by household. These had to have at least 3 people living in the household, with at least 1 being a preschool or elementary school child, speaking English or Spanish, having a telephone willingness to complete symptom assessments and having bimonthly home visits and not using alcohol-based hand sanitiser routinely 617 households were randomised, 211 to the education, 205 to the hand sanitiser and 201 to the hand sanitiser and mask groups. The participants were 2708, mostly adult Latino immigrants to the USA

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Larson 2010 *(Continued)*

	Intracluster correlation coefficients are reported on page 179 of the manuscript
Interventions	Written Spanish or English language educational materials regarding the prevention and treatment of URTIs and influenza or the same educational materials and hand sanitiser (Purell, J&J), in large (8- and 4-ounce) and small (1-ounce) containers to be carried by individual household members to work or school or the same interventions as well as regular surgical face masks (Procedure Face Masks for adults and children, Kimberly-Clark) with instructions for both the caretaker and the ill person to wear them when an ILI occurred in any household member. Replenishment of intervention stocks was done at the bimonthly home visit Caretakers had to wear a mask for 7 days when within 3 feet of a symptomatic case. These were also encouraged to wear masks within 3 feet of any household member. Reinforcing phone calls were made 3 times in 6 days The text clearly reports active influenza vaccine promotion during the bi-monthly visits ("The home visit to each household was made every 2 months to minimise study dropout, reinforce adherence to the assigned intervention, replenish product supplies and record use of supplies, answer questions, and correct ongoing misconceptions. At each visit, new educational materials regarding URTI prevention and treatment and influenza vaccination were distributed." (PDF page 3). Also just before the Discussion as follows: "Influenza vaccination rates: There was an increase between the baseline and exit interview in all three groups that reported 50% of more of members receiving influenza vaccine (pre- versus post-intervention for each group: 21.1% and 40.8% in the Education group, 19.0% and 57.1% in the hand sanitiser group, and 22.4% and 43.5% in the hand sanitiser and face mask group (P = 0.001). Additionally, those in the hand sanitiser group reported a significantly greater increase than the other 2 groups, controlling for baseline rates (P = 0.002)" Coverage was unequal across groups, no information on the progressive impact of the vaccine, or indeed the nature of the vaccine(s) is reported. Apparently the first season was mild and the vaccine mismatched, compliance with the trial interventions was low in Arm 3 and a local epidemic of *S. aureus* meant that the control group started washing hands The authors report no effect on reporting rates of vaccine coverage by arms but with so many confounders who knows?
Outcomes	Laboratory: PCR carried out on samples from deep nasal swabs for influenza and the most common other pathogens (RSV, rhinovirus, enterovirus, parainfluenza viruses etc.). The text describing the results of the swabbing is confusing but in general appears to be non-random "Households reported 669 episodes of ILI (0 to 5 per individual)". Of the 234 deep nasal swabs obtained, 33.3% (n = 78) tested positive for influenza; 43.6% (n = 34) were influenza A and 56.4% (n = 44) were influenza B. Among the 66.7% who tested negative for influenza, 30.8% (48/156) tested positive for other viruses: 7 for respiratory syncytial virus, 9 for parainfluenza, 11 for enterovirus, 10 for rhinovirus, 6 for adenovirus, and 5 for metapneumovirus. Swabs were not obtained from the remaining 435 reported ILI episodes for the following reasons: 72.0% (n = 313) did not meet the CDC definition of an ILI and were therefore included in the URTI symptom count, 21.4% of episodes (n = 93) were reported after 48 hours of ILI onset or the participant refused to be swabbed, and the research staff were unable to reach the participant in 6.7% of episodes (n = 29) As no definition of URTI is given it is unclear what kind of biases are introduced by the non-swabbing of the 313/435 "not meeting CDC definition". Effectiveness: ILI (CDC definition): "temperature of 37.8°C or more and cough and/or sore throat in the absence of a known cause other than influenza" URTI only referred to as "Viral upper respiratory infections (URTIs)" Safety: N/A
Notes	The authors conclude that "the Hand Sanitizer group was significantly more likely to report that no household member had symptoms (P,0.01), but there were no significant differences in rates of infection by intervention group in multivariate analyses. Knowledge improved significantly more in the Hand Sanitizer group (P,0.0001). The proportion of households that reported >50% of members receiving influenza vaccine increased during the study (P,0.001). Despite the fact that compliance with mask wearing was poor, mask wearing as well as increased crowding, lower education levels of caretakers,

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Larson 2010 *(Continued)*

and index cases 0–5 years of age (compared with adults) were associated with significantly lower secondary transmission rates (all P,0.02). In this population, there was no detectable additional benefit of hand sanitiser or face masks over targeted education on overall rates of URTIs, but mask wearing was associated with reduced secondary transmission and should be encouraged during outbreak situations. During the study period, community concern about methicillin-resistant *Staphylococcus aureus* was occurring, perhaps contributing to the use of hand sanitiser in the Education control group, and diluting the intervention's measurable impact".

The study is at high risk of bias. Randomisation and reasons for dropout are not described. Differentials in cluster characteristics across arms point to randomisation not having worked and the confounding effects of a post-randomisation staphylococcal scare is difficult to judge. Symptom-driven follow up gives no idea of the effects on asymptomatic ILI/influenza. Poor definitions (URTI?). There are unexplained dropouts and the analysis plan is unclear. Finally the very small number of cases of influenza and an unclear swabbing attrition may introduce further elements of confounding

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"Cluster block randomised, controlled trial", but sequence generation not reported
Allocation concealment (selection bias)	Unclear risk	"Households were block randomised into one of three groups:" Allocation concealment not reported
Blinding (performance bias and detection bias) All outcomes	High risk	Not possible
Incomplete outcome data (attrition bias) All outcomes	High risk	In 211 control group HH 26 dropped out and 37 did not consent In 205 hand sanitiser group HH 21 dropped out and 36 did not consent In 201 hand sanitiser and face mask group HH 19 dropped out and 35 did not consent Reasons for dropout not described
Selective reporting (reporting bias)	Unclear risk	617 of 772 eligible households were randomised HH in groups comparable

Lau 2004a

Methods	Case-control study carried out in Hong Kong, SARS of China during 4 April to 10 June 2003, at the height of the SARS outbreak. The aim was to describe the defined and undefined sources of SARS cases groups and assess the protective effects of various public health measures Defined sources were classified as being a healthcare worker in a hospital, living in Amoy Gardens (a known focus of infection) having had a contact with a member of the household with SARS of earlier onset, hospital in patients infected with SARS by other hospital inpatients and contacts of SARS cases before the onset of their own symptoms The undefined sources group of cases were all the other categories Cases in general were identified and interviewed on the phone. Households with more than 1 index case were considered as having 2 index cases. Of the 1690 identified cases, 1214 from 996 households were enrolled in the study. 140 cases could not be contacted as they had a wrong phone number, 163 were uncontactable after at least 5 attempts, 163 refused to take part and 10 did not speak either Chinese or English. 17 were further excluded because they were aged less than 16. 22 questionnaires were

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Lau 2004a *(Continued)*

	unusable. (This makes 1175, obviously the 17 minors are included in the case-control study, as adding them makes a total of 1192)
Participants	Description of cases: 330 probable cases of SARS selected as follows. From 1192 people with probable SARS reported to the Department of Health in the territory of HK up to 16 May 2003, 1175 were entered in the case-control analysis. SARS cases were defined as Xray evidence of pulmonary infiltration consistent with pneumonia with a temperature of > 38°C or a history of such in the previous 2 days and at least 2 of the following: history of chills in the previous 2 days new or increased cough, breathing difficulty, general malaise of myalgia, typical signs of consolidation and known exposure to SARS. The authors say that this definition is the same the WHO's case definition of probable SARS. At interview, risk factors were elicited and identified. There were 727 cases in the defined source category and 347 in the undefined sources category (330 after exclusion of 17 minors) Description of controls: 660 controls of undefined origin and with no description of selection
Interventions	Natural exposure to SARS during a serious epidemic
Outcomes	Community transmission of SARS reduced OR 0.30 (95% CI 0.23 to 0.39)
Notes	Risk of bias: medium (inconsistencies in the text: lack of description of controls) Notes: the authors conclude that community transmission was of less importance than previously thought and public health measures worked. The following risk factors were significantly associated with SARS (matched multivariate analysis OR with 95% CIs): - Visit to mainland China 1.95 (1.11 to 3.42) - Visited Prince of Wales Hospital 7.07 (1.62 to 30.75) - Visited other hospitals 3.70 (2.54 to 5.39) - Visited Amoy Gardens 7.63 (3.77 to 15.43) The following activities/interventions had a significant protective function: - Thorough disinfection of living quarters 0.41 (0.29 to 0.58) - Wore a mask in public places frequently 0.36 (0.25 to 0.52) - Washed hands 11 or more times a day 0.58 (0.38 to 0.87) Potentially a very interesting study possibly rigorously conducted let down by a very confusingly written text. The biggest problem is lack of clarity as to who the controls were. This may be a reflection of the pressure of carrying out a study in the midst of a serious epidemic

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	N/A
Allocation concealment (selection bias)	Unclear risk	N/A
Blinding (performance bias and detection bias) All outcomes	Unclear risk	N/A
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	N/A
Selective reporting (reporting bias)	Unclear risk	N/A

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Leclair 1987

Methods	Controlled before and after study conducted in children's hospital of Boston, USA, to determine whether increased compliance with a policy of glove and gown isolation precautions could reduce the high rate of nosocomial RSV infection on an infant and toddler ward. All patients admitted to the 28-bed infant and toddler medical ward during 3 consecutive RSV seasons (1982 to 1985) were included in the study. When patients with known or suspected RSV infection were admitted, an attempt was made to place them in single rooms or to group them together, but infected patients were frequently required to share rooms with susceptible patients during the winter months, when the prevalence of RSV on the wards is highest. The RSV season was defined as the 24 weeks each year starting at the beginning of November and continuing through the end of April. All the documented cases of RSV infection occurred during that period, and all the patients and patient-days during that interval on the study ward were recorded. RSV infections were classified as nosocomial if symptoms developed 5 or more days after the patient's admission to the hospital. All cases of RSV infection were confirmed virologically. During the first half of the study nursing staff wore both gloves and gowns for only 20 of 52 observed contacts. During and after the second compliance survey, compliance rapidly increased: nursing staff wore both gloves and gowns for 73 of 90 of their contacts
Participants	695 patients aged from 5 days to 4 years and 11 months. The distribution of ages was similar in the 2 periods. 37 acquired nosocomial RSV infections
Interventions	Infection-control intervention to increase use of gloves and gowns versus no intervention
Outcomes	Laboratory: yes Effectiveness: RSV infection Safety: N/A
Notes	Risk of bias: low Notes: the authors concluded that the incidence of nosocomial RSV infection rose with the intensity of hospital exposure and that this rise was markedly different in the periods before and after intervention. The use of gloves and gowns can reduce the nosocomial transmission of RSV, particularly with increasing exposure to patients shedding the virus (RR for pre and post-intervention periods infection rates 2.9, 1.5 to 5.7). Compliance by the staff improved dramatically after the intervention and it continued even after the end of the study, probably because the favourable results of the intervention were well-publicised, the head nurse introduced an educational programme emphasising the appropriate application of isolation precautions, and gowns and gloves became more accessible to care givers. The study, although prone to selection bias, is better designed than some of it peers as there is an attempt at adjusting for different levels of RSV circulation by sub-analysis by virus shedding days by the infected participants

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	N/A
Allocation concealment (selection bias)	Unclear risk	N/A
Blinding (performance bias and detection bias) All outcomes	Unclear risk	N/A
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	N/A
Selective reporting (reporting bias)	Unclear risk	N/A

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Leung 2004

Methods	Prospective cohort study conducted during 13 March to 29 June 2003 in the paediatric department of the Prince of Wales Hospital at the height of the SARS epidemic in Hong Kong, China. The aim of the study was to test the effectiveness of procedures to stop transmission of SARS from infected children to carers and visitors
Participants	26 HCWs in close contact with probable or suspected SARS and 88 HCWs in contact with patients in other study areas during the study period
Interventions	Triage and UHR-S isolation and strict infection control procedures versus triage and UHR-S isolation and less strict infection control procedures Healthcare workers were exposed to 9 children with probable SARS and 29 with suspected SARS admitted into the Ultra High Risk SARS (UHR-S) areas with a mean age of 8.9 years, 88 children with pneumonia but no SARS contact with a mean age of 8.2 admitted to the isolation cubicle of the Ultra High Risk Infection (UHR-I) area, 227 with febrile illness and normal chest radiograph aged 4.9 years treated in an open cubicle in the UHR-I area and 274 non-febrile children with a mean age of 7.5 years admitted into the High Risk (HR) area. The study tested the effectiveness of triage and UHR-S isolation + strict infection control procedures versus triage and UHR-S isolation + less strict infection control procedures Triage at admission aimed at identifying children aged less than 18 who: - were febrile or afebrile with a known SARS contact who were admitted to the UHR-S area - with a positive CXR and a SARS contact who were admitted to the UHR-S area - with CXR changes but no SARS contact who were admitted to the UHR-I area - were febrile or afebrile but no SARS contact who were admitted to the HR area Very strict infection control measures were implemented on entry and exit from the UHR-S area (handwashing, gown, caps, goggles, mask, upper and trousers of cloth operating theatre garments and N95 face respirator for HCWs, all measures but no goggles or undergarments for visitors and handwashing and mask for patients) Less strict infection control measures were implemented on entry and exit from the UHR-I area (handwashing, gown, goggles, mask, upper and trousers of cloth operating theatre garments and N95 face respirator for HCWs, and handwashing and mask for visitors and patients), Even less strict infection control measures were implemented on entry and exit from the HR area (handwashing, gown, caps, goggles, mask, upper and trousers of cloth operating theatre garments and mask of N95 face respirator for HCWs and handwashing and paper mask for visitors and patients) Enforcement was directed by a police nurse in the UHR areas
Outcomes	Laboratory: laboratory confirmation of SARS Effectiveness: probable or suspected SARS according to WHO definitions Safety: N/A
Notes	Risk of bias: low Note: the authors conclude that the measures worked well as no HCW or visitor became ill. This is a remarkably well-conducted and clearly reported study in the midst of a major infectious disease outbreak with a previously unknown agent. The Prince of Wales Hospital had previously witnessed an outbreak in which an index patient had infected 138 healthcare workers. All the more remarkable as the paediatric department had not been built as isolation facility and had to be rapidly reorganised

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	N/A
Allocation concealment (selection bias)	Unclear risk	N/A

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Leung 2004 *(Continued)*

Blinding (performance bias and detection bias) All outcomes	Unclear risk	N/A
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	N/A
Selective reporting (reporting bias)	Unclear risk	N/A

Liu 2009

Methods	The paper is a re-analysis and publication in English of Ma 2004, a case-control study carried out shortly after the SARS outbreak at the Armed Forces Hospital (AFH) in Beijing in which 16 HCW died. The data from Ma 2004 had been published in Chinese only. The paper assesses relationships between protective and risk factors in cases and controls using a 2-step analysis procedure: univariate analysis and then multivariate analysis for those associations found significant up to the 10% level
Participants	Description of cases - 51 HCW (age mean 29.5 years) who were admitted to AFH during 5 March to 17 May 2003 with clinical features fitting WHO's SARS criteria. All enrolled analysed cases subsequently proved to be IgG SARS positive (1 case was excluded because he/she was negative). Probable cases of SARS are defined as: documented fever (temperature > 38°C), presence of cough, shortness of breath or breathing difficulty, and a significant history of exposure to a SARS patient not more than 10 days prior to onset of symptoms, plus radiographic evidence of infiltrates consistent with pneumonia or respiratory distress syndrome (RDS) on chest X-ray (CXR) (World Health Organization criteria, 2003). The text mentions that cases were 76% (51 of the 67) "survived" staff in the AFH Description of controls; 426 HCW (age mean 31.4 years) working in AFH during the same period as cases with self-reported exposure to SARS but had no symptoms (the text says "uninfected"). All enrolled analysed controls subsequently proved to be IgG SARS negative and their exposure within 1 month of a SARS case was confirmed. These are 90% of AFH employees exposed to SARS.
Interventions	Exposure and risk or protective factors were subsequently elicited by questionnaire and interviews in June to July 2003: gender, age, ethnic group, educational level, co-morbidity, smoking status, alcohol intake, contact date, occupation, department, contacts with SARS and exposure time. None of these factors proved to be significant in a multivariate analysis. At univariate analysis 17 variables were significantly associated with SARS, 10 of which were protective (i.e. negative association): - wearing a 12-layer cotton surgical mask - wearing 16-layer cotton surgical mask (and wearing layers of mask) - wearing glasses - wearing gloves - wearing goggles - wearing multiple layers of protective clothing - taking "prophylactic medicine" (such as "antivirals" and vitamin supplements), performing nose washes after contact and having training prior to exposure N95 mask use was non-significant probably because of the rarity of its use At multivariate analysis level, 12 and 16-layer mask non-use and not undergoing training, not taking medicine and not wearing multiple layers of masks were found to be associated with SARS onset
Outcomes	Laboratory: all clinically diagnosed hospital-acquired SARS cases confirmed by + SARS-CoV IgG ELISA and all controls confirmed by a - SARS-CoV IgG ELISA Effectiveness: univariate and multivariate analysis among the 28 variables elicited in questionnaires and by interview

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Liu 2009 *(Continued)*

Notes	The authors conclude that "this study identified exposure to high-risk procedures (such as chest compression), and contact with respiratory secretions to be significant risk factors for SARS infection among HCWs in a hospital in Beijing. These results also provide confirmation that personal protective measures against droplet spread, such as wearing multiple layers of mask, are effective against the nosocomial spread of SARS" The main points to bear in mind when interpreting this study are: - the possibility of selection bias in cases (only living cases were recruited whereas we know that 16 HCWs in AFH died) - protective variables are not well-defined (i.e. the make or type of masks used, whether fitted or not) - information on the 10 protective interventions (variables) was elicited post hoc with a possibility of recall bias (mentioned by the authors in their Discussion) - the lack of reporting of numerator and denominator data for cases and controls - the apparent lack of mention of data assessment and analysis blinded to case or control status - failure to attempt matching between cases and controls and the partly prospective nature of the study design

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	N/A
Allocation concealment (selection bias)	Unclear risk	N/A
Blinding (performance bias and detection bias) All outcomes	Unclear risk	N/A
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	N/A
Selective reporting (reporting bias)	Unclear risk	N/A

Loeb 2009

Methods	Open non-inferiority randomised, controlled trial carried out to compare the surgical mask with the N95 respirator in protecting healthcare workers against influenza. The trial was carried out between 2008 (enrolment started in September and follow up on 12 January 2009) and 23 April 2009 (when all HCWs were told to wear a N95 respirator for all HCWs caring for febrile patients because of the appearance of novel A/H1N1). The trial trigger was the beginning of the influenza season defined as isolation of 2 or more viruses in a district in the same week. Following the 2003 SARS outbreak all Ontario nurses caring for febrile patients (38 °C or more and new onset cough or SOB) had to wear surgical masks. The randomisation (carried out in blocks of 4 by centre) then consisted of either confirmation to same-maker surgical mask wear or N95 respirator wear. Investigators and laboratory staff were blind to allocation status, but for obvious reasons (the visible difference in interventions), participants were unblinded. "The criterion for non-inferiority was met if the lower limit of the 95% confidence interval (CI) for the reduction in incidence (N95 respirator minus surgical group) was greater than -9%". So this is the non-inferiority margin. It is assumed that the "minus surgical group" means minus surgical mask group.
Participants	Consenting nurses (n = 446 randomised) aged a mean of 36.2 years working full time (≥ 37 hours/week) in 23 acute units (a mix of paediatric, A&E and acute medical units) in 8 hospitals in Ontario, Canada. 225 were randomised to the surgical mask and 221 to the N95 respirator. There were 13 and 11

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Loeb 2009 *(Continued)*

	dropouts respectively from each arm (all accounted for) plus 21 and 19 lost to follow up. 11 in each arm gave no reason, the others are accounted for. There were no deaths. The final total of 212 and 210 was included in the analysis. Table 1 reports the demographic data of participants by arm, which appear comparable
Interventions	Surgical masks (as standard wear by the standard distributor) or fit–tested N95 respirator. All nurses wore gloves or gowns in the presence of a febrile patient
Outcomes	Laboratory RT-PCR paired sera with 4-fold antibody rise from baseline (only for unvaccinated) nurses Effectiveness: follow up (lasting a mean of around 97 days for both arms) was carried out twice-weekly on a web-based instrument. Nurses with new symptoms were asked to swab a nostril if any of the following signs or symptoms had developed: fever (temperature ≥ 38°C), cough, nasal congestion, sore throat, headache, sinus problems, muscle aches, fatigue, earache, ear infection or chills The text defines influenza with laboratory-confirmation and separately reports criteria for swab triggering and a definition of ILI ("Influenza-like illness was defined as the presence of cough and fever: a temperature ≥ 38°C"). But this is not formally linked to influenza in the text as it appears that primary focus was the detection of laboratory-confirmed influenza (either by RT-PCR or serology) Additional outcome data sought were work-related absenteeism and physician visits for respiratory illness Secondary outcomes included detection of the following non-influenza viruses by PCR: parainfluenza virus types 1, 2, 3 and 4; respiratory syncytial virus types A and B; adenovirus; metapneumovirus; rhinovirus-enterovirus; and coronaviruses OC43, 229E, SARS, NL63 and HKU1 Audits to assess nurse compliance with the interventions were carried out in the room of each patient cared for. The text reports that 50 and 48 nurses in the surgical mask and N95 groups respectively had laboratory confirmation of influenza infection, indicating non-inferiority. Interestingly non-inferiority seemed to be applicable both to seasonal viruses and nH1N1 viruses (as 8% and 11.9% were serologically positive to nH1N1). This finding is explained either by seeding or cross reaction with seasonal H1N1. Equivalent conclusions could be drawn for nurses with complete follow up. Non-inferiority was applicable also to other ILI agents identified. None of the 52 persons with positive isolates met the criteria for ILI All cases of ILI were confirmed as having influenza (9 and 2 respectively). This means that all the 11 cases of ILI had influenza but that most of those with a laboratory diagnosis of influenza did not have cough and fever. For example the text reports that "Of the 44 nurses in each group who had influenza diagnosed by serology, 29 (65.9%) in the surgical mask group and 31 (70.5%) in the N95 respirator group had no symptoms". By implication of the 88 nurses with antibody rises 28 had symptoms of some kind, i.e. two-thirds were asymptomatic. Absenteeism was 1 versus 39 episodes in the mask versus respirator arms. No episodes of LRTI were recorded. The number of family contacts with ILI were the same for each arm (45 versus 47). Physician visits were similar in both groups Safety: no AEs are reported
Notes	The authors conclude that "Among nurses in Ontario tertiary care hospitals, use of a surgical mask compared with a N95 respirator resulted in non-inferior rates of laboratory-confirmed influenza" This a well-designed and conducted trial with credible conclusions. The only comment is that the focus in the analysis on influenza (symptomatic and asymptomatic) is not well-described, although the rationale is clear (interruption of transmission)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Randomisation was performed centrally ...."

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Loeb 2009 *(Continued)*

Allocation concealment (selection bias)	Low risk	"...by an independent clinical trials coordinating group such that investigators were blind to the randomisation procedure and group assignment and was stratified by centre in permuted blocks of 4 participants."
Blinding (performance bias and detection bias) All outcomes	Low risk	Outcome assessment blinded: "It was not possible to conceal the identity of the N95 respirator or the surgical mask since manipulating these devices would interfere with their function. Laboratory personnel conducting hemagglutinin inhibition assays, polymerase chain reaction (PCR), and viral culture for influenza were blinded to allocation."
Incomplete outcome data (attrition bias) All outcomes	Low risk	21 of 225 randomised in mask group and 19 of 221 randomised in N95 group were lost to follow up, reasons reported Study stopped early: "We had planned to stop the study at the end of influenza season. However, because of the 2009 influenza A(H1N1) pandemic, the study was stopped on April 23, 2009, when the Ontario Ministry of Health and Long-Term Care recommended N95 respirators for all healthcare workers taking care of patients with febrile respiratory illness."
Selective reporting (reporting bias)	Low risk	All outcomes reported

Longini 1988

Methods	Cluster-controlled, double-blind, randomised trial to assess the efficacy of virucidal tissues in interrupting family transmission of rhinovirus and influenza virus. The study was carried out in the community of Tecumseh, Michigan, USA during the period 25 November 1984 to 28 April 1985. However, the authors only report results for the period 13 January to 23 March 1985, when a high circulation of influenza A H3N2 and rhinovirus was detected
Participants	296 households were enrolled but for "technical reasons" 5 household were eliminated from the analysis. The analysis was carried out in households with 3 to 5 members. The authors report data on 143 households randomised to virucidal tissues and 148 to placebo tissue. Average age in households was around 22 and the difference between arms was not significant. Randomisation was carried out by the sponsor and tissues were pre-packed in coded boxes with no other identifying features and delivered to households at the beginning of the study period
Interventions	Disposable 3-layered virucidal tissues (citric and malic acids with sodium lauryl sulphate in the middle layer) or placebo (succinic acid in the middle layer) tissues. They were used to blow the nose and for coughing or sneezing into Households were also stratified by level of tissue use. Tissue use was significantly higher in the intervention arm (82% versus 71%)
Outcomes	Laboratory: yes - viral culture from nasal and throat swabs from symptomatic participants Effectiveness: ARI (with a proportion of laboratory-confirmed diagnosis in non-randomly chosen participants with symptoms lasting 2 days or more) Follow up and surveillance was carried out using a telephone questionnaire Safety: N/A
Notes	Risk of bias: high (inappropriate choice of placebo) Notes: the authors conclude that virucidal tissues were up to 36.9% effective in preventing transmission of ARIs as measured by secondary attack rates (18.7% versus 11.8%). This was not significant but may well have been affected by the lack of do-nothing community controls. This a well-designed, well-written study despite the unexplained attrition of 5 families, the lack of reporting of cluster coefficients and the differential in tissue use between the 2 arms which raises questions about the robustness of double-blinding. Particularly notable is the discussion on the low generalisability of results from the study from the placebo arm given that even the inert barrier of the tissues is a likely to have limited

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Longini 1988 *(Continued)*

	spread. Also the lengths to which the authors went to obtain allocation concealment and maintenance of double-blind conditions

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"Treated and placebo tissues were randomly assigned ..." Sequence generation not reported
Allocation concealment (selection bias)	Low risk	"Treated and placebo tissues were randomly assigned by the sponsor to 296 participating households stratified by household size, such that roughly half the households would receive treated tissues. Thus, the investigators were unaware of the assignment of treated tissues."
Blinding (performance bias and detection bias) All outcomes	Low risk	"The type of tissue was identified by code, and the boxes in which tissues were contained were not marked with any specific identifiers. Therefore, the study was double-blinded."
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	296 HH eligible. "The final sample used for analysis consisted of 143 households in the treatment group and 148 households in the placebo group."
Selective reporting (reporting bias)	High risk	"The analysis of secondary spread was restricted to households of three to five members for technical reasons, which eliminated five households." "The two groups were almost identical in composition."

Luby 2005

Methods	Partly double-blind, cluster-randomised controlled trial carried out during 15 April 2002 to 5 April 2003 in Karachi, Pakistan. The trial assessed the effects of mother and child handwashing on the incidence of respiratory infections, impetigo (data not extracted) and diarrhoea (data not extracted) Randomisation took place by computer-generated random numbers in 3 phases: - 25 neighbourhoods were assigned to handwashing and 11 to standard practice - 300 households assigned to using antiseptic soap - 300 households assigned to using plain soap - 306 households assigned to standard practice - 1523 children younger than 15 years assigned to using antiseptic soap - 1640 children younger than 15 years assigned to using plain soap - 1528 children younger than 15 years assigned to standard practice Soaps were identical weight, colour and smell and were packed centrally with a coded packing case matched to households containing 96 bars. Neither field workers not participants were aware of the content. Control arm households were visited with the same frequency as intervention household but were given books and pens. Codes were held centrally by the manufacturer and broken after the end of the trial to allow analysis
Participants	Householders of slums in Karachi. Of the 1523 children younger then 15 years assigned to using antiseptic soap 117 dropped out (1 died, 51 were born in and 65 aged out) = 1406; 504 were aged less than 5 Of 1640 children younger then 15 years assigned to using plain soap 117 dropped out (3 died, 44 were born in and 70 aged out) = 1523; 517 were aged less than 5 1528 children younger then 15 years assigned to standard practice 125 dropped out (3 died, 40 were born in and 82 aged out) = 1403; 489 were aged less than 5

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Luby 2005 *(Continued)*

Interventions	Instruction programme and antibacterial soap containing 1.2% triclocarban, or ordinary soap to be used throughout the day by householders or standard procedure
Outcomes	Laboratory: N/A Effectiveness: - Number of new respiratory illness per person per week - Pneumonia (cough or difficulty in breathing with a respiratory rate of > 60 min in children less than 60 days old, > 50 min in those less than 1 year old and > 40 min for those aged 1 to 5 years) Follow up was weekly with household interview and direct observation. Children aged less than 5 were weighed and the report presents stratification of results by child weight Safety: N/A
Notes	Risk of bias: low (cluster coefficients and analysis by unit of randomisation provided) Notes: the authors conclude that "handwashing" neighbourhoods has significantly less episodes of respiratory disease than controls (e.g. 50% less cough). "Handwashing" children aged less than 5 had 50% less episodes of pneumonia than controls (-65% to -35%). However there was no difference in respiratory illness between types of soap. The report is confusing, with a shifting focus between children age groups. The impression reading is of an often re-written manuscript. There is some loss of data (for example in the results by weight, i.e. risk group) because of lack of clarity on denominators. Despite this, the trial is a landmark.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation took place by computer-generated random numbers in 3 phases:
Allocation concealment (selection bias)	Low risk	"One of the investigators (SL) who did not participate in recruiting neighbourhoods or households programmed a spreadsheet to randomly generate the integers of a 1 or a 2. He applied the random numbers sequentially to the list of neighbourhoods. Neighbourhoods with a 1 were assigned to control, and those with a 2 were assigned to handwashing promotion. Random assignment continued until neighbourhoods consisted of at least 600 handwashing promotion households and 300 control households were assigned."
Blinding (performance bias and detection bias) All outcomes	High risk	Not blinded
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	89% of the study population followed up, but no data on the clusters
Selective reporting (reporting bias)	Low risk	"At baseline, households in the three intervention groups were similar."

Macartney 2000

Methods	Controlled before and after study with economic evaluation (data not extracted) carried out over 8 RSV seasons in 1988 to 1996. The study assessed the impact of a programme for the interruption of transmission of RSV in a children hospital in Philadelphia, USA. Analyses are presented both by risk group (exposure to patients by days of viral shedding) and as aggregate. Only for the latter numerators and denominators are provided, whereas for the former figures are presented in bar chart format

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Macartney 2000 *(Continued)*

Participants	Children with community-acquired RSV infection and the inpatient children exposed to them (1604 in 4 seasons before and 2065 in the "after the intervention" seasons. Children were aged around 1 year and those with risk factors were equally spread (51% versus 54%) in the 2 periods
Interventions	Education with high index of suspicion for case-finding with barriers (but no goggles or masks) and handwashing for patients and staff with contact precautions for RSV + patients for 2 weeks with isolation (when possible) with cohorting of patients and staff with enhanced surveillance with restriction of visits with discouragement of staff with ARIs from working unprotected in SCBU
Outcomes	Laboratory: ELISA confirmation of RSV infection on all children admitted with respiratory symptoms. In a proportion of cases RSV culture was undertaken, although this had a minimal practical impact as any child with respiratory symptoms was considered as a RSV case Effectiveness: clinically-defined RSV cases contracted nosocomially (with symptoms appearing after at least 6 days from admission) Safety: N/A
Notes	Risk of bias: low Notes: the authors conclude that 10 RSV infections were prevented per season (RR for post-intervention compared to pre-intervention periods 0.61, 95% CI 0.53 to 0.69). The study is well-reported and the conclusions appear reasonable, but no information is given on the background rate of infection and the impact of the intervention on HCW morbidity is not analysed

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	N/A
Allocation concealment (selection bias)	Unclear risk	N/A
Blinding (performance bias and detection bias) All outcomes	Unclear risk	N/A
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	N/A
Selective reporting (reporting bias)	Unclear risk	N/A

MacIntyre 2009

Methods	Prospective cluster-randomised trial carried out in Sydney, Australia, to assess the use of surgical masks, P2 masks and no masks in preventing influenza-like illness (ILI) in households. The study was carried out during the 2 winter seasons of 2006 and 2007 (August to the end of October 2006 and June to the end of October 2007). “Gaussian random effects were incorporated in the model to account for the natural clustering of persons in households"
Participants	290 adults from 145 families; 47 households (94 enrolled adults and 180 children) were randomised to the surgical mask group, 46 (92 enrolled adults and 172 children) to the P2 mask group, and 52 (104 enrolled adults and 192 children) to the no-mask (control) group
Interventions	Use of surgical masks and P2 mask versus no mask. The P2 mask is described as very cumbersome

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MacIntyre 2009 *(Continued)*

Outcomes	Laboratory: serological evidence Effectiveness: Influenza-like illness (ILI) (described as fever, history of fever or feeling feverish in the past week, myalgia, arthralgia, sore throat, cough, sneezing, runny nose, nasal congestion, headache) However, a positive laboratory finding for influenza converts the ILI definition into one of influenza Safety:N/A
Notes	The authors conclude that adherence to mask use significantly reduced the risk for ILI-associated infection, but < 50% of participants wore masks most of the time. We concluded that household use of face masks is associated with low adherence and is ineffective for controlling seasonal respiratory disease. Compliance was by self-report – therefore likely to be an underestimate The primary outcome was ILI or lab-positive illness. This showed no effect Sensitivity analysis by adherence showed that under the assumption that the incubation period is equal to 1 day (the most probable value for the 2 most common viruses isolated, influenza (21) and rhinovirus (26)), adherent use of P2 or surgical masks significantly reduces the risk for ILI infection, with a hazard ratio equal to 0.26 (95% CI 0.09 to 0.77; P = 0.015). No other covariate was significant. Under the less likely assumption that the incubation period is equal to 2 days, the quantified effect of complying with P2 or surgical mask use remains strong, although borderline significant; hazard ratio was 0.32 (95% CI 0.11 to 0.98; P = 0.046). The study was underpowered to determine if there was a difference in efficacy between P2 and surgical masks (Table 5). The study conclusion appears to be a post-hoc data exploration. Regardless of this the study message is that respirator use in a family setting is unlikely to be effective as compliance is difficult unless there is a situation of real impending risk

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Participating households were randomised to 1 of 3 arms by a secure computerised randomisation process:"
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding (performance bias and detection bias) All outcomes	Low risk	"Study participants and trial staff were not blinded, as it is not technically possible to blind the mask type to which participants were randomised. However, laboratory staff were blinded to the arm of randomisation."
Incomplete outcome data (attrition bias) All outcomes	Low risk	143 families of 145 randomised were analysed; 2 families in the control group were lost to follow up during the study. No reason was given for this
Selective reporting (reporting bias)	Low risk	No differences between groups at baseline

Madge 1992

Methods	Prospective cohort study conducted in 4 medical wards of the Royal Hospital for Sick Children in Glasgow, UK, to evaluate the effectiveness of 4 infection control procedures in preventing nosocomial infection with RSV. This is an interruption of transmission study. Every child up to 2, irrespective of clinical presentation, had respiratory secretions tested for RSV antigen within 18 hours of admission. Nosocomial infection was assumed if a child become RSV positive 7 days or more after admission. Children after discharge from hospital were not studied

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Madge 1992 *(Continued)*

Participants	No special precaution group 152 (winter 1); gowns/gloves 337 (winter 1 and 2); cohort nursing 265 (winter 1 and 2); cohort nursing and gowns/gloves 310 (winter 1 and 2); 1001 (winter 3)
Interventions	Stepwise intervention programmes: gowns/gloves; cohort nursing + gowns/gloves; cohort nursing, versus no special precautions. The procedures evaluated in the 2 winter periods were gowns/gloves; cohort nursing + gowns/gloves; cohort nursing, versus no special precautions. In the third year the most effective strategy was introduced into all ward areas and its efficacy in clinical practice was assessed. There was not separate area for managing children with infections
Outcomes	Laboratory: yes - culture, antibodies titres, serological studies Effectiveness: RSV infections (seroconversion within 7 days of admission) Safety: N/A
Notes	Risk of bias: low Notes: the authors conclude that combined with rapid laboratory diagnosis, cohort nursing and the wearing of gowns and gloves for all contacts with RSV-infected children can significantly reduce the risk of nosocomial RSV infection (odds reduced to between 1.27% to 75.6%). One confounding effect that was not accounted for in the study design was a possible "ward effect". For practical reasons, 2 wards (3 and 4) continued with the same policy over the first 2 years of the study. Since it was also necessary apply policies to whole wards there is a possibility that ward 4 might have been especially effective at implementing their assigned policy

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	N/A
Allocation concealment (selection bias)	Unclear risk	N/A
Blinding (performance bias and detection bias) All outcomes	Unclear risk	N/A
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	N/A
Selective reporting (reporting bias)	Unclear risk	N/A

Makris 2000

Methods	Prospective cohort study carried out in 8 private, freestanding long-term care facilities located in New Jersey and Delaware, to determine the impact of an ongoing infection control intervention programme in reducing the incidence of nosocomial infections. The 8 facilities were selected on the basis of similarity with respect to admission rate, size, acuity levels, availability of services, overall infection rates, in-house environmental service departments. Resident populations were comparable in terms of age, sex and underlying disease. The 8 facilities were grouped into 4 sets of matched pairs. Within each pair, each home was designated at random as either a test site or a control site. The results was that 4 facilities (2 urban and 2 suburban, with a total of 443 beds), were selected as test sites and another 4 facilities, 2 urban and 2 suburban, with a total of 447 beds, were selected as control sites

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Makris 2000 *(Continued)*

Participants	443 beds (patients) in the test group, 447 beds (patients) in the control group. We assumed number of beds as number of participants.
Interventions	Infection-control education programme reinforcing handwashing and other hygienic measures versus normal care
Outcomes	Laboratory: no Effectiveness: upper respiratory infections Safety: N/A
Notes	Risk of bias: high (internal inconsistencies) Notes: the authors conclude that infection control education measures that reinforce handwashing and other hygienic measures helps reduce the number of organisms present on hands and surfaces and may have contributed to the non-significant reduction of URTIs (the opposite is reported in the paper: incidence density rate of 4.15/1000 patient days in the test homes versus 3.15/1000 patient days in the control homes) showed in this study. We assumed number of beds as number of participants to the study, but we do not know the characteristics of the patients (age, sex, underlying conditions, etc.). The authors confuse a cohort design with a before and after design and in the report they confusingly use both terms and reach conclusions not supported by the evidence presented

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	N/A
Allocation concealment (selection bias)	Unclear risk	N/A
Blinding (performance bias and detection bias) All outcomes	Unclear risk	N/A
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	N/A
Selective reporting (reporting bias)	Unclear risk	N/A

Master 1997

Methods	Prospective cohort study conducted in an elementary school, Detroit, to evaluate the effect of a mandatory scheduled handwashing programme on absenteeism due to acute communicable illness (including upper respiratory disease). Classrooms were divided into either control or experimental groups without formal randomisation. Six classrooms were assigned to the handwashing group and 8 classrooms were assigned to the control group. Data were collected for 37 school days. Information about absent children was recorded daily by the school secretary. Symptoms were used to classify students as having respiratory or gastrointestinal illness. Upper respiratory infections and gastrointestinal symptoms (data not extracted) were not considered mutually exclusive
Participants	14 classrooms including 305 healthy, predominantly upper middle-class children ranging from ages 5 to 12. All grade levels from kindergarten through fifth grade were included. Six classrooms (143 students) were the handwashing group and 8 classrooms (162 students) were the control group

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Master 1997 *(Continued)*

Interventions	Handwashing programme versus usual practice. Children in the handwashing group were asked to wash their hands after arrival at school, before eating lunch, after lunch recess, and before going home. Children in the control group washed at their normal frequency. All children in both groups washed with the school soap, which was not antibacterial
Outcomes	Laboratory: no Effectiveness: upper respiratory infections (URTI) - cough sneeze, pink eye, headache, mononucleosis, acute exacerbation of asthma, sinus trouble, fever alone, bronchitis Safety: N/A
Notes	Risk of bias: high Notes: the authors conclude that handwashing among children can be effective in preventing transmission of disease, but the difference in days of absence is statistically significant only for gastrointestinal symptoms (RR for ARIs 0.79, P = 0.756). Limitations in the study design are: use of a discrete population without socio-economically diverse backgrounds, use of a single institution, lack of blind assessment, low specificity of symptoms, and lack of accurate symptom definition

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	N/A
Allocation concealment (selection bias)	Unclear risk	N/A
Blinding (performance bias and detection bias) All outcomes	Unclear risk	N/A
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	N/A
Selective reporting (reporting bias)	Unclear risk	N/A

Morton 2004

Methods	Cross-over study to evaluate the effectiveness of an alcohol gel as an adjunct to regular handwashing for decreasing absenteeism among elementary children by reducing specific communicable diseases such cold, flu and conjunctivitis. The study was conducted in an elementary school in New England, US. In the cross-over design classrooms in each grade level were randomised to begin as the experimental group (alcohol gel) or the control group (regular handwashing). A study protocol for hand hygiene was introduced following the germ unit education. The handwashing product was a soap and water alternative that is approximately 60% ethyl alcohol. In phase 1 (46 days) children in 9 classrooms were in the experimental group, and children in 8 classrooms were in the control group. After a 1 week washout period when no children had access to the alcohol gel, Phase 2 (47 days) started, and the classroom that had participated before as an experimental group passed in the control group and vice versa. Data were collected by the parents that informed the secretary or the school nurse of the reasons for a child's absence, including symptoms of any illness. Respiratory illnesses were defined by symptoms of URTI
Participants	253 children, 120 girls and 133 boys, from kindergarten to 3rd grade. 32 children dropped out (10 due to skin irritation and 22 because of lack of parental consent)

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Morton 2004 *(Continued)*

Interventions	Use of an alcohol gel as an adjunct to regular handwashing and educational programme versus regular handwashing and educational program
Outcomes	Laboratory: no Effectiveness: days of absences from school for respiratory illness Safety: N/A
Notes	Risk of bias: high (no description of randomisation; partial reporting of outcomes, numerators and denominators) Notes: the authors conclude that significantly fewer children became ill while using the alcohol gel as an adjunct to regular handwashing than when using regular handwashing only (decreased school absenteeism of 43% with the use of alcohol gel on top of handwashing). The authors also described, as a limitation of the study, the fact that the school nurse served as the data collector, and this could be perceived as bias in measurement of the outcome variable Randomisation and allocation are not described, there are no cluster coefficients reported and attrition is not taken into consideration during the analysis. Unit of randomisation and analysis are different. No reporting by arm. No ORs, no CIs reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	N/A
Allocation concealment (selection bias)	Unclear risk	N/A
Blinding (performance bias and detection bias) All outcomes	Unclear risk	N/A
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	N/A
Selective reporting (reporting bias)	Unclear risk	N/A

Murphy 1981

Methods	Prospective cohort study carried out in the Children's Hospital, Denver, to examine the effect of using gowns, masks and handwashing on the acquisition of symptomatic respiratory infections by medical personnel caring for infants with respiratory disease
Participants	58 people of nursing, medical, respiratory therapy personnel; 30 in the handwashing group, 28 in the handwashing, masks and gowns. Seventy HCWs initially were available for enrolment, 9 refused to take part and 3 withdrew
Interventions	Handwashing versus handwashing, masks and gowns
Outcomes	Laboratory: yes Effectiveness: viral infections (including RSV) Safety: N/A
Notes	Risk of bias: medium

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Murphy 1981 *(Continued)*

	Notes: the authors conclude that there was no difference between the 2 groups with respect to number of viral infections (i.e. 4/30 in the handwashing group versus 5/28 in the handwashing gown and masking group (P > 0.20). The findings cannot demonstrate any effect of adding the use of both gown and mask to the usual handwashing routine on the development of illness in personnel caring for infants with respiratory disease. Possible reasons for lack of effect are: the heavy exposure all adults have to respiratory viral illness in the community at large; poor compliance to the study protocol, modes of virus spread which would not be blocked by the use of mask and gown

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	N/A
Allocation concealment (selection bias)	Unclear risk	N/A
Blinding (performance bias and detection bias) All outcomes	Unclear risk	N/A
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	N/A
Selective reporting (reporting bias)	Unclear risk	N/A

Niffenegger 1997

Methods	Prospective 2-centre cohort study assessing the effects of a handwashing programme in Indiana, USA. Two centres were enrolled for the August to December 1994 (21 weeks) study: a test and a control centre
Participants	Eight teachers and 26 children (aged 3 to 5) in the test group and 12 children and 8 teachers in the control group. According to the authors, age, experience gender and socioeconomic variables were equally distributed between the 2 groups, but data are not shown. No attrition is mentioned
Interventions	Three weekly cycles of teachings, handwashing routine encouragement for children, parents and staff and correct sneezing and coughing procedure. Follow up was weekly filling in of a teacher report. It is unclear from the text what happened in the control site, or indeed if they were fully aware of the project
Outcomes	Laboratory: N/A Effectiveness: colds and ARIs no better defined Safety: N/A
Notes	Risk of bias: high (wide range of incidence of infections) Notes: the authors conclude that during the first 11 weeks of the study the test centre had double the incidence of colds compared to the control centre this is explained by the author as caused by the influx of new children bringing in new viruses in the test centre. In the second period the reverse was true, explained as the stabilising of the population and the taking effect of the programme. The list of potential confounders and biases is countless. For example there is only a very cursory description of participants in both arms and the role of teachers especially in the control centre is not explained

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Niffenegger 1997 *(Continued)*

The test group had significantly fewer colds than the control group (P < 0.05)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	N/A
Allocation concealment (selection bias)	Unclear risk	N/A
Blinding (performance bias and detection bias) All outcomes	Unclear risk	N/A
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	N/A
Selective reporting (reporting bias)	Unclear risk	N/A

Nishiura 2005

Methods	Case-control study carried out during the SARS outbreak (26 February 2003 to 28 April 2003) in Hanoi, Vietnam. The study aimed at assessing the relationship between SARS infection and behaviour. The study population was based at the Hanoi French Hospital (HFH) and followed the outbreak during 3 phases. The first phase (26 February to 4 March 2006) in which an index case and 9 suspected secondary cases were admitted/cared for. The second phase (8 March to 11 March 2003) in which outpatients were closed and staff no longer returned home as the outbreak spread and the third phase (11 March 2003 to 28 April 2003) in which the HFH was closed to all other then SARS cases who were isolated
Participants	Description of cases: 29 surviving people with laboratory confirmed SARS cases either admitted and retained or transferred to other hospitals. Nine cases did not take part (5 died, 1 refused and 3 had relocated). Twenty-eight were HCWs employees of the HFH and 1 a relative of a patient. Substantial exposure and behaviour were documented through observation and questionnaires Description of controls: 90 people aged > 20 who provided written consent with substantial SARS exposure, 57 of whom were HFH employees
Interventions	Handwashing before contact with SARS patient Handwashing after contact with SARS patient Masks Gloves Gowns All measures combined Analysis by epidemic stage is reported
Outcomes	SARS infection
Notes	Risk of bias: low Notes: the authors conclude that masks (OR 0.3, 95% CI 0.1 to 0.7) and gowns (OR 0.2, 95% CI 0.0 to 0.8) were significantly associated with protection during phase 1 but in Phase 2 masks (OR 0.1, 95% CI 0.0 to 0.3) and all measures (OR 0.1, 95% CI 0.0 to 0.3) were associated with protection probably because of

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Nishiura 2005 *(Continued)*

	the increased awareness of the danger of the outbreak and increase us of measures - this is confirmed by the results of the mathematical model in the second part of the study. A well-written and reported study

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	N/A
Allocation concealment (selection bias)	Unclear risk	N/A
Blinding (performance bias and detection bias) All outcomes	Unclear risk	N/A
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	N/A
Selective reporting (reporting bias)	Unclear risk	N/A

Ou 2003

Methods	Retrospective cohort study carried out in selected precincts of Haidian district of Beijing, People's Republic of China between March and May 2003 during the epidemic of SARS (attack rate 19/100,000 population in the period March to July). Precincts were chosen on the basis of the highest number of quarantinees. The study aimed at assessing the risk of acquiring SARS among quarantinees. A better definition of the risk would help in future to identify better candidates for quarantine and target resources accordingly. The study was based on a questionnaire-based survey on the reasons for quarantine. SARS diagnosis for contacts was independently carried out from lists
Participants	171 SARS cases (29% of total) were identified in the precincts and 1210 persons (23%) quarantined from the selected districts (contacts). These were sampled from a total population of 2.24 million, with 5.186 quarantinees. Response rate was 85% (1.028 quarantinees who completed the questionnaire, of which 232 developed probable SARS while in quarantine)
Interventions	Quarantine at home or hospital for 14 days post-exposure (reduced to 10 and then to 3). Quarantine is defined as the separation and or restriction of movement of persons who due to recent exposure to a communicable disease risk acquiring the disease and transmitting to third parties. A contact was defined as: - Healthcare worker not using personal protective equipment (PPE) when caring for/assessing a SARS case: - other persons caring for a SARS case - persons sharing accommodation with a SARS case - persons visiting a SARS case - persons working with a SARS case - classmates or teachers of a SARS case - persons sharing the same means of public transport with a SARS case All quarantinees were followed up daily and were admitted to hospital if they developed fever (38 °C or more)
Outcomes	Laboratory: no

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Ou 2003 *(Continued)*

	Effectiveness: definition of SARS was based on criteria of Chinese Ministry of Health. Definition was clinical and not based on laboratory isolation of the SARS-CoV Safety: N/A
Notes	Risk of bias: high Notes: the authors conclude that only those quarantinees who actually had home or hospital contact with a symptomatic SARS patient developed the illness (attack rate 31.1, 95% CI 20.2 to 44.4 for carers, 8.9%, 95% CI 2.9 to 22.1 for visitors, 4.6%, 95% CI 2.3 to 8.9 for those who lived with a SARS case) but not those living in the same building or working with them and not contacts of any SARS case during the incubation period. Fever was also not a good reason to quarantine people (attack rate nil). Quarantine also appeared to prevent transmission, although there were numerous cases in which quarantine was not required. There are several limitations to the conclusion of the study Non-random basis for the sample, selection bias of the sample and responders, recall bias of responders and the absence of a laboratory-confirmed diagnosis may have affected the conclusion one way or another Overall, not enough denominator data, non-exposed data are given to allow data extraction or calculate OR

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	N/A
Allocation concealment (selection bias)	Unclear risk	N/A
Blinding (performance bias and detection bias) All outcomes	Unclear risk	N/A
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	N/A
Selective reporting (reporting bias)	Unclear risk	N/A

Pang 2003

Methods	Ecological study describing and analysing the effects of public health measures on the SARS epidemic between 5 March and 29 May 2003 in Beijing, China. Data were collected from centralised notification and close contact databases
Participants	2521 probable SARS cases mostly hospitalised aged around 33 (407 or 16% were HCWs) and 192 of these who died out of a total population of 13.6 million people. The peak took place on 25 April with 173 hospitalised cases
Interventions	SARS was made notifiable on 9 April and contact tracing commenced a day later. On 18 April 62,363 of the estimated 85,000 Beijing HCWs received training in the management of SARS cases and were issued gowns, gloves, masks. By 17 April, 123 fever clinics were opened, however these were contiguous to hospitals and it is thought that some transmission occurred By 21 April quarantine of close contacts was underway (these were only allowed to leave quarantine in exceptional circumstances and only wearing a mask) and fever check at airports were begun the day after. By 24 April all schools and universities closed. Two days later public meeting places (bars, libraries etc) were closed. From 27 April all SARS cases were placed in designated hospital wards and by 8 May SARS cases were only sent to designated hospitals. By 1 May a SARS hospital of 1000 beds built in 1

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Pang 2003 *(Continued)*

	week was opened and received only SARS cases (40% of total cases). The last cases were registered on 26 May. The highest attack rate (14.5%) of quarantined people was those of spouses of SARS cases
Outcomes	Laboratory: laboratory testing for the presence of SARS-CoV was not part of the case definition Effectiveness: probable SARS cases (close contact of a SARS sufferer with signs and symptoms of febrile respiratory disease and chest X-ray changes, or person visiting of residing in an area with recent SARS activity and with signs and symptoms of febrile respiratory disease and chest X-ray changes and lack of response to antibiotics or person visiting of residing in an area with recent SARS activity and with signs and symptoms of febrile respiratory disease and chest X-ray changes and normal or decreased WBC count) Safety: N/A
Notes	Risk of bias: low Notes: the authors conclude that in virtue of the shape of the epidemic curve it is likely that the combination of measures taken before the 25 April helped contain the spread of SARS. Although there may be alternative explanations this appears to be the most likely explanation of the facts. Hospitals were seen early on as sources of transmission of the SARS Co-V. The authors seem to doubt the direct effectiveness of entry port (for example, airports, stations, etc.) checks (12 cases identified out of over 13 million people screened). They think screening was more useful to keep away sick people

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	N/A
Allocation concealment (selection bias)	Unclear risk	N/A
Blinding (performance bias and detection bias) All outcomes	Unclear risk	N/A
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	N/A
Selective reporting (reporting bias)	Unclear risk	N/A

Pelke 1994

Methods	Controlled before and after study conducted in a neonatal intensive care unit (NICU) of Kapiolani medical centre, Honolulu, Hawaii, to assess the effect of gowning on RSV and other infections, on traffic and handwashing patterns. Alternate 2-month gowning and no-gowning cycles were established in a 24-bed NICU for 8 months. One entire 4-month cycle was repeated to eliminate the potential for seasonal variables and outbreaks. All the people entering into the NICU (physicians, nursing staff, ward clerks, families and visitors) wore gowns. During the no-gowning periods nursing staff wore hospital-issued pantsuit, washed at home through ordinary methods and worn from home. Ward clerks, physicians, hospital staff, families and visitors wore street clothes without gowns. Throughout the entire 8-month period, there was the recommendation for all staff and visitors to enforce initial 2-minute hand-scrub. Nails were cleaned before scrubbing, and a minimum 15-second handwash between infants or equipment was expected. Surveillance cultures were done weekly on all patients. Without the knowledge of the NICU staff, a neonatal research nurse scheduled observations of traffic patterns, while ostensibly reviewing charts, to determine if a lack of gowning procedures encourage more traffic. Handwashing

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Pelke 1994 *(Continued)*

	compliance was studied, again without staff awareness, by 30 minutes direct observation. Follow up of infection rates was planned through standard infection control surveillance
Participants	230 infants, aged 22 to 42 weeks, with birth a weight of 464 to 6195 grams. Overall there were 330 infants admitted to NICU during the study period. Thus 17% of participants had no RSV cultures taken. The reasons given are vague (transfer or death)
Interventions	Use of gowns and standard procedures (handwashing) versus standard procedures
Outcomes	Laboratory: serological evidence: yes Effectiveness: RSV infection Safety: N/A
Notes	Risk of bias: medium (17% loss to follow up) Notes: the authors conclude that gowning did not protect NICU infants from any type of infection or affect mortality (1.21 versus 1.38/100 patient-days of gowning and no-gowning periods respectively). Gowning procedures did not deter staff or visitors from entering the unit, since traffic was also unchanged between periods. Finally the results showed no change in handwashing patterns between periods. Besides the advantage of eliminating a potentially unnecessary ritual that may be perceived as a psychological barrier to families visiting their infants, other benefits to discontinuing gowning include saving staff time involved in various gowning procedures and costs. If gowns are eliminated, it is recommended to perform careful follow up. The study conclusions must be taken with caution given the likely selection bias introduced by the missing 17% of children

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	N/A
Allocation concealment (selection bias)	Unclear risk	N/A
Blinding (performance bias and detection bias) All outcomes	Unclear risk	N/A
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	N/A
Selective reporting (reporting bias)	Unclear risk	N/A

Roberts 2000

Methods	Open cluster-RCT carried out between March and November 1996 (the southern hemisphere winter season) in 23 child care centres caring for a minimum of 50 children 10 hours a day, 5 days a week in Australia. The study assessed the effects of an Australian national handwashing programme compared to standard procedure. Randomisation was according to a random number table and cluster coefficients are reported
Participants	Children (299 in the intervention arm and 259 in the control arm) aged 3 or younger attending the centres at least 3 days a week. Attrition was 51 children in the intervention arm and 72 children in the control arm due mainly to staff leaving the centres

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Roberts 2000 *(Continued)*

Interventions	Handwashing programme with training for staff and children. It is unclear whether any extra hand cleansing agents were used, as GloGerm (?) is mentioned when it was used in a preliminary study
Outcomes	Laboratory: N/A Effectiveness: ARI (runny nose, cough and blocked nose) Follow up was via a parental phone interview every 2 weeks Safety: N/A
Notes	Risk of bias: low (cluster coefficients and analysis by unit of randomisation) Notes: the authors conclude that although there was no overall decrease in respiratory illness (RR 0.95, 95% CI 0.89 to 1.01), in children up to 24 months the decrease was significant (RR 0.90, 95% CI 0.83 to 0.97). The authors speculated that this was because maximum benefits are likely from this age group because of their limited ability to wipe their nose and hands without a structured programme. Analyses by 3 compliance levels are also reported. A so-so reported and well-conducted trial

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation was according to a random number table
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding (performance bias and detection bias) All outcomes	High risk	Not possible to blind the intervention
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Recruitment rate 88% (23 of 26 CCCs); loss to follow up not clear as no denominator given
Selective reporting (reporting bias)	Low risk	Centres comparable at baseline

Ryan 2001

Methods	Retrospective and prospective, controlled, before and after study carried out at the US Navy's Great Lakes recruit training centre in Illinois. Rates of respiratory disease were retrospectively calculated for recruits undergoing training for 3 periods: 1996, before the implementation of "Operation Stop Cough" and 1997 and 1998. To compare rates of respiratory illness with a similar community the authors also looked at the incidence of respiratory illness in a population of phase II sailors undergoing the second part of their training in the same camp. In addition a compliance questionnaire was also carried out during the latter 2 years of the study
Participants	Recruits undergoing training (44,797 in 1996; 47,300 in 1997; and 44,128 in 1998) mainly men, aged around 19 to 20 and a control population of phase II training sailors (no precise denominators given but around 10,000 yearly) who did not have a programme of handwashing
Interventions	Structured top-down programme of handwashing at least 5 times daily
Outcomes	Laboratory: N/A Effectiveness: respiratory illness detected from sick parade records and outgoing recruits questionnaire on a sample survey Safety: N/A

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Ryan 2001 *(Continued)*

Notes	Risk of bias: low Notes: the authors conclude that implementation of the control programme has seen near-halving of incidence of ARIs (based on 3 stratified samples of recruits infrequent handwashers had more self-reported episodes of ARIs (4.7 versus 3.2 per recruit, OR 1.5, 95% CI 1.2 to 1.8) and reported more hospitalisations (OR 10.9, 95% CI 2.7 to 46.2). Despite dramatic results, implementation was and continues to be difficult

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	N/A
Allocation concealment (selection bias)	Unclear risk	N/A
Blinding (performance bias and detection bias) All outcomes	Unclear risk	N/A
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	N/A
Selective reporting (reporting bias)	Unclear risk	N/A

Sandora 2005

Methods	Single-blind, cluster-randomised controlled trial carried around the Boston area, USA, in the period November 2002 to April 2003. The trial tested the effects of using a hand sanitiser and a programme of instruction on the transmissions of GI infections (data not extracted) and ARIs in families. Units of randomisation were childcare centres and were carried out on enrolment by an investigator using random block size generated by computer. Assignment was single-blind (i.e. investigator blinded to the status of the centre). Cluster correlation was 0.01
Participants	292 families with 1 or more children aged 6 months to 5 years who were in child care for 10 or more hours a week. There were 155 children in 14 centres allocated to the intervention arm and 137 children in 12 centres allocated to the control arm. The mean age was 3 to 2.7 years. Attrition was respectively 15 (3 lost to follow up and 12 who discontinued the intervention) and 19 (8 lost to follow up and 11 who discontinued the intervention). ITT analysis was carried out
Interventions	Alcohol-based hand sanitiser with bi-weekly hand hygiene educational materials over 5 months versus bi-weekly educational material on healthy diet
Outcomes	Effectiveness: ARI (2 of the following symptoms for 1 day or 1 of the following symptoms for 2 days: runny nose, cough, sneezing, stuffy or blocked nose, fever, sore throat). An illness episode had to be separated by 2 symptom-free days from a previous episode. A secondary illness was when it followed a similar illness in another family member by 2 to 7 days Follow up was by means of bi-weekly phone calls to care givers Safety: dry skin (71 reports), stinging (11 reports), bad smell (7 reports), dislike (2 reports), allergic reaction (2 reports), slippery feel (1 report) and irritation (20 reports)
Notes	Risk of bias: low

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Sandora 2005 *(Continued)*

	Notes: the authors conclude that although the rate of GI illnesses was significantly lower in the intervention group, the incidence rate ratio - IRR was not significantly different for ARIs (0.97, 95% CI 0.72 to 1.30). Compliance and droplet route spread may account for this apparent lack of effect. A well-reported trial

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Random assignments were generated by computer using a permuted-blocks design with random block sizes."
Allocation concealment (selection bias)	Low risk	"Assignments were concealed in opaque envelopes, and centers were assigned to control or intervention groups by a study investigator as they were enrolled."
Blinding (performance bias and detection bias) All outcomes	High risk	Blinding not possible
Incomplete outcome data (attrition bias) All outcomes	Low risk	Attrition was 15 in intervention arm (3 lost to follow up and 12 who discontinued the intervention) and 19 in the control arm (8 lost to follow up and 11 who discontinued the intervention). ITT analysis was carried out
Selective reporting (reporting bias)	Unclear risk	Well-reported

Sandora 2008

Methods	Cluster-randomised, controlled trial carried out in a single elementary school system located in Avon, Ohio, USA to assess the effectiveness of a multifactorial infection-control intervention, including alcohol-based hand sanitiser and surface disinfection, in reducing absenteeism caused by gastrointestinal and respiratory illnesses among elementary school students. The study also aimed to describe the viral and bacterial contamination of common surfaces in the school classroom and to assess the impact of an environmental disinfectant on the presence of selected viruses and bacteria on these surfaces. Clustering was described as "teams of 3-4 classes depending on the class year"
Participants	A total of 363 students in 15 different classrooms were eligible to participate and received letters about the study. A total of 285 of these students provided written informed consent and were randomly assigned to the intervention group (146) or to the control group (139). No students were lost to follow up or discontinued the intervention during the study period. Baseline demographic characteristics were similar in the intervention and control groups. Most families were white and non-Hispanic and in excellent or very good health at baseline
Interventions	Alcohol-based hand sanitiser to use at school and quaternary ammonium wipes to disinfect classroom surfaces daily for 8 weeks versus usual handwashing and cleaning practices
Outcomes	Laboratory: Serological evidence: no Swabs for bacteria and viruses from 3 types of classroom surfaces were taken Effectiveness: Respiratory illness defined as days absent as measured by a (blinded) school worker who routinely recorded reason for absenteeism either for gastrointestinal or respiratory causes Safety: N/A

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Sandora 2008 *(Continued)*

Notes	The authors conclude that multifaceted intervention that included alcohol-based hand sanitiser use and disinfection of common classroom surfaces reduced absenteeism from gastrointestinal illness among elementary school students. The intervention did not impact on absenteeism from respiratory illness. In addition, norovirus was detected less frequently on classroom surfaces in the group receiving the intervention. The study is good quality with low risk of bias. The authors checked compliance by counting discarded wipes. Reasons given for the apparent lack of effect against ARIs but good effect on GI illness are that disinfecting the classroom surfaces (daily at lunchtime with alkali) was important – as well as the alcohol wipes. The authors measured the norovirus concentration on surfaces and found this reduced. Other reasons may be that droplets are not affected by this method or that contamination of hands by respiratory infections is likely to be continuous (in orofaecal transmission is mostly at the time of defecation)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"The allocation sequence was generated by computer ..."
Allocation concealment (selection bias)	Unclear risk	"...and teams were assigned to study groups by a study investigator (Dr Shih)." Blinding of allocation cannot be guaranteed
Blinding (performance bias and detection bias) All outcomes	High risk	Not possible
Incomplete outcome data (attrition bias) All outcomes	Low risk	No students were lost to follow up or discontinued the intervention during the study period
Selective reporting (reporting bias)	Unclear risk	Well-reported

Satomura 2005

Methods	Randomised controlled trial, randomisation was achieved by simple computer-generated random digit. Allocation was concealed using sealed opaque envelopes. Not clear if there was a central randomisation centre. Post hoc exchange of envelopes was prevented by writing both the name of each subject and the number on the envelope he/she drew before breaking the seal. Participants were not blinded to the intervention, however, disease incidence was determined by 1 study physician who was not informed of the results of assignment. Analysis was done based on the intention-to-treat principle. The study targeted community healthcare all over Japan and was conducted between December 2002 and March 2003 for a follow-up period of 60 days
Participants	Three hundred and eighty-seven participants at 18 sites were recruited. Included in the analysis 384, follow up was completed on 338 participants. Attrition was fully explained for URTI analysis, however, 2 subjects were not accounted for in the ILI analysis. Forty-six participants did not complete the follow up due to either discontinuation of diary use (n = 9) or contracting influenza-like illness (ILI) (n = 37) Of the 37 participants with ILI, 11 were in povidone-iodine group, 12 in water group and 14 in control. Analysis was performed on 35 participants (Kitamura 2007)
Interventions	Participants were randomised to 1 of the following: water gargling, n = 122 (20 mL of water for about 15 seconds 3 times consecutively, at least 3 times a day); povidone-iodine gargling, n = 133 (20 mL of 15 to 30 times diluted 7% povidone-iodine (as indicated by the manufacturer) in the same way as water gargling); and control, n = 132 (retain their previous gargling habits)

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Satomura 2005 *(Continued)*

	All groups were asked to fill a daily gargling diary (standardised form to record: gargling habits, handwashing and influenza complaints) The frequency of gargling in the water group was higher (3.6), frequency of handwashing was similar between the 3 groups URTI symptom was classified according to Jackson methods. Diary recording was continued throughout the follow-up period and for 1 week after the onset of URTI. ILI were reported separately
Outcomes	Laboratory: none Effectiveness: primary outcome: incidence of first URTI. Index cases were defined as all of the following conditions: (1) both nasal and pharyngeal symptoms, (2) severity of at least 1 symptom increased by 2 grades or more, and (3) worsening of a symptom of 1 increment or more for > 3 days Secondary outcome: severity of URTI of the incident cases was assessed by grading each symptom during the initial 7 days after the onset of URTI in numeric scores: none = 0, mild = 1, moderate = 2 and severe = 3 ILI was defined as both developing a fever of 38 °C or higher, and worsening arthralgia in addition to some respiratory symptoms (Kitamura 2007) Safety: no harm was reported. However, 2 patients in the povidone group switched to water gargling (analysed in their assignment group)
Notes	The authors conclude that simple water gargling is effective to prevent URTIs among healthy people. However, no significant difference was observed against ILIs Study was well-conducted, blinding would have added to the validity of the results. In addition, the study was not powered enough to detect significant preventative effect against ILI The study demonstrated that in addition to handwashing, simple gargling even with simple water can reduce URTI but not ILI. However, during periods of endemic influenza, multiple inexpensive and simple modalities (handwashing, masks, gargling) can be utilised together to reduce infection and transmission. Overall, the reporting of the 2 combined studies together is highly confusing. In the first study (Satomura 2005) the main outcome is URTI defined as fever and arthralgia. The second study (which is a presentation of further data from the 2005 publication in the guise of a short report) introduces the outcome ILI with a definition similar to that of URTI in the first study but referring to the earlier outcome as common cold. Also of note is reporting of significance without confidence intervals. Overall this potentially important study should be repeated with a larger denominator Medium risk of bias because of confused reporting and absence of double-blinding

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Group assignment was based on simple computer-generated random digits..."
Allocation concealment (selection bias)	Low risk	"By an individual drawing of sealed opaque envelopes, subjects were randomly assigned to the following three groups" "allocation was completely concealed from study administrators"
Blinding (performance bias and detection bias) All outcomes	High risk	Not blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	338 of 385 randomised followed up; reasons reported

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Satomura 2005 *(Continued)*

Selective reporting (reporting bias)	Unclear risk	Confusing reporting

Seto 2003

Methods	Case-control study Hong Kong, China, conducted during the period 15 March to 24 March 2003 in 5 hospitals. The study aims were to assess the effectiveness of protective procedures for contracting SARS in HCWs exposed to 11 index cases in 3 of the 5 hospitals during the SARS epidemic
Participants	Description of cases: 13 HCWs infected with confirmed SARS within 2 to 7 days of exposure with no community exposure, 4 males and 9 females 2 doctors, 6 nurses, 4 healthcare assistants and 1 domestic staff who came into contact with SARS index cases. Only one used no protection measures and all omitted at least one of the protective measures required (handwashing, masks, gloves, gowns). Cases were identified through notification, which has been active since early February A SARS cases was defined as having fever of 38 °C or more, radiological infiltrates, and 2 of either: new cough, malaise, signs of consolidation Description of controls: 241 staff from the 5 hospitals who were not infected. The authors report that use of measures was elicited using questionnaires, 365 of which were returned (85% response rate). Non-responders were likely to be on leave or night shift. Data for 102 staff were excluded because they had no exposure to SARS
Interventions	Exposure was defined as coming within 0 to 91 metres (3 feet) of an index case with SARS symptoms when providing care. Recommended measures were handwashing, masks, gloves and gowns
Outcomes	SARS
Notes	Risk of bias: medium (inconsistencies in the text: lack of description of controls) Notes: the authors conclude that the 69 staff reporting use of all 4 measures were not infected, whereas all infected staff had omitted at least one measure. Simple analysis showed that masks, gowns and handwashing (OR 5, 95% CI 1 to 19) were effective but only masks (OR 13, 95% CI 3 to 60) were significant at logistic regression, possibly through lack of power. No blind assessment of cases and control data was carried out and 15% attrition of questionnaires may have introduced bias. The study was published as research letter in the Lancet, so possible lack of space may have affected reporting clarity

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	N/A
Allocation concealment (selection bias)	Unclear risk	N/A
Blinding (performance bias and detection bias) All outcomes	Unclear risk	N/A
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	N/A
Selective reporting (reporting bias)	Unclear risk	N/A

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Simon 2006

Methods	Prospective cohort surveillance study conducted in the University Children's Hospital in Bonn, Germany, to assess the global efficacy of a complex intervention programme to contain nosocomial transmission of RSV infections. This is a before-after design, with a multifactorial intervention carried out in one hospital
Participants	6548 paediatric patients admitted at the University Children's Hospital in the period of study (2200 in 1999 to 2000; 2298 in 2000 to 2001; 1959 in 2001 to 2002). 283 RSV infections were documented in 278 hospitalised paediatric patients: 138 in 1999 to 2000, 89 in 2000 to 2001, 56 in 2001 to 2002. Of the general population 244 events were ambulatory RSV infections and 39 nosocomial RSV infections
Interventions	Intervention strategy aimed at increasing vigilance to identify and isolate RSV-infected patients together with enforced contact precautions versus standard procedures. Interventions are not described very well: vigilance + cohorting versus vigilance versus standard practice
Outcomes	Laboratory: All RSV infections were confirmed by antigen detection or cell culture using MS cells Effectiveness: RSV infections no better defined clinically Safety: N/A
Notes	Risk of bias: low The authors conclude that the multi-factorial prevention strategy (early diagnosis, a strict cohorting and contact isolation policy, and prospective surveillance) probably contributed significantly to the reduced risk of nosocomial RSV infections in the hospital. In the pre-intervention period there were 39 cases (13.8%) nosocomial infections with an incidence density of 0.99/1000 patient-days; following the introduction of the surveillance and prevention policy there was a 9-fold decrease of the incidence (1.67 versus 0.18/1000 patient-days)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	N/A
Allocation concealment (selection bias)	Unclear risk	N/A
Blinding (performance bias and detection bias) All outcomes	Unclear risk	N/A
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	N/A
Selective reporting (reporting bias)	Unclear risk	N/A

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Snydman 1988

Methods	Controlled before and after study conducted during the winters of 1983-84 (retrospectively), 1984 to 1985 and 1985 to 1986 (prospectively) to assess whether the introduction of infection control measures halted transmission of RSV in a special nursery in Boston, USA. Record review for the retrospective part and prospective study for the 2 seasons following the introduction of infection control measures
Participants	HCW and patients in the special care baby unit
Interventions	From the 1984 to 1985 season the following were introduced: Active surveillance Extensive cohorting of patients and staff Respiratory precautions on suspicion of respiratory case Gown, mask and gloves used on contact Restricted visiting policy Segregation of cases
Outcomes	Laboratory: RSV culture Effectiveness: RSV cases with symptoms and laboratory confirmation Safety: N/A
Notes	Risk of bias: high Notes: the authors conclude that there were 7 cases in the season "before" and no cases in the following seasons (no transmission per 1000 patient days in the post-intervention period compared 8 per 1000 patient-days in the pre-intervention period). No denominators are provided (hence no data can be extracted) and exposure is generically quantified by aggregate patient-days of exposure. It is unclear how the circulation of RSV outside related to the claimed success of the measures, as no information is provided

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	N/A
Allocation concealment (selection bias)	Unclear risk	N/A
Blinding (performance bias and detection bias) All outcomes	Unclear risk	N/A
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	N/A
Selective reporting (reporting bias)	Unclear risk	N/A

Somogyi 2004

Methods	Prospective cohort study of 9 observations (3 each when using 3 different masks). The authors observed and photographed droplet dispersal while a volunteer breathed out 3 times in 3 different types of mask
Participants	1 volunteer

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Somogyi 2004 *(Continued)*

Interventions	Three masks, 2 without air filter and allowing external exhalation, 1 with manifold and air filter
Outcomes	Effectiveness: plume of droplets as observed and photographed: masks were poor at preventing droplet spread
Notes	Risk of bias: low Notes: the authors conclude that the mask with manifold and air filter did not allow dispersal of droplets and was far safer in an epidemic such as SARS to contain the spread. Simple, safe and effective study

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	N/A
Allocation concealment (selection bias)	Unclear risk	N/A
Blinding (performance bias and detection bias) All outcomes	Unclear risk	N/A
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	N/A
Selective reporting (reporting bias)	Unclear risk	N/A

Teleman 2004

Methods	Case-control study assessing risk and protective factors in HCWs during the SARS outbreak in Singapore (1 to 22 March 2003)
Participants	Description of cases: 36 HCWs admitted with probable SARS (according to WHO definition) during 1 to 31 March 2003. Six others were too ill to speak and 2 others died Description of controls: 50 HCWs working on the same wards who had definite exposure to SARS (physical proximity of 1 metre or less of a patient subsequently diagnosed as having SARS) but did not develop SARS
Interventions	Data on personal details and symptoms and exposure were gathered via a closed phone questionnaire. The 2 groups were comparable for demographic and epidemiological characteristics except that non-Chinese ethnic groups were twice as common among controls The following risk factors were assessed: Distance from source of infection < 1 metre Duration of exposure 60 or more minutes Wearing N95 respirator Wearing gloves Wearing gown Touched patients Touched patients' personal belongings Contact with respiratory secretions Performed venepuncture

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Teleman 2004 *(Continued)*

	Performed or assisted in intubation Performed suction of body fluids Administered oxygen Handwashing after each patient
Outcomes	SARS
Notes	Risk of bias: low Notes: the authors conclude that 3 factors were associated with significant risks or protection: Wearing N95 respirator OR 0.1 (95% CI 0.02 to 0.86) Contact with respiratory secretions OR 21.8 (95% CI 1.7 to 274.8) Handwashing after each patient OR 0.07 (95% CI 0.008 to 0.66) A well-reported study, let down by the failure to indicate whether assessment of risk factors had been carried out blindly to cases or control status. We wonder how much of the non-significance for certain factors is due to lack of statistical power

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	N/A
Allocation concealment (selection bias)	Unclear risk	N/A
Blinding (performance bias and detection bias) All outcomes	Unclear risk	N/A
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	N/A
Selective reporting (reporting bias)	Unclear risk	N/A

Turner 2004a

Methods	Double-blind randomised controlled trial conducted by Hill Top Research, Inc. Winnipeg, Canada, to assess the efficacy of acids with virucidal activity for the inactivation of virus and prevention of experimental rhinovirus colds. Subjects in good health, aged 18 to 60, were recruited from Winnipeg and surrounding communities for participation. Qualified subjects were randomised to treatment with vehicle (62% ethanol, 1% ammonium lauryl sulfate and 1% Klucel), vehicle containing 3.5% salicylic acid or vehicle containing 1% salicylic acid and 3.5% pyroglutamic acid. The volunteers' hands were disinfected and then test product was applied to both hands of each subject. Fifteen minutes after application, the fingerprints of each hand were contaminated with Rhinovirus type 39. The volunteers touched conjunctiva and the nasal mucosa only with the right hand. Viral contamination of the fingers was assessed in the left hands of the volunteers, and viral infection was assessed by culture of nasal lavage specimens and blood samples
Participants	85 volunteers, 31 control group, 27 used vehicle with 3.5% salicylic acid, 27 used vehicle with 1% salicylic acid and 3.5% pyroglutamic acid
Interventions	Use of salicylic acid versus salicylic acid and pyroglutamic acid versus "placebo" substance

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Turner 2004a *(Continued)*

Outcomes	Laboratory: yes Effectiveness: rhinovirus type 39 infection Safety: N/A
Notes	Risk of bias: unclear (no description of randomisation process, concealment or allocation) Notes: the authors concluded that organic acids commonly used in over-the-counter skin care and cosmetic products have substantial virucidal activity against rhinovirus. These preparations provided effective residual antiviral activity on the hands. The virucidal effect of these hand treatments resulted in a reduction in the incidence of rhinovirus infection in the treated volunteers (P = 0.025). The utility of this observation in the natural setting remains to be determined. The volunteers were not allowed to use their hands in the interval between the hand treatment and the virus challenge, so the effect of normal use of the hands on the virucidal activity of these organic acids is not known. Similarly, the virus challenge method used in these experiments may not simulate the natural setting in all aspects. The effect of nasal secretions that would be transferred with the virus in the natural setting on the activity of the acids or on the transmission of virus was not tested in the model We are unsure as to the practical significance of this study and the generalisability of its results to the real world. Poorly-reported study

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"randomised" Sequence generation not described
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding (performance bias and detection bias) All outcomes	Unclear risk	"double blind" but no description
Incomplete outcome data (attrition bias) All outcomes	Low risk	All accounted for (short study)
Selective reporting (reporting bias)	High risk	Poorly reported

Turner 2004b

Methods	Double-blind, randomised controlled trial conducted by Hill Top Research, Inc. Winnipeg, Canada, to assess the residual virucidal activity of a skin cleanser wipe and its effectiveness in preventing experimental rhinovirus colds. Subjects in good health and from 18 to 60 were recruited from Winnipeg and surrounding communities for participation The residual activity of a skin cleanser wipe containing 4% pyroglutamic acid formulated with 0.1% benzalkonium chloride was tested. The negative control treatment was 62% ethanol. Benzalkonium chloride had been previously tested and was found to have no virucidal activity. Volunteers were randomly assigned to use the control preparation or the active preparation. The study material was applied to hands with a towelette. Fifteen minutes later, when the fingers were completely dry, the fingertips of each hand of the control subjects and the volunteers in the active treatment group were contaminated with rhinovirus type 39. An additional volunteer in the active group were challenged with virus 1 hour after application and the final group of volunteers was challenged 3 hours after application. Viral infection was assessed by culture of nasal lavage specimens and blood samples

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Turner 2004b *(Continued)*

Participants	122 volunteers, 30 control group, 92 active group (30 tested after 15 minutes, 30 after 1 hour, 32 after 2 hours)
Interventions	Use of a skin cleanser wipe containing 4% pyroglutamic acid formulated with 0.1% benzalkonium chloride versus skin cleanser wipe containing ethanol
Outcomes	Laboratory: yes Effectiveness: rhinovirus type 39 infection Safety: N/A
Notes	Risk of bias: unclear (no description of randomisation process, concealment or allocation)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"randomised" Sequence generation not described
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding (performance bias and detection bias) All outcomes	Unclear risk	"double blind" but no description given
Incomplete outcome data (attrition bias) All outcomes	Low risk	All accounted for (short study)
Selective reporting (reporting bias)	High risk	Poorly reported

Wang 2007

Methods	Prospective cohort, surveillance study carried out to identify risk factors for development of SARS among quarantined persons in Taiwan. Two types of quarantine were implemented during the SARS outbreak in Taiwan: level A and level B quarantine. Level A quarantine was designed for persons who had known and, at times, had close exposure to persons infected with SARS in healthcare facilities and other community and domestic areas. Level B quarantine was designed for travellers who sat on the same flight within 3 rows of a person infected with SARS or were returning from World Health Organization–designated SARS-affected areas
Participants	During the study period 52,255 persons were placed under level A quarantine and 95,271 persons were placed under level B quarantine
Interventions	Exposure to level A quarantine versus level B
Outcomes	Laboratory: Serological evidence: yes Effectiveness: SARS (definition not reported) Safety: N/A

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Wang 2007 *(Continued)*

Notes	The authors conclude that focusing quarantine efforts on persons with known or suspected exposure can greatly decrease the number of persons placed under quarantine, without substantially compromising its yield and effectiveness. This is an important study, as it implies that risk banding can increase effectiveness and efficiency of quarantine procedures. The risk of bias is high as most of the answers to the NOS items are clearly no, however it is very difficult to get answers to a question such as the effectiveness of quarantine using any other design

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	N/A
Allocation concealment (selection bias)	Unclear risk	N/A
Blinding (performance bias and detection bias) All outcomes	Unclear risk	N/A
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	N/A
Selective reporting (reporting bias)	Unclear risk	N/A

White 2001

Methods	Double-blind, placebo-controlled, cluster-randomised trial that took place in 3 schools in California during March to April 1999. The study assessed the incremental value of using an alcohol hand rub together with water and soap handwashing. Both arms had been given an educational programme starting 2 weeks prior to the beginning of the trial. Randomisation was by classroom and the placebo hand rub was indistinguishable from the active ingredient. Details of randomisation are not given
Participants	Of the 72 classes originally recruited, lack of compliance (use of supplementary product at least 3 times a day), reduced the classes to 32 (16 in both arms) with 769 participants aged 5 to 12
Interventions	Pump-activated antiseptic hand rub with benzalkonium chloride (SAB) (Woodward Laboratories) or inert placebo that "virtually" looked the same in batches of 4 colour-coded bottles containing both. School staff, parents and participants were blinded
Outcomes	Laboratory: testing of virucidal and bactericidal activity of the active compound Effectiveness: ARI (cough, sneezing, sinus trouble, bronchitis, fever, red eye, headache, mononucleosis, acute exacerbations of asthma) Gastrointestinal and other illnesses (data not extracted) Follow up and observation was carried out by classroom staff and illnesses were described by parents Safety: 7 students dropped out because of mild sensitivity to the rub
Notes	Risk of bias: high (no description of randomisation; partial reporting of outcomes, numerators and denominators) Notes: the authors conclude that addition of the rub led to a 30% to 38% decrease of illness and absenteeism (RR for illness absence incidence 0.69, RR for absence duration 0.71). Very high attrition, unclear randomisation procedure, educational programme and use of placebo hand rub make generalisability of the results debatable. No confidence intervals reported

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White 2001 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"randomised trial", but sequence generation not described
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding (performance bias and detection bias) All outcomes	Low risk	Double-blind, placebo-controlled, cluster-randomised trial. Randomisation was by classroom and the placebo hand rub was indistinguishable from the active ingredient
Incomplete outcome data (attrition bias) All outcomes	High risk	Partial reporting of outcomes, numerators and denominators
Selective reporting (reporting bias)	High risk	Poor reporting

White 2003

Methods	Prospective, open, cohort study carried out at the University of Colorado, Boulder campus during 8 weeks in the autumn-winter of 2002. The study aimed at assessing the effects of hand hygiene on URTIs and absenteeism. Allocation was by residence hall with 2 halls doing "knowledge studies" being allocated, one to each arm
Participants	430 students aged around 18 mainly females were recruited but only 188 in the intervention cluster and 203 in the control cluster completed at least 3 weeks' follow up. Students were recruited with cash incentives. No reasons for attrition are given
Interventions	Education programme and alcohol gel adjunct to handwashing in residence halls versus standard hygiene
Outcomes	Laboratory: in vitro testing of the antibacterial and antiviral properties of the hand rub Effectiveness: URTI (at least 2 symptoms with one of them lasting at least 2 to 3 days. List of symptoms as follows: sore throat, stuffy nose, ear pain, painful/swollen neck, cough, chest congestion, sinus pain, fever, working days lost). Weekly surveys were carried out before during and after the study Safety: N/A
Notes	Risk of bias: medium Notes: the authors conclude that the intervention resulted in significantly fewer symptoms (reductions of 14.8% to 39.9 %) and absenteeism (40% reduction). Unexplained attrition and unknown effect of cash incentives. Relatively unclear definition of illness with a hint of a sensitivity analysis in the footer to a table

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	N/A

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White 2003 *(Continued)*

Allocation concealment (selection bias)	Unclear risk	N/A
Blinding (performance bias and detection bias) All outcomes	Unclear risk	N/A
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	N/A
Selective reporting (reporting bias)	Unclear risk	N/A

Wu 2004

Methods	Case-control study carried out on the Beijing SARS outbreak to assess the reasons for the insurgence of SARS cases in people who had no apparent contact with a SARS case
Participants	Description of cases: 94 probable or suspected SARS cases (Ministry of Health of China definitions) hospitalised during the period 28 April 2003 to 9 June 2003, aged 14 or more and non-HCWs with no known or reported no close contact with probably or suspected SARS cases. Fifty percent of cases were males with a median age of 29 years. The definition changed after 3 May to include those with symptoms who travelled to or resided in areas with known recent SARS activity but did not necessarily have contact with an index case. No laboratory confirmation of SARS was included in the definition which was purely practical (i.e. clinical-anamnestic). However antibody titres were taken several weeks after symptoms had abated. Close contacts (which played a part in the earlier case definition) were defined as persons who shared utensils, meals, residence hospital room or transportation vehicle with a suspected SARS or those who visited or came into contact with body fluids up to 14 days prior to the development of the index case's symptoms. Cases and controls were interviewed during the period 3 to 16 June Description of controls: 281 controls selected each by telephone random number change of last digits of the cases' phone numbers. This was aimed at providing neighbouring matching. Controls were interviewed by 4 July 2003 Seven controls (2 matched sets) were excluded because they were aged less than 14 and 7 matched sets were excluded because the case was reclassified as a HCW Cases and controls were interviewed for the 2 weeks preceding symptoms
Interventions	Always wearing a mask Intermittently wearing a mask Washing hands Owning a pet Visiting a farmer's market Visited clinics, eaten out or taken taxis
Outcomes	SARS
Notes	Risk of bias: medium (inconsistencies in the text: lack of description of controls) Notes: the authors conclude that cases were more likely than controls to have chronic pathologies (OR 4.1, 95% CI 1.8 to 9.3) or have visited fever clinics (OR 13.4, 95% CI 3.8 to 46.7), eaten out (OR 2.3, 95% CI 1.2 to 4.5) or taken taxis more than once a week (OR 3.2, 95% CI 1.3 to 8.0). In other words, unrecognised sources of transmission were present in the community. Always wearing a mask use was strongly protective (70% reduction in risk OR 0.3, 95% CI 0.2 to 0.7) and even wearing one intermittently with a smaller significant reduction in risk (OR 0.5, 95% CI 0.2 to 0.9) and so was always washing hands after returning home (OR 0.3, 95% CI 0.2 to 0.7) and owning a pet (OR 0.4, 95% CI 0.2 to 0.9) and visiting a

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Wu 2004 *(Continued)*

farmer's market (OR 0.4, 95% CI 0.2 to 0.8). Of great interest is the role of fever clinics in spreading the disease, probably because of poorly-implemented isolation and triage procedures. A fascinating study

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	N/A
Allocation concealment (selection bias)	Unclear risk	N/A
Blinding (performance bias and detection bias) All outcomes	Unclear risk	N/A
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	N/A
Selective reporting (reporting bias)	Unclear risk	N/A

Yen 2006

Methods	Prospective cohort study performed in a 67-bed military hospital in Taiwan to assess the effectiveness of the integrated infection control strategy by comparing the rate of SARS transmission in HCWs in the study hospital with that in other major hospitals in Taiwan without the integrated infection control strategy
Participants	Healthcare workers (HCWs) of a 67-bed military hospital, that was the study hospital. Eighty-six hospitals were used as comparison hospitals with a total of 746 negative pressure isolation rooms (NPIR beds), caring for SARS patients without the integrated infection control strategy. All HCWs in this group were trained before the SARS epidemic in Taiwan through a national regulation for a standard nosocomial infection control programme, with infectious diseases physicians/infection control nurses available in each regional and tertiary hospital
Interventions	Integrated infection control strategy (consisting of patient traffic into hospital, zone of risks and extensive installation of alcohol dispensers for glove-on hand-rubbing) versus standard nosocomial infection control programme
Outcomes	Serological evidence: yes Effectiveness: SARS (definition?) Safety: N/A
Notes	Risk of bias: high The authors conclude that the integrated infection control strategy appeared to be effective in reducing the incidence of HCWs contracting SARS. Point estimates? 95% CIs. The advantages included rapid implementation without negative pressure isolation rooms, flexibility to transfer patients, and re-enforcement for HCWs to comply with infection control procedures, especially handwashing. The efficacy and low cost are major advantages, especially in countries with large populations at risk and fewer economic resources

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Yen 2006 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	N/A
Allocation concealment (selection bias)	Unclear risk	N/A
Blinding (performance bias and detection bias) All outcomes	Unclear risk	N/A
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	N/A
Selective reporting (reporting bias)	Unclear risk	N/A

Yin 2004

Methods	Case-control study carried out in 10 hospitals of Guangdong province, China, comparing the rate of usage of protective measures in HCWs with SARS and without SARS. The rate of exposure to SARS between 2 groups was similar. The data were obtained by questionnaire. Limited information is available from the abstract and from partial translation of the original text in Chinese
Participants	Description of cases: 77 HCWs who had contracted SARS Description of controls: 180 HCWs who had not contracted SARS Both cases and controls had been working in isolation units and took part in delivering first aid and caring for SARS patients. No significant differences were noted between cases and controls for a series of variables
Interventions	Mouth mask Thick mouth mask (more than 12 layers of cloths) Use one-off paper mouth mask Never use mouth mask Wear eye mask if necessary Protecting for nose and eyes mucosa Wear shoe gloves Wear barrier gown Wear hand gloves Rinse out mouth Take bath and change clothes before home Check mouth mask Intake oseltamivir phosphate orally Never eating and smoking in the ward Handwashing and disinfection Using nose clamp Intake herbal Banlangen (Indigowoad Root) orally
Outcomes	SARS
Notes	Risk of bias: medium (inconsistencies in the text: lack of description of controls)

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Yin 2004 *(Continued)*

	Notes: the authors conclude that the combination of mouth mask, barrier gown, gloves, goggles, footwear, rinse out mouth and take bath and change clothes before provided significant protection and that there was a dose-response relation with the more interventions used in combination the better the protection. Single measures such as wearing of a mask (OR 0.78, 95% CI 0.60 to 0.99), goggles (OR 0.20, 95% CI 0.10 to 0.41) and footwear (OR, 0.58 95% CI 0.39 to 0.86) were effective Limited information is available from the abstract and from partial translation of the original text in Chinese

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	N/A
Allocation concealment (selection bias)	Unclear risk	N/A
Blinding (performance bias and detection bias) All outcomes	Unclear risk	N/A
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	N/A
Selective reporting (reporting bias)	Unclear risk	N/A

Yu 2007

Methods	Case-control study to analyse the risk factors associated with nosocomial outbreaks of SARS in hospital wards in Guangzhou and Hong Kong, China. The study was designed with the individual hospital wards as the units for data collection and analysis. Case wards were hospital wards in which super spreading events of SARS occurred, and control wards were hospital wards in which patient(s) with SARS were admitted, but no super spreading events occurred. A super spreading event is defined as the development of ≥ 3 new cases of SARS in a ward during the period from 2 to 10 days after the admission of an identifiable index patient or as the development of a cluster of ≥ 3 new cases of SARS in a ward during a period of 8 days but without any known sources of SARS
Participants	Eighty-six wards in 21 hospitals in Guangzhou and 38 wards in 5 hospitals in Hong Kong were included in the study. One ward in Guangzhou and 2 wards in Hong Kong did not participate and they were excluded from the analysis
Interventions	Information related to 2 factors was collected: (1) environmental and administrative factors and (2) host factors. Environmental and administrative factors included physical factors, procedural or situational factors, and administrative factors pertaining to each ward. Host factors included symptoms, severity or dependency (for activities of daily living and behaviour changes), treatment or intervention, and comorbidity of the identified index patient in a case ward or in the first patient with SARS admitted in a control ward
Outcomes	Laboratory: serological evidence: no Effectiveness: SARS (no definition) Safety: N/A

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Yu 2007 *(Continued)*

Notes	The authors conclude that environmental risk factors were significantly associated with the occurrence of a super spreading event (clustering of ≥ 3 cases) included minimum distance between beds of ≤ 1 m and performance of resuscitation in the ward. Use of BIPAP ventilation and use of oxygen were the significant risk factors associated with the host patient. Of the administrative factors, allowing staff with symptoms to work also increased the risk. Providing adequate washing or changing facilities for staff was protective As disaggregate data are not reported we did not extract numerator/denominator data

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	N/A
Allocation concealment (selection bias)	Unclear risk	N/A
Blinding (performance bias and detection bias) All outcomes	Unclear risk	N/A
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	N/A
Selective reporting (reporting bias)	Unclear risk	N/A

AEs: adverse events
AFH: Armed Forces Hospital
ARI: acute respiratory infection
ASR: adverse skin reactions
A&E: accident and emergency
BIPAP: Bilevel Positive Airway Pressure
CCC: Child Care Centre
CIs: confidence intervals
CDC: Centers for Disease Control and Prevention
CMF:citric acid: malic acid: sodium lauryl sulfate (a virucidal mixture added to tissue paper)
CoV: coronavirus
C-RCT: cluster-randomised controlled trial
CXR: chest X-ray
DCC: daycare centre
FRI: febrile respiratory illness
GI: gastro-intestinal
HCW: healthcare worker
HFH: Hanoi French Hospital
HH: hand hygiene
HR: high risk
ICU: intensive care unit
ILI: influenza-like illness
IRR: incident rate ratio
ITT: intention-to-treat
LRTI: lower respiratory tract infection
m: metre
MCU: medical convalescent unit
MDCK: Madin Darby canine kidney cell line
MS: monkey-derived cell line

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N/A: not applicable
NICU: neonatal intensive care unit
NOS: Newcastle-Ottawa Scales
NTS: National Skin Centre
OR: odds ratio
PCR: polymerase chain reaction
PCU: physical conditioning unit
PPE: personal protective equipment
RCT: randomised controlled trial
RDS: respiratory distress syndrome
RR: risk ratio
RTI: respiratory tract infection
RT-PCR: reverse-transcriptase polymerase chain reaction
RSV: respiratory syncytial virus
SAB: surfactant, allantoin and benzalkonium chloride
SARS: severe acute respiratory syndrome
SD: standard deviation
SOPs: standard operating procedures
S/S: signs/symptoms
SOB: shortness of breath
SCBU: special care baby unit
UHR-I: ultra high-risk infection
UHR-S: ultra high-risk SARS
URTI: upper respiratory tract infection
WBC: white blood cell
WHO: World Health Organization

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Abou El Hassan 2004	Topic completely extraneous
Amirav 2005	Randomised controlled trial of aerosol treatment
Anderson 2004	Mathematical model with interesting discussion of interaction between public health measures
Anonymous 2002	News item
Anonymous 2003	No data presented
Anonymous 2004	News item
Anonymous 2005a	News item
Anonymous 2005b	News item
Anonymous 2005c	News item
Apisarnthanarak 2009	Intervention bundle not broken down
Apisarnthanarak 2010	Participants took antivirals
Aragon 2005	Descriptive paper (non-comparative). Has no viral outcomes
Barros 1999	Correlational study between incidence of upper respiratory tract infection (URTI) and factors such as overcrowding

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Study	Reason for exclusion
Bauer 2009	Historical comparison with RSV gammaglobulin among interventions
Bell 2004	Has unpublished entry exit screening data and extensive references but no comparative data
Bellissimo-Rodrigues 2009	Intervention is chlorexidine
Ben-Abraham 2002	Exclude - bacterial illness only
Black 1981	Diarrhoea only outcome
Borkow 2010	No human beings involved
Bouadma 2010	Hospital based ventilator routine
Breugelmans 2004	Description of risk factors in aircraft
Cai 2009	Compliance study
Cantagalli 2010	Outcome outside inclusion criteria
Carbonell-Estrany 2008	Immunoglobulin intervention and descriptive review
Carter 2002	News item
Castillo-Chavez 2003	Editorial
Cava 2005a	Survey of quarantinees' views
Cava 2005b	Personal experiences of quarantine
CDC 2003	Case reports
Chai 2005	Letter - about MRSA
Chaovavanich 2004	Case report
Chau 2003	No original retrievable data. Mathematical model fitting expected to observed cases with quarantine in the SARS of Hong Kong
Chau 2008	Audit of infection control procedures and compliance with guidelines
Chen 2007	An assessment of the impact of different handwashing teaching methods. No clinical outcomes
Cheng 2010	Confounded by antiviral use for post-exposure prophylaxis
Chia 2005	Knowledge survey
Clynes 2010	Letters
Cowling 2007	Epidemiology, non-comparative, non-interventions study
Daniels 2010	Commentary
Daugherty 2008	No free data presented

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Study	Reason for exclusion
Davies 1994	Antibody titres as outcomes with so many biases that interpretation of study is problematic
Day 1993	No acute respiratory infection outcome data
Day 2006	Mathematical model; no new data
Dell'Omodarme 2005	Probabilistic and Bayesian mathematical model of screening at entry
Desenclos 2004	Description of transmission
DiGiovanni 2004	Qualitative study of compliance factors in quarantine
Doebbeling 1992	RCT respiratory data not present. Only 3 viruses isolated in total with no viral typing available
Dwosh 2003	Case series
Edmonds 2010	Lab study
Fendler 2002	Cohort study badly biased with differential health profiles and healthcare workers dependency in intervention and control semi-cohorts. No attempt at adjusting for confounders was made. No denominators available
Flint 2003	Description of spread in aircraft and non-comparative data
Fung 2004	Non-comparative
Garcia 2010	Commentary
Gaydos 2001	Editorial linked to Ryan 2001
Gensini 2004	Interesting historical review
Giroud 2002	Non-clinical outcomes
Glass 2006	Mathematical model - no original data presented
Goel 2007	Non-comparative study
Gomersall 2006	Non-comparative study
Gore 2001	Summary of Dyer 2000 (already included)
Gostin 2003	Not an analytical study
Gralton 2010	Review
Guinan 2002	It would appear that 9 classes took part and "acted as their own controls", but it is not clear if there was cross-over of classes or not. In addition the outcome is combined gastrointestinal/respiratory. The clue lies in the presence of a nested economic analysis which shows considerable savings in time for staff and pupils if the soap is used: in other words this is a (covert) publicity study
Gupta 2005	Economic model - no new data
Gwaltney 1982	No breakdown of cases by arm given

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Study	Reason for exclusion
Han 2003	Non-comparative
Hayden 1985	This is a RCT with laboratory-induced colds, small numbers and uncertain numerators but almost certainly because of the unique laboratory conditions (placebo tissues not being a placebo at all) of impossible generalisation. It was a pilot to the far bigger trial by Farr 1988a; Farr 1988b
Hendley 1988	Inappropriate intervention
Hens 2009	Model
Heymann 2009	Already in review as Heymann 2004
Hilburn 2003	No ARI/viral outcomes (e.g. URTIs)
Hilmarsson 2007	Animal study
Hirsch 2006	Study tested pharmacological interventions
Ho 2003	Descriptive review
Hsieh 2007	Mathematical model
Hugonnet 2007	Letter without any data
Jiang 2003	Two papers probably the same paper in different versions: Jiang SP, Huang LW, Wang JF, Wu W, Yin SM, Chen WX, et al. [A study of the architectural factors and the infection rates of healthcare workers in isolation units for severe acute respiratory syndrome]. [Chinese] Chung-Hua Chieh Ho Ho Hu Hsi Tsa Chih [Chinese Journal of Tuberculosis & Respiratory Diseases]. 26(10):594-7, 2003 Oct
Johnson 2009	Outcomes are non-clinical
Jones 2005	Historical account
Kaydos-Daniels 2004	Not an analytical study
Kelso 2009	Model
Khaw 2008	Assessing the efficacy of O_2 delivery
Kilabuko 2007	Aetiological study
Kosugi 2004	Non-comparative study
Lam 2004	Outcomes were generic (infection rates). No laboratory data available for viral diagnosis
Lange 2004	No data presented
Larson 2004	Inappropriate outcomes
Larson 2005	Cluster-RCT comparing the effects of 2 hand hygiene regimens on infection rates and skin condition and microbial counts of nurses' hands in neonatal intensive care units. Outcomes were generic (for example, pneumonia and microbial counts of participants' skin). No laboratory data available for viral diagnosis
Lau 2004b	Attitude survey

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Study	Reason for exclusion
Lau 2005	Herbal remedy effectiveness assessment
Lee 2005	Descriptive study of risk and protective factors of transmission in households. No assignment took place
Lee 2010	Cohort study; unclear numbers were vaccinated against influenza
Lipsitch 2003	Mathematical model fit to evidence
Luckingham 1984	Historical report on Tucson experience during Spanish flu pandemic
Ma 2004	Case-control study of risk factors for SARS
MacIntyre 2010	Commentary on Cowling 2009
Malone 2009	Model
Marin 1991	Viral resistance study
McSweeny 2007	Historical description
Mielke 2009	Review
Mikolajczyk 2008	No intervention
Monsma 1992	Non-comparative study
Nishiura 2009	Model
O'Callaghan 1993	Letter linked to Isaacs 1991
Olsen 2003	Description of transmission
Ooi 2005	Descriptive study but with interesting organisational chart
Orellano 2010	Confounded by antiviral use
Panchabhai 2009	Pharma intervention
Pang 2004	Descriptive study of Beijing outbreak. Some duplicate data in common with Pang 2003
Pittet 2000	Analysis of relationship between handwashing compliance campaign and nosocomial bacterial infections (e.g. MRSA)
Prasad 2004	Letter about retrospective cohort - behavioural
Rabenau 2005	In vitro test of several disinfectants
Reynolds 2008	Describes the psychological effects of quarantine
Richardson 2010	Non-clinical study
Riley 2003	Mathematical model fit to evidence
Rodriguez 2009	A “reasonable attempt at minimizing bias” (see inclusion criteria) does not include absenteeism

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Study	Reason for exclusion
Rosenthal 2005	Outcomes were generic (for example, pneumonia, URTIs). No laboratory data available for viral diagnosis
Safiulin 1972	Non-comparative set of studies with no clinical outcomes
Sandrock 2008	Review
Satter 2000	Experiment assessing virucidal activity of finger tip surface - no clinical outcome data
Schull 2007	Describes the impact of SARS in a Toronto study
Seal 2010	Lab study
Seale 2009	Study looking at whether using respirators in A&E department is feasible
Sizun 1996	This is a review, with no original data presented
Stebbins 2009	Attitude survey
Stoner 2007	No study data available
Stukel 2008	Impact of the SARS disruption on care/mortality for other pathologies (for example, acute myocardial infarction). There are no interventions and outcomes are unrelated to acute respiratory infections
Svoboda 2004	Descriptive study with before and after data but shifting denominators
Tracht 2010	Model
Ueno 1990	Experimental study. No clinical intervention
van der Sande 2008	Laboratory study without any clinical outcomes
Viscusi 2009a	Lab study
Viscusi 2009b	Lab study
Wang 2003	Descriptive study
Wang 2005	Case-control study of susceptibility factors
Weber 2004	Editorial linked to Larson 2004
Wen 2010	Lab study
White 2005	Redundant publication of White 2003
Wilczynski 1997	Clinical trial of the effects of breast feeding
Wilder-Smith 2003	Description of risk factors in aircraft
Wilder-Smith 2005	Descriptive review
Wong 2005	Attitude survey

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Study	Reason for exclusion
Yen 2010	Model
Yu 2004	Description of transmission
Zamora 2006	Head-to-head comparison of two sets of PPEs with no controls and no clinical outcomes
Zhai 2007	Non-comparative study
Zhao 2003	CCT of SARS treatment

A&E: accident and emergency
ARI: acute respiratory infection
CCT: controlled clinical trial
MRSA: methicillin-resistant *Staphylococcus aureus*
RCT: randomized controlled trial
RSV: respiratory syncytial virus
PPE: personal protective equipment
PEP: post-exposure prophylaxis
SARS: severe acute respiratory syndrome
URTI: upper respiratory tract infection

DATA AND ANALYSES

Comparison 1. Case-control studies

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Thorough disinfection of living quarters	1	990	Odds Ratio (M-H, Fixed, 95% CI)	0.30 [0.23, 0.39]
2 Frequent handwashing	7	2825	Odds Ratio (M-H, Fixed, 95% CI)	0.54 [0.44, 0.67]
3 Wearing mask	7	3216	Odds Ratio (M-H, Fixed, 95% CI)	0.32 [0.26, 0.39]
4 Wearing N95 respirator	3	817	Odds Ratio (M-H, Fixed, 95% CI)	0.17 [0.07, 0.43]
5 Wearing gloves	6	1836	Odds Ratio (M-H, Fixed, 95% CI)	0.32 [0.23, 0.45]
6 Wearing gowns	5	1460	Odds Ratio (M-H, Fixed, 95% CI)	0.33 [0.24, 0.45]
7 All interventions	2	369	Odds Ratio (M-H, Fixed, 95% CI)	0.09 [0.02, 0.35]
8 Use of eye protection (mask/goggles)	3	1482	Odds Ratio (M-H, Fixed, 95% CI)	0.10 [0.05, 0.17]
9 Nose wash	2	1225	Odds Ratio (M-H, Fixed, 95% CI)	0.30 [0.16, 0.57]

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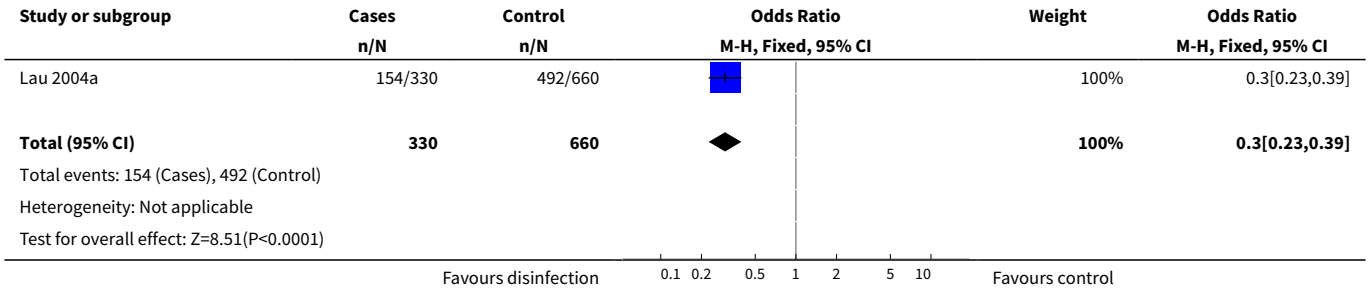
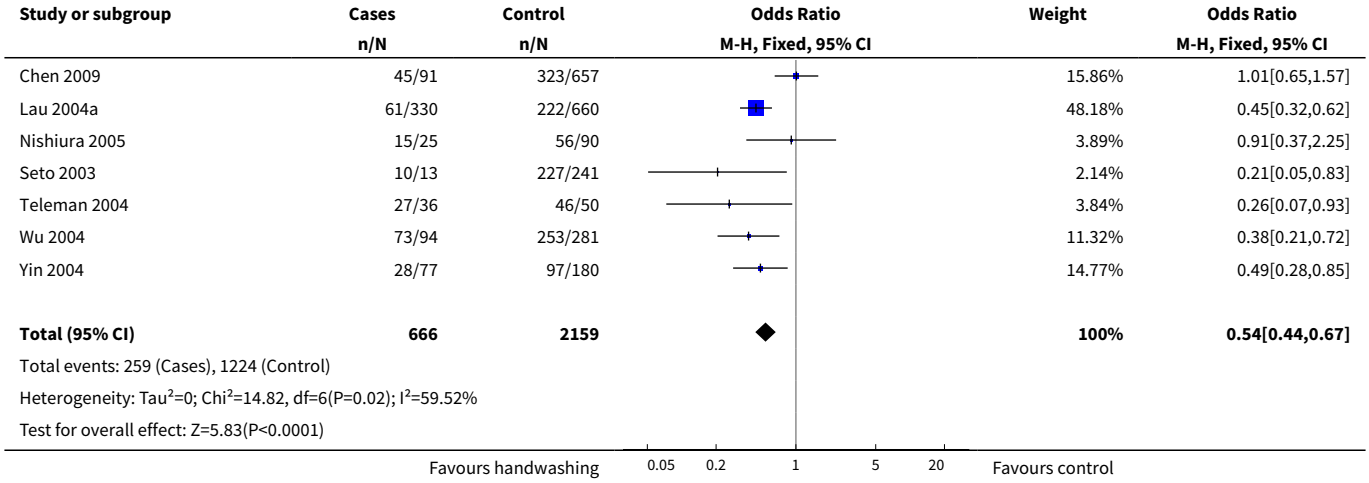
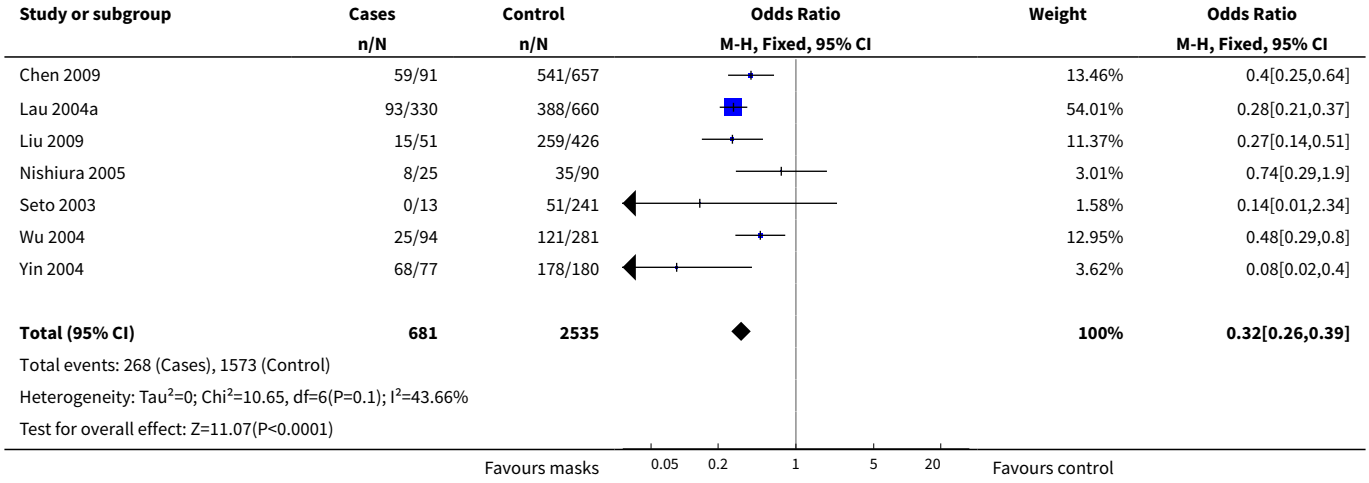
Analysis 1.1. Comparison 1 Case-control studies, Outcome 1 Thorough disinfection of living quarters.



Analysis 1.2. Comparison 1 Case-control studies, Outcome 2 Frequent handwashing.



Analysis 1.3. Comparison 1 Case-control studies, Outcome 3 Wearing mask.



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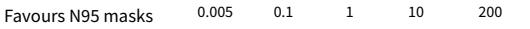
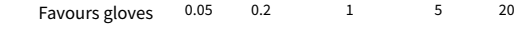
Analysis 1.4. Comparison 1 Case-control studies, Outcome 4 Wearing N95 respirator.

Study or subgroup	Cases n/N	Control n/N	Odds Ratio M-H, Fixed, 95% CI	Weight	Odds Ratio M-H, Fixed, 95% CI
Liu 2009	2/51	31/426		18.86%	0.52[0.12,2.24]
Seto 2003	0/13	92/241		28.88%	0.06[0,1.02]
Teleman 2004	3/36	23/50		52.26%	0.11[0.03,0.39]
Total (95% CI)	**100**	**717**		**100%**	**0.17[0.07,0.43]**
Total events: 5 (Cases), 146 (Control)					
Heterogeneity: Tau^2=0; Chi^2=3.26, df=2(P=0.2); I^2=38.56%					
Test for overall effect: Z=3.72(P=0)					



Analysis 1.5. Comparison 1 Case-control studies, Outcome 5 Wearing gloves.

Study or subgroup	Cases n/N	Control n/N	Odds Ratio M-H, Fixed, 95% CI	Weight	Odds Ratio M-H, Fixed, 95% CI
Chen 2009	10/91	257/657		41.59%	0.19[0.1,0.38]
Liu 2009	27/30	337/346		4.02%	0.24[0.06,0.94]
Nishiura 2005	8/25	30/90		6.63%	0.94[0.36,2.43]
Seto 2003	4/13	117/241		6.2%	0.47[0.14,1.57]
Teleman 2004	10/36	22/50		9.94%	0.49[0.2,1.23]
Yin 2004	37/77	136/180		31.63%	0.3[0.17,0.52]
Total (95% CI)	**272**	**1564**		**100%**	**0.32[0.23,0.45]**
Total events: 96 (Cases), 899 (Control)					
Heterogeneity: Tau^2=0; Chi^2=8.57, df=5(P=0.13); I^2=41.63%					
Test for overall effect: Z=6.61(P<0.0001)					



Analysis 1.6. Comparison 1 Case-control studies, Outcome 6 Wearing gowns.

Study or subgroup	Cases n/N	Control n/N	Odds Ratio M-H, Fixed, 95% CI	Weight	Odds Ratio M-H, Fixed, 95% CI
Chen 2009	49/91	468/657		40.26%	0.47[0.3,0.74]
Nishiura 2005	2/25	25/90		7.66%	0.23[0.05,1.03]
Seto 2003	0/13	83/241		6.75%	0.07[0,1.2]
Teleman 2004	5/36	13/50		7.18%	0.46[0.15,1.43]
Yin 2004	27/77	128/180		38.15%	0.22[0.12,0.39]
Total (95% CI)	**242**	**1218**		**100%**	**0.33[0.24,0.45]**
Total events: 83 (Cases), 717 (Control)					
Heterogeneity: Tau^2=0; Chi^2=6.16, df=4(P=0.19); I^2=35.07%					
Test for overall effect: Z=6.83(P<0.0001)					

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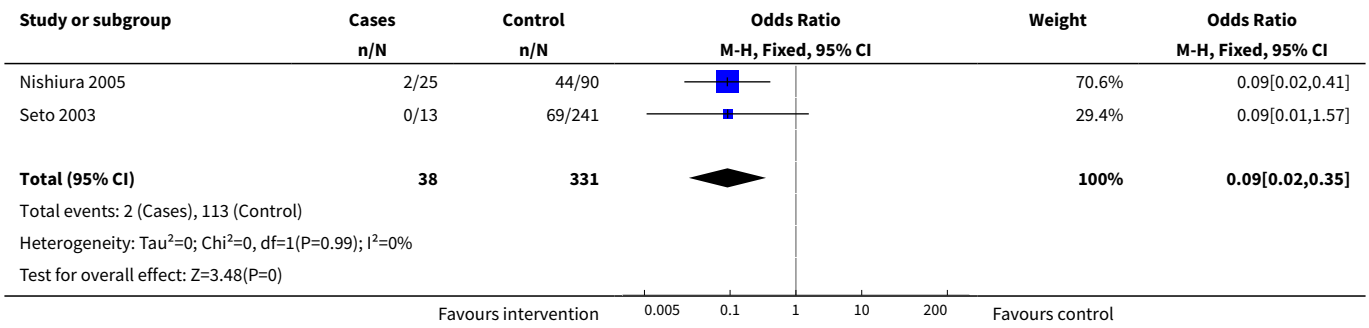
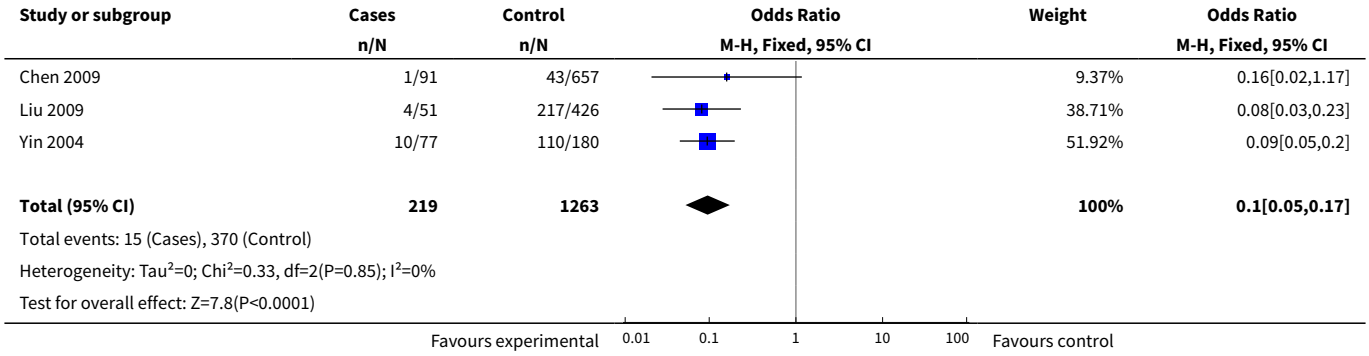
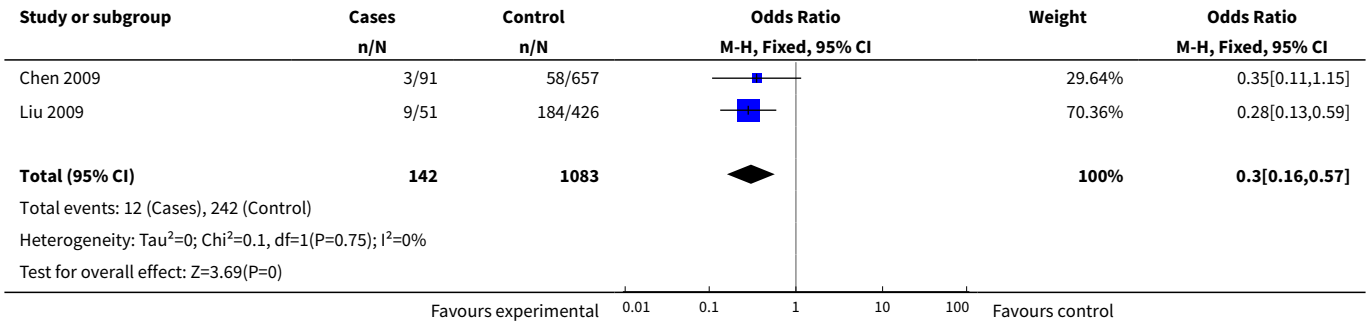
Analysis 1.7. Comparison 1 Case-control studies, Outcome 7 All interventions.



Analysis 1.8. Comparison 1 Case-control studies, Outcome 8 Use of eye protection (mask/goggles).



Analysis 1.9. Comparison 1 Case-control studies, Outcome 9 Nose wash.



ADDITIONAL TABLES

Table 1. Significance in multivariable analysis of interventions to prevent SARS

Outcome or subgroup	Studies	How many statistically significant on multivariable analysis

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Table 1. Significance in multivariable analysis of interventions to prevent SARS *(Continued)*

1.1 Thorough disinfection of living quarters	1	1
1.2 Frequent handwashing	7	4
1.3 Wearing mask	7	6
1.4 Wearing N95 respirator	3	2
1.5 Wearing gloves	6	2
1.6 Wearing gowns	5	2
1.7 All interventions	2	1
1.8 Use of eye protection (mask/goggles)	3	1
1.9 Nose wash	2	1

Table 2. Summary of main results

	RCT (N = 6)	C-RCT (N = 17)	Case-control (N = 9)	Prospective cohort (N = 16)	Retrospective cohort (N = 6)	Before-after (N = 13)
Handwashing	-	3 trials in children effective 1 trial in households effective if implemented < 36 hours after onset	7 studies OR 0.54 (95% CI 0.44 to 0.67)	2 studies found effect, 2 no effect on ARIs	-	1 study in military recruits: > 5 times per day effective
Handwashing with antiseptic	-	3 trials in children: 2 antiseptic more effective 1 antiseptic = soap	-	2 studies added effect of antiseptic 1 study: no difference	-	-
Handwashing and surface disinfection	-	4 trials in children and families: 2 studies effective	-	-	-	1 study in school effective
Hand disinfection	3 trials effective	-	-	-	-	-
Gargling with iodine	1 trial effective	-	-	-	-	-
Nose wash	-	-	2 studies OR 0.30 (95% CI 0.16 to 0.57)	-	-	-
Virucidal tissues	-	1 trial: small effect 2 trials: non-significant	-	1 study effective	-	-

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Table 2. Summary of main results *(Continued)*

Disinfection of living quarters	-	-	1 study OR 0.30 (95% CI 0.23 to 0.39)	-	-	-
Use of eye protection			3 studies OR 0.10 (95% CI 0.05 to 0.17)			
Barriers (masks, gloves, gowns combined)	-	-	2 studies OR 0.09 (95% CI 0.02 to 0.35)	1 study: masks + gowns no added effect to handwashing	-	3 studies: combined with isolation effective 1 study: mask and gown added to isolation not effective 1 study: gowns and gloves effective in paediatric ward
Mask	1 trial: surgical masks no effect	1 trial: no effect added to handwashing 1 trial: no effect of P2 mask 1 trial: added to handwashing effective if implemented < 36 hours after onset of illness 1 trial: added to handwashing effective during weeks 4 to 6 1 trial: no effect added to handwashing	7 studies OR 0.32 (95% CI 0.26 to 0.39)	3 studies: masks effective (with air filter safer)	1 study: harm related to mask wearing	1 study in children's hospital effective
N95 respirator	1 trial: surgical masks non-inferior to N95 respirators	-	3 studies OR 0.17 (95% CI 0.07 to 0.43)	-	1 study: harm related to N95 respirator wearing	-
Gloves	-	-	6 studies OR 0.32 (95% CI 0.23 to 0.45)	-	1 study: harm related to gloves	-
Gowns	-	-	5 studies OR 0.33 (95% CI 0.24 to 0.45)	-	1 study: harm related to gown wearing	1 study: no added effect in neonatal ICU

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Table 2. Summary of main results *(Continued)*

Distancing	-	-	-	1 study: no effect in military recruits 2 studies: cohorting in hospitals effective	1 study: cohorting in paediatric wards effective 1 study in military hospital cohorting with handwashing and gowns effective	6 studies: early identification of cases and isolation effective
Quarantine	-	-	-	1 study: isolation of close contacts effective	1 study: isolation of close contacts effective 1 study: marginal non-significant benefit of border entry screening	-

ARI: acute respiratory infection
C-RCT: cluster-randomised controlled trial
ICU: intensive care unit
OR: odds ratio
RCT: randomised controlled trial

APPENDICES

Appendix 1. Previous search strategy

(Details of the search strategy used in the original review and the 2009 search strategy updates for MEDLINE, CENTRAL, EMBASE and CINAHL)

In the first publication of this review we searched the Cochrane Central Register of Controlled Trials (CENTRAL) (*The Cochrane Library* 2006, issue 4); MEDLINE (1966 to November 2006); OLDMEDLINE (1950 to 1965); EMBASE (1990 to November 2006) and CINAHL (1982 to November 2006). The MEDLINE search terms were modified for OLDMEDLINE, EMBASE and CINAHL.

In this 2009 update we searched the Cochrane Central Register of Controlled Trials (CENTRAL) (*The Cochrane Library* 2009, issue 2); Ovid MEDLINE (2006 to May Week 1 2009); OLDMEDLINE (1950 to 1965); Ovid EMBASE (2006 to Week 18, 2009) and Ovid CINAHL (2006 to May Week 1 2009).

Ovid MEDLINE
1 exp Influenza/
2 influenza.tw.
3 flu.tw.
4 exp Common Cold/
5 common cold.tw.
6 exp Rhinovirus/
7 rhinovirus*.tw.
8 exp Adenoviridae/
9 adenovirus*.tw.
10 exp Coronavirus/
11 exp Coronavirus Infections/
12 coronavirus*.tw.
13 exp Respiratory Syncytial Viruses/
14 exp Respiratory Syncytial Virus Infections/
15 respiratory syncytial virus*.tw.
16 respiratory syncythial virus.tw.
17 exp Parainfluenza Virus 1, Human/
18 exp Parainfluenza Virus 2, Human/
19 exp Parainfluenza Virus 3, Human/
20 exp Parainfluenza Virus 4, Human/

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21 (parainfluenza or para-influenza or para influenza).tw.
22 exp Severe Acute Respiratory Syndrome/
23 (severe acute respiratory syndrome or SARS).tw.
24 acute respiratory infection*.tw.
25 acute respiratory tract infection*.tw.
26 or/1-25 (59810)
27 exp Hand Washing/
28 (handwashing or hand washing or hand-washing).tw.
29 hand hygiene.tw.
30 (sanitizer* or sanitiser*).tw.
31 (cleanser* or disinfectant*).tw.
32 exp Gloves, Protective/
33 exp Gloves, Surgical/
34 glov*.tw.
35 exp Masks/
36 mask*1.tw.
37 exp Patient Isolators/
38 exp Patient Isolation/
39 patient isolat*.tw.
40 (barrier* or curtain* or partition*).tw.
41 negative pressure room*.tw.
42 reverse barrier nursing.tw.
43 Cross Infection/pc [Prevention]
44 school closure*.tw.
45 (clos* adj3 school*).tw.
46 mass gathering*.tw.
47 public gathering*.tw.
48 (ban or bans or banned or banning).tw.
49 (outbreak* adj3 control*).tw.
50 distancing.tw.
51 exp Quarantine/
52 quarantine*.tw.
53 or/27-49
54 26 and 53
55 (animals not (humans and animals)).sh.
56 54 not 55

CENTRAL search strategy

#1 MeSH descriptor Influenza, Human explode all trees
#2 influenza:ti,ab,kw
#3 flu:ti,ab,kw
#4 MeSH descriptor Common Cold explode all trees
#5 "common cold":ti,ab,kw
#6 MeSH descriptor Rhinovirus explode all trees
#7 rhinovirus*:ti,ab,kw
#8 MeSH descriptor Adenoviridae explode all trees
#9 adenovirus*:ti,ab,kw
#10 MeSH descriptor Coronavirus explode all trees
#11 MeSH descriptor Coronavirus Infections explode all trees
#12 coronavirus*:ti,ab,kw
#13 MeSH descriptor Respiratory Syncytial Viruses explode all trees
#14 MeSH descriptor Respiratory Syncytial Virus Infections explode all trees
#15 respiratory syncytial virus*:ti,ab,kw
#16 respiratory syncythial virus*:ti,ab,kw
#17 MeSH descriptor Parainfluenza Virus 1, Human explode all trees
#18 MeSH descriptor Parainfluenza Virus 2, Human explode all trees
#19 MeSH descriptor Parainfluenza Virus 3, Human explode all trees
#20 MeSH descriptor Parainfluenza Virus 4, Human explode all trees
#21 (parainfluenza or para-influenza or para influenza):ti,ab,kw
#22 MeSH descriptor Severe Acute Respiratory Syndrome explode all trees
#23 (severe acute respiratory syndrome or SARS):ti,ab,kw

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#24 acute respiratory infection*:ti,ab,kw
#25 acute respiratory tract infection*:ti,ab,kw
#26 (#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25)
#27 MeSH descriptor Handwashing explode all trees
#28 (handwashing or hand washing or hand-washing):ti,ab,kw
#29 hand hygiene:ti,ab,kw
#30 (sanitizer* or sanitiser*):ti,ab,kw
#31 (cleanser* or disinfectant*):ti,ab,kw
#32 MeSH descriptor Gloves, Protective explode all trees
#33 MeSH descriptor Gloves, Surgical explode all trees
#34 glov*:ti,ab,kw
#35 MeSH descriptor Masks explode all trees
#36 mask*:ti,ab,kw
#37 MeSH descriptor Patient Isolators explode all trees
#38 MeSH descriptor Patient Isolation explode all trees
#39 (barrier* or curtain* or partition*):ti,ab,kw
#40 negative NEXT pressure NEXT room*:ti,ab,kw
#41 "reverse barrier nursing":ti,ab,kw
#42 MeSH descriptor Cross Infection explode all trees with qualifier: PC
#43 school NEXT closure*:ti,ab,kw
#44 (clos* NEAR/3 school*):ti,ab,kw
#45 mass NEXT gathering*:ti,ab,kw
#46 public NEXT gathering*:ti,ab,kw
#47 ("ban" or "bans" or banned or banning):ti,ab,kw
#48 (outbreak* NEAR/3 control*):ti,ab,kw
#49 distancing:ti,ab,kw
#50 MeSH descriptor Quarantine explode all trees
#51 quarantine*:ti,ab,kw
#52 (#27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35 OR #36 OR #37 OR #38 OR #39 OR #40 OR #41 OR #42 OR #43 OR #44 OR #45 OR #46 OR #47 OR #48 OR #49 OR #50 OR #51)
#53 (#26 AND #52)

Ovid EMBASE search strategy

1 exp Influenza/
2 influenza.tw.
3 flu.tw.
4 exp Common Cold/
5 common cold.tw.
6 exp Human Rhinovirus/
7 rhinovirus*.tw.
8 exp Adenovirus/
9 adenovirus*.tw.
10 exp Coronavirus/
11 coronavirus*.tw.
12 exp Respiratory Syncytial Pneumovirus/
13 respiratory syncytial virus*.tw.
14 respiratory syncythial virus.tw.
15 (parainfluenza or para-influenza or para influenza).tw.
16 exp Severe Acute Respiratory Syndrome/
17 (severe acute respiratory syndrome or SARS).tw.
18 acute respiratory infection*.tw.
19 acute respiratory tract infection*.tw.
20 or/1-19
21 exp Hand Washing/
22 (handwashing or hand washing or hand-washing).tw.
23 hand hygiene.tw.
24 (sanitizer$ or sanitiser$).tw.
25 (cleanser$ or disinfectant$).tw.
26 exp Glove/
27 exp Surgical Glove/

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28 glov*.tw.
29 exp Mask/
30 mask*1.tw.
31 patient isolat*.tw.
32 (barrier* or curtain* or partition*).tw.
33 negative pressure room*.tw.
34 reverse barrier nursing.tw.
35 Cross Infection/pc [Prevention]
36 school closure*.tw.
37 (clos* adj3 school*).tw.
38 mass gathering*.tw.
39 public gathering*.tw. (5)
40 (ban or bans or banned or banning).tw.
41 (outbreak* adj3 control*).tw.
42 distancing.tw.
43 quarantine*.tw.
44 or/21-43
45 20 and 44

EBSCO CINAHL search strategy

S26 S10 and S24
S25 S10 and S24
S24 S11 or S12 or S13 or S14 or S15 or S16 or S17 or S18 or S19 or S20 or S21 or S22 or 23 or S24
S23 TI outbreak* N3 control* or AB outbreak* N3 control*
S22 TI (school closure* or mass gathering* or public gathering* or ban or bans or banned or banning or distancing or quarantine*) or AB (school closure* or mass gathering* or public gathering* or ban or bans or banned or banning or distancing or quarantine*)
S21 TI (patient isolat* or barrier* or curtain* or partition* or negative pressure room* or reverse barrier nursing) or AB (patient isolat* or barrier* or curtain* or partition* or negative pressure room* or reverse barrier nursing)
S20 TI (glov* or mask*) or AB (glov* or mask*)
S19 TI (handwashing or hand washing or hand-washing or hand hygiene) or AB (handwashing or hand washing or hand-washing or hand hygiene)
S18 (MH "Quarantine")
S17 (MM "Cross Infection")
S16 (MH "Isolation, Reverse")
S15 (MH "Patient Isolation+")
S14 (MH "Respiratory Protective Devices")
S13 (MH "Masks")
S12 (MH "Gloves")
S11 (MH "Handwashing+")
S10 S1 or S2 or S3 or S4 or S5 or S6 or S7 or S8 or S9
S9 TI (influenza or flu or rhinovirus* or adenovirus* or coronavirus* or respiratory syncytial virus* or respiratory syncythial virus* or parainfluenza or para-influenza or para influenza or severe acute respiratory syndrome or SARS or respiratory viral infection* or viral respiratory infection*) or AB (influenza or flu or rhinovirus* or adenovirus* or coronavirus* or respiratory syncytial virus* or respiratory syncythial virus* or parainfluenza or para-influenza or para influenza or severe acute respiratory syndrome or SARS or respiratory viral infection* or viral respiratory
infection*)TI (influenza or flu or rhinovirus* or adenovirus* or coronavirus* or respiratory syncytial virus* or respiratory syncythial virus* or parainfluenza or para-influenza or para influenza or severe acute respiratory (syndrome or SARS or respiratory viral infection* or viral respiratory infection*) or AB (influenza or flu or rhinovirus* or adenovirus* or coronavirus* or respiratory syncytial virus* or respiratory syncythial virus* or parainfluenza or para-influenza or para influenza or severe acute respiratory syndrome or SARS or respiratory viral infection* or viral
respiratory infection*)
S8 (MH "SARS Virus")
S7 (MH "Severe Acute Respiratory Syndrome")
S6 (MH "Respiratory Syncytial Virus Infections")
S5 (MH "Respiratory Syncytial Viruses")
S4 (MH "Coronavirus+")
S3 (MH "Coronavirus Infections+")
S2 (MH "Common Cold")
S1 (MH "Influenza+")

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Appendix 2. Embase.com search strategy, October 2010

The search strategy was broadened in 2010 to be more inclusive of new and emerging viruses.

'influenza'/exp AND [embase]/lim OR ('influenza virus a'/exp OR 'influenza virus b'/de OR 'influenza virus c'/de AND [embase]/lim) OR (influenza*:ab,ti OR flu:ab,ti AND [embase]/lim) OR ('common cold'/de AND [embase]/lim) OR ('common cold':ab,ti OR 'common colds':ab,ti AND [embase]/lim) OR ('human rhinovirus'/de AND [embase]/lim) OR (rhinovir*:ab,ti AND [embase]/lim) OR ('rhinovirus infection'/de AND [embase]/lim) OR ('adenovirus'/de OR 'human adenovirus'/exp AND [embase]/lim) OR ('human adenovirus infection'/exp AND [embase]/lim) OR (adenovir*:ab,ti AND [embase]/lim) OR ('coronavirus'/de OR 'sars coronavirus'/de AND [embase]/lim) OR (coronavir*:ab,ti AND [embase]/lim) OR ('coronavirus infection'/de AND [embase]/lim) OR ('severe acute respiratory syndrome'/de AND [embase]/lim) OR ('severe acute respiratory syndrome':ab,ti OR sars:ab,ti AND [embase]/lim) OR ('respiratory syncytial pneumovirus'/de AND [embase]/lim) OR ('respiratory syncytial virus infection'/de AND [embase]/lim) OR ('respiratory syncytial virus':ab,ti OR 'respiratory syncytial viruses':ab,ti OR rsv:ab,ti OR 'respiratory syncytial pneumovirus':ab,ti OR 'respiratory syncytial pneumoviruses':ab,ti AND [embase]/lim) OR ('parainfluenza virus'/exp AND [embase]/lim) OR (parainfluenza*:ab,ti OR 'para influenza':ab,ti OR 'para-influenza':ab,ti AND [embase]/lim) OR ('enterovirus'/de OR 'enterovirus infection'/de AND [embase]/lim) OR (enterovir*:ab,ti AND [embase]/lim) OR ('human parvovirus b19'/de OR 'bocavirus'/de AND [embase]/lim) OR (parvovirus*:ab,ti OR bocavirus*:ab,ti AND [embase]/lim) OR ('human metapneumovirus'/de AND [embase]/lim) OR (metapneumovir*:ab,ti AND [embase]/lim) OR ('parechovirus'/de AND [embase]/lim) OR (parechovirus*:ab,ti AND [embase]/lim) OR ('acute respiratory infection':ab,ti OR 'acute respiratory infections':ab,ti OR 'acute respiratory tract infection':ab,ti OR 'acute respiratory tract infections':ab,ti AND [embase]/lim) AND ('hand washing'/de AND [embase]/lim OR (handwashing:ab,ti OR 'hand washing':ab,ti OR 'hand-washing':ab,ti AND [embase]/lim) OR ('hand hygiene':ab,ti AND [embase]/lim) OR (sanitiser*:ab,ti OR sanitizer*:ab,ti OR cleanser*:ab,ti OR disinfectant*:ab,ti AND [embase]/lim) OR ('glove'/de OR 'surgical glove'/de AND [embase]/lim) OR (glov*:ab,ti AND [embase]/lim) OR ('mask'/de OR 'face mask'/de OR 'surgical mask'/de AND [embase]/lim) OR (mask:ab,ti OR masks:ab,ti OR respirator:ab,ti OR respirators:ab,ti AND [embase]/lim) OR ('protective clothing'/de OR 'protective equipment'/de AND [embase]/lim) OR ('patient isolator':ab,ti OR 'patient isolators':ab,ti OR 'patient isolation':ab,ti AND [embase]/lim) OR (cohorting:ab,ti OR 'cohort isolation':ab,ti AND [embase]/lim) OR (barrier*:ab,ti OR curtain*:ab,ti OR partition*:ab,ti AND [embase]/lim) OR ('negative pressure room':ab,ti OR 'negative pressure rooms':ab,ti AND [embase]/lim) OR ('reverse barrier nursing':ab,ti OR 'reverse-barrier nursing':ab,ti OR 'reverse barrier unit':ab,ti OR 'reverse-barrier unit':ab,ti AND [embase]/lim) OR (('cross infection' NEAR/2 prevent*):ab,ti AND [embase]/lim) OR ('infection control'/de AND [embase]/lim) OR ((school* NEAR/3 (clos* OR dismissal*)):ab,ti AND [embase]/lim) OR ('temporary closure':ab,ti OR 'temporary closures':ab,ti AND [embase]/lim) OR ('mass gathering':ab,ti OR 'mass gatherings':ab,ti AND [embase]/lim) OR ((public NEAR/2 (gathering* OR event*)):ab,ti AND [embase]/lim) OR (bans:ab,ti OR banning:ab,ti OR banned:ab,ti OR ban:ab,ti AND [embase]/lim) OR ((outbreak* NEAR/3 control*):ab,ti AND [embase]/lim) OR (distancing*:ab,ti AND [embase]/lim) OR (quarantine*:ab,ti AND [embase]/lim) OR ((protective NEAR/2 (cloth* OR garment* OR gown* OR device* OR equipment)):ab,ti AND [embase]/lim) OR (((protective OR preventive) NEAR/2 (procedure* OR behavior* OR behaviour*)):ab,ti AND [embase]/lim) OR ('personal protective':ab,ti OR 'personal protection':ab,ti AND [embase]/lim) OR ('isolation room':ab,ti OR 'isolation rooms':ab,ti OR 'isolation strategy':ab,ti OR 'isolation strategies':ab,ti AND [embase]/lim) OR ((distance NEAR/2 patient*):ab,ti AND [embase]/lim) OR (((spatial OR patient) NEAR/1 separation):ab,ti AND [embase]/lim)) AND ('randomized controlled trial'/exp OR 'single blind procedure'/exp OR 'double blind procedure'/exp OR 'crossover procedure'/exp AND [embase]/lim OR (random*:ab,ti OR placebo*:ab,ti OR factorial*:ab,ti OR crossover*:ab,ti OR 'cross over':ab,ti OR 'cross-over':ab,ti OR volunteer*:ab,ti OR assign*:ab,ti OR allocat*:ab,ti OR ((singl* OR doubl*) NEAR/2 (blind* OR mask*)):ab,ti AND [embase]/lim) OR ('controlled study'/de OR 'treatment outcome'/de OR 'major clinical study'/de OR 'clinical trial'/de AND [embase]/lim) OR (chang*:ab,ti OR evaluat*:ab,ti OR reviewed:ab,ti OR baseline:ab,ti OR compare*:ab,ti OR compara*:ab,ti OR consecutive:ab,ti OR retrospective:ab,ti AND [embase]/lim))

Appendix 3. CINAHL (EBSCO) search strategy, October 2010

The search strategy was broadened in 2010 to be more inclusive of new and emerging viruses.

S54 S32 and S53
S53 S44 or S52
S52 S45 or S46 or S47 or S48 or S49 or S50 or S51
S51 TI observational stud* or AB observational stud*
S50 TI cohort stud* or AB cohort stud*
S49 (MH "Cross Sectional Studies")
S48 (MH "Nonconcurrent Prospective Studies")
S47 (MH "Correlational Studies")
S46 (MH "Case Control Studies+")
S45 (MH "Prospective Studies")
S44 S33 or S34 or S35 or S36 or S37 or S38 or S39 or S40 or S41 or S42 or S43
S43 TI allocat* N1 random* or AB allocat* N1 random*
S42 (MH "Quantitative Studies")
S41 TI placebo* or AB placebo*
S40 (MH "Placebos")
S39 TI random* allocation* or AB random* allocation*
S38 (MH "Random Assignment")

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S37 TI (randomised control* trial* or randomized control* trial*) or AB (randomised control* trial* or randomized control* trial*)
S36 TI ((singl* W1 blind*) or (singl* W1 mask*) or (doubl* W1 blind*) or (doubl* W1 mask*) or (trebl* W1 blind*) or (trebl* W1 mask*) or (tripl* W1 blind*) or (tripl* W1 mask*)) or AB ((singl* W1 blind*) or (singl* W1 mask*) or (doubl* W1 blind*) or (doubl* W1 mask*) or (trebl* W1 blind*) or (trebl* W1 mask*) or (tripl* W1 blind*) or (tripl* W1 mask*))
S35 TI clinic* W1 trial* or AB clinic* W1 trial*
S34 PT clinical trial
S33 (MH "Clinical Trials+")
S32 S15 and S31
S31 S16 or S17 or S18 or S19 or S20 or S21 or S22 or S23 or S24 or S25 or S26 or S27 or S28 or S29 or S30
S30 TI (bans or banning or banned or ban or "outbreak control" or "outbreak controls" or distancing* or quarantine* or "protective clothing" or "protective garment" or "protective garments" or "protective gown" or "protective gowns" or "protective device" or "protective devices" or "protective equipment" or "protective behaviour" or "protective behavior" or "protective behaviours" or "protective behaviors" or "protective procedure" or "protective procedures" or "preventive behaviours" or "preventive behaviour" or "preventive behavior" or "preventive behaviors" or "preventive procedure" or "preventive procedures" or "personal protective" or "isolation room" or "isolation rooms" or "isolation strategy" or "isolation strategies" or "patient distance" or "patient distancing" or "patient separation" or "spatial separation") or AB (handwashing or "hand washing" or hand-washing or "hand hygiene" or sanitiser or sanitizer or cleanser* or disinfectant* or glov* or mask or masks or respirator or respirators or "patient isolation" or "patient isolators" or barrier* or curtain* or partition* or "negative pressure room" or "negative pressure rooms" or "reverse barrier nursing" or "reverse barrier unit" or "reverse barrier isolation" or "cross infection" or "infection control" or "disease control" or "school closure" or "school closures" or "school dismissal" or "school dismissals" or "temporary closure" or "temporary closures" or "mass gathering" or "mass gatherings" or "public gathering" or "public gatherings" or "public event" or "public events")
S29 TI (handwashing or "hand washing" or hand-washing or "hand hygiene" or sanitiser or sanitizer or cleanser* or disinfectant* or glov* or mask or masks or respirator or respirators or "patient isolation" or "patient isolators" or barrier* or curtain* or partition* or "negative pressure room" or "negative pressure rooms" or "reverse barrier nursing" or "reverse barrier unit" or "reverse barrier isolation" or "cross infection" or "infection control" or "disease control" or "school closure" or "school closures" or "school dismissal" or "school dismissals" or "temporary closure" or "temporary closures" or "mass gathering" or "mass gatherings" or "public gathering" or "public gatherings" or "public event" or "public events") or AB (handwashing or "hand washing" or hand-washing or "hand hygiene" or sanitiser or sanitizer or cleanser* or disinfectant* or glov* or mask or masks or respirator or respirators or "patient isolation" or "patient isolators" or barrier* or curtain* or partition* or "negative pressure room" or "negative pressure rooms" or "reverse barrier nursing" or "reverse barrier unit" or "reverse barrier isolation" or "cross infection" or "infection control" or "disease control" or "school closure" or "school closures" or "school dismissal" or "school dismissals" or "temporary closure" or "temporary closures" or "mass gathering" or "mass gatherings" or "public gathering" or "public gatherings" or "public event" or "public events")
S28 (MH "Sterilization and Disinfection")
S27 (MH "Quarantine")
S26 (MH "Area Restriction (Iowa NIC)") OR (MH "Infection Protection (IowaNIC)")
S25 (MH "Infection Control")
S24 (MH "Cross Infection/PC")
S23 (MH "Isolation, Reverse")
S22 (MH "Patient Isolation")
S21 (MH "Protective Devices")
S20 (MH "Protective Clothing")
S19 (MH "Respiratory Protective Devices")
S18 (MH "Masks")
S17 (MH "Gloves")
S16 (MH "Handwashing+")
S15 S1 or S2 or S3 or S4 or S5 or S6 or S7 or S8 or S9 or S10 or S11 or S12 or S13 or S14
S14 TI ("acute respiratory tract infection" or "acute respiratory tract infections" or "acute respiratory infection" or "acute respiratory infections") or AB (influenza* or flu or "common cold" or "common colds" or rhinovir* or adenovir* or coronavir* or sars or "severe acute respiratory syndrome" or "respiratory syncytial virus" or "respiratory syncytial viruses" or rsv or pneumovir* or parainfluenza* or "para influenza" or para-influenza or enterovir* or bocavir* or metapneumovir* or parvovir* or parechovir*)
S13 TI (influenza* or flu or "common cold" or "common colds" or rhinovir* or adenovir* or coronavir* or sars or "severe acute respiratory syndrome" or "respiratory syncytial virus" or "respiratory syncytial viruses" or rsv or pneumovir* or parainfluenza* or "para influenza" or para-influenza or enterovir* or bocavir* or metapneumovir* or parvovir* or parechovir*) or AB (influenza* or flu or "common cold" or "common colds" or rhinovir* or adenovir* or coronavir* or sars or "severe acute respiratory syndrome" or "respiratory syncytial virus" or "respiratory syncytial viruses" or rsv or pneumovir* or parainfluenza* or "para influenza" or para-influenza or enterovir* or bocavir* or metapneumovir* or parvovir* or parechovir*)
S12 (MH "Respiratory Tract Infections+")
S11 (MH "Parvovirus Infections+")
S10 (MH "Enterovirus Infections+")
S9 (MH "Enteroviruses+")
S8 (MH "Respiratory Syncytial Virus Infections")
S7 (MH "Respiratory Syncytial Viruses")

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S6 (MH "SARS Virus")
S5 (MH "Severe Acute Respiratory Syndrome")
S4 (MH "Coronavirus Infections+")
S3 (MH "Coronavirus+") OR (MH "Coronavirus Infections")
S2 (MH "Common Cold")
S1 (MH "Influenza+") OR (MH "Influenza A H5N1") OR (MH "Influenza A

Appendix 4. LILACS (Latin America and Caribbean) search strategy

Tw acute respiratory tract infection$ or Tw acute respiratory infection$ or Mh human influenza or Mh influenza a virus or Mh influenza a virus, h1n1 subtype or Mh influenza a virus, h3n2 subtype or Mh influenza a virus, h3n8 subtype or Mh influenza a virus, h5n1 subtype or Mh influenza b virus or Mh influenza c virus or Mh influenza in humans or Mh influenza viruses type a or Mh influenza viruses type b or Mh influenza viruses type c or Mh influenza, human or Tw influenza$ or Tw flu or Mh influenzavirus a or Mh influenzavirus b or Mh influenzavirus c or Mh adenoviridae or Mh adenoviridae infections or Mh adenovirus infections or Mh adenovirus infections, human or Mh adenoviruses, human or Tw rhinovir$ or Tw adenovir$ or Tw common cold$ or Tw resfriado comum or Tw resfriado comun or Mh coronavirus or Mh sars-associated coronavirus or Mh human coronavirus 229e or Mh coronavirus 229e, human or Mh coronavirus infections or Tw coronavir$ or Mh severe acute respiratory syndrome or Mh severe acute respiratory syndrome virus or Tw severe acute respiratory syndrome or Tw sars or Tw sindrome respirat$ agudo grave or Mh human respiratory syncytial virus or Mh respiratory syncytial virus infections or Mh respiratory syncytial virus, human or Mh respiratory syncytial viruses or Tw respiratory syncytial virus$ or Tw rsv or Tw virus sincitiales respiratorios or Tw virus sinciciais respiratorios or Mh pneumovirus or Tw pneumovir$ or Mh human parainfluenza virus 1 or Mh parainfluenza virus 1, human or Mh human parainfluenza virus 2 or Mh parainfluenza virus 2, human or Mh human parainfluenza virus 3 or Mh parainfluenza virus 3, human or Mh parainfluenza virus infections Tw parainfluenza$ or Tw para influenza or Tw para-influenza or Mh enterovirus or Mh human enterovirus b or Mh enterovirus b, human or Mh enterovirus infections or Tw enterovir$ or Mh bocavirus or Tw bocavir$ or Mh metapneumovirus or Mh human metapneumovirus or Mh metapneumovirus, human or Tw metapneumovir$ or Mh parvovirus or Mh human parvovirus b19 or Mh parvovirus b19, human or Mh parvovirus infections or Tw parvovir$ or Mh parvoviridae or Mh parvoviridae infections or Tw parechovir$ [Words]

and

Mh Handwashing or Tw handwashing or Tw hand washing or Tw hand-washing or Tw lavado de manos or Tw lavagem de maos or Tw hand hygiene or Tw higiene or Tw sanitiser$ or Tw sanitizer or Tw cleanser$ or Tw disinfectant$ or Tw esteriliza$ or Tw desinfectar$ or Mh protective gloves or Mh surgical gloves or Mh gloves, protective or Mh gloves, surgical or Tw glov$ or Tw guantes or Tw luvas or Mh masks or Mh facial masks or Tw mask or Tw masks or Tw mascaras or Mh respiratory protective devices or Tw respirator or Tw respirators or Mh protective clothing or Mh protective devices or Mh patient isolation or Tw patient isolat$ or Tw aisladores de pacientes or Tw aislamiento de pacientes or Tw isoladores de pacientes or Tw isolamento de pacientes or Tw barrier$ or Tw curtain$ or Tw partition$ or Tw barrera or Tw barreira or Tw cortina or Tw tabique or Tw protective clothing or Tw protective devices or Tw ropa de protec$ or Tw equipos de seguridad or Tw roupa de prote$ or Tw equipamentos de prote$ or Mh cross infection or Tw cross infection or Tw infec$ hospital$ or Tw infection control$ or Tw control$ de infec$ or Mh communicable disease control or Tw communicable disease control or Tw control de enfermedades transmisibles or Tw controle de doen$ transmiss$ or Mh infection control or Mh quarantine Tw quarantine$ or Tw cuarentena or Tw quarentena or Tw protective devices or Tw dispositivos de prtoecc$ or Tw personal protect$ or Tw equipamentos de protec$ or Tw equipo de protecc$ or Tw isolation room or Tw sala de aislamiento or Tw quarto de isolamento or Tw patient distance or Tw distancia del paciente or Tw spatial separation or Tw separa$ especial or Tw cohort isolation or Tw cohort$ or Tw ban or Tw bans or Tw banning or Tw banned or Tw prohibici$ or Tw proibi$ or Tw outbreak control or Tw distanc$ or Tw school closure or Tw temporary closure or Tw cierre de la escuela or Tw fechamento da escola or Tw public gathering or Tw reunion publica or Tw reuni$ publica or Tw reverse barrier nursing or Tw reverse barrier unit or Tw reverse barrier isolation or Tw negative pressure room$ or Tw patient separation [Words]

Appendix 5. Indian MEDLARS search strategy

(influenza$ or flu or common cold$ or rhinovir$ or coronavir$ or adenovir$ or severe acute respiratory syndrome$ or sars or respiratory syncytial virus$ or rsv or parainfluenza$ or enterovir$ or metapneumovir$ or parvovir$ or bocavir$ or parechovir$) and (handwashing or hand washing or mask$ or glov$ or protect$ or isolat$ or barrier$ or curtain$ or partition$ or cross infection$ or infection control$ or disease control$ or school$ or quarantine$ or ban$ or cohort$ or distanc$ or spatial separation$)

Appendix 6. IMSEAR (Index Medicus for the South East Asia Region) search strategy

(influenza or flu or common cold or rhinovirus or coronavirus or adenovirus or severe acute respiratory syndrome or sars or respiratory syncytial virus or rsv or parainfluenza or enterovirus or bocavirus or metapneumovirus or parvovirus or parechovirus) and (handwashing or hand washing or hand hygiene or sanitiser or sanitizer or cleanser or disinfectant or gloves or masks or mask or protective clothing or protective devices or patient isolation or barrier or curtain or partition or cross infection or disease control or infection control or school or schools or bans or banning or banned or ban or distancing or quarantine or isolation or spatial separation or cohorting or cohort isolation)

WHAT'S NEW

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Date	Event	Description
1 April 2020	Amended	We deleted the table 'GRADE evidence profiles physical barriers/handwashing and related interventions in hospital and community settings' because the table is not rendering correctly when downloading the PDF.

HISTORY

Protocol first published: Issue 4, 2006
Review first published: Issue 4, 2007

Date	Event	Description
22 October 2010	New citation required but conclusions have not changed	We updated the review again at the behest of the World Health Organization (WHO). External sources of support amended. External support from the WHO. The WHO interim guidelines document on 'Infection Prevention and Control of Epidemic and Pandemic Prone Acute Respiratory Diseases in Health Care' was published in 2007 to provide infection control guidance to help prevent the transmission of acute respiratory diseases (ARD) in health care. The update of these guidelines will be evidence-based and an update of this review was requested to assist in informing the evidence base for the revision of the WHO guidelines. Dr John Conly, Dr Mark Jones and Sarah Thorning joined the review team.
22 October 2010	New search has been performed	Searches conducted. We included seven new trials; four randomised controlled trials and three non-randomised comparative studies. We excluded 36 new trials.
7 May 2009	New search has been performed	For the 2009 update we included three cluster-randomised controlled trials (Sandora 2008; Cowling 2009; MacIntyre 2009) and one individual randomised controlled trial (Satomura 2005, with its linked publication Kitamura 2007). We also included one retrospective cohort study (Foo 2006), one case-control study (Yu 2007) and two prospective cohort studies (Wang 2007; Broderick 2008). The content and conclusions of the 2007 review changed little, but the additional eight studies add more information and certainty. Our meta-analysis remains unchanged as there were no new studies for pooling.
30 April 2009	New citation required but conclusions have not changed	New author joined the review team.
8 July 2008	Amended	Converted to new review format.
20 August 2007	Amended	Review first published Issue 4, 2007.

CONTRIBUTIONS OF AUTHORS

Tom Jefferson (TOJ), Chris Del Mar (CDM) and Liz Dooley (LD) were responsible for drafting the protocol.

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TOJ, Eliana Ferroni (EF), Bill Hewak (BH) and Adi Prabhala (AP) extracted study data and Sree Nair (SN) performed the analyses in the original review.

TOJ, EF, Lubna A Al-Ansary (LA), Ghada A Bawazeer (GB) and CDM adjudicated in data extraction in the 2009 update, and Mieke van Driel (MvD) assisted in the writing, construction of the summary of results table and updating with the most recent studies. All 2009 review authors contributed to the final report.

For the 2010 update TOJ and John Conly (JMC) extracted data and CDM checked extractions and arbitrated. All three checked the search strategy terms. Sarah Thorning designed and carried out the searches. All 2010 review authors contributed to the final report.

DECLARATIONS OF INTEREST

Chris Del Mar provided expert advice to GlaxoSmithKline about vaccination against acute otitis media in 2008-2009. He receives royalties from books published through Blackwell, BMJ Books and Elsevier.

SOURCES OF SUPPORT

Internal sources

- The Cochrane Collaboration Steering Group, UK.

External sources

- National Institute of Health Research (NIHR), UK.

  Competitive grant awarded through the Cochrane Collaboration
- National Health and Medical Research Council (NHMRC), Australia.

  Competitive grant to Chris Del Mar and Tom Jefferson, 2009
- Sabbatical year for John Conly while at the WHO in Geneva, Switzerland was supported by the University of Calgary, Calgary, Canada.
- World Health Organization, Geneva, Switzerland.

  Requested and provided support to the Cochrane Collaboration for current update

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

None, apart from the change in the title (see Published notes, below).

NOTES

In Issue 1, 2010, the title was changed from *Interventions for the interruption or reduction of the spread of respiratory viruses* to *Physical interventions to interrupt or reduce the spread of respiratory viruses.*

The original review was subsequently published as Jefferson T, Foxlee R, Del Mar C, Dooley L, Ferroni E, Hewak B, Prabhala A, Nair S, Rivetti A. Physical interventions to interrupt or reduce the spread of respiratory viruses: systematic review. BMJ 2008;336:77-80 and Jefferson T, Del Mar C, Dooley L, Ferroni E, Al-Ansary LA, Bawazeer GA, van Driel ML, Foxlee R, Rivetti A. Physical interventions to interrupt or reduce the spread of respiratory viruses: systematic review. BMJ 2009 Sep 21;339:b3675. doi: 10.1136/bmj.b3675.

INDEX TERMS

Medical Subject Headings (MeSH)

*Virus Shedding; Case-Control Studies; Influenza, Human [transmission] [virology]; Randomized Controlled Trials as Topic; Respiratory Tract Infections [*prevention & control] [transmission] [virology]; Virus Diseases [*prevention & control] [transmission]

MeSH check words

Humans

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Physical interventions to interrupt or reduce the spread of respiratory viruses (Review)

Jefferson T, Dooley L, Ferroni E, Al-Ansary LA, van Driel ML, Bawazeer GA, Jones MA, Hoffmann TC, Clark J, Beller EM, Glasziou PP, Conly JM

Jefferson T, Dooley L, Ferroni E, Al-Ansary LA, van Driel ML, Bawazeer GA, Jones MA, Hoffmann TC, Clark J, Beller EM, Glasziou PP, Conly JM.
Physical interventions to interrupt or reduce the spread of respiratory viruses.
Cochrane Database of Systematic Reviews 2023, Issue 1. Art. No.: CD006207.
DOI: 10.1002/14651858.CD006207.pub6.

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[Intervention Review]

Physical interventions to interrupt or reduce the spread of respiratory viruses

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Editorial group: Cochrane Acute Respiratory Infections Group.
Publication status and date: Edited (no change to conclusions), published in Issue 4, 2023.

Citation: Jefferson T, Dooley L, Ferroni E, Al-Ansary LA, van Driel ML, Bawazeer GA, Jones MA, Hoffmann TC, Clark J, Beller EM, Glasziou PP, Conly JM. Physical interventions to interrupt or reduce the spread of respiratory viruses. *Cochrane Database of Systematic Reviews* 2023, Issue 1. Art. No.: CD006207. DOI: 10.1002/14651858.CD006207.pub6.

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ABSTRACT

Background

Viral epidemics or pandemics of acute respiratory infections (ARIs) pose a global threat. Examples are influenza (H1N1) caused by the H1N1pdm09 virus in 2009, severe acute respiratory syndrome (SARS) in 2003, and coronavirus disease 2019 (COVID-19) caused by SARS-CoV-2 in 2019. Antiviral drugs and vaccines may be insufficient to prevent their spread. This is an update of a Cochrane Review last published in 2020. We include results from studies from the current COVID-19 pandemic.

Objectives

To assess the effectiveness of physical interventions to interrupt or reduce the spread of acute respiratory viruses.

Search methods

We searched CENTRAL, PubMed, Embase, CINAHL, and two trials registers in October 2022, with backwards and forwards citation analysis on the new studies.

Selection criteria

We included randomised controlled trials (RCTs) and cluster-RCTs investigating physical interventions (screening at entry ports, isolation, quarantine, physical distancing, personal protection, hand hygiene, face masks, glasses, and gargling) to prevent respiratory virus transmission.

Data collection and analysis

We used standard Cochrane methodological procedures.

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Main results

We included 11 new RCTs and cluster-RCTs (610,872 participants) in this update, bringing the total number of RCTs to 78. Six of the new trials were conducted during the COVID-19 pandemic; two from Mexico, and one each from Denmark, Bangladesh, England, and Norway. We identified four ongoing studies, of which one is completed, but unreported, evaluating masks concurrent with the COVID-19 pandemic.

Many studies were conducted during non-epidemic influenza periods. Several were conducted during the 2009 H1N1 influenza pandemic, and others in epidemic influenza seasons up to 2016. Therefore, many studies were conducted in the context of lower respiratory viral circulation and transmission compared to COVID-19. The included studies were conducted in heterogeneous settings, ranging from suburban schools to hospital wards in high-income countries; crowded inner city settings in low-income countries; and an immigrant neighbourhood in a high-income country. Adherence with interventions was low in many studies.

The risk of bias for the RCTs and cluster-RCTs was mostly high or unclear.

Medical/surgical masks compared to no masks

We included 12 trials (10 cluster-RCTs) comparing medical/surgical masks versus no masks to prevent the spread of viral respiratory illness (two trials with healthcare workers and 10 in the community). Wearing masks in the community probably makes little or no difference to the outcome of influenza-like illness (ILI)/COVID-19 like illness compared to not wearing masks (risk ratio (RR) 0.95, 95% confidence interval (CI) 0.84 to 1.09; 9 trials, 276,917 participants; moderate-certainty evidence. Wearing masks in the community probably makes little or no difference to the outcome of laboratory-confirmed influenza/SARS-CoV-2 compared to not wearing masks (RR 1.01, 95% CI 0.72 to 1.42; 6 trials, 13,919 participants; moderate-certainty evidence). Harms were rarely measured and poorly reported (very low-certainty evidence).

N95/P2 respirators compared to medical/surgical masks

We pooled trials comparing N95/P2 respirators with medical/surgical masks (four in healthcare settings and one in a household setting). We are very uncertain on the effects of N95/P2 respirators compared with medical/surgical masks on the outcome of clinical respiratory illness (RR 0.70, 95% CI 0.45 to 1.10; 3 trials, 7779 participants; very low-certainty evidence). N95/P2 respirators compared with medical/surgical masks may be effective for ILI (RR 0.82, 95% CI 0.66 to 1.03; 5 trials, 8407 participants; low-certainty evidence). Evidence is limited by imprecision and heterogeneity for these subjective outcomes. The use of a N95/P2 respirators compared to medical/surgical masks probably makes little or no difference for the objective and more precise outcome of laboratory-confirmed influenza infection (RR 1.10, 95% CI 0.90 to 1.34; 5 trials, 8407 participants; moderate-certainty evidence). Restricting pooling to healthcare workers made no difference to the overall findings. Harms were poorly measured and reported, but discomfort wearing medical/surgical masks or N95/P2 respirators was mentioned in several studies (very low-certainty evidence).

One previously reported ongoing RCT has now been published and observed that medical/surgical masks were non-inferior to N95 respirators in a large study of 1009 healthcare workers in four countries providing direct care to COVID-19 patients.

Hand hygiene compared to control

Nineteen trials compared hand hygiene interventions with controls with sufficient data to include in meta-analyses. Settings included schools, childcare centres and homes. Comparing hand hygiene interventions with controls (i.e. no intervention), there was a 14% relative reduction in the number of people with ARIs in the hand hygiene group (RR 0.86, 95% CI 0.81 to 0.90; 9 trials, 52,105 participants; moderate-certainty evidence), suggesting a probable benefit. In absolute terms this benefit would result in a reduction from 380 events per 1000 people to 327 per 1000 people (95% CI 308 to 342). When considering the more strictly defined outcomes of ILI and laboratory-confirmed influenza, the estimates of effect for ILI (RR 0.94, 95% CI 0.81 to 1.09; 11 trials, 34,503 participants; low-certainty evidence), and laboratory-confirmed influenza (RR 0.91, 95% CI 0.63 to 1.30; 8 trials, 8332 participants; low-certainty evidence), suggest the intervention made little or no difference. We pooled 19 trials (71, 210 participants) for the composite outcome of ARI or ILI or influenza, with each study only contributing once and the most comprehensive outcome reported. Pooled data showed that hand hygiene may be beneficial with an 11% relative reduction of respiratory illness (RR 0.89, 95% CI 0.83 to 0.94; low-certainty evidence), but with high heterogeneity. In absolute terms this benefit would result in a reduction from 200 events per 1000 people to 178 per 1000 people (95% CI 166 to 188). Few trials measured and reported harms (very low-certainty evidence).

We found no RCTs on gowns and gloves, face shields, or screening at entry ports.

Authors' conclusions

The high risk of bias in the trials, variation in outcome measurement, and relatively low adherence with the interventions during the studies hampers drawing firm conclusions. There were additional RCTs during the pandemic related to physical interventions but a relative paucity given the importance of the question of masking and its relative effectiveness and the concomitant measures of mask adherence which would be highly relevant to the measurement of effectiveness, especially in the elderly and in young children.

There is uncertainty about the effects of face masks. The low to moderate certainty of evidence means our confidence in the effect estimate is limited, and that the true effect may be different from the observed estimate of the effect. The pooled results of RCTs did not show a clear reduction in respiratory viral infection with the use of medical/surgical masks. There were no clear differences between the use

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of medical/surgical masks compared with N95/P2 respirators in healthcare workers when used in routine care to reduce respiratory viral infection. Hand hygiene is likely to modestly reduce the burden of respiratory illness, and although this effect was also present when ILI and laboratory-confirmed influenza were analysed separately, it was not found to be a significant difference for the latter two outcomes. Harms associated with physical interventions were under-investigated.

There is a need for large, well-designed RCTs addressing the effectiveness of many of these interventions in multiple settings and populations, as well as the impact of adherence on effectiveness, especially in those most at risk of ARIs.

PLAIN LANGUAGE SUMMARY

Do physical measures such as hand-washing or wearing masks stop or slow down the spread of respiratory viruses?

Key messages
We are uncertain whether wearing masks or N95/P2 respirators helps to slow the spread of respiratory viruses based on the studies we assessed.

Hand hygiene programmes may help to slow the spread of respiratory viruses.

How do respiratory viruses spread?
Respiratory viruses are viruses that infect the cells in your airways: nose, throat, and lungs. These infections can cause serious problems and affect normal breathing. They can cause flu (influenza), severe acute respiratory syndrome (SARS), and COVID-19.

People infected with a respiratory virus spread virus particles into the air when they cough or sneeze. Other people become infected if they come into contact with these virus particles in the air or on surfaces on which they land. Respiratory viruses can spread quickly through a community, through populations and countries (causing epidemics), and around the world (causing pandemics).

Physical measures to try to prevent respiratory viruses spreading between people include:

· washing hands often;

· not touching your eyes, nose, or mouth;

· sneezing or coughing into your elbow;

· wiping surfaces with disinfectant;

· wearing masks, eye protection, gloves, and protective gowns;

· avoiding contact with other people (isolation or quarantine);

· keeping a certain distance away from other people (distancing); and

· examining people entering a country for signs of infection (screening).

What did we want to find out?
We wanted to find out whether physical measures stop or slow the spread of respiratory viruses from well-controlled studies in which one intervention is compared to another, known as randomised controlled trials.

What did we do?
We searched for randomised controlled studies that looked at physical measures to stop people acquiring a respiratory virus infection.

We were interested in how many people in the studies caught a respiratory virus infection, and whether the physical measures had any unwanted effects.

What did we find?
We identified 78 relevant studies. They took place in low-, middle-, and high-income countries worldwide: in hospitals, schools, homes, offices, childcare centres, and communities during non-epidemic influenza periods, the global H1N1 influenza pandemic in 2009, epidemic influenza seasons up to 2016, and during the COVID-19 pandemic. We identified five ongoing, unpublished studies; two of them evaluate masks in COVID-19. Five trials were funded by government and pharmaceutical companies, and nine trials were funded by pharmaceutical companies.

No studies looked at face shields, gowns and gloves, or screening people when they entered a country.

We assessed the effects of:

· medical or surgical masks;

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· N95/P2 respirators (close-fitting masks that filter the air breathed in, more commonly used by healthcare workers than the general public); and

· hand hygiene (hand-washing and using hand sanitiser).

We obtained the following results:

Medical or surgical masks

Ten studies took place in the community, and two studies in healthcare workers. Compared with wearing no mask in the community studies only, wearing a mask may make little to no difference in how many people caught a flu-like illness/COVID-like illness (9 studies; 276,917 people); and probably makes little or no difference in how many people have flu/COVID confirmed by a laboratory test (6 studies; 13,919 people). Unwanted effects were rarely reported; discomfort was mentioned.

N95/P2 respirators

Four studies were in healthcare workers, and one small study was in the community. Compared with wearing medical or surgical masks, wearing N95/P2 respirators probably makes little to no difference in how many people have confirmed flu (5 studies; 8407 people); and may make little to no difference in how many people catch a flu-like illness (5 studies; 8407 people), or respiratory illness (3 studies; 7799 people). Unwanted effects were not well-reported; discomfort was mentioned.

Hand hygiene

Following a hand hygiene programme may reduce the number of people who catch a respiratory or flu-like illness, or have confirmed flu, compared with people not following such a programme (19 studies; 71,210 people), although this effect was not confirmed as statistically significant reduction when ILI and laboratory-confirmed ILI were analysed separately. Few studies measured unwanted effects; skin irritation in people using hand sanitiser was mentioned.

What are the limitations of the evidence?
Our confidence in these results is generally low to moderate for the subjective outcomes related to respiratory illness, but moderate for the more precisely defined laboratory-confirmed respiratory virus infection, related to masks and N95/P2 respirators. The results might change when further evidence becomes available. Relatively low numbers of people followed the guidance about wearing masks or about hand hygiene, which may have affected the results of the studies.

How up to date is this evidence?
We included evidence published up to October 2022.

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SUMMARY OF FINDINGS

Summary of findings 1. Medical/surgical masks compared to no masks for preventing the spread of viral respiratory illness

Randomised studies: medical/surgical masks compared to no masks for preventing the spread of viral respiratory illness

Patient or population: general population
Setting: community and hospitals
Intervention: medical/surgical masks
Comparison: no masks

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with no masks	Risk with randomised studies: masks				
Viral respiratory illness - influenza/COVID-like illness	Study population 160 per 1000	152 per 1000 (134 to 174)	RR 0.95 (0.84 to 1.09)	276,917 (9 RCTs)	⊕⊕⊕⊖ Moderate[a]	
Viral respiratory illness - laboratory-confirmed influenza/SARS-CoV-2	Study population 40 per 1000	40 per 1000 (29 to 57)	RR 1.01 (0.72 to 1.42)	13,919 (6 RCTs)	⊕⊕⊕⊖ Moderate[b]	
Adverse events	-		-	(3 RCTs)	⊕⊖⊖⊖ Very low[a,c]	Adverse events were not reported consistently and could not be meta-analysed. Adverse events reported for masks included warmth, discomfort, respiratory difficulties, humidity, pain, and shortness of breath, in up to 45% of participants.

***The risk in the intervention group** (and its 95% confidence interval) is based on the median observed risk in the comparison group of included studies and the **relative effect** of the intervention (and its 95% CI).
CI: confidence interval; **RCT:** randomised controlled trial; **RR:** risk ratio

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.

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Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

[a]Downgraded one level for study limitations (lack of blinding).
[b]Downgraded one level for imprecision (wide confidence intervals).
[c]Downgraded two levels for imprecision (only three studies enumerated adverse events; another study mentioned no adverse events).

Summary of findings 2. N95 respirators compared to medical/surgical masks for preventing the spread of viral respiratory illness

Randomised studies: N95 respirators compared to medical/surgical masks for preventing the spread of viral respiratory illness

Patient or population: general population and healthcare workers
Setting: hospitals and households
Intervention: N95 masks
Comparison: medical/surgical masks

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with medical masks	Risk with randomised studies: N95				
Viral respiratory illness - clinical respiratory illness	Study population 120 per 1000	84 per 1000 (54 to 132)	RR 0.70 (0.45 to 1.10)	7799 (3 RCTs)	⊕⊝⊝⊝ Very Low[a,b,c]	All studies were conducted in hospital settings with healthcare workers.
Viral respiratory illness - influenza-like illness	Study population 50 per 1000	41 per 1000 (33 to 52)	RR 0.82 (0.66 to 1.03)	8407 (5 RCTs)	⊕⊕⊝⊝ Low[a,b]	1 study was conducted in households (MacIntyre 2009).
Viral respiratory illness - laboratory-confirmed influenza	Study population 70 per 1000	77 per 1000 (63 to 94)	RR 1.10 (0.90 to 1.34)	8407 (5 RCTs)	⊕⊕⊕⊝ Moderate[b]	1 study was conducted in households (MacIntyre 2009).
Adverse events	-		-	(5 RCTs)	⊕⊝⊝⊝ Very Low[a,b,c]	There was insufficient consistent reporting of adverse events to enable meta-analysis. Only 1 study reported detailed adverse events: discomfort was reported in 41.9% of N95 wearers versus 9.8% of medical mask wearers (P < 0.001); headaches

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were more common with N95 (13.4% versus 3.9%; P < 0.001); difficulty breathing was reported more often in the N95 group (19.4% versus 12.5%; P = 0.01); and N95 caused more problems with pressure on the nose (52.2% versus 11.0%; P < 0.001). 4 RCTs either reported no adverse events or only reported on comfort wearing masks.

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the median risk in the comparison group and the observed __relative effect__ of the intervention (and its 95% CI).
CI: confidence interval; **RCT:** randomised controlled trial; **RR:** risk ratio

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

[a]Downgraded one level for study limitations (lack of blinding).
[b]Downgraded one level for imprecision (wide confidence interval or no meta-analysis conducted).
[c]Downgraded one level for inconsistency of results (heterogeneity).

Summary of findings 3. Hand hygiene compared to control for preventing the spread of viral respiratory illness

Hand hygiene compared to control for preventing the spread of viral respiratory illness

Patient or population: general population and healthcare workers
Setting: schools, childcare centres, homes, offices, nursing homes
Intervention: hand hygiene
Comparison: control

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with control	Risk with hand hygiene				
Acute respiratory illness	Study population		RR 0.86 (0.81 to 0.90)	52,105 (9 RCTs)	⊕⊕⊕⊖ Moderate[a]	
	380 per 1000	327 per 1000 (308 to 342)				

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Influenza-like illness	Study population		RR 0.94 (0.81 to 1.09)	34,503 (11 RCTs)	⊕⊕⊖⊖ Low[a,b]	
	90 per 1000	85 per 1000 (73 to 98)				
Laboratory-confirmed influenza	Study population		RR 0.91 (0.63 to 1.30)	8332 (8 RCTs)	⊕⊕⊖⊖ Low[b,c]	
	80 per 1000	73 per 1000 (50 to 104)				
Composite of acute respiratory illness, influenza-like illness, laboratory-confirmed influenza	Study population		RR 0.89 (0.83 to 0.94)	71,210 (19 RCTs)	⊕⊕⊖⊖ Low[a,b]	
	200 per 1000	178 per 1000 (166 to 188)				
Adverse events	-		-	(2 RCTs)	⊕⊖⊖⊖ Very low[a,b,c]	Data were insufficient to conduct meta-analysis. 1 study reported that no adverse events were observed, and another study reported that skin reaction was recorded for 10.4% of participants in the hand sanitiser group versus 10.3% in the control group.

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the median observed risk in the comparison groups of included studies and the __relative effect__ of the intervention (and its 95% CI).
CI: confidence interval; **RCT:** randomised controlled trial; **RR:** risk ratio

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

[a]Downgraded one level for study limitation (majority of studies were unblinded, with participant-assessed outcome).
[b]Downgraded one level for inconsistent results across studies.
[c]Downgraded one level for imprecision (wide confidence interval or no meta-analysis conducted).

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BACKGROUND

Description of the condition

Epidemic and pandemic viral infections pose a serious threat to people worldwide. Epidemics of note include severe acute respiratory syndrome (SARS) in 2003 and the Middle East respiratory syndrome (MERS), which began in 2012, and the current SARS-CoV-2 pandemic. Major pandemics include the H1N1 influenza caused by the H1N1pdm09 virus in 2009 and the coronavirus disease 2019 (COVID-19) caused by SARS-CoV-2.

Even non-epidemic acute respiratory infections (ARIs) place a huge burden on healthcare systems around the world, and are a prominent cause of morbidity (WHO 2017). Furthermore, ARIs are often antecedents to lower respiratory tract infections (RTIs) caused by bacterial pathogens (i.e. pneumonia), which cause millions of deaths worldwide, mostly in low-income countries (Schwartz 2018).

High viral load, high levels of transmissibility, susceptible populations, and symptomatic patients are considered to be the drivers of such epidemics and pandemics (Jefferson 2006a). Preventing the spread of respiratory viruses from person to person may be effective at reducing the spread of outbreaks.

Physical interventions, such as the use of masks and physical distancing measures, might prevent the spread of respiratory viruses which are considered to be transmitted by multiple modes of transmission including by respiratory particles of varying sizes spreading from infected to susceptible people and through direct and indirect contact (Kutter 2018; Leung 2021). It is recognised that there is a continuum of respiratory particle sizes varying between large droplet to fine aerosols, which is an important concept. Particles of a variety of sizes may be expelled from the human airway during coughing, sneezing, singing, talking, and during certain medical procedures (WHO 2021). In addition, transmission of respiratory viruses is likely highly complex, dependent on multiple host, virus and environmental factors, plus the myriad of interactions between these factors, which may influence the predominant modes of transmission in any given setting (Broderick 2008; Hendley 1988; Kutter 2018; Leung 2021). Current evidence suggests that the virus responsible for the current COVID-19 pandemic spreads mainly between people who are in close contact with each other (Onakpoya 2022a).

It is also unknown if all respiratory viruses or different strains of a specific respiratory virus transmit in a similar manner, further adding to the complexity of respiratory virus transmission.

Description of the intervention

Single measures of intervention such as the use of vaccines or antivirals, may be insufficient to contain the spread of influenza, but combinations of interventions may reduce the reproduction number to below 1 (Demicheli 2018a; Demicheli 2018b; Jefferson 2014; Jefferson 2018; Thomas 2010). When the reproduction number (or R0) is below 1, each infection causes less than one new secondary infection and the disease will eventually die out. For some respiratory viruses there are no licensed interventions, and a combination of social and physical interventions may be the only option to reduce the spread of outbreaks, particularly those that may be capable of becoming epidemic or pandemic in nature (Luby 2005). Such interventions were emphasised in the World Health Organization's latest Global Influenza Strategy 2019 to 2030, and have several possible advantages over other methods of suppressing ARI outbreaks since they may be instituted rapidly and may be independent of any specific type of infective agent, including novel viruses. In addition, the possible effectiveness of public health measures during the Spanish flu pandemic of 1918 to 1919 in US cities supports the impetus to investigate the existing evidence on the effectiveness of such interventions (Bootsma 2007), including quarantine (such as isolation, physical distancing) and the use of disinfectants. We also considered the major societal implications for any community adopting these measures (CDC 2005a; CDC 2005b; WHO 2006b; WHO 2020a; WHO 2020b).

How the intervention might work

Epidemics and pandemics are more likely during antigenic change (changes in the viral composition) in the virus or transmission from animals (domestic or wild) when there is no natural human immunity (Bonn 1997). High viral load, high levels of transmissibility, and symptomatic patients are considered to be the drivers of such epidemics and pandemics (Jefferson 2006b).

Physical interventions, such as the use of masks (Greenhalgh 2020; Howard 2020), physical distancing measures, school closures, and limitations of mass gatherings, might prevent the spread of the virus transmitted by infectious respiratory particles from infected to susceptible individuals. The use of hand hygiene, gloves, and protective gowns can also prevent the spread by limiting the transfer of viral particles onto and from fomites (inanimate objects such as flat surfaces, tabletops, utensils, porous surfaces, or nowadays cell phones, which can transmit the agent if contaminated) (Onakpoya 2022b). Such public health measures were widely adopted during the Spanish flu pandemic and have been the source of considerable debate (Bootsma 2007).

Why it is important to do this review

Although the benefits of physical interventions seem self-evident, given the global importance of interrupting respiratory virus transmission, having up-to-date estimates of their effectiveness is necessary to inform planning, decision-making, and policy. The continuance of outbreaks of COVID-19 and the reporting of several new trials assessing different barrier interventions in preventing the spread of SARS-COV-2 virus, have prompted this update (WHO 2022). Physical methods have several possible advantages over other methods of suppressing ARI outbreaks, including their rapid deployment and ability to be independent of the infective agent, including novel viruses.

The hallmark of the 2020 update was shifting from including all types of studies to a focus on randomised controlled trials (RCTs) only, which had substantially increased in number. This change enabled more robust evidence summaries from high-quality studies, which are much less prone to the risk of the multiple biases associated with observational studies, to help policy and decision makers in making national and global recommendations. The 2020 update identified 67 relevant studies, but none were carried out during the COVID-19 pandemic (Jefferson 2020). The three key messages of that update were: (1) hand hygiene programmes may help to slow the spread of respiratory viruses; (2) uncertainty whether wearing masks or N95/P2 respirators would help in slowing the spread of respiratory viruses; and (3) few studies were identified for other interventions. One study looked

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at quarantine, and none looked at eye protection, gowns and gloves, or screening people when they entered a country. However, during the last search of the 2020 update, six ongoing, unpublished studies were identified; three of them evaluate masks in COVID-19. The review authors are aware that several trials have now been published since the publication of the 2020 update, warranting this new update.

This is the fifth update (Jefferson 2009; Jefferson 2010; Jefferson 2011; Jefferson 2020) of a Cochrane Review first published in 2007 (Jefferson 2007).

OBJECTIVES

To assess the effectiveness of physical interventions to interrupt or reduce the spread of acute respiratory viruses.

METHODS

Criteria for considering studies for this review

Types of studies

For this 2022 update we only considered individual-level randomised controlled trials (RCTs), or cluster-RCTs, or quasi-RCTs for inclusion.

In versions of this review prior to 2020 we also included observational studies (cohorts, case-controls, before-after, and time series studies). However, for this update there were sufficient randomised studies to address our study aims, so we excluded observational studies because randomisation is the optimal method to prevent systematic differences between participants in different intervention groups and, further, deciding who receives an intervention and who does not is influenced by many factors, including prognostic factors (Higgins 2011). This point is particularly relevant here because individuals who chose to implement physical interventions are likely to use multiple interventions, thus making it difficult to separate out the effect of single interventions. Further, they are likely to be different from individuals who do not implement physical interventions in ways that are difficult to measure.

Types of participants

People of all ages.

Types of interventions

We included RCTs and cluster-RCTs of trials investigating physical interventions or combinations of interventions to prevent respiratory virus transmission compared with doing nothing or with other interventions. The interventions of interest included: screening at entry ports, isolation, quarantine, physical distancing, personal protection (clothing, gloves, devices), hand hygiene, face masks, gargling, nasal washes, eye protective devices, face shields, disinfecting, and school closure.

Types of outcome measures

For the outcomes listed below we had no predetermined key time points of interest or adverse events of special interest, however, methods of assessment of cases of viral respiratory illness based on laboratory-confirmation needed to be based on an accurate test in combination with critical additional information. For example, a polymerase chain reaction (PCR) test in combination with symptoms of disease, or a serological test at baseline as well as at the end of follow-up were acceptable methods. Further, we stratified analyses by study-specific definitions for cases of viral respiratory illness which included a broad definition of acute respiratory infection (ARI), a more specific definition of influenza-like-illness (ILI), and the most precise definition of a laboratory-confirmed respiratory infection that identified the actual viral pathogen. For the studies conducted during the COVID-19 pandemic, we assumed that COVID-like illness was interchangeable with ILI. In the case of laboratory-confirmed respiratory infection we separated out SARS-CoV-2/influenza and other viral pathogens. We did not pool these outcomes as it cannot be assumed that the effects of physical interventions will be the same for the different viral pathogens. The one exception was for the comparison of hand-hygiene versus control where the estimated effects for ARI, ILI and laboratory-confirmed infection were highly consistent.

Primary outcomes

1. Numbers of cases of viral respiratory illness (including acute respiratory infections (ARI), influenza-like illness (ILI), COVID-like illness and laboratory-confirmed influenza, SARS-CoV-2 or other viral pathogens).
2. Adverse events related to the intervention.

Secondary outcomes

1. Deaths.
2. Severity of viral respiratory illness as reported in the studies.
3. Absenteeism.
4. Hospital admissions.
5. Complications related to the illness, e.g. pneumonia.

Search methods for identification of studies

Electronic searches

For this 2022 update, we refined the original search strategy using a combination of previously included studies and automation tools (Clark 2020). We converted this search using the Polyglot Search Translator (Clark 2020), and ran the searches in the following databases:

1. the Cochrane Central Register of Controlled Trials (CENTRAL) (2022, Issue 09), which includes the Acute Respiratory Infections Group's Specialised Register (searched 04 October 2022) (Appendix 1);
2. PubMed (01 January 2020 to 04 October 2022) (Appendix 2);
3. Embase (01 January 2020 to 04 October 2022) (Appendix 3);
4. CINAHL (Cumulative Index to Nursing and Allied Health Literature) (01 January 2020 to 04 October) (Appendix 4);
5. US National Institutes of Health Ongoing Trials Register ClinicalTrials.gov (January 2010 to 04 October 2022); and
6. World Health Organization International Clinical Trials Registry Platform (January 2010 to 04 October 2022).

We combined the database searches with the Cochrane Highly Sensitive Search Strategy for identifying randomised trials in MEDLINE: sensitivity- and precision-maximising version (2008 revision) (Lefebvre 2011). Details of previous searches are available in Appendix 5.

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Searching other resources

We conducted a backwards-and-forwards citation analysis in Scopus on all newly included studies to identify other potentially relevant studies.

Data collection and analysis

Selection of studies

The search and citation analysis results were initially screened via the RobotSearch tool (Marshall 2018) to exclude all studies that were obviously not RCTs. We scanned the titles and abstracts of studies identified by the searches. We obtained the full-text articles of studies that either appeared to meet our eligibility criteria or for which there was insufficient information to exclude it. We then used a standardised form to assess the eligibility of each study based on the full article.

Data extraction and management

Five review authors (LA/GB/EF/EB/TOJ) independently applied the inclusion criteria to all identified and retrieved articles, and extracted data using a standard template that had been developed for and applied to previous versions of the review, but was revised to reflect our focus on RCTs and cluster-RCTs for this update. We resolved any disagreements through discussion with either PG or JMC acting as arbiter. We extracted and reported descriptions of interventions using the Template for Intervention Description and Replication (TIDieR) template (Table 1).

Assessment of risk of bias in included studies

Four review authors (EF/EB/GB/MJ) independently assessed risk of bias for the method of random sequence generation and allocation concealment (selection bias), blinding of participants and personnel (performance bias), blinding of outcome assessment (detection bias), outcome reporting (attrition bias), and selective reporting (reporting bias). In addition, for the cluster trials, we assessed selection bias due to how recruitment of participants was conducted. Participants should be identified before the cluster is randomised or, if not, recruitment should be by someone masked to the cluster allocation. Further, we considered whether there were sufficient numbers of clusters in each treatment group to ensure comparable groups, and excluded one study from the analysis due to insufficient number of clusters. We used the Cochrane risk of bias tool to assess risk of bias, classifying each risk of bias domain as 'low', 'high', or 'unclear'. The following were indications for low risk of bias:

1. method of random sequence generation: the method was well-described and is likely to produce balanced and truly random groups;
2. allocation concealment: the next treatment allocation was not known to participant/cluster or treating staff until after consent to join the study;
3. blinding of participants and personnel: the method is likely to maintain blinding throughout the study;
4. blinding of outcome assessors: all outcome assessors were unaware of treatment allocation;
5. outcome reporting: participant attrition throughout the study is reported, and reasons for loss are appropriately described; and
6. selective reporting: all likely planned and collected outcomes have been reported.

Measures of treatment effect

When possible, we performed meta-analysis and summarised effectiveness as risk ratio (RR) using 95% confidence intervals (CIs). For studies that could not be pooled, we used the effect measures reported by the trial authors (such as RR or incidence rate ratio (IRR) with 95% CI or, when these were not available, relevant P values). Where multiple analyses were reported on the same outcome we chose the analysis based on preferences for: (1) an adjusted analysis (over an unadjusted analysis), and (2) an analysis based on a longer follow-up period, or a greater number of outcomes events.

Unit of analysis issues

Many of the included studies were cluster-RCTs. To avoid any unit of analysis issues, we only included treatment effect estimates that were based on methods that were appropriate for the analysis of cluster trials, such as mixed models and generalised estimating equations. Given this restriction, we used the generalised inverse-variance method of meta-analysis. Some cluster-RCTs that did not report cluster-adjusted treatment effects provided sufficient data (number of events and participants by treatment group and intraclass correlations) for us to calculate appropriate treatment effect estimates and standard errors using the methods described in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2021a). For studies with multiple treatment groups but only one control group, where appropriate, we adjusted standard errors upwards to avoid unit of analysis errors in the meta-analyses. We did this by splitting the control group into equal sized groups and adjusting standard errors upwards to account for the reduced sample size of the control subgroups (Higgins 2021b).

Dealing with missing data

Previously, whenever details of studies were unclear, or studies were only known to us by abstracts or communications at meetings, we corresponded with first or corresponding authors. For this 2022 review, we did not contact authors of studies.

Assessment of heterogeneity

Aggregation of data was dependent on types of comparisons, sensitivity and homogeneity of definitions of exposure, populations and outcomes used. We calculated the I^2statistic and Chi^2 test for each pooled estimate to assess the presence of statistical heterogeneity (Higgins 2002; Higgins 2003).

Assessment of reporting biases

Given the widely disparate nature of our evidence base, we limited our assessment of possible reporting biases to funnel plot visual inspection if we had > 10 included studies for any single meta-analysis.

Data synthesis

If possible and appropriate, we combined studies in a meta-analysis. We used the generalised inverse-variance random-effects model where cluster-RCTs were included in the analysis. We chose the random-effects model because we expected clinical heterogeneity due to differences in pooled interventions and outcome definitions, and methodological heterogeneity due to pooling of RCTs and cluster-RCTs.

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Subgroup analysis and investigation of heterogeneity

We conducted one post hoc subgroup analyses of adults (18 years +) versus children (0 to 18 years) for the comparison of hand hygiene versus control.

We did not conduct further investigation of heterogeneity due to insufficient numbers of studies included in the comparisons.

Sensitivity analysis

We conducted a sensitivity analysis for hand hygiene versus control where we included the most precise and unequivocal measure of viral respiratory illness reported for each included study.

Summary of findings and assessment of the certainty of the evidence

We created three summary of findings tables using the following outcomes: numbers of cases of viral respiratory illness (including ARIs, ILI, COVID-like illness and laboratory-confirmed influenza/SARS-CoV-2 or other respiratory viruses), and adverse events related to the intervention (Summary of findings 1; Summary of findings 2; Summary of findings 3). We planned to include the secondary outcomes of deaths; severity of viral respiratory illness as reported in the studies; absenteeism; hospital admissions; and complications related to the illness (e.g. pneumonia). However, these data were poorly reported in the included studies. We used the five GRADE considerations (study limitations, consistency of effect, imprecision, indirectness, and publication bias) to assess the certainty of evidence as it related to the studies which contributed data to the meta-analyses for the prespecified outcomes (Atkins 2004). We used the methods and recommendations described in Section 8.5 and Chapter 12 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011), employing GRADEpro GDT software (GRADEpro GDT). We justified all decisions to down- or upgrade the certainty of the evidence in footnotes, and made comments to aid the reader's understanding of the review where necessary.

RESULTS

Description of studies

See Characteristics of included studies and Characteristics of excluded studies tables. Five trials were funded by government and pharmaceutical companies (Aiello 2010; Aiello 2012; Chard 2019; Yeung 2011; Zomer 2015), and nine trials were funded by pharmaceutical companies (Arbogast 2016; Carabin 1999; Luby 2005; Nicholson 2014; Sandora 2005; Sandora 2008; Turner 2004a; Turner 2004b; Turner 2012).

Results of the search

For this 2022 update we found 2667 records through database and trial registry searching, as well as 738 record through citation searching. After removing duplicates we had 2936 records that underwent title and abstract screening.
We identified a total of 202 titles in this 2022 update. We excluded 180 titles and retrieved the full papers of 35 studies, to include 11 new studies. See Figure 1.

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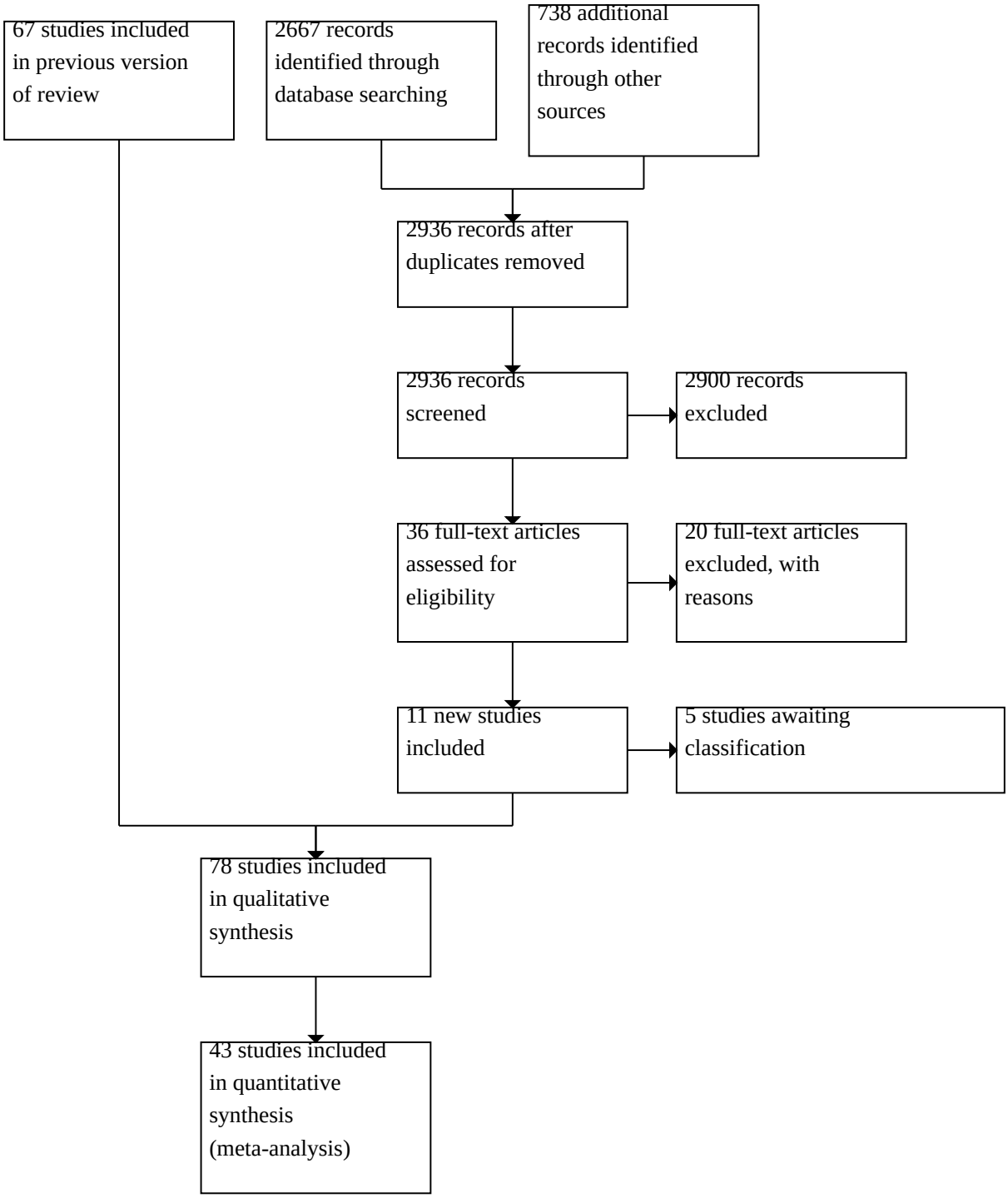
Figure 1. Study flow diagram.



Included studies

In this 2022 update we included 11 new studies (610,872 participants); randomised controlled trials (RCTs) (n = 5) or cluster-RCTs (n = 6) published between 2020 and 2022. In total 78 studies are included in this review update. For detailed descriptions of the interventions of the included studies, see Table 1.

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Eighteen trials focused on using masks (Abaluck 2022; Aiello 2010; Aiello 2012; Alfelali 2020; Barasheed 2014; Bundgaard 2021; Canini 2010; Cowling 2008; Ide 2016; Jacobs 2009; Loeb 2009; MacIntyre 2009; MacIntyre 2011; MacIntyre 2013; MacIntyre 2015; MacIntyre 2016; Radonovich 2019; Suess 2012). Thirteen of the 18 trials compared medical/surgical masks to no mask (control) (Abaluck 2022; Aiello 2010; Aiello 2012; Alfelali 2020; Barasheed 2014; Bundgaard 2021; Canini 2010; Cowling 2008; Jacobs 2009; MacIntyre 2009; MacIntyre 2015; MacIntyre 2016; Suess 2012). One study compared catechin-treated masks to no mask (Ide 2016), and one study included cloth masks versus control (third arm in MacIntyre 2015). Three of the 18 trials were in healthcare workers (Ide 2016; Jacobs 2009; MacIntyre 2015), whilst the remaining trials were in non-healthcare workers (students, households, families, or pilgrims). Only one trial was conducted during the H1N1 pandemic season (Suess 2012), and two trials were conducted during the SARS-CoV-2 pandemic (Abaluck 2022; Bundgaard 2021).

Five of the 18 trials compared N95 masks or P2 masks to medical/surgical masks (Loeb 2009; MacIntyre 2009; MacIntyre 2011; MacIntyre 2013; Radonovich 2019). All of these trials, except for one study that was conducted on household individuals (MacIntyre 2009), included healthcare workers either in a hospital setting, Loeb 2009; MacIntyre 2011; MacIntyre 2013, or an outpatient setting (MacIntyre 2009; Radonovich 2019).

One trial evaluated the effectiveness of quarantining workers of one of two sibling companies in Japan whose family members had developed an influenza-like illness (ILI) during the 2009 to 2010 H1N1 influenza pandemic (Miyaki 2011). Another trial conducted during the SARS-CoV-2 pandemic in Norway investigated fitness centre access with physical distancing compared to no access (Helsingen 2021); and one cluster trial compared daily testing for contacts of individuals with SARS-CoV-2 compared to self-isolation at home in English secondary schools (Young 2021).

Nineteen trials compared hand hygiene interventions with no hand hygiene (control) and provided data suitable for meta-analysis. The populations in these trials included adults, children, and families, in settings such as schools (Biswas 2019; Stebbins 2011), childcare centres (Azor-Martinez 2018; Correa 2012; Roberts 2000; Zomer 2015), homes/households (Cowling 2008; Cowling 2009; Larson 2010; Little 2015; Nicholson 2014; Ram 2015; Sandora 2005; Simmerman 2011), offices (Hubner 2010), military trainees (Millar 2016), villages (Ashraf 2020; Swarthout 2020), and nursing homes (Teesing 2021). None of the trials were conducted during a pandemic, although some of the studies were conducted during peak influenza seasons.

A further 10 trials that compared a variety of hand hygiene modalities to control provided insufficient information to include in meta-analyses. Three trials were in children: one was conducted in daycare centres in Denmark examining a multimodal hygiene programme (Ladegaard 1999), and two trials compared a hand hygiene campaign or workshop in an elementary school environment in Saudi Arabia, Alzaher 2018, and Egypt, Talaat 2011. Three trials tested virucidal hand treatment in an experimental setting, Gwaltney 1980; Turner 2004a, and in a community, Turner 2012, in the USA. Feldman 2016 compared hand-washing with chlorhexidine gluconate amongst Israeli sailors. One trial compared hand sanitiser packaged in a multimodal hygiene programme amongst office employees in the USA (Arbogast 2016). Two trials were conducted in a long-term facility setting: one trial examined the effect of a bundled hand hygiene programme on infectious risk in nursing home residents in France (Temime 2018), and the other trial compared the effect of using hand sanitisers in healthcare workers on the rate of infections (including respiratory infections) in nursing home residents in Hong Kong (Yeung 2011).

Five trials compared different hand hygiene interventions in a variety of settings such as schools (Morton 2004, in kindergartens and elementary schools in the USA; Priest 2014, in primary schools in New Zealand; and Pandejpong 2012 in kindergartens in Thailand). One study was conducted in low-income neighbourhoods in Karachi, Pakistan (Luby 2005), and one was conducted in a workplace environment in Finland (Savolainen-Kopra 2012). A variety of interventions were used across these trials such as soap and water (Luby 2005; Savolainen-Kopra 2012), hand sanitiser (Morton 2004; Pandejpong 2012; Priest 2014; Savolainen-Kopra 2012), body wash (Luby 2005), and alcohol-based hand wipes (Morton 2004), with or without additional hygiene education. There was considerable variation in interventions, and the information in the trial reports was insufficient to permit meta-analysis.

Seven trials compared a combined intervention of hand hygiene and face masks with control. Four of these trials were carried out in households in Germany (Suess 2012), Thailand (Simmerman 2011), Hispanic immigrant communities in the USA (Larson 2010), and households in Hong Kong (Cowling 2009). Two trials were conducted amongst university student residences (Aiello 2010; Aiello 2012), and two trials in groups of pilgrims at the annual Hajj (Aelami 2015; Alfelali 2020). Moreover, six trials evaluated the incremental benefit of combining surgical masks in addition to hand hygiene with soap (Simmerman 2011), hand sanitiser (Aiello 2010; Aiello 2012; Larson 2010; Suess 2012), or both (Cowling 2009), versus mask or hand hygiene alone on the outcomes of ILI and influenza. Aelami 2015 investigated a hygienic package (alcohol-based hand rub (gel or spray), surgical masks, soap, and paper handkerchiefs) with a control group.

Seven trials compared a multimodal combination of hand hygiene and disinfection of surfaces, toys, linen, or other components of the environment with a control (Ban 2015; Carabin 1999; Ibfelt 2015; Kotch 1994; McConeghy 2017; Sandora 2008; White 2001). Variation in scope and type of interventions and insufficient data in trial reports precluded meta-analysis. All studies except for one were in children (McConeghy 2017), which was in a nursing home population).

Three trials included in two papers investigated the role of virucidal tissues in interrupting transmission of naturally occurring respiratory infections in households (Farr 1988a; Farr 1988b; Longini 1988). Four cluster-RCTs implemented complex, multimodal sanitation, education, cooking, and hygiene interventions (Chard 2019; Hartinger 2016; Huda 2012; Najnin 2019). All four of these trials were conducted in low-income countries in settings with minimal to no access to basic sanitation.

Three trials assessed the effect of gargling on the incidence of upper respiratory tract infections (URTIs) or influenza: gargling with povidone-iodine (Satomura 2005), green tea (Ide 2014), and tap water (Goodall 2014). Two trials investigated the use of mouth/nasal washes on the incidence of SARS-CoV-2 infection in healthcare workers during the COVID-19 pandemic (Almanza-Reyes 2021; Gutiérrez-García 2022). One trial investigated the use of glasses against the transmission of SARS-CoV-2 (Fretheim 2022a).

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Ongoing studies

We identified four ongoing studies during the course of the COVID-19 pandemic, of which one is completed, but unreported (NCT04471766). The trials evaluated masks concurrent with the COVID-19 pandemic. Three trials on other interventions are ongoing (Brass 2021; NCT03454009; NCT04267952).

Studies awaiting classification

We identified five studies awaiting classification (Contreras 2022; Croke 2022; Delaguerre 2022; Loeb 2022; Varela 2022).

A previous RCT (NCT04296643) reported as ongoing in the last version has now been recently published but was not able to be included in the summary of findings pooled results (Loeb 2022). In a multicentre, randomised non-inferiority trial of 1009 healthcare workers (HCWs) across four countries randomised to medical mask versus fit-tested N95 respirators for direct care of COVID-19 patients or long-term care residents, laboratory-confirmed SARS-CoV-2 was found in 10.46% (52/497) versus 9.27% (47/507) in the medical/surgical mask group and fit-tested N95 respirator group (hazard ratio 1.14 (95% CI 0.77 to 1.69), respectively. There was a 1.19% absolute increase in risk of COVID-19 with medical masks versus N95 respirator 95% CI (-2.5% to 4.9%). There were 47 (10.8%) adverse events related to the intervention reported in the medical mask group and 59 (13.6%) in the N95 respirator group. The use of medical masks was found to be non-inferior to N95 respirators in the direct care of COVID-19 patients and the study crossed over into the more transmissible Omicron variant period of the COVID-19 pandemic.

Excluded studies

We excluded a total of 180 studies. We identified 20 new studies for exclusion at the data extraction stage of this 2022 update, all of which appeared to be eligible at screening. Five of the 20 studies were ineligible due to evaluating treatments for patients with disease (Cyril Vitug 2021; Ferrer 2021; Meister 2022; Sanchez Barrueco 2022; Sevinc Gul 2022), two were excluded because they did not assess clinical outcomes (Costa 2021; Seneviratne 2021), four were excluded due to not assessing viral outcomes (Gharebaghi 2020; Giuliano 2021; Karakaya 2021; Kawyannejad 2020), five were excluded as they were experiments that did not measure any of our outcomes of interest (Ahmadian 2022; Dalakoti 2022; Egger 2022; Malaczek 2022; Montero-Vilchez 2022); three were excluded because they were not RCTs (Chen 2022; Lim 2022; Mo 2022), and one was excluded as it was a report of another study (Munoz-Basagoiti 2022).

Risk of bias in included studies

The overall risk of bias is presented graphically in Figure 2 and summarised by included study in Figure 3. Details on the judgements can be found in the descriptions of individual included studies (Characteristics of included studies table). Out of 78 included studies, only two were rated as low risk of bias for all domains. One of those studies compared two different types of masks (Radonovich 2019), and the other compared hand sanitiser to no treatment (Turner 2012). Notably, neither of these two studies was blinded, however, trial procedures were sufficiently robust that the risk of performance bias was low. Overall,approximately only 20% of the studies were rated as low risk of performance bias. This risk of bias domain was particularly problematic because most interventions studied could not be blinded from participants and/or investigators. The two risks of bias domains that were rated the least problematic were attrition bias and random sequence generation where around 50% of studies were rated as low risk of bias. Allocation concealment, blinded outcome assessment and selective reporting were rated as low risk of bias for around 40% of the included studies. Many of the included studies were cluster-RCTs where the randomisation process was not well reported leading to ratings of unclear risk of bias.

Figure 2. 'Risk of bias' graph: review authors' judgements about each risk of bias item presented as percentages across all included trials.

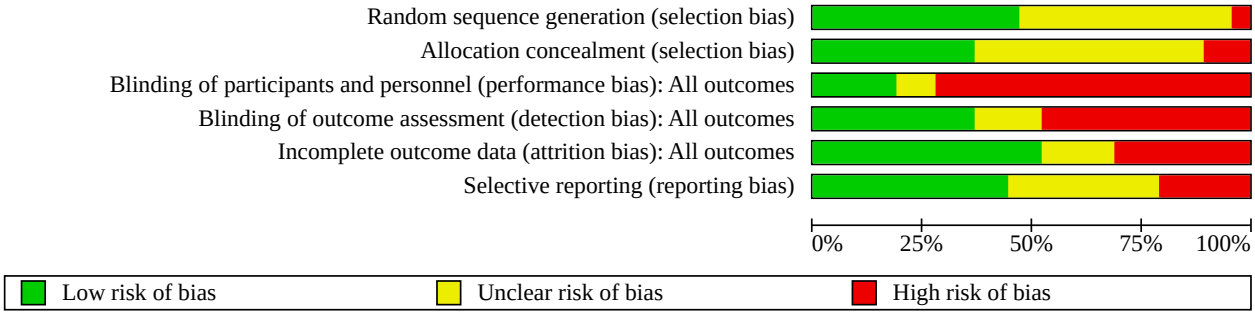

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Figure 3. 'Risk of bias' summary: review authors' judgements about each risk of bias item for each included trial.

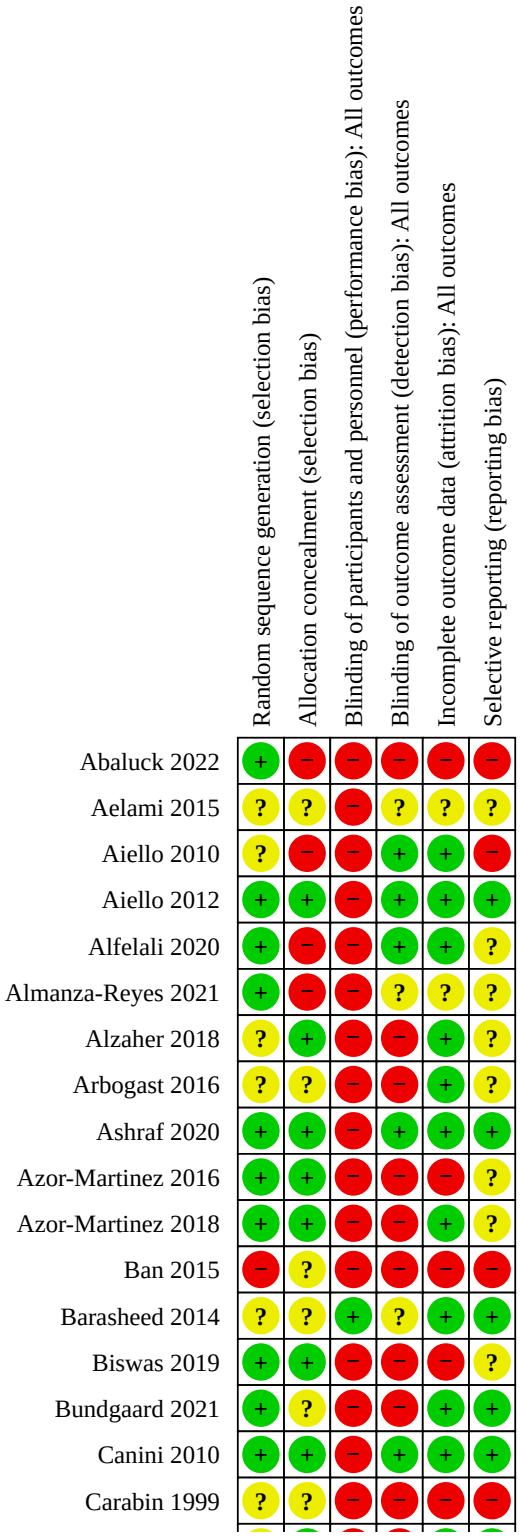

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Figure 3. (Continued)

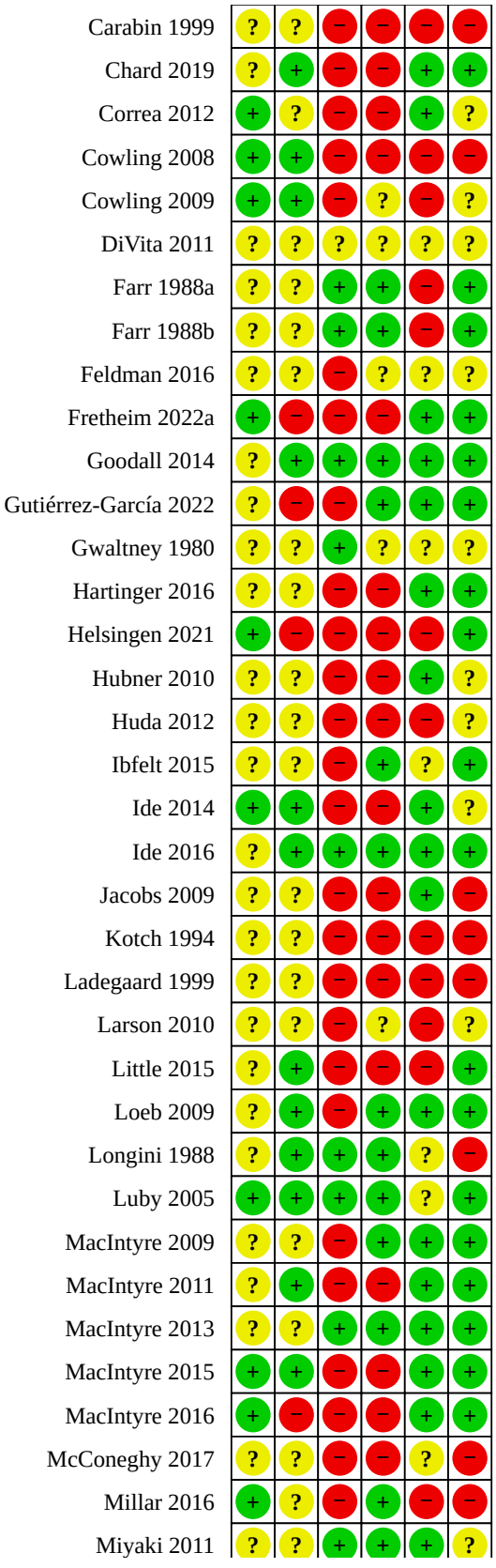

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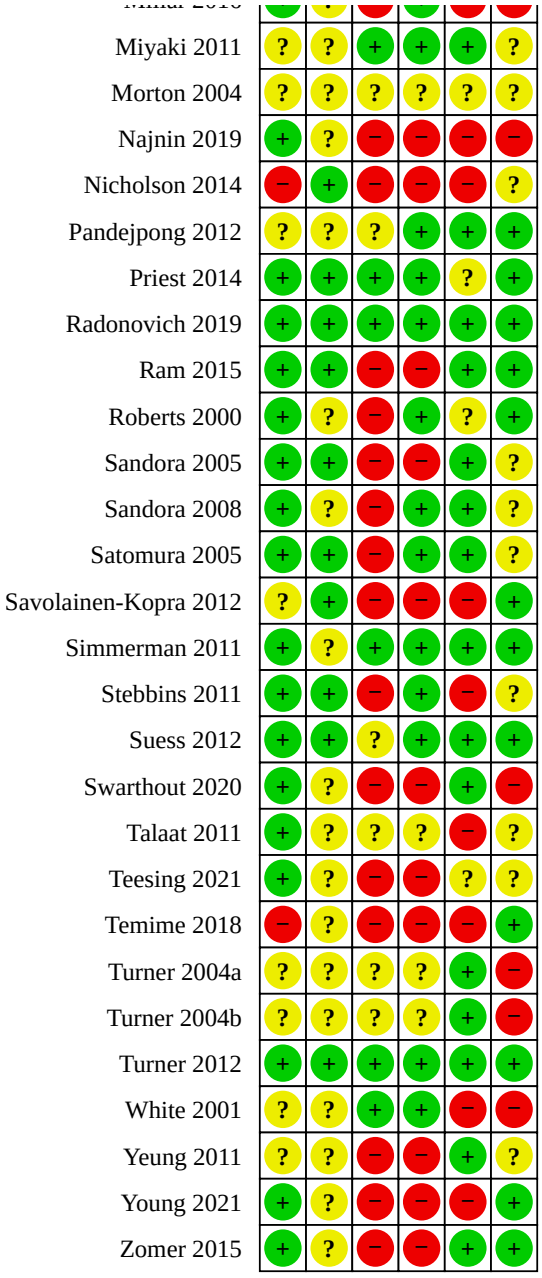
Figure 3. (Continued)



Allocation

For this 2022 review, 10 of the 11 newly included studies provided adequate information on randomisation and were judged to have low risk of bias (Abaluck 2022; Alfelali 2020; Almanza-Reyes 2021; Ashraf 2020; Bundgaard 2021; Fretheim 2022a; Helsingen 2021; Swarthout 2020; Teesing 2021; Young 2021). Six of these studies described the use of a computerised random number generator (Almanza-Reyes 2021; Bundgaard 2021; Helsingen 2021; Swarthout 2020; Teesing 2021; Young 2021). Almanza-Reyes 2021 described the use of computer-generated stratified block scheme, while Bundgaard 2021 reported the use of a computer algorithm stratified by the five regions of Denmark. In Fretheim 2022a, the investigators used a digital platform (Nettskjema) for recruitment, randomisation and allocation. Three studies mentioned the use of a random number generator, with no additional specifics (Helsingen 2021; Swarthout 2020; Teesing 2021), while Young 2021 mentioned that randomisation was performed in blocks of two and stratified using nine strata to ensure a sample representative of schools and colleges in England. Abaluck 2022 reported pairwise cross randomisation, whilst Ashraf 2020 reported using a block random number generator. Alfelali 2020 described using coin-tossing by an individual who was not a member of the research team (i.e. a fellow pilgrim who was not a participant in the trial, a tour operator, or a medical volunteer). One study provided insufficient information to judge the sequence generation bias (Gutiérrez-García 2022).

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The success of randomisation was judged as low risk of bias in one study only that used an off-site investigator to allocate groups (Ashraf 2020). Four new studies provided insufficient information to make a judgment on the adequacy of the process (Bundgaard 2021; Swarthout 2020; Teesing 2021; Young 2021). The remaining six newly included studies were judged as high risk of allocation bias (Abaluck 2022; Alfelali 2020; Almanza-Reyes 2021; Fretheim 2022a; Gutiérrez-García 2022; Helsingen 2021). In Abaluck 2022, there was a significant difference in the numbers of households included in each treatment group, suggestive of a lack of allocation concealment. Alfelali 2020 used coin tossing, which can lead to a large imbalance. In Almanza-Reyes 2021 baseline prognostic factors (vaccination and frequency of handwashing) were unbalanced between the two arms. In Fretheim 2022a, a higher number of participants used face masks in the intervention group. In Gutiérrez-García 2022 there as a significant age difference between the two groups. Helsingen 2021 described assigning the randomised sequence by a member of the research team, with no further description.

For the review published in 2020, information on sequence generation was overall poorly reported in most of the included studies. Nineteen of the included studies provided adequate information on the randomisation scheme and were judged as at low risk of bias (Aiello 2012; Azor-Martinez 2016; Azor-Martinez 2018; Biswas 2019; Canini 2010; Correa 2012; Ide 2014; MacIntyre 2015; MacIntyre 2016; Millar 2016; Najnin 2019; Radonovich 2019; Ram 2015; Simmerman 2011; Stebbins 2011; Suess 2012; Talaat 2011; Turner 2012; Zomer 2015). Nine studies described the use of computerised sequence generation program/software (Aiello 2012; Azor-Martinez 2018; Biswas 2019; Canini 2010; Millar 2016; Najnin 2019; Radonovich 2019; Talaat 2011; Turner 2012). One study used random number tables for sequence generation (Azor-Martinez 2016). Three studies described using the random function in Microsoft Excel (Microsoft Excel 2018) (Correa 2012; MacIntyre 2016; Suess 2012). Two studies used statistical software to generate a randomisation allocation (MacIntyre 2015; Priest 2014). Two studies reported using block randomisation: Ram 2015 used block randomisation, and an independent investigator-generated the list of random assignments, whilst Simmerman 2011 performed block randomisation. Stebbins 2011 used constrained randomisation, and Zomer 2015 reported using stratified randomisation by means of computer generation with a 1:1 ratio in each of the strata.

Fourteen studies reported insufficient information to permit a judgement on the adequacy of the process to minimise selection bias (Aelami 2015; Alzaher 2018; Arbogast 2016; Barasheed 2014; Chard 2019; DiVita 2011; Feldman 2016; Hubner 2010; Ibfelt 2015; McConeghy 2017; Miyaki 2011; Pandejpong 2012; Savolainen-Kopra 2012; Yeung 2011). Six studies provided some description about sequence generation, but it was still unclear (Hartinger 2016; Huda 2012; Ide 2016; Little 2015; MacIntyre 2011; MacIntyre 2013). Huda 2012 mentioned random number tables, but it was unclear if this was for random selection or randomisation. Ide 2016 used computer-generated randomisation, but the method was not stated. Hartinger 2016 used covariate-constrained randomisation, but the method was not described. In Little 2015, participants were automatically randomly assigned by the intervention software, but the sequence generation was not described. Two studies used a secure computerised randomisation program (MacIntyre 2011; MacIntyre 2013), but the sequence generation was not described.

Three of the studies included in the 2020 review, were poorly randomised (Ban 2015; Nicholson 2014; Temime 2018). Ban 2015 included only two clusters, and the randomisation scheme was not reported. Nicholson 2014 used coin tossing, which can lead to a large imbalance. Temime 2018 used “simple randomisation” with no further description.

For the RCTs included in previous versions of the review, three were poorly reported with no description of randomisation sequence or concealment of allocation (Gwaltney 1980; Turner 2004a; Turner 2004b). The quality of the cluster-RCTs varied, with four studies not providing a description of the randomisation procedure (Carabin 1999; Kotch 1994; Morton 2004; White 2001). We rated seven studies as at low risk of bias for sequence generation (Cowling 2008; Cowling 2009; Luby 2005; Roberts 2000; Sandora 2005; Sandora 2008; Satomura 2005), and a further six studies as at unclear risk of bias (Farr 1988a; Farr 1988b; Ladegaard 1999; Loeb 2009; Longini 1988; MacIntyre 2009).

Many of the newly included cluster-RCTs did not report adequately on allocation concealment. Twenty-one of these studies reported adequate allocation and were judged as at low risk of bias (Aiello 2012; Alzaher 2018; Azor-Martinez 2016; Azor-Martinez 2018; Biswas 2019; Canini 2010; Chard 2019; Goodall 2014; Ide 2014; Ide 2016; Little 2015; MacIntyre 2011; MacIntyre 2015; Nicholson 2014; Priest 2014; Radonovich 2019; Ram 2015; Savolainen-Kopra 2012; Stebbins 2011; Suess 2012; Turner 2012). Aiello 2012 randomised all residence houses in each of the residence halls prior to the intervention implementation. Alzaher 2018 allocated schools prior to all schoolgirls attending selected schools being invited to participate. Azor-Martinez 2016 allocated schools/classes prior to children's recruitment. Azor-Martinez 2018 assigned clusters prior to recruitment. Biswas 2019 completed the allocation prior to individuals being recruited. Chard 2019 allocated schools prior to individuals being recruited. Goodall 2014 used opaque, sealed, serially numbered envelopes that were only accessed when two study personnel were present. Ide 2014 also reported using individual drawing of sealed, opaque envelopes to randomly assign participants to the study groups. MacIntyre 2011 randomised hospitals prior to inclusion of participants. In MacIntyre 2015, hospital wards were randomised prior to recruitment of individuals. Nicholson 2014 used coin tossing to assign communities to intervention or control arms. Radonovich 2019 used constrained randomisation to resolve any potential imbalance between covariates between the trial arms. Four studies reported the use of central randomisation: Canini 2010 used central randomisation by employing an interactive voice response system; Ide 2016 used central randomisation services; Little 2015 participants were automatically randomly assigned by the intervention software; and Ram 2015 described a central allocation through data collectors notifying the field research officer, who consulted the block randomisation list to make the assignment of the household compound to intervention or control. Savolainen-Kopra 2012 randomised clusters by matching prior to the onset of the interventions. Four studies reported that allocation was assigned by personnel (investigator, physician, or statistician) unaware of the randomisation sequence (Priest 2014; Stebbins 2011; Suess 2012; Turner 2012). Twenty-two studies reported insufficient information to permit a judgement on the adequacy of the process to minimise selection bias (Aelami 2015; Arbogast 2016; Ban 2015; Barasheed 2014; Correa 2012; DiVita 2011; Feldman 2016; Hartinger 2016; Hubner 2010; Huda 2012; Ibfelt 2015; MacIntyre

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2013; McConeghy 2017; Millar 2016; Miyaki 2011; Najnin 2019; Pandejpong 2012; Simmerman 2011; Talaat 2011; Temime 2018; Yeung 2011; Zomer 2015). Two studies provided some information about allocation, but it was not enough to permit a judgement on the risk of bias (Barasheed 2014; Simmerman 2011). Barasheed 2014 randomised pilgrim tents using an independent study co-ordinator who was not an investigator, but did not describe how this was done. Simmerman 2011 described using a study co-ordinator to assign households to the study arm (after consent was obtained). Only one of the newly added studies was judged as at high risk of bias, where the random assignment was allocated by doctors enrolling the participants (MacIntyre 2016). Of the previously included RCTs, 14 provided no or an insufficient description of concealment of allocation (Carabin 1999; Farr 1988a; Farr 1988b; Gwaltney 1980; Kotch 1994; Ladegaard 1999; Larson 2010; MacIntyre 2009; Morton 2004; Roberts 2000; Sandora 2008; Turner 2004a; Turner 2004b; White 2001). We assessed all of the remaining studies as at low risk of bias (Canini 2010; Cowling 2008; Cowling 2009; Loeb 2009; Longini 1988; LLuby 2005; Sandora 2005;Satomura 2005). Aiello 2010 used the drawing of a uniform ticket with the name of each hall out of a container and was rated as at high risk of bias.

Blinding

Although blinding is less of a concern in cluster-RCTs, the risk of bias is substantial when the outcomes are subjective and the outcome assessor is not blinded.

In this 2022 review, five RCTs (Almanza-Reyes 2021; Bundgaard 2021; Fretheim 2022a; Gutiérrez-García 2022; Helsingen 2021), and six cluster-RCTs were all judged to have a high risk of detection bias (Abaluck 2022; Alfelali 2020; Ashraf 2020; Swarthout 2020; Teesing 2021; Young 2021).

We judged two of the newly included studies to have a low risk of detection bias as the outcome is laboratory-confirmed (Alfelali 2020; Gutiérrez-García 2022). One study provided insufficient information to enable judgment (Almanza-Reyes 2021). The remaining eight of the 11 new studies have a high risk of detection bias (Abaluck 2022; Ashraf 2020; Bundgaard 2021; Fretheim 2022a; Helsingen 2021; Swarthout 2020; Teesing 2021; Young 2021). In Abaluck 2022, investigators dropped individuals for whom symptom data were missing. In addition, other outcomes were subjective and can be influenced by the unblinded mask promoters, and mask surveillance staff. Moreover, blood testing in the protocol specified baseline testing which was not done, and no further explanation was provided. In Ashraf 2020, although the data collection team was separate from the intervention team, they were not blinded, and the outcome was respiratory illness measured through caregiver-reported symptoms. In Bundgaard 2021, case detection was based on patient-reported symptoms on home tests. In Fretheim 2022a, the outcome was self-reported positive COVID-19 test result, notified to the Norwegian Surveillance System for Communicable Diseases (MSIS). However, the public policy requiring confirmatory PCR-test had changed during the study, which may have affected reporting. In Helsingen 2021, although the outcome was a positive test for COVID-19 based on SARS-CoV-2 ribonucleic acid, the samples were collected and sent by participants, and there was a difference in adherence in testing between the two groups. Swarthout 2020, Teesing 2021, and Young 2021 all had subjective outcomes and assessors were not blinded. As for the detection bias, six of the newly included studies were considered to have a high risk of detection bias (Bundgaard 2021; Gutiérrez-García 2022; Helsingen 2021; Swarthout 2020; Teesing 2021; Young 2021. In Bundgaard 2021, case detection was based on patient-reported symptoms and results from home point-of-care (POCT) testing. The primary outcome of Gutiérrez-García 2022 was participants' self-reported symptoms. Case detection in Helsingen 2021 was based on a home-test kit. Swarthout 2020, Teesing 2021, and Young 2021 had subjective outcomes.

In the 2020 review, we judged 36 studies to have a high risk of bias (Aiello 2012; Abaluck 2022; Alfelali 2020; Almanza-Reyes 2021; Alzaher 2018; Arbogast 2016; Ashraf 2020; Azor-Martinez 2016; Azor-Martinez 2018; Ban 2015; Biswas 2019; Bundgaard 2021; Carabin 1999; Chard 2019; Correa 2012; Cowling 2008; Gutiérrez-García 2022; Helsingen 2021; Ide 2014; Kotch 1994; Ladegaard 1999; Little 2015; MacIntyre 2011; MacIntyre 2015; MacIntyre 2016; McConeghy 2017; Najnin 2019; Nicholson 2014; Ram 2015; Sandora 2008; Savolainen-Kopra 2012; Swarthout 2020; Teesing 2021; Temime 2018; Young 2021; Zomer 2015). We assessed five cluster-RCTs as at low risk of bias. Farr 1988a and Farr 1988b were double-blinded studies and were judged as at low risk of bias. MacIntyre 2013 and Simmerman 2011 reported laboratory-confirmed influenza, and blinding would not have affected the result. In Miyaki 2011 the self-reported respiratory symptoms were confirmed by a physician.

We judged four cluster-RCTs to have a low risk of detection bias because the outcome was laboratory-confirmed influenza (Alfelali 2020; Barasheed 2014; Suess 2012), or physician-confirmed ILI, Pandejpong 2012. Another two cluster-RCTs were judged to have a low risk of bias because outcome assessors were blinded (Abaluck 2022; Ashraf 2020). One RCT (Almanza-Reyes 2021) and two cluster-RCTs (Talaat 2011; Yeung 2011) provided insufficient data to judge the effect of non-blinding. Talaat 2011 included outcomes that were both self-reported ILI and laboratory-confirmed influenza. In Yeung 2011 the detection of cases was based on records for hospitalisation related to infection (including pneumonia). Eleven cluster-RCTs were not blinded, but we judged the primary outcome to be unaffected by non-blinding. Seven trials reported laboratory-confirmed influenza (Aiello 2012; Cowling 2009; Larson 2010; Loeb 2009; MacIntyre 2009; Millar 2016; Stebbins 2011). Four studies reported self-reported outcomes (Canini 2010; Priest 2014; Roberts 2000; Sandora 2008), but outcome assessors were not aware of the intervention assignment. Five RCTs were double-blinded and were judged as at low risk of bias (Goodall 2014; Ide 2016; Longini 1988; Luby 2005; White 2001), whilst two studies were single-blinded where investigators, Radonovich 2019, or laboratory personnel, Turner 2012, were blinded. Four RCTs were not blinded and were judged as at high risk of bias given the subjective nature of the outcome assessed (Hubner 2010; Ibfelt 2015; Jacobs 2009; Satomura 2005). Turner 2004a and Turner 2004b were double-blind studies, but insufficient information was provided to assess the risk of bias.

Incomplete outcome data

In this 2022 review, six of the 11 newly included studies had reasonable attrition and provided sufficient evidence about participant flow throughout the study and reasons of loss to follow-up, and hence were assessed as having a low risk of attrition bias (Alfelali 2020; Ashraf 2020; Bundgaard 2021; Fretheim 2022a; Gutiérrez-García 2022; Swarthout 2020). Two studies provided insufficient information to assess the attrition risk (Almanza-

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Reyes 2021; Teesing 2021). The remaining three studies were judged at high risk of attrition bias. In Abaluck 2022, laboratory testing results were only available for 40% of the symptomatic participants. In Helsingen 2021, more people in the control group withdrew from the study and reasons for withdrawal were not provided. In the Young 2021 study there was high attrition at different rates between the two groups.

In the 2020 review, we assessed 26 newly included trials as having a low risk of attrition bias, with sufficient evidence from the participant flow chart, and explanation of loss to follow-up (which was minimal) similar between groups (Aiello 2012; Alzaher 2018; Arbogast 2016; Azor-Martinez 2018; Barasheed 2014; Canini 2010; Chard 2019; Correa 2012; Goodall 2014; Hartinger 2016; Hubner 2010; Ide 2014; Ide 2016; MacIntyre 2011; MacIntyre 2013; MacIntyre 2015; MacIntyre 2016; Miyaki 2011; Pandejpong 2012; Radonovich 2019; Ram 2015; Simmerman 2011; Suess 2012; Turner 2012; Yeung 2011; Zomer 2015). Seven studies did not report sufficient information on incomplete data (attrition bias) (Aelami 2015; DiVita 2011; Feldman 2016; Hartinger 2016; Ibfelt 2015; McConeghy 2017; Priest 2014). Twelve studies had a high risk of attrition bias (Azor-Martinez 2016; Ban 2015; Biswas 2019; Huda 2012; Little 2015; Millar 2016; Najnin 2019; Nicholson 2014; Savolainen-Kopra 2012; Stebbins 2011; Talaat 2011; Temime 2018). In Azor-Martinez 2016, attrition levels were high and differed between the two groups. Ban 2015 did not report on reasons for loss to follow-up. Biswas 2019 did not provide information on missing participants (28 children in the control schools and two children in the intervention schools). Huda 2012 did not provide a flow diagram of study participants. Little 2015 had high attrition that differed between the two groups. Attrition in Millar 2016 differed amongst the three groups. In addition, ARI cases were captured utilising clinic-based medical records for those participants who sought hospital care only. In Najnin 2019, there was high migration movement during the study, which could have distorted the baseline characteristics even more. There was no description of how such migration and changes in the intervention group were dealt with. In Nicholson 2014, households were removed from the study if they provided no data for five consecutive weeks. Although attrition was reported in Savolainen-Kopra 2012, and 76% of volunteers who were recruited at the beginning of the reporting period completed the study, new recruits were added during the study to replace volunteers lost in most clusters. The total number of reporting participants at the end of the trial was 626 (91.7%) compared to the beginning, meaning that 15.7% of participants were replaced during the study. In Stebbins 2011,reasons for episodes of absence in 66% of the study participants were not reported. Talaat 2011 did not provide a flow chart of clusters flow during the study period and provided no information on withdrawal. Temime 2018 was greatly biased due to underreporting of outcomes in the control groups. Furthermore, no study flow chart was provided, and there was no reporting on any exclusions.

Selective reporting

For this 2022 review update, six of the 11 newly included studies reported all specified outcomes and were judged to have a low risk of selective reporting (Ashraf 2020; Bundgaard 2021; Fretheim 2022a; Gutiérrez-García 2022; Helsingen 2021; Young 2021). Three studies had no published protocol and were considered to have an unclear risk of selective reporting (Alfelali 2020; Almanza-Reyes 2021; Teesing 2021). The remaining two new included studies are considered to have a high risk of bias in this domain. Abaluck 2022 did not report on prespecified seroconversion, while in Swarthout 2020, none of the outcomes reported were prespecified in the trial registry.

In the 2020 review, 22 included studies reported all specified outcomes and were judged as at low risk of reporting bias (Aiello 2012; Barasheed 2014; Canini 2010; Chard 2019; Goodall 2014; Hartinger 2016; Ibfelt 2015; Ide 2016; Little 2015; MacIntyre 2011; MacIntyre 2013; MacIntyre 2015; MacIntyre 2016; Pandejpong 2012; Priest 2014; Radonovich 2019; Savolainen-Kopra 2012; Simmerman 2011; Suess 2012; Temime 2018; Turner 2012; Zomer 2015). For 18 studies, it is unlikely that other outcomes were measured and not reported, although no protocol was available to assess reporting bias (Aelami 2015; Alzaher 2018; Arbogast 2016; Azor-Martinez 2016; Azor-Martinez 2018; Ban 2015; Biswas 2019; Correa 2012; DiVita 2011; Feldman 2016; Hubner 2010; Huda 2012; Ide 2014; Miyaki 2011; Nicholson 2014; Stebbins 2011; Talaat 2011; Yeung 2011). Three studies were at high risk of reporting bias (McConeghy 2017; Millar 2016; Najnin 2019). In McConeghy 2017, URTI was mentioned in the methods (the intervention presumably would have targeted these), but only lower respiratory tract infection (LRTI) and overall infection were reported. Millar 2016 was originally conducted for another purpose; we could not find the respiratory outcomes reported in the study as part of the original study protocol. In Najnin 2019, the published study protocol did not include respiratory illness as an outcome.

Other potential sources of bias

An additional consideration for cluster-RCTs is identification/recruitment bias, where individuals are recruited in the trial after clusters are randomised. Such bias can introduce an imbalance amongst groups.

In this 2022 review, of the six cluster-RCTs included, we judged four to have a low risk of identification/recruitment bias (Abaluck 2022; Ashraf 2020; Swarthout 2020; Teesing 2021). In Abaluck 2022, all of people in the village were assigned to one study arm (control, cloth mask or surgical mask villages). In Ashraf 2020, participants were unaware of their intervention group assignment until after the baseline survey and randomisation. In Swarthout 2020, village clusters comprised of 12 enrolled households, while in Teesing 2021 randomisation was done per nursing home. Alfelali 2020 recruited individuals after cluster-randomisation and is judged to have a high risk of recruitment bias, while in Young 2021, participation of students and staff contacts were made after random assignment of the school through written consent or electronic completion of a consent form.

Of the cluster-RCTs included in our 2020 review, we judged 13 to have a low risk of identification/recruitment bias (Arbogast 2016; Biswas 2019; Canini 2010; Cowling 2008; Longini 1988; Luby 2005; MacIntyre 2015; MacIntyre 2016; Roberts 2000; Sandora 2005; Suess 2012; Temime 2018; White 2001). In Arbogast 2016, all identified individuals (office workers) were included in the assigned cluster. Schools were identified and then randomised to the clusters; students were then randomly selected from each classroom and school. Nine studies described the identification of participants, consenting/enrolling, and then randomising to the clusters (Canini 2010; Cowling 2008; Longini 1988; Luby 2005; MacIntyre 2015; MacIntyre 2016; Roberts 2000; Sandora 2005; White 2001). Suess 2012 identified and consented patients, then recruitment was performed by physicians unaware of cluster assignment. In Temime

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2018, directors of the included nursing homes agreed to participate in the study before randomisation, and written consent was not required from the residents.

Amongst the newly included studies, we judged four cluster-RCTs as at low risk of identification/recruitment bias (Abaluck 2022; Swarthout 2020; Teesing 2021; Young 2021). In Abaluck 2022, the village was the unit of randomisation and all households received one arm of the study (control, surgical mask or cloth mask). In Swarthout 2020, village clusters were each randomised by blocks (group of nine adjacent clusters) into eight groups. In Teesing 2021 nursing homes were computer randomised after baseline hand hygiene measurements to either the intervention arm or the control arm. In Young 2021, schools were randomly assigned (1:1) to either a policy of offering contacts daily testing over seven days to allow continued school attendance (intervention group) or to follow the usual policy of isolation of contacts for 10 days (control group). In two studies there were insufficient details to permit a judgement of the risk of bias (Alfelali 2020; Ashraf 2020).

In the 2020 review, we judged 11 cluster-RCTs as at high risk of identification/recruitment bias (Aiello 2010; Aiello 2012; Azor-Martinez 2018; Chard 2019; Correa 2012; Cowling 2009; Larson 2010; McConeghy 2017; Nicholson 2014; Priest 2014; Savolainen-Kopra 2012). In Aiello 2010 and Aiello 2012, recruitment continued for two weeks after the start of the study, which could have introduced bias. Six trials identified and recruited participants after cluster randomisation (Azor-Martinez 2018; Chard 2019; Cowling 2009; Larson 2010; McConeghy 2017; Nicholson 2014). Three trials recruited new participants after the start of the study to replace those lost to follow-up (Correa 2012; Priest 2014; Savolainen-Kopra 2012). We judged five cluster-RCTs to have probable identification/recruitment bias (Alzaher 2018; Barasheed 2014; MacIntyre 2011; Najnin 2019; Radonovich 2019), whereas in 19 studies there were insufficient details to permit a judgement of risk of bias (Carabin 1999; DiVita 2011; Feldman 2016; Hartinger 2016; Huda 2012; Ibfelt 2015; Kotch 1994; Ladegaard 1999; MacIntyre 2009; MacIntyre 2013; Millar 2016; Miyaki 2011; Pandejpong 2012; Radonovich 2019; Sandora 2008; Stebbins 2011; Talaat 2011; Yeung 2011; Zomer 2015).

Two of the newly included cluster-RCTs reported intracluster correlation coefficient (ICC) to adjust sample size, taking into consideration clustering effects, and described adjusting outcomes for clustering effect using different statistical methods, or provided justification for not performing adjusted analysis for clustering (Alfelali 2020; Swarthout 2020). For four studies there were insufficient details to permit a judgement of risk of bias (Abaluck 2022; Ashraf 2020; Teesing 2021; Young 2021) since they provided insufficient details on ICC and/or did not perform adjusted analysis or justified the absence of it.

Twenty-six cluster-RCTs identified in the 2020 review reported intracluster correlation coefficient (ICC) to adjust sample size, taking into consideration clustering effects, and described adjusting outcomes for clustering effect using different statistical methods, or provided justification for not performing adjusted analysis for clustering (Aiello 2010; Aiello 2012; Arbogast 2016; Canini 2010; Carabin 1999; Correa 2012; Cowling 2008; Cowling 2009; Hartinger 2016; Huda 2012; Little 2015; Luby 2005; MacIntyre 2009; MacIntyre 2011; MacIntyre 2013; MacIntyre 2015; MacIntyre 2016; McConeghy 2017; Priest 2014; Radonovich 2019; Ram 2015; Roberts 2000; Stebbins 2011; Suess 2012; Talaat 2011; Temime 2018). Five cluster-RCTs did not report the ICC but described adjusting outcomes for clustering effect using different statistical methods, or explained why adjusted analysis for clustering was not performed (Biswas 2019; Chard 2019; McConeghy 2017; Simmerman 2011; Zomer 2015). Thirteen cluster-RCTs provided insufficient details on ICC and/or did not perform adjusted analysis or justified the absence of it (Alzaher 2018; Azor-Martinez 2016; Azor-Martinez 2018; Barasheed 2014; Feldman 2016; Larson 2010; Millar 2016; Miyaki 2011; Najnin 2019; Nicholson 2014; Pandejpong 2012; Savolainen-Kopra 2012; Yeung 2011). Two cluster-RCTs reported the ICC but did not perform adjusted analysis or justified the absence of it (Sandora 2005; Sandora 2008).

Effects of interventions

See: **Summary of findings 1** Medical/surgical masks compared to no masks for preventing the spread of viral respiratory illness; **Summary of findings 2** N95 respirators compared to medical/surgical masks for preventing the spread of viral respiratory illness; **Summary of findings 3** Hand hygiene compared to control for preventing the spread of viral respiratory illness

Comparison 1: Medical/surgical masks compared to no masks

We included 12 trials (10 of which were cluster-RCTs) comparing medical/surgical masks versus no masks (Abaluck 2022; Alfelali 2020; Aiello 2012; Barasheed 2014; Bundgaard 2021; Canini 2010; Cowling 2008; Jacobs 2009; MacIntyre 2009; MacIntyre 2015; MacIntyre 2016; Suess 2012). Two trials were conducted with healthcare workers (HCWs) (Jacobs 2009; MacIntyre 2015), whilst the other 10 studies included people living in the community. In the acute care hospital setting, as opposed to the community setting, variable mask use occurred, according to usual practices in the settings where the studies were undertaken, varying from just under 16% most of the time to 23.6% wearing for > 70% of all working hours (Jacobs 2009; MacIntyre 2015). We therefore excluded the two studies in the acute care hospital setting from the meta-analysis, and report results from these studies narratively. Ten trials were conducted in non-pandemic settings, and two were conducted during the SARS-CoV-2 pandemic (Abaluck 2022; Bundgaard 2021).

Primary outcomes

1. Numbers of cases of viral respiratory illness

Influenza/COVID-like illness

Pooling of nine trials conducted in the community found an estimate of effect for the outcomes of influenza/COVID-like illness cases (risk ratio (RR) 0.95, 95% confidence interval (CI) 0.84 to 1.09; 9 trials; 276,917 participants; moderate-certainty evidence; Analysis 1.1) suggesting that wearing a medical/surgical mask will probably make little or no difference for this outcome. Two studies in healthcare workers provided inconclusive results with very wide confidence intervals: RR 0.88, 95% CI 0.02 to 32; and RR 0.26, 95% CI 0.03 to 2.51, respectively (Jacobs 2009; MacIntyre 2015).

Laboratory-confirmed influenza/SARS-CoV-2 cases

Similarly, the estimate of effect for laboratory-confirmed influenza/SARS-CoV-2 cases (RR 1.01, 95% CI 0.72 to 1.42; 6 trials, 13,919 participants; moderate-certainty evidence; Analysis 1.1) suggests that wearing a medical/surgical mask probably makes little or no difference compared to not wearing a mask for this outcome.

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Laboratory-confirmed other respiratory viruses

One community study reported on laboratory-confirmed other respiratory viruses, showing RR 0.58, 95% CI 0.25 to 1.31; Analysis 1.1, and another study in healthcare workers reported RR 0.79, 95% CI 0.42 to 1.52 (MacIntyre 2015).

Assessing both source control and personal protection

The design of most trials assessed whether masks protected the wearer. Six trials were cluster-RCTs, with all participants in the intervention clusters required to wear masks, thus assessing both source control and personal protection. In two trials the clusters were households with a member with new influenza; neither of these studies found any protective effect (RR 1.03 in 105 households (Canini 2010); RR 1.21 in 145 households (MacIntyre 2009)). In two trials the clusters were college dormitories during the influenza season; neither study found any reduction (RR 1.10 in 37 dormitories (Aiello 2012); RR 0.90 in three dormitories (Aiello 2010)).

Studies conducted during the SARS-CoV-2 pandemic

Two studies were conducted during the SARS-CoV-2 pandemic (Abaluck 2022; Bundgaard 2021), with the former being a very large cluster-RCT of villages in Bangledesh and the latter a large RCT conducted in Denmark.

Exclusion of study due to insufficient number of clusters

We excluded Aiello 2010 from the meta-analysis since we did not consider 'randomisation' of three clusters to three arms to be a proper randomised trial.

2. Adverse events related to the intervention

Canini 2010 reported that 38 (75%) of participants in the intervention arm experienced discomfort with the mask use due to warmth (45%), respiratory difficulties (33%), and humidity (33%). Children reported feeling pain more frequently (3/12) than other participants wearing adult face masks (1/39; P = 0.04). In MacIntyre 2015, adverse events associated with face mask use were reported in 40.4% (227/562) of HCWs in the medical-mask arm. General discomfort (35.1%; 397/1130) and breathing problems (18.3%; 207/1130) were the most frequently reported adverse events. Suess 2012 reported that the majority of participants (107/172; 62%) did not report any problems with mask-wearing. More adults reported no problems (71%) compared to children (36/72; 50%; P = 0.005). The main issues when wearing a face mask for adults as well as for children were "heat/humidity" (18/34; 53% of children; 10/29; 35% of adults; P = 0.1), followed by "pain" and "shortness of breath". Alfelali 2020 reported the most common side effects of wearing a mask in Hajj pilgrims were difficulty in breathing (26%) and discomfort (22%). Although no details were provided, Bundgaard 2021 mentioned that 14% of participants had adverse reactions. Cowling 2008 and Abaluck 2022 mentioned that no adverse events were reported. The other trials did not report measuring adverse outcomes.

Secondary outcomes

1. Deaths

Not reported.

2. Severity of viral respiratory illness as reported in the studies

Jacobs 2009 reported that participants in the mask group were significantly more likely to experience more days with headache and feeling bad. They found no significant differences between the two groups for symptom severity scores. None of the other trials reported this outcome.

3. Absenteeism

Not reported.

4. Hospital admissions

Not reported.

5. Complications related to the illness (e.g. pneumonia)

Not reported.

Comparison 2: N95/P2 respirators compared to medical/surgical masks

We included five trials comparing medical/surgical masks with N95/P2 respirators (Loeb 2009; MacIntyre 2009; MacIntyre 2011; MacIntyre 2013; Radonovich 2019). All of these trials except MacIntyre 2009 included HCWs. MacIntyre 2009 included carers and household members of children with a respiratory illness recruited from a paediatric outpatient department and a paediatric primary care practice in Sydney, Australia. None of the trials were conducted during the SARS-CoV-2 pandemic.

Primary outcomes

1. Numbers of cases of viral respiratory illness

Clinical respiratory illness

Pooling of three trials found an estimate of effect suggesting considerable uncertainty as to whether an N95/P2 respirator provides any benefit compared to medical/surgical masks for the outcome of clinical respiratory illness (RR 0.70, 95% CI 0.45 to 1.10; 7799 participants, very low-certainty evidence; Analysis 2.1) (MacIntyre 2011; MacIntyre 2013 (two arms); Radonovich 2019).

Influenza-like-illness

Based on five trials conducted in four healthcare settings and one household, the estimates of effect for the outcome of ILI (RR 0.82, 95% CI 0.66 to 1.03; 8407 participants, low-certainty evidence; Analysis 2.1) suggest that N95/P2 respirators may make little or no difference for this outcome (Loeb 2009; MacIntyre 2009; MacIntyre 2011; MacIntyre 2013; Radonovich 2019).

Laboratory-confirmed influenza

The estimate of the effect for the outcome of laboratory-confirmed influenza infection (RR 1.10, 95% CI 0.90 to 1.34; 8407 participants, moderate-certainty evidence; Analysis 2.1) suggests that the use of a N95/P2 respirator compared to a medical/surgical mask probably makes little or no difference for this more precise and objective outcome.

The outcomes clinical respiratory illness and ILI were reported separately. Considering how these outcomes were defined, it is highly likely that there was considerable overlap between the two, therefore these outcomes were not combined into a single clinical outcome (Analysis 2.1). The laboratory-confirmed viral respiratory infection outcome included influenza primarily but multiple other

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common viral respiratory pathogens were also included in several studies. The laboratory-confirmed viral infection outcome was considered more precise and objective in comparison to the clinical outcomes, which were more subjective and considered to be less precise. The findings did not change when we restricted the evidence to HCWs (Analysis 2.2).

2. Adverse events related to the intervention

Harms were poorly reported, but generally discomfort wearing medical/surgical masks and N95/P32 respirators was mentioned in several studies. Radonovich 2019 mentioned that participants wearing the N95 respirator reported skin irritation and worsening of acne. MacIntyre 2011 reported that adverse events were more common with N95 respirators; in particular, discomfort was reported in 41.9% of N95 wearers versus 9.8% of medical-mask wearers (P < 0.01); headaches were more common with N95 (13.4% versus 3.9%; P < 0.01); difficulty breathing was reported more often in the N95 group (19.4% versus 12.5%; P = 0.01); and N95 caused more problems with pressure on the nose (52.2% versus 11.0%; P < 0.01). In MacIntyre 2013, fewer participants using the N95 respirator reported problems (38% (195/512) versus 48% (274/571) of participants in the medical-mask arm; P = 0.001). Loeb 2009 mentioned that no adverse events were reported.

The one trial conducted in the community mentioned that more than 50% of participants reported concerns with both types of masks, mainly that wearing them was uncomfortable, but there were no significant differences between the P2 (N95) and surgical-mask groups (MacIntyre 2009).

Secondary outcomes

1. Deaths

Not reported.

2. Severity of viral respiratory illness as reported in the studies

Not reported.

3. Absenteeism

Loeb 2009 reported that 42 participants (19.8%) in the surgical-mask group reported an episode of work-related absenteeism compared with 39 (18.6%) of participants in the N95 respiratory group (absolute risk difference −1.24%, 95% CI −8.75% to 6.27%; P = 0.75).

4. Hospital admissions

Not reported.

5. Complications related to the illness (e.g. pneumonia)

Loeb 2009 reported that there were no episodes of LRTIs.

Comparison 3: Hand hygiene compared to control

Nineteen trials compared hand hygiene interventions with control and provided sufficient data to include in meta-analyses (Ashraf 2020; Azor-Martinez 2018; Biswas 2019; Correa 2012; Cowling 2008; Cowling 2009; Hubner 2010; Larson 2010; Little 2015; Millar 2016; Nicholson 2014; Ram 2015; Roberts 2000; Sandora 2005; Simmerman 2011; Stebbins 2011; Swarthout 2020; Teesing 2021; Zomer 2015). The populations of these studies included adults, children, and families, in settings such as schools, childcare centres, homes, and offices. None of the studies was conducted during a pandemic, although a few studies were conducted during peak influenza seasons. A further 16 trials comparing hand hygiene to a control had other outcomes or insufficient information to include in meta-analyses (Alzaher 2018; Arbogast 2016; Azor-Martinez 2016; DiVita 2011; Feldman 2016; Gwaltney 1980; Ladegaard 1999; Luby 2005; Morton 2004; Priest 2014; Savolainen-Kopra 2012; Talaat 2011; Temime 2018; Turner 2012; White 2001; Yeung 2011). The results of these trials were consistent with the findings of our meta-analyses. The results for all outcomes from the 19 trials that were meta-analysed and the 16 trials that were not meta-analysed are shown in Table 2.

Primary outcomes

1. Numbers of cases of viral respiratory illness

Acute respiratory infection (ARI)

Pooling of nine trials for the broad outcome of ARI showed a 14% relative reduction in the numbers of participants with ARI (RR 0.86, 95% CI 0.81 to 0.90; 52,105 participants, moderate-certainty evidence; Analysis 3.1.1) in the hand hygiene group (Analysis 3.1), suggesting a probable benefit (Ashraf 2020; Azor-Martinez 2018; Correa 2012; Larson 2010; Little 2015; Millar 2016; Nicholson 2014; Sandora 2005; Swarthout 2020).

Influenza-like-illness (ILI) and laboratory-confirmed influenza

When considering the more strictly defined outcomes of ILI (Biswas 2019; Cowling 2008; Cowling 2009; Hubner 2010; Larson 2010; Little 2015; Ram 2015; Roberts 2000; Simmerman 2011; Teesing 2021; Zomer 2015), and laboratory-confirmed influenza (Biswas 2019; Cowling 2008; Cowling 2009; Hubner 2010; Larson 2010; Ram 2015; Simmerman 2011; Stebbins 2011) the estimates of the effect were heterogeneous, suggesting that hand hygiene may make little or no difference (RR 0.94, 95% CI 0.81 to 1.09 for ILI; 34,503 participants, low-certainty evidence; Analysis 3.1.2); (RR 0.91, 95% CI 0.63 to 1.30 for laboratory-confirmed influenza; 8332 participants; low-certainty evidence; Analysis 3.1.3).

Composite outcome ‘ARI or ILI or influenza'

All 19 trials could be pooled for analysis of the composite outcome ‘ARI or ILI or influenza’, with each study only contributing once with the most comprehensive outcome (in terms of number of events) reported showing an 11% relative reduction in participants with a respiratory illness, suggesting that hand hygiene may offer a benefit (RR 0.89, 95% CI 0.83 to 0.94; low-certainty evidence; Analysis 3.2), but with high heterogeneity. A funnel plot of the 19 trial results did not appear to suggest any small study effects for this outcome (Figure 4).

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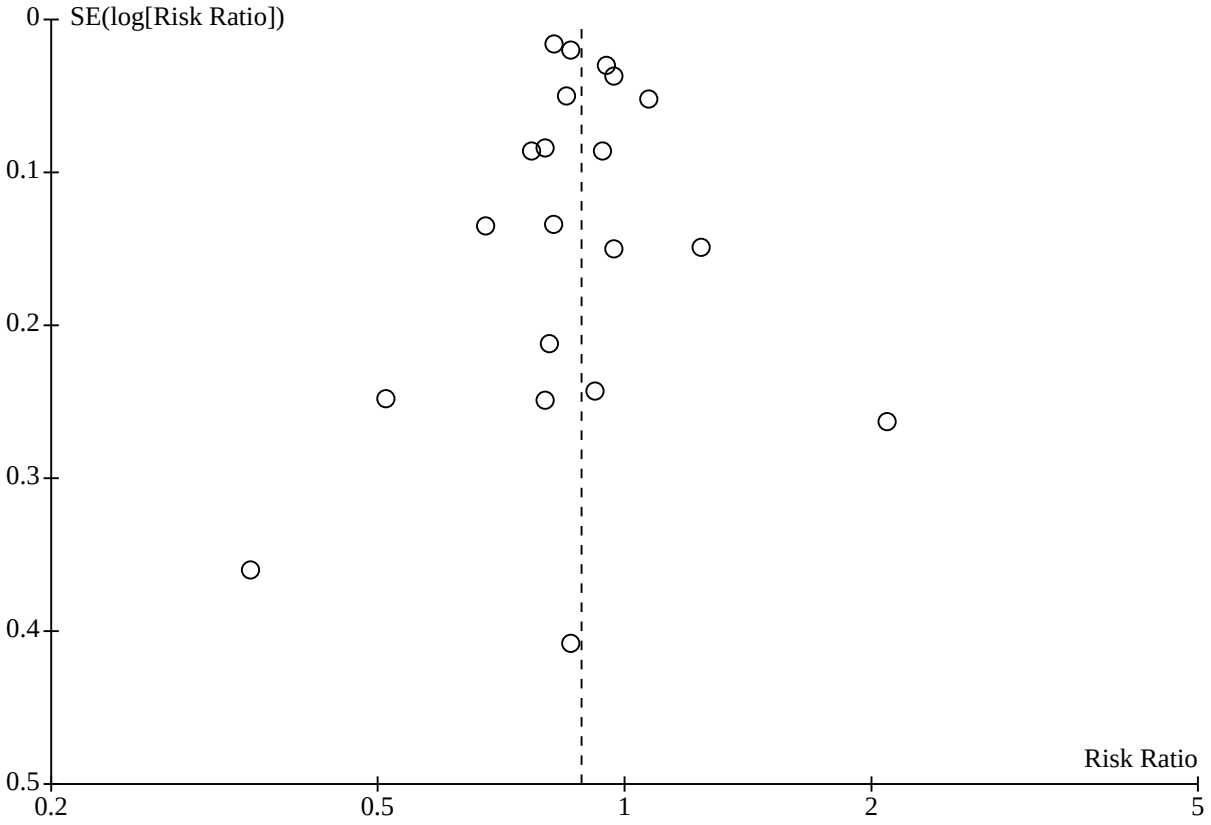
Figure 4.



Sensitivity analysis

In a sensitivity analysis we used only the most precise and unequivocal (with laboratory confirmed considered the most precise and an undefined ARI considered the least precise) outcome reported in each of 12 studies identified by JMC, an infectious disease physician, and found an estimate of effect in favour of hand hygiene, but with wider CIs (RR 0.88, 95% CI 0.77 to 1.02; Analysis 3.3).

Subgroup analysis by age group

We considered that studies in children might have a different effect than studies in adults, so we conducted subgroup analysis by age group. We found no evidence of a difference in treatment effect by age group (P = 0.18; Analysis 3.4).

2. Adverse events related to the intervention

Correa 2012 reported that no adverse events were observed; in the study by Priest 2014, skin reaction was recorded for 10.4% of participants in the hand sanitiser group versus 10.3% in the control group (RR 1.01, 95% CI 0.78 to 1.30).

Secondary outcomes

1. Deaths

Not reported.

2. Severity of viral respiratory illness as reported in the studies

Not reported.

3. Absenteeism

Three trials measured absenteeism from school or work and demonstrated a 36% relative reduction in the numbers of participants with absence in the hand hygiene group (RR 0.64, 95% CI 0.58 to 0.71; Analysis 3.5) (Azor-Martinez 2016; Hubner 2010; Nicholson 2014).

4. Hospital admissions

Not reported.

5. Complications related to the illness (e.g. pneumonia)

Not reported.

Comparison 4: Hand hygiene + medical/surgical masks compared to control

Primary outcomes

1. Numbers of cases of viral respiratory illness (including ARIs, ILI, and laboratory-confirmed influenza)

Six trials (Aelami 2015; Aiello 2012; Cowling 2009; Larson 2010; Simmerman 2011; Suess 2012) were able to be pooled to compare the use of the combination of hand hygiene and medical/surgical masks with control. Four of these trials were in households, two in university student residences, and one at the annual Hajj pilgrimage. For the outcomes ILI and laboratory-confirmed influenza, pooling demonstrated an estimate of effect suggesting little or no difference between the hand hygiene and medical/surgical mask combination and control. The number of trials and

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events was lower than for comparisons of hand hygiene alone, or medical/surgical masks alone, and the confidence interval was wide. For ILI, the RR for intervention compared to control was 1.03 (95% CI 0.77 to 1.37; 4504 participants; Analysis 4.1.1), and for influenza it was 0.97 (95% CI 0.69 to 1.36; 3121 participants; Analysis 4.1.2). Full results of these trials are shown in Table 3

2. Adverse events related to the intervention

Adverse events related to mask wearing in the study by Suess 2012 are reported under Comparison 1 (medical/surgical masks). There was no mention of adverse events related to hand hygiene.

Secondary outcomes

1. Deaths

Not reported.

2. Severity of viral respiratory illness as reported in the studies

Not reported.

3. Absenteeism

Not reported.

4. Hospital admissions

Not reported.

5. Complications related to the illness, e.g. pneumonia

Not reported.

Comparison 5: Hand hygiene + medical/surgical masks compared to hand hygiene

Primary outcomes

1. Numbers of cases of viral respiratory illness (including ARIs, ILI and laboratory-confirmed influenza)

Three trials studied the addition of medical/surgical masks to hand hygiene (Cowling 2009; Larson 2010; Simmerman 2011). All three trials had three arms, and are also included in the comparison of hand hygiene plus medical/surgical mask versus control (Comparison 4). All three studies showed no difference between hand hygiene plus medical/surgical mask groups and hand hygiene alone, for all outcomes. The estimates of effect suggested little or no difference when adding masks to hand hygiene compared to hand hygiene alone: for the outcome ILI (RR 1.03, 95% CI 0.69 to 1.53; 3 trials) and the outcome laboratory-confirmed influenza (RR 0.99, 95% CI 0.69 to 1.44), the estimates of effect were not different and the CIs were relatively wide, suggesting little or no difference (Analysis 5.1). However, the CIs around the estimates were wide and do not rule out an important benefit.

2. Adverse events related to the intervention

Not reported.

Secondary outcomes

1. Deaths

Not reported.

2. Severity of viral respiratory illness as reported in the studies

Not reported.

3. Absenteeism

Not reported.

4. Hospital admissions

Not reported.

5. Complications related to the illness (e.g. pneumonia)

Not reported.

Comparison 6: Medical/surgical masks compared to other (non-N95) masks

One trial compared medical/surgical masks with cloth masks in hospital healthcare workers (MacIntyre 2015), and another trial compared catechin-treated masks versus control masks in healthcare workers and staff of hospitals, rehabilitation centres, and nursing homes in Japan (Ide 2016).

Primary outcomes

1. Numbers of cases of viral respiratory illness (including ARIs, ILI, and laboratory-confirmed influenza)

MacIntyre 2015 found that the rate of ILI was higher in the cloth mask arm compared to the medical/surgical masks arm (RR 13.25, 95% CI 1.74 to 100.97).

Ide 2016 did not find a benefit from the catechin-treated masks over untreated masks on influenza infection rates (adjusted odds ratio (OR) 2.35, 95% CI 0.40 to 13.72; P = 0.34).

2. Adverse events related to the intervention

In MacIntyre 2015 adverse events associated with face mask use were reported in 40.4% (227/562) of HCWs in the medical/surgical mask arm and 42.6% (242/568) in the cloth mask arm (P = 0.45). The most frequently reported adverse events were general discomfort (35.1%; 397/1130) and breathing problems (18.3%; 207/1130). Laboratory tests showed the penetration of particles through the cloth masks to be very high (97%) compared with medical/surgical masks (44%). Ide 2016 reported that there were no serious adverse events associated with the intervention.

Secondary outcomes

1. Deaths

Not reported.

2. Severity of viral respiratory illness as reported in the studies

Not reported.

3. Absenteeism

Not reported.

4. Hospital admissions

Not reported.

5. Complications related to the illness (e.g. pneumonia)

Not reported.

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Comparison 7: Soap + water compared to sanitiser, and comparisons of different types of sanitiser

Two trials compared soap and water with sanitiser (Azor-Martinez 2018; Savolainen-Kopra 2012). Another trial compared different types of hand sanitiser in a virus challenge study (Turner 2004a; Turner 2004b), and one trial studied the frequency of use of hand sanitiser (Pandejpong 2012). The full results of these four trials are shown in Table 4.

Primary outcomes

1. Numbers of cases of viral respiratory illness (including ARIs, ILI, and laboratory-confirmed influenza)

In the trial by Azor-Martinez 2018, ARI incidence was significantly higher in the soap-and-water group compared with the hand sanitiser group (rate ratio 1.21, 95% CI 1.06 to 1.39). In contrast, there was no significant difference between interventions in Savolainen-Kopra 2012. In the rhinovirus challenge study (Turner 2004a; Turner 2004b), all hand sanitisers tested led to a significant lowering of infection rates, but no differences between sanitisers were observed. The study sample size was small.

2. Adverse events related to the intervention

Two trials stated that no adverse events were observed (Pandejpong 2012; Savolainen-Kopra 2012).

Secondary outcomes

1. Deaths

Not reported.

2. Severity of viral respiratory illness as reported in the studies

Not reported.

3. Absenteeism

The authors of Azor-Martinez 2018 also observed a significant benefit for hand sanitiser in reduction in days absent, whereas there was no difference between intervention groups in the Savolainen-Kopra 2012 trial. The study on frequency of use of sanitiser found that use of sanitiser every hour significantly reduced days absent compared with use every two hours or with use only before the lunch break (Pandejpong 2012).

4. Hospital admissions

Not reported.

5. Complications related to the illness (e.g. pneumonia)

Not reported.

Comparison 8: Surface/object disinfection (with or without hand hygiene) compared to control

Primary outcomes

1. Numbers of cases of viral respiratory illness (including ARIs, ILI, and laboratory-confirmed influenza)

Six trials contributed data to this comparison (Ban 2015; Carabin 1999; Ibfelt 2015; Kotch 1994; McConeghy 2017; Sandora 2008). Full results of these trials are shown in Table 5. Five of the six trials combined disinfection with other interventions such as hand hygiene education, provision of hand hygiene products, and audits. Ban 2015 utilised a combination of provision of hand hygiene products, and cleaning and disinfection of surfaces, and demonstrated a significant reduction in ARI in the intervention group (OR 0.47, 95% CI 0.48 to 0.65). A similar result was seen in Carabin 1999, with a significant reduction in episodes of ARI. Two studies tested multi component interventions and observed no significant difference in ARI outcomes (Kotch 1994; McConeghy 2017).

One trial compared disinfection alone to usual care (Ibfelt 2015). This study demonstrated a significant reduction in some viruses detected on surfaces in the childcare centres (adenovirus, rhinovirus, respiratory syncytial virus (RSV), and metapneumovirus), but not in other viruses, including coronavirus.

2. Adverse events related to the intervention

Not reported.

Secondary outcomes

1. Deaths

Not reported.

2. Severity of viral respiratory illness as reported in the studies

Not reported.

3. Absenteeism

Only one study measured this outcome (Sandora 2008), observing no significant difference between groups for the outcome of absence due to respiratory illness (rate ratio for intervention to control 1.10, 95% CI 0.97 to 1.24).

4. Hospital admissions

Not reported.

5. Complications related to the illness (e.g. pneumonia)

Not reported.

Comparison 9: Complex interventions compared to control

Complex interventions are either multifaceted environmental programmes (such as those in low-income countries) or combined interventions including hygiene measures and gloves, gowns, and masks.

Four trials studied complex hygiene and sanitation interventions in low-income country settings (Chard 2019; Hartinger 2016; Huda 2012; Najnin 2019). Full results from these studies are given in Table 6.

Primary outcomes

1. Numbers of cases of viral respiratory illness (including ARIs, ILI, and laboratory-confirmed influenza)

All four trials of complex interventions observed no significant differences between groups in rates of viral respiratory illness.

2. Adverse events related to the intervention

Not reported.

Secondary outcomes

1. Deaths

Not reported.

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2. Severity of viral respiratory illness as reported in the studies

Not reported.

3. Absenteeism

Not reported.

4. Hospital admissions

Not reported.

5. Complications related to the illness (e.g. pneumonia)

Not reported.

Comparison 10: Physical distancing/quarantine

We found three RCTs that assessed physical distancing/quarantine interventions. A quasi-cluster-RCT assessed the effectiveness of quarantining workers of one of two sibling companies in Japan whose family members developed an ILI during the 2009 to 2010 H1N1 influenza pandemic (Miyaki 2011). Workers in the intervention group were asked to stay home on full pay until five days after the household member(s) showed resolution of symptoms or two days after alleviation of fever. A second RCT conducted during the SARS-CoV-2 pandemic investigated whether attending fitness centres with physical distancing was non-inferior compared to no access in terms of COVID-19 transmission (Helsingen 2021). The third study was a cluster-RCT conducted during the SARS-CoV-2 pandemic that compared voluntary daily lateral flow device testing for seven days with negative contacts remaining at school to self-isolation of school-based COVID-19 contacts for 10 days in a non-inferiority design (Young 2021).

Primary outcomes

1. Numbers of cases of viral respiratory illness (including laboratory-confirmed influenza and SARS-CoV-2)

Miyaki 2011 reported adherence with the intervention was 100%. In the intervention group 2.75% of workers contracted influenza, compared with 3.18% in the control group (Cox hazard ratio 0.799, 95% CI 0.66 to 0.97; P = 0.02), indicating that the rate of infection was reduced by 20% in the intervention group. However, the risk of a worker being infected was 2.17-fold higher in the intervention group where workers stayed at home with their infected family members. The authors concluded that quarantining workers who have infected household members could be a useful additional measure to control the spread of respiratory viruses in an epidemic setting.

Helsingen 2021 reported 3016 participants were tested for SARS-CoV-2 resulting in one positive case in the fitness centre access arm versus zero in the no access arm at 14 days (risk difference (RD) 0.053%, 95% CI − 0.050 to 0.156%; P = 0.32). In addition, 11 in the fitness centre access arm versus 27 in the no access arm tested positive for SARS-CoV-2 antibodies at one month (RD − 0.87%, 95% CI − 1.52% to − 0.23%; P = 0.001). The authors concluded that access to fitness centres with physical distancing and low population prevalence of SARS-CoV-2 infection did not increase risk of SARS-CoV-2 infection.

Results from Young 2021 suggested no difference between the two treatment arms for SARS-CoV-2 infection (RR 0.96, 95% CI 0.75 to 1.22) leading the study authors to conclude non-inferiority of daily contact testing of school-based contacts (intervention) compared to self-isolation (control).

2. Adverse events related to the intervention

Not reported.

Secondary outcomes

1. Deaths

Not reported.

2. Severity of viral respiratory illness as reported in the studies

Not reported.

3. Absenteeism

Young 2021 reported COVID-19 related absences from school were similar in the two treatment groups (RR 0.80, 95% CI 0.54 to 1.19).

4. Hospital admissions

Helsingen 2021 reported no hospital admissions in either treatment arm.

5. Complications related to the illness (e.g. pneumonia)

Not reported.

Comparison 11: Eye protection compared to control

Primary outcomes

1. Numbers of cases of viral respiratory illness (including laboratory-confirmed influenza and SARS-CoV-2)

We only identified one trial of eye protection which was a preprint only (Fretheim 2022a). This was a pragmatic RCT conducted in Norway from 2 February to 24 April 2022, where 3717 participants were randomised to an intervention group asked to wear glasses (e.g. sunglasses) for two weeks when close to others in public spaces. COVID-19 cases in the national registry were 3.7% in the intervention group (68/1852) and 3.5% (65/1865) in the control group (RR 1.10, 95% CI 0.75 to 1.50). Positive COVID-19 tests based on self-reporting were 9.6% and 11.5% (RR 0.83, 95% CI 0.69 to 1.00). Given the high risk of bias and wide CIs, no policy conclusions can be drawn, but replication studies are clearly warranted. Almost a third of the participants reported respiratory infections. However, a lower proportion of those (215 participants) were in the intervention group compared to the control group (RR 0.90; 95% CI 0.82 to 0.99).

2. Adverse events related to the intervention

A total of 76 participants reported a negative experience from participating in the trial (53 in the intervention group and 23 in the control group). The most common complaint related to the combination of wearing glasses and face masks, and 21 participants in the intervention group cited fogging as an issue. Some participants reported feeling tired or uncomfortable wearing glasses, and a few participants complained of reduced vision when wearing sunglasses or reading glasses. In the control group some participants reported headaches from not being able to wear glasses, and one participant in the intervention group reported a fall due to reduced vision.

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Secondary outcomes

1. Deaths

Not reported.

2. Severity of viral respiratory illness as reported in the studies

Not reported.

3. Absenteeism

Not reported.

4. Hospital admissions

Not reported.

5. Complications related to the illness, e.g. pneumonia

Not reported.

Comparison 12: Gargling/nose rinsing compared to control

Five trials investigated the effect of gargling/nose rinsing. Satomura 2005 compared throat gargling with povidone-iodine versus tap water in healthy adults. Ide 2014 compared gargling with green tea versus tap water in high school students, and Goodall 2014 compared gargling with tap water with no gargling in university students. Two additional trials were conducted during the SARS-CoV-2 pandemic: Almanza-Reyes 2021 compared silver mouth wash/nose rinse versus conventional mouthwashes and nose rinse in health workers; and Gutiérrez-García 2022 compared neutral electrolysed water mouth and nose rinses versus no rinses in health workers.

Primary outcomes

1. Numbers of cases of viral respiratory illness (including ARIs, ILI, and laboratory-confirmed influenza and SARS-CoV-2)

Satomura 2005 reported that gargling with tap water reduced the incidence of URTIs compared to the control group (usual care) (hazard ratio (HR) 0.60, 95% CI 0.39 to 0.95). Gargling with povidone-iodine did not reduce the incidence of URTIs compared to the control group (HR 0.88, 95% CI 0.58 to 1.34).

Goodall 2014 found no difference in laboratory-confirmed URTIs between the gargling (tap water) and no-gargling groups (RR for gargling versus no gargling 0.82, 95% CI 0.53 to 1.26; P = 0.36).

In a meta-analysis of gargling versus control based on two trials the pooled estimate of effect suggested little or no difference for the outcome of clinical URTI due to gargling (RR 0.91, 95% CI 0.63 to 1.31; 830 participants; Analysis 6.1) (Goodall 2014; Satomura 2005).

There was no difference in the incidence of laboratory-confirmed influenza between high school students gargling with green tea compared with those using tap water (adjusted OR 0.69, 95% CI 0.37 to 1.28; P = 0.24) (Ide 2014). There was also no difference in the incidence of clinically defined influenza (adjusted OR 0.75, 95% CI 0.50 to 1.13; P = 0.17). However, the authors reported that adherence to the interventions amongst students was low.

Almanza-Reyes 2021 reported the incidence of SARS-CoV-2 infection was statistically significantly lower in the silver mouth wash/nose rinse group (two out of 114, 1.8%) compared to the conventional mouthwash group (33 out of 117, 28.2%), and Gutiérrez-García 2022 reported the incidence of COVID-19-positive cases in the nasal and oral rinses group was 1% compared to 13% in the control group (RR 0.09, 95% CI of 0.01 to 0.72). A meta-analysis of these two studies showed a 93% reduction in risk of SARS-CoV-2 (RR 0.07, 95% CI 0.02 to 0.23; 394 participants; Analysis 6.2).

2. Adverse events related to the intervention

Satomura 2005 reported no adverse events during the 60-day intervention period. Ide 2014 also did not observe any adverse events during the study. Goodall 2014 did not report on adverse effects. There were no adverse reactions in the study by Almanza-Reyes 2021 or side effects in the study by Gutiérrez-García 2022.

Secondary outcomes

1. Deaths

Not reported.

2. Severity of viral respiratory illness as reported in the studies

Satomura 2005 reported that the mean peak score in bronchial symptoms was lower in the water gargling group (0.97) than in the povidone-iodine gargling group (1.41) and the control group (1.40), P = 0.055. Other symptoms were not significantly different between groups. Goodall 2014 reported that symptom severity was greater in the gargling group for clinical and laboratory-confirmed URTI, but this was not statistically significant (225.3 versus 191.8, and 210.5 versus 191.8, respectively). Ide 2014 did not report symptom or illness severity.

3. Absenteeism

Not reported.

4. Hospital admissions

Not reported.

5. Complications related to the illness (e.g. pneumonia)

Not reported.

Comparison 13: Virucidal tissues compared to control

Two reports (three trials) conducted in the USA studied the effect of virucidal tissues (Farr 1988a; Farr 1988b; Longini 1988). Full results from these studies are given in Table 7.

Primary outcomes

1. Numbers of cases of viral respiratory illness (including ARIs, ILI, and laboratory-confirmed influenza)

The three trials of virucidal tissues reported no differences in infection rates between tissues and placebo, and between tissues and no tissues (Farr 1988a; Farr 1988b; Longini 1988).

2. Adverse events related to the intervention

Farr 1988b reported cough in 4% of participants using virucidal tissues versus 57% in the placebo group, but 24% reported nasal burning in the virucidal tissue group versus 8% in the placebo group. Longini 1988 did not report on adverse effects.

Secondary outcomes

1. Deaths

Not reported.

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2. Severity of viral respiratory illness as reported in the studies

Not reported.

3. Absenteeism

Not reported.

4. Hospital admissions

Not reported.

5. Complications related to the illness (e.g. pneumonia)

Not reported.

DISCUSSION

Summary of main results

See Table 8.

1. Medical/surgical masks compared to no masks

The pooled estimates of effect from randomised controlled trials (RCTs) and cluster-RCTs for wearing medical/surgical masks compared to no masks in the community suggests probably little or no difference in interrupting the spread of influenza-like illness (ILI)/COVID-19 like illness (risk ratio (RR) 0.95, 95% confidence interval (CI) 0.84 to 1.09; moderate-certainty evidence), or laboratory-confirmed influenza/SARS-CoV-2 (RR 1.01, 95% CI 0.72 to 1.42; moderate-certainty evidence). Six trials were cluster-RCTs, with all participants in the intervention clusters required to wear masks, thus assessing both source control and personal protection. In two trials the clusters were households with a member with new influenza; neither trial found any protective effect (RR 1.03 in 105 households (Canini 2010); RR 1.21 in 145 households (MacIntyre 2009). In two trials the clusters were college dormitories during the influenza season; neither trial found any reduction (RR 1.10 in 37 dormitories (Aiello 2012); RR 0.90 in three dormitories (Aiello 2010)). Two studies were conducted during the COVID-19 pandemic and their addition had minimal impact on the pooled estimate of effect previously reported from the earlier studies focused on influenza (Abaluck 2022; Bundgaard 2021). We excluded Aiello 2010 from meta-analysis since we did not consider 'randomisation' of three clusters to three arms was a proper randomised trial.

Less than half of the trials comparing masks with no masks addressed harms of mask wearing (Canini 2010; Cowling 2008; MacIntyre 2015; Suess 2012). Warmth, respiratory difficulties, humidity, and general discomfort were the most frequently reported adverse events. Neither of the RCTs conducted during the COVID-19 pandemic directly assessed harms of mask wearing. More adults reported no harms compared to children.

In one trial cloth masks were associated with a significantly higher risk of both ILI and laboratory-confirmed respiratory virus infection in healthcare workers (HCWs) (MacIntyre 2015). In addition, filtration capacity of the two-ply cotton cloth masks was found to be only 3% and markedly less than with medical/surgical masks based on standardised particle testing. The authors suggested moisture retention, poor filtration, and penetration of the virus through the mask as plausible explanations for the increased risk of infection.

We did not find any randomised trials assessing the effectiveness of barrier interventions using a combination of masks, gloves, and gowns.

2. N95 respirators compared to medical/surgical masks

Comparisons between N95 respirators and medical/surgical masks, used as needed for exposure to at-risk patients, for the outcomes of clinical respiratory illness and the outcome of laboratory-confirmed influenza showed estimates of effect suggesting considerable uncertainty for any benefit of N95 respirators for the former outcome and probably little or no difference for the latter outcome. Five trials (four in healthcare settings and one in a household setting) compared N95/P2 respirators with medical/surgical masks. Pooling of three of these trials showed an estimate of effect suggesting considerable uncertainty as to whether there was any benefit comparing N95 respirators and medical/surgical face masks for the outcome of clinical respiratory illness (RR 0.70, 95% CI 0.45 to 1.10; very low-certainty evidence), and that N95 respirators may make little or no difference for the outcome of ILI (RR 0.82, 95% CI 0.66 to 1.03; low-certainty evidence), and probably little or no difference for the outcome of laboratory-confirmed influenza (RR 1.10, 95% CI 0.90 to 1.34; moderate-certainty evidence). The presence of imprecision (wide CIs) and heterogeneity, particularly for the more subjective and less precise outcomes of clinical respiratory illness and ILI compared to laboratory-confirmed influenza infection, makes it difficult to assess whether there may be a benefit of either medical/surgical masks or N95/P2 respirators. Restricting the pooling to HCWs made no difference to the overall findings. The two trials with the largest event rates were quite consistent in their findings of no significant differences between N95 and medical/surgical masks for the outcomes of laboratory-confirmed influenza and all laboratory-confirmed viral infections (Loeb 2009; Radonovich 2019). Three of the trials contributing to this analysis were carried out by members of the same group (MacIntyre 2009; MacIntyre 2011; MacIntyre 2013).

In general, harms were poorly reported or not reported at all in trials comparing N95 respirators with surgical masks. General discomfort resulting in reduced wear adherence was the most frequently reported harm.

3. Hand hygiene compared to control

We found that the estimate of effect may offer a benefit for hand hygiene for the composite outcome 'acute respiratory infections (ARI) or ILI or influenza' (RR 0.89, 95% CI 0.83 to 0.94; low-certainty evidence), and probably offers a benefit for the outcomes ARI alone (RR 0.86, 95% CI 0.81 to 0.90; moderate-certainty evidence), and absenteeism (RR 0.64, 95% CI 0.58 to 0.71). An observed estimate of effect in favour of hand hygiene for laboratory-confirmed influenza, but with wider CIs may be a consequence of smaller sample sizes in conjunction with a more rigorous outcome measure.

4. Hand hygiene + medical/surgical masks compared to control

The estimate of effect of combined hand hygiene and medical/surgical mask interventions compared to control in six (mostly small) trials suggested that the intervention may make little or no difference for the outcomes ILI (RR 1.03, 95% CI 0.77 to 1.37), and laboratory-confirmed influenza (four trials) (RR 0.97, 95% CI 0.69 to 1.36).

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5. Hand hygiene + medical/surgical masks compared to hand hygiene

We also found an estimate of effect suggesting that adding medical/surgical masks to hand hygiene compared to hand hygiene alone may make little or no difference for the outcomes ILI (RR 1.03, 95% CI 0.69 to 1.53; 3 trials), and laboratory-confirmed influenza (RR 0.99, 95% CI 0.69 to 1.44).

6. Medical/surgical masks compared to other (non-N95) masks

One trial found that medical/surgical masks were more effective than cloth masks at reducing the rate of ILI (RR 13.25, 95% CI 1.74 to 100.97) (MacIntyre 2015), but the extremely wide CIs make this finding difficult to interpret. One trial did not find a benefit from catechin-treated masks over untreated masks on influenza infection rates (adjusted odds ratio (OR) 2.35, 95% CI 0.40 to 13.72; P = 0.34) (Ide 2016).

Harms of wearing masks were reported in 40.4% of HCWs using medical/surgical masks, and in 42.6% of those wearing cloth masks (P = 0.45) (MacIntyre 2015). The penetration of particles was higher in cloth masks (97%) compared to medical/surgical masks (44%).

7. Soap + water compared to sanitiser, and comparisons of different types of sanitiser

There were too few trials comparing different types of hand hygiene interventions to be certain of any true differences between soap and water, alcohol-based hand sanitisers, or other types of interventions. Also, it is uncertain whether the incremental effect of adding virucidals or antiseptics to hand-washing actually decreased the respiratory disease burden outside the confines of the rather atypical studies. The extra benefit may have been, at least in part, accrued by confounding additional routines.

8. Surface/object disinfection (with or without hand hygiene) compared to control

We identified six trials on surface/object disinfection (with or without hand hygiene), and although they were heterogeneous (and therefore could not be pooled), three of them showed a clear benefit compared to controls (Ban 2015; Carabin 1999; Ibfelt 2015).

We found no RCTs of nose disinfection, or disinfection of living quarters, as described in observational studies reported in Jefferson 2011.

9. Complex interventions compared to control

Four trials studied complex hygiene and sanitation interventions, all in low-income country settings (Chard 2019; Hartinger 2016; Huda 2012; Najnin 2019). These trials could not be pooled due to the heterogeneity of the interventions and settings. All four trials found no significant differences between groups in the rates of viral respiratory illness.

10. Physical distancing/quarantine compared to control

We identified one trial that evaluated the effect of quarantine and found a reduction in influenza transmission to co-workers when those with infected household members stayed home from work (Miyaki 2011). However, staying home increased their risk of being infected two-fold. Two studies conducted during the COVID-19 pandemic on SARS-cov-2 transmission showed (1) non-inferiority of daily contact testing of school-based contacts (intervention) compared to self-isolation (control) (Young 2021); and (2) access to fitness centres with physical distancing and low population prevalence of SARS-CoV-2 infection did not increase risk of SARS-cov-2 infection (Helsingen 2021).

11. Eye protection compared to control

We only identified one trial of eye protection which was a preprint only (Fretheim 2022a).

12. Gargling compared to control

Three trials addressed the use of gargling in preventing respiratory infections (Goodall 2014; Ide 2014; Satomura 2005). Although the trials used a variety of liquids and different outcomes, pooling the results of the two trials that compared gargling with tap water versus control did not show a favourable effect in reducing URTIs (RR 0.91, 95% CI 0.63 to 1.31) (Goodall 2014; Satomura 2005). Two trials of mouthwash/nose rinse were conducted during the SARS-cov-2 pandemic in HCWs: Almanza-Reyes 2021 compared silver mouth wash/nose rinse versus conventional mouthwashes and nose rinse; and Gutiérrez-García 2022 compared neutral electrolysed water mouth and nose rinses versus no rinses. Both studies reported large protective effects of the intervention on SARS-CoV-2 infection with reported outcomes of SARS-C0V-2 infection in 28.2% and 12.7% in the HCWs not using the interventions versus 1.8% and 1.2% in those using the intervention, despite the use of full personal protective equipment (PPE) and the high outcome rates raise questions about risk of bias, and no data were provided about baseline rates in other settings with full use of PPE.

13. Virucidal tissues compared to control

Two reports (three trials) identified in Jefferson 2011 studied the effect of virucidal tissues compared to placebo or no tissues (Farr 1988a; Farr 1988b; Longini 1988). These trials found no differences in infection rates and could not be pooled.

Overall completeness and applicability of evidence

Several features need consideration before making generalisations based on the included studies.

The settings of the included studies, which were conducted over five decades, were heterogeneous and ranged from suburban schools, Carabin 1999, to emergency departments, intensive care units, and paediatric wards, Loeb 2009, in high-income countries; slums in low-income countries (Luby 2005); and an upper Manhattan immigrant Latino neighbourhood (Larson 2010). Few attempts were made to obtain socio-economic diversity by (for example) involving more schools in the evaluations of the same programme. We identified only a few studies from low-income countries, where the vast majority of the burden of ARIs lies and where inexpensive interventions are so critical. Additionally, limited availability of over-the-counter medications and national universal comprehensive health insurance provided with consequent physician prescription of symptomatic treatment may further limit the generalisability of findings.

The included trials generally reported few events and were conducted mostly during non-epidemic periods with the exception of the trials carried out during the influenza H1N1 and SARS-CoV-2 pandemics. The large study by Radonovich 2019 is an exception as it crossed over two of the highest reporting years for influenza in

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the USA between 2010 and 2017 (Elflein 2019). None of the trials were conducted during pandemics of SARS-CoV-1or in outbreaks of Middle East respiratory syndrome (MERS).

Of the trials assessing the effect of masks, six were carried out in those at greater exposure (i.e. HCWs) (Jacobs 2009; Loeb 2009; MacIntyre 2011; MacIntyre 2013; MacIntyre 2015; Radonovich 2019). None of these studies included HCWs undertaking aerosol-generating procedures, for which the World Health Organization (WHO) currently recommends the N95 or equivalent mask. Three trials on hand hygiene interventions were carried out in nursing homes, and included HCWs (McConeghy 2017; Temime 2018; Yeung 2011). The scarcity of RCTs on HCWs limits the generalisability of such results.

The variable quality of the methods of some studies is striking. Incomplete or no reporting of randomisation (Turner 2004a), blinding (Farr 1988a; Farr 1988b), numerators and denominators (Carabin 1999; Kotch 1994), interventions, and cluster coefficients in the relevant trials (Carabin 1999), led to a considerable loss of information. Potential biases were often not discussed.

Inappropriate placebos caused design problems. In some studies the placebo probably carried sufficient effect to dilute the intervention effects (Longini 1988). Two valiant attempts with virucidal tissues probably failed because placebo handkerchiefs were impregnated with a dummy compound that stung the users' nostrils (Farr 1988a; Farr 1988b).

Some studies used impractical interventions. Volunteers subjected to the intervention hand cleaner (organic acids) were not allowed to use their hands between cleaning and virus challenge, so the effect of normal use of the hands on the intervention remains unknown (Turner 2004a; Turner 2004b). Two per cent aqueous iodine painted on the hands, although a successful antiviral intervention, causes unacceptable cosmetic staining, which is impractical for all but those at the highest risk of epidemic contagion (Gwaltney 1980).

Adherence with interventions, especially educational programmes, was a problem for many studies despite the importance of many such low-cost interventions. Adherence with mask wearing varied; it was generally around 60% to 80%, but was reported to be as low as 40% (see Table 1). Overall, the logistics of carrying out trials that involve sustained behaviour change are demanding, particularly in challenging settings such as immigrant neighbourhoods or students' halls of residence.

The identified trials provided sparse and unsystematic data on adverse effects of the intervention, and few of the RCTs measured or reported adherence with the intervention, which is especially important for the use of medical/surgical masks or N95 respirators. No studies investigated how the level of adherence may have influenced the effect size.

We identified one study assessing the effects of eye protection (Fretheim 2022a), and we identified three studies on physical distancing/quarantine (Helsingen 2021; Miyaki 2011; Young 2021). The dearth of evidence and predominant setting of seasonal viral circulation limits generalisability of our findings to other contexts and any future epidemics due to other respiratory viruses such as the COVID-19 pandemic although there have been increasing numbers of RCTs and cluster-RCTs in the latter setting which are adding to the evidence base.

The two recent small trials from Mexico assessing local mouth/nose rinses airways prophylactic as interventions treatments report large but uncertain reductions in transmission to healthcare workers which warrant further study and replication by other investigator (Almanza-Reyes 2021; Gutiérrez-García 2022).

Certainty of the evidence

We found the available evidence base identified through our search processes to be of variable quality. Reporting of sequence generation and allocation concealment were poor in 30% to 50% of studies across the categories of intervention comparisons. Given the nature of the intervention comparison, blinding of treatment allocation after randomisation was rarely achieved. Although blinding of outcome assessment is highly feasible and desirable, most outcomes were assessed by self-reports. Outcomes in some studies were poorly defined, with a lack of clarity as to the possible aetiological agents (bacterial versus viral). Some studies used laboratory-confirmed outcomes, both adding precision and avoiding indirectness by having an accurate outcome measure and lowering the risk of bias (see Table 9 for heterogeneity of trial outcome definitions). We found no evidence of selective reporting of outcomes within the included studies. We believe publication bias is unlikely, as the included studies demonstrated a range of effects, both positive and negative, over all study sizes. The variable quality of the studies hampers drawing any firm conclusions.

Potential biases in the review process

The non-drug (and often locally manufactured) nature of most of the interventions in this review, the lack of effective regulation in some settings, and the possible endless number of manufacturers make it difficult to gauge the existence of unpublished data. Non-drug interventions typically have no or very loose regulation.

In this 2022 update, we again focused on RCTs and cluster-RCTs, providing a higher level of evidence compared with the previous version of the review, which also meta-analysed observational studies when appropriate (Jefferson 2011). However, many of the trials were small and hence underpowered, and at high or unclear risk of bias due to poor reporting of methods and lack of blinding. The populations, outcomes, comparators, and interventions tested were heterogeneous.

Due to the urgency of this update in the context of the COVID-19 pandemic, we did not contact trial authors to request missing data. This means that we have not considered studies that included other non-respiratory infections, and did not provide stratified data by type of infection.

Agreements and disagreements with other studies or reviews

Several reviews of RCTs have found broadly similar results to this review for face masks. In a meta-analysis comparing surgical masks with N95 respirators, Smith 2016 pooled three trials and found an estimate of effect suggesting no difference for laboratory-confirmed respiratory infections (OR 0.89, 95% CI 0.64 to 1.24) or ILI (OR 0.51, 95% CI 0.19 to 1.41) (Loeb 2009; MacIntyre 2011; MacIntyre 2013). A similar meta-analysis, Offeddu 2017, based on two trials concluded that masks (either N95/P2 respirators or medical/surgical masks) were effective against clinical respiratory infections (RR 0.59, 95% CI 0.46 to 0.77) and ILI (RR 0.34, 95% CI 0.14

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to 0.82) (MacIntyre 2011; MacIntyre 2015). Pooling of two studies (MacIntyre 2011; MacIntyre 2013) also found an estimate of effect that favoured N95 respirators to medical/surgical masks for clinical respiratory infections (RR 0.47, 95% CI 0.36 to 0.62), but not for ILI, (RR 0.59, 95% CI 0.27 to 1.28) based on three studies (Loeb 2009: MacIntyre 2011; MacIntyre 2013). The outcome of clinical respiratory infection is considered to be the most subjective and least precise outcome.

A recent meta-analysis included five trials comparing N95/P2 respirators with medical/surgical masks and found no difference between groups for either influenza (RR 1.09, 95% CI 0.92 to 1.28), or respiratory viral infections (RR 0.89, 95% CI 0.70 to 1.11) (Long 2020). By excluding Loeb 2009 (an open, non-inferiority RCT that compared medical/surgical masks with N95 respirators in protecting HCWs against influenza), the authors reported a significant protective effect against viral infections (RR 0.61, 95% CI 0.39 to 0.98). The authors do not report a rationale for the exclusion in the sensitivity analysis, and do not report on exclusion of the studies with low weighting, which arguably would be more relevant in a sensitivity analysis. The two trials that make up 96% of the weighting demonstrated no significant differences in the outcome events (Loeb 2009; Radonovich 2019). A recent meta-analysis of four RCTs adjusting for clustering, which compared N95 respirators with the use of medical/surgical masks, found pooled estimates of effect that did not demonstrate any difference in any laboratory-confirmed viral respiratory infection (OR 1.06, 95% CI 0.90 to 1.25), laboratory-confirmed influenza (OR 0.94, 95% CI 0.73 to 1.20), or clinical respiratory illness (OR 1.49, 95% CI 0.98 to 2.28), with the evidence profile suggesting that there was greater imprecision and inconsistency in the outcome of clinical respiratory illness (Bartoszko 2020). Moreover, in another recent systematic review that assessed the effectiveness of personal protective and environmental measures in non-healthcare settings (funded by the WHO), 10 RCTs reporting estimates of the effectiveness of face masks in reducing laboratory-confirmed influenza virus infections in the community were identified (Xiao 2020). The evidence from these RCTs suggested that the use of face masks either by infected persons or by uninfected persons does not have a substantial effect on influenza transmission.

The findings from several systematic reviews and meta-analyses over the last decade have not demonstrated any difference in the clinical effectiveness of N95 respirators or equivalent compared to the use of surgical masks when used by HCWs in multiple healthcare settings for the prevention of respiratory virus infections, including influenza.

Reviews based on observational studies have usually found a stronger protective effect for face masks, but have important biases. The review by Chu 2020 did not consider RCTs of influenza transmission, but only the observational studies examining impact on SARS, MERS, or SARS-CoV-2. For N95 masks versus no mask in HCWs, there was a large protective effective with an OR of 0.04 (95% CI 0.004 to 0.30); for surgical masks versus no masks, there was an OR of 0.33 (0.17 to 0.61) overall, but four of these studies were in healthcare settings. Chu 2020 has been criticised for several reasons: use of an outdated 'Risk of bias' tool; inaccuracy of distance measures; and not adequately addressing multiple sources of bias, including recall and classification bias and in particular confounding. Confounding is very likely, as preventive behaviours such as mask use, social distancing, and hand hygiene are correlated behaviours, and hence any effect estimates are likely to be overly optimistic.

The two RCTs of medical/surgical masks during the SARS-CoV-2 pandemic found uncertain evidence of a small or no effect (Abaluck 2022; Bundgaard 2021). The study by Abaluck 2022 found a statistically significant benefit of masks versus no masks for COVID-like-illness, however, this study was rated at high risk of bias for five of the six domains due to issues including baseline imbalance, subjective outcome assessment and incomplete follow-up across the groups. Despite this study contributing 45% of the weight towards the meta-analysis of influenza/COVID-like-illness for masks versus no masks, the updated conclusions from the analysis strengthened around little or no effect of mask use.

Also based on observational studies, Jefferson 2011 found a protective effect of wearing surgical masks with hygienic measures compared to not wearing masks in the SARS 2003 outbreak (OR 0.32, 95% CI 0.26 to 0.39). However, the evidence was based on case-control studies carried out during the outbreak. There was some additional but very limited supportive evidence from the cohort studies in Jefferson 2011.

Although the use of eye protection and physical distancing measures are widely believed to be effective in reducing transmission of respiratory viruses and mitigating the impact of an influenza pandemic, we found only one trial investigating the role of self-quarantine in reducing the incidence of H1N1 influenza events in the workplace, and no trials examining the effect of eye protection. The evidence for these measures was derived largely from observational studies and simulation studies, and the overall certainty of supporting evidence is relatively low. The finding of limited evidence evaluating these interventions was also consistent with a recent review funded by the WHO for the preparation of its guidelines on the use of non-pharmaceutical interventions for pandemic influenza in non-medical settings (Fong 2020).

There are several previous systematic reviews on hand hygiene and respiratory infections. Five of them reviewed the evidence in a community setting (Moncion 2019; Rabie 2006; Saunders-Hastings 2017; Warren-Gash 2013: Wong 2014), and three focused on children (Mbakaya 2017; Willmott 2016; Zivich 2018). The earliest review in 2006 included eight studies, three of which were RCTs (Rabie 2006). The pooled estimate of seven studies was described as “indicative” of the effect of hand hygiene, but the studies were of poor quality. The Warren-Gash 2013 review included 16 studies (10 of which were RCTs) and reported mixed and inconclusive results. A 2014 review identified 10 RCTs and reported that the combination of hand hygiene with face masks in high-income countries (five trials) significantly reduced the incidence of laboratory-confirmed influenza and ILI, whilst hand hygiene alone did not (Wong 2014). This significant reduction in laboratory-confirmed influenza and ILI for hand hygiene and face masks may have been based on the raw numbers without adjusting for any clustering effects in the included cluster trials, which produced inappropriately narrow CIs, and possibly biased treatment effect estimates. Moreover, trials from the low-income countries were not included in the review, and this significant effect was not demonstrated when all the trials identified in the review were combined. The Saunders-Hastings 2017 review of studies evaluating the effectiveness of personal protective measures in interrupting pandemic influenza transmission only

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identified two RCTs (Azor-Martinez 2014; Suess 2012), which reported a significant effect of hand hygiene. The Moncion 2019 review identified seven RCTs of hand hygiene compared to control, with mixed results for preventing the transmission of laboratory-confirmed or possible influenza. Systematic reviews of RCTs of hand hygiene interventions amongst children, Mbakaya 2017 and Willmott 2016, or at a non-clinical workplace, Zivich 2018, identified heterogeneous trials with quality problems including small numbers of clusters and participants, inadequate randomisation, and self-reported outcomes. Evidence of impact on respiratory infections was equivocal.

A rapid search for other systematic reviews of RCTs was conducted in September 2022, and none of high quality were found.

AUTHORS' CONCLUSIONS

Implications for practice

The evidence summarised in this review on the use of masks is largely based on studies conducted during traditional peak respiratory virus infection seasons up until 2016. Two relevant randomised trials conducted during the COVID-19 pandemic have been published, but their addition had minimal impact on the overall pooled estimate of effect. The observed lack of effect of mask wearing in interrupting the spread of influenza-like illness (ILI) or influenza/COVID-19 in our review has many potential reasons, including: poor study design; insufficiently powered studies arising from low viral circulation in some studies; lower adherence with mask wearing, especially amongst children; quality of the masks used; self-contamination of the mask by hands; lack of protection from eye exposure from respiratory droplets (allowing a route of entry of respiratory viruses into the nose via the lacrimal duct); saturation of masks with saliva from extended use (promoting virus survival in proteinaceous material); and possible risk compensation behaviour leading to an exaggerated sense of security (Ammann 2022; Brosseau 2020; Byambasuren 2021; Canini 2010; Cassell 2006; Coroiu 2021; MacIntyre 2015; Rengasamy 2010; Zamora 2006).

Our findings show that hand hygiene has a modest effect as a physical intervention to interrupt the spread of respiratory viruses, but several questions remain. First, the high heterogeneity between studies may suggest that there are differences in the effect of different interventions. The poor reporting limited our ability to extract the information needed to assess any 'dose response' relationship, and there are few head-to-head trials comparing hand hygiene materials (such as alcohol-based sanitiser or soap and water). Second, the sustainability of hand hygiene is unclear where participants in some studies achieved 5 to 10 hand-washings per day, but adherence may have diminished with time as motivation decreased, or due to adverse effects from frequent hand-washing. Third, there is little evidence about the effectiveness of combinations of hand hygiene with other interventions, and how those are best introduced and sustained. Finally, some interventions were intensively implemented within small organisations, and involved education or training as a component, and the ability to scale these up to broader interventions is unclear.

Our findings with respect to hand hygiene should be considered generally relevant to all viral respiratory infections, given the diverse populations where transmission of viral respiratory infections occurs. The participants were adults, children and families, and multiple congregation settings including schools, childcare centres, homes, and offices. Most respiratory viruses, including the pandemic SARS-CoV-2, are considered to be predominantly spread via respiratory particles of varying size or contact routes, or both (WHO 2020c). Data from studies of SARS-CoV-2 contamination of the environment based on the presence of viral ribonucleic acid and infectious virus suggest significant fomite contamination (Lin 2022; Onakpoya 2022b; Ong 2020; Wu 2020). Hand hygiene would be expected to be beneficial in reducing the spread of SARS-CoV-2 similar to other beta coronaviruses (SARS-CoV-1, Middle East respiratory syndrome (MERS), and human coronaviruses), which are very susceptible to the concentrations of alcohol commonly found in most hand-sanitiser preparations (Rabenau 2005; WHO 2020c). Support for this effect is the finding that poor hand hygiene, despite the use of full personal protective equipment (PPE), was independently associated with an increased risk of SARS-CoV-2 transmission to healthcare workers in a retrospective cohort study in Wuhan, China in both a high-risk and low-risk clinical unit for patients infected with COVID-19 (Ran 2020). The practice of hand hygiene appears to have a consistent effect in all settings, and should be an essential component of other interventions.

The highest-quality cluster-RCTs indicate that the most effect on preventing respiratory virus spread from hygienic measures occurs in younger children. This may be because younger children are least capable of hygienic behaviour themselves (Roberts 2000), and have longer-lived infections and greater social contact, thereby acting as portals of infection into the household (Monto 1969). Additional benefit from reduced transmission from them to other members of the household is broadly supported by the results of other study designs where the potential for confounding is greater.

Routine long-term implementation of some of the interventions covered in this review may be problematic, particularly maintaining strict hygiene and barrier routines for long periods of time. This would probably only be feasible in highly motivated environments, such as hospitals. Many of the trial authors commented on the major logistical burdens that barrier routines imposed at the community level. However, the threat of a looming epidemic may provide stimulus for their inception.

Implications for research

Public health measures and physical interventions can be highly effective to interrupt the spread of respiratory viral infections, especially when they are part of a structured and co-ordinated programme that includes instruction and education, and when they are delivered together and with high adherence. Our review has provided important insights into research gaps that need to be addressed with respect to these physical interventions and their implementation and have been brought into a sharper focus as a result of the COVID-19 pandemic. The 2014 WHO document 'Infection prevention and control of epidemic - and pandemic-prone acute respiratory infections in health care' identified several research gaps as part of their GRADE assessment of their infection prevention and control recommendations, which remain very relevant (WHO 2014). Research gaps identified during the course of our review and the WHO 2014 document may be considered from the perspective of both general and specific themes.

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A general theme identified was the need to provide outcomes with explicitly defined clinical criteria for acute respiratory infections (ARIs) and discrete laboratory-confirmed outcomes of viral ARIs using molecular diagnostic tools which are now widely available. Our review found large disparities between studies with respect to the clinical outcome events, which were imprecisely defined in several studies, and there were differences in the extent to which laboratory-confirmed viruses were included in the studies that assessed them. Another general theme identified was the lack of consideration of sociocultural factors that might affect adherence with the interventions, especially those employed in the community setting. A prime example of this latter point was illustrated by the observations of the use of masks versus mask mandates during the COVID-19 pandemic. In addition, the cost and resource implications of the physical interventions employed in different settings would have important relevance for low- to middle-income countries. Resources have been a major issue with the COVID-19 pandemic, with global shortages of several components of PPE. Several specific research gaps related to physical interventions were identified within the WHO 2014 document and are congruent with many of the findings of this 2022 update, including the following: transmission dynamics of respiratory viruses from patients to healthcare workers during aerosol-generating procedures; a continued lack of precision with regards to defining aerosol-generating procedures; the safety of cohorting of patients with the same suspected but unconfirmed diagnosis in a common unit or ward with patients infected with the same known pathogen in healthcare settings; the optimal duration of the use of physical interruptions to prevent spread of ARI viruses; use of spatial separation or physical distancing (in healthcare and community settings, respectively) alone versus spatial separation or physical distancing with the use of other added physical interventions coupled with examining discrete distance parameters (e.g. one metre, two metres, or > two metres); the effectiveness of respiratory etiquette (i.e. coughing/sneezing into tissues or a sleeved bent elbow); the effectiveness of triage and early identification of infected individuals with an ARI in both hospital and community settings; the utility of entrance screening to healthcare facilities; use of frequent disinfection techniques appropriate to the setting (high-touch surfaces in the environment, gargling with oral disinfectants, and virucidal tissues or clothing) alone or in combination with facial masks and hand hygiene; the use of visors, goggles or other eyewear; the use of ultraviolet light germicidal irradiation for disinfection of air in healthcare and selected community settings; the use of air scrubbers and /or high-efficiency particulate absorbing filters and the use of widespread adherence with effective vaccination strategies.

There is a clear requirement to conduct large, pragmatic trials to evaluate the best combinations in the community and in healthcare settings with multiple respiratory viruses and in different sociocultural settings. Randomised controlled trials (RCTs) with a pragmatic design, similar to the Luby 2005 trial or the Bundgaard 2020 trial, should be conducted whenever possible. Similar to what has been observed in pharmaceutical interventions where multiple RCTs were rapidly and successfully completed during the COVID-19 pandemic, proving they can be accomplished, there should be a deliberate emphasis and directed funding opportunities provided to conduct well-designed RCTs to address the effectiveness of many of the physical interventions in multiple settings and populations, especially in those most at risk, and in very specific well-defined populations with monitoring of the adherence to the interventions.

Several specific research gaps deserve expedited attention and may be highlighted within the context of the COVID-19 pandemic. The use of face masks in the community setting represents one of the most pressing needs to address, given the polarised opinions around the world, and the increasing concerns over widespread microplastic pollution from the discarding of masks (Shen 2021). Both broad-based ecological studies, adjusting for confounding and high quality RCTs, may be necessary to determine if there is an independent contribution to their use as a physical intervention, and how they may best be deployed to optimise their contribution. The type of fabric and weave used in the face mask is an equally pressing concern, given that surgical masks with their cotton-polypropylene fabric appear to be effective in the healthcare setting, but there are questions about the effectiveness of simple cotton masks. In addition, any masking intervention studies should focus on measuring not only benefits but also adherence, harms, and risk compensation if the latter may lead to a lower protective effect. In addition, although the use of medical/surgical masks versus N95 respirators demonstrates no differences in clinical effectiveness to date, their use needs to be further studied within the context of a well-designed RCT in the setting of COVID-19, and with concomitant measurement of harms, which to date have been poorly studied. The recently published Loeb RCT conducted over a prolonged course in the current pandemic has provided the only evidence to date in this area (Loeb 2022).

Physical distancing represents another major research gap which needs to be addressed expediently, especially within the context of the COVID-19 pandemic setting as well as in future epidemic settings. The use of quarantine and screening at entry ports needs to be investigated in well-designed, high-quality RCTs given the controversies related to airports and travel restrictions which emerged during the COVID-19 pandemic. We found only one RCT investigating quarantine, and no trials of screening at entry ports or physical distancing. Given that these and other physical interventions are some of the primary strategies applied globally in the face of the COVID-19 pandemic, future trials of high quality should be a major global priority to be conducted within the context of this pandemic, as well as in future epidemics with other respiratory viruses of less virulence.

The variable quality and small scale of some studies is known from descriptive studies (Aiello 2002; Fung 2006; WHO 2006b), and systematic reviews of selected interventions (Meadows 2004). In summary, more high-quality RCTs are needed to evaluate the most effective strategies to implement successful physical interventions in practice, both on a small scale and at a population level. It is very unfortunate that more rigorous planning, effort and funding was not provided during the current COVID-19 pandemic towards high-quality RCTs of the basic public health measures. Finally, we emphasise that more attention should be paid to describing and quantifying the harms of the interventions assessed in this review, and their relationship with adherence.

ACKNOWLEDGEMENTS

This 2022 review update is funded by the National Institute for Health and Care Research (NIHR) ESP Incentive Award Scheme NIHR150879. The views expressed are those of the authors and

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not necessarily those of the NIHR or the Department of Health and Social Care.

We wish to acknowledge the late Chris del Mar for his substantial contributions as an author on previous versions of this review. We also thank Sarah Thorning for designing and updating searches from the 2011 publication to the 2020 publication. We thank Jessika Wejfalk for translating the funding source in a Danish trial in this 2022 update.

The following people conducted the editorial process for this 2022 update:

- Sign-off Editor (final editorial decision): Michael Brown (Michigan State University College of Human Medicine, USA).
- Managing Editor (selected peer reviewers, collated peer reviewer comments, provided editorial guidance to authors): Fiona Russell (Bond University, Australia).
- Contact Editor (assessed peer review comments and recommended an editorial decision): Allen Cheng (Monash University, Australia).
- Statistical Editor (provided comments): Teresa Neeman (Biological Data Science Institute, Australian National University, Australia).
- Copy Editor (copy-editing and production): Heather Maxwell.

Peer reviewers (provided comments and recommended an editorial decision):

- Clinical/content review: Roderick P. Venekamp.
- Consumer review: Janet Wale (Independent consumer representative).
- Methods review: Leslie Choi (Evidence Synthesis Development Editor, Cochrane Central Executive Team).

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Abaluck 2022

Study characteristics	
Methods	Cluster-RCT Randomisation unit: villages (N = 600) Intervention duration: 8 weeks “Our intervention was designed to last 8 weeks in each village”
Participants	Inclusion criteria: community level participants Intervention = 178,322 individuals, control = 163,861 individuals (Total N = 342,183 adults)
Interventions	2 types of mask used: surgical and cloth masks PLUS a brief video of notable public figures discussing why, how, and when to wear a mask, PLUS a brochure based on WHO materials depicting proper mask-wearing. Control villages: the control group did not receive any interventions See Table 1 for details.
Outcomes	Effectiveness: primary outcome: symptomatic seroprevalence (symptomatic and seropositive) Laboratory: seropositivity was defined by having detectable IgG antibodies against SARS-CoV-2 Symptoms defined as per WHO-defined COVID-19 symptoms: (a) fever and cough; (b) 3 or more of the following symptoms (fever, cough, general weakness/fatigue, headache, myalgia, sore throat, coryza, dyspnoea, anorexia/nausea/vomiting, diarrhoea, altered mental status); or (c) loss of taste or smell. Secondary outcomes: prevalence of proper mask-wearing as wearing either a project mask or an alternative face-covering over the mouth and nose and improper mask-wearing as wearing a mask in any way that did not fully cover the mouth and nose; prevalence of physical distancing per WHO guideline that defines physical distancing as one meter of separation; prevalence of symptoms consistent with COVID-19: definition (see above) Safety not assessed. However, study mentioned that there was no adverse events reported during the study period

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Abaluck 2022 *(Continued)*

Notes	The authors conclude that: a randomised trial of community-level mask promotion in rural Bangladesh during the COVID-19 pandemic shows that the intervention increased mask usage and reduced symptomatic SARS-CoV-2 infections, demonstrating that promoting community mask-wearing can improve public health (a scalable and effective method to promote mask adoption and reduce symptomatic SARS-CoV-2 infections.) Funding: this trial was financially supported by a grant from GiveWell.org to Innovations for Poverty Action. The trial authors declare no competing interests.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Random number generator used
Allocation concealment (selection bias)	High risk	Significant differences in the numbers of households included in each treatment group suggestive of a lack of allocation concealment
Blinding of participants and personnel (performance bias) All outcomes	High risk	Participants, mask promoters, and mask surveillance staff were not blinded as intervention materials were clearly visible
Blinding of outcome assessment (detection bias) All outcomes	High risk	Although the pre-specified analyses and sample exclusions were made by analysts blinded to the treatment assignment, investigators dropped individuals who were missing symptom data or who did not consent to blood spot collection from the primary outcome. One of the outcomes is COVID-19 symptoms reported by participants. Mask promoters, and mask surveillance staff were not blinded
Incomplete outcome data (attrition bias) All outcomes	High risk	Laboratory testing results were only available for around 40% of the symptomatic participants
Selective reporting (reporting bias)	High risk	Primary outcome of seroconversion was not reported

Aelami 2015

Study characteristics

Methods	A prospective cross-sectional study conducted during the Hajj season 2012. Pilgrims were randomised into 2 groups. The intervention group received education on personal hygiene including a hygienic package containing alcohol-based hand rub (gel or spray), surgical masks, soap, paper handkerchiefs, and user instructions; the control group did not receive any intervention. ILI was defined as the presence of at least 2 of the following during their stay: fever, cough, and sore throat. Questionnaires including demographic and clinical information were distributed amongst trained physicians before departure from Iran.
Participants	Total enrolled: 664 Iranian pilgrims (306 in the intervention group and 358 in the control group) Inclusion criteria: not reported Exclusion criteria: not reported

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Aelami 2015 *(Continued)*

Interventions	Hygiene education and package. See Table 1 for details.
Outcomes	ILI defined as the presence of at least 2 of the following during their stay: fever, cough, and sore throat. No safety outcomes were reported.
Notes	This is an abstract, therefore few details were reported. Funding not mentioned. Disclosure of interest: none declared.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient details provided
Allocation concealment (selection bias)	Unclear risk	Insufficient details provided
Blinding of participants and personnel (performance bias) All outcomes	High risk	Unblinded study
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient details provided
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Insufficient details provided
Selective reporting (reporting bias)	Unclear risk	Insufficient details provided

Aiello 2010

Study characteristics

Methods	Cluster-RCT assessing the effects of hand sanitiser and masks versus masks or no intervention on ILI symptoms. The trial was conducted in university halls of residence with more than 100 student residents in a US university during the 2006 to 2007 influenza “season”. The study lasted 6 weeks. The units of randomisation were 7 of the 15 halls. 1 hall was very large (1240 residents), and the 6 remaining ones, which had between 110 and 830 residents, were combined into 2 clusters roughly equivalent in size. The 3 clusters were then randomised by random extraction of the clustered halls’ names out of a container. The largest hall (single-cluster) was randomised to the mask and hand sanitiser arm; the 4-halls cluster received masks; and the remaining 2 halls were assigned as controls.
Participants	A total of 1297 with completed baseline survey and at least 1 weekly survey result were analysed (face mask and hand hygiene group = 367; face mask–only group = 378; control group = 552). Inclusion criteria: aged 18 or more, willing to wear mask and use alcohol-based hand sanitiser, have a throat swab specimen collected when ill, and complete the baseline and weekly surveys over the 6-week study period

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Aiello 2010 *(Continued)*

	Exclusion criteria: individuals reporting a skin allergy to alcohol were excluded Recruitment of students began in 26 November, but the trial did not go "live" with distribution of intervention materials until 22 January 2007 when the first case of influenza was confirmed on campus by laboratory tests. Enrolment continued until 16 February 2007, and the study was completed on 16 March 2007. During the study period there was a 1-week break when the majority of residents left campus. There were 1327 eligible participants, 1297 of which had a complete baseline survey and at least 1-weekly survey result. It is unclear what the ineligibility criteria were for the 30 missing (1327 minus 1297), but the explanation may be in the appendix.
Interventions	Alcohol-based hand sanitiser (62% ethyl alcohol in a gel base) in a squeeze bottle and TECNOL procedure masks with ear loops (KC Ltd) and educational material or masks and educational material or no intervention. Compliance was encouraged within halls and outside. Sleep wearing was optional. All participants received basic video-linked instruction on cough etiquette and hand sanitation. At baseline and weekly during the study, participants were asked to fill in a web-based survey collecting demographic and ILI symptom data. This was supplemented by direct observation of compliance by staff. Compliance with "optimal handwashing" (at least 20 seconds 5 or more times a day) was significantly higher in the sanitiser-and-mask arm. See Table 1 for details.
Outcomes	Laboratory details are described in appendix. Effectiveness: ILI, defined as cough and at least 1 constitutional symptom (fever/feverishness, chills, headache, myalgia). ILI cases were given contact nurses' phone numbers to record the illness and paid USD 25 to provide a throat swab. 368 participants had ILI, and 94 of these had a throat swab analysed by PCR. 10 of these were positive for influenza (7 for A and 3 for B). Safety: N/A
Notes	The authors conclude that "These findings suggest that face masks and hand hygiene may reduce respiratory illnesses in shared living settings and mitigate the impact of the influenza A (H1N1) pandemic". This conclusion is based on a significantly lower level of ILI incidence in the mask and hand sanitiser arm compared to the other 2 arms after adjustment for covariates (30% to 50% less in arm 1 compared to controls in the last 2 weeks of the study). Comparison with the ILI rate of the control arm may not be a reflection of the underlying rate of ILI because the intervention arm received instruction on hand sanitation and hand etiquette. The play of adjustments is unclear. The intracluster correlation coefficient is reported in the footer of Table 4. Its very small size suggests lack of clustering within halls. The role of spring break is mentioned in the Discussion, as are the results of this study compared to other studies included in our review (Cowling 2008 and MacIntyre 2009). The authors report that 147 of 1297 participants (11.3%) had ILI symptoms "at baseline" and were excluded from analysis. During the 6 weeks of the study, 368 of 1150 participants (32%) had ILI. This averages out at about 5% per week. It is unclear what the term "at baseline" means; presumably this means during the 2 to 3 weeks of participant enrolment. If this is so, the reason for the triggering of the interventions (tied to influenza isolation) are obscure, as the trial is supposedly about ILI, and an ILI outbreak was already under way "at baseline". This study has the same trial registration number as the Aiello 2012 study; the study was funded by government and pharmaceutical industry, i.e. this work was supported by funding from the Centers for Disease Control (CDC) and Prevention Grant U01 C1000441 (www.cdc.gov). Disclosure of interest: none declared.
Risk of bias	

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Aiello 2010 *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Described as randomised, but sequence generation not reported
Allocation concealment (selection bias)	High risk	The residence hall units were randomised by blindly selecting a uniform ticket with the name of each hall out of a container (A.S.M. and A.A.) for randomisation assignment to each study arm.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Unblinded study
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Outcome assessors blinded.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Attrition is reported as follows: 9, 11, and 19 ineligible and 26, 52, and 21 lost to follow-up (respectively by arm), for a total of 39 and 99 for each reason for attrition. In total, 1297 (97%) of 1331 participants completed a baseline and at least 1-weekly survey. The text reports an ITT analysis with only 1 ILI episode included by participant. No reasons for the attrition of participants and swab volunteers are reported (were the swabs taken from a random sample or not?).
Selective reporting (reporting bias)	High risk	There is no information on the causes of ILI other than the reporting on the 10 influenza PCR-positive swabs of 94 out of 368 students with ILI. This is a very low rate (and the Discussion confirms that the influenza season was mild), but investigation of the other known causes of ILI is not even mentioned in the text. This is especially important because stress, alcohol intake levels, and influenza vaccination were a significant predictor of ILI symptoms (Table 1). The reason for selective testing and/or reporting of influenza viruses tests over the other causes of ILI are unclear, especially as the study objective was focused on ILI. The text is also difficult to follow, weaving the reporting of ILI and influenza without a clear rationale.

Aiello 2012

Study characteristics	
Methods	During the 2007 to 2008 influenza season, 1111 students residing in university residence halls were cluster-randomised by residence house (N = 37) to either face mask and hand hygiene, face mask only, or control arms. Discrete time survival analysis using generalised models estimated rate ratios according to study arm, each week and cumulatively over the 6-week intervention period, for clinically verified ILI and laboratory-confirmed influenza A or B.
Participants	A total of 1187 young adults living in 37 residence halls, randomly assigned to 1 of 3 groups for 6 weeks: face mask use (n = 392), face masks with hand hygiene (n = 349), control (n = 370) Inclusion criteria: aged 18 or more, willing to wear mask and use alcohol-based hand sanitiser, have a throat swab specimen collected when ill, and complete the baseline and weekly surveys over the 6-week study period Exclusion criteria: individuals reporting a skin allergy to alcohol were excluded

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Aiello 2012 *(Continued)*

Interventions	Participants were assigned to face mask and hand hygiene, face mask only, or control group during the study. See Table 1 for details.
Outcomes	Clinically verified ILI: case definition (presence of cough and at least 1 or more of fever/feverishness, chills, or body aches) Laboratory-confirmed influenza A or B. Throat swab specimens were tested for influenza A or B using RT-PCR. No safety outcomes reported.
Notes	This study has the same trial registration number as the Aiello 2010 study; the study was funded by government and pharmaceutical industry, i.e. this work was supported by funding from the Centers for Disease Control (CDC) and Prevention Grant U01 C1000441 (www.cdc.gov). Disclosure of interest: none declared.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer generation of sequence described.
Allocation concealment (selection bias)	Low risk	All residence houses in each of the residence halls were randomised prior to the intervention implementation.
Blinding of participants and personnel (performance bias) All outcomes	High risk	No blinding for study participants and personnel
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Outcome assessors blinded.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Attrition low and similar in each group
Selective reporting (reporting bias)	Low risk	2 outcomes specified and reported.

Alfelali 2020

Study characteristics

Methods	Cluster open-label RCT Location: Mina, Greater Makkah, Saudi Arabia Follow up for 4 days
Participants	Arabic or English speaking Hajj pilgrims aged > 18 years from participating countries (Australia, Qatar and KSA) staying in allocated tents and able to provide signed informed consent were included.

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Alfelali 2020 *(Continued)*

Interventions	Mask wearing. See Table 1 for details.
Outcomes	Effectiveness: Laboratory: laboratory-confirmed viral respiratory infections (nasal swab on 650 participants only) Secondary outcomes: clinical respiratory infections in participants Safety reported on side effects of mask wearing The most common side effects: difficulty in breathing (26.2%); discomfort (22%); a small minority (3%) reported feeling hot, sweating, a bad smell or blurred vision with eyeglasses
Notes	The authors conclude that this trial was unable to provide conclusive evidence on facemask efficacy against viral respiratory infections most likely due to poor adherence to protocol. Funding: this report was made possible by a National Priorities Research Program grant (NPRP 6-1505-3-358) from the Qatar National Research Fund, a member of Qatar Foundation. Disclosure of interests: the other authors have no competing interests to declare.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Coin-tossing by an individual who was not a member of the research team
Allocation concealment (selection bias)	High risk	Used coin tossing which can introduce imbalance
Blinding of participants and personnel (performance bias) All outcomes	High risk	No blinding
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Laboratory staff were blinded to the assigned intervention group
Incomplete outcome data (attrition bias) All outcomes	Low risk	Reported both intention-to-treat and per-protocol analysis and participant flow chart
Selective reporting (reporting bias)	Unclear risk	Insufficient information available.

Almanza-Reyes 2021

Study characteristics

Methods	RCT randomised using a computer-generated block scheme and stratified according to duty position, work shifts and the area/department of the service FU duration: 9 weeks
Participants	Workers (doctors, nurses, administrators) in a hospital for the exclusive recruitment of patients diagnosed with COVID-19 “General Tijuana Hospital”

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Almanza-Reyes 2021 *(Continued)*

Interventions	Experimental group: mouthwash and nose rinse Silver mouth wash: 50 mL spray bottle containing AgNPs solution with 1 wt% concentration (0.6 mg/mLmetallic silver). Mix 4 to 6 spray shots (corresponding to volume ~ 0.5 mL) of this solution with 20 mL of water and to gargle with obtained solution for 15 to 30 seconds at least 3 times a day. Or use as nasal lavages on the inner part of the nasal alae and nasal passage with the same solution using a cotton swab twice a day. Mouth spray: cover evenly the oral cavity with the direct 1 to 2 spray shots of solution without its previous dilution in water. Control group: instructed to do mouth wash and nose rinse with a conventional mouthwash the way they normally did before the study See Table 1 for details.
Outcomes	Effectiveness: Laboratory: Lab-confirmed infection using RT-PCR; symptoms of respiratory tract infection (RTI) no definition given; clinical Evacuation: CT (Toshiba Aquilion 16, Japan) chest scan (random selection) Safety: done using self-reported by participants using a questionnaire. “The present study also showed that no harmful side effects were observed in the 114 participants who used AgNPs as a mouthwash and nose rinse solution for 9 weeks”
Notes	Authors conclude that the mouth and nasal rinse with AgNPs helps in the prevention of SARS-CoV-2 infection in health personnel who are exposed to patients diagnosed with COVID-19. Funding: Funded studies A. Pestryakov Development Program "Priority 2030" Tomsk Polytechnic University https://tpu.ru/en. Conflict of interest statement: the authors have declared that no competing interests exist.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated stratified block scheme
Allocation concealment (selection bias)	High risk	Unbalanced baseline prognostic factors (vaccination and frequency of handwashing)
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not blinded.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information provided.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No participant flow chart reported.
Selective reporting (reporting bias)	Unclear risk	No protocol available

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Alzaher 2018

Study characteristics	
Methods	A cluster-RCT conducted amongst girls attending 4 primary schools between January and March 2018. The participants attended a hand-hygiene workshop. The schoolgirls' absences were followed up for 5 weeks. Incidence rate, percentage of absence days, and absence rate were calculated for total and upper respiratory infections absences.
Participants	A total of 496 schoolgirls aged of 6 to 12 years, attending 4 public primary girls' schools in the city of Riyadh, Saudi Arabia between January and March 2018. Students were randomised to education group (n = 234) or control group (n = 262). Exclusion criteria: not reported
Interventions	Hand hygiene workshop. See Table 1 for details.
Outcomes	Incidence rate, percentage of absence days, and absence rate were calculated for total and upper respiratory infections absences. The episode of URIs was defined as having 2 of the following symptoms for a day or 1 of the symptoms for 2 or more consecutive days: 1) a runny nose, 2) a stuffy or blocked nose or noisy breathing, 3) sneezing, 4) a cough, 5) a sore throat, and 6) feeling hot, having a fever or a chill. No safety outcomes reported.
Notes	Source of funding is unclear. Disclosure of interest: none mentioned.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient detail provided.
Allocation concealment (selection bias)	Low risk	Schools allocated prior to all schoolgirls attending selected schools were invited to participate.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Unblinded study
Blinding of outcome assessment (detection bias) All outcomes	High risk	Unblinded study
Incomplete outcome data (attrition bias) All outcomes	Low risk	No loss to follow-up
Selective reporting (reporting bias)	Unclear risk	No protocol available

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Arbogast 2016

Study characteristics	
Methods	A 13.5-month prospective cluster-RCT executed with alcohol-based hand sanitiser in strategic workplace locations and personal use (intervention group) and brief hand hygiene education (both groups). Four years of retrospective data were collected for all participants.
Participants	Data for a total of 1183 participants were analysed (intervention group = 525, control group = 607). Inclusion criteria: all employees at 3 facilities who were 18 years of age or older, were enrolled in the company health insurance coverage, did not transfer between sites, and worked onsite full time (≥ 32 hours) were eligible for the study Exclusion criteria: not reported
Interventions	Alcohol-based hand sanitiser in strategic workplace locations and personal use (intervention group) and brief hand hygiene education (both groups). See Table 1 for details.
Outcomes	1. The number of healthcare insurance claims, for a defined set of preventable illnesses, per participant per year 2. Absenteeism, defined as the number of sick episodes per participant per year Claims based on ICD-9 codes No safety outcomes reported.
Notes	Only 2 clusters (1 per group) included, hence study data not included in meta-analysis. Industry funded. Disclosure of interest: none mentioned.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	No details provided.
Allocation concealment (selection bias)	Unclear risk	No details provided.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Unblinded study
Blinding of outcome assessment (detection bias) All outcomes	High risk	Unblinded study
Incomplete outcome data (attrition bias) All outcomes	Low risk	Attrition minimal and similar in 2 groups
Selective reporting (reporting bias)	Unclear risk	No protocol available

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Ashraf 2020

Study characteristics	
Methods	Geographically pair-matched community-based cluster-randomised trial Used a random number generator to block Open-label Block randomised: unit of randomisation was a group of compounds visited by a single local promoter
Participants	1. Infants (target child) will be eligible to participate in the study if: a. they are in utero at the baseline survey. b. their parents/guardians are planning to stay in the study village for the next 12 months (if a mother is planning to give birth at her natal home and then return, she will still be a candidate for enrolment) 2. Children < 36 months old at baseline that are living in the compound of a target child will be eligible to participate in diarrhoea measurement if: a. they are < 36 months old at the baseline survey; b. their parents/guardians are planning to stay in the study village for the next 12 months. 3. Children 18 to 27 months old at baseline that are living in the compound of a target child will be eligible to participate in intestinal parasite specimen collection if: a. they are 18 to 27 months old at the baseline survey; b. their parents/guardians are planning to stay in the study village for the next 12 months.
Interventions	6 intervention arms: water quality, sanitation, hand washing, combined WSH, nutrition, nutrition + WSH Intervention was delivered at the household or the compound level See Table 1 for details.
Outcomes	Effectiveness: Primary outcome: 7-day prevalence of acute respiratory illness (ARI). Defined as: caregiver-reported symptoms of persistent cough or panting, wheezing, or difficulty breathing (1 or 2) in the 7 days before the interview. No clinical data were collected Secondary analyses: alternate combinations of the measured symptoms: 7-day prevalence of only panting, wheezing, or difficulty breathing (2) and ARI plus fever ([1 or 2] and 3) Outcomes were measured approximately 12 and 24 months following intervention roll out. Safety not assessed
Notes	The authors conclude that: single targeted water, sanitation, and hygiene interventions reduced reported respiratory illness in young children. There was no apparent respiratory health benefit from combining WASH interventions. Financial support: this research was funded by Global Development grant OPPGD759 from the Bill & Melinda Gates Foundation to the University of California, Berkeley, CA. S. P. L., S. A., M. I., B. F. A., and J. M. C. report grants from the Bill & Melinda Gates Foundation during the conduct of the study. P. K. R. reports grants from Leland Stanford University during the conduct of the study for support to the WASH Benefits project. M. R. reports grants and non financial support from the Bill & Melinda Gates Foundation (through a subcontract from UC Berkeley) during the conduct of the study. Disclosure of interest: none mentioned.

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Ashraf 2020 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Random number generator
Allocation concealment (selection bias)	Low risk	Random allocation by an offsite investigator
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not blinded
Blinding of outcome assessment (detection bias) All outcomes	Low risk	The research team who implemented the intervention was separate from the data collection team. The analysis was carried out masked to the allocated group.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Provided participants flow diagram showing minimal attrition.
Selective reporting (reporting bias)	Low risk	Reported the pre-specified outcomes.

Azor-Martinez 2016

Study characteristics	
Methods	Randomised, controlled, and open study with an 8-month follow-up. The experimental group washed their hands with soap and water, together with using hand sanitiser, and the control group followed their usual handwashing procedures. Absenteeism rates due to URIs were compared between the 2 groups through a multivariate Poisson regression analysis. The per cent of days missed in both groups were compared with a z test.
Participants	A sample of 1341 (intervention group = 621, control group = 720) Inclusion criteria: children 4 to 12 years old, attending 5 state schools in Almeria (Spain) whose parents/guardians had signed an informed consent document Exclusion criteria: children who had any of the following chronic illnesses that predisposed them to infection: neoplasia, primary and secondary immunodeficiencies, cystic fibrosis, chronic treatment with high doses of steroids or immunosuppressants
Interventions	Hand-washing workshops of 2-hour duration. The experimental group washed their hands with soap and water together with using hand sanitiser, whilst the control group followed usual hand-washing procedures. See Table 1 for details.
Outcomes	Absenteeism rates due to URIs Per cent of days missed Respiratory illness was defined by 2 of the following symptoms during 1 day, or 1 of the symptoms for 2 consecutive days: (1) runny nose; (2) stuffy or blocked nose or noisy breathing; (3) cough; (4) feeling hot or feverish or having chills; (5) sore throat; or (6) sneezing.

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Azor-Martinez 2016 *(Continued)*

	A school absenteeism case (episode) was defined as when a child failed to attend school due to an URI. Common infectious illnesses, such as conjunctivitis, and skin infections were not included. Other causes for absenteeism, such as doctors' appointments, family vacations, and accident injuries, were also excluded. No safety outcomes reported.
Notes	Government funded Disclosure of interest: none mentioned.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	A random number table was used.
Allocation concealment (selection bias)	Low risk	Schools/classes allocated prior to children recruited.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Unblinded study
Blinding of outcome assessment (detection bias) All outcomes	High risk	Unblinded study
Incomplete outcome data (attrition bias) All outcomes	High risk	Attrition levels high and different in the 2 groups
Selective reporting (reporting bias)	Unclear risk	No protocol available

Azor-Martinez 2018

Study characteristics

Methods	A cluster-RCT, controlled, and open study of 911 children aged 0 to 3 years attending 24 DCCs in Almería, Spain, with an 8-month follow-up. 2 intervention groups of DCC families performed educational and hand hygiene measures, 1 with soap and water (n = 274), another with hand sanitiser (n = 339), and the control group followed usual hand-washing procedures (n = 298). Respiratory infection (RI) episode rates were compared through multilevel Poisson regression models. The percentage of days missed were compared with Poisson exact tests.
Participants	A total of 911 children attending 24 DCCs in Almería (Spain). Inclusion criteria: children between 0 and 3 years old enrolled in DCCs and attending for at least 15 hours per week whose parents or guardians had signed an informed consent Exclusion criteria: children with chronic illness or medication that could affect their likelihood of contracting an infection

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Azor-Martinez 2018 *(Continued)*

	Data were analysed for 911 participants: hand sanitiser group (n = 339), soap and water group (n = 274), and control group (n = 298).
Interventions	2 intervention groups. 1 group used soap and water, another used hand sanitiser, whilst the control group followed usual hand-washing procedures. Groups received 1-hour hand hygiene workshop. See Table 1 for details.
Outcomes	Primary: RI incidence rate Secondary: (1) the presence or absence of at least 1 antibiotic prescription for each new RI episode during the study period (topical antibiotics were excluded), and (2) the percentage of RI absenteeism days in the 3 groups calculated as the ratio of RI absenteeism days to all possible days of attendance DCC absenteeism episode was defined as when a child failed to attend a DCC because of an RI. Respiratory illness was defined as the presence of 2 of the following symptoms during 1 day or the presence of 1 of the symptoms for 2 consecutive days: (1) runny nose, (2) stuffy or blocked nose or noisy breathing, (3) cough, (4) feeling hot or feverish or having chills, (5) sore throat, or (6) sneezing. No safety outcomes reported.
Notes	Government funded. This work was supported by a grant from the Andalusia Department of Health. Competing interests: the authors have indicated they have no potential conflicts of interest to disclose.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer randomisation using statistical software for the sequence
Allocation concealment (selection bias)	Low risk	Clusters assigned prior to recruitment.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Unblinded study
Blinding of outcome assessment (detection bias) All outcomes	High risk	Unblinded study
Incomplete outcome data (attrition bias) All outcomes	Low risk	Attrition minimal and similar in 3 groups
Selective reporting (reporting bias)	Unclear risk	No protocol available

Ban 2015

Study characteristics

Methods	Quote: "Group randomised" trial. Only 2 clusters, which were 2 kindergartens in Xiantao City, Hubei Province, China.

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Ban 2015 *(Continued)*

Participants	Data for a total of 393 participants were analysed (intervention group = 194, control group = 199). 5 classes (221 children) randomly selected from 1 kindergarten in the intervention group and 6 classes (244 children) randomly selected from another kindergarten in the control group. Children were aged 5 or under. There were 72 exclusions from the analysis.
Interventions	Intervention group: hand hygiene and surface-cleaning education and provision of products for kindergarten and home use. Control group: usual practice. See Table 1 for details.
Outcomes	Respiratory illness, defined as: 2 or more of the following: fever, cough and expectoration, runny nose and nasal congestion, collected by parental questionnaire. Axillary temperature higher than 37.3 °C or the range of temperature fluctuation is more than 1 °C. 'Cough and expectoration' were defined as 3 or more coughs in a single hour and lasting for 4 or more hours in a single day, with or without expectoration. 'Runny nose and nasal congestion' were defined as a runny nose lasting for 4 or more hours in 1 day, with or without nasal congestion.
Notes	Funding not mentioned. Disclosure of interest: none mentioned.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Method not described, and only 2 clusters.
Allocation concealment (selection bias)	Unclear risk	Method not described.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Unblinded study
Blinding of outcome assessment (detection bias) All outcomes	High risk	Unblinded study
Incomplete outcome data (attrition bias) All outcomes	High risk	Parental report, and parents were aware of treatment allocation
Selective reporting (reporting bias)	High risk	Attrition reported and balanced between groups, but high rate of attrition in a trial with small numbers of participants.

Barasheed 2014

Study characteristics

Methods	Pilot, non-blinded, parallel, cluster-RCT
Participants	22 tents were randomly selected from the Australian pilgrims camped in Mina, during Hajj in 2011; 12 tents were allocated to the mask group and 10 tents to the control group. A total of 164 Australian pilgrims were recruited: 75 in the mask group (39 ‘cases’ and 36 ‘contacts’) and 89 in the control group (36 ‘cases’ and 53 ‘contacts’).

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Barasheed 2014 *(Continued)*

	Inclusion criteria for index case: 1) Australian pilgrims of any gender aged > 15 years who attend the Hajj 2011, and 2) have symptoms of respiratory infection for 3 days. For close tent contact: 1) Australian pilgrims of any gender aged 15 years or more who attend the Hajj 2011, and 2) pilgrims who share the same tent and sleep "immediately close" to the index case. Exclusion criteria: for index case: 1) pilgrims who do not suffer from symptoms of respiratory infection, 2) pilgrims who present with symptoms of respiratory infection for > 3 days, and 3) children aged less than 15 years. For close tent contact: 1) pilgrims who are symptomatic at presentation, 2) pilgrims who are not close tent contacts of an index case, and 3) children aged less than 15 years. Only 10% to 15% of potential participants took part in the study.
Interventions	"supervised mask use" versus "no supervised mask use". See Table 1 for details.
Outcomes	Laboratory: 2 nasal swabs from all ILI cases and contacts, 1 for influenza POCT using the QuickVue Influenza (A+B) assay (Quidel Corporation, San Diego, USA) and 1 for later nucleic acid testing for influenza and other respiratory viruses. However, there was a problem with getting POCT on time during Hajj. Effectiveness: to assess the effectiveness of face masks in the prevention of transmission of ILI. ILI was defined as subjective (or proven) fever plus 1 respiratory symptom (e.g. dry or productive cough, runny nose, sore throat, shortness of breath). Safety: none planned or reported
Notes	The study was conducted from 4 November 2011 to 10 November 2011. Compliance with face mask use by pilgrims was 56 of 75 (76%) in the mask group and 11 of 89 (12%) in the control group (P < 0.001). The proportion of face mask user in the 'mask' tents was 76% for both males (19/25) and females (38/50). The most often reported reason for not wearing face masks was discomfort (15%). Government funded: Qatar National Research Fund (QNRF). The other authors have declared no conflict of interest in relation to this work.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information provided.
Allocation concealment (selection bias)	Unclear risk	Quote: "tents were randomised to either intervention group (supervised mask tent) or control group (no supervised mask tent) by an independent study coordinator who was not an investigator", but did not mention how
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "Because advice from the Saudi Ministry of Hajj to all pilgrims included recommending the wearing of masks, all pilgrims, both cases and controls, were asked about mask-wearing"
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Self-reported outcomes (nasal swab was performed for those who reported ILI symptoms and was not intended as systematic detection). ILI was defined as subjective (or proven) fever plus 1 respiratory symptom.
Incomplete outcome data (attrition bias) All outcomes	Low risk	No loss to follow-up, all numbers were reported from enrolment to analysis
Selective reporting (reporting bias)	Low risk	All planned outcomes were reported.

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Biswas 2019

Study characteristics	
Methods	Cluster-RCT in 24 primary schools in Dhaka to assess the effectiveness of hand sanitiser and a respiratory hygiene education intervention in reducing ILI and laboratory-confirmed influenza during June to September 2015. 12 schools were randomly selected to receive hand sanitiser and respiratory hygiene education, and 12 schools received no intervention. Field staff actively followed children daily to monitor for new ILI episodes (cough with fever) through school visits and by phone if a child was absent. When an illness episode was identified, medical technologists collected nasal swabs to test for influenza viruses.
Participants	A total of 10,855 students were enrolled in the study (intervention schools = 5077 children; control schools = 5778 children). Children aged 5 to 10 years educated in 24 randomly selected primary schools in Dhaka, Bangladesh Exclusion: schools that offered education above grade 5 because of differences in student populations, as well as schools that had previously received a hand or respiratory hygiene intervention
Interventions	Hand sanitiser and respiratory hygiene education versus no intervention. See Table 1 for details.
Outcomes	Incidence of ILI Incidence of laboratory-confirmed influenza (RT-PCR) An ILI episode was defined as measured fever ≥ 38 °C or subjective fever and cough. If a child was absent, the field staff followed up by phone to identify the reason for absenteeism and to determine if the child met the ILI case definition. If a child in a participating school had an ILI episode, a trained medical technologist visited the child's household to obtain consent from the child's parent/guardian and collect a nasal swab from the child within 48 hours of symptom onset. If it was outside the 48-hour window, the sample was not collected. No safety outcomes reported.
Notes	Government funded. Disclosure of interest: none mentioned.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Sequence generated using a computer-based random number generator.
Allocation concealment (selection bias)	Low risk	Allocation completed prior to individuals being recruited.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Unblinded study
Blinding of outcome assessment (detection bias) All outcomes	High risk	Unblinded study
Incomplete outcome data (attrition bias)	High risk	Information missing for 30 children (28 children in the control schools and 2 children in the intervention schools)

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Biswas 2019 *(Continued)*
All outcomes

Selective reporting (reporting bias)	Unclear risk	No protocol available

Bundgaard 2021

Study characteristics

Methods	Investigator-initiated, nationwide, unblinded, randomised controlled trial stratified by the 5 regions of Denmark
Participants	Inclusion criteria: community-dwelling adults aged 18 years or older without current or prior symptoms or diagnosis of COVID-19 reported being outside the home amongst others for at least 3 hours per day, and who did not wear masks during their daily work. Exclusion criteria: previously tested positive for SARS-CoV-2 and wear face masks at work
Interventions	Exposure: mask (N = 2392) Control group: no mask (N = 2470) Both groups received materials and instructions for antibody testing on receipt and at 1 month; materials and instructions for collecting an oropharyngeal/nasal swab sample for polymerase chain reaction (PCR) testing at 1 month and whenever symptoms compatible with COVID-19 occurred during follow-up. They registered symptoms and results of the antibody test in the online REDCap system. Written instructions and instructional videos guided antibody testing, oropharyngeal/nasal swabbing, and proper use of masks, and a help line was available to participants. See Table 1 for details.
Outcomes	Study duration: 1 month Effectiveness: primary outcome (composite) SARS-CoV-2 infection, defined as a positive result on an oropharyngeal/nasal swab test for SARS-CoV-2, development of a positive SARS-CoV-2 antibody test result (IgM or IgG) during the study period, or a hospital-based diagnosis of SARS-CoV-2 infection or COVID-19. Secondary outcome: PCR evidence of infection with other respiratory viruses Safety: adverse reaction: 14% in mask group (no further descriptions)
Notes	The authors conclude that inconclusive results, missing data, variable adherence, patient-reported findings on home tests, no blinding, and no assessment of whether masks could decrease disease transmission from mask wearers to others. Funding: the primary funding source was The Salling Foundations. Disclsure can be viewed at www.acponline.org /authors/icmje/ConflictOfInterestForms.do?msNum=M20-6817.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer algorithm stratified by the 5 regions of Denmark
Allocation concealment (selection bias)	Unclear risk	Insufficient information reported

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Bundgaard 2021 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	High risk	Not blinded
Blinding of outcome assessment (detection bias) All outcomes	High risk	Not blinded. Patient reported symptoms, POCT testing, patient-reported findings on home tests.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Participant flow chart showed acceptable attrition
Selective reporting (reporting bias)	Low risk	All pre-specified outcomes reported.

Canini 2010

Study characteristics	
Methods	A cluster-RCT conducted in France during the 2008 to 2009 influenza season. Households were recruited during a medical visit of a household member with a positive rapid influenza A test and symptoms lasting less than 48 hours. Households were randomised either to the mask or control group for 7 days. In the intervention arm, the index case had to wear a surgical mask from the medical visit and for a period of 5 days. The trial was initially intended to include 372 households, but was prematurely interrupted after the inclusion of 105 households (306 contacts) following the advice of an independent steering committee. Generalised estimating equations were used to test the association between the intervention and the proportion of household contacts who developed an ILI during the 7 days following the inclusion.
Participants	A total of 105 households were randomised, which represented 148 contacts in the intervention arm and 158 in the control arm. The study was conducted in 3 French regions (Ile de France, Aquitaine, and Franche-Comté) and included households of size 3 to 8. Exclusion criteria: if index patient was treated for asthma or chronic obstructive pulmonary disease or was hospitalised
Interventions	Surgical mask versus no mask. See Table 1 for details.
Outcomes	The primary endpoint was the proportion of household contacts who developed an ILI during the 7 days following inclusion. Exploratory cluster-level efficacy outcome, the proportion of households with 1 or more secondary illness in household contacts. A temperature over 37.8 °C with cough or sore throat was used as primary clinical case definition. Adverse reactions due to mask-wearing
Notes	Government funded. Competing interests: the authors have declared that no competing interests exist.
Risk of bias	

Bias	**Authors' judgement**	**Support for judgement**

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Canini 2010 *(Continued)*

Random sequence generation (selection bias)	Low risk	Randomisation lists were generated by a computerised program.
Allocation concealment (selection bias)	Low risk	Randomisation was performed centrally by the GP after written consent on an interactive voice response system dedicated to the study.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Unblinded study
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Outcome assessors blinded.
Incomplete outcome data (attrition bias) All outcomes	Low risk	All households included in analysis.
Selective reporting (reporting bias)	Low risk	All specified outcomes reported.

Carabin 1999

Study characteristics	
Methods	Cluster-RCT carried out in DCCs in the Canadian province of Quebec between 1 September 1996 and 30 November 1997 (15 months). The aim was to test the effects of a hygiene programme on the incidence of diarrhoea and fecal contamination (data not extracted) and on colds and URTIs. The design included before and after periods analysed to assess the Hawthorne effect of study participation on control DCCs. The unit of randomisation was DCC, but analysis was also carried out at classroom and single-child level. This is a common mistake in cluster-RCT analysis. DCCs were stratified by URTI incidence preceding the trial and randomised by location. Cluster coefficients are not reported.
Participants	A total of 1729 children aged 18 to 36 months in 47 DCCs (83 toddler classrooms) Inclusion criteria: presence of at least 1 sandbox and 1 play area and of at least 12 available toddler places For the autumn of 1997 intervention group (24 DCCs, 43 classrooms, and 414 children), control group (23 DCCs, 23 classrooms, and 374 children). It is not clear what is the distribution and data for the autumn of 1996.
Interventions	Training session (1 day) with washing of hands, toy cleaning, window opening, sand pit cleaning, and repeated exhortations to hand wash. See Table 1 for details.
Outcomes	Laboratory: N/A Effectiveness: diarrhoea and coliform contamination (data not extracted) Colds (nasal discharge with at least 1 of the following: fever, sneezing, cough, sore throat, earache, malaise, irritability) URTI (cold of at least 2 days' duration) Surveillance was carried out by educators, annotating absences or illness on calendars. Researchers also filled in a phone questionnaire with answers by DCC directors. Safety: N/A
Notes	Risk of bias: high (no description of randomisation; partial reporting of outcomes, numerators, and denominators)

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Carabin 1999 *(Continued)*

Notes: the authors conclude that the intervention reduced the incidence of colds (IRR 0.80, 95% CI 0.68 to 0.93). This was a confusingly written study with unclear interweaving of 2 study designs. For unclear reasons analysis was only carried out for the first autumn. Unclear why colds are not reported in the results. Cluster-coefficients and randomisation process were not described.

Support for the study was provided by the Rhone-Poulenc Rorer Canada Ltd.

Disclosure of interest: none mentioned.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Block randomisation of DCC according to region, but sequence generation not reported
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias) All outcomes	High risk	Blinding not possible (hygiene session plus educational material versus none)
Blinding of outcome assessment (detection bias) All outcomes	High risk	Unblinded
Incomplete outcome data (attrition bias) All outcomes	High risk	Originally 52 eligible DCCs with 89 classrooms agreed to take part, but 5 dropped out (2 closed, 1 was sold, 2 either did not provide data or the data were "unreliable", and 6 classrooms had insufficient data). 43 children failing to attend DCC for at least 5 days in the autumn were also excluded. ITT analysis was carried out including an additional DCC whose director refused to let staff attend the training session. No correction made for clustering.
Selective reporting (reporting bias)	High risk	Denominators unclear and not explained

Chard 2019

Study characteristics

Methods	Cluster-RCT conducted amongst 100 randomly selected primary schools lacking functional WASH facilities in Saravane Province, Lao People's Democratic Republic. Schools were randomly assigned to either the intervention (n = 50) or comparison (n = 50) arm. Intervention schools received a school water supply, sanitation facilities, hand-washing facilities, drinking water filters, and behaviour change education and promotion. Comparison schools received the intervention after research activities had ended. At unannounced visits every 6 to 8 weeks, enumerators recorded pupils' roll-call absence, enrolment, attrition, progression to the next grade, and reported illness (diarrhoea, respiratory infection, conjunctivitis), and conducted structured observations to measure intervention fidelity and adherence. Stool samples were collected annually prior to de-worming and analysed for soil-transmitted helminth (STH) infection. In addition to our primary ITT analysis, we conducted secondary analyses to quantify the role of intervention fidelity and adherence on project impacts.
Participants	100 primary schools (50 intervention, 50 comparison) with a total of 3993 pupils were enrolled throughout the study period (intervention schools = 2021 pupils, control schools = 1972 pupils). Up to 40 pupils

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Chard 2019 *(Continued)*

	selected from grades 3 to 5 in each school using systematic stratified sampling, with grade and sex as the stratification variables. Pupils selected at baseline were followed throughout the entire study period; pupils who left the school due to abandonment or transfer were replaced at the beginning of the following academic year, maintaining equal grade and sex ratios when possible. Pupils who progressed from fifth to the sixth grade were replaced with pupils from grade 3 the following academic year.
Interventions	Water supply, sanitation facilities, hand-washing facilities, drinking water filters, and behaviour change education and promotion versus control. See Table 1 for details.
Outcomes	Primary impact of interest was pupil absence, measured by school-wide roll-call at each visit. Secondary health impacts included diarrhoea, symptoms of respiratory infection, and conjunctivitis/non-vision-related eye illness collected through pupil interviews. Pupils were considered to have symptoms of respiratory infection if they reported cough, runny nose, stuffy nose, or sore throat. No safety outcomes reported.
Notes	Funded by government and pharmaceutical industry. Competing interests: all authors have completed the ICMJE uniform disclosure form at http://www.icmje.org/ coi_disclosure.pdf (available upon request from the corresponding author) and declare no conflicts of interest.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient details provided.
Allocation concealment (selection bias)	Low risk	Schools allocated prior to recruitment of individuals.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Unblinded study
Blinding of outcome assessment (detection bias) All outcomes	High risk	Unblinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	Exclusions were due to participants leaving school, hence unlikely to cause bias.
Selective reporting (reporting bias)	Low risk	All specified outcomes reported.

Correa 2012

Study characteristics

Methods	Cluster-RCT in childcare facilities in Colombia from 16 April to 18 December 2008 (3 school terms) testing the effects of hand hygiene using an alcohol-based hand rub versus standard practice

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Correa 2012 *(Continued)*

Participants	42 childcare facilities in 6 towns in Colombia. A total of 1727 were enrolled (intervention group = 794 from 21 centres, control group = 933 from 21 centres). Inclusion criteria: licensed to care for 12 or more children aged 1 to 5 years for 8 hours a day, 5 times per week, and where availability of tap water was limited
Interventions	Intervention: alcohol-based hand wash as an addition to hand-washing Control: usual hand-washing practice See Table 1 for details.
Outcomes	ARI defined as: 2 or more of the following symptoms for at least 24 hours, lasting at least 2 days: runny, stuffy, or blocked nose or noisy breathing; cough; fever, hot sensation, or chills; and/or sore throat. Ear pain alone was considered an ARI.
Notes	This work was supported by a grant from the Global Development Network (New Delhi, India), "Fifth Global Research Project: Promoting Innovative Programs from the Developing World: Towards Realizing the Health MDG's in Africa and Asia," and the Bill and Melinda Gates Foundation (Seattle, Washington, United States). Authors declare to have no conflicts of interest.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"...using the random function in Microsoft Excel™ (Microsoft Corp., Redmond, Washington, United States), random numbers (1 or 2) were generated and allotted 1:1 within each group. Finally, a researcher flipped a coin to decide which number would correspond to either arm (heads = 1, intervention; tails = 2, control)."
Allocation concealment (selection bias)	Unclear risk	Method not described
Blinding of participants and personnel (performance bias) All outcomes	High risk	Unblinded study
Blinding of outcome assessment (detection bias) All outcomes	High risk	Unblinded study
Incomplete outcome data (attrition bias) All outcomes	Low risk	Lost to follow-up similar in each group and not substantial
Selective reporting (reporting bias)	Unclear risk	No protocol available

Cowling 2008

Study characteristics

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Cowling 2008 *(Continued)*

Methods	Cluster-RCT carried out in Hong Kong SARS between February and September 2007. The study assessed the effects of non-pharmaceutical interventions on the household transmission of influenza over a 9-day period. ILI cases whose family contacts had been symptom-free for at least 2 weeks rapid-tested for influenza A and B were used and randomised to 3 interventions. Randomisation was carried out in 2 different schedules (2:1:1 for the first 100 households, and subsequently 8:1:1), but it is unclear why and how this was done.
Participants	A total of 350 of 944 originally enrolled participants representing 122 households were analysed (control group = 71 households with 205 household contacts, face mask = 21 households with 61 household contacts, HH = 30 households with 84 household contacts). Inclusion criteria: residents of Hong Kong aged at least 2 years, reporting at least 2 symptoms of ILI ((such as fever ≥ 38 degrees, cough, headache, coryza, sore throat, muscle aches and pains) and positive influenza A+B rapid test and living in a household with at least 2 other individuals, none of whom had ILI in the preceding 14 days Households were excluded because subsequent laboratory testing (culture) was negative. Attrition was not explained.
Interventions	Households were randomised to either wearing face masks with education (as the control group plus education about face mask use) or hand-washing with special medicated soap (with alcohol sanitiser) with education (as the control group plus education about hand-washing) or education about general healthy lifestyle and diet (control group). The soap was distributed in special containers that were weighed at the start and end of the study. Interventions visits to the households were done on average 1 day after randomisation of index case household. See Table 1 for details.
Outcomes	Laboratory: QuickVue RTI MDCK culture Samples were harvested using NTS, but the text refers to a second procedure from June 2007 onwards testing for non-influenza viruses, with no data reported. Effectiveness: secondary attack ratios (SAR): SAR is the proportion of household contacts of an index case who were subsequently ill with influenza (symptomatic contact individuals with at least 1 NTS positive for influenza by viral culture or PCR) 3 clinical definitions were used for secondary analysis: 1. Fever ≥ 38 degrees, or at least 2 of following symptoms: headache, coryza, sore throat, muscle aches and pains 2. At least 2 of the following S/S: fever ≥ 37.8 degrees, cough, headache, sore throat, muscle aches and pains 3. Fever ≥ 37.8 degrees plus cough or sore throat Safety: no harms were reported in any of the arms
Notes	The trial authors conclude that “The secondary attack ratios were lower than anticipated, and lower than reported in other countries, perhaps due to differing patterns of susceptibility, lack of significant antigenic drift in circulating influenza virus strains recently, and/or issues related to the symptomatic recruitment design. Lessons learnt from this pilot have informed changes for the main study in 2008”. Although billed as a pilot study, the text is highly confusing and at times contradictory. The intervention was delivered at a home visit up to 36 hours after the index case was seen in the outpatients. This is a long time and perhaps the reason for failure of the intervention. Practically, the intervention will have to be organised before even seeking medical care, i.e. people know to do it when the child gets sick at home. This work has received financial support from the US Centers for Disease Control and Prevention (grant no. 1 U01 CI000439-01), the Research Fund for the Control of Infectious Disease, Food and Health Bu-

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Cowling 2008 *(Continued)*

reau, Government of the Hong Kong SAR, and the Area of Excellence Scheme of the Hong Kong University Grants Committee (grant no. AoE/M-12/06).

Competing Interests: the authors have declared that no competing interests exist.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation was computer generated by a biostatistician. Quote:"A pre-specified table of random numbers will be used to assign one of the three interventions to the household of the index case."
Allocation concealment (selection bias)	Low risk	The households of eligible study index patients were allocated to 3 groups in a 1:1:1 ratio under a block randomisation structure with randomly permuted block sizes of 18, 24, and 30 using a random-number generator. Allocation was concealed from treating physicians and clinics and implemented by study nurses at the time of the initial household visit.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Participants and people who administered the interventions were not blinded to the interventions, but participants were not informed of the specific nature of the interventions applied to other participating households.
Blinding of outcome assessment (detection bias) All outcomes	High risk	Unblinded
Incomplete outcome data (attrition bias) All outcomes	High risk	Dropout was accounted for. Dropout from the randomised population was high: 32% in control group, 37.5% in hand hygiene group, and 39.4% in face mask and hand hygiene group. Reasons for dropout were distributed evenly across the 3 groups. Authors report follow-up as proportion of patients remaining in the study after initial dropout.
Selective reporting (reporting bias)	High risk	The choice of season, change in randomisation schedules, and unexplained dropouts amongst contacts; the use of QuickVue, which proved unreliable, reporting bias on non-influenza isolates resulted in a judgement of high risk of bias.

Cowling 2009

Study characteristics

Methods	Cluster-RCT
Participants	A total of 407 index cases and 794 household contacts were analysed. Of 407 enrolled households, 322 received the allocated interventions as follows: 1. control group = 112 households with 346 contacts (only 91 households analysed with 279 contacts); 2. hand hygiene = 106 households with 329 contacts (only 85 households analysed with 257 contacts); 3. face mask + hand hygiene = 104 households with 340 contacts (only 83 households analysed with 258 contacts).

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Cowling 2009 *(Continued)*

	Inclusion criteria: households in Hong Kong. Index cases from 45 outpatient clinics in both the private and public sectors across Hong Kong. They enrolled individuals who reported at least 2 symptoms of ARI (temperature 37.8 °C, cough, headache, sore throat, or myalgia); had symptom onset within 48 hours; and lived in a household with at least 2 other people, none of whom had reported ARI in the preceding 14 days. After giving informed consent, participants provided nasal and throat swab specimens. 2750 patients were eligible and tested between 2 January and 30 September 2008.
Interventions	Participants with a positive rapid-test result and their household contacts were randomly assigned to 1 of 3 study groups: control (lifestyle measures - 134 households), control plus enhanced hand hygiene only (136 households), and control plus face masks and enhanced hand hygiene (137 households) for all household members. No detailed description of the instructions was given to participants. See Table 1 for details.
Outcomes	Influenza virus infection in household contacts, as confirmed by RT-PCR or diagnosed clinically after 7 days "The primary outcome measure was the secondary attack ratio at the individual level: that is, the proportion of household contacts infected with influenza virus. We evaluated the secondary attack ratio using a laboratory definition (a household contact with a nose and throat swab specimen positive for influenza by RT-PCR) as the primary analysis and 2 secondary clinical definitions of influenza based on self-reported data from the symptom diaries as secondary analyses." Statistical analysis: adjusted for clustering Results: no statistically significant difference in secondary attack ratio between groups in total population. Statistically significant reduction in RT-PCR confirmed influenza virus infections in the household contacts in 154 households in which the intervention was applied within 36 hours of symptom onset in the index patient. Adherence to hand hygiene was between 44% and 62%. Adherence of index patient to wearing a face mask between 15% and 49%.
Notes	"In an unintentional deviation from that protocol, 49 of the 407 randomly allocated persons had a household contact with influenza symptoms at recruitment (a potential co-index patient). We also randomly assigned 6 of 407 persons who had symptoms for slightly more than 48 hours." The trial authors conclude that "Hand hygiene and face masks seemed to prevent household transmission of influenza virus when implemented within 36 hours of index patient symptom onset. These findings suggest that non-pharmaceutical interventions are important for mitigation of pandemic and interpandemic influenza". Primary funding source: Centers for Disease Control and Prevention. Potential conflicts of interest: none disclosed.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation was computer generated by a biostatistician. Quote:"A pre-specified table of random numbers will be used to assign one of the three interventions to the household of the index case."
Allocation concealment (selection bias)	Low risk	The households of eligible study index patients were allocated to 3 groups in a 1:1:1 ratio under a block randomisation structure with randomly permuted block sizes of 18, 24, and 30 using a random-number generator. Allocation was concealed from treating physicians and clinics and implemented by study nurses at the time of the initial household visit.
Blinding of participants and personnel (performance bias)	High risk	Quote: "Participants and personnel administering the interventions were not blinded to group assignment."

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Cowling 2009 *(Continued)*
All outcomes

Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	It is not stated if the outcome assessor was blinded.
Incomplete outcome data (attrition bias) All outcomes	High risk	Dropout was accounted for. Dropout from the randomised population was high: 32% in control group, 37.5% in hand hygiene group, and 39.4% in face mask and hand hygiene group. Reasons for dropout were distributed evenly across the 3 groups. Trial authors report follow-up as proportion of patients remaining in the study after initial dropout.
Selective reporting (reporting bias)	Unclear risk	In general good reporting

DiVita 2011

Study characteristics

Methods	The impact of hand-washing promotion on the risk of household transmission of influenza, ILI, and fever was tested in rural Bangladesh. ILI was defined as fever in children < 5 years old and fever with cough or sore throat in individuals > 5 years old. Households were randomised to intervention or control. The intervention group received hand-washing stations with soap and daily hand-washing motivation at critical times for pathogen transmission, such as after coughing or sneezing. Daily surveillance was conducted, and household members with fever were tested for influenza viruses by PCR. Secondary attack ratios (SAR) were calculated for influenza, ILI, and fever in each arm. Logistic regression with generalised estimating equations was used to estimate the significance of the SAR comparison whilst controlling for clustering by household.
Participants	The study included 233 patient index cases (intervention group = 100, control group 133) with 2540 household contacts (intervention group = 134, control group = 1226). Inclusion criteria: index case patients (individuals who developed ILI within the previous 2 days and were the only symptomatic person in their household) as well as their household contacts
Interventions	Hand-washing stations with soap and daily hand-washing motivation versus control. See Table 1 for details.
Outcomes	SAR were calculated for influenza, ILI, and fever. ILI was defined as fever in children < 5 years old and fever with cough or sore throat in individuals > 5 years old. No safety outcomes reported.
Notes	Funding source unknown. Disclosure of interest: none declared.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient details provided

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DiVita 2011 *(Continued)*

Allocation concealment (selection bias)	Unclear risk	Insufficient details provided
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Insufficient details provided
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient details provided
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Insufficient details provided
Selective reporting (reporting bias)	Unclear risk	Insufficient details provided

Farr 1988a

Study characteristics	
Methods	6-month cluster-RCT, controlled, double-blind of the efficacy of virucidal nasal tissues in the prevention of natural cold, conducted in Charlottesville, Virginia, USA. Many of the families were enrolled because 1 or more family members worked at the State Farm Insurance Company; the remaining families were recruited from the Charlottesville community by advertisement in a local newspaper. Families were randomly assigned by the sponsoring company to receive boxes of treated tissues, placebo tissues, or no tissues. The randomisation was performed by computer. Study participants and investigators were unaware of the type of tissues each family was randomised to receive. Blinding efficacy was tested using a questionnaire: the mothers in each family were asked twice if she believed her family was using virucidal or placebo tissues. Participants in the treated and placebo groups were instructed to use only tissues received through the study, whilst families in the additional control group without tissues were allowed to continue their usual practice of personal hygiene. Each family member kept a daily listing of respiratory symptoms on a record card. A nurse epidemiologist visited each family monthly to encourage recording.
Participants	186 families, 58 in the active group, 59 in the placebo group, and 69 in the no-tissues group. A total of 302 families were originally recruited; 116 families who did not comply with the study protocol, lost their surveillance cards, could not complete the protocol were excluded from the analysis.
Interventions	Use of virucidal tissues versus placebo tissues versus no tissues. The treated tissues were impregnated with malic and citric acids and sodium lauryl sulphate, whilst placebo tissues contained saccharin. See Table 1 for details.
Outcomes	Laboratory: serological evidence: no Effectiveness: respiratory illness Safety: N/A
Notes	The authors concluded that virucidal tissues have only a small impact on the overall rate of natural acute respiratory illnesses. The total illness rate was lower in families using virucidal tissues than in both of the other study groups, but only the difference between active and placebo groups was statistically significant (3.4 illness per person versus 3.9 for placebo group, P = 0.04, and 3.6 for the no-tissue control group, P = 0.2, and overall 14% to 5% reduction). The questionnaire results suggest that some bias may have been present since a majority of mothers in the virucide group believed they were receiving the 'active' tissues. Another possible explanation of the low effectiveness of virucidal tissues

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Farr 1988a *(Continued)*

	is poor compliance by children in use of the virucidal tissues. A well-designed and honestly reported study. Funding source not reported. Potential conflicts of interest: none disclosed.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote:"The randomisation was performed by computer in each trial." However, method of sequence generation is not stated.
Allocation concealment (selection bias)	Unclear risk	Quote: "In trial I, families were randomly assigned by the sponsoring company to receive boxes of treated tissues, placebo tissues or no tissues." Quote: "Families with one or two children were randomised in one stratum, and families with three or more children were randomised in a second stratum in trial I." Concealment of allocation not described
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "Study participants and investigators were unaware of the type of tissues which each family was randomised to receive in both trials. In trial I, the mother in each family was asked twice if she believed her family was using active or placebo tissues, first after three months and then at the end of the study."
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "Study participants and investigators were unaware of the type of tissues which each family was randomised to receive in both trials. In trial I, the mother in each family was asked twice if she believed her family was using active or placebo tissues, first after three months and then at the end of the study."
Incomplete outcome data (attrition bias) All outcomes	High risk	Quote: "A total of 116 of the 302 families were excluded from the analysis. Families were excluded if they lost their surveillance cards or did not conscientiously record data, did not comply with the study protocol, or simply could not complete the protocol for family reasons. It was discovered that families with five or more members had so many colds that it was not possible to distinguish primary and secondary illnesses. These large families were therefore excluded from the analysis in trial I and were excluded from enrolment in trial II."
Selective reporting (reporting bias)	Low risk	All indicated outcomes are reported.

Farr 1988b

Study characteristics

Methods	Six-month randomised, controlled, double-blind trial of the efficacy of virucidal nasal tissues in the prevention of natural cold, conducted in Charlottesville, Virginia, USA. Families were recruited from the Charlottesville community by advertisement in a local newspaper. Families were randomly assigned by the sponsoring company to receive either virucidal tissues or placebo-treated tissues. Stratified randomisation was performed by computer, and the strata were defined by total number in the family. Study participants and investigators were unaware of the type of tissues each family was randomised to receive. Each family member kept a daily listing of respiratory symptoms on a record card. A nurse

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Farr 1988b *(Continued)*

	epidemiologist visited each family monthly to encourage recording. In addition, a study monitor visited each family bimonthly to further encourage compliance and reporting of symptoms.
Participants	98 families, 58 in the active group and 40 in the placebo group. 231 families were initially recruited, 222 completed the trial, data of 98 families were analysed. The other families were excluded from the analysis because they complained of side effects (sneezing, etc.) or reported not using the tissues regularly. See Table 1 for details.
Interventions	Use of virucidal tissues versus placebo tissues. The treated tissues were impregnated with malic and citric acids and sodium lauryl sulphate, whilst the placebo tissues contained succinic acid. Participants in the treated and placebo groups were instructed to only use tissues received through the study.
Outcomes	Laboratory: serological evidence: no Effectiveness: respiratory illness Safety: N/A
Notes	The study suggests that virucidal tissues have only a small impact on the overall rate of natural acute respiratory illnesses. The total illness rate was lower in families using virucidal tissues than in the other study group, but the difference between active and placebo groups was not statistically significant. There was a small, non-significant drop in illness rates across families (5%). The tissues appeared to be ineffective as the drop was confined to primary illness unaffected by tissue use. The placebo (succinic acid) was not inert, and was associated with cough and nasal burning. This impacted on allocation concealment. A well-designed and honestly reported study marred by transparent allocation. Funding source not reported. Potential conflicts of interest: none disclosed.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"The randomisation was performed by computer in each trial." However, method of sequence generation is not stated.
Allocation concealment (selection bias)	Unclear risk	Quote: "In trial II, families were randomly assigned by the sponsor to receive either virucidal tissues or placebo treated tissues." Quote:"In trial II, stratified randomisation was again used, but this time the strata were defined by total number in the family (i.e., one stratum for two-member families, another stratum for three-member families, and a final one for four-member families)." Concealment of allocation not described
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote:"Study participants and investigators were unaware of the type of tissues which each family was randomised to receive in both trials."
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote:"Study participants and investigators were unaware of the type of tissues which each family was randomised to receive in both trials."
Incomplete outcome data (attrition bias) All outcomes	High risk	Quote:"A total of 222 (of 231) families completed trial II; 9 families were terminated early (table 1). In 124 families, one or more family members reported not using the tissues regularly and/or reported having significant side effects. The data from these families were not analysed, leaving 58 families (177 persons) and 40 families (114 persons) for analysis in the virucide and placebo groups, respectively."

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Farr 1988b *(Continued)*

Selective reporting (reporting bias)	Low risk	All indicated outcomes are reported.

Feldman 2016

Study characteristics	
Methods	Prospective cluster-RCT. Ships from a single, central naval base. Ships were stratified by vessel classes (corvette, fast missile boat, and patrol boat).
Participants	All people participating in security operations, routine exercises, and patrol at a single, central naval base were eligible. The actual number of participants in the groups is not reported.
Interventions	Chlorhexidine gluconate (CHG) dispensers in addition to soap-and-water hand-washing versus soap-and-water hand-washing. See Table 1 for details.
Outcomes	Laboratory: bacterial palm cultures from 30 sailors from each group using a modified bag broth technique with sterile brain-heart broth, at 0 and 4 months (sample participants) Effectiveness: Primary outcome: incidence of infectious diseases reported by the computerised patient records system using ICD-9 diagnoses and grouped into diarrhoeal, respiratory, and skin infections; the number of sick call visits; and the number of sick leave and light-duty days incurred by the sailors Secondary outcome: subclinical morbidity (i.e. symptoms of self-reported infectious diseases) Safety: not reported
Notes	No report on adherence Study was conducted between May and September 2014 (4 months follow-up). CHG availability onboard the ships did not reduce the transmission of infectious diseases or colonisation. Government funded (Israeli Defense Force Medical Corps). Potential conflicts of interest: none disclosed.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	No description of randomisation
Allocation concealment (selection bias)	Unclear risk	No description of allocation
Blinding of participants and personnel (performance bias) All outcomes	High risk	Unblinded. Self-reported outcomes
Blinding of outcome assessment (detection bias)	Unclear risk	No information if personnel collecting data for ICD-9 diagnosis were blinded

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Feldman 2016 *(Continued)*
All outcomes

Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No participants flow chart, no attrition data
Selective reporting (reporting bias)	Unclear risk	No protocol to compare

Fretheim 2022a

Study characteristics	
Methods	Pragmatic RCT
Participants	3717 participants in Norway (glasses n = 1852; no glasses n = 1865) Inclusion criteria: 1. were at least 18 years of age; 2. did not regularly wear glasses; 3. owned or could borrow glasses that they could use (e.g. sun-glasses); 4. had not contracted COVID-19 in the 6 weeks prior to participation; 5. did not have COVID-19 symptoms when providing consent; 6. were willing to be randomised to wear, or not wear glasses outside their home when close to others for a 2-week period; 7. provided informed consent; and 8. contact lenses were allowed in the control group for those dependent on this visual aid. Exclusion criteria: 1. does regularly wear glasses (contact lenses are accepted); and 2. contracted COVID-19 after December 15th 2021.
Interventions	Intervention group: wearing eyeglasses (any type) when close to other people outside their home (on public transport, in shopping malls etc.), over a 14-day period. The control: encouraged not to wear glasses when close to others outside their home. See TIDieR Table (Table 1) for details.
Outcomes	Primary outcome 1. Any positive COVID-19 test result reported to the Norwegian Surveillance System for Communicable Diseases (MSIS), from day 3 to day 17 of the study period. Secondary outcomes 1. Any positive COVID-19 test result based on self-report, from day 1 to day 17 of the study period. 2. Episode of respiratory infection based on self-report of symptoms from day 1 to day 17 of the study period. Respiratory infection was defined as having 1 respiratory symptom (stuffed or runny nose, sore throat, cough, sneezing, heavy breathing) and fever, or 1 respiratory symptom and at least 2 more symptoms (body ache, muscular pain, fatigue, reduced appetite, stomach pain, headache, loss of smell). 3. Healthcare use for respiratory symptoms, self-reported, from day 1 to day 17 of the study period. 4. Healthcare use for injuries, self-reported, from day 1 to day 17 of the study period. 5. Healthcare use (all causes), self-reported, from day 1 to day 17 of the study period. 6. Healthcare use for respiratory symptoms as registered in Norwegian Patient Registry (NPR), from day 3 to day 28 of the study period.

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Fretheim 2022a *(Continued)*

	7. Healthcare use for injuries (from day 1 to day 21 as registered in NPR and the Norwegian Registry for Primary Health Care (KPR), from day 3 to day 28 of the study period. 8. Healthcare use (all causes) as registered in NPR and KPR from day 1 to day 21 of the study period.
Notes	The study did not report on the latter 4 outcomes due to lack of access to this data at the time of publication. Negative experiences of using the eyeglasses were reported: fogging, feeling uncomfortable and tiring, reduced vision, fall, feeling silly when wearing glasses indoor, headache. Funding: the costs of running the trial were covered by the Centre for Epidemic Interventions Research (CEIR), Norwegian Institute of Public Health. Competing interests: all authors declare: no competing interests.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Automatically randomised after signing the consent form in the online recruitment platform (Nettskjema).
Allocation concealment (selection bias)	High risk	A digital recruitment platform (Nettskjema) was used to generate allocation. However, more participants in the intervention group wore face masks.
Blinding of participants and personnel (performance bias) All outcomes	High risk	An open-label study. Participants and investigators were not blinded.
Blinding of outcome assessment (detection bias) All outcomes	High risk	Outcome is self-reported positive COVID-19 test result reported to the Norwegian Surveillance System for Communicable Diseases (MSIS). However, the public policy requiring confirmatory PCR-test had changed during the study conduct which may have affected case detection.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Participants flow chart was provided.
Selective reporting (reporting bias)	Low risk	No deviation from the published protocol.

Goodall 2014

Study characteristics

Methods	A 2X2 factorial RCT with 4 treatment arms 1. Vitamin D_3 and gargling 2. Placebo and gargling 3. Vitamin D_3 and no gargling 4. Placebo and no gargling
Participants	600 students from McMaster University, Hamilton, Ontario, Canada, randomised to the following. 1. Vitamin D and gargling (N = 150, analysed 135) 2. Vitamin D and no gargling (N = 150, 123 outcomes included in analysis)

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Goodall 2014 *(Continued)*

	3. Placebo and gargling (N = 150, 121 known outcomes included in analysis) 4. Placebo and no gargling (N = 150, 113 known outcomes included in analysis) Inclusion criteria: aged ≥ 17 years and lived with at least 1 student house mate. Exclusion criteria: students with contraindicated medical conditions (hypercalcaemia, parathyroid disorder, chronic kidney disease, use of anticonvulsants, malabsorption syndromes, sarcoidosis), who were currently or planning to become pregnant, who were taking ≥ 1000 international units (IU)/day vitamin D, or who were unable to swallow capsules
Interventions	See Table 1 for details.
Outcomes	Laboratory (influenza assessed via weekly self-collected nasal swabs; only swabs for symptomatic participants were assessed). Lab-confirmed influenza was determined by testing the Day 1 nasal swabs using an in-house enterovirus/rhinovirus PCR and, if negative, a commercial multiplex PCR able to detect 16 respiratory viruses and viral subtypes (xTAG RVP FAST, Luminex, Austin TX). Clinical URTI assessed via weekly online surveys. Clinical URTI is defined as the participant's perception of cold in conjunction with 1 or more symptoms (runny/stuffy nose, congestion, cough, sneezing, sore throat, muscle aches, or fever). When participants reported symptoms but were uncertain if they were ill, adjudication was applied by 2 clinicians. Safety: None assessed/reported by the investigators.
Notes	Study was conducted during 2 periods: September to October in 2010 and 2011. Partial governmental funding. Competing interests: the authors declare that they have no competing interests.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No description on how the randomisation sequence was generated
Allocation concealment (selection bias)	Low risk	Study used opaque, sealed, serially numbered envelopes. Envelopes were only accessed when both personnel were present.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Due to the nature of gargling with tap water, this intervention was not blinded. However, all other aspects of the study were blinded. Self-reported symptoms were adjudicated by 2 clinicians.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Except for gargling, all other participants and study personnel were blinded.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Study flow chart and reasons for lost to follow-up are provided, imputation used for missing outcomes.
Selective reporting (reporting bias)	Low risk	All planned study outcomes were reported and match the published study protocol.

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Gutiérrez-García 2022

Study characteristics	
Methods	Single-blind (analyst) randomised controlled trial carried out in a single centre in Mexico City during September to November 2020. Randomisation was through tokens in opaque envelopes but the trial was open to all except the data analysts. There were some imbalances in age groups post-randomisation at baseline in age and comorbidities
Participants	85 front line healthcare workers, unvaccinated and with no history of COVID infection in each arm. 6 and 1 were excluded from the analysis as they tested positive to CUVID within 14 days of recruitment. Follow-up was 2 weeks
Interventions	Neutral electrolysed water (SES) (pH 6.5 to 7.5) nasal and oral rinses 3 times daily and PPE versus PPE only for the prevention of SARS-CoV-2 infection. See Table 1 for details.
Outcomes	Laboratory RT-PCR no further described "according to the WHO guidelines", once only presumably with symptoms. Effectiveness COVID-19 disease confirmed by RT-PCR, between the 14th day since their recruitment and the 28th day of follow-up. The following are listed as COVID-19 signs and symptoms: dry cough, fever > 37.5℃, headache, myalgia, arthralgia, rhinorrhoea, conjunctivitis, pharyngodynia, odynophagia. 1 and 10 participants were positive in the intervention and control arms respectively. All 11 were nurses. Safety Local harms from SES applications – none reported
Notes	The authors conclude that quote: "the prophylactic protocol was demonstrated as a protective factor, in more than 90%, for developing the disease, and without adverse effects. Nasal and oral rinses with SES maybe an efficient alternative to reinforce the protective measures against COVID-19 disease and should be further investigated." Funding: no funding was received. Competing interests: the authors RGG, JCA and IDE declare that they have no competing interests. ACL, NMS and BPM state that they are employees at Esteripharma S.A. de C.V. company but did not participate in the decision to publish the results of the study, nor in the selection of the volunteers or in its development.

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Insufficient information provided.
Allocation concealment (selection bias)	High risk	Nurse or doctor chose one of two identical tokens that were placed inside an opaque plastic container. One token was labelled 'with SES' (treatment group) and the other 'without SES' (control group).
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not blinded.
Blinding of outcome assessment (detection bias)	Low risk	Primary endpoint was the number of healthcare professionals, nurses, or physicians, with COVID-19 disease confirmed by

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Gutiérrez-García 2022 *(Continued)*

All outcomes		RT-PCR. Researchers that performed the statistical analyses were blinded.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Minimal exclusions from the analysis.
Selective reporting (reporting bias)	Low risk	Pre-specified outcomes reported.

Gwaltney 1980

Study characteristics	
Methods	Study assessed the effectiveness of aqueous iodine applied to the fingers in blocking hand transmission of experimental infection with rhinovirus from 1 volunteer to another. Healthy, young adult volunteers were recruited from the general population at the University of Virginia, Charlottesville. Volunteers were not informed about the contents of the hand preparation until after the study. 2 experiments were conducted to evaluate the virucidal activity of aqueous iodine applied to the fingers immediately before viral contamination. Another 2 experiments were conducted to determine whether there was sufficient residual activity of aqueous iodine after 2 hours to interrupt viral spread by the hand route. Volunteers who were donors of virus for the hand exposures were challenged intranasally on 3 consecutive days with the rhinovirus strain HH. Recipients were randomly assigned to receive iodine or placebo. The donors contaminated their hands with nasal secretions by finger to nose contact before the exposure. Hand contact was made between a donor and a recipient by stroking of the fingers for 10 seconds. Donors and recipients wore masks during the exposure period.
Participants	15 and 20 volunteers in 2 experiments
Interventions	Treatment of fingers with iodine versus placebo. The virucidal preparation used was aqueous iodine (2% iodine and 4% potassium iodide). The placebo was an aqueous solution of food colours. See Table 1 for details.
Outcomes	Experimental rhinovirus infection reduced (P = 0.06) Laboratory: serological evidence Effectiveness: rhinovirus infection (based on serology, isolation, and clinical symptoms) with high-score clinical illness. Score was published elsewhere. Safety: N/A
Notes	Risk of bias: high (poor description of randomisation process, concealment, or allocation) Notes: the study suggests that aqueous iodine applied to the fingers was effective in blocking transmission by hand contact of experimental infection with rhinovirus for up to 2 hours after application (1 out 10 volunteers were infected compared to 6 out of 10 in the placebo preparation arm, P = 0.06 with Fisher's exact test). The effectiveness of iodine treatment of the fingers in interrupting viral transmission in volunteers recommends its use for attempting to block transmission of rhinovirus under natural conditions. Although the cosmetic properties of 2% aqueous iodine make it impractical for routine use, it can be used as an epidemiologic tool to study the importance of the hand transmission route and to develop an effective cosmetically acceptable hand preparation. A summarily reported study. Funding source not reported. Disclosure of interest: none mentioned.

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**

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Gwaltney 1980 *(Continued)*

Random sequence generation (selection bias)	Unclear risk	Insufficient information
Allocation concealment (selection bias)	Unclear risk	insufficient information
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote:Quote: "The viricidal preparation used was aqueous iodine... . The placebo was an aqueous solution of food colors... mixed to resemble the color of iodine. An odor of iodine was given to the placebo... . Volunteers were not informed about the contents of the hand preparation until after the study."
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	It is not stated whether the outcome assessor was blinded or not.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Insufficient information
Selective reporting (reporting bias)	Unclear risk	Insufficient information

Hartinger 2016

Study characteristics	
Methods	Communities were randomised to a comprehensive intervention was an improved solid-fuel stove, installation of a kitchen sink with running water, solar drinking water disinfection, education on handwashing, and separating animals from the kitchen environment.
Participants	534 children (267 in each group) in 51 communities (25 in intervention, 26 in control group). 250 children/households in the intervention group and 253 children/households in the control group were available for follow-up. Conducted in a rural farming area
Interventions	Environmental home-based intervention package consisting of improved solid-fuel stoves, kitchen sinks, solar disinfection of drinking water, and hygiene promotion. See Table 1 for details.
Outcomes	Laboratory: *Escherichia coli* (not relevant to this review) Effectiveness: weekly collection of daily diary data on illness. ARI was defined as child presenting cough or difficulty breathing, or both. ALRI was defined as child presenting cough or difficulty breathing, with a raised respiratory rate (> 50 per min in children aged 6 to 11 months and > 40 per min in children aged 12 months) on 2 consecutive measurements. Safety: none described in methods and none reported
Notes	The authors conclude that “combined home-based environmental interventions slightly reduced childhood diarrhoea, but the confidence interval included unity. Effects on growth and respiratory outcomes were not observed, despite high user compliance of the interventions. The absent effect on respiratory health might be due to insufficient household air quality improvements of the improved stoves and additional time needed to achieve attitudinal and behaviour change when providing composite interventions”. Well-reported trial. Age of children not reported. Funding: this work was supported by the UBS Optimus Foundation, Freiwillige Akademische Gesellschaft, Basel, Stiftung EmiliaGuggenheim-Schnurr, Basel.

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Hartinger 2016 *(Continued)*

Conflict of interest: the authors have no conflicts of interest to declare.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Covariate-constrained randomisation is mentioned, but method not described.
Allocation concealment (selection bias)	Unclear risk	Method not mentioned
Blinding of participants and personnel (performance bias) All outcomes	High risk	Unblinded
Blinding of outcome assessment (detection bias) All outcomes	High risk	Data collected by field worker and recorded by parent. All would be aware of allocation.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Low attrition rate, reasons stated, balanced between groups.
Selective reporting (reporting bias)	Low risk	It is unlikely that other outcomes were measured but not reported.

Helsingen 2021

Study characteristics

Methods	Non-inferiority open randomised trial carried out in May 25 to June 15 2020 during the first lockdown in Norway. Eligible individuals were randomised 1:1 stratified by fitness centre by a computerised random number generator to no access to fitness centre or access to fitness centre with “mitigation measures”
Participants	3825 people aged 18 to 65 with no risk factors for Covid 19 (diabetes, cardiovascular disease including hypertension, age > 65). 61 randomised participants (18 and 43, respectively) withdrew consent before start of the intervention with 3764 remaining
Interventions	The intervention consisted in gym access with: avoidance of body contact; 1 m distance between individuals at all times; 2 m distance for high intensity activities; disinfection of all work stations; cleaning of all equipment after use by participant; regular cleaning of facilities and access control by facility employees to ensure distance measures and avoid overcrowding; open changing rooms with showers and saunas remained closed; staff was present during all opening hours; lids on trash cans removed; individuals were instructed to stay home if they had any Covid-19 related symptoms, participants were advised to avoid touching their eyes, nose and mouth. See Table 1 for details.
Outcomes	Laboratory Self-administered (at times facilitated by HCW) NP, saliva or OP swabs in transport medium taken at day 14 to 15 from beginning sent to central lab. RT-RPC performed. Testing of antibodies (IGG) was carried out in late June with a mailed self-administered spot slide which was then mailed and analysed centrally. Effectiveness

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Helsingen 2021 *(Continued)*

	Primary: PCR positivity in both arms Co-primary: hospital admission in the two arms at 21 days (via data linkage) Secondary: proportion of participants with SARS-CoV-2 antibodies in the 2 study arms at 30 days. Testing also carried out for gym staff. Safety NR
Notes	The authors conclude that "Provided good hygiene and physical distancing measures and low population prevalence of SARS-CoV-2infection, there was no increased infection risk of SARS-CoV-2 in fitness centres in Oslo, Norway for individuals without Covid-19-relevant comorbidities." There was low and declining incidence on C19 in the Oslo area during the time of the trial as reported by the authors. The authors call the analysis set ITT but consent withdrawal individuals were not part of the analysis. There was marked difference in PCR uptake (88.7% in the training arm; 71.4% in the no-training arm) and no cycle thresholds are reported. Funding: this study was funded by the Norwegian Research Council, grant no. 312757. The grant paid for necessary equipment, study personnel and researchers. Competing interests: Dr. Lise M. Helsingen reports grants from Norwegian Research Council (grant no. 312757), during the conduct of the study. All other authors declare no competing interests in relation to this work.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer random-number generator
Allocation concealment (selection bias)	High risk	Allocation performed by one of the study authors
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not blinded.
Blinding of outcome assessment (detection bias) All outcomes	High risk	Not blinded.
Incomplete outcome data (attrition bias) All outcomes	High risk	More women were compliant with SARS-CoV2 testing in the training arm as compared to the no-training arm, and compliant individuals were somewhat younger in the training arm compared to the non-training arm.
Selective reporting (reporting bias)	Low risk	All pre-specified outcomes reported

Hubner 2010

Study characteristics

Methods	A prospective, controlled, intervention-control group design to assess the epidemiological and economical impact of alcohol-based hand disinfectants use at workplace. Volunteers in public administra-

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Hubner 2010 *(Continued)*

	tions in the municipality of the city of Greifswald were randomised into 2 groups. Participants in the intervention group were provided with alcoholic hand disinfection, the control group was unchanged. In all, 1230 person-months were evaluated.
Participants	Employees (n = 134) from the administration of the Ernst-Moritz-Arndt University Greifswald, the municipality of Greifswald and the state of Mecklenburg-Pomerania, were recruited for the study and randomised to intervention (N = 67) or control (N = 67). Final analysis was performed on 64 from the intervention and 65 from the control group. Inclusion criteria: all administrative officers, who did not already apply hand disinfection at work, were considered for participation and were invited by email or mail (n = 850). The 134 participants declared their written consent to participate and completed a pre-study survey with demographic, social, health, and work-related questions to provide data for randomisation. Exclusion criteria: employees that were already using hand disinfectants at work
Interventions	Alcohol-based hand disinfectants use at workplace versus usual hygiene. See Table 1 for details.
Outcomes	Respiratory and gastrointestinal symptoms and days of work were recorded based on a monthly questionnaire over 1 year.
Notes	Funding source not mentioned. Competing interests: the authors declare a financial competing interest: GK is employed by Bode Chemie GmbH, Hamburg, Germany. NOH and AK received financial support for research from Bode Chemie in the past. All other authors declare no conflict of interest.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No details provided.
Allocation concealment (selection bias)	Unclear risk	No details provided.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Unblinded study
Blinding of outcome assessment (detection bias) All outcomes	High risk	Self-reported outcomes
Incomplete outcome data (attrition bias) All outcomes	Low risk	Lost to follow-up minimal and similar in 2 groups
Selective reporting (reporting bias)	Unclear risk	No protocol available

Huda 2012

Study characteristics

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Huda 2012 *(Continued)*

Methods	Poorly described cluster-RCT. Partial report of the SHEWA-B trial focused on changing 11 targeted behaviours in villages to measure the impact on diarrhoea and respiratory illness amongst children. Unit of randomisation is not clear, but was probably a village. A group of 10 to 17 households within a village were the participants, based on the household having at least 1 child under the age of 5.
Participants	A total of 1692 participants (intervention = 848, control = 844) at baseline and 1699 participants at 18 months (intervention = 849, control = 850) Households were eligible if they have a child < 5 years of age and a guardian agreed to participate.
Interventions	SHEWA-B programme targeting improved latrine coverage and usage, access to and use of arsenic-free water, and improved hygiene practices using soaps. See Table 1 for details.
Outcomes	Laboratory: none described in methods and none reported Effectiveness: ARI and diarrhoea. ARI defined as cough and fever or difficulty breathing and fever within 48 hours prior to interview. Safety: none described in methods and none reported
Notes	The authors conclude that quote: “The prevalence of childhood diarrhea and respiratory illness was similar in the intervention and control communities”. Poorly reported trial. This research activity was funded by the United Kingdom's Department for International Development (DFID). Disclosure of interest: none mentioned.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Mentions random-number tables, but not clear if this was for random selection or randomisation
Allocation concealment (selection bias)	Unclear risk	Method not described
Blinding of participants and personnel (performance bias) All outcomes	High risk	Unblinded
Blinding of outcome assessment (detection bias) All outcomes	High risk	Data on illness were collected by a resident of the village, who was likely to know treatment allocation.
Incomplete outcome data (attrition bias) All outcomes	High risk	Not reported. No flow diagram
Selective reporting (reporting bias)	Unclear risk	Unlikely that other outcomes were measured and not reported

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Ibfelt 2015

Study characteristics	
Methods	Cluster-RCT in 12 daycare nurseries in Denmark. Centres in the intervention group had their linen and children's toys commercially cleaned and disinfected every 2 weeks. Control group centres had usual practice. Swabbing for bacteria and respiratory viruses was conducted at baseline and the end of the intervention period.
Participants	12 nurseries in Copenhagen (intervention = 6, control = 6) with a total of 587 children aged 6 months to 3 years Not clear how many children were in each group. Data on illness collected at the individual level, and on presence of bacteria and viruses at the cluster level.
Interventions	Washing and disinfection of toys and linen every 2 weeks for 3 months. See Table 1 for details.
Outcomes	Laboratory: counts of bacteria (not relevant to this review) and 11 respiratory viruses at baseline and end of intervention period, taken from swabs of 10 predefined locations in playroom (7 locations) and toilet area (3 locations). Viruses were influenza A and B; coronavirus NL63229E, OC43, and HKU1; parainfluenza virus 1, 2, 3, and 4; rhinovirus; RSV A/B; adenovirus; enterovirus; parechovirus; metapneumovirus; and bocavirus. Testing by PCR Effectiveness: illness counts in the children. Absence due to sickness recorded daily with reason categorised, but no definitions of illness provided. Safety: none mentioned in methods and none reported
Notes	The authors conclude that "Although cleaning and disinfection of toys every two weeks can decrease the microbial load in nurseries, it does not appear to reduce sickness absence among nursery children". The results of the disinfection are reported as follows: "The most prevalent virus was coronavirus (97% positive samples), followed by bocavirus (96%), adenovirus (73%) and rhinovirus (46%). The intervention reduced the presence of adenovirus, rhinovirus and RSV approximately two- to five-fold [odds ratio (OR) 2.4, 95% confidence interval (CI) 1.1-5.0 for adenovirus; OR 5.3, 95% CI 2.3-12.4 for rhinovirus; OR 4.1, 95% CI 1.5-11.2 for RSV] compared with the control group. On the other hand, metapneumovirus was found significantly less often in the control group than in the intervention group. The intervention had no effect on the detection of other viruses. The fomites with the highest presence of respiratory virus were pillows and sofas, followed by toys and playroom tables. When looking at the samples from the toys alone, there was a significant decrease following the intervention in the intervention group compared with the control group for rhinovirus (OR 3.8, 95% CI 1.3-10.5; P = 0.01) and RSV (OR 5.2, 95% CI 1.1-23.8; P = 0.04), but not adenovirus". This a poorly reported cluster-RCT. Its importance lies in the surface viral prevalence data (which could have been overestimated by PCR) and the finding that even in the presence of high viral prevalence, sickness was lower in the control (no surface disinfection) arm. This suggests the absence of other factors that could activate surface respiratory viruses. Funding: this work was supported by the Danish Council for Technology and Innovation under the Ministry of Science, Innovation and Higher Education as part of the Sundhed i Børneinstitutioner innovation consortium. Conflict of interest statement: Ecolab Denmark, Berendsen Denmark and 3M Denmark supplied materials and cleaning free of charge, but had no influence on the analysis of the data or the writing of the manuscript.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Method not mentioned

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Ibfelt 2015 *(Continued)*

Allocation concealment (selection bias)	Unclear risk	Method not mentioned
Blinding of participants and personnel (performance bias) All outcomes	High risk	Unblinded
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Objective measure of bacterial and viral counts. However, illness reporting is unclear.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No attrition or denominators given for results.
Selective reporting (reporting bias)	Low risk	Unlikely that other outcomes were measured but not reported

Ide 2014

Study characteristics	
Methods	Randomised, open-label, 2-group parallel study of 757 high school students (15 to 17 years of age) conducted for 90 days during the influenza epidemic season from 1 December 2011 to 28 February 2012, in 6 high schools in Shizuoka Prefecture, Japan. The green tea gargling group gargled 3 times a day with bottled green tea, and the water gargling group did the same with tap water. The water group was restricted from gargling with green tea.
Participants	A total of 747 students were enrolled (green tea gargling group = 384, water gargling group = 363) High school students (15 to 17 years of age) who attended 6 high schools in the Kakegawa and Ogasa districts of Shizuoka Prefecture, Japan
Interventions	See Table 1 for details.
Outcomes	Incidence of laboratory-confirmed influenza Incidence of clinically defined influenza infection Time for which the participant was free from clinically-defined influenza infection Clinically-defined influenza infection, specified as fever (≥ 37.8 °C) plus any 2 of the following additional symptoms: cough, sore throat, headache, or myalgia. Influenza infection with viral antigen was detected by immunochromatographic assay. No safety data reported.
Notes	Funding: this work was supported by Grants-in-Aid for Scientific Research (KAKENHI) Grant Number 23590887. Competing Interests: the authors have declared that no competing interests exist.

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**

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Ide 2014 *(Continued)*

Random sequence generation (selection bias)	Low risk	Computer-generated permuted block randomised schema
Allocation concealment (selection bias)	Low risk	Randomised at the Data Management Center of Shizuoka General Hospital in Japan
Blinding of participants and personnel (performance bias) All outcomes	High risk	Unblinded study
Blinding of outcome assessment (detection bias) All outcomes	High risk	Unblinded study
Incomplete outcome data (attrition bias) All outcomes	Low risk	Minimal attrition
Selective reporting (reporting bias)	Unclear risk	Protocol not available

Ide 2016

Study characteristics	
Methods	Randomised controlled study in Japan. Participants were randomly allocated into the catechin-treated (epigallocatechin gallate-treated) or non-treated face mask groups for 60 days from January to March 2016. Incidence of laboratory-confirmed influenza infection was measured and compared between groups using Fisher's exact test. Multivariate analysis was performed to calculate adjusted ORs and associated 95% CIs.
Participants	Participants included workers in a nursing home, a rehabilitation facility, and a hospital. A total of 234 participants were eligible for the study (catechin group, n = 118; control group, n = 116).
Interventions	Catechin-treated mask versus non-treated face mask. See Table 1 for details.
Outcomes	Incidence of laboratory-confirmed influenza infection Laboratory-confirmed influenza infection with viral antigen detected by immunochromatographic assay performed when participants reported ILI. No safety outcomes reported.
Notes	Funding: this work was supported in part by a grant from the Japan Society for the Promotion of Science (JSPS), through the Grant-in-Aid for JSPS Fellows (No. 15J10190 to KI) and Grants-in-Aid for Scientific Research (C) (15K08924 to HY). Conflict of Interest: the authors declare that they have no conflicts of interest.
Risk of bias	
Bias	**Authors' judgement** / **Support for judgement**

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Ide 2016 *(Continued)*

Random sequence generation (selection bias)	Unclear risk	Computer-generated randomisation, but method not stated
Allocation concealment (selection bias)	Low risk	Central randomisation service at Data Management Centre of Shizouka General Hospital
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blinded
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Attrition minimal
Incomplete outcome data (attrition bias) All outcomes	Low risk	Attrition minimal
Selective reporting (reporting bias)	Low risk	Specified outcomes reported.

Jacobs 2009

Study characteristics	
Methods	Open-RCT lasting 77 days from January 2008 to test “superiority” of face masks in preventing "URTI". This term appears as an acronym in the introduction and is not explained. It is assumed that it stands for 'upper respiratory infections', but it is preceded in the text by the term 'common cold', which is also lacking a definition. Randomisation was carried out in blocks within each of 3 professional figures (physicians, nurses, and “co-medical” personnel).
Participants	33 HCWs mainly females aged around 34 to 37 in a tertiary healthcare hospital in Tokyo, Japan. HCW with quote: “predisposing conditions” (undefined) to “URTI” and those taking antibiotics were excluded. A baseline descriptive survey was carried out including “quality of life”. 1 participant dropped out at end of week 1, but no reason is reported nor the allocation arm. Analysis was performed on 32 participants (mask = 17, no mask = 15).
Interventions	Surgical mask MA-3 (Osu Sangyo, Japan) during all phases of hospital work (n = 17) or no mask (n = 15) (except when specifically required by hospital SOPs). See Table 1 for details.
Outcomes	Laboratory: N/A Effectiveness: URTI is defined on the basis of a symptoms score, with a score > 14 being a URTI according to Jackson’s 1958 criteria (“Jackson score”). These are not explained in text, although the symptoms are listed in Table 3 (any, sore throat, runny nose, stuffy nose, sneeze, cough, headache, ear ache, feel bad) together with their mean and scores SD by intervention arm. Safety: the text does not mention or report harms. These appear to be indistinguishable from URTI symptoms (e.g. headache which is reported as of significantly longer duration in the intervention arm). Compliance is self-reported as high (84.3% of participants).

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Jacobs 2009 *(Continued)*

Notes	The authors conclude that quote: “Face mask use in healthcare workers has not been demonstrated to provide benefit in terms of cold symptoms or getting colds. A larger study is needed to definitively establish non-inferiority of no mask use”. This is a small, badly reported trial. The purpose of trials is to test hypotheses not to prove or disprove 'superiority' of interventions. There is no power calculation, and CIs are not reported (although there is a mention in Discussion). No accurate definitions of a series of important variables (e.g. URTI, runny nose, etc.) are reported, and the Jackson scores are not explained, nor their use in Japanese personnel or language validated. Intervention arm data not extracted due to the uncertainty of its meaning. Funding source not mentioned. Conflicts of interest: none to report

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Open RCT, but sequence generation not reported
Allocation concealment (selection bias)	Unclear risk	"Mask and no mask groups were formed using block randomisation of participants within their respective job categories: nurses, doctors, and co-medical personnel." Concealment of allocation not described
Blinding of participants and personnel (performance bias) All outcomes	High risk	Unblinded study. Blinding not possible, as 1 group wore face masks
Blinding of outcome assessment (detection bias) All outcomes	High risk	Unblinded study
Incomplete outcome data (attrition bias) All outcomes	Low risk	1 dropout in each group accounted for.Quote: "Analyses were performed following the principles of intention-to-treat."
Selective reporting (reporting bias)	High risk	NB: influenza vaccine coverage was 100% in mask group and only 81% in the non-mask-wearing group.

Kotch 1994

Study characteristics

Methods	Pair-matched, cluster-RCT conducted from 19 October 1988 to 23 May 1989 in 24 childcare centres in North Carolina, USA The trial tested the effects of a hand-washing and environment sterilising programme on diarrhoea (data not extracted) and ARIs. Child daycare centres had to care for 30 children or less, at least 5 of whom had to be in nappies, and intending to stay open for at least another 2 years. Randomisation is not described, nor are cluster coefficients reported.
Participants	389 children aged 3 years or less in daycare for at least 20 hours a week. There were some withdrawals, but attrition of participants is not stated, only that in the end data for 31 intervention classrooms and 36 control classrooms were available. 291 children aged up to 24 months and 80 over 24 months took part. The text is very confusing, as 371 seems to be the total of the number of families that took part.

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Kotch 1994 *(Continued)*

	No denominator breakdown by arm is reported, and numerators are only reported as new episodes per child-year.
Interventions	Structured hand-washing and environment (including surfaces, sinks, toilets, and toys) disinfecting programme with waterless disinfectant scrub. See Table 1 for details.
Outcomes	Laboratory: N/A Effectiveness: ARI (coughing, runny nose, wheezing, sore throat, or earache) Safety: N/A
Notes	Risk of bias: high (poor reporting of randomisation, outcomes, numerators and denominators) Note: the authors conclude that the fully adjusted RR for prevention of ARIs was 0.94 (−2.43 to 0.66). A poorly reported study. This study was supported in part by grant MCJ-373111 from the Maternal and Child Health Program (Title V. Social Security Act), Health Resources and Services Administration, Department of Health and Human Services. Cal Stat™ was contributed by Cal- gon Vestal Laboratories, a subsidiary of Merck and Co, Inc, St Louis, MO. Conflicts of interest: none to report.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "Pair-matched cluster-randomised, controlled trial", but sequence generation not reported
Allocation concealment (selection bias)	Unclear risk	Centres were matched in pairs and then randomly allocated to either intervention or control programmes. Allocation concealment was not reported.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not possible (intervention was training session)
Blinding of outcome assessment (detection bias) All outcomes	High risk	"The same staff who conducted the training unobtrusively recorded observations at 5-week intervals"
Incomplete outcome data (attrition bias) All outcomes	High risk	18 families were dropped, denominator not clear.
Selective reporting (reporting bias)	High risk	Denominators not clearly reported

Ladegaard 1999

Study characteristics

Methods	RCT with cluster-randomisation to intervention or control. Of 10 institutions, 2 were excluded because they wanted institutions to be comparable in uptake area (i.e. housing and income). Interventions were administered to children, parents, and teachers at the institutions.
Participants	Children 0 to 6 years old

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Ladegaard 1999 *(Continued)*

Interventions	Multifaceted: information, t-shirts to the children with: "Clean hands - yes, thank you", performance of a fairytale "The princess who did not want to wash her hands", exercise in hand-washing, importance of clean and fresh air. The aims of the intervention were to: 1. increase the hygiene education of the daycare teachers; 2. motivate the children by practical learning to have better hand hygiene; and 3. inform the parents about better hand hygiene. See Table 1 for details.
Outcomes	34% decrease in "sickness" (probably mostly gastroenteritis)
Notes	Risk of bias: only limited data available Note: the authors conclude that there was a 34% decrease in sickness in the intervention arm; this is probably overall sickness, as gastroenteritis is part of the outcomes (data not extracted). Only limited data available from translation by Jørgen Lous. Funding was received from a local part of the Danish Health Authority (Forebyggelsesrådet för Fyns Amt).

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Unclear risk	Randomisation by "lottery", the same as "flip the coin". Concealment not reported
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not possible
Blinding of outcome assessment (detection bias) All outcomes	High risk	Not possible
Incomplete outcome data (attrition bias) All outcomes	High risk	Total numbers of children included in each arm Not reported.
Selective reporting (reporting bias)	High risk	Limited data reported, in particular denominators missing.

Larson 2010

Study characteristics

Methods	Cluster block-randomised, controlled trial carried out between 20 November 2006 and 20 June 2008 in an upper Manhattan immigrant Latino neighbourhood (“19 month data collection period”). The study aimed at assessing the effects of education versus education and hand sanitiser use versus education and hand sanitiser use and common mask use against upper respiratory infections over a period of under 2 years. Follow-up was through an automated telephone system with a small financial incentive (USD 20) for those with 75% or more compliance. Those reporting an ILI received a visit within 48 hours for swabbing.

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Larson 2010 *(Continued)*

	An index case was someone who at the "onset day of illness nobody else in the household had been symptomatic within the previous five days". A secondary case for each episode quote: "was any member of the household who developed symptoms within five days following the index case"; "The secondary attack rate was defined as the number of secondary cases recorded within 5 days of the onset of symptoms in the index case divided by the number of household members minus one". The text implies that the unit of observation was the episode ("study subjects contributed more than one episode in which they were considered to be the index case").
Participants	617 households were randomised to the education group (n = 211), the hand-sanitiser group (n = 205), and the hand-sanitiser and mask group (n = 201). There were 2708 participants, mostly adult Latino immigrants to the USA. Recruitment and allocation were carried out by household. There had to be at least 3 people living in the household, with at least 1 being a preschool or elementary school child, speaking English or Spanish, having a telephone, willingness to complete symptom assessments and have bimonthly home visits, and not using alcohol-based hand sanitiser routinely. Intracluster correlation coefficients are reported on page 179 of the manuscript.
Interventions	Written Spanish or English language educational materials regarding the prevention and treatment of URTIs and influenza or the same educational materials and hand sanitiser (Purell, J&J), in large (8- and 4-ounce) and small (1-ounce) containers to be carried by individual household members to work or school, or the same interventions as well as regular surgical face masks (Procedure Face Masks for adults and children, Kimberly-Clark) with instructions for both the caretaker and the ill person to wear them when an ILI occurred in any household member. Replenishment of intervention stocks was done at the bimonthly home visit. Caretakers had to wear a mask for 7 days when within 3 feet of a symptomatic case. They were also encouraged to wear masks within 3 feet of any household member. Reinforcing phone calls were made 3 times in 6 days. The text clearly reports active influenza vaccine promotion during the bimonthly visits. ("The home visit to each household was made every 2 months to minimise study dropout, reinforce adherence to the assigned intervention, replenish product supplies and record use of supplies, answer questions, and correct ongoing misconceptions. At each visit, new educational materials regarding URTI prevention and treatment and influenza vaccination were distributed." (PDF page 3). Also just before the Discussion as follows: "Influenza vaccination rates: There was an increase between the baseline and exit interview in all three groups that reported 50% of more of members receiving influenza vaccine (pre- versus post-intervention for each group: 21.1% and 40.8% in the Education group, 19.0% and 57.1% in the hand sanitiser group, and 22.4% and 43.5% in the hand sanitiser and face mask group (P = 0.001). Additionally, those in the hand sanitiser group reported a significantly greater increase than the other 2 groups, controlling for baseline rates (P = 0.002)") Coverage was unequal across groups, no information on the progressive impact of the vaccine, or indeed the nature of the vaccine(s) is reported. Apparently the first season was mild and the vaccine mismatched, compliance with the trial interventions was low in Arm 3, and a local epidemic of *Staphylococcus aureus* meant that the control group started washing hands. The trial authors report no effect on reporting rates of vaccine coverage by arms, but with so many confounders who knows? See Table 1 for details.
Outcomes	Laboratory: PCR carried out on samples from deep nasal swabs for influenza and the most common other pathogens (RSV, rhinovirus, enterovirus, parainfluenza viruses, etc.). The text describing the results of the swabbing is confusing, but in general appears to be non-random "Households reported 669 episodes of ILI (0 to 5 per individual)". Of the 234 deep nasal swabs obtained, 33.3% (n = 78) tested positive for influenza: 43.6% (n = 34) were influenza A and 56.4% (n = 44) were influenza B. Amongst the 66.7% who tested negative for influenza, 30.8% (48/156) tested positive for other viruses: 7 for respiratory syncytial virus, 9 for parainfluenza, 11 for enterovirus, 10 for rhinovirus, 6 for adenovirus, and 5 for metapneumovirus. Swabs were not obtained from the remaining 435 reported ILI episodes for the fol-

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Larson 2010 *(Continued)*

	lowing reasons: 72.0% (n = 313) did not meet the CDC definition of an ILI and were therefore included in the URTI symptom count; 21.4% of episodes (n = 93) were reported after 48 hours of ILI onset or the participant refused to be swabbed; and the research staff were unable to reach the participant in 6.7% of episodes (n = 29). As no definition of URTI is given, it is unclear what kind of biases were introduced by the non-swabbing of the 313/435 "not meeting CDC definition". Effectiveness: ILI (CDC definition): "temperature of 37.8°C or more and cough and/or sore throat in the absence of a known cause other than influenza" URTI only referred to as "Viral upper respiratory infections (URTIs)". Safety: N/A
Notes	The authors conclude that quote: "the Hand Sanitizer group was significantly more likely to report that no household member had symptoms (P,0.01), but there were no significant differences in rates of infection by intervention group in multivariate analyses. Knowledge improved significantly more in the Hand Sanitizer group (P,0.0001). The proportion of households that reported >50% of members receiving influenza vaccine increased during the study (P.0.001). Despite the fact that compliance with mask wearing was poor, mask wearing as well as increased crowding, lower education levels of caretakers, and index cases 0–5 years of age (compared with adults) were associated with significantly lower secondary transmission rates (all P,0.02). In this population, there was no detectable additional benefit of hand sanitiser or face masks over targeted education on overall rates of URTIs, but mask wearing was associated with reduced secondary transmission and should be encouraged during outbreak situations. During the study period, community concern about methicillin-resistant *Staphylococcus aureus* was occurring, perhaps contributing to the use of hand sanitiser in the Education control group, and diluting the intervention's measurable impact". The study is at high risk of bias. Randomisation and reasons for dropout are not described. Differentials in cluster characteristics across arms point to randomisation not having worked, and the confounding effects of a post randomisation staphylococcal scare are difficult to judge. Symptom-driven follow-up gives no idea of the effects on asymptomatic ILI/influenza. Poor definitions (URTI?). There are unexplained dropouts, and the analysis plan is unclear. Finally, the very small number of cases of influenza and an unclear swabbing attrition may introduce further elements of confounding. Funding: this study was funded by grant #1 U01 CI000442-01, "Stopping URIs and Flu in the Family: The Stuffy Trial." Conflicts of interest: none reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "Cluster block randomised, controlled trial", but sequence generation not reported
Allocation concealment (selection bias)	Unclear risk	Quote:"Households were block randomised into one of three groups" Allocation concealment not reported
Blinding of participants and personnel (performance bias) All outcomes	High risk	Blinding of participants and personnel was not possible.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Blinding of outcome assessment is not stated.

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Larson 2010 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	High risk	In control group households (n = 211), 26 dropped out and 37 did not consent. In hand-sanitiser group households (n = 205), 21 dropped out and 36 did not consent. In hand-sanitiser and face mask group households (n = 201), 19 dropped out and 35 did not consent. Reasons for dropout were not described.
Selective reporting (reporting bias)	Unclear risk	617 of 772 eligible households were randomised.

Little 2015

Study characteristics	
Methods	Individuals sharing a household by mailed invitation through general practices in England were recruited. After consent, participants were randomised online by an automated computer-generated random-number program to receive either no access or access to a bespoke automated web-based intervention that maximised hand-washing intention, monitored hand-washing behaviour, provided tailored feedback, reinforced helpful attitudes and norms, and addressed negative beliefs. Participants were enrolled into an additional cohort (randomised to receive intervention or no intervention) to assess whether the baseline questionnaire on hand-washing would affect hand-washing behaviour. Participants were not masked to intervention allocation, but statistical analysis commands were constructed masked to group. The primary outcome was number of episodes of RTIs in index participants in a modified intention-to-treat population of randomly assigned participants who completed follow-up at 16 weeks.
Participants	344 physician offices were recruited over a wide area of England, and 20,066 participants were enrolled and randomised to intervention (N = 16,086) and control (N = 10,026). Modified ITT was performed on 16,908 participants who completed the follow-up questionnaire at 16 weeks (intervention = 8241 and control = 8667). Inclusion criteria: adult patients (aged 18 years or older) identified from computerised lists in general practitioner (GP) practices in England, for whom there was at least 1 other individual living in the household who was willing to report illness to the index person Exclusion criteria: patients with severe mental problems (e.g. major uncontrolled depression or schizophrenia, dementia, or severe mental impairment) or who were terminally ill, and those reporting a skin complaint that would restrict hand-washing
Interventions	Automated web-based intervention that maximised hand-washing intention, monitored hand-washing behaviour, provided tailored feedback, reinforced helpful attitudes and norms, and addressed negative beliefs. Control no access to intervention web pages. See Table 1 for details.
Outcomes	The primary outcome was the number of index individuals that reported 1 or more RTIs (including ILI) at 16 weeks. Secondary: duration of symptoms, transmission of respiratory infections, gastrointestinal infections, attendance at the practice, and use of health service resources Infections self-reported by participants. RTI defined as 2 symptoms of an RTI for at least 1 day or 1 symptom for 2 consecutive days. Definition of ILI was a high temperature (feeling very hot or very cold; or measured temperature > 37.5 °C), a respiratory symptom (sore throat, cough, or runny nose), and a systemic symptom (headache, severe fatigue, severe muscle aches, or severe malaise).

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Little 2015 *(Continued)*

	No safety outcomes reported.
Notes	Government funded. The study was funded by the Medical Research Council (study number 09/800/22). Declaration of interests: the authors declare no competing interests.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Participants were automatically randomly assigned by the intervention software, but sequence generation not described.
Allocation concealment (selection bias)	Low risk	Participants were automatically randomly assigned by the intervention software.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Unblinded study
Blinding of outcome assessment (detection bias) All outcomes	High risk	Unblinded study
Incomplete outcome data (attrition bias) All outcomes	High risk	High attrition that was different in the 2 groups
Selective reporting (reporting bias)	Low risk	Specified outcomes reported.

Loeb 2009

Study characteristics

Methods	Open non-inferiority RCT carried out to compare the surgical mask with the N95 respirator in protecting healthcare workers against influenza. The trial was carried out between 2008 (enrolment started in September and follow-up on 12 January 2009) and 23 April 2009 (when all HCWs caring for febrile patients were told to wear an N95 respirator) because of the appearance of novel A/H1N1). The trial trigger was the beginning of the influenza season, defined as isolation of 2 or more viruses in a district in the same week. Following the 2003 SARS outbreak, all Ontario nurses caring for febrile patients (38 °C or more and new onset cough or SOB) had to wear surgical masks. The randomisation (carried out in blocks of 4 by centre) then consisted of either confirmation to same-maker surgical mask wear or N95 respirator wear. Investigators and laboratory staff were blind to allocation status, but for obvious reasons (the visible difference in interventions), participants were unblinded. “The criterion for non-inferiority was met if the lower limit of the 95% confidence interval (CI) for the reduction in incidence (N95 respirator minus surgical group) was greater than -9%”. So this is the non-inferiority margin. It is assumed that the “minus surgical group” means minus surgical mask group.
Participants	Consenting nurses (n = 446 randomised) aged a mean of 36.2 years working full time (≥ 37 hours/week) in 23 acute units (a mix of paediatric, A&E, and acute medical units) in 8 hospitals in Ontario, Canada. 225 were randomised to the surgical mask and 221 to the N95 respirator. There were 13 and 11 dropouts, respectively from each arm (all accounted for), plus 21 and 19 lost to follow-up; 11 in each arm gave no reason, the others are accounted for. There were no deaths. The final total of 212 and 210 was included in the analysis. Table 1 reports the demographic data of participants by arm, which appear comparable.

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Loeb 2009 *(Continued)*

Interventions	Surgical masks (as standard wear by the standard distributor) or fit–tested N95 respirator. All nurses wore gloves or gowns in the presence of a febrile patient. See Table 1 for details.
Outcomes	Laboratory RT-PCR paired sera with 4-fold antibody rise from baseline (only for unvaccinated) nurses Effectiveness: follow-up (lasting a mean of around 97 days for both arms) was carried out twice-weekly on a web-based instrument. Nurses with new symptoms were asked to swab a nostril if any of the following signs or symptoms had developed: fever (temperature ≥ 38 °C), cough, nasal congestion, sore throat, headache, sinus problems, muscle aches, fatigue, earache, ear infection, or chills. The text defines influenza with laboratory confirmation, and separately reports criteria for swab triggering and a definition of ILI ("Influenza-like illness was defined as the presence of cough and fever: a temperature ≥ 38°C"). But this is not formally linked to influenza in the text, as it appears that primary focus was the detection of laboratory-confirmed influenza (either by RT-PCR or serology). Additional outcome data sought were work-related absenteeism and physician visits for respiratory illness. Secondary outcomes included detection of the following non-influenza viruses by PCR: parainfluenza virus types 1, 2, 3, and 4; respiratory syncytial virus types A and B; adenovirus; metapneumovirus; rhinovirus-enterovirus; and coronaviruses OC43, 229E, SARS, NL63, and HKU1. Audits to assess nurse compliance with the interventions were carried out in the room of each patient cared for. The text reports that 50 and 48 nurses in the surgical mask and N95 groups, respectively, had laboratory confirmation of influenza infection, indicating non-inferiority. Interestingly, non-inferiority seemed to be applicable both to seasonal viruses and nH1N1 viruses (as 8% and 11.9% were serologically positive to nH1N1). This finding is explained either by seeding or cross reaction with seasonal H1N1. Equivalent conclusions could be drawn for nurses with complete follow-up. Non-inferiority was applicable also to other ILI agents identified. None of the 52 individuals with positive isolates met the criteria for ILI. All cases of ILI were confirmed as having influenza (9 and 2 respectively). This means that all the 11 cases of ILI had influenza, but that most of those with a laboratory diagnosis of influenza did not have cough and fever. For example, the text reports that "Of the 44 nurses in each group who had influenza diagnosed by serology, 29 (65.9%) in the surgical mask group and 31 (70.5%) in the N95 respirator group had no symptoms". By implication, of the 88 nurses with antibody rises, 28 had symptoms of some kind, i.e. two-thirds were asymptomatic. Absenteeism was 1 versus 39 episodes in the mask versus respirator arms. No episodes of LRTI were recorded. The number of family contacts with ILI were the same for each arm (45 versus 47). Physician visits were similar in both groups. Safety: no AEs are reported
Notes	The authors conclude that "Among nurses in Ontario tertiary care hospitals, use of a surgical mask compared with a N95 respirator resulted in non-inferior rates of laboratory-confirmed influenza". This a well-designed and conducted trial with credible conclusions. The only comment is that the focus in the analysis on influenza (symptomatic and asymptomatic) is not well-described, although the rationale is clear (interruption of transmission). Funding/Support: this study was supported by the Public Health Agency of Canada. Financial disclosures: none reported.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"Randomisation was performed centrally ....", but method of sequence generation not described.

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Loeb 2009 *(Continued)*

Allocation concealment (selection bias)	Low risk	"...by an independent clinical trials coordinating group such that investigators were blind to the randomisation procedure and group assignment and was stratified by centre in permuted blocks of 4 participants."
Blinding of participants and personnel (performance bias) All outcomes	High risk	"It was not possible to conceal the identity of the N95 respirator or the surgical mask since manipulating these devices would interfere with their function"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Outcome assessment blinded: "Laboratory personnel conducting hemagglutinin inhibition assays, polymerase chain reaction (PCR), and viral culture for influenza were blinded to allocation."
Incomplete outcome data (attrition bias) All outcomes	Low risk	21 of 225 randomised to mask group and 19 of 221 randomised to N95 group were lost to follow-up, reasons reported. Study stopped early: Quote: We had planned to stop the study at the end of influenza season. However, because of the 2009 influenza A(H1N1) pandemic, the study was stopped on April 23, 2009, when the Ontario Ministry of Health and Long-Term Care recommended N95 respirators for all healthcare workers taking care of patients with febrile respiratory illness."
Selective reporting (reporting bias)	Low risk	All outcomes reported.

Longini 1988

Study characteristics	
Methods	Cluster-controlled, double-blind, randomised trial to assess the efficacy of virucidal tissues in interrupting family transmission of rhinovirus and influenza virus. The study was carried out in the community of Tecumseh, Michigan, USA during the period of 25 November 1984 to 28 April 1985. However, the authors only report results for the period of 13 January to 23 March 1985, when a high circulation of influenza A H3N2 and rhinovirus was detected.
Participants	296 households were enrolled, but 5 households were eliminated from the analysis for "technical reasons". The analysis was carried out in households with 3 to 5 members. The authors report data on 143 households randomised to virucidal tissues and 148 to placebo tissue. The average age in households was around 22, and the difference between arms was not significant. Randomisation was carried out by the sponsor, and tissues were pre-packed in coded boxes with no other identifying features and delivered to households at the beginning of the study period.
Interventions	Disposable 3-layered virucidal tissues (citric and malic acids with sodium lauryl sulphate in the middle layer) or placebo (succinic acid in the middle layer) tissues. They were used to blow the nose and for coughing or sneezing into. Households were also stratified by level of tissue use. Tissue use was significantly higher in the intervention arm (82% versus 71%). See Table 1 for details.
Outcomes	Laboratory: yes - viral culture from nasal and throat swabs from symptomatic participants Effectiveness: ARI (with a proportion of laboratory-confirmed diagnosis in non-randomly chosen participants with symptoms lasting 2 days or more) Follow-up and surveillance was carried out using a telephone questionnaire. Safety: N/A
Notes	Risk of bias: high (inappropriate choice of placebo) Note: the authors conclude that virucidal tissues were up to 36.9% effective in preventing transmission of ARIs as measured by secondary attack rates (18.7% versus 11.8%). This finding was not statistical-

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Longini 1988 *(Continued)*

ly significant, but may well have been affected by the lack of do-nothing community controls. This a well-designed, well-written study despite the unexplained attrition of 5 families, the lack of reporting of cluster coefficients, and the differential in tissue use between the 2 arms, which raises questions about the robustness of double-blinding. Particularly notable is the discussion on the low generalisability of results from the study from the placebo arm given that even the inert barrier of the tissues is likely to have limited spread. Also, the lengths to which the authors went to obtain allocation concealment and maintenance of double-blind conditions.

Funding: The Kimberly-Clark Corporation sponsored this research. This research was also partially supported by National Institutes of Health Grant 1-RO1-AI22877-01 and General Clinical Research Center Public Health Research Grant 5-MO1-RR000039.
Declaration of interests: none declared.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "Treated and placebo tissues were randomly assigned ..." Sequence generation not reported
Allocation concealment (selection bias)	Low risk	Quote:"Treated and placebo tissues were randomly assigned by the sponsor to 296 participating households stratified by household size, such that roughly half the households would receive treated tissues. Thus, the investigators were unaware of the assignment of treated tissues."
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"Treated and placebo tissues were randomly assigned by the sponsor to the randomly assigned 296 households stratified by household size... The type of tissue was identified by code, and the boxes in which tissues were contained were not marked with any specific identifiers. Therefore, the study was double-blinded."
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote:"The investigators were unaware of the assignment of the treated tissues"
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	296 households eligible. "The final sample used for analysis consisted of 143 households in the treatment group and 148 households in the placebo group."
Selective reporting (reporting bias)	High risk	Quote:"The analysis of secondary spread was restricted to households of three to five members for technical reasons, which eliminated five households." "The two groups were almost identical in composition."

Luby 2005

Study characteristics

Methods	Partly double-blind, cluster-RCT carried out during 15 April 2002 to 5 April 2003 in Karachi, Pakistan. The trial assessed the effects of mother and child hand-washing on the incidence of respiratory infections, impetigo (data not extracted), and diarrhoea (data not extracted). Randomisation took place by computer-generated random numbers in 3 phases. 1. 25 neighbourhoods were assigned to hand-washing and 11 to standard practice. 2. 300 households were assigned to using antiseptic soap. 3. 300 households were assigned to using plain soap.

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Luby 2005 *(Continued)*

4. 306 households were assigned to standard practice.
5. 1523 children younger than 15 years were assigned to using antiseptic soap.
6. 1640 children younger than 15 years were assigned to using plain soap.
7. 1528 children younger than 15 years were assigned to standard practice.

Soaps were of identical weight, colour, and smell and were packed centrally with a coded packing case matched to households containing 96 bars. Neither field workers nor participants were aware of the content. Control arm households were visited with the same frequency as intervention household but were given books and pens. Codes were held centrally by the manufacturer and broken after the end of the trial to allow analysis.

Participants	Householders of slums in Karachi. Of the 1523 children younger then 15 years assigned to using antiseptic soap, 117 dropped out (1 died, 51 were born in, and 65 aged out) = 1406; 504 were aged less than 5. Of 1640 children younger then 15 years assigned to using plain soap, 117 dropped out (3 died, 44 were born in, and 70 aged out) = 1523; 517 were aged less than 5. Of 1528 children younger then 15 years assigned to standard practice, 125 dropped out (3 died, 40 were born in, and 82 aged out) = 1403; 489 were aged less than 5.
Interventions	Instruction programme and antibacterial soap containing 1.2% triclocarban, or ordinary soap to be used throughout the day by householders, or standard procedure. See Table 1 for details.
Outcomes	Laboratory: N/A Effectiveness: 1. Number of new respiratory illness per person per week 2. Pneumonia (cough or difficulty in breathing with a respiratory rate of > 60 min in children less than 60 days old, > 50 min in those less than 1 year old, and > 40 min for those aged 1 to 5 years) Follow-up was weekly with household interview and direct observation. Children aged less than 5 were weighed, and the report presents stratification of results by child weight. Safety: N/A
Notes	Risk of bias: low (cluster coefficients and analysis by unit of randomisation provided) Note: the authors conclude that "handwashing" neighbourhoods has significantly fewer episodes of respiratory disease than controls (e.g. 50% less cough). "Handwashing" children aged less than 5 had 50% fewer episodes of pneumonia than controls (−65% to −35%). However, there was no difference in respiratory illness between types of soap. The report is confusing, with a shifting focus between children age groups. The impression reading is of an often rewritten manuscript. There is some loss of data (e.g. in the results by weight, i.e. risk group) because of lack of clarity on denominators. Despite this, the trial is a landmark. Funding: most of the funding for this study was provided by Procter and Gamble, manufacturer of Safeguard Bar Soap. The balance of the funding was provided by the Centers for Disease Control and Prevention. Conflict of interest statement: S Luby was supported by the grant from the Procter & Gamble company that funded this study. W Billhimer is an employee of the Procter & Gamble company. The other authors declare that they have no conflict of interest.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation took place by computer-generated random numbers in 3 phases.
Allocation concealment (selection bias)	Low risk	Quote:"One of the investigators (SL) who did not participate in recruiting neighbourhoods or households programmed a spreadsheet to randomly gen-

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Luby 2005 *(Continued)*

		erate the integers of a 1 or a 2. He applied the random numbers sequentially to the list of neighbourhoods. Neighbourhoods with a 1 were assigned to control, and those with a 2 were assigned to handwashing promotion. Random assignment continued until neighbourhoods consisted of at least 600 handwashing promotion households and 300 control households were assigned."
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote:"The antibacterial soap ... contained 1-2% triclocarban as an antibacterial substance. The plain soap was identical to the antibacterial soap except that it did not contain triclocarban... . Neither the fieldworkers nor the families knew whether soaps were antibacterial or plain."
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote:"Neither the fieldworkers nor the families knew whether soaps were antibacterial or plain."
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	89% of the study population followed up, but no data on the clusters.
Selective reporting (reporting bias)	Low risk	Quote:"At baseline, households in the three intervention groups were similar."

MacIntyre 2009

Study characteristics	
Methods	Prospective cluster-RCT carried out in Sydney, Australia, to assess the use of surgical masks, P2 masks, and no masks in preventing ILI in households. The study was carried out during the 2 winter seasons of 2006 and 2007 (August to the end of October 2006 and June to the end of October 2007). “Gaussian random effects were incorporated in the model to account for the natural clustering of persons in households"
Participants	290 adults from 145 families. 47 households (94 enrolled adults and 180 children) were randomised to the surgical mask group, 46 (92 enrolled adults and 172 children) to the P2 mask group, and 52 (104 enrolled adults and 192 children) to the no-mask (control) group.
Interventions	Use of surgical masks and P2 mask versus no mask. The P2 mask is described as very cumbersome. See Table 1 for details.
Outcomes	Laboratory: serological evidence Effectiveness: ILI (described as fever, history of fever or feeling feverish in the past week, myalgia, arthralgia, sore throat, cough, sneezing, runny nose, nasal congestion, headache) However, a positive laboratory finding for influenza converts the ILI definition into one of influenza. Safety: N/A
Notes	The study authors conclude that adherence to mask use significantly reduced the risk for ILI-associated infection, but < 50% of participants wore masks most of the time. They concluded that household use of face masks is associated with low adherence and is ineffective for controlling seasonal respiratory disease. Compliance was by self-report, therefore likely to be an underestimate. The primary outcome was ILI or lab-positive illness. This showed no effect. Sensitivity analysis by adherence showed that under the assumption that the incubation period is equal to 1 day (the most probable value for the 2 most common viruses isolated, influenza (21) and rhinovirus (26)), adherent use of P2 or surgical masks significantly reduces the risk for ILI infection, with a hazard ratio = 0.26 (95% CI 0.09 to 0.77; P = 0.015). No other covariate was significant. Under the less likely assumption that the incubation period is equal to 2 days, the quantified effect of complying with P2 or surgical mask use remains strong, although borderline significant; hazard ratio was 0.32 (95% CI

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MacIntyre 2009 *(Continued)*

0.11 to 0.98; P = 0.046). The study was underpowered to determine if there was a difference in efficacy between P2 and surgical masks (Table 5). The study conclusion appears to be a post hoc data exploration. Regardless of this, the study message is that respirator use in a family setting is unlikely to be effective as compliance is difficult unless there is a situation of real impending risk.

Funding: the Office of Health Protection, Department of Health and Ageing, Australia, 3M Australia, and Medical Research Council (UK).
Disclosure: Simon Cauchemez, PhD; Dominic E. Dwyer, BSc(Med), MBBS, FRACP, FRCPA, MD; Holly Seale, BSc, PhD; Pamela Cheung, RN; Gary Browne, MBBS; James Wood, BSc, PhD; and Zhanhai Gao, BSc, MSc, PhD, have disclosed no relevant financial relationships. C. Raina MacIntyre, MBBS, FRACP, FAFPHM, M App Epid, PhD, has disclosed that she has received grants for clinical research from 3M. Michael Fasher, MBBS, PhD, has disclosed that he has received grants for educational activities from and has served as an advisor or consultant to GlaxoSmithKline. Robert Booy, MBBS, FRACP, FRCPCH, MSc, MD, has disclosed that he has received grants for clinical research and educational activities from, and has served as an advisor or consultant to, CSL, Roche, Sanofi, GlaxoSmithKline, and Wyeth. All funding received is directed to a research account at The Children's Hospital at Westmead, Sydney, Australia, and is not personally accepted by Dr. Booy. Neil Ferguson, FmedSci, DPhi, has disclosed that he has served as an advisor or consultant to Crucell Inc.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"Participating households were randomised to 1 of 3 arms by a secure computerised randomisation process", but sequence generation not described.
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding of participants and personnel (performance bias) All outcomes	High risk	"Study participants and trial staff were not blinded, as it is not technically possible to blind the mask type to which participants were randomised."
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"However, laboratory staff were blinded to the arm of randomisation."
Incomplete outcome data (attrition bias) All outcomes	Low risk	143 of 145 randomised families were analysed; 2 families in the control group were lost to follow-up during the study, for which no reasons were given.
Selective reporting (reporting bias)	Low risk	No differences between groups at baseline

MacIntyre 2011

Study characteristics

Methods	A cluster-RCT of 1441 HCWs in 15 Beijing hospitals was performed during the 2008 to 2009 winter. Participants wore masks or respirators during the entire work shift for 4 weeks. Outcomes included CRI, ILI, laboratory-confirmed respiratory virus infection, and influenza. A convenience no-mask/respirator group of 481 health workers from 9 hospitals was compared.
Participants	Participants (N = 1441) were hospital HCWs aged > 18 years from the emergency departments and respiratory wards of 15 hospitals. These wards were selected as high-risk settings in which repeated and multiple exposures to respiratory infections are expected.

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MacIntyre 2011 *(Continued)*	
	Participants were randomised to medical mask (N = 492 staff from 5 hospitals), N95 fit-tested masks (N = 461 staff from 5 hospitals), and N95 non-fit-tested mask (N = 488 staff from 5 hospitals).
Interventions	Fit-tested N95 respirators versus non-fit-tested N95 respirators versus medical masks. See Table 1 for details.
Outcomes	Clinical respiratory illness, defined as 2 or more respiratory symptoms or 1 respiratory symptom and a systemic symptom Influenza-like illness, defined as fever ≥ 38 °C plus 1 respiratory symptom (i.e. cough, runny nose, etc.) Laboratory-confirmed viral respiratory infection (detection of adenoviruses, human metapneumovirus, coronavirus 229E/NL63, parainfluenza viruses 1, 2, and 3, influenza viruses A and B, respiratory syncytial virus A and B, rhinovirus A or B, and coronavirus OC43/HKU1 by multiplex PCR) Laboratory-confirmed influenza A or B Adherence with mask or respirator use. Reported problems associated with using the masks or respirators
Notes	Control arm not randomised so has been ignored. Funding source unknown. Conflict of interests: Raina MacIntyre receives funding from influenza vaccine manufacturers GSK and CSL Biotherapies for investigator-driven research. She has also been on advisory boards for Wyeth, GSK and Merck. Dr Simon Cauchemez received consulting fees from MacIntyre et al. 178 [a] 2011 Blackwell Publishing Ltd, Influenza and Other Respiratory Viruses, 5, 170–179 Sanofi-Pasteur MSD on the modelling of varicella zoster virus. The remaining authors declare that they have no competing interests. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication. Prior to the start of this study, NMF acted as a consultant for Roche, Novartis and GSK Biologicals (ceasing in 2007).

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomisation process (using a secure computerised randomisation program), but sequence generation not described
Allocation concealment (selection bias)	Low risk	Hospitals randomised prior to inclusion of participants.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Unblinded study
Blinding of outcome assessment (detection bias) All outcomes	High risk	Unblinded study
Incomplete outcome data (attrition bias) All outcomes	Low risk	No loss to follow-up
Selective reporting (reporting bias)	Low risk	Specified outcomes reported.

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MacIntyre 2013

Study characteristics	
Methods	A cluster-RCT
Participants	A total of 1669 nurses and doctors from 68 emergency departments and respiratory wards of 19 Beijing hospitals were included. Inclusion criteria: any nurse or doctor aged 18 years or older who worked full time in the emergency or respiratory wards was eligible. Exclusion: HCWs if they (1) were unable or refused to consent; (2) had beards, long moustaches, or long facial hair stubble; (3) had a current respiratory illness, rhinitis, and/or allergy; or (4) worked part time or did not work in the aforementioned wards or departments Final analysis was performed on 572 staff and 24 wards in medical mask group, 516 staff and 20 wards in the targeted N95 mask group, and 581 staff and 24 wards in the N95 mask group.
Interventions	Quote: "Masks used in the study were the 3M Standard Tie-On Surgical Mask (catalog number mask 1817; 3M, St. Paul, MN) and the 3M Health Care N95 Particulate Respirator (catalog number 1860; 3M)... . Participants wore the mask or respirator on every shift after being shown how to fit and wear it. Participants were supplied daily with either three masks for the medical mask arm or two N95 respirators. Participants using N95 respirators underwent a fit testing procedure using a 3M FT-30 Bitrex Fit Test Kit according to the manufacturer's instructions (3M)." See Table 1 for details.
Outcomes	Laboratory: 1. Laboratory-confirmed viral respiratory infection in symptomatic participants, defined as detection of adenoviruses; human metapneumovirus; coronaviruses 229E/NL63 and OC43/HKU1; parainfluenza viruses 1, 2, and 3; influenza viruses A and B; respiratory syncytial viruses A and B; or rhinoviruses A/B by nucleic acid testing (NAT) using a commercial multiplex polymerase chain reaction (Seegen, Inc., Seoul, Korea). 2. Laboratory-confirmed influenza A or B in symptomatic participants. 3. Laboratory-confirmed bacterial colonisation in symptomatic participants, defined as detection of *Streptococcus pneumoniae*, *Legionella*, *Bordetella pertussis*, chlamydia, *Mycoplasma pneumoniae*, or *Haemophilus influenzae* type B by multiplex polymerase chain reaction (Seegen, Inc.). Effectiveness: CRI, defined as 2 or more respiratory symptoms or 1 respiratory symptom and a systemic symptom. ILI, defined as fever (38 °C) plus 1 respiratory symptom Safety: adverse effects measured using a semi-structured questionnaire. Investigators stated that there was higher reported adverse effects and discomfort of N95 respirators compared with the other 2 arms. In terms of comfort, 52% (297 of 571) of the medical mask arm reported no problems, compared with 62% (317 of 512) of the targeted arm and 38% (217 of 574) of the N95 arm (P < 0.001).
Notes	Compliance with the product was highest in the targeted N95 arm (82%; 422 of 516), then the medical mask arm (66%; 380 of 572), and the N95 arm (57%; 333 of 581); these differences were statistically significant (P < 0.001). The period study conducted: 28 December 2009 to 7 February 2010 Funding: unclear Declaration of interests: none declared.

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	"using a secure computerized randomization program", but sequence generation not described

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MacIntyre 2013 *(Continued)*

Allocation concealment (selection bias)	Unclear risk	No information provided.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Outcome was objectively assessed with lab confirmation in addition to clinical illness.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"Laboratory outcomes are reported for all subjects (with at least one respiratory symptom or fever) tested, and then for the subset meeting the CRI definition"
Incomplete outcome data (attrition bias) All outcomes	Low risk	No loss to follow-up. Flow chart and text match, investigators conducted ITT and PP analysis. All the outcomes were accounted for amongst all participants.
Selective reporting (reporting bias)	Low risk	All outcomes were reported as planned.

MacIntyre 2015

Study characteristics	
Methods	A cluster-RCT of cloth masks compared with medical masks in healthcare workers in 14 secondary-/tertiary-level hospitals in Hanoi, Vietnam. Hospital wards were randomised to: medical masks, cloth masks, or a control group (usual practice, which included mask wearing). Participants used the mask on every shift for 4 consecutive weeks.
Participants	1607 hospital HCWs aged ≥ 18 years working full time in selected high-risk wards. Medical mask group (n = 580 HCWs), cloth mask group (n = 569 HCWs), control group (n = 458 HCWs)
Interventions	Medical masks, cloth masks, or a control group. See Table 1 for details.
Outcomes	Clinical respiratory illness, influenza-like illness, and laboratory-confirmed respiratory virus infection 1. Clinical respiratory illness, defined as 2 or more respiratory symptoms or 1 respiratory symptom and a systemic symptom 2. Influenza-like illness, defined as fever ≥ 38 °C plus 1 respiratory symptom 3. Laboratory-confirmed viral respiratory infection. Laboratory confirmation was by nucleic acid detection using multiplex reverse transcriptase PCR (RT-PCR) for 17 respiratory viruses. Adverse events associated with mask use
Notes	Government funded. Competing interests: CRM has held an Australian Research Council Linkage Grant with 3M as the industry partner, for investigator-driven research. 3M has also contributed masks and respirators for investigator-driven clinical trials. CRM has received research grants and laboratory testing as in-kind support from Pfizer, GSK and Bio-CSL for investigator-driven research. HS had a NHMRC Australian-based Public Health Training Fellowship at the time of the study (1012631). She has also received funding from vaccine manufacturers GSK, bio-CSL and Sanofi Pasteur for investigator-driven research and presentations. AAC used filtration testing of masks for his PhD thesis conducted by 3M Australia.

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**

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MacIntyre 2015 *(Continued)*

Random sequence generation (selection bias)	Low risk	Epi info V.6 was used to generate a randomisation allocation.
Allocation concealment (selection bias)	Low risk	74 wards randomised prior to recruitment of individuals.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Unblinded study
Blinding of outcome assessment (detection bias) All outcomes	High risk	Unblinded study
Incomplete outcome data (attrition bias) All outcomes	Low risk	No loss to follow-up
Selective reporting (reporting bias)	Low risk	Specified endpoints reported.

MacIntyre 2016

Study characteristics	
Methods	Cluster-RCT to examine medical mask use as source control for people with respiratory illness in 6 major hospitals in 2 districts of Beijing, China. Index cases with ILI were randomly allocated to medical mask (n = 123) and control arms (n = 122). Since 43 index cases in the control arm also used a mask during the study period, an as-treated post hoc analysis was performed by comparing outcomes amongst household members of index cases who used a mask (mask group) with household members of index cases who did not use a mask (no mask group).
Participants	245 index cases with ILI (medical mask = 123, control group = 122) and 597 household contacts (medical mask = 302, control group = 295)
Interventions	Medical mask versus no mask (control). See Table 1 for details.
Outcomes	Clinical respiratory illness, ILI, and laboratory-confirmed viral respiratory infection 1. Clinical respiratory illness, defined as 2 or more respiratory symptoms (cough, nasal congestion, runny nose, sore throat, or sneezes) or 1 respiratory symptom and a systemic symptom (chill, lethargy, loss of appetite, abdominal pain, muscle or joint aches). 2. ILI, defined as fever ≥ 38 °C plus 1 respiratory symptom. 3. Laboratory-confirmed viral respiratory infection, defined as detection of adenoviruses, human metapneumovirus, coronaviruses 229E/NL63 and OC43/HKU1, parainfluenza viruses 1, 2, and 3, influenza viruses A and B, respiratory syncytial virus A and B, or rhinovirus A/B by nucleic acid testing using a commercial multiplex PCR. No safety outcomes reported.
Notes	Government funded. Competing interests: all authors have completed the Unified Competing Interests form (available on request from the corresponding author) and declare that: CRM has held an Australian Research Council Linkage Grant with 3M as the industry partner, for investigator driven research. 3M have also contributed supplies of masks and respirators for investigator-driven clinical trials. She has received re-

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MacIntyre 2016 *(Continued)*

search grants and laboratory testing as in-kind support from Pfizer, GSK and Bio-CSL for investigator-driven research. HS had an NHMRC Australian based Public Health Training Fellowship at the time of the study (1012631). She has also received funding from vaccine manufacturers GSK, bio-CSL and Saniofi Pasteur for investigator-driven research and presentations. AAC had testing of filtration of masks by 3M for PhD.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Random allocation sequence using Microsoft Excel
Allocation concealment (selection bias)	High risk	Doctors enrolled the participants randomly to intervention and control arms.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Unblinded study
Blinding of outcome assessment (detection bias) All outcomes	High risk	Clinical endpoints assessed unblinded.
Incomplete outcome data (attrition bias) All outcomes	Low risk	No loss to follow-up
Selective reporting (reporting bias)	Low risk	Specified outcomes reported.

McConeghy 2017

Study characteristics

Methods	Pilot study of comprehensive intervention (education, cleaning of surfaces, audit and feedback) to staff of nursing homes versus usual care. Pair-matched cluster-randomised design with only 5 clusters (nursing homes) in each group
Participants	10 nursing homes in Colorado, USA Intervention group = 481 long-stay residents and control group = 380 'Long-stay' defined as resident at least 90 days prior to baseline, or recently readmitted after previous long stay.
Interventions	A multifaceted hand-washing/surface-cleaning intervention comprised of 1) 1-hour online educational module focused on how to prevent infections; 2) provided with an “essential bundle” of 7 products, ranging from hand sanitiser gel and foam to antiviral facial tissues, disinfecting spray, and hand and face wipe and recommendation to use 4 skin cream and wipe products; 3) audit and feedback system. See Table 1 for details.
Outcomes	Laboratory: surface cultures mentioned in Methods, but no results given Effectiveness: LRTI, all infections, hospitalisation, use of antibiotics (not relevant to this review)

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McConeghy 2017 *(Continued)*

	Safety: none mentioned in Methods and no results given
Notes	The authors conclude that Quote: "This multifaceted hand-washing and surface cleaning intervention was designed to reduce infection rates among nursing homes residents. In our 10-facility randomized, matched pair pilot study, we observed program compliance and satisfaction along with reductions in surface bacterial counts, but did not observe a statistically significant reduction in infection rates, antimicrobial use, or hospitalizations". Very poorly reported study with results not explained, summarised in Table 3 as RDs. Denominators and attrition are unclear. This work was supported by Kimberly-Clark Corporation (Contract # 14792008). Declaration of interests: none declared.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Method not described
Allocation concealment (selection bias)	Unclear risk	Method not described
Blinding of participants and personnel (performance bias) All outcomes	High risk	Unblinded
Blinding of outcome assessment (detection bias) All outcomes	High risk	Illness and absenteeism reported by treating staff.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No attrition given. Data were collected from e-medical record at baseline, but not clear whether illness data during the study were collected by the same method.
Selective reporting (reporting bias)	High risk	Upper respiratory tract infection was mentioned in the Methods (intervention presumably would target these), but only LRTI and overall infection reported.

Millar 2016

Study characteristics

Methods	Cluster-RCT, open-label study, factorial design
Participants	Around 30,000 healthy, male army trainees aged 18 to 42 years at Fort Benning, Georgia were included. Inclusion criteria: trainees assigned to 1 of the 6 selected training battalions, trainees who present with an SSTI at the clinic or the hospital, provide informed consent. Exclusion criteria: fails to meet inclusion criteria. No denominator breakdown by arm is reported.
Interventions	Promotion of hand-washing in addition to a once-weekly application of chlorhexidine-based body wash. See Table 1 for details.
Outcomes	This study was nested in a large field-based RCT and utilised clinic-based medical records. Laboratory: none

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Millar 2016 *(Continued)*

	Effectiveness: incidence of ARI at 20 months. The case definition was any occurrence of the following ICD-9 symptom or disease-specific codes: 460 to 466, 480 to 488, and specifically 465.9, 482.9, 486, and 487.1. Safety: adverse effects neither planned nor reported by the investigators
Notes	The period study conducted: May 2010 to January 2012 Government funded. Declaration of interests: none declared.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	quote: "computer-generated random numbers to 1 of the 3 study groups"
Allocation concealment (selection bias)	Unclear risk	No information provided.
Blinding of participants and personnel (performance bias) All outcomes	High risk	The study was open-label and self-reporting of ARI. It is planned as secondary objective of an original trial. Data abstractors were blinded to group assignment.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Data abstractors were blinded to group assignment.
Incomplete outcome data (attrition bias) All outcomes	High risk	There is a statistically significant difference between attrition rates in the 3 groups. The reasons for attrition are briefly reported in Table 1 of the original study (Ellis and colleagues 2014), but are unlikely to be related to the outcomes of this study. ARI cases were captured utilising clinic-based medical records, but this outcome is not prespecified in the protocol.
Selective reporting (reporting bias)	High risk	The study was conducted for another purpose. According to the study protocol, the outcomes of interest in the current report were not mentioned as outcomes when the study was planned. ARI is not prespecified as an outcome in the protocol published on ClinicalTrials.gov.

Miyaki 2011

Study characteristics

Methods	A quasi-cluster-RCT
Participants	A total of 15,134 assigned to intervention (N = 6634 workers) and control (N = 8500 workers) Inclusion criteria: all general employees (aged 19 to 72 years in 2009) of 2 sibling companies of a major car industry in Kanagawa Prefecture, Japan. All workers who regularly reported to the workplace were included, regardless of treatment for chronic diseases. All employees have the same health insurance plan and were followed up in the same way.
Interventions	Quote: "The intervention involved asking workers whose family members developed an influenza-like illness (ILI) to stay at home. If any co-habiting family members showed signs of influenza-like illness

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Miyaki 2011 *(Continued)*

	(ILI), employees ... were asked to stay at home voluntarily until 5 days has passed since the resolution of the ILS symptoms or 2 days after alleviation of fever." See Table 1 for details.
Outcomes	Workroom: influenza A test kit (rapid test) Effectiveness: assess the effectiveness of household quarantine in reducing the incidence of influenza A H1N1. ILI was defined as a body temperature greater than 38 °C or more than 1 °C above the normal temperature accompanied with more than 2 of these symptoms: nasal mucus, pharyngeal pain, cough, chills or heat sensation Safety: the incidence of influenza A H1N1 amongst workers who were told to stay home if a family member developed ILI was higher (relative risk of 2.17; P < 0.001) compared to control group. No other safety measures/harms reported. Compliance: quote: "our intervention was not compulsory; we only asked the employees to leave the workplace for a while on full pay, and we succeeded in getting all workers' agreement. In our case, explaining that the home waiting policy might be beneficial to the whole workers and help to avoid stopping the manufacturing lines (explaining it is for the benefit of the public) and guaranteeing payment during the leave (financial support) helped them to obey our request."
Notes	Period study conducted: 1 July 2009 to 19 February 2010 Unfunded There are no conflicts of interest to declare.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No information given.
Allocation concealment (selection bias)	Unclear risk	No information given.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	The nature of the intervention (stay at home) was confirmed in the intervention group, where all workers agree as they were financially supported during absences due to ILI.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"Company doctors diagnosed the disease through a positive result of an influenza A test or clinical symptoms", but not clear if they were blinded to assignment; however, the diagnostic process is meticulous and objectively confirmed.
Incomplete outcome data (attrition bias) All outcomes	Low risk	All cases are included in the analysis, and none were lost to follow-up.
Selective reporting (reporting bias)	Unclear risk	Although all outcomes of interest are clearly specified, described, and followed up, and text and numbers checked out well and based on the outcome stated for the study, there is no published protocol to match the planned vs the reported outcomes.

Morton 2004

Study characteristics

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Morton 2004 *(Continued)*

Methods	Cross-over study to evaluate the effectiveness of an alcohol gel as an adjunct to regular hand-washing for decreasing absenteeism amongst elementary children by reducing specific communicable diseases such cold, flu, and conjunctivitis. The study was conducted in an elementary school in New England, USA. In the cross-over design, classrooms in each grade level were randomised to begin as the experimental group (alcohol gel) or the control group (regular hand-washing). A study protocol for hand hygiene was introduced following the germ unit education. The hand-washing product was a soap-and-water alternative that is approximately 60% ethyl alcohol. In phase 1 (46 days) children in 9 classrooms were in the experimental group, and children in 8 classrooms were in the control group. After a 1-week washout period when no children had access to the alcohol gel, phase 2 (47 days) started, and the classroom that had participated before as experimental group passed into the control group and vice versa. Data were collected by the parents, who informed the secretary or the school nurse of the reasons for a child's absence, including symptoms of any illness. Respiratory illnesses were defined by symptoms of URTI.
Participants	253 children, 120 girls and 133 boys, from kindergarten to 3rd grade. Of the eligible 285 students, 32 children dropped out (10 due to skin irritation and 22 because of lack of parental consent). No denominator breakdown by arm is reported because the study used a cross-over design.
Interventions	Use of an alcohol gel as an adjunct to regular hand-washing and educational programme versus regular hand-washing and educational programme. See Table 1 for details.
Outcomes	Laboratory: no Effectiveness: days of absences from school for respiratory illness Safety: N/A
Notes	Risk of bias: high (no description of randomisation; partial reporting of outcomes, numerators and denominators) Note: the authors conclude that significantly fewer children became ill whilst using the alcohol gel as an adjunct to regular hand-washing than when using regular hand-washing only (decreased school absenteeism of 43% with the use of alcohol gel on top of hand-washing). The authors also described, as a limitation of the study, the fact that the school nurse served as the data collector, which could be perceived as bias in measurement of the outcome variable. Randomisation and allocation are not described; no cluster coefficients were reported; and attrition was not taken into consideration during the analysis. Unit of randomisation and analysis are different. No reporting by arm. No ORs, no CIs reported. Funding: Maine Administrative School District #35 in Eliot, Maine, and South Berwick, Maine. Conlicts of interest: none declared.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information
Allocation concealment (selection bias)	Unclear risk	Insufficient information
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Quote: "A cross-over design was used. In the crossover design, classrooms in each grade level were randomized to begin as the experimental group (regular hand washing)."
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Quote:"The school nurse served as the data collector for the duration of the study. This could be perceived as bias in the measurement of the outcome variable, absenteeism related to infectious illness."

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Morton 2004 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Insufficient information
Selective reporting (reporting bias)	Unclear risk	Insufficient information

Najnin 2019

Study characteristics	
Methods	Cluster-RCT, parallel assignment
Participants	Residents of the high-risk, cholera-prone study areas. Low-income communities in Mirpur area of urban Dhaka defined by low per capita income, poor sanitation, unsafe water use, sharing of water source, and poor living conditions. 90 geographic clusters were included, with 30-metre buffer zones. A total of 7842 households, with 52,237 individuals analysed Vaccine-only area: data were analysed for 1965 households consisting of 13,148 individuals Vaccine-plus-behaviour-change area: data were analysed for 3886 households consisting of 25,566 individuals Control area: data were analysed for 1991 households consisting of 13,523 individuals Study criteria from published protocol: Inclusion criteria: apparently healthy residents of selected vaccination sites, aged 1 year and above, non-pregnant women, written informed consent Exclusion criteria: age less than 1 year and pregnant women
Interventions	Hand-washing and water treatment promotion. See Table 1 for details.
Outcomes	Laboratory: none used Effectiveness: prevalence of respiratory illness. People were classified as having respiratory illness if they reported having fever plus either cough or nasal congestion or fever plus breathing difficulty in the past 2 days of unannounced home visits: in each intervention group and amongst those who had soap/soapy water with water present in the hand-washing station (35% of all groups combined) versus those without this (regardless of the intervention group). Planned secondary outcome: prevalence of reported respiratory illness during 2-year intervention period Safety: no adverse effects planned or reported
Notes	The period study conducted: 2011 to 2013 Funding: government and private Bill & Melinda Gates Foundation Conlicts of interest: none declared.

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Computer-generated randomisation sequence was used to allocate 90 geographical clusters to 1 of 3 groups. Before randomisation, clusters were strat-

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Najnin 2019 *(Continued)*

		ified blocked into 2 categories according to the distance to the hospital. (parent article: Lancet. 2015 Oct 3;386(10001):1362-1371)
Allocation concealment (selection bias)	Unclear risk	No information provided.
Blinding of participants and personnel (performance bias) All outcomes	High risk	All trial participants and investigators were aware of group assignment. Several in and out migrations across all groups before, after, and during outcome monitoring, and large number of changes in intervention areas
Blinding of outcome assessment (detection bias) All outcomes	High risk	Several in and out migrations across all groups before, after, and during outcome monitoring, and large number of changes in intervention areas
Incomplete outcome data (attrition bias) All outcomes	High risk	High migration movement. This could have distorted the baseline characteristics even more. Very hard to assess because the numbers in the index paper are different from the parent paper (Qadri 2015). In addition to that, for each intervention, data were analysed for 15% to 30% of those allocated on start date. Each group started with approximately 80,000 people; the number analysed is much lower (237,216 people were in the study area on start date of outcome monitoring, the total number analysed across all groups was 52,237). No info about data on migrated individuals or on those who changed intervention areas was dealt with? Also data for prevalence of ARI adjusted for age and wealth were not shown. The outcome is addressed in the 2 days preceding an unannounced visit. This means that if there was a respiratory illness in the past week it would not have been reported. Moreover, these monthly unannounced visits were done to a different set of participants in each group!
Selective reporting (reporting bias)	High risk	Published protocol does not include respiratory illness as an outcome.

Nicholson 2014

Study characteristics	
Methods	Cluster-RCT
Participants	70 low-income communities in Mumbai, India (35 communities per arm) were randomised to intervention arm (N = 1025) and control arm (N = 1026). Households located in low-income urban communities in west and south Mumbai, India. Each household contains 1 target child in the first year of a municipal school (typically aged 5 years).
Interventions	Combination of hand-washing promotion with provision of free soap aimed at 5-year-olds with provision of free soap. See Table 1 for details.
Outcomes	Laboratory: none reported Effectiveness: Primary outcomes: episodes of diarrhoea, ARIs, and school absences amongst target children, and episodes of diarrhoea and ARIs among their families Secondary outcomes: episodes of eye infections, vomiting, abscesses or boils, headaches, and earache

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Nicholson 2014 *(Continued)*

	Operational defiinitions for all the illnesses were taken from *Black's Medical Dictionary* (MacPherson 1999). ARIs as "pneumonia, cough, fever, chest pain and shortness of breath, cold, inflammation of any or all of the airways, that is, nose, sinuses, throat, larynx, trachea and bronchi" Safety: no safety measures planned or reported by the investigators
Notes	The period study conducted: 22 October 2007 to 2 August 2008 Funding: multinational corporate company (Unilever plc.) Conlicts of interest: none declared.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Coin tossing used, which could have led to a large imbalance.
Allocation concealment (selection bias)	Low risk	"a coin toss was used to assign one community in each pair to intervention and one to control"
Blinding of participants and personnel (performance bias) All outcomes	High risk	Participants knew to which arm they had been recruited. Households were removed from the study if they provided no data for 5 consecutive weeks.
Blinding of outcome assessment (detection bias) All outcomes	High risk	Data collectors were independent of the behaviour change intervention. Each was assigned exclusively to either households in the intervention group or to control households. However, communities, where very low literacy levels exist, were replaced after randomisation.
Incomplete outcome data (attrition bias) All outcomes	High risk	Data for non-completers were available and similar across groups. ITT and PP were performed. However, households were removed from the study if they provided no data for 5 consecutive weeks.
Selective reporting (reporting bias)	Unclear risk	No information to judge

Pandejpong 2012

Study characteristics

Methods	Cluster-RCT, single study centre
Participants	Children (total number = 1437) were randomised to alcohol hand gel every 60 minutes (N = 452 children), every 120 minutes (N = 447 children), and once before lunch (N = 540 children). Inclusion criteria: all children in a large private school in suburban Bangkok, Thailand, all ages, both genders with parental consent to participate. Exclusion criteria: an allergy to alcohol hand gel
Interventions	3 disinfection interventions: Alcohol hand gel applied every 60 minutes vs every 120 minutes vs once before lunch (3 groups). The current school standard for hand hygiene (q lunch group). See Table 1 for details.
Outcomes	Laboratory: none

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Pandejpong 2012 *(Continued)*

	Effectiveness: Primary: rates of absenteeism from physician-confirmed ILI Secondary: rate of absenteeism caused by total reported ILI (with and without a doctor's confirmation) In case the child was sick but did not see a doctor, the parents were asked to report any of the following symptoms: runny nose or cough, fever or chills, sore throat, headache, diarrhoea, and presence of hand, foot, or mouth ulcers. If 2 or more of these symptoms were reported, then the child's illness was documented as an ILI. Safety: investigators reported that no adverse reaction to the alcohol hand gel was reported in any participants
Notes	The period study conducted: December 2009 to February 2010 Funding: Royal College of Physicians of Thailand Conflict of interest: none to report

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No information provided.
Allocation concealment (selection bias)	Unclear risk	No information provided.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Parents and teachers are aware of the assignment. Teachers were responsible for recording the absenteeism case record forms. Parents would report child sickness. No diagnostic tests, even in the case of physician-confirmed ILI
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Outcome is physician-confirmed ILI.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: "No students were lost to follow-up or discontinued the intervention during the study period."
Selective reporting (reporting bias)	Low risk	All outcomes were reported.

Priest 2014

Study characteristics

Methods	A cluster-RCT
Participants	Study included children aged 5 to 11 years at 68 primary schools in New Zealand. Schools were randomised to hand sanitiser + education session arm (34 schools and 8859 children) and education session arm (34 schools and 7386 children). Inclusion criteria:

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Priest 2014 *(Continued)*

	School-level inclusion: at least 100 children of primary school age (school years 1 to 6; children will generally range in age from 5 years to 11 years) at November 2008. Schools that are not currently using hand-sanitiser products or are willing to not use them for the period of the trial. Schools are within the City boundaries of Christchurch, Dunedin, or Invercargill in New Zealand. The principal of the school consents to the school being included in the trial. Not ''special schools'' (e.g. schools for children with deafness or disability) and either not currently using hand-sanitiser products or willing to not use them for the period of the trial if they were randomised to the control group were eligible to participate in the trial. Student-level inclusion (follow-up children): children were eligible to participate in the follow-up group, for whom more detailed information on absences was collected, if they attended a school year 1 to 6 class in 1 of the included schools at the beginning of the second school term in 2009 (the end of April), and their caregivers completed the consent form indicating that they were willing to be telephoned following their child's absences and that they were able to take part in telephone interviews in English Exclusion criteria: School-level exclusion: special needs schools Student-level exclusion (follow-up children): children of the principal investigators and study personnel of the trial. Or, children of families that the principal of the primary school directs us not to approach
Interventions	Hand sanitiser provision (in addition to hand hygiene education session also provided to control group) in schoolchildren. See Table 1 for details.
Outcomes	Laboratory: none Effectiveness: Primary outcome: the incidence rate of absence episodes from school (reported by the parents during telephone calls) due to any illness during the study period (winter term) Secondary outcomes: assessing whether hand sanitiser was effective in reducing the: 1. incidence rate of respiratory illness absence episodes, 2. incidence rate of gastrointestinal illness absence episodes, 3. incidence rate of absence for any reason, 4. length of illness episode, 5. length of illness absence episode, and 6. incidence rate of subsequent illness amongst other children or adults in the household. Definition of respiratory illness: at least 2 of the following caregiver-reported symptoms for 1 day, or 1 of the following symptoms for 2 days (but not fever alone): runny nose, stuffy or blocked nose or noisy breathing, cough, fever, sore throat, or sneezing Safety: examined whether the use of hand sanitiser was associated with an increased risk of any skin reactions during the intervention period. Skin reactions: dryness, redness, flakiness, itchiness, eczema, and any other skin reactions
Notes	The period study conducted: 27 April to 25 September 2009 Government funded: Health Research Council of New Zealand Competing Interests: the authors have declared that no competing interests exist. All authors affirm that they are not involved in any other trials on the same or a related intervention.

Risk of bias

Bias	Authors' judgement	Support for judgement

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Priest 2014 *(Continued)*

Random sequence generation (selection bias)	Low risk	Quote: "Stata/MP 10.1 for Windows was used to generate the random numbers"
Allocation concealment (selection bias)	Low risk	Done by trial statistician provided with school codes and district and randomised the schools to either "A" or "B"
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Outcome assessors were blinded to the group allocation until the analysis was completed.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Outcome assessors were blinded to the group allocation until the analysis was completed.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	The study flow diagram gives a clear account on follow-up, with numbers of those lost to follow-up and those who discontinued the intervention along with the reasons for doing so. No child was excluded from the analysis. Only PP analysis was reported.
Selective reporting (reporting bias)	Low risk	All outcomes stated in the published protocol were reported in the study. The exception was quote: "1 planned secondary outcome (that is irrelevant to our study) that was not collected and 2 collected secondary outcomes that were not planned in the original protocol".

Radonovich 2019

Study characteristics	
Methods	Cluster-RCT, multicentre, pragmatic effectiveness trial
Participants	Study included 280 clusters randomly assigned to N95 respirators (189 clusters and 1993 HCPs) and medical masks (191 clusters and 2058 HCPs). All participants in a cluster worked in the same outpatient clinic or outpatient setting. All participants were permitted to participate for 1 or more years and gave written consent for each year of participation. Inclusion criteria: healthcare workers in outpatient settings serving adult and paediatric patients with a high prevalence of acute respiratory illness. Participants were aged at least 18 years and employed at 1 of the 7 participating health systems, and self-identified as routinely positioned within 6 feet (1.83 m) of patients. Participants were full-time employees (defined as direct patient care for approximately ≥ 24 hours weekly) and worked primarily at the study site (defined as ≥ 75% of working hours). Exclusion criteria: medical conditions precluding safe participation or anatomic features that could interfere with respirator fit, such as facial hair or third-trimester pregnancy. Participants self-identified race and sex using fixed categories; these variables were collected because facial anthropometrics related to race and sex may influence N95 respirator fit.
Interventions	Fit-tested N95 respirators versus medical masks when near patients with respiratory illness. See Table 1 for details.
Outcomes	Laboratory. Primary outcome: the incidence of laboratory-confirmed influenza, defined as: 1. detection of influenza A or B virus by RT-PCR in an upper respiratory specimen collected within 7 days of symptom onset; 2. detection of influenza from a randomly obtained swab from an asymptomatic participant; and

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Radonovich 2019 *(Continued)*

3. influenza seroconversion (symptomatic or asymptomatic), defined as at least a 4-fold rise in haemagglutination inhibition antibody titres to influenza A or B virus between pre-season and postseason serological samples deemed not attributable to vaccination.

Effectiveness. Secondary outcomes: the incidence of 4 measures of viral respiratory illness or infection as follows:

1. acute respiratory illness with or without laboratory confirmation;
2. laboratory-detected respiratory infection, defined as detection of a respiratory pathogen by PCR or serological evidence of infection with a respiratory pathogen during the study surveillance period(s), which was added to the protocol prior to data analysis;
3. laboratory-confirmed respiratory illness, identified as previously described (defined as self-reported acute respiratory illness plus the presence of at least PCR–confirmed viral pathogen in a specimen collected from the upper respiratory tract within 7 days of the reported symptoms and/or at least a 4-fold rise from pre-intervention to postintervention serum antibody titres to influenza A or B virus; and
4. influenza-like illness, defined as temperature of at least 100 °F (37.8 °C) plus cough and/or a sore throat, with or without laboratory confirmation.

Safety: no serious study-related adverse events were reported. 19 participants reported skin irritation or worsening acne during years 3 and 4 at 1 site in the N95 respirator group.

Notes

The study was conducted from September 2011 to May 2015, with final follow-up on 28 June 2016.

Compliance: adherence was reported on daily surveys 22,330 times in the N95 respirator group and 23,315 times in the medical mask group. Quote: “Always” was reported 14,566 (65.2%) times in the N95 respirator group and 15,186 (65.1%) times in the medical mask group; “sometimes” 5407 (24.2%) times in the N95 respirator group and 5853 (25.1%) times in the medical mask group; “never” 2272 (10.2%) times in the N95 respirator group and 2207 (9.5%) times in the medical mask group; and “did not recall” 85 (0.4%) times in the N95 respirator group and 69 (0.3%) times in the medical mask group. Participant-reported adherence could not be assessed in 784 participants (31.2%) in the N95 respirator group and 822 (30.8%) in the medical mask group (P = 0.84) because of lack of response to surveys or lack of adherence opportunities (i.e. participants did not encounter an individual with respiratory signs or symptoms). Analysed post hoc, participant adherence was reported as always or sometimes 89.4% of the time in the N95 respirator group and 90.2% of the time in the medical mask group.

Government funded.
Conflict of interest disclosures: Dr Bessesen reported receiving grants from the Department of Veterans Affairs during the conduct of the study. Dr Brown reported receiving grants from the US Department of Veterans Affairs during the conduct of the study. Dr Cummings reported receiving grants from the Centers for Disease Control and Prevention, the National Institutes of Health, and MedImmune outside the submitted work and the Biomedical Advanced Research and Development Authority during the conduct of the study. Ms Los reported receiving grants from Centers for Disease Control and Prevention, the Veterans Health Administration, and the Biodefense Advanced Research and Development Agency during the conduct of the study. Dr Gibert reported receiving financial support for the conduct of the study, including research personnel, from the Veterans Health Administration during the conduct of the study. Dr Gorse reported receiving grants from the US Department of Veterans Affairs during the conduct of the study. Dr Nyquist reported receiving grants from the Centers for Disease Control and Prevention/Division of Healthcare Quality Promotion, the National Institute for Occupational Safety and Health, and the Veterans Health Administration during the conduct of the study; personal fees and nonfinancial support from Sequirus outside the submitted work; and serving on a policy making committee regarding infectious disease for the American Academy of Pediatrics Committee on Infectious Diseases. Dr Reich reported receiving grants from Veterans Health Administration during the conduct of the study. Dr Rodriguez-Barradas reported receiving grants from Veterans Affairs Central Office during the conduct of the study. Dr Perl reported receiving grants from the Centers for Disease Control and Prevention and Biomedical Advanced Research and Development Authority during the conduct of the study and grants from Medimmune outside the submitted work. No other disclosures were reported.

Risk of bias

Bias	Authors' judgement	Support for judgement

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Radonovich 2019 *(Continued)*

Random sequence generation (selection bias)	Low risk	Computer-generated random sequences by an individual not involved in the study implementation and data analyses. Used stratified randomisation
Allocation concealment (selection bias)	Low risk	Used constrained randomisation
Blinding of participants and personnel (performance bias) All outcomes	Low risk	The participants cannot be blinded, but it seems that all the measures otherwise were the same with meticulous follow-up. Besides, the primary outcome was lab based (an objective outcome), which is unlikely to be affected by of lack of blinding. Investigators were blinded to the randomisation until completion of the study and analysis.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Primary outcome is laboratory-confirmed diagnosis.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: "Missing outcomes were imputed using standard multiple imputation techniques, creating multiple imputed data sets with no missing values for each analysis"
Selective reporting (reporting bias)	Low risk	Reported study outcomes matched the published protocol. Every outcome was accounted for.

Ram 2015

Study characteristics	
Methods	RCT
Participants	377 household compounds (index cases) completed the study. Control arm has 184 compounds with 1607 contacts, and intervention group has 193 compounds with 1814 contacts. Final analysis was performed on 193 index cases and 1661 contacts in the intervention group and 184 index cases and 1498 contacts in the control group. In 2009, index case-patients with symptom onset within 7 days preceding enrolment were eligible. Eligibility criteria changed in 2010 to include index case-patient with symptom onset within 48 hours preceding enrolment. Inclusion criteria: 1. Individuals ≥ 5 years old: ILI, defined as history of fever and either cough or sore throat with fever onset within the previous 24 hours. 2. Individuals < 5 years old: any child with acute fever with onset within the previous 24 hours. 3. Return to home within 24 hours of presentation to Upazilla Health Complex, Jahurul Islam Medical College Hospital or the local pharmacies, i.e. the index case cannot be admitted for treatment. If admitted, the patient would not be eligible. 4. No fever in any bari resident during the 7 days preceding the patient's presentation to hospital (see definition below). 5. At least 2 individuals (in addition to the index case-patient) who intend to reside in the bari during the subsequent 20 days. 6. Residence within 30 minutes travel time (1-way) from the Upazilla Health Complex or Jahurul Islam Medical College Hospital or the local pharmacy. Exclusion criteria: compounds were excluded if any compound member(s) was reported to have fever within 3 days before index case-patient enrolment. At another time point, compounds were excluded

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Ram 2015 *(Continued)*

	if any primary household member was reported to have fever (fever occurring within 48 hours prior to enrolment recorded).
Interventions	Promoting intensive hand-washing in households to prevent transmission of ILI. See Table 1 for details.
Outcomes	Laboratory: PCR for influenza A and B, with further subtyping of influenza A isolates for all ILI amongst contacts Effectiveness: incidence of ILI. An age-based definition of ILI was used as follows. 1. For individuals > 5 years old, ILI was defined as history of fever with cough or sore throat. 2. For children < 5 years old, ILI was defined as fever (the authors used this relatively liberal case definition in order to include influenza cases with atypical presentations in children). Safety: no safety data planned or reported by investigators
Notes	Inclusion/exclusion criteria changed 3 times during the study conduct. The period study conducted: June 2009 to December 2010 Government funded Competing interests: the authors have declared that no competing interests exist.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Block randomisation, with a block size of 4, in order to promote random and even allocation of household compounds to the 2 treatment arms. The list of random assignments was generated by an investigator with no contact with the participants.
Allocation concealment (selection bias)	Low risk	Once baseline data collection was complete, the data collector notified the field research officer, who consulted the block randomisation list to make the assignment of the household compound to intervention or control.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Relied on symptom reporting from the head of family. Inclusion/exclusion criteria changed 3 times during the study conduct. Given the provision of a hand-washing station as part of the intervention, it was not possible to ensure blinding of participants, intervention staff, or data collectors.
Blinding of outcome assessment (detection bias) All outcomes	High risk	Relied on symptom reporting from the head of family. Inclusion/exclusion criteria changed 3 times during the conduct of the study. Given the provision of a hand-washing station as part of the intervention, it was not possible to ensure blinding of participants, intervention staff, or data collectors.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Flow chart followed all households an individuals from recruitment to analysis.
Selective reporting (reporting bias)	Low risk	The specified outcomes are clearly accounted for Investigators report all outcomes for each modified enrolment.

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Roberts 2000

Study characteristics	
Methods	Open cluster-RCT carried out between March and November 1996 (the Southern Hemisphere winter season) in 23 childcare centres caring for a minimum of 50 children 10 hours a day, 5 days a week in Australia. The study assessed the effects of an Australian national hand-washing programme compared to standard procedure. Randomisation was according to a random-number table, and cluster coefficients are reported.
Participants	Children (299 in the intervention arm and 259 in the control arm) aged 3 or younger attending the centres at least 3 days a week. Attrition was 51 children in the intervention arm and 72 children in the control arm due mainly to staff leaving the centres.
Interventions	Hand-washing programme with training for staff and children. It is unclear whether any extra hand-cleansing agents were used, as GloGerm (?) is mentioned when it was used in a preliminary study. See Table 1 for details.
Outcomes	Laboratory: N/A Effectiveness: ARI (runny nose, cough, and blocked nose) Follow-up was via a parental phone interview every 2 weeks. Safety: N/A
Notes	Risk of bias: low (cluster coefficients and analysis by unit of randomisation) Note: the authors conclude that although there was no overall decrease in respiratory illness (RR 0.95, 95% CI 0.89 to 1.01), in children up to 24 months the decrease was statistically significant (RR 0.90, 95% CI 0.83 to 0.97). The authors speculated that this was because maximum benefits are likely from this age group due to their limited ability to wipe their nose and hands without a structured programme. Analyses by 3 compliance levels are also reported. A so-so reported and well-conducted trial. This work was supported by a grant from the Commonwealth Department of Family Services and Health, Research and Development Scheme. Conflict of interest: none to report.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation was according to a random-number table.
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding of participants and personnel (performance bias) All outcomes	High risk	It was not possible to blind the intervention.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "The observer was not informed of the content of the training sessions or the intervention status of the centres."
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Recruitment rate 88% (23 of 26 CCCs); loss to follow-up not clear, as no denominator given
Selective reporting (reporting bias)	Low risk	Centres were comparable at baseline.

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Sandora 2005

Study characteristics	
Methods	Single-blind, cluster-RCT carried around the Boston area, USA, in the period of November 2002 to April 2003. The trial tested the effects of using a hand sanitiser and a programme of instruction on the transmissions of GI infections (data not extracted) and ARIs in families. Units of randomisation were child-care centres and were carried out on enrolment by an investigator using random block size generated by computer. Assignment was single-blind (i.e. investigator blinded to the status of the centre). Cluster correlation was 0.01.
Participants	292 families with 1 or more children aged 6 months to 5 years who were in child care for 10 or more hours a week 155 children in 14 centres were allocated to the intervention arm and 137 children in 12 centres to the control arm**.** The mean age was 3 to 2.7 years. Attrition was respectively 15 (3 lost to follow-up and 12 who discontinued the intervention) and 19 (8 lost to follow-up and 11 who discontinued the intervention). ITT analysis was carried out.
Interventions	Alcohol-based hand sanitiser with biweekly hand hygiene educational materials over 5 months versus biweekly educational material on healthy diet. See Table 1 for details.
Outcomes	Effectiveness: ARI (2 of the following symptoms for 1 day or 1 of the following symptoms for 2 days: runny nose, cough, sneezing, stuffy or blocked nose, fever, sore throat). An illness episode had to be separated by 2 symptom-free days from a previous episode. A secondary illness was when it followed a similar illness in another family member by 2 to 7 days. Follow-up was by means of biweekly phone calls to caregivers. Safety: dry skin (71 reports), stinging (11 reports), bad smell (7 reports), dislike (2 reports), allergic reaction (2 reports), slippery feel (1 report), and irritation (20 reports).
Notes	Risk of bias: low Note: the authors conclude that although the rate of GI illnesses was significantly lower in the intervention group, the IRR was not significantly different for ARIs (0.97, 95% CI 0.72 to 1.30). Compliance and droplet route spread may account for this apparent lack of effect. A well-reported trial. Study funds and hand sanitiser were provided by GOJO Industries, Inc (Akron, OH). No conflict of interest declared.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "Random assignments were generated by computer using a permuted-blocks design with random block sizes."
Allocation concealment (selection bias)	Low risk	Low riskUnclear riskHigh risk
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote: "Teachers in the intervention classrooms were responsible for encouraging the use of the disinfecting wipes and hand sanitizer according to the study protocol ... Given that no placebo was provided and sanitizer use was recorded, neither families nor data collectors could be blinded as to the group assignment of the family."
Blinding of outcome assessment (detection bias) All outcomes	High risk	Quote: "Given that no placebo was provided and sanitizer use was recorded, neither families nor data collectors could be blinded as to the group assignment of the family."

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Sandora 2005 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	Low risk	Attrition was 15 in intervention arm (3 lost to follow-up and 12 who discontinued the intervention) and 19 in the control arm (8 lost to follow-up and 11 who discontinued the intervention). ITT analysis was carried out.
Selective reporting (reporting bias)	Unclear risk	Well-reported

Sandora 2008

Study characteristics	
Methods	Cluster-RCT carried out in a single elementary school system located in Avon, Ohio, USA to assess the effectiveness of a multifactorial infection-control intervention, including alcohol-based hand sanitiser and surface disinfection, in reducing absenteeism caused by gastrointestinal and respiratory illnesses amongst elementary school students. The study also aimed to describe the viral and bacterial contamination of common surfaces in the school classroom and to assess the impact of an environmental disinfectant on the presence of selected viruses and bacteria on these surfaces. Clustering was described as "teams of 3-4 classes depending on the class year".
Participants	A total of 363 students in 15 different classrooms were eligible to participate and received letters about the study. A sample of 285 of these students provided written informed consent and were randomly assigned to the intervention group (146) or to the control group (139) and contributed to final analysis. No students were lost to follow-up or discontinued the intervention during the study period. Baseline demographic characteristics were similar in the intervention and control groups. Most families were white and non-Hispanic and in excellent or very good health at baseline.
Interventions	Alcohol-based hand sanitiser to use at school and quaternary ammonium wipes to disinfect classroom surfaces daily for 8 weeks versus usual hand-washing and cleaning practices. See Table 1 for details.
Outcomes	Laboratory: Serological evidence: no Swabs for bacteria and viruses from 3 types of classroom surfaces were taken. Effectiveness: Respiratory illness defined as days absent as measured by a (blinded) school worker who routinely recorded reason for absenteeism either for gastrointestinal or respiratory causes. Safety: N/A
Notes	The authors conclude that the multifaceted intervention that included alcohol-based hand sanitiser use and disinfection of common classroom surfaces reduced absenteeism from gastrointestinal illness amongst elementary school students. The intervention did not impact on absenteeism from respiratory illness. In addition, norovirus was detected less frequently on classroom surfaces in the group receiving the intervention. The study is of good quality with low risk of bias. The authors checked compliance by counting discarded wipes. Reasons given for the apparent lack of effect against ARIs but good effect on GI illness are that disinfecting the classroom surfaces (daily at lunchtime with alkali) was important, as were the alcohol wipes. The authors measured the norovirus concentration on surfaces and found this to be reduced. Other reasons may be that droplets are not affected by this method, or that contamination of hands by respiratory infections is likely to be continuous (in orofaecal transmission is mostly at the time of defecation). Study funds, hand-sanitiser, and disinfecting wipes were provided by The Clorox Company (Oakland, CA).

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Sandora 2008 *(Continued)*

	Financial disclosures: Drs Sandora and Goldmann received a consulting fee from The Clorox Company for their efforts in designing and conducting this study; Dr Shihh as indicated she has no financial relationships relevant to this article to disclose.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "The allocation sequence was generated by computer ..."
Allocation concealment (selection bias)	Unclear risk	Quote: "...and teams were assigned to study groups by a study investigator (Dr Shih)." Blinding of allocation cannot be guaranteed.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not possible
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: " All of the students absences were recorded in the usual fashion by the school employee who normally answers this dedicated telephone line. This employee was blinded to the group assignment of the child."
Incomplete outcome data (attrition bias) All outcomes	Low risk	No students were lost to follow-up or discontinued the intervention during the study period.
Selective reporting (reporting bias)	Unclear risk	Well-reported

Satomura 2005

Study characteristics

Methods	RCT. Randomisation was achieved by simple computer-generated random digit. Allocation was concealed using sealed, opaque envelopes. Not clear if there was a central randomisation centre. Post hoc exchange of envelopes was prevented by writing both the name of each participant and the number on the envelope he/she drew before breaking the seal. Participants were not blinded to the intervention; however, disease incidence was determined by 1 study physician who was not informed of the results of assignment. Analysis was done based on the intention-to-treat principle. The study targeted community healthcare all over Japan and was conducted between December 2002 and March 2003 for a follow-up period of 60 days.
Participants	387 participants at 18 sites were recruited, 384 were included in the analysis: water gargling (N = 122), povidone-iodine gargling (N = 132), and control (N = 130). Follow-up was completed on 338 participants. Attrition was fully explained for URTI analysis; however, 2 participants were not accounted for in the ILI analysis. 46 participants did not complete the follow-up due to either discontinuation of diary use (n = 9) or contracting ILI (n = 37). Of the 37 participants with ILI, 11 were in the povidone-iodine group, 12 in the water group, and 14 in the control group. Analysis was performed on 35 participants (Kitamura 2007 [Kitamura 2007]).
Interventions	Participants were randomised to 1 of the following: water gargling, n = 122 (20 mL of water for about 15 seconds 3 times consecutively, at least 3 times a day); povidone-iodine gargling, n = 133 (20 mL of 15 to

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Satomura 2005 *(Continued)*

	30 times diluted 7% povidone-iodine (as indicated by the manufacturer) in the same way as water gargling); and control, n = 132 (retain their previous gargling habits). All groups were asked to fill a daily gargling diary (standardised form to record: gargling habits, hand-washing, and influenza complaints). The frequency of gargling in the water group was higher (3.6); the frequency of hand-washing was similar amongst the 3 groups. URTI symptom was classified according to Jackson methods. Diary recording was continued throughout the follow-up period and for 1 week after the onset of URTI. ILI was reported separately. See Table 1 for details.
Outcomes	Laboratory: none Effectiveness: Primary outcome: incidence of first URTI. Index cases were defined as all of the following conditions: 1. both nasal and pharyngeal symptoms, 2. severity of at least 1 symptom increased by 2 grades or more, and 3. worsening of a symptom of 1 increment or more for > 3 days. Secondary outcome: severity of URTI of the incident cases was assessed by grading each symptom during the initial 7 days after the onset of URTI in numeric scores: none = 0, mild = 1, moderate = 2, and severe = 3 ILI was defined as both developing a fever of 38 °C or higher and worsening arthralgia in addition to some respiratory symptoms (Kitamura 2007). Safety: no harm was reported. However, 2 participants in the povidone-iodine group switched to water gargling (analysed in their assignment group).
Notes	The authors concluded that simple water gargling is effective in preventing URTIs amongst healthy people. However, no statistically significant difference was observed against ILIs. The study was well-conducted; blinding would have added to the validity of the results. In addition, the study was not powered enough to detect a statistically significant preventative effect against ILI. The study demonstrates that in addition to hand-washing, simple gargling even with water can reduce URTI, but not ILI. However, during periods of endemic influenza, multiple inexpensive and simple modalities (hand-washing, masks, gargling) can be utilised together to reduce infection and transmission. Overall, the reporting of the 2 combined studies together is highly confusing. In the first study (Satomura 2005), the main outcome is URTI defined as fever and arthralgia. The second study (which is a presentation of further data from the 2005 publication in the guise of a short report) introduces the outcome ILI with a definition similar to that of URTI in the first study but referring to the earlier outcome as common cold. Also of note is reporting of significance without confidence intervals. Overall, this potentially important study should be repeated with a larger denominator. Unclear risk of bias because of confused reporting and absence of double-blinding. Partial financial support was provided by the Suzuken Memorial Foundation (2002) and Uehara Memorial Foundation (2003) (trial registry, ISRCTN67680497). No financial conflict of interest was reported by the authors of this paper.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Group assignment was based on simple computer-generated random digits..."
Allocation concealment (selection bias)	Low risk	Quote: "By an individual drawing of sealed opaque envelopes, subjects were randomly assigned to the following three groups" Quote: "allocation was completely concealed from study administrators"

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Satomura 2005 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	High risk	Not blinded
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "To prevent post hoc exchange of the envelopes, local administrators wrote down both the name of each subject and the number on the envelope he/she drew before breaking the seal."
Incomplete outcome data (attrition bias) All outcomes	Low risk	338 of 385 randomised followed up; reasons reported.
Selective reporting (reporting bias)	Unclear risk	Confusing reporting

Savolainen-Kopra 2012

Study characteristics	
Methods	Open cluster-RCT, 3-arm intervention trial
Participants	A total of 21 clusters (683 individuals) were randomised to implement hand hygiene with soap and water (257 individuals), alcohol-based hand rub (202 individuals), or control (224 individuals). The study was conducted in distinct office work units in 6 corporations in the Helsinki Region that together employed some 10,000 staff. All employees (age ≥ 18 years, both genders) were contacted by email survey. Inclusion criteria: quote: "Volunteers working in defined units" Exclusion criteria: quote:"Persons with open wounds or chronic eczema in hands" The designated 21 study clusters were identified as operationally distinct working units, each containing at least 50 people.
Interventions	Hand hygiene with soap and water and standardised instructions on how to limit the transmission of infections. Usual hand hygiene (control). See Table 1 for details.
Outcomes	Laboratory: Quote: "Between November 2008 and May 2010, the seven occupational health clinics serving the six participating corporations were advised to collect, using standard techniques, two to three respiratory samples per week from typical RTI patients and also faecal samples from a few representative patients with gastrointestinal symptoms when a GIT outbreak was suspected. The samples could originate from the study participants and also from work units not included in the study. In the laboratory, viral nucleic acids were extracted with well-characterized commercial kits and tested by validated real-time PCR methods to detect influenza A and B viruses, respiratory syncytial virus, parainfluenza virus types 1, 2, and 3, adenoviruses, human rhinoviruses and human enteroviruses from respiratory specimens, and norovirus from faecal specimens (detailed descriptions of the test procedures are available from the authors)." Effectiveness: Predefined primary endpoints: 1. Number of reported infection episodes in a cluster per total reported weeks. 2. Number of reported sick leave episodes in a cluster per total reported weeks. Secondary endpoints and outcome measures:

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Savolainen-Kopra 2012 *(Continued)*

	1. Number of days with reported symptoms of RTI and/or GTI in a cluster within a time frame of 100 reporting weeks. 2. Number of days-off due to own RTI or GTI in a cluster within a time frame of 100 reporting weeks. Safety: reported 0 adverse events
Notes	The period study conducted: January 2009 to May 2010 Government funded. Competing interests: the authors declare that they have no competing interests.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information
Allocation concealment (selection bias)	Low risk	Quote:"clusters were matched and randomized prior to onset of the interventions"
Blinding of participants and personnel (performance bias) All outcomes	High risk	The interventions were not blinded to any party involved (i.e. the study group, participants, or the occupational health services). Subjective reporting of disease episodes
Blinding of outcome assessment (detection bias) All outcomes	High risk	Subjective reporting of disease episodes
Incomplete outcome data (attrition bias) All outcomes	High risk	24% loss to follow-up. However, new recruiting in most clusters; the total number of reporting participants at the end of the trial was 91.7% compared to that at the beginning. Attrition was reported, and 76% of volunteers who started reporting continued to do so until the end of the study. Because of new recruiting in most clusters, the total number of reporting participants at the end of the trial was 626, or 91.7%, compared to that at the beginning. This means that 15.7% of the participants were replaced during the study!!! Raw data on the effects of the interventions on the occurrence of respiratory infections and vomiting/diarrhoea diseases were not reported. Zero adverse effects were reported.
Selective reporting (reporting bias)	Low risk	All planned outcomes were reported.

Simmerman 2011

Study characteristics

Methods	Randomised controlled study
Participants	Study recruited 348 households and 885 members and randomised them as follows: 1. Control (index household = 119, with 302 family members) 2. Hand-washing (index household = 119, with 292 family members) 3. Hand-washing and face mask (index household = 110, with 291 family members)

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Simmerman 2011 *(Continued)*

	The household members of children (index cases) presenting with ILI at the outpatient department of the Queen Sirikit National Institute of Child Health (QSNICH) in Bangkok, the largest public paediatric hospital in Thailand Inclusion criteria: For index cases: children aged 1 month through 15 years, residents of the Bangkok metropolitan area, and had an onset of illness < 48 hours before respiratory specimens tested positive for influenza by an RIDT that was later confirmed by qualitative real-time RT-PCR (rRT-PCR) Eligible index cases' households must have had at least 2 other members aged ≥ 1 month who planned to sleep inside the house for a period of at least 21 days from the time of enrolment. Exclusion criteria: For index cases: children at high risk for severe influenza complications (e.g. chronic lung disease, renal disease, and long-term aspirin therapy) and those treated with influenza antiviral medications Excluded households: those with any member reporting an ILI that preceded the index case by 7 days or less and households where any member had received influenza vaccination during the preceding 12 months
Interventions	Hand-washing, or hand-washing plus paper surgical face mask, or control. See Table 1 for details.
Outcomes	Laboratory: To identify index cases: QuickVue Influenza A+B rapid diagnostic kit (Quidel Co., San Diego, CA, USA), followed by rRT-PCR for influenza viral RNA Index cases and contacts tested with nasal swab and throat swab both processed for rRT-PCR. 2 blood samples for antibody seroconversion collected on Days 1 and 21 (seroconversion defined as a fourfold rise in HI titre between paired sera for any of the antigens assayed). Effectiveness: Laboratory-confirmed secondary influenza virus infections amongst household members described as the secondary attack rate (SAR). A secondary influenza virus infection was defined as a positive rRT-PCR result on Days 3 or 7 or a fourfold rise in influenza HI antibody titres with the virus type and subtype matching the index case. SAR for ILI defined by the WHO as fever plus cough or sore throat, based on self-reported symptoms. Safety: no safety measures planned or reported by the investigators Adherence: participants in the control arm reported an average of 3.9 hand-washing episodes/day (on Day 7), whilst participants in the hand-washing arm reported an average of 4.7 hand-washing episodes/day (95% CI 4.3 to 5.0; P = 0.002 compared to controls), and participants in the hand-washing plus face mask arm reported 4.9 episodes/day (95% CI 4.5 to 5.3; P < 0.001 compared to controls). In the intervention arms, parents had the highest reported daily hand-washing frequency (5.7, 95% CI 5.3 to 6.0) followed by others (4.8, 95% CI 4.3 to 5.3), siblings (4.3, 95% CI 3.7 to 4.8), and the index cases (4.1, 95% CI 3.8 to 4.4). There was no difference in the average amount of soap used in a week in the hand-washing arm (54 mL per person) and the hand-washing plus face mask arm (58.1 mL per person) (P = 0.15). 289 participants in the hand-washing plus face mask arm used an average of 12 masks per person per week (median 11, IQR 7 to 16) and reported wearing a face mask a mean of 211 minutes/day (IQR 17 to 317 minutes/day). Parents wore their masks for a median of 153 (IQR 40 to 411) minutes per day, far more than other relations (median 59; IQR 9 to 266), the index patients themselves (median 35; IQR 4 to 197), or their siblings (median 17; IQR 6 to 107). The study authors note that differences in average usage may be an attenuated measure of appropriate use in relation to the actual unmeasured exposure risk such as proximity to the index case.
Notes	The period study conducted: April 2008 and August 2009

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Simmerman 2011 *(Continued)*

	Government funded. BJC has received research funding from MedImmune Inc. No other declarations are reported.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Randomization was achieved using a block randomization method using a list of blocks each with 12 household IDs, four of which were assigned to each of the three study arms."
Allocation concealment (selection bias)	Unclear risk	Quote: "A study coordinator assigned each household to one study arm after consent was obtained"
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Recruiting clinicians were blinded to the allocation of the specific intervention. The participants were not blinded, but it is unlikely that the outcome would have been affected by lack of blinding.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	The primary outcome is a laboratory-confirmed influenza.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Household flow chart provided with reasons for exclusions, all numbers provided. Analysis was done by ITT and PP.
Selective reporting (reporting bias)	Low risk	All outcomes are accounted for in the ITT analysis of the results.

Stebbins 2011

Study characteristics

Methods	Cluster-RCT, open-label
Participants	Study included 3360 students from 10 Pittsburgh elementary schools. Intervention arm (5 schools, 1695 people) and control arm (5 schools, 1665 people) No inclusion or exclusion criteria were provided.
Interventions	Training in hand and respiratory (cough) hygiene. Hand-sanitiser was provided and encouraged to be used regularly. See Table 1 for details.
Outcomes	Laboratory: Primary outcome: laboratory-confirmed influenza (RT-PCR) amongst children presenting with ILIs leading to their absence from school 2 nasal swabs were obtained using test manufacturer-approved sterile Dacron swabs. 1 swab was employed for influenza testing using the QuickVue Influenza A+B test (Quidel Corp, San Diego, CA). The second nasal swab was delivered on cold pack to the University of Pittsburgh Medical Center Clinical Virology Laboratory, Pittsburgh, PA for RT-PCR testing (performed within 48 hours). The RT-PCR used viral nucleic acid extract (EasyMag; bioMerieux, Durham, NC) and primer/probe sequences for influenza A, influenza B, and influenza A H1 and H3

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Stebbins 2011 *(Continued)*

	subtypes (CDC, Atlanta GA). Effectiveness: Secondary outcome: absence episodes and cumulative days of absence due to ILI, any illness, and all causes Safety: none mentioned
Notes	The period study conducted: 1 November 2007 through 24 April 2008 Funding: this research was supported by Cooperative Agreement number 5UCI000435-02 from the Centers for Disease Control and Prevention (CDC). DC and DB received support from the NIH MIDAS program (1U01-GM070708). DC holds a Career Award at the Scientific Interface from the Burroughs Welcome Fund. No other conflicts declared.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "constrained randomization algorithm"
Allocation concealment (selection bias)	Low risk	Quote: "Random allocation of schools to two arms was created by Dr. Cummings and concealed until intervention assignment". "At the beginning of the school year parents and guardians were given the opportunity to decline participation"
Blinding of participants and personnel (performance bias) All outcomes	High risk	Unblinded
Blinding of outcome assessment (detection bias) All outcomes	Low risk	In 76% and 78% of illness in intervention and control group were laboratory confirmed. ILI is objectively defined.
Incomplete outcome data (attrition bias) All outcomes	High risk	Only episodes of identified causes were analysed. Causes of absence episodes in 66% of the study participants were not identified (2092 in the intervention group and 2232 in the control group). The parents could be contacted in only 34% cases of absence. About half of them had an illness, and in one-third of these cases the illness met the criteria of ILI (361 cases (33%)). Of these, 279 (77%) were tested for influenza.
Selective reporting (reporting bias)	Unclear risk	Insufficient information to judge

Suess 2012

Study characteristics

Methods	Cluster-RCT, open-label, parallel design
Participants	Study sample included 84 households randomised as follows: 1. 30 control (index cases = 30, household contact = 82) 2. 26 mask group (index cases = 26, household contact = 69)

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Suess 2012 *(Continued)*

	3. 28 mask and hand hygiene group (index cases = 28, household contact = 67) Inclusion criteria: patients presenting to general practitioners or family physicians at the study sites within 2 days of symptom onset; had a positive rapid antigen test for influenza (later to be confirmed by quantitative RT-PCR (qRT-PCR); and was at least 2 years old. Index cases also had to be the only household member suffering from respiratory disease within 14 days prior to symptom onset. Exclusion criteria were pregnancy, severely reduced health status, and HIV infection. 1-person households were also not eligible or inclusion.
Interventions	Quote: "facemask and practising intensified hand hygiene (MH group), wearing facemask only (M group) and none of the 2 (control group)". See Table 1 for details.
Outcomes	Primary outcomes: SAR of laboratory-confirmed (qRT-PCR) influenza infection amongst household members (secondary infection cases) presenting with ILI within the observation period (8 days from the date of onset). ILI was defined as fever (> 38.0 °C) + cough or sore throat. Nasal wash specimens (or if these were not possible, nasal swabs) from all participating household members Effectiveness: Secondary outcomes: laboratory-confirmed influenza infection in a household contact (secondary infection cases). The study authors defined a symptomatic secondary influenza virus infection as a laboratory-confirmed influenza infection in a household member who developed fever (> 38.0 °C), cough, or sore throat during the observation period. They termed all other secondary cases as subclinical. A secondary outcome measure was the occurrence of ILI as defined by WHO as fever plus cough or sore throat. Safety: study reported that the majority of participants (107/172, 62%) did not report any problems with mask-wearing. This proportion was significantly higher in the group of adults (71/100, 71%) compared to the group of children (36/72, 50%) (P = 0.005). The main problem reported by participants (adults as well as children) was "heat/humidity" (18/34, 53% of children; 10/29, 35% of adults) (P = 0.1), followed by "pain" and "shortness of breath" when wearing a face mask.
Notes	Period study conducted: November 2009 to April 2011 Adherence: in general, daily adherence was good, reaching a plateau of over 50% in nearly all groups (M and MH groups; 2009/10 and 2010/11) from the third day on (by then the intervention had been implemented in all households). A gradual decline towards lower adherence began around the sixth day of the index patient's illness. Government funded. The authors declare that they have no competing interests.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "prepared lists of random numbers with Microsoft Excel 2003 (Mircosoft™ Cooperation, Seattle, USA) which were divided between the three intervention groups. Each participating physician received a list of random numbers with the interventions represented in a 1:1:1 ratio"
Allocation concealment (selection bias)	Low risk	Quote: "the participating physician received a list of random numbers with the interventions represented in a 1:1:1 ratio. Eligible index patients were randomly assigned a number, which was then communicated to the study center. The resulting intervention was only communicated to the households with the physicians. Intervention material was given to the study sites in closed boxes marked only with the randomisation number. Recruiting physicians were not aware of the allocation of the numbers to the interventions and the boxes for the three intervention arms looked identical. After randomisation, participants were given their box by the physician's assistants"

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Suess 2012 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Outcomes are very objective and therefore unlikely to be influenced by lack of blinding. In addition, Quote: "physicians (as well as laboratory personnel) blinded from the randomisation results".
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: physicians (as well as laboratory personnel) blinded from the randomisation results". Outcomes are very objective and therefore unlikely to be influenced by lack of blinding.
Incomplete outcome data (attrition bias) All outcomes	Low risk	No loss to follow-up. Daily follow-up home visits over the short period of data collection (8 days)
Selective reporting (reporting bias)	Low risk	The follow-up period is very short (8 days) with very good coverage, and the criteria for defining the outcome are highly objective. All planned outcomes were reported.

Swarthout 2020

Study characteristics	
Methods	Cluster randomised open-label controlled trial carried out over 18 months in Kenyan geographically near villages to test the effect of a package of measures on pregnant mothers and then on prevalence of ARIs in their young children
Participants	7246 pregnant women in 702 clusters were enrolled, with 6960 children in year 1 and 7088 in year 2 children with available ARI data. The mean ages of index children and siblings younger than 3 years were 14.2 months (SD: 6.77 months) and 22.9 months (SD: 5.70 months) for years 1 and 2, respectively. The cluster-level intra-cluster correlation coefficient for ARIs was 0.026 for both years. There were 2212 households with 2279 children lost to follow-up by year 2 for unspecified reasons
Interventions	There were 6 intervention groups: chlorinated drinking water (W), improved sanitation (S), handwashing with soap (H), combined WSH, improved nutrition (N) through counselling lipid based nutrient supplementation (LNS) combined WSHN There were 2 control groups passive control (no promotional visits), a double-sized active control (monthly visits to measure mid–upper arm circumference) All were done through health promoters with follow up 1 or 2 years after intervention. See Table 1 for details.
Outcomes	Laboratory NR Effectiveness Prevalence of ARIs in children (defined as cough or difficulty breathing, including panting or wheezing, within 7 days before the interview - in children younger than 3 years). Secondary outcomes included difficulty breathing, including panting or wheezing, in the past 7 days (a more specific indicator of respiratory infection than a cough alone); ARI symptoms presenting with fever in the past 7 days (a potentially more severe infection); and facilitator observed runny nose. As this was a rare outcome, caregiver-reported runny nose was analysed post hoc Safety NR
Notes	Quote: "The authors conclude that Water, sanitation, and handwashing interventions with behaviour change messaging did not reduce ARIs. Nutrition counselling and LNS modestly reduced ARI symptoms compared with controls in year 1 [prevalence ratio (PR): 0.87, 95% confidence interval (CI): 0.77–0.99], but no effect in the combined WSHN group weakens this finding" Financial support: this work was supported by the Bill & Melinda Gates Foundation (OPPGD759).

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Swarthout 2020 *(Continued)*

The authors declare no further competing interests.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer random-number generator
Allocation concealment (selection bias)	Unclear risk	Insufficient information provided.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not blinded
Blinding of outcome assessment (detection bias) All outcomes	High risk	Not blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	Attrition balanced across groups and < 20%
Selective reporting (reporting bias)	High risk	None of the outcomes reported were prespecified in the trial registry

Talaat 2011

Study characteristics

Methods	Cluster-RCT
Participants	Children (N = 44,451) in the first 3 primary grades from 60 governmental elementary schools in Cairo, Egypt were included and randomised to 30 schools in the intervention arm (N = 20,882 students) and 30 control schools (N = 23,569 students). No exclusion criteria provided.
Interventions	Students were required to wash their hands at least twice during the school days for about 45 seconds, followed by proper rinsing and drying on a clean towel. Campaign material was developed, and posters were placed near sinks in the classroom and playground to encourage hand-washing with soap and water upon arriving at school, before and after meals, using the bathroom, and after coughing and sneezing. See Table 1 for details.
Outcomes	Laboratory: point-of-care influenza A and B viruses using QuickVue (QuickVue; Quidel Corp., San Diego, CA, USA). School nurses collected nasal swabs from children who visited the school clinic with ILI, and only for students who had prior written approval of a parent. Effectiveness: rates of absenteeism caused by ILI and laboratory-confirmed influenza. ILI defined as fever > 38 °C and either cough or sore throat. Safety: none planned or reported by the investigators
Notes	The period study conducted: 16 February to 12 May 2008

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Talaat 2011 *(Continued)*

Funding: this work was supported by the Centers of Diseases Prevention and Control, Work Unit no. 6000.000.000.E0016.

No interests declared.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "computer-generated random number table"
Allocation concealment (selection bias)	Unclear risk	No information given.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	The participants and study personnel were not blinded, although lack of blinding is unlikely to have influenced the outcome. Laboratory-confirmed influenza was only conducted only for students who had prior written approval of a parent.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Quote: “Differential interest of study teams may have contributed to the low rate of testing in students who were absent because of ILI in the control schools compared to the intervention schools (12% vs 22%)”
Incomplete outcome data (attrition bias) All outcomes	High risk	No flow chart of clusters flow during the study period. No information on withdrawal. Differential interest of study teams may have contributed to the low rate of testing in students who were absent because of ILI in the control schools compared to the intervention schools (12% vs 22%) incomplete or loss of data. The total number ILI episodes could be an underestimate, as there is no proactive method to look for symptoms of ILI amongst the students; it depends on the student being absent or in class with symptoms that are picked up by the teachers at school.
Selective reporting (reporting bias)	Unclear risk	Insufficient information to judge

Teesing 2021

Study characteristics

Methods	Cluster - trial taking place in 66 nursing homes units (33 nursing homes) in the Netherlands during October to December 2016 with 2 follow-up periods (January to April 2017, May to October 2017). Randomisation was carried out by computer and there were some post-randomisation imbalances: the intervention arm had more small and medium-sized nursing homes (< 88 beds, 88 to 118 beds) and the control arm had more large nursing homes (> 118 beds).
Participants	Nursing home staff whose compliance was measured with direct observation according to the WHO-defined HH moments and recorded in a novel app. “The nurses were blinded by giving distinct names to the lessons (The New Way of Working) and the observations (HANDSOME), so that they appeared to be different projects. Nurses were told that the observers were registering the frequency of health care activities (in general)”. Staff worked in 66 nursing home units, 36 (976 beds, median 25 per unit) in the intervention arm, and 30 (886 beds, median 28 per unit) in the control arm. During the trial 8 (12%) units left the study during the follow-up for various reasons: 6 intervention units (four during Follow-up 1 and 2 during Follow-up 2) and 2 control units (both during Follow-up 2)

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Teesing 2021 *(Continued)*

Interventions	Hand hygiene (HH) enhancement activities versus no activities. Activities for staff were: an e-learning session, 3 live lessons, posters, and a photo competition. See Table 1 for details.
Outcomes	Laboratory NR Effectiveness Incidence of gastroenteritis*, influenza-like illness (ILI), assumed pneumonia*, urinary tract infections (UTIs)*, and infections caused MRSA* in residents *Data not extracted Safety NR
Notes	The authors conclude that quote: "This study, similarly to comparable studies, could not conclusively demonstrate the effectiveness of an HH intervention in reducing HAIs among residents of nursing homes, despite the use of clearly defined outcome measures, a standardized illness incident reporting instrument, and directly observed HH in a multicenter cluster-RCT. This could be due to an insufficient increase in HH compliance and/or other factors in the nursing home environment that need to be addressed concurrently in order to decrease illness rates" The trend of ILI incidence reflects that of the outside community at a higher level. This is probably due to ascertainment bias in the nursing homes in the trial. The trend is seasonal and could be accounted for by visitor transmission. Funding: this study was funded by the Netherlands Organization for Health Research and Development (ZonMw). Non-financial support was received from Essity during the conduct of the study. Competing interests: the authors declare that they have no competing interests.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer random-number generator
Allocation concealment (selection bias)	Unclear risk	Insufficient information provided.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Nurses blinded but participants and other staff members not blinded.
Blinding of outcome assessment (detection bias) All outcomes	High risk	Staff members of nursing homes in the intervention arm were potentially extra alert to infections and more motivated to register them.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Participant flow diagram not reported.
Selective reporting (reporting bias)	Unclear risk	Insufficient information available

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Temime 2018

Study characteristics	
Methods	2-arm cluster-RCT
Participants	All residents and staff of 27 privately held chains of nursing homes owned by Korian. 26 nursing homes (13 per arm), with an average of 80 residents per nursing home, were included in the study.
Interventions	Quote: "The intervention was based on a bundle of HH-related measures aimed at NH staff, residents, visitors, and outside care providers. These measures included facilitated access to handrub solution using pocket-sized containers and new dispensers, a campaign to promote HH with posters and event organization, the formation of local work groups in each NH to work on HH guidelines, and staff education using e-learning on infection control and HH training performed by the same nurse for all NHs." See Table 1 for details.
Outcomes	Laboratory: none used Effectiveness: Primary outcomes: incidence rate of ARIs and AGE reported in the context of episodes of clustered cases, defined as at least 5 cases within 4 days amongst nursing home residents or staff. ARIs were defined as the combination of at least 1 respiratory symptom with 1 symptom of systemic infection. AGE was defined as the sudden onset of diarrhoea or vomiting in the absence of a non-infectious aetiology. Secondary endpoints were mortality rate, hospitalisation rate, and antibiotic prescription rate (measured in defined daily doses (DDDs) per 100 resident days). Safety: no adverse event surveillance planned or reported by the investigators
Notes	The period study conducted: 1 April 2014 to 1 April 2015 Funding: private (Institute of Ageing Well Korian (Institut du bien vieillir Korian), which runs the nursing homes included in the study) Conflicts of interest: none to report.

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	High risk	"simple" randomisation is used
Allocation concealment (selection bias)	Unclear risk	No information provided.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote: "we suspected that underreporting occurred. The data were verified qualitatively after the end of the intervention through individual phone interviews with each participating NH. Based on these interviews, ARI clustered cases episodes had actually occurred in 12 out of 13 control NHs; however, only 1 had been notified to health authorities. No unreported clustered cases episodes were identified in the intervention NHs"
Blinding of outcome assessment (detection bias) All outcomes	High risk	Data were collected at NH level and reported to centralised by the NH group headquarters in Paris through computerised databases. There was underreporting of ARI and AGE in the control groups. The trial authors suspected that underreporting occurred. Primary outcome: high risk. Secondary outcomes: low risk

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Temime 2018 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	High risk	For the primary outcome, there was underreporting of ARI and AGE in the control groups; no study flow chart was provided; and no reporting on any exclusions. Surveillance is based on voluntary and standardised notifications to health authorities of any AGE or ARI clustered case episode.
Selective reporting (reporting bias)	Low risk	Reported outcomes match planned outcomes published in the protocol.

Turner 2004a

Study characteristics	
Methods	Double-blind RCT conducted by Hill Top Research, Inc., Winnipeg, Canada, to assess the efficacy of acids with virucidal activity for the inactivation of virus and prevention of experimental rhinovirus colds. Participants in good health, aged 18 to 60, were recruited from Winnipeg and surrounding communities for participation. Qualified participants were randomised to treatment with vehicle (62% ethanol, 1% ammonium lauryl sulphate, and 1% Klucel), vehicle containing 3.5% salicylic acid, or vehicle containing 1% salicylic acid and 3.5% pyroglutamic acid. The volunteers' hands were disinfected, and then test product was applied to both hands of participant. 15 minutes after application, the fingerprints of each hand were contaminated with rhinovirus type 39. The volunteers touched conjunctiva and the nasal mucosa only with the right hand. Viral contamination of the fingers was assessed in the left hands of the volunteers, and viral infection was assessed by culture of nasal lavage specimens and blood samples.
Participants	85 volunteers; 31 control group, 27 used vehicle with 3.5% salicylic acid, 27 used vehicle with 1% salicylic acid and 3.5% pyroglutamic acid
Interventions	Use of salicylic acid versus salicylic acid and pyroglutamic acid versus "placebo" substance. See Table 1 for details.
Outcomes	Laboratory: yes Effectiveness: rhinovirus type 39 infection Safety: N/A
Notes	Risk of bias: unclear (no description of randomisation process, concealment or allocation) Note: the authors concluded that organic acids commonly used in over-the-counter skin care and cosmetic products have substantial virucidal activity against rhinovirus. These preparations provided effective residual antiviral activity on the hands. The virucidal effect of these hand treatments resulted in a reduction in the incidence of rhinovirus infection in the treated volunteers (P = 0.025). The utility of this observation in the natural setting remains to be determined. The volunteers were not allowed to use their hands in the interval between the hand treatment and the virus challenge, so the effect of normal use of the hands on the virucidal activity of these organic acids is not known. Similarly, the virus challenge method used in these experiments may not simulate the natural setting in all aspects. The effect of nasal secretions that would be transferred with the virus in the natural setting on the activity of the acids or on the transmission of virus was not tested in the model. We are unsure as to the practical significance of this study and the generalisability of its results to the real world. Poorly reported study Funding for this study was provided by the Procter & Gamble Co., Cincinnati, Ohio. No interests declared.

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**

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Turner 2004a *(Continued)*

Random sequence generation (selection bias)	Unclear risk	Quote: "randomised" Sequence generation not described.
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Quote: "double blind", but no description
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Quote: "double blind", but no description
Incomplete outcome data (attrition bias) All outcomes	Low risk	All accounted for (short study).
Selective reporting (reporting bias)	High risk	Poorly reported

Turner 2004b

Study characteristics	
Methods	Double-blind RCT conducted by Hill Top Research, Inc., Winnipeg, Canada, to assess the residual virucidal activity of a skin cleanser wipe and its effectiveness in preventing experimental rhinovirus colds. Participants in good health, aged 18 to 60 years, were recruited from Winnipeg and surrounding communities for participation. The residual activity of a skin cleanser wipe containing 4% pyroglutamic acid formulated with 0.1% benzalkonium chloride was tested. The negative control treatment was 62% ethanol. Benzalkonium chloride had been previously tested and was found to have no virucidal activity. Volunteers were randomly assigned to use the control preparation or the active preparation. The study material was applied to hands with a towelette. 15 minutes later, when the fingers were completely dry, the fingertips of each hand of the control participants and the volunteers in the active treatment group were contaminated with rhinovirus type 39. An additional volunteer in the active group was challenged with virus 1 hour after application, and the final group of volunteers was challenged 3 hours after application. Viral infection was assessed by culture of nasal lavage specimens and blood samples.
Participants	122 volunteers; 30 in control group, 92 in active group (30 tested after 15 minutes, 30 after 1 hour, 32 after 2 hours)
Interventions	Use of a skin cleanser wipe containing 4% pyroglutamic acid formulated with 0.1% benzalkonium chloride versus skin cleanser wipe containing ethanol. See Table 1 for details.
Outcomes	Laboratory: yes Effectiveness: rhinovirus type 39 infection Safety: N/A
Notes	Risk of bias: unclear (no description of randomisation process, concealment or allocation) Funding for this study was provided by the Procter & Gamble Co., Cincinnati, Ohio. No interests declared.

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Turner 2004b *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "randomised" Sequence generation not described.
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Quote: "double blind", but no description given
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Quote: "double blind", but no description given
Incomplete outcome data (attrition bias) All outcomes	Low risk	All accounted for (short study).
Selective reporting (reporting bias)	High risk	Poorly reported

Turner 2012

Study characteristics	
Methods	Randomised controlled clinical trial
Participants	A total of 212 participants were enrolled (116 in the treatment group, 96 in the control group). Healthy adult volunteers aged > 18 years from the University of Virginia community Written informed consent was obtained, and volunteers were compensated for participation. Exclusion: individuals with skin conditions that would interfere with safety evaluations or medical conditions that could impact the person's well-being or affect study results, and those whose occupations required frequent hand-washing
Interventions	Antiviral hand treatment containing 2% citric acid, 2% malic acid, and 62% ethanol (n = 116) or to a no-treatment control group (n = 96). The hand treatment was applied every 3 hours and after hand-washing whilst the participants were awake. See Table 1 for details.
Outcomes	Laboratory: PCR using AmpliTaq Gold DNA Polymerase from Applied Biosystems Effectiveness: reduction of rhinovirus-induced common colds; comparison of the number of RV-associated illnesses per 100 participants in the control group with that in the treatment group over 9 weeks. Definitions: a common cold illness was defined as the presence of any of the symptoms of nasal obstruction, rhinorrhoea, sore throat, or cough on at least 3 consecutive days. Illnesses separated by at least 3 symptom-free days were considered to be separate illnesses. Rhinovirus infection was defined as the detection of RV in nasal lavage. All volunteers were seen weekly for nasal lavage, and specimens were assayed by PCR for the presence of RV. PCR–positive specimens separated by at least 8 days and at least 1 negative PCR specimen were considered to be separate infections. RV-associated illnesses were based on detection of RV either at the time of the illness or at the first weekly visit after the illness.

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Turner 2012 *(Continued)*

	Safety: hand irritation occurred in 11 of the 116 volunteers (9%) in the treatment group, which met protocol criteria for removal from the study. An additional 8 participants who did not meet these protocol criteria voluntarily withdrew due to hand irritation. There was no hand irritation in the control group. No other adverse effects of the study treatment were noted.
Notes	The period study conducted: August 2009 to November 2009 Funding: The Dial Corporation - a Henkel Company, Scottsdale, Arizona, USA Potential conflicts of interest: R. B. T. is a consultant to Henkel and received grant funding to conduct these studies. All other authors are current or former employees of Henkel. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "A randomization code generated using commercially available software was provided by the sponsor"
Allocation concealment (selection bias)	Low risk	Quote: "staff at the study site assigned sequential subject numbers as they enrolled volunteers into the study, and treatment assignment was determined by the subject number."
Blinding of participants and personnel (performance bias) All outcomes	Low risk	The outcomes are unlikely to be influenced by lack of blinding.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "Personnel who conducted the laboratory assays were blinded to study groups and to whether the specimen was from a routine or illness related visit"
Incomplete outcome data (attrition bias) All outcomes	Low risk	Attrition (and reasons for it) was reported. Study outcomes reported as ITT and PP.
Selective reporting (reporting bias)	Low risk	All planned outcomes in study protocol were reported on.

White 2001

Study characteristics

Methods	Double-blind, placebo-controlled, cluster-RCT that took place in 3 schools in California during March to April 1999. The study assessed the incremental value of using an alcohol hand rub together with water-and-soap hand-washing. Both arms were administered an educational programme beginning 2 weeks prior to start of the trial. Randomisation was by classroom, and the placebo hand rub was indistinguishable from the active ingredient. Details of randomisation are not given.
Participants	Of the 72 classes originally recruited, lack of compliance (use of supplementary product at least 3 times a day) reduced the classes to 32 (16 in both arms) and a total of 769 participants aged 5 to 12 (381 students who received the sanitiser, and 388 who received the placebo).

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White 2001 *(Continued)*

Interventions	Pump-activated antiseptic hand rub with benzalkonium chloride (SAB) (Woodward Laboratories) or inert placebo that "virtually" looked the same in batches of 4 colour-coded bottles. School staff, parents, and participants were blinded. See Table 1 for details.
Outcomes	Laboratory: testing of virucidal and bactericidal activity of the active compound Effectiveness: ARI (cough, sneezing, sinus trouble, bronchitis, fever, red eye, headache, mononucleosis, acute exacerbations of asthma) Gastrointestinal and other illnesses (data not extracted) Follow-up and observation was carried out by classroom staff, and illnesses were described by parents. Safety: 7 students dropped out because of mild sensitivity to the rub
Notes	Risk of bias: high (no description of randomisation; partial reporting of outcomes, numerators and denominators) Note: the authors conclude that addition of the rub led to a 30% to 38% decrease of illness and absenteeism (RR for illness absence incidence 0.69, RR for absence duration 0.71). Very high attrition, unclear randomisation procedure, educational programme and use of placebo hand rub make generalisability of the results debatable. No confidence intervals reported. This study was supported by an Orange County School Nurses Organization Health Promotion Grant. No interests declared.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "randomised trial", but sequence generation not described
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "To distinguish content, both the active and placebo formulations were distributed in four color-coded groups of 1oz spritz bottles. The content were and distribution patters were only know to the researchers and were indecipherable by the school staff or students."
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "Teachers were responsible for recording attendance for each day during the study"
Incomplete outcome data (attrition bias) All outcomes	High risk	Partial reporting of outcomes, numerators and denominators
Selective reporting (reporting bias)	High risk	Poor reporting

Yeung 2011

Study characteristics

Methods	Clustered-RCT of a hand hygiene intervention involving pocket-sized containers of alcohol-based hand rub for the control of infections in long-term care facilities. Staff hand hygiene adherence was directly observed, and residents' infections necessitating hospitalisation were recorded. After a 3-month pre-intervention period, long-term care facilities (LTCFs) were randomised to receive pocket-sized containers of alcohol-based gel, reminder materials, and education for all HCWs (treatment group) or to re-

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Yeung 2011 *(Continued)*

	ceive basic life support education and workshops for all HCWs (control group). A 2-week intervention period (1 to 15 April 2007) was followed by 7 months of postintervention observations.
Participants	6 out of 7 community-based, private or semiprivate, residential LTCFs in Hong Kong agreed to participate and were randomised to: 1. hand hygiene group (3 LTCFs, 73 nursing staff and 244 residents analysed); or 2. control group (3 LTCFs, 115 nursing staff and 379 residents analysed). All were nursing homes serving an elderly population. All LTCFs were situated in different regions of Hong Kong, including urban and rural areas. The targets of the intervention were all full- and part-time HCWs at these LTCFs. The LTCFs employed 3 types of HCWs: nurses, nursing assistants, and physiotherapists.
Interventions	Pocket-sized containers of alcohol-based gel, reminder materials, and education (intervention group) or basic life-support education and workshop (control group). See Table 1 for details.
Outcomes	Rates of infection (requiring hospitalisation) Outbreaks Death due to infection Diagnoses of infection coded into 6 categories, all of which were common endemic infections in LTCFs: 1. pneumonia, 2. urinary tract infection, 3. septicaemia, 4. skin or soft-tissue infection (including cellulitis or pressure sores), 5. gastroenteritis, and 6. fever. Infections recorded in death certificates were also included, regardless of whether the resident had been hospitalised. The causes of death were categorised as due to infection, not due to infection, or unknown. If the primary or the secondary diagnosis on the death certificate belonged to 1 of the 6 endemic infection categories, the death was coded as due to infection. No safety outcomes reported.
Notes	University and industry funded.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No details provided.
Allocation concealment (selection bias)	Unclear risk	No details provided.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Unblinded study
Blinding of outcome assessment (detection bias) All outcomes	High risk	Unblinded study

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Yeung 2011 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	Low risk	No loss to follow-up
Selective reporting (reporting bias)	Unclear risk	No protocol available

Young 2021

Study characteristics	
Methods	Cluster-randomised, controlled trial of daily contact testing in students and staff at secondary schools and colleges in England to show whether daily contact testing increases school attendance and to assess the impact of daily contact testing on SARS-CoV-2 transmission within schools.
Participants	201 schools, of which 99 were randomly assigned to self-isolation of school-based COVID-19 contacts for 10 days (control) and 102 to voluntary daily lateral flow device (LFD) testing for 7 days with LFD-negative contacts remaining at school (intervention)
Interventions	All schools in the intervention and control groups followed the national policy of offering twice weekly asymptomatic testing with LFDs. Individuals with positive LFD results were required to self-isolate immediately and requested to obtain a confirmatory PCR test within 2 days. Those with indicator symptoms of possible COVID-19 (new cough, fever, loss or change in taste or smell) were required to self-isolate along with their household and obtain an urgent PCR test. If a student or staff member tested positive by LFD or PCR, close contacts (hereafter referred to as contacts) were identified by schools using national guidelines. Those in close contact with a case less than 48 hours before symptom onset (or a positive test if asymptomatic) were required to self-isolate for 10 days. At schools in the intervention group, contacts were offered daily contact testing as an alternative to self-isolation, provided the contact was school-based (i.e. with a staff member or student), the contact did not have indicator symptoms of COVID-19, and contacts were able to attend for on-site testing at school. See Table 1 for details.
Outcomes	Laboratory PCR confirmed infections Effectiveness COVID-19-related school absence and symptomatic PCR-confirmed COVID-19. Safety NR
Notes	The authors conclude that quote: “Daily contact testing of school-based contacts was non-inferior to self-isolation for control of COVID-19 transmission, with similar rates of symptomatic infections among students and staff with both approaches." Funding: UK Government Department of Health and Social Care. Declaration of interests: DWE reports lecture fees from Gilead outside the submitted work. VB, RO, and DC are consultants employed by Department of Health and Social Care as part of Deloitte’s broader project work supporting the delivery of NHS Test and Trace. TF reports honoraria from Qatar National Research Fund outside the submitted work. All other authors declare no competing interests. Potential conflicts of interest: all authors report no conflicts of interest relevant to this article.

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Computer random-number generator

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Young 2021 *(Continued)*

Allocation concealment (selection bias)	Unclear risk	Insufficient information reported
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not blinded.
Blinding of outcome assessment (detection bias) All outcomes	High risk	Not blinded.
Incomplete outcome data (attrition bias) All outcomes	High risk	Participant flow diagram reported showing high attrition at different rates in the 2 groups
Selective reporting (reporting bias)	Low risk	Prespecified outcomes reported

Zomer 2015

Study characteristics	
Methods	Cluster-RCT
Participants	71 daycare centres (36 intervention DCCs, and 35 control) in Rotterdam-Rijnmond, Gouda and Leiden in the Netherlands Study enrolled 545 children (intervention = 278, control = 267). Inclusion/exclusion criteria: children who attended the DCC at least 2 days a week; were aged between 6 months and 3.5 years at start of the trial; intended to attend the DCC throughout the study period; and if their parents consented, were Dutch-speaking, and had access to email or regular post. Children were excluded if they had a chronic illness or medication that predisposed them to infection, a sibling taking part in the trial (i.e. 1 child per family could be included), or if they started attending CCC after the beginning of the trial).
Interventions	4 components: 1. HH products, paper towel dispensers, soap, alcohol-based hand sanitiser, and hand cream were provided for 6 months. 2. Training and a booklet outlining the training. 3. 2 team training sessions aimed at specific HH improvement activities. 4. Posters and stickers for caregivers and children as reminders. See Table 1 for details.
Outcomes	Laboratory: none Effectiveness: incidence of respiratory infections in children monitored by parents. The common cold was defined as a blocked or runny nose with at least 1 of the following symptoms: coughing, sneezing, fever, sore throat, or earache. Safety: none planned or reported by the investigators
Notes	The period study conducted: September 2011 to April 2012

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Zomer 2015 *(Continued)*

Funding: mixed. The Netherlands Organisation for Health Research and Development (ZonMw). Dispensers and refills were sponsored by SCA Hygiene Products, Sweden.

Declaration of interest: none.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Stratified randomization is performed by assigning each DCC to one of six strata based on size (i.e. small < 46 children per day versus large ≥ 46 children per day) and geographic location (i.e. highly urban versus urban versus slightly/non-urban). DCCs are assigned to either intervention or control group by means of computer generation with a 1:1 ratio in each of the strata"
Allocation concealment (selection bias)	Unclear risk	No information provided.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Outcome is subjective.
Blinding of outcome assessment (detection bias) All outcomes	High risk	Symptoms were reported by parents, no validation.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Very few children were excluded or lost to follow-up (reasons for exclusions provided).
Selective reporting (reporting bias)	Low risk	All planned outcomes are reported. However, between published protocol and the paper, secondary outcomes became the primary outcome in the published paper!

AEs: adverse events
AFH: Armed Forces Hospital
AGE: acute gastroenteritis
AgNPs: ARGOVIT silver nanoparticles
ALRI: acute lower respiratory infection
ARI: acute respiratory infection
ASR: adverse skin reactions
A&E: accident and emergency
BIPAP: bilevel positive airway pressure
CCC: childcare centre
CDC: Centers for Disease Control and Prevention
CG: control group
CHG: chlorhexidine gluconate
CI: confidence interval
CMF: citric acid: malic acid: sodium lauryl sulphate (a virucidal mixture added to tissue paper)
CoV: coronavirus
cluster-RCT: cluster-randomised controlled trial
CRI: clinical respiratory illness
CXR: chest X-ray
DCC: daycare centre
EG: experimental group
FRI: febrile respiratory illness
FU: follow up
GI: gastrointestinal

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GTI: gastrointestinal infection
GP: general practitioner
HCW: healthcare worker
HFH: Hanoi French Hospital
HH: hand hygiene
HR: high risk
HSG: hand sanitiser group
ICD-9: International Classification of Disease, 9th Revision, Clinical Modification
IgG: immunoglobulin G
ICU: intensive care unit
ILI: influenza-like illness
IQR: interquartile range
IRR: incident rate ratio
ITT: intention-to-treat
KSA: Kingdom of Saudi Arabia
LFD: lateral flow device
LNS: lipid based nutrient supplementation
LRTI: lower respiratory tract infection
LTCF: long-term care facility
m: metre
MCU: medical convalescent unit
MDCK: Madin Darby canine kidney cell line
M group: face mask group
MH group: face mask and hand hygiene group
MS: monkey-derived cell line
N/A: not applicable
NAT: nucleic acid testing
NH: nursing home
NICU: neonatal intensive care unit
NOS: Newcastle-Ottawa Scales
NP: non-pharmaceutical
NR: not reported
NTS: nasal and throat swab
OR: odds ratio
PCR: polymerase chain reaction
PCU: physical conditioning unit
POCT: point-of-care testing
PP: per protocol
PPE: personal protective equipment
QNAF: Qatar National Research Fund
RCT: randomised controlled trial
RDS: respiratory distress syndrome
RI: respiratory infection
RIDT: rapid influenza diagnostic test
RNA: ribonucleic acid
RR: risk ratio
rRT-PCR: real-time reverse transcription-polymerase chain reaction
RTI: respiratory tract infection
RT-PCR: reverse-transcriptase polymerase chain reaction
RSV: respiratory syncytial virus
RV: rhinovirus
SAB: surfactant, allantoin, and benzalkonium chloride
SAR: secondary attack rate
SARS: severe acute respiratory syndrome
SCBU: special care baby unit
SD: standard deviation
SES: electrolysed water
SHEWA-B: Sanitation, Hygiene Education and Water Supply in Bangladesh
SOB: shortness of breath
SOPs: standard operating procedures
S/S: signs/symptoms
SSTI: skin and soft-tissue infection

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STH: soil-transmitted helminth
SWG: soap and water group
TIDieR: Template for Intervention Description and Replication
UHR-I: ultra high-risk infection
UHR-S: ultra high-risk SARS
URI: upper respiratory infection
URTI: upper respiratory tract infection
WBC: white blood cell
WHO: World Health Organization
WSH: water, sanitation, and handwashing (combined)

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Abou El Hassan 2004	Topic completely extraneous
Ahmadian 2022	Excluded as study is an experiment that did not measure any of our outcomes of interest.
Amirav 2005	Randomised controlled trial of aerosol treatment
Anderson 2004	Mathematical model with interesting discussion of interaction between public health measures
Anonymous 2002	News item
Anonymous 2004	News item
Anonymous 2005a	News item
Anonymous 2005b	News item
Anonymous 2005c	News item
Apisarnthanarak 2009	Intervention bundle not broken down.
Apisarnthanarak 2010	Participants took antivirals.
Aragon 2005	Descriptive paper (non-comparative). Has no viral outcomes
Azor-Martinez 2014	Results reported as respiratory and gastrointestinal infections. No extractable respiratory data
Barros 1999	Correlational study between incidence of URTI and factors such as overcrowding
Bauer 2009	Historical comparison with RSV gammaglobulin amongst interventions
Bell 2004	Has unpublished entry exit screening data and extensive references but no comparative data
Bellissimo-Rodrigues 2009	Intervention is chlorhexidine.
Ben-Abraham 2002	Exclude - bacterial illness only
Black 1981	Diarrhoea only outcome
Borkow 2010	No human beings involved.
Bouadma 2010	Hospital-based ventilator routine

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Study	Reason for exclusion
Bowen 2007	Outcomes of composite infections. Respiratory infections are not reported separately.
Breugelmans 2004	Description of risk factors in aircraft
Cai 2009	Compliance study
Cantagalli 2010	Outcome outside inclusion criteria
Carbonell-Estrany 2008	Immunoglobulin intervention and descriptive review
Carter 2002	News item
Castillo-Chavez 2003	Editorial
Cava 2005a	Survey of quarantinees' views
Cava 2005b	Personal experiences of quarantine
CDC 2003a	Case reports
CDC 2003b	No data presented.
Chai 2005	Letter - about MRSA
Chami 2012	Outcomes of composite infections. Respiratory infections are not reported separately.
Chaovavanich 2004	Case report
Chau 2003	No original retrievable data. Mathematical model fitting expected to observed cases with quarantine in the SARS of Hong Kong
Chau 2008	Audit of infection control procedures and compliance with guidelines
Chen 2007	An assessment of the impact of different hand-washing teaching methods. No clinical outcomes
Chen 2022	Not a RCT.
Cheng 2010	Confounded by antiviral use for postexposure prophylaxis
Chia 2005	Knowledge survey
Clynes 2010	Letters
Costa 2021	No clinical outcome assessed
Cowling 2007	Epidemiology, non-comparative, non-interventions study
Cyril Vitug 2021	Is a treatment for COVID-19 infection
Dalakoti 2022	Excluded as study is an experiment that did not measure any of our outcomes of interest.
Daniels 2010	Commentary
Daugherty 2008	No free data presented.

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Study	Reason for exclusion
Davies 1994	Antibody titres as outcomes with so many biases that interpretation of study is problematic
Day 1993	No acute respiratory infection outcome data
Day 2006	Mathematical model; no new data
Dell'Omodarme 2005	Probabilistic and Bayesian mathematical model of screening at entry
Denbak 2018	Outcomes of composite infections. Respiratory infections are not reported separately.
Desenclos 2004	Description of transmission
DiGiovanni 2004	Qualitative study of compliance factors in quarantine
Doebbeling 1992	RCT respiratory data not present. Only 3 viruses isolated in total with no viral typing available.
Dwosh 2003	Case series
Edmonds 2010	Lab study
Egger 2022	Excluded as study is an experiment that did not measure any of our outcomes of interest.
Fendler 2002	Cohort study badly biased with differential health profiles and healthcare workers dependency in intervention and control semi-cohorts. No attempt to adjust for confounders was made. No de-nominators available.
Ferrer 2021	Is a treatment (not something to interrupt transmission)
Flint 2003	Description of spread in aircraft and non-comparative data
Fung 2004	Non-comparative
Garcia 2010	Commentary
Gaydos 2001	Editorial linked to Ryan 2001. (Ryan 2001 was an included trial in a previous version of this review (2011). Non-RCTs were removed in this 2020 update).
Gensini 2004	Interesting historical review
Gharebaghi 2020	Study on the prevention of ventilator associated pneumonia in mechanical ventilatory patients
Girou 2002	Non-clinical outcomes
Giuliano 2021	Outcome is hospital aquired pneumonia which is a syndrome with multiple aetiologies, mainly bacterial and mycotic
Glass 2006	Mathematical model - no original data presented
Goel 2007	Non-comparative study
Gomersall 2006	Non-comparative study
Gore 2001	Summary of Dyer 2000. (Dyer 2000 was a prospective, cluster open-label cross-over cohort study included in the previous version of this review (2011). Non-RCTs were removed in this 2020 update).

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Study	Reason for exclusion
Gostin 2003	Not an analytical study
Gralton 2010	Review
Guinan 2002	It would appear that 9 classes took part and "acted as their own controls", but it is not clear if there was cross-over of classes or not. In addition, the outcome is combined gastrointestinal/respiratory. The clue lies in the presence of a nested economic analysis which shows considerable savings in time for staff and pupils if the soap is used: in other words this is a (covert) publicity study.
Gupta 2005	Economic model - no new data
Gwaltney 1982	No breakdown of cases given by arm.
Han 2003	Non-comparative
Hayden 1985	This is an RCT with laboratory-induced colds, small numbers, and uncertain numerators, but almost certainly because of the unique laboratory conditions (placebo tissues not being a placebo at all) of impossible generalisation. It was a pilot to the far bigger trial by Farr 1988a; Farr 1988b.
Hendley 1988	Inappropriate intervention
Hens 2009	Model
Heymann 2009	Already included in review as Heymann 2004. (Heymann 2004 was a controlled before and after study included in the previous version of this review (2011). Non-RCTs were removed in this 2020 update).
Hilburn 2003	No ARI/viral outcomes (e.g. URTIs)
Hilmarsson 2007	Animal study
Hirsch 2006	Study tested pharmacological interventions.
Ho 2003	Descriptive review
Hsieh 2007	Mathematical model
Hugonnet 2007	Letter without any data
Jiang 2003	Two papers that are probably different versions of the same paper: Jiang SP, Huang LW, Wang JF, Wu W, Yin SM, Chen WX, et al. A study of the architectural factors and the infection rates of health-care workers in isolation units for severe acute respiratory syndrome. Chung-Hua Chieh Ho Ho Hu Hsi Tsa Chih [Chinese Journal of Tuberculosis & Respiratory Diseases]. 26(10):594-7, 2003 Oct
Johnson 2009	Outcomes are non-clinical.
Jones 2005	Historical account
Karakaya 2021	Outcome is ventilator associated pneumonia which is a syndrome with multiple aetiologies, mainly bacterial and mycotic
Kawyannejad 2020	Trial on mouthwash for VAP patients with no viral infection outcomes
Kaydos-Daniels 2004	Not an analytical study
Kelso 2009	Model

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Study	Reason for exclusion
Khaw 2008	Assessing the efficacy of O_2 delivery
Kilabuko 2007	Aetiological study
Kosugi 2004	Non-comparative study
Lam 2004	Outcomes were generic (infection rates). No laboratory data available for viral diagnosis.
Lange 2004	No data presented.
Larson 2004a	Inappropriate outcomes
Larson 2004b	Inappropriate outcomes
Larson 2005	Cluster-RCT comparing the effects of 2 hand hygiene regimens on infection rates and skin condition and microbial counts of nurses' hands in neonatal intensive care units. Outcomes were generic (e.g. pneumonia and microbial counts of participants' skin). No laboratory data available for viral diagnosis.
Lau 2004	Attitude survey
Lau 2005	Herbal remedy effectiveness assessment
Lee 2005	Descriptive study of risk and protective factors of transmission in households. No assignment took place.
Lee 2010	Cohort study; unclear numbers were vaccinated against influenza
Lennell 2008	Measured absenteeism due to non-specific infection
Lim 2022	Not a RCT.
Lipsitch 2003	Mathematical model fit to evidence
Luckingham 1984	Historical report on Tucson experience during Spanish flu pandemic
Ma 2004	Case-control study of risk factors for SARS
MacIntyre 2010	Commentary on Cowling 2009
Malaczek 2022	Excluded as study is an experiment that did not measure any of our outcomes of interest.
Malone 2009	Model
Marin 1991	Viral resistance study
McSweeny 2007	Historical description
Meister 2022	Excluded as this is a treatment trial (all participants had COVID).
Mielke 2009	Review
Mikolajczyk 2008	No intervention
Mo 2022	Not a RCT.

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Study	Reason for exclusion
Monsma 1992	Non-comparative study
Montero-Vilchez 2022	Excluded as study is an experiment that did not measure any of our outcomes of interest.
Munoz-Basagoiti 2022	Excluded as this is a report of another study.
Nandrup-Bus 2009	The trial had only 2 clusters.
Nishiura 2009	Model
O'Callaghan 1993	Letter linked to Isaacs 1991. (Isaacs 1991 was a retrospective and prospective cohort study included in a previous version of this review (2011). Non-RCTs were removed in the 2020 update).
Olsen 2003	Description of transmission
Ooi 2005	Descriptive study, but with interesting organisational chart
Orellano 2010	Confounded by antiviral use
Panchabhai 2009	Pharma intervention
Pang 2004	Descriptive study of Beijing outbreak. Some duplicate data in common with Pang 2003. (Pang 2003 was an eclogical study included in a previous version of this review (2011). Non-RCTs were removed in the 2020 update).
Patel 2012	Although within each district the participating schools and households were randomly selected, the allocation of districts to the intervention and comparison arms was not randomly assigned.
Pittet 2000	Analysis of relationship between hand-washing compliance campaign and nosocomial bacterial infections (e.g. MRSA)
Prasad 2004	Letter about retrospective cohort - behavioural
Rabenau 2005	In vitro test of several disinfectants
Reynolds 2008	Describes the psychological effects of quarantine
Richardson 2010	Non-clinical study
Riley 2003	Mathematical model fit to evidence
Rodriguez 2009	A “reasonable attempt at minimizing bias” (see inclusion criteria) does not include absenteeism
Rosen 2006	Non-specific outcome. Measured absenteeism
Rosenthal 2005	Outcomes were generic (e.g. pneumonia, URTIs). No laboratory data available for viral diagnosis.
Safiulin 1972	Non-comparative set of studies with no clinical outcomes
Sanchez Barrueco 2022	Excluded as this is a treatment trial (all participants had COVID)
Sandrock 2008	Review
Sattar 2000	Experiment assessing virucidal activity of fingertip surface - no clinical outcome data

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Study	Reason for exclusion
Schull 2007	Describes the impact of SARS in a Toronto study
Seal 2010	Lab study
Seale 2009	Study looking at whether using respirators in A&E department is feasible
Seneviratne 2021	Not an intervention to reduce transmission and they did not look at ARIs or other clinically relevant outcomes
Sevinc Gul 2022	Excluded as this is a treatment trial (all participants had COVID)
Sizun 1996	This is a review; no original data presented.
Slayton 2016	Compares hand-washing plus (antibacterial) towel versus hand-washing without towel
Stebbins 2009	Attitude survey
Stedman-Smith 2015	Composite outcome. No data on separate respiratory illnesses reported.
Stoner 2007	No study data available.
Stukel 2008	Impact of the SARS disruption on care/mortality for other pathologies (e.g. acute myocardial infarction). There are no interventions, and outcomes are unrelated to acute respiratory infections.
Svoboda 2004	Descriptive study with before-and-after data but shifting denominators
Tracht 2010	Model
Ueno 1990	Experimental study. No clinical intervention
Uhari 1999	No respiratory illness data to be extracted
van der Sande 2008	Laboratory study without any clinical outcomes
Vessey 2007	Composite outcome. No data on separate respiratory illnesses reported.
Viscusi 2009a	Lab study
Viscusi 2009b	Lab study
Wang 2003	Descriptive study
Wang 2005	Case-control study of susceptibility factors
Weber 2004	Editorial linked to Larson 2004a
Wen 2010	Lab study
White 2005	Redundant publication of White 2003. (White 2003 was a prospective, open, cohort study included in a previous version of this review (2011). Non-RCTs were removed in the 2020 update).
Wilczynski 1997	Clinical trial of the effects of breastfeeding
Wilder-Smith 2003	Description of risk factors in aircraft

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Study	Reason for exclusion
Wilder-Smith 2005	Descriptive review
Wong 2005	Attitude survey
Yen 2010	Model
Yu 2004	Description of transmission
Zamora 2006	Head-to-head comparison of 2 sets of PPEs with no controls and no clinical outcomes
Zhai 2007	Non-comparative study
Zhao 2003	CCT of SARS treatment

A&E: accident and emergency
ARI: acute respiratory infection
CCT: controlled clinical trial
MRSA: methicillin-resistant *Staphylococcus aureus*
RCT: randomised controlled trial
RSV: respiratory syncytial virus
PPE: personal protective equipment
SARS: severe acute respiratory syndrome
URTI: upper respiratory tract infection
VAP: ventilator associated pneumonia

Characteristics of studies awaiting classification *[ordered by study ID]*

Contreras 2022

Methods	Follow-up of the WASH Benefits Bangladesh cluster-randomised controlled trial. Access to and reported use of latrines was high in both arms, and latrine quality was significantly improved by the intervention, while use of child faeces management tools was low. A random subset of households from the sanitation and control arms was enrolled into a longitudinal substudy, which measured child health with quarterly visits between 1 to 3.5 years after implementation.
Participants	9800 observations on children < 5 years through intention-to-treat analysis using generalised linear models with robust standard errors. 720 households (360 per arm) from the parent trial were enrolled and made 9800 child observations between June 2014 and December 2016.
Interventions	Multicomponent sanitation intervention including periods with differing intensity of behavioural promotion: water, sanitation, hygiene, and nutrition interventions. The sanitation intervention included provision of or upgrades to improved latrines, sani-scoops for faeces removal, children's potties, and in-person behavioural promotion. Promotion was intensive up to 2 years after intervention initiation, decreased in intensity between years 2 to 3, and stopped after 3 years. The study period included approximately 1 year of high-intensity promotion, 1 year of low-intensity promotion, and 6 months with no promotion.
Outcomes	Diarrhoea and ARI, at 1 to 2 years after intervention implementation to 3.5 years (follow-up). Outcomes were caregiver-reported and there were limited data collected after promotion ceased.
Notes	Trial registration: ClinicalTrials.gov; NCT01590095; https://clinicaltrials.gov/ct2/show/NCT01590095

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Croke 2022

Methods	Cluster-randomised trial assessing the effect of a national water, sanitation, and hygiene program on adherence with COVID-19 policies in Congo. The trial is a follow-up of the Villages et Ecoles Assainis programme which was running prior to the COVID-19 pandemic.
Participants	332 communities were randomly assigned to the Villages et Ecoles Assainis program or control. (590/1312; 45%) individuals who owned phones were surveyed by phone 3 times between May 2020 to August 2021.
Interventions	Large-scale water and sanitation programme not described in detail.
Outcomes	Primary outcomes were COVID symptoms, non- COVID illness symptoms, child health, psychological well-being, and vaccine acceptance. Secondary outcomes included COVID-19 preventive behaviour and knowledge, and perceptions of governmental performance, including COVID response. All outcomes were self-reported. COVID symptoms were defined as the number of household members in the past week with fever, dry cough, difficulty breathing/shortness of breath, or fatigue, while non-COVID illness variable was defined as the number of sick household members in the last 7 days (excluding those with COVID symptoms). The child health index was created using the proportion of children under 5 with fever/cough/diarrhoea in the last 2 weeks. The mental health index is a summary index of scores from answers to questions.
Notes	Cannot find NCT and unclear funders although acknowledgments list a potential load of funders. Probably public.

Delaguerre 2022

Methods	Prospective, open-label, non-inferiority randomised (2:1), controlled trial
Participants	Study included healthy individuals aged 18 to 45 years, with negative RADT test 3 days prior to concert event, with no risk factors and not living with someone with risk factors, and residing in Paris. Study excluded people with positive RADT test within 3 days before the gathering. People with clinical signs suggestive of an infectious respiratory disease, or with risk factor for severe COVID-19, or living with someone with risk factors for severe COVID-19. Persons not covered by French National Health Insurance or who cannot stand for the duration of the experiment (about 5 hours from entry line to exit) were excluded. Person under legal guardianship, pregnant woman or woman orally declaring non-use of effective contraception and breastfeeding woman were also excluded.
Interventions	Participants were randomly assigned to: 1. medical face mask wearing during an indoor concert event, or 2. not attending. Both groups had RADT test 3 days before the event Saliva samples for RT-PCR were collected from both groups on D0 and D7 using self-saliva-collection kits
Outcomes	Primary outcome: 1. the number of SARS-CoV-2-positive RT-PCR tests on self-collected saliva at day 7. Secondary outcomes: 1. the conversion rate of salivary carriage between the day 0 and day 7 visits;

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Delaguerre 2022 *(Continued)*

	2. the percentages of adequately masked (nose and mouth covered) faces over the total 4-hour period gathering.
Notes	1. French Ministry of Health. 2. ITT and PP analysis were used. Several imputation for missing data. 3. It is not clear if participants had COVID-19 in the past (in the table with baseline characteristics it is reported quote: “”declared Covid-19 history”: what does it mean? 4. Surgical masks were worn also by all attendees, regardless of study participation? 5. What is the intervention? Combined screening test + surgical mask?

Loeb 2022

Methods	Multicentre, randomised, non-inferiority trial
Participants	1009 healthcare workers who provided direct care to patients with suspected or confirmed COVID-19. Conducted in 29 healthcare facilities in Canada, Israel, Pakistan, and Egypt from 4 May 2020 to 29 March 2022.
Interventions	Use of medical masks versus fit-tested N95 respirators for 10 weeks, plus universal masking, which was the policy implemented at each site.
Outcomes	The primary outcome was confirmed COVID-19 on reverse transcriptase polymerase chain reaction (RT-PCR) test.
Notes	Financial support was given by the Canadian Institutes of Health Research, World Health Organization, and Juravinski Research Institute. Disclosures can be viewed at www.acponline.org/authors/icmje/ConflictOfInterestForms.do?msNum=M22-1966

Varela 2022

Methods	Open-label non-inferiority randomised controlled trial
Participants	Study was conducted in Colombia Inclusion criteria: people aged ≥ 18 years of both genders and who: (a) lived in a geographic area with active COVID-19 transmission and in areas with medium, medium-high, and high vulnerability index; and (b) worked outside their homes for at least 2 days during the last week. Exclusion criteria: retirement, unemployment, home-based working, history of laboratory-confirmed COVID-19, working in health care, and daily N95 mask or face shield use. In addition, during follow-up if participants reported an occupation change from work outside the home to home-based work, or became unemployed
Interventions	1. Intervention group (IG): instructed to wear closed face shields with surgical face masks 2. Active control group (ACG): instructed to wear only surgical face mask

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Varela 2022 *(Continued)*

	PPE was sent to their home address for each day of participation All participants received a follow-up twice a week by phone All participants received recorded educational intervention via email or phone that provided recommendations about COVID-19 prevention measures, guidance to ensure adherence, and appropriate handling of the assigned PPE. Weekly short questionnaire was performed on days 7, 14, and 21 to evaluate health status SARS-CoV-2 symptoms, PPE use, and adherence.
Outcomes	Primary outcome was the composite result of positive RT-PCR or seroconversion during follow-up Secondary outcomes including PPE use and adherence
Notes	1. Study was nested within an observational study (CoVIDA project). 2. Funding was provided by donors administered by the philanthropy department at the Universidad de Los Andes, external financing from the United Nations Development Programme (UNDP), and donations of diagnostic material from the Engineering Services Laboratory S.A.S. (LABSERVING S.A.S. Colombia). Funders had no input on the study at any stage. 3. Provided analysis as ITT and PP. 4. Missing data were imputed with negative results.

ARI: acute respiratory infection
h: hours
ITT: intention-to-treat
NCT: trial register number
PPE: personal protective equipment
PP: per protocol
RADT: rapid antigen detection test
RT-PCR: reverse-transcriptase polymerase chain reaction

Characteristics of ongoing studies *[ordered by study ID]*

Brass 2021

Study name	Prevention of SARS-CoV-2 (COVID-19) transmission in residential aged care using ultraviolet light (PETRA)
Methods	A multicentre, 2-arm double-cross-over, randomised controlled trial will be conducted to determine the efficacy of GUV devices to reduce respiratory viral transmission in RACF, as an adjunct to existing infection control measures. The study will be conducted in partnership with 3 aged care providers in metropolitan and regional South Australia. RACF will be separated into paired within-site zones, then randomised to intervention order (GUV or control). The initial 6-week period will be followed by a 2-week washout before cross-over to the second 6-week period. After accounting for estimated within-zone and within-facility correlations of infection, and baseline infection rates (10 per 100 person-days), a sample size of n = 8 zones (n = 40 residents/zone) will provide 89% power to detect a 50% reduction in symptomatic infection rate.
Participants	RACF within metropolitan and regional South Australia will be considered for recruitment if they possess the ability to sub-divide communal living areas into discrete areas that enable a concurrent comparison of interventions, with the facility cohorts otherwise subject to the same facility practices (e.g. environmental cleaning, staffing, and social distancing).
Interventions	The intervention will involve the commercially available Laftech GUV appliances: UV-FLOW-C wall- and ceiling-mounted system, UV-FAN-XS wall-mounted air purifier, and UV-FAN M2/95HP air purification device (LAF Technologies, Melbourne, Australia).

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Brass 2021 *(Continued)*

Outcomes	The primary outcome will be the incidence rate ratio of combined symptomatic respiratory infections for intervention versus control. Secondary outcomes include incidence rates of hospitalisation for complications associated with respiratory infection; respiratory virus detection in facility air and fomite samples; rates of laboratory-confirmed respiratory illnesses and genomic characteristics.
Starting date	
Contact information	Andrew P. Shoubridge • The South Australian Health and Medical Research Institute (SAHMRI), Adelaide, SA, Australia • The Microbiome and Host Health Programme, College of Medicine and Public Health, Flinders University, Bedford Park, SA, Australia
Notes	

NCT03454009

Study name	Appropriate time-interval application of alcohol hand gel on reducing influenza-like illness amongst preschool children: a randomised, controlled trial
Methods	This is a comprehensive randomised cluster hand-hygiene improvement intervention to reduce self-reported ARI/ILI and GI illness, absenteeism, presenteeism and related behavioural and attitudinal change over a 90-day trial. The intervention group will receive hand hygiene supplies and a variety of educational materials, including environmental posters in common areas. The control group will perform their usual hygiene activities and will not receive an intervention. Identical weekly surveys will be administered to the intervention and control groups to measure self-reported illness, absenteeism, presenteeism, along with behaviour and attitudes measured at specified intervals during the study. The intervention and control groups were randomised by work floors before the onset of the enrolment period. It is hypothesised that employees in the intervention group will experience reduced self-reported illness, absenteeism, and presenteeism along with improved protective hygiene behaviours and related attitudes, relative to those in the control group over the 90-day trial.
Participants	Inclusion criteria 1. At least 18 years of age or older 2. No known allergies to alcohol or surface disinfecting wipes 3. Works at least 30% of office hours at the study host site 4. Consent to receiving emails from Kent State University Exclusion criteria 1. Under 18 years of age 2. Known allergies to alcohol or surface disinfecting wipes 3. Works less than 30% of office hours at the study host site 4. Does not consent to receiving emails from Kent State University
Interventions	The intervention group will receive hand hygiene supplies and a variety of educational materials, including environmental posters in common areas. The control group will perform their usual hygiene activities and will not receive an intervention.
Outcomes	Self-reported ARI/ILI and GI illness, absenteeism, presenteeism and related behavioural and attitudinal change over a 90-day trial

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NCT03454009 *(Continued)*

Starting date	5 February 2018
Contact information	Maggie Stedman-Smith, PhD, Kent State University College of Public Health
Notes	Recruitment completed. Last update in ClinicalTrials.gov was 1 May 2019. NCT03454009

NCT04267952

Study name	Hand hygiene intervention program on primary school students' health outcomes and absenteeism in school
Methods	Study Type: interventional (clinical trial) Estimated enrolment: 200 participants Allocation: randomised Intervention model: parallel assignment Masking: single (participant) Masking description: participation will not know whether they are in the experimental or control group
Participants	Inclusion criteria: primary school student (especially third- and fourth-class student) Exclusion criteria: people with chronic disease
Interventions	Experimental: first group Hand hygiene intervention programme prepared by using planned behaviour theory will be applied to the students in this group. Active comparator: second group Students in this group will be given classic hand hygiene training.
Outcomes	Primary outcome measure: children with symptoms of infection will be referred to the family physician to have a rapid antigen test and to report the result to the researcher. 10 identified upper respiratory tract symptoms (fever, sore throat, runny nose, etc.) will be recorded weekly by family of children. The researcher will receive symptom information from the family via weekly SMS. The number of days the child does not attend school due to illness and the percentage of absenteeism 1. Group A streptococcal infections in rapid antigen test (time frame: total 20 weeks) 2. Incidence of symptoms of acute upper respiratory tract infection (time frame: total 20 weeks) 3. School absenteeism (time frame: total 20 weeks) Secondary outcome measures: Glogerm gel applied hands will shine areas containing micro-organisms. Contamination rate will be calculated by taking a photo of the hands and performing brightness analysis in Adobe Photoshop program. 1. Pollution rate of hands (time frame: from date of randomisation until the date of first documented progression assessed up to 7 months)
Starting date	9 September 2019

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NCT04267952 *(Continued)*

Contact information	Contact: Uyanık +905068949969; gulcinyelten@hotmail.com
Notes	Recruitment is ongoing. Last update in ClinicalTrials.gov was 13 February 2020. NCT04267952

NCT04471766

Study name	Evaluation of locally produced cloth face mask on COVID-19 and respiratory illnesses prevention at the community level - a cluster-RCT
Methods	Study type: interventional (clinical trial) Estimated enrolment: 66,000 participants Allocation: randomised Intervention model: parallel assignment Masking: single (outcomes assessor) Primary purpose: prevention
Participants	Ages eligible for study: 10 years and older (child, adult, older adult) Sexes eligible for study: all Accepts healthy volunteers: no Criteria Inclusion criteria: 1. Household resident 2. Age 10 years and older Exclusion criteria: 1. Refusal to participate
Interventions	Experimental: certified cloth face mask plus preventive information Active comparator: information on COVID-19 prevention
Outcomes	Self-reported main symptoms of COVID-19 (3 or more of fever, cough, fatigue, shortness of breath, loss of smell/taste) Consultation for COVID-19 like illness or reported positive test, or both Self reported COVID-19 like illness plus hospitalisation or death Any death during the follow-up period: 1. Reported COVID-19 like illness (time frame: 4 months' follow-up) 2. Consultation (time frame: 4 months' follow-up) 3. Severe illness (time frame: 4 months' follow-up) 4. Mortality (time frame: 4 months' follow-up)
Starting date	Estimated study start date: July 2020
Contact information	Amabelia Rodrigues, PhD, 00245966078659; a.rodrigues@bandim.org

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NCT04471766 *(Continued)*

Notes	The number of cases of COVID-19 is still increasing, and transmission of SARS-CoV-2 seems to occur mainly through person-to-person transmission through respiratory droplets, indirect contact with infected people and surfaces. The use of face masks is recommended as a public health measure, but in many settings only domestic cloth made masks are available to the majority of the people. However, masks can be of different quality, and very little is known about the utility of cloth face masks at the community level. In Bandim Health Project's Health and Demographic Surveillance System we evaluated the effect of providing locally produced cloth face masks on the severity of COVID-19 like illness and mortality in an urban population. The locally produced cloth mask is made according to a laboratory-certified model and was provided to the intervention group alongside information of how the risk of transmission can be reduced. The control group received information alone. Follow-up will be implemented through telephone calls and post epidemic home visits.

ARI: acute respiratory tract infections
GUV: germicidal ultraviolet
ILI: influenza-like illness
GI: gastrointestinal
n: number
RACF: residential aged care facilities
RCT: randomised controlled trial
SARS: severe acute respiratory syndrome

DATA AND ANALYSES

Comparison 1. Randomised trials: medical/surgical masks versus no masks

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.1 Viral illness	10		Risk Ratio (IV, Random, 95% CI)	Subtotals only
1.1.1 Influenza/COVID-like illness	9	276917	Risk Ratio (IV, Random, 95% CI)	0.95 [0.84, 1.09]
1.1.2 Laboratory-confirmed influenza or SARS-cov-2	6	13919	Risk Ratio (IV, Random, 95% CI)	1.01 [0.72, 1.42]
1.1.3 Laboratory-confirmed other respiratory viruses	1	4862	Risk Ratio (IV, Random, 95% CI)	0.58 [0.25, 1.31]

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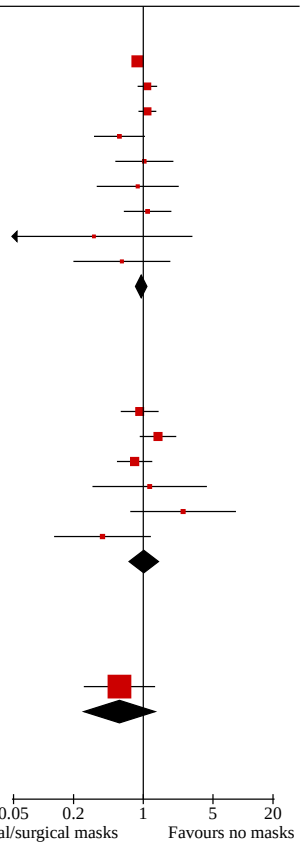
Analysis 1.1. Comparison 1: Randomised trials: medical/surgical masks versus no masks, Outcome 1: Viral illness

Study or Subgroup	log[Risk Ratio]	SE	Medical/surgical masks Total	No masks Total	Weight	Risk Ratio IV, Random, 95% CI
1.1.1 Influenza/COVID-like illness						
Abaluck 2022 (1)	-0.135	0.036	111525	155268	41.4%	0.87 [0.81 , 0.94]
Aiello 2012	0.095	0.115	392	370	19.8%	1.10 [0.88 , 1.38]
Alfelali 2020	0.095	0.105	3864	3823	21.9%	1.10 [0.90 , 1.35]
Barasheed 2014	-0.55	0.3	75	89	4.6%	0.58 [0.32 , 1.04]
Canini 2010	0.025	0.342	148	158	3.6%	1.03 [0.52 , 2.00]
Cowling 2008	-0.128	0.483	61	205	1.9%	0.88 [0.34 , 2.27]
MacIntyre 2009	0.1	0.28	186	100	5.2%	1.11 [0.64 , 1.91]
MacIntyre 2016	-1.139	1.16	302	295	0.3%	0.32 [0.03 , 3.11]
Suess 2012	-0.494	0.571	26	30	1.4%	0.61 [0.20 , 1.87]
Subtotal (95% CI)			**116579**	**160338**	**100.0%**	**0.95 [0.84 , 1.09]**
Heterogeneity: Tau² = 0.01; Chi² = 11.44, df = 8 (P = 0.18); I² = 30%						
Test for overall effect: Z = 0.71 (P = 0.48)						
1.1.2 Laboratory-confirmed influenza or SARS-cov-2						
Aiello 2012	-0.083	0.223	392	370	25.9%	0.92 [0.59 , 1.42]
Alfelali 2020	0.34	0.215	3864	3823	26.7%	1.40 [0.92 , 2.14]
Bundgaard 2021 (2)	-0.2	0.208	2392	2470	27.4%	0.82 [0.54 , 1.23]
Cowling 2008	0.148	0.674	61	205	5.8%	1.16 [0.31 , 4.34]
MacIntyre 2009	0.92	0.6225	186	100	6.6%	2.51 [0.74 , 8.50]
Suess 2012	-0.942	0.57	26	30	7.7%	0.39 [0.13 , 1.19]
Subtotal (95% CI)			**6921**	**6998**	**100.0%**	**1.01 [0.72 , 1.42]**
Heterogeneity: Tau² = 0.07; Chi² = 8.52, df = 5 (P = 0.13); I² = 41%						
Test for overall effect: Z = 0.07 (P = 0.95)						
1.1.3 Laboratory-confirmed other respiratory viruses						
Bundgaard 2021	-0.55	0.42	2392	2470	100.0%	0.58 [0.25 , 1.31]
Subtotal (95% CI)			**2392**	**2470**	**100.0%**	**0.58 [0.25 , 1.31]**
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.31 (P = 0.19)						



Footnotes
(1) Covid-like-illness
(2) SARS-cov-2

Comparison 2. Randomised trials: N95 respirators compared to medical/surgical masks

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.1 Viral illness	5		Risk Ratio (IV, Random, 95% CI)	Subtotals only
2.1.1 Clinical respiratory illness	3	7799	Risk Ratio (IV, Random, 95% CI)	0.70 [0.45, 1.10]
2.1.2 Influenza-like illness	5	8407	Risk Ratio (IV, Random, 95% CI)	0.82 [0.66, 1.03]
2.1.3 Laboratory-confirmed influenza	5	8407	Risk Ratio (IV, Random, 95% CI)	1.10 [0.90, 1.34]
2.2 Viral illness in healthcare workers	4		Risk Ratio (IV, Random, 95% CI)	Subtotals only
2.2.1 Clinical respiratory illness	3	7799	Risk Ratio (IV, Random, 95% CI)	0.70 [0.45, 1.10]
2.2.2 Influenza-like illness	4	8221	Risk Ratio (IV, Random, 95% CI)	0.81 [0.59, 1.11]

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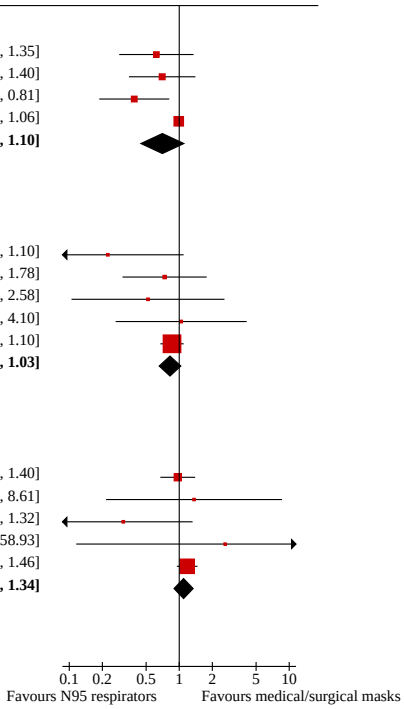
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.2.3 Laboratory-confirmed influenza	4	8221	Risk Ratio (IV, Random, 95% CI)	1.05 [0.79, 1.40]

Analysis 2.1. Comparison 2: Randomised trials: N95 respirators compared to medical/surgical masks, Outcome 1: Viral illness

Study or Subgroup	log[Risk Ratio]	SE	N95 respirators Total	Medical/surgical masks Total	Weight	Risk Ratio IV, Random, 95% CI
2.1.1 Clinical respiratory illness						
MacIntyre 2011	-0.478	0.397	949	492	18.5%	0.62 [0.28 , 1.35]
MacIntyre 2013 (1)	-0.357	0.355	516	286	20.8%	0.70 [0.35 , 1.40]
MacIntyre 2013	-0.942	0.374	581	286	19.7%	0.39 [0.19 , 0.81]
Radonovich 2019	-0.01	0.035	2243	2446	41.0%	0.99 [0.92 , 1.06]
Subtotal (95% CI)			**4289**	**3510**	**100.0%**	**0.70 [0.45 , 1.10]**
Heterogeneity: Tau² = 0.13; Chi² = 8.37, df = 3 (P = 0.04); I² = 64%						
Test for overall effect: Z = 1.54 (P = 0.12)						
2.1.2 Influenza-like illness						
Loeb 2009	-1.496	0.81	210	212	2.0%	0.22 [0.05 , 1.10]
MacIntyre 2009	-0.306	0.45	92	94	6.6%	0.74 [0.30 , 1.78]
MacIntyre 2011	-0.654	0.817	949	492	2.0%	0.52 [0.10 , 2.58]
MacIntyre 2013	0.04	0.7	1097	572	2.7%	1.04 [0.26 , 4.10]
Radonovich 2019	-0.151	0.124	2243	2446	86.7%	0.86 [0.67 , 1.10]
Subtotal (95% CI)			**4591**	**3816**	**100.0%**	**0.82 [0.66 , 1.03]**
Heterogeneity: Tau² = 0.00; Chi² = 3.19, df = 4 (P = 0.53); I² = 0%						
Test for overall effect: Z = 1.68 (P = 0.09)						
2.1.3 Laboratory-confirmed influenza						
Loeb 2009	-0.031	0.186	210	212	27.7%	0.97 [0.67 , 1.40]
MacIntyre 2009 (2)	0.31	0.94	92	94	1.2%	1.36 [0.22 , 8.61]
MacIntyre 2011	-1.171	0.74	949	492	1.9%	0.31 [0.07 , 1.32]
MacIntyre 2013	0.96	1.59	1097	572	0.4%	2.61 [0.12 , 58.93]
Radonovich 2019	0.166	0.11	2243	2446	68.8%	1.18 [0.95 , 1.46]
Subtotal (95% CI)			**4591**	**3816**	**100.0%**	**1.10 [0.90 , 1.34]**
Heterogeneity: Tau² = 0.00; Chi² = 4.15, df = 4 (P = 0.39); I² = 4%						
Test for overall effect: Z = 0.89 (P = 0.37)						



Footnotes

(1) MacIntyre 2013 includes 2 comparisons: N95 vs surgical masks and targeted N95 vs surgical masks

(2) MacIntyre 2009 reported on outcome laboratory confirmed infections

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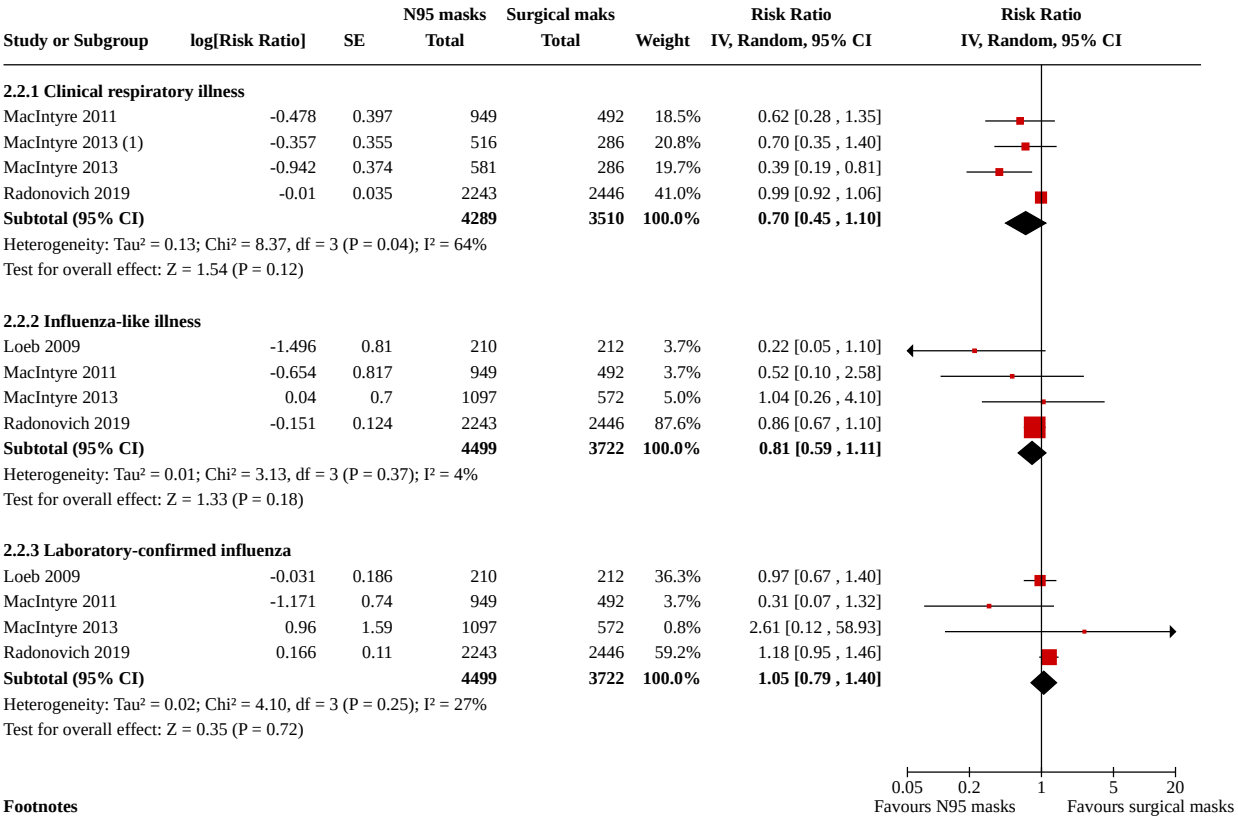
Analysis 2.2. Comparison 2: Randomised trials: N95 respirators compared to medical/surgical masks, Outcome 2: Viral illness in healthcare workers



Footnotes

(1) MacIntyre 2013 includes 2 comparisons: N95 vs surgical masks and targeted N95 vs surgical masks

Comparison 3. Randomised trials: hand hygiene compared to control

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3.1 Viral illness	19		Risk Ratio (IV, Random, 95% CI)	Subtotals only
3.1.1 Acute respiratory illness	9	52105	Risk Ratio (IV, Random, 95% CI)	0.86 [0.81, 0.90]
3.1.2 Influenza-like illness	11	34503	Risk Ratio (IV, Random, 95% CI)	0.94 [0.81, 1.09]
3.1.3 Laboratory-confirmed influenza	8	8332	Risk Ratio (IV, Random, 95% CI)	0.91 [0.63, 1.30]
3.2 ARI or ILI or influenza (including outcome with most events from each study)	19	71210	Risk Ratio (IV, Random, 95% CI)	0.89 [0.83, 0.94]
3.3 Influenza or ILI: sensitivity analysis including outcomes with the most precise and unequivocal definitions	12	28205	Risk Ratio (IV, Random, 95% CI)	0.88 [0.77, 1.02]

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Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3.4 ARI or ILI or influenza: subgroup analysis	19	71210	Risk Ratio (IV, Random, 95% CI)	0.89 [0.83, 0.94]
3.4.1 Children	11	29259	Risk Ratio (IV, Random, 95% CI)	0.91 [0.84, 0.98]
3.4.2 Adults	8	41951	Risk Ratio (IV, Random, 95% CI)	0.84 [0.78, 0.91]
3.5 Absenteeism	3	3150	Risk Ratio (IV, Random, 95% CI)	0.64 [0.58, 0.71]

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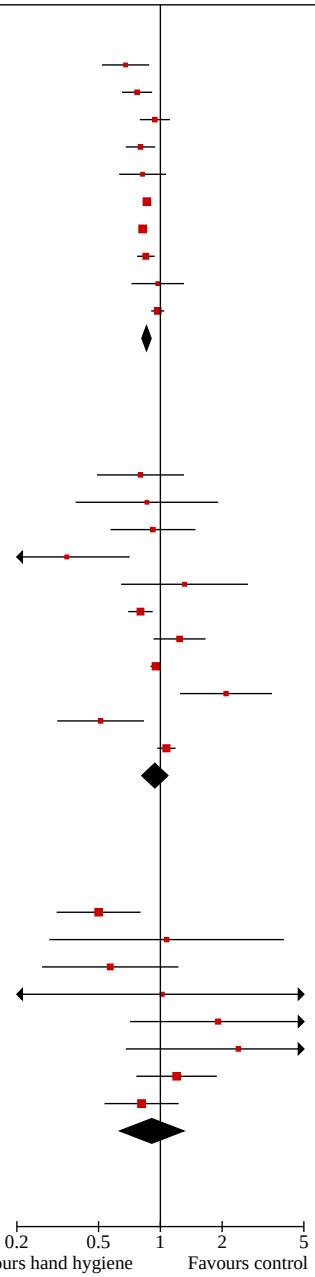
Analysis 3.1. Comparison 3: Randomised trials: hand hygiene compared to control, Outcome 1: Viral illness

Study or Subgroup	log[Risk Ratio]	SE	Hand hygiene Total	Control Total	Weight	Risk Ratio IV, Random, 95% CI
3.1.1 Acute respiratory illness						
Ashraf 2020	-0.39	0.135	588	1123	3.3%	0.68 [0.52 , 0.88]
Azor-Martinez 2018 (1)	-0.261	0.086	339	149	6.7%	0.77 [0.65 , 0.91]
Azor-Martinez 2018	-0.062	0.086	274	149	6.7%	0.94 [0.79 , 1.11]
Correa 2012	-0.223	0.084	794	933	6.9%	0.80 [0.68 , 0.94]
Larson 2010	-0.199	0.134	946	904	3.3%	0.82 [0.63 , 1.07]
Little 2015	-0.151	0.02	8241	8667	20.5%	0.86 [0.83 , 0.89]
Millar 2016	-0.198	0.016	10000	10000	21.4%	0.82 [0.80 , 0.85]
Nicholson 2014	-0.163	0.05	847	833	12.6%	0.85 [0.77 , 0.94]
Sandora 2005	-0.03	0.15	602	451	2.7%	0.97 [0.72 , 1.30]
Swarthout 2020	-0.03	0.037	1496	4769	15.9%	0.97 [0.90 , 1.04]
Subtotal (95% CI)			**24127**	**27978**	**100.0%**	**0.86 [0.81 , 0.90]**
Heterogeneity: Tau² = 0.00; Chi² = 24.86, df = 9 (P = 0.003); I² = 64%						
Test for overall effect: Z = 5.93 (P < 0.00001)						
3.1.2 Influenza-like illness						
Biswas 2019	-0.223	0.249	5077	5778	6.2%	0.80 [0.49 , 1.30]
Cowling 2008	-0.151	0.408	84	205	2.8%	0.86 [0.39 , 1.91]
Cowling 2009	-0.083	0.243	257	279	6.4%	0.92 [0.57 , 1.48]
Hubner 2010	-1.05	0.36	64	65	3.5%	0.35 [0.17 , 0.71]
Larson 2010	0.271	0.363	946	904	3.5%	1.31 [0.64 , 2.67]
Little 2015	-0.223	0.07	8241	8667	17.0%	0.80 [0.70 , 0.92]
Ram 2015	0.215	0.149	193	184	11.1%	1.24 [0.93 , 1.66]
Roberts 2000	-0.051	0.03	299	259	19.4%	0.95 [0.90 , 1.01]
Simmerman 2011	0.737	0.263	292	302	5.7%	2.09 [1.25 , 3.50]
Teesing 2021	-0.67	0.248	976	886	6.2%	0.51 [0.31 , 0.83]
Zomer 2015	0.068	0.052	278	267	18.2%	1.07 [0.97 , 1.19]
Subtotal (95% CI)			**16707**	**17796**	**100.0%**	**0.94 [0.81 , 1.09]**
Heterogeneity: Tau² = 0.03; Chi² = 38.62, df = 10 (P < 0.0001); I² = 74%						
Test for overall effect: Z = 0.83 (P = 0.41)						
3.1.3 Laboratory-confirmed influenza						
Biswas 2019	-0.693	0.24	508	689	19.8%	0.50 [0.31 , 0.80]
Cowling 2008	0.07	0.671	84	205	6.0%	1.07 [0.29 , 4.00]
Cowling 2009	-0.562	0.39	257	279	12.7%	0.57 [0.27 , 1.22]
Hubner 2010	0.02	0.834	64	65	4.2%	1.02 [0.20 , 5.23]
Larson 2010	0.648	0.504	946	904	9.2%	1.91 [0.71 , 5.13]
Ram 2015	0.875	0.644	193	184	6.4%	2.40 [0.68 , 8.48]
Simmerman 2011	0.182	0.23	292	302	20.4%	1.20 [0.76 , 1.88]
Stebbins 2011	-0.211	0.212	1695	1665	21.4%	0.81 [0.53 , 1.23]
Subtotal (95% CI)			**4039**	**4293**	**100.0%**	**0.91 [0.63 , 1.30]**
Heterogeneity: Tau² = 0.11; Chi² = 13.58, df = 7 (P = 0.06); I² = 48%						
Test for overall effect: Z = 0.53 (P = 0.60)						



Footnotes

(1) Azor 2018 included 2 hand-washing groups: one using soap and water (RR 0.94) and the other using hand sanitizer (RR 0.77)

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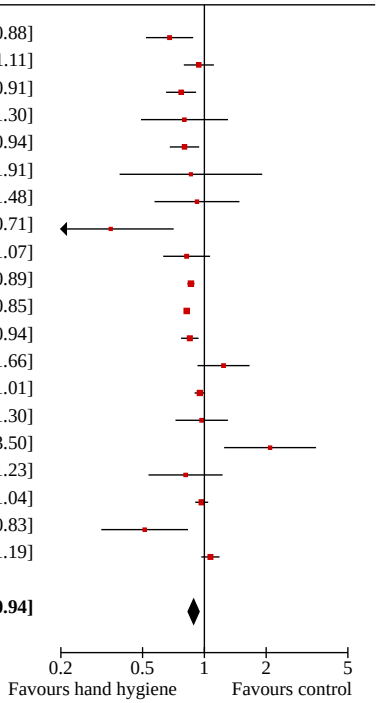
Analysis 3.2. Comparison 3: Randomised trials: hand hygiene compared to control, Outcome 2: ARI or ILI or influenza (including outcome with most events from each study)

Study or Subgroup	log[Risk Ratio]	SE	Hand hygiene Total	Control Total	Weight	Risk Ratio IV, Random, 95% CI
Ashraf 2020	-0.39	0.135	588	1123	3.7%	0.68 [0.52 , 0.88]
Azor-Martinez 2018 (1)	-0.062	0.086	274	149	6.1%	0.94 [0.79 , 1.11]
Azor-Martinez 2018	-0.261	0.086	339	149	6.1%	0.77 [0.65 , 0.91]
Biswas 2019	-0.223	0.249	5077	5778	1.4%	0.80 [0.49 , 1.30]
Correa 2012	-0.223	0.084	794	933	6.3%	0.80 [0.68 , 0.94]
Cowling 2008	-0.151	0.408	84	205	0.6%	0.86 [0.39 , 1.91]
Cowling 2009	-0.083	0.243	257	279	1.5%	0.92 [0.57 , 1.48]
Hubner 2010	-1.05	0.36	64	65	0.7%	0.35 [0.17 , 0.71]
Larson 2010	-0.199	0.134	946	904	3.7%	0.82 [0.63 , 1.07]
Little 2015	-0.151	0.02	8241	8667	10.8%	0.86 [0.83 , 0.89]
Millar 2016	-0.198	0.016	10000	10000	11.0%	0.82 [0.80 , 0.85]
Nicholson 2014	-0.163	0.05	847	833	8.8%	0.85 [0.77 , 0.94]
Ram 2015	0.215	0.149	193	184	3.2%	1.24 [0.93 , 1.66]
Roberts 2000	-0.051	0.03	299	259	10.2%	0.95 [0.90 , 1.01]
Sandora 2005	-0.03	0.15	602	451	3.2%	0.97 [0.72 , 1.30]
Simmerman 2011	0.737	0.263	292	302	1.3%	2.09 [1.25 , 3.50]
Stebbins 2011	-0.211	0.212	1695	1665	1.8%	0.81 [0.53 , 1.23]
Swarthout 2020	-0.03	0.037	1496	4769	9.8%	0.97 [0.90 , 1.04]
Teesing 2021	-0.67	0.248	976	886	1.4%	0.51 [0.31 , 0.83]
Zomer 2015	0.068	0.052	278	267	8.6%	1.07 [0.97 , 1.19]
Total (95% CI)			**33342**	**37868**	**100.0%**	**0.89 [0.83 , 0.94]**

Heterogeneity: Tau² = 0.01; Chi² = 83.20, df = 19 (P < 0.00001); I² = 77%
Test for overall effect: Z = 3.83 (P = 0.0001)
Test for subgroup differences: Not applicable

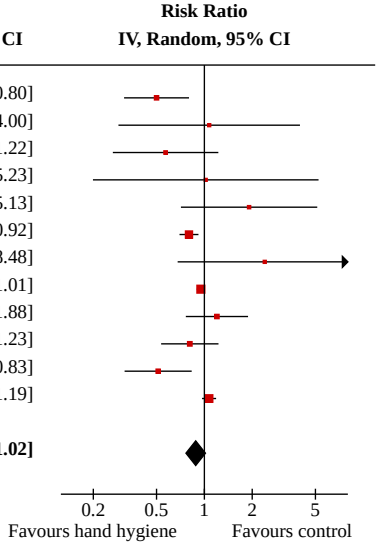


Footnotes
(1) Azor 2018 included 2 treatment groups: soap and water (RR 0.94); and hand sanitizer (RR 0.77)

Analysis 3.3. Comparison 3: Randomised trials: hand hygiene compared to control, Outcome 3: Influenza or ILI: sensitivity analysis including outcomes with the most precise and unequivocal definitions

Study or Subgroup	log[Risk Ratio]	SE	Hand hygiene Total	Control Total	Weight	Risk Ratio IV, Random, 95% CI
Biswas 2019	-0.693	0.24	508	689	6.6%	0.50 [0.31 , 0.80]
Cowling 2008	0.07	0.671	84	205	1.1%	1.07 [0.29 , 4.00]
Cowling 2009	-0.562	0.39	257	279	3.0%	0.57 [0.27 , 1.22]
Hubner 2010	0.02	0.834	64	65	0.7%	1.02 [0.20 , 5.23]
Larson 2010	0.648	0.504	946	904	1.9%	1.91 [0.71 , 5.13]
Little 2015	-0.223	0.07	8241	8667	19.7%	0.80 [0.70 , 0.92]
Ram 2015	0.875	0.644	193	184	1.2%	2.40 [0.68 , 8.48]
Roberts 2000	-0.051	0.03	299	259	23.3%	0.95 [0.90 , 1.01]
Simmerman 2011	0.182	0.23	292	302	7.0%	1.20 [0.76 , 1.88]
Stebbins 2011	-0.211	0.212	1695	1665	7.8%	0.81 [0.53 , 1.23]
Teesing 2021	-0.67	0.248	976	886	6.3%	0.51 [0.31 , 0.83]
Zomer 2015	0.068	0.052	278	267	21.5%	1.07 [0.97 , 1.19]
Total (95% CI)			**13833**	**14372**	**100.0%**	**0.88 [0.77 , 1.02]**

Heterogeneity: Tau² = 0.02; Chi² = 31.95, df = 11 (P = 0.0008); I² = 66%
Test for overall effect: Z = 1.75 (P = 0.08)
Test for subgroup differences: Not applicable



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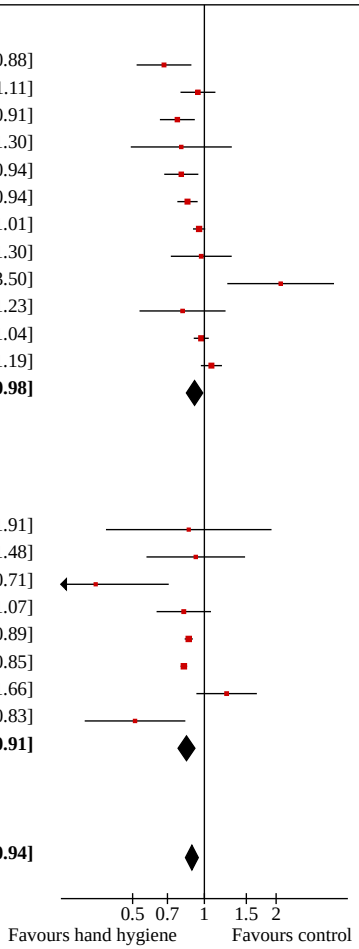
Analysis 3.4. Comparison 3: Randomised trials: hand hygiene compared to control, Outcome 4: ARI or ILI or influenza: subgroup analysis

Study or Subgroup	log[Risk Ratio]	SE	Hand hygiene Total	Control Total	Weight	Risk Ratio IV, Random, 95% CI
3.4.1 Children						
Ashraf 2020	-0.39	0.135	588	1123	3.7%	0.68 [0.52 , 0.88]
Azor-Martinez 2018	-0.062	0.086	274	149	6.1%	0.94 [0.79 , 1.11]
Azor-Martinez 2018 (1)	-0.261	0.086	339	149	6.1%	0.77 [0.65 , 0.91]
Biswas 2019	-0.223	0.249	5077	5778	1.4%	0.80 [0.49 , 1.30]
Correa 2012	-0.223	0.084	794	933	6.3%	0.80 [0.68 , 0.94]
Nicholson 2014	-0.163	0.05	847	833	8.8%	0.85 [0.77 , 0.94]
Roberts 2000	-0.051	0.03	299	259	10.2%	0.95 [0.90 , 1.01]
Sandora 2005	-0.03	0.15	602	451	3.2%	0.97 [0.72 , 1.30]
Simmerman 2011	0.737	0.263	292	302	1.3%	2.09 [1.25 , 3.50]
Stebbins 2011	-0.211	0.212	1695	1665	1.8%	0.81 [0.53 , 1.23]
Swarthout 2020	-0.03	0.037	1496	4769	9.8%	0.97 [0.90 , 1.04]
Zomer 2015	0.068	0.052	278	267	8.6%	1.07 [0.97 , 1.19]
Subtotal (95% CI)			**12581**	**16678**	**67.2%**	**0.91 [0.84 , 0.98]**
Heterogeneity: Tau² = 0.01; Chi² = 36.24, df = 11 (P = 0.0002); I² = 70%						
Test for overall effect: Z = 2.36 (P = 0.02)						
3.4.2 Adults						
Cowling 2008	-0.151	0.408	84	205	0.6%	0.86 [0.39 , 1.91]
Cowling 2009	-0.083	0.243	257	279	1.5%	0.92 [0.57 , 1.48]
Hubner 2010	-1.05	0.36	64	65	0.7%	0.35 [0.17 , 0.71]
Larson 2010	-0.199	0.134	946	904	3.7%	0.82 [0.63 , 1.07]
Little 2015	-0.151	0.02	8241	8667	10.8%	0.86 [0.83 , 0.89]
Millar 2016	-0.198	0.016	10000	10000	11.0%	0.82 [0.80 , 0.85]
Ram 2015	0.215	0.149	193	184	3.2%	1.24 [0.93 , 1.66]
Teesing 2021	-0.67	0.248	976	886	1.4%	0.51 [0.31 , 0.83]
Subtotal (95% CI)			**20761**	**21190**	**32.8%**	**0.84 [0.78 , 0.91]**
Heterogeneity: Tau² = 0.00; Chi² = 20.32, df = 7 (P = 0.005); I² = 66%						
Test for overall effect: Z = 4.17 (P < 0.0001)						
Total (95% CI)			**33342**	**37868**	**100.0%**	**0.89 [0.83 , 0.94]**
Heterogeneity: Tau² = 0.01; Chi² = 83.20, df = 19 (P < 0.00001); I² = 77%						
Test for overall effect: Z = 3.83 (P = 0.0001)						
Test for subgroup differences: Chi² = 1.83, df = 1 (P = 0.18), I² = 45.2%						

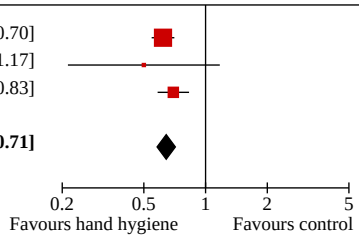


Footnotes

(1) Azor 2018 includes 2 intervnetion groups: soap and water (RR 0.94) and hand sanitizer (RR 0.77)

Analysis 3.5. Comparison 3: Randomised trials: hand hygiene compared to control, Outcome 5: Absenteeism

Study or Subgroup	log[Risk Ratio]	SE	Hand Hygiene Total	Control Total	Weight	Risk Ratio IV, Random, 95% CI
Azor-Martinez 2016	-0.478	0.065	621	720	64.8%	0.62 [0.55 , 0.70]
Hubner 2010	-0.693	0.435	64	65	1.4%	0.50 [0.21 , 1.17]
Nicholson 2014	-0.362	0.09	847	833	33.8%	0.70 [0.58 , 0.83]
Total (95% CI)			**1532**	**1618**	**100.0%**	**0.64 [0.58 , 0.71]**
Heterogeneity: Tau² = 0.00; Chi² = 1.43, df = 2 (P = 0.49); I² = 0%						
Test for overall effect: Z = 8.45 (P < 0.00001)						
Test for subgroup differences: Not applicable						



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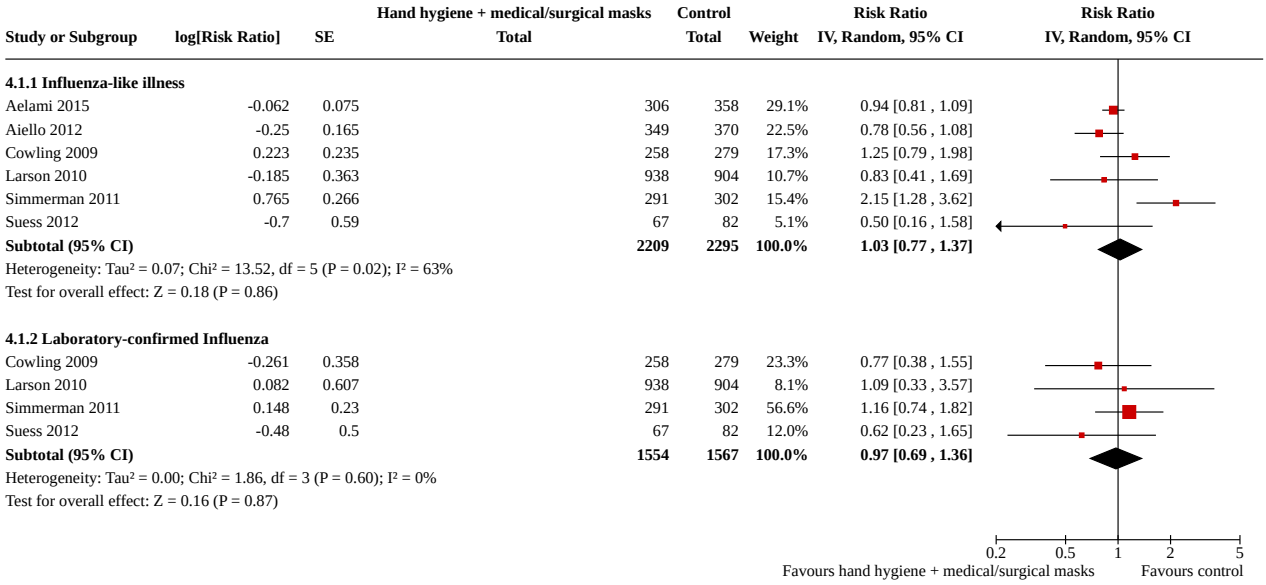
Comparison 4. Randomised trials: hand hygiene + medical/surgical masks compared to control

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
4.1 Viral illness	6		Risk Ratio (IV, Random, 95% CI)	Subtotals only
4.1.1 Influenza-like illness	6	4504	Risk Ratio (IV, Random, 95% CI)	1.03 [0.77, 1.37]
4.1.2 Laboratory-confirmed Influenza	4	3121	Risk Ratio (IV, Random, 95% CI)	0.97 [0.69, 1.36]

Analysis 4.1. Comparison 4: Randomised trials: hand hygiene + medical/surgical masks compared to control, Outcome 1: Viral illness



Comparison 5. Randomised trials: hand hygiene + medical/surgical masks compared to hand hygiene

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
5.1 Viral illness	3		Risk Ratio (IV, Random, 95% CI)	Subtotals only
5.1.1 Influenza-like illness	3	2982	Risk Ratio (IV, Random, 95% CI)	1.03 [0.69, 1.53]
5.1.2 Laboratory-confirmed influenza	3	2982	Risk Ratio (IV, Random, 95% CI)	0.99 [0.69, 1.44]

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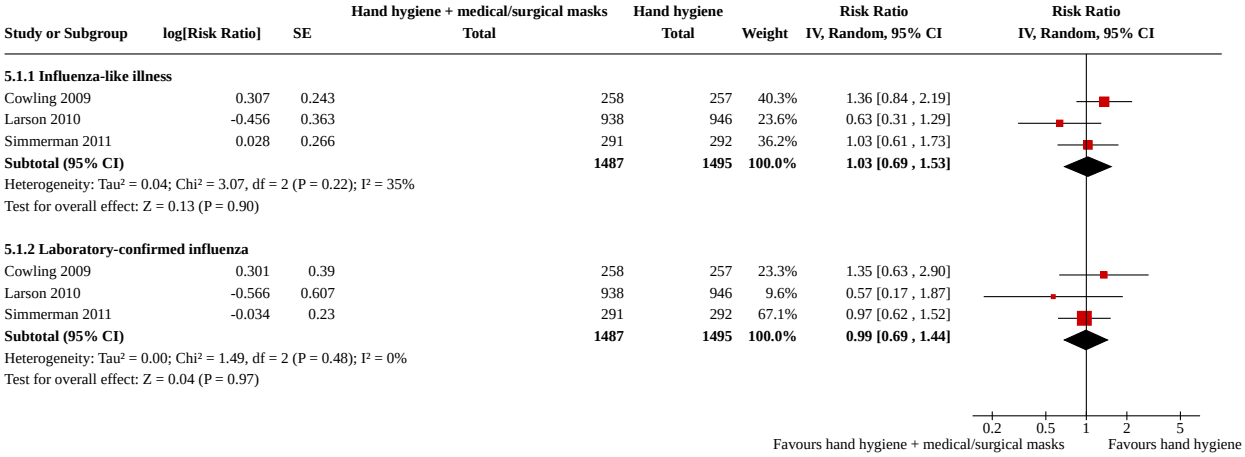
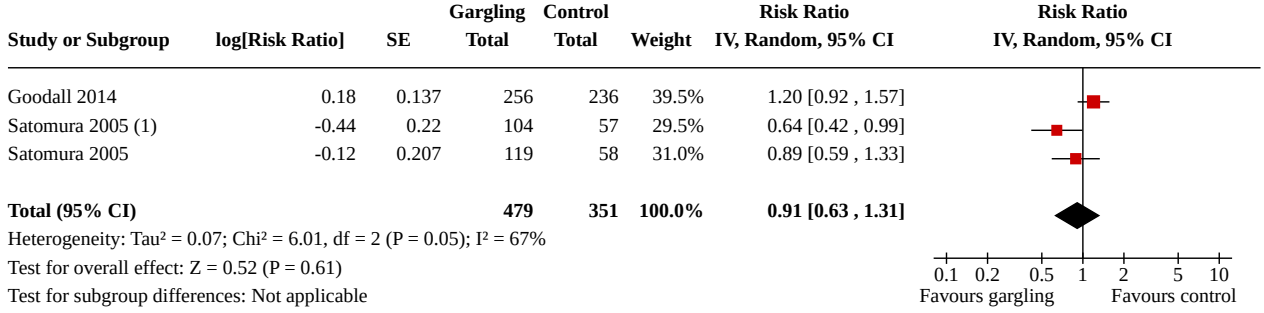
Analysis 5.1. Comparison 5: Randomised trials: hand hygiene + medical/surgical masks compared to hand hygiene, Outcome 1: Viral illness



Comparison 6. Randomised trials: gargling compared to control

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
6.1 Viral illness	2	830	Risk Ratio (IV, Random, 95% CI)	0.91 [0.63, 1.31]
6.2 SARS-CoV-2	2	394	Risk Ratio (IV, Random, 95% CI)	0.07 [0.02, 0.23]

Analysis 6.1. Comparison 6: Randomised trials: gargling compared to control, Outcome 1: Viral illness



Footnotes

(1) Satomura 2005 included 2 intervention groups

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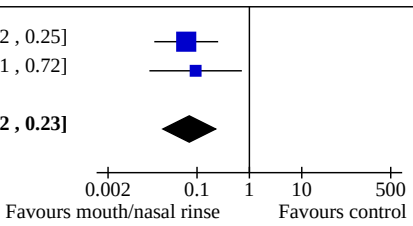
Analysis 6.2. Comparison 6: Randomised trials: gargling compared to control, Outcome 2: SARS-CoV-2

Study or Subgroup	Mouth/nose rinse Events	Total	Control Events	Total	Weight	Risk Ratio IV, Random, 95% CI
Almanza-Reyes 2021	2	114	33	117	67.7%	0.06 [0.02 , 0.25]
Gutiérrez-García 2022	1	84	10	79	32.3%	0.09 [0.01 , 0.72]
Total (95% CI)		**198**		**196**	**100.0%**	**0.07 [0.02 , 0.23]**
Total events:	3		43			

Heterogeneity: Tau² = 0.00; Chi² = 0.11, df = 1 (P = 0.74); I² = 0%
Test for overall effect: Z = 4.49 (P < 0.00001)
Test for subgroup differences: Not applicable



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ADDITIONAL TABLES

Table 1. Description of interventions in included studies, using the items from the Template for Intervention Description and Replication (TIDieR) checklist

Author, year	Brief name	Recipient	Why	What (materials)	What (procedures)	Who provided	How	Where	When and how much	Tailoring	Modification of intervention throughout trial	Strategies to improve or maintain intervention fidelity	Extent of intervention fidelity
Masks compared to either no masks or different mask types													
Abaluck 2022 (additional sources: Abaluck 2021a, Abaluck 2021b, Kwong 2021)	Community-level mask promotion and distribution of free masks. A. Cloth masks or B. Surgical masks with possible additional village level elements: i) incentive	Leaders and adult householders of rural and peri-urban villages	Increase large-scale adoption and proper wearing of face masks to slow the spread of COVID-19 and save lives informed by research in public health, psychology, eco-	Masks colour-coded by households, either: A. cloth masks: an exterior layer of 100% non-woven polypropylene (70 grams/m^2 [gsm]), 2 interior layers of 60% cotton/40% polyester interlocking knit (190 gsm), an elastic loop that goes around the head above and below the ears, and a nose bridge; filtration efficiency: 37%[1] B. 3 layers of 100% non woven polypropy-	All villages: 1. household distribution of surgical or cloth masks and showing of mask-wearing video; 2. distribution and promotion of masks at village markets; 3. mask distribution at mosques; 4. mask promotion in public spaces; 5. role modelling and advocacy by local leaders, including Imams during Friday prayers using a scripted speech. Periodic monitoring of passers-by and reminding people to put on masks	Local NGO staff and volunteers (Bangladesh NGO Green-Voice)[5] and Innovations for Poverty Action (IPA) Village Imams and police officers No "spe-	Masks and promotion delivered face to face in households, markets, mosques and streets of villages both as groups and individually Text messages delivered by	Households, markets, mosques and streets of 572 villages (in rural Bangladesh)	8 weeks per village rolled out over a 6 week period (November 2020 to January 2021) 1 day of training per village Once off mask distribution and promotion at households (4 days / village)	Periodic monitoring and then additional training of staff provided as needed Different locations and timing of observation across different days	In the first 5 weeks of the study staff found low engagement in some villages with local mask use, so mask promotion staff were retrained by researcher partway through the in-	Numbers of masks distributed was noted Promoters periodically monitored passers-by and reminded peoople to put on masks Direct surveillance of mask wearing, correct mask-	Numbers of masks distributed: A. 370,643 B. 924,849 Mask-wearing: IGs: 42.3% CG: 13.3% Increase was largest in mosques (37% points) and 25% to 29% points in

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Table 1. Description of interventions in included studies, using the items from the Template for Intervention Description and Replication (TIDieR) checklist *(Continued)*

	ii) signage iii) text message reminder and household elements: i) altruism or self-protection messages ii) amount of households receiving texts iii) commitment to mask-wearing	nomics, marketing, and other social sciences on product promotion and dissemination strategies	lene[2], elastic ear loops, and a nose bridge; filtration efficiency: 95%. Sticker that had a logo of a mask with an outline of the Bangladeshi flag and a phrase in Bengali that noted the mask could be washed and reused[3]; filtration efficiency of 76% Initial 3 masks per household Video of notable public figures[4] discussing why, how, and when to wear a mask Brochure based on WHO materials depicting proper mask-wearing Scripted speeches for	Some villages: village police accompanying mask promoters, providing monetary rewards or certificates to villages if mask-wearing rate improves. Some villages: public signalling of mask-wearing via signage, text message reminders, messaging emphasizing either altruistic or self-protection motives for mask-wearing, and extracting verbal commitments from households. Modelling of safe mask wearing by study staff Detailed procedures outlined in online protocol supplement osf.io/23mws/	cialized skills" needed as intervention designed to be easily adopted by other NGOs or agencies Training of staff provided by researchers for mask promotion	phone and individually	Mask distribution 3 to 6 days / week at markets and on 3 Fridays at mosques during the first 4 weeks Weekly or biweekly mask promotion Role-modelling and leader advocacy at Friday prayers Periodic monitoring: 1/ week on weeks 1, 2, 4, 6, 8, and 10;	tervention "to work more closely with local leaders and set specific milestones for that partnership" After 5 weeks, monitoring of mask-wearing was limited to those who appeared to be 18 years or older.	wearing (wearing either a project mask or an alternative face-covering over the mouth and nose) and physical distancing (if s/he was at least one arm's length away from the nearest person)[6] Monetary rewards or certificates to villages if mask-wearing rate improved Additional training	other locations Proper mask-wearing increased by 29.0% Physical distancing increased from 24.1% in CG villages to 29.2% in IG villages No difference between IGs and CGs in number of people observed in public areas, as an indication of social distancing.

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Table 1. Description of interventions in included studies, using the items from the Template for Intervention Description and Replication (TIDieR) checklist *(Continued)*

	use by role models and local leaders at Friday prayers		daily schedule provided in Protocol – 1 hour per site for 9 sites 8am to 5pm		for mask promotion staff	
	Scripted text messages				Recording of activities undertaken by intervention staff including the degree to which leaders or imams understood the script, sites observed etc (see p.9 of Protocol osf.io/23mws/) "consistent with the WHO guideline that defines physical distancing as one meter of separation."
	Monetary rewards (USD 190) or non-monetary reward (certificate) for villages		Each village observed on 2 alternating days of the week.			
	Signage for household doors declaring they are a mask-wearing household		Observations occurred 7 days of the week (9 am to 7 pm)			
	Smart phone for delivery and receipt of text message reminders		Detailed schedules provided in online protocol supplement via osf.io/23mws/			
	Loudspeaker for announcements in markets by research staff					

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							Masks woven by and procured from local Bangladeshi garment factories within 6 weeks after ordering: $0.50 per cloth mask and $0.13 per surgical mask
							Masks and hand sanitiser for staff delivering intervention Costs: Cloth masks: $275.10/village Surgical masks: $88.90/village PPE for staff: $70/village Media costs: $100/village Transport and other costs: $30/village
							Handouts and written and some audio scripts for role

www.who.int/western-pacific/emergencies/covid-19/information/physical-distancing (accessed 13 June 2022).

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Table 1. Description of interventions in included studies, using the items from the Template for Intervention Description and Replication (TIDieR) checklist *(Continued)*

				models, leaders, surveillance officers and texts etc provided by the research team and in online protocol supplement via osf.io/23mws/									
Alfelali 2020	Face masks	Hajj pilgrims aged ≥ 18 years	Prevent and control viral respiratory infections at mass gatherings	50 surgical face masks per participant (3M™ Standard Tie-On surgical mask, Cat No: 1816) Written instructions for mask use (See S1 Appendix)	Provide masks and verbal and printed instructions, rules for mask use and demonstration of appropriate mask usage provided (See S1 Appendix) Rules for mask use: • "Try to avoid touching the front of the mask. • Change your mask if it is damp, wet or dirty. • Always clean your hands before and after changing the masks. • Put used masks in a plastic bag and throw it into a rubbish bin. You will find bins somewhere close to your tent in Mina."	464 volunteer trained research team members approached pilgrims in their tents Training included how to approach pilgrims and explanation and demonstration of	Individually and face to face to groups of pilgrims in tents	Tents of pilgrims for Hajj in Makkah (Saudi Arabia) 50 to 150 pilgrims per large tent, sleeping head-to-head and sharing meals and rites	Mask wearing for 24 hours if possible, over days of Hajj season inside and outside assigned tents 3 consecutive Hajj seasons (5 to 6 days, October 2013 to 2015)	Written information provided in preferred language (Arabic or English) Pilgrims who used at least 1 mask each day were considered to have used the mask during that day (i.e.	None described	4 day diaries of mask use: number of masks used and hours worn each day (see S1 Appendix)	Mask use: IG: Daily: 24.7% Intermittently: 47.7% None: 20.9% CG: Daily: 14.3% Intermittently: 34.9% None: 43.7% Mask use of at least 4 hours consistently greater

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Table 1. Description of interventions in included studies, using the items from the Template for Intervention Description and Replication (TIDieR) checklist *(Continued)*

						mask use				could be < 24 hours)			in IG than CG
Barasheed 2014	Supervised mask use	Religious pilgrims ≥ 15 years	Prevent respiratory virus infections at mass gatherings through mask use	Plain surgical face masks (3M Standard Tie-On Surgical Mask, Cat No: 1816) manufactured by 3M company, USA; 5 masks per day Written instructions on face mask use Special polythene bags for disposal	Masks provided to index case and their contacts with advice on mask use (before prayers, in seminars, and after meals). Written instructions provided on face mask use, need to change them, and disposal.	Not described, presumably the medical researchers	Face-to-face provision of masks, instructions, and reminders	Tents of pilgrimage site (Mina Valley, Saudi Arabia)	Advice on mask use given throughout pilgrimage stay (5 days)	None reported.	None reported.	The medical researchers followed pilgrims each day to remind participants about recording their mask usage in health diary.	Face mask use: mask group: 56/75 (76%), control group: 11/89 (12%) (P < 0.001) 76% of intervention tents wore masks. 10 of 75 (13%) pilgrims in 'mask' tents wore face masks during sleep.
Bundgaard 2021 (additional source- Bundgaard 2020)	Face masks (surgical)	Community-dwelling adults aged 18 years or older with inter-	Reduce wearers' risk for SARS-CoV-2 infection out-	Per participant: 50 x 3-layer, disposable, surgical face masks with ear loops (TYPE II EN 14683 (Abena, Denmark); filtration rate,	Supply of masks sent to home address by courier Provision of written instructions sent by courier about how and when to wear masks including	Researchers provided the masks (funded by Salling Group), in-	Individually by mail, email, online and telephone	Mask wearing: when outside the home - and in the	Mask wearing: whenever outside the home or when guests in the home,	Changing of mask if worn for more than 8 hours	None described	Face mask adherence: Self-report (Yes / Partial / No) (Suppl 4)	Face mask adherence: % Adhere: 46% Partial: 47% No: 7%

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Table 1. Description of interventions in included studies, using the items from the Template for Intervention Description and Replication (TIDieR) checklist *(Continued)*

	net access	side the home through protection of the nose and mouth from droplets or aerosols or contaminated fingers and hands	98%; made in China) 1 badge (saying: "I am testing face masks – for you and me") Written instructions and instructional videos for proper use of masks (See supplement 8) of published paper including link to video for proper face mask use [in Danish] vimeo.com/406952695	links to instructional video for face mask use Instruction to follow advice of local health authorities (in Denmark) Provision of follow-up support by email and a phone help-line for questions	structions and follow-up support Background and training of researcher not described Hotline provided medical expertise and guidance, (qualification and training needed for this support not specified)	home when they had guests (in Denmark) Instructions and support at home and online	up to 8 hours for 1 mask, for 1 month (April to May 2020) 1 off instructions for mask use and again as needed Weekly follow-up emails Hotline available at all times during study period	If guests in the home, wear mask Individualised support as needed via email or telephone	Average mask use per day Self-assessed adherence with health authority guideline on social distancing and hygiene (Suppl)	Mean face masks used: Weekdays: 1.7 Weekends: 1.3 Health authority guidance adherence not reported

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Canini 2010	Surgical face masks	Householders (over 5 years)	Limit transmission of influenza transmission by large droplets produced during coughing in households	Initial supply of 30 masks: for adults and children > 10: surgery masks with ear loops, 3 plys, anti fog (AEROKYN, LCH medical products, Paris, France) Children 5 to 10: face mask KC47127, (Kimberly-Clark, Dallas, TX, USA) Closed plastic bags for disposal	Masks given immediately on home visit by attending general practitioner with demonstration of proper use and instruction to be worn for 5 days in presence of another household member or in confined space (e.g. car) and to change every 3 hours or if damaged.	General practitioners	Face-to-face individually	Households in France	One-off provision of masks worn for 5 days	None described.	None described.	Not described, but reported mask usage was measured	34/51 (66%) wore masks > 80% of the duration. Reported mask-wearing: 11 ± 7.2 masks during 4.0 ± 1.6 days with an average use of 2.5 ± 1.3 masks per day and duration of use of 3.7 ± 2.7 hours/day
Jacobs 2009	Face masks	Hospital healthcare providers (nurses, doctors, and co-medical personnel)	Decrease risk of infection through limiting droplet spread through masks	Hospital-standard disposable surgical Mask MA-3 (Ozu Sangyo, Tokyo, Japan); quantity not specified	Provision of masks and instructions for use	Not described, presumably research team	Face-to-face	Tertiary care hospital in Tokyo, Japan Face masks worn whilst on hospital property.	77 days	None described.	None described.	Self-reported adherence	Self-reported adherence for both groups reported as good, with full adherence by 84.3% and remainder complying

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Table 1. Description of interventions in included studies, using the items from the Template for Intervention Description and Replication (TIDieR) checklist *(Continued)*

													79.2% to 98.7%.
Loeb 2009	2 active interventions A. surgical masks B. N95 respirators	Healthcare workers (nurses)	Reduce transmission of influenza in healthcare settings through coughing or sneezing with protective masks	A. Surgical masks B. N95 respirators	Provision of masks or N95 respirators Instruction in use and proper placement of devices Fit-testing and demonstration of positioning of N95 using standard protocol and procedure (details provided) Qualitative fit-testing using saccharin or Bitrex protocol[7]	Provided by research team (not further described) Fit-testing by technician for N95	In-person face-to-face	Tertiary hospitals in Ontario, Canada	1 influenza season (12 weeks) Use of mask as required[8] when providing care to or within 1 m of patient with febrile respiratory illness, ≥ 38 °C, and new or worsening cough or shortness of breath Nurses to wear N95 when caring for patients with "febrile respira-	Fit-testing of nurses not already fit-tested	Ceased before end of season	Adherence audits during peak of season by trained auditor who stood short distance from patient isolation room	18 episodes: N95: 6/7 participants (85.7%) wearing assigned device versus 100% for masks

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									tory illness"				
MacIntyre 2009	2 active interventions in addition to infection control guidelines A. Surgical masks (SM) B. P2 masks (P2)	Householders with a child with fever and respiratory symptoms	Prevent or reduce respiratory virus transmission in the community through non-pharmaceutical interventions	A. 3M surgical mask, catalogue no. 1820; St Paul, MN, USA for adults B. P2 masks (3M flat-fold P2 mask, catalogue no. 9320; Bracknell, Berkshire, UK) A and B: health guidelines and pamphlets about infection control	Provision of masks and pamphlets and education about infection prevention and mask use Telephone calls and exit interviews to record adherence to mask use All groups: health guidelines, pamphlets about infection control were provided	Not described, presumably research team	Face-to-face and by telephone	Households in Sydney, Australia	2 winter seasons (3 months and 6 months) 2 weeks of follow-up Masks to be worn at all times when in same room as index child, regardless of distance from child	None described.	None described.	Daily telephone calls to record mask use throughout day Exit interviews about adherence	Reported mask use: Day 1 SM: 36/94 (38%) P2: 42/92 (46%) stated wearing "most or all" of the time. Other participants were wearing face masks rarely or never. Day 5: SM: 29/94 (31%) P2: 23/92 (25%)
MacIntyre 2011	3 active interventions A. Medical masks	Healthcare workers	Protect HCWs by preventing transmis-	Daily supply of A. 3 medical masks (3M medical mask, catalogue number 1820, St Paul, MN, USA)	Supply of masks or respirators. Instruction in when to wear it, correct fitting, and storage (in paper bag in personal locker)	Masks provided to hospitals. Training of	Masks and training provided face-	Emergency departments and respi-	Entire work shift for 4 weeks	Taken off for toilet and meal breaks and at	None described.	Mask/respirator use monitored by: (i) observed	Adherence for usage was high for all and not

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	B. N95 respirators fit-tested C. N95 respirators non-fit-tested		sion of influenza and other respiratory viruses from patients through mask wearing	2 respirators: B. N95 fit-tested mask (3M flat-fold N95 respirator, catalogue number 9132) fit-tested with 3M FT-30 Bitrex Fit Test kit according to manufacturer's instructions (3M, St Paul, MN, USA) C. N95 non-fit-tested mask (3M flat-fold N95 respirator, catalogue number 9132) Diary cards for usage recording	Instruction in importance of hand hygiene before and after removal For fit-tested group: fit-testing procedure	staff provided by 1 member of research team.	to-face, not described if training was individually or in groups.	ratory wards in hospitals in Beijing, China		end of shift		adherence by head ward nurse recorded daily; (ii) self-report diary cards carried during day recording; (i) no. hours; (ii) usage. Exit interviews	significantly different amongst arms. Medical mask: 76%, 5 hours N95 fit-tested: 74%, 5.2 hours N95 non-fit-tested: 68%, 4.9 hours
MacIntyre 2013	3 active interventions A. N95 respirators at all times B. N95 respirators targeted use C. Medical masks	Healthcare workers (nurses and doctors)	Protect HCWs from respiratory infections from patients through mask use	Daily supply of: A. and B. 2 respirators (3M Health Care N95 Particulate Respirator; catalogue number 1860) 3M FT-30 Bitrex Fit Test Kit C. 3 masks 3 masks (3M Standard Tie-On Surgical Mask catalogue number mask 1817; 3M, St Paul, MN, USA) Pocket-sized diary card with	Supply of respirators Instructions in use including times and fit Fit-testing procedure according to the manufacturer's instructions (3M) For targeted N95: checklist of defined high-risk procedures, including common aerosol-generating procedures	3M supplied respirators and masks. Provider of instructions not specified.	Masks and training provided face-to-face, not described if training was individually or in groups.	Emergency departments and respiratory wards of tertiary hospitals in Beijing, China	For 4 weeks, A and B worn at all times on shift; B. targeted (intermittent) use of N95 respirators only whilst performing high-risk procedures or barrier.	None described.	None described.	Self-reported daily record of number of hours worked, mask or respirator use, number of high-risk procedures undertaken collected by study staff.	Adherence highest for targeted N95 (82%; 422/516) versus N95 (57%; 333/581) versus medical mask (66%; 380/572).

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				tick boxes for mask use									
MacIntyre 2015	2 active interventions A. Cloth masks B. Medical masks	Hospital healthcare workers	Prevent respiratory infections in HCWs from patients through mask-wearing	A. 5 cloth masks for study duration (2- layer, cotton) B. 2 medical masks daily for each 8-hour shift for study duration (3 layers, non-woven material) All masks locally manufactured. Written instructions on cleaning cloth masks	Cloth or medical masks to be worn at all times on shift. Cloth masks to be washed with soap and water daily after shifts, and the process of cleaning to be documented. Provision of written instructions for cloth mask cleaning	Researchers arranged supply of masks and instructions and any training of staff assisting the delivery.	Masks and written instructions provided face-to-face.	Hospital wards in Vietnam	4 weeks (25 days) of face mask use	Masks not worn while in the toilet or during tea or lunch breaks.	None described.	Monitored adherence with mask use by self-report diary card and exit survey and interviews with a subsample (ACTRN12610000887077)	Mask-wearing adherence: cloth mask: 56.8% medical mask: 56.6% Reported cloth mask washing: 23/25 days (92%)
MacIntyre 2016	Medical mask use	Sick householders with ILI (index cases) and their well contacts of the same household	Protect well people in the community from transmission of respiratory pathogens by contacts with ILI through mask use	21 medical masks (3M 1817 surgical mask) Diary cards for mask use	Supply of masks Instructions for mask wearing and handwashing protocol Provision of diary cards	Study staff member provided masks and instructions in use.	Masks and instructions provided face-to-face and individually.	Fever clinics of major hospitals in Beijing, China	3 masks/day for 21 days Mask wearing: whenever in the same room as a household member or a visitor to the household Handwashing: before	Allowed to remove their masks during mealtimes and whilst asleep and to cease wearing once symptoms	None reported.	Self-reported daily record of mask use using diary card	Mask use: mask group: 4.4 hours; control group: 1.4 hours

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									putting on and after taking off	resolved		
Radonovich 2019	2 active interventions A. N95 respirators (N95) B. Medical masks (MM)	Healthcare personnel of outpatient sites within medical centres	Prevent HCP from acquiring workplace viral respiratory infections and transmitting them to others by effective respiratory protection by N95 respirators which reduce aerosol exposure and inhalation of small airborne	A. N95 respirators: 3M Corporation 1860, 1860S, and 1870 (St Paul, MN, USA) or Kimberly Clark Technol Fluidshield PFR95-270, PFR95-274 (Dallas, TX, USA) B. Medical mask Precept 15320 (Arden, NC, USA) or Kimberly Clark Technol Fluidshield 47107 (Dallas, TX, USA). Reminder signs posted at each site A portable computer equipped with data recording software (HandyAudit; Toronto, Canada) to document adherence	Participants instructed to wear assigned protective devices whenever they were positioned within 6 feet (1.83 m) of patients with suspected or confirmed respiratory illness and to don a new N95/MM with each patient interaction. Hand hygiene recommended to all participants in accordance with Centers for Disease Control and Prevention guidelines. Infection prevention policies were followed at each study site. Reminder signs posted at sites and emails sent. Annual fit-testing conducted for all participants.	Centres provided device supplied by study to HCP. Study personnel posted reminder signs and emails and conducted adherence observations.	Face-to-face individual provision of devices and adherence observations Onsite posting of signs Other reminders by email	Outpatient sites within medical centres in USA	As instructed, for each new patient interaction during 12-week period of peak viral respiratory illness each year for 4 years (total of 48 weeks)	Fitting of N95 masks	None described.	Reminder signage posted at study sites, and emails sent by study personnel. Self-reported daily device wearing of “always”, “sometimes”, “never”, or “did not recall" Observation of device-wearing behaviours as participants entered and exited care rooms conducted	Device wearing: N95: 89.4% reported “always” or “sometimes” versus MM: 90.2% “Never” N95: 10.2% MM: 9.5%

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			particles, meet filtration requirements, and fit tightly	(Radonovich 2016)	Filtration testing performed on the device models in the study. Further details in protocol (Radonovich 2016).							during unannounced, inconspicuous visits to randomly selected sites documented on portable computer	
Hand hygiene													
Alzaher 2018	Hand hygiene workshop	Primary school girls	Targeted school children to improve hand hygiene to reduce school absences due to upper respiratory infection and spread of infection in	6-minute video-clip of 2 siblings that attended school-based health education about hand hygiene Short interactive lecture about: common infections in schools, methods of transmission, hand-washing procedure using soap and water including when to wash hands	Delivery of workshop and distribution of supporting materials (games and posters) to school and students	Study investigator delivered workshop.	Delivered face-to-face in group format for the workshop	2 primary girls' schools in Saudi Arabia	1-hour once-off workshop; posters and games provided to school	Not described	Not described	Posters in restrooms as reminders of hand-washing hygiene during 5-week follow-up period after workshop	Not reported

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			schools and to families	Puzzle games related to hand hygiene Posters with cartoon princesses' picture promoting hand-washing									
Arbogast 2016	Multimodal hand hygiene intervention programme in addition to control of brief video	Office buildings and the employees of health insurance company	Reduce hand-to-mouth germ transmission from shared workspaces and workplace facilities and thereby healthcare claims and absenteeism through improved workplace hand	Alcohol-based hand sanitiser (PURELL Advanced, GOJO Industries Inc, Akron, OH, USA) installed as wall-mounted dispensers, stands, or free-standing bottles One 8-ounce bottle of hand sanitiser (PURELL Advanced) per cubicle One 100-count canister of hand wipes (PURELL Wipes) per cubicle	Hand hygiene supplies installed in offices. Replenishment product was made easily available to individual employees upon request via a simple process. Monitoring of product shipments into sites Physical collection and full replacement of soap, sanitiser, and wipes Intervention and control group: educational video embedded at end of baseline online knowledge survey	Not described, presumably study investigators arranged installations	Hand hygiene supplies provided in office environments and individually at staff cubicles/offices. Video provided individually via email.	High-traffic common areas of 2 US health insurance company offices (e.g. near elevators, at entrances) and appropriate public spaces (e.g. coffee area, break rooms, conference rooms, training	13.5 months overall One-off email video 11 days before study hand hygiene supplies installed. 13 months of provision of supplies 2 times evening collection and	Sanitiser installed in high-use areas of the offices.	Not described	Employee survey at 4 months included questions about hand hygiene practice adherence. Monitoring of product shipments into the sites and physical collection of the soap, sanitiser, and wipes products 2 times	Intervention group employees: reported 40% more cleaning of work area regularly; significantly more likely to keep the hand sanitiser with them and use it throughout the day; significant increases in hand sanitiser use for at-risk

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	hygiene	Replenishment products stored in supply room (in addition to existing foam hand wash (GOJO Green Certified Foam Handwash) and an alcohol-based hand sanitiser foam wall-mounted dispenser (PURELL, GOJO Industries) already provided near the restroom exits prior to intervention) Identical soap in all restrooms Intervention and control group: brief (< 1-minute educational video) about proper hand hygiene technique, for both washing and sanitising hands	rooms, lobbies, reception areas); individual staff cubicles of mostly open plan offices (average 309 square feet). Office restrooms	full replacement of products	in the study; collected samples were measured and usage rates were estimated	activities[9] Estimated use by average employee from sample collection: sanitiser 1.8 to 3.0 times/day, soap 2.1 to 4.4 times/day, wipes at their desk 1.4 to 1.5 times/week

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Table 1. Description of interventions in included studies, using the items from the Template for Intervention Description and Replication (TIDieR) checklist *(Continued)*

				''Wash Your Hands'', signage promoting hand hygiene adherence, was already posted next to restroom exits at both the control and intervention sites.									
Azor-Martinez 2016	Handwashing programme	Primary school children and their parents and teachers	Prevent transmission of upper respiratory infections in schools and to families through non-pharmaceutical intervention of handwashing programme in schools	Brochure about hand-washing awareness and habits Workshop content materials Stories, songs, and classroom posters about hand hygiene and infection transmission Hand sanitiser (ALCO ALOE GEL hand sanitiser by Americo Govantes Burguete, S.L. Madrid, Spain containing 0.2% chlorhexidine digluconate, 1% phenoxyethanol,	Brochure sent to parents by mail with study information sheet. Workshop provided for pupils and teachers: frequent infections in schools, transmission and prevention, instructions on correct hand-washing (water and soap, soaping > 20 s, drying hands), use of hand sanitisers and possible side effects Classroom activities linked to hand hygiene and infection transmission	Brochure sent by school administration. Workshop and verbal and written information presumably provided by the study research assistant. Classroom	Brochure sent by mail to individual parents. Workshops and classroom activities delivered in groups face-to-face. Teacher reinforcement of hand hy-	Primary school classes in Spain (details not provided)	8 months overall One-off brochure and installation of hand sanitiser dispensers 2-hour workshop held 1 month before study commencement Fortnightly class-	Supervision and administration of hand sanitiser as needed by teachers, especially for younger children	Not described	Daily reinforcement by teachers of hand hygiene Fortnightly support by research assistant promoting handwashing Self-reported correct handwashing procedure (water and soap, soaping	Self-reported correct handwashing included in analysis but not separately reported.

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Table 1. Description of interventions in included studies, using the items from the Template for Intervention Description and Replication (TIDieR) checklist *(Continued)*

				0.1% benzalkonium chloride, 5% aloe barbadensis, 70% denat ethyl alcohol, excipients quantity sufficient for 100 mL alcohol 70%, pH 7.0 to 7.5) Informational poster about when and how to wash hands Written and verbal guidance to teachers, parents, and students on properties, possible side effects, and precautionary measures for gel use and storage	Reinforcement of hand hygiene by teachers Hand sanitiser dispensers fixed to walls with an informational poster about hand-washing Supervision of younger children when using hand sanitiser and administration of sanitiser if needed Instruction of children in hand-washing procedures after toilet and when dirty and correct hand sanitiser use[10]	activities provided by research assistant and teachers. Supervision and administration of hand sanitiser for younger children by teachers	giene provided to class face-to-face. Hand sanitiser use supervision was provided individually and face-to-face.		room activities As required, teacher supervision and administration of hand sanitiser Daily reinforcement of hand hygiene by teachers			> than 20 s, drying hands)	
Azor-Martinez 2018	Educational and hand hygiene programme 2 active in-	Day care centres and their attending children, their parents,	Prevent transmission of respiratory infections by improved hand	A. Liquid soap (no specific antibacterial components (pH = 5.5)) OR B. Hand sanitiser (70% ethyl alcohol (pH = 7.0 to 7.5)) for home use and	Installation of liquid soap or hand sanitiser dispensers in classrooms Supervision and administration of hand sanitiser if required	Workshop delivered by researchers. Research assistant	Workshops delivered face-to-face in groups to parents and staff.	Classroom of DCCs (in Spain) for child interventions	8 months overall Initial 1-hour workshop 1 month before study	Administration of hand sanitiser in the case of young children	Not described	Not described Reported that no monitoring of adherence	Families or DCC staff, or both, used 1660 L of hand sanitiser, estimated use by each child of

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	terventions: A. soap and water B. hand sanitiser	and DCC staff	hygiene of children, parents, and staff through handwashing practices and use of hand sanitiser due to its bactericide and virucide properties	in dispensers for school classroom Workshop content handout Stories, songs, and posters about hand hygiene and infection transmission	3 hand hygiene workshops for parents and DCC staff: 1. Hand-washing practices, hand sanitiser use, possible side effects and precautionary measures (HSG only) 2. RIs and their treatments 3. Fever Instructions to children, parents, and DCC staff on usual hand-washing practices and protocol[11] Classroom activities (stories and songs) about hand hygiene and infection transmission	provided hand hygiene materials to DCCs and parents. Parents and staff supervised and administered sanitiser where indicated.	Workshop content emailed to attendees individually. Individual face-to-face supervision of hand sanitiser use, as indicated	Workshops provided at DCCs.	commencement 3 further identical sessions/DCC provided again 1 month apart Fortnightly classrooms and DCC activities One-off installation of dispensers As-needed supervision of hand sanitiser use Dose of sanitiser: 1 to 2	DCC staff could attend training at other DCC if unable to attend at own DCC.	through continuous observation of hand hygiene behaviours was done, but amount of hand sanitiser was measured	dose 6 to 8 times/day.

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Table 1. Description of interventions in included studies, using the items from the Template for Intervention Description and Replication (TIDieR) checklist *(Continued)*

									mL/disinfection				
Biswas 2019	Hand sanitiser and respiratory hygiene education	Primary schools and their students and staff	Reduce community-wide influenza virus transmission by improving handwashing and respiratory hygiene and use of sanitiser in schoolchildren as contributors to community-wide virus transmission	Hand sanitiser (63% ethyl alcohol) in colourless, transparent 1.5-litre local plastic bottles (manufactured by a local pharmaceutical company and was available commercially in Bangladesh (price: USD 5.75/L)) Video clip on respiratory hygiene practices Behavioural change materials – 3 colour posters (see Appendix of paper) Curriculum materials for hygiene classes	Installation of hand sanitiser in wall dispensers in all classrooms and outside all toilets, refilled by field staff as needed Encouragement of use of sanitiser at 5 key times during the day[12] Hand and respiratory hygiene education provided.[13] Integration of hygiene messages into school's hygiene curriculum Delivery of video clip on respiratory hygiene practice Behaviour change materials distributed and placed around schools.	Selected teachers responsible for dissemination of intervention messages throughout were trained over 2 days in these messages, behaviour change communication, sanitiser use, and practices for preventing spread of respiratory	Hand sanitiser and education materials provided to schools. Education provided in classrooms in groups and face-to-face.	Primary schools (in Bangladesh) Sanitiser in each classroom and outside toilets Education in classroom	10 weeks Intervention messages conveyed in classrooms 3 times/week.	Refills provided as needed.	Not described	Structured field observation by 2 field staff of 5 hours/school observing handwashing and respiratory hygiene behaviours of children at 2 different locations in a classroom or outside Every other day, field staff measured the level of hand sanitiser in the morning and in the af-	Handwashing observed opportunities: IG 604/921 (66%) versus CG 171/802 (21%) Hand sanitiser used in 91% of observed handwashing events in intervention schools. Average consumption of hand sanitiser/child/day: 4.3 mL

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					Use of sanitiser by classroom teachers after training Training of selected teachers in consultation with head of school and management committee in key messages Communication of key messages by the selected teachers to other teachers	secretions. Classroom teachers conveyed intervention messages during regular hygiene classes. Field staff replaced supplies as needed.						ternoon to calculate amount of hand sanitiser used/day/school and enrolled children.	Observation of proper cough or sneeze etiquette: IG: 33% versus CG: 2%
Correa 2012	Alcohol-based hand rubs	Childcare centres and their staff and children	Reduce incidence and transmission of infection in chil-	Dispensers of alcohol-based hand rubs with ethanol 62.0% (PURELL, GOJO Industries, Akron, OH, USA) Workshop materials[14]	ABH and training on proper use to staff and children Pre-trial ABH use workshop to teachers that followed recommended HH teaching tech-	Local representative of GOJO Industries Inc.	Face-to-face training and provision of materials; group training	Childcare centres in Colombia (centres or community homes)	8 months overall 1 ABH dispenser per centre with	Refilled ABH as needed	Not described	Visual reminders and monthly refresher training Monitoring	Teachers at 7 intervention centres reported almost complete substi-

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	dren by improved hand hygiene where water is scarce including provision of ABH and training in hand hygiene teaching techniques	Visual reminders on ABH techniques in bathrooms and next to dispensers	niques and instructed teachers to add ABH to routine HH and give preference to hand-washing with soap and water if hands visibly soiled Continuous refilling of ABH ABH technique refresher workshops (8/centre) Monitoring of safety, proper use of ABH, amount of ABH used	provided dispensers and dispenser installations free of charge. Fieldwork team delivered other components.	ABH in centres, classrooms, and common areas depending on size Visual reminders in bathrooms and next to dispensers Workshops and training presumably provided in centres.	< 14 children; 1 per classroom in larger centres; 1 per classroom + 1 for common areas in centres with > 28 children 1 workshop pre-trial to staff Monthly 30-minute ABH technique refresher training (8 per centre) Biweekly monitoring	of safety, proper use of ABH, amount of ABH used Semi-structured survey on completion of teachers' perceptions about changes in HH practices and use of HSW and ABH. Measurement of consumption of resources and costs related to ABH use and HSW	tution of HSW with ABH, and HSW decreased from 3 times per day to 1 per day, and ABH rose to 6 per day. Teachers at remaining 14 centres reported partial substitution of HSW with ABH. Controls reported HSW 3 times per day. Median number of ABH applications per child rose from 3.5

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													to 4.5 in preschools and 3.5 to 5.5 in community centres.
DiVita 2011	Household handwashing promotion	Householders with index patient with ILI	Prevent influenza transmission in households in resource-poor settings through provision of handwashing facilities and use of them at critical times for pathogen transmission	Hand-washing stations with soap	Provision of hand-washing stations Hand-washing motivation to wash at critical times for pathogen transmission (e.g. after coughing or sneezing)	Not specifically described, presumably the researchers	Face-to-face provision of facilities in households "Motivation" not described	Household in Bangladesh	Over 2 influenza seasons One-off provision of handwashing facilities Frequency of "motivation" not described	Not described	Not described	Not described	Not described
Feldman 2016	2 active interventions	Naval ships and	Reduced infection	Septadine solution (Floris, Misgav, Israel) 70% alcohol	Installation of CHG disinfection devices on ships alongside	Provision of CHG pre-	CHG sent to ships	Navy fast missile boats	4 months	CHG replenished	Not described	Total amount of CHG dis-	Mean volume CHG:

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	A. Hand disinfection with chlorhexidine gluconate + hygiene education B. Hygiene education	their sailors	transmission and improved hand hygiene in sailors who are at increased risk due to closed environments, contact with shared surfaces, and poor HH culture	and 0.5% CHG; inactive materials: purified water, glycerin, propylene glycol, and methylene blue	regular soap and water Supply and replenishment of CHG (sent to ships regardless of replenishment demands) Hygiene instruction by a naval physician (to both intervention groups and study control group)	sumably by study team and funds Hygiene instruction by naval physician	directly. Mode of hygiene instruction not described.	and patrol boats of naval base in Israel Dispensers installed in key locations on-board (adjacent to heads (toilets), mess decks (dining rooms), common areas).	Unlimited supply of CHG replenished on demand for 4 to 5 months. Automatic amount dispensed: 3 mL	on demand.		pensed was tallied.	8.2 mL per sailor per day (projected yearly cost USD 45 per sailor)
Gwaltney 1980	A. Virucidal hand preparation B. Placebo (no control)	Healthy young adults	Reduce infection rates by interrupting viral spread by hand	A. Virucidal hand preparation: aqueous iodine (2% iodine and 4% potassium iodide)	Immersion of each finger and thumb of both hands to proximal interphalangeal joint (interphalangeal joint of thumb) into designated preparation for 5 seconds then air-dried for 5 to 6 min	Researchers	Face-to-face and individually	US university	Exposure to donors on 3 consecutive days (days 2, 3, and 4) after initial exposure	Not described	Not described	Reported knowledge of hand preparation use as active, placebo, or don't know	Active (n = 24): 6 active 2 placebo 16 don't know Placebo (n = 22):

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				or self-inoculation route	B. Placebo: aqueous solution of food colours (Kroger; Kroger Co., Cincinnati, OH, USA) mixed to resemble the colour of iodine with 0.01% iodine and 0.02% potassium iodide to give an odour of iodine Masks	Exposure of recipients to donors either immediately after treatment or after 2-hour delay by hand contact with donor stroking fingers for 10 s Masks worn by donors and recipients during procedure. Recipients placed in single isolation rooms after second exposure till end of experiment.							6 active 7 placebo 9 don't know
Hubner 2010	Alcoholic hand disinfection	Employees (administrative officers)	Reduce absenteeism and spread of infection in administration employees with frequent customer	2 alcohol-based hand rubs (500 mL bottles) for desktop use to ensure minimal effort for use: 1. Amphisept E (Bode Chemie, Hamburg, Germany) ethanol (80% w/w) based formula with antibacterial, antifungal, and limited virus inactivating activity.	Provision of hand rub and instruction on use as needed at work only and in accordance with prevailing standard[15]: at least 5 times per day, especially after toileting, blowing nose, before eating, and after contact with ill colleagues, customers, and archive material	Presumably provided or arranged by study team	In person to staff	Administration offices in Germany Hand rubs used at desk or work (not outside of work).	12 months overall Hand rub used as much needed for complete wetting of the hands (at least 3 mL or a palmful)[16] at least	Hand rub use especially after toileting, blowing nose, before eating, and after contact with ill colleagues,	Not described	Self-reported adherence with hand hygiene measures	Reported mean hand disinfection frequency times per day: > 5: 19% 3 to 5: 59.8% 1 to 2: 20.5% < 1: 0.7%

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			con-tact and work with paper docu-ments through im-proved hand hy-giene	2. For partici-pants with skin problems: Sterillium (Bode Chemie, Hamburg, Germany) 2-propanol (45% w/w), 1-propanol (30% w/w), and mecetro-nium etilsul-fate (0.2% w/w), with a refatting effect and has activity against bacteria, fungi and enveloped viruses. Hand cream: Baktolan balm, water-in-oil emulsion with no non-antibac-terial properties (Bode Chemie, Hamburg, Ger-many)				5 times per day.	cus-tomers, and archive mater-ial			
Lade-gaard 1999 (trans-lated from Dan-ish)	Hand hy-giene pro-gramme	Day-care centres and their staff, chil-dren, and par-ents	Re-duce risk of infec-tion in child care through in-creased hy-	Personnel guide on rec-ommendations for: hygiene, ventilation, out-of-stay care, stricter hygien-ic regulations in cases with se-lected diseases	Staff meeting in each DCC and training in microbiological cause of infection spread guided by National Board of Health and Hygiene	Re-search team pre-sum-ably pro-vided train-ing.	Face-to-face with train-ing and activi-ties by group with staff and	On-site in DCCs	2-month interven-tion peri-od 1-hour training of chil-dren	None de-scribed.	None de-scribed.	None de-scribed.	None re-ported.

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	of children	genic education of daycare professionals, motivation of daycare facilities for regular hand hygiene, and informing parents about hand hygiene	Fairy tale and poster "The Princess Who Won't Wash Hands" Colouring in drawings "Wash hands" song and rhymes T-shirt for children with the inscription "Clean hands - yes thank you" Diploma for children and book "The Princess Who Won't Wash Hands" to also be used by parents with their child Informational leaflet for parents in envelope	Education of children in hand-washing (about bacteria and why and when to wash hands) Practical hand-washing classes with 4 to 5 children at a time Provision of t-shirt, book, and diploma to children Provision of leaflet for parents	children Information sent home to parents via children.

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Little 2015	Web-based hand-washing in-tervention	House-holders (over 18) who were gen-eral prac-tice pa-tients	Pre-vent trans-mission of respi-ratory tract infec-tions through im-proved hand hy-giene to re-duce spread via close con-tact (via droplets) and hand-to-face con-tact	Website-based programme: provided infor-mation about the importance of influenza and role of hand-washing; developed a plan to max-imise intention formation for hand-washing; reinforced help-ful attitudes and norms; addressed neg-ative beliefs (URL provid-ed for demon-stration ver-sion no longer active; see www.lifeguideon-line.org)	Provision of link to website for direct log in Automated emails prompted partic-ipants to use ses-sions and complete monthly question-naires and maintain hand-washing.	Re-searchers deliv-ered web-based pro-gramme and emails.	Online indi-vidual-ly	House-holds in Eng-land	4 months overall 4 week-ly web-based sessions Month-ly email ques-tions to maintain hand-washing over 4 months	Tai-lored feed-back pro-vided with-in web pro-gramme	None de-scribed.	Emailed ques-tions month-ly to maintain hand-washing	None re-ported.
Luby 2005	Hand-wash-ing pro-mo-tion at neigh-bour-hood level with 2 inter-ven-	Neigh-bour-hoods and their house-holds	Im-prove hand-wash-ing and bathing with soap in set-tings where com-mu-	Slide shows, videotapes, and pamphlets illus-trating health problems from contaminat-ed hands and specific hand-washing in-structions	Hand-washing pro-motion to neigh-bourhoods: Neighbourhood meetings of 10 to 15 householders (moth-ers) from nearby homes and monthly meetings for men Soap to households	Re-search team in col-labo-ration with Health Orient-ed Pre-ventive Edu-	Face-to-face in small groups and in-dividu-ally	Neigh-bour-hoods and homes in Karachi, Pak-istan	1-year weekly house-hold vis-its 30-to 45-minute neigh-bour-	Soap re-placed regu-larly.	None de-scribed.	None de-scribed, though soap use mea-sured.	House-holds' mean use of study soap per week: 3.3 bars Average use per resident

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	tions at household level A. Antibacterial soap B. Plain soap	nicable diseases are leading causes of childhood morbidity and mortality	Soaps: 90-gram white bars without brand names or symbols, same smell with identical generic white wrappers with serial numbers matched to households A. Households: 2 to 4 white bars of 90-gram antibacterial soap containing 1.2% triclocarban (Safeguard Bar Soap: Procter & Gamble Company (Cincinnati, OH, USA) B. Households: plain soap (no triclocarban) Soap packets	Fieldworker home visits: discussed importance of and correct hand-washing (wet hands, lather them completely with soap, rub them together for 45 seconds, and rinse off completely) technique and promote regular hand-washing habits[17] Encouragement of daily bathing with soap and water	cation (HOPE)[18] Fieldworkers were trained in interviewing and handwashing promotion.	hood meetings 2 to 3 times/week first 2 months then weekly for months 2 to 9, then monthly Monthly men's meetings first 3 months Weekly household visits					per day: 4.4 g
Millar 2016 additional details from Ellis 2010	Skin and soft-tissue infection prevention	Military trainees	Improve personal hygiene practices	A. Enhanced standard: supplemental materials (a pocket card and posters in the barracks)	Provision of education and hygiene-based measures in addition to standard SSTI prevention brief upon entry:	Not described, presumably the researchers	Face-to-face and individually for body wash and	US military training base	One-off education on entry to training	None described.	None described.	None described.	None described.

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	tion intervention in addition to SSTI brief on entry also provided to control A. Enhanced standard B. Chlorhexidine		to prevent infection, especially acute respiratory infection in military trainees who are at increased risk	B. CHG: CHG-based body wash (Hibiclens, Mölnlycke Heath Care, Norcross, GA, USA)	Enhanced standard: supplemental materials CHG: as for enhanced standard group, plus a CHG-based body wash and instructions for use			pocket card Mode of education not described.	CHG: use of wash 1 per week for entire training period (14 weeks)				
Morton 2004	Healthy hands (alcohol gel as handwashing adjunct)	Elementary schools and their children and staff	Prevent infections in elementary school-age children who are particularly vulnerable through adjunct use of alcohol gel and	Alcohol gel and dispensers: AlcoSCRUB (60% ethyl alcohol) supplied by Erie Scientific Company, Portsmouth, NH, USA "Healthy Hands Rules" protocol[19] (Figure 3 in paper) Healthy Hand Resource Man-	Healthy hands protocol introduced after "Germ unit" education in classes Daily reminders to children on public address system (in first week) then weekly reminders Review of protocol in each classroom after vacation by school nurse 2 classroom visits from school nurse	Gel provided by suppliers. Research team provided educational aspects. Classroom teach-	Face-to-face training in classes and individual information giving and monitoring	Elementary schools in USA Wall-mounted near door entrance of each classroom at age-appropriate height	46 days 0.5 mL dispensed per application. Use of "special soap" according to "Healthy Hands Protocol" (Fig-	Reinforcement teaching provided if gel usage indicated that it was needed. Germ unit education tailored	1 student was concerned gel was making her sick, so school nurse provided additional classroom visit to allay concerns.	Usage of gel calculated.	5 gel applications per day 1 dispenser lasted 1 month.

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			education based on Health Belief Model (HBM) (Kirscht 1974)	ual for school nurse, available for parents Monthly newsletters to parents ''Healthy Hands'' refrigerator magnet for families (see Figure 2 in paper) Informational letter to local primary care providers, paediatricians, family practitioners, and advanced practice nurses "Germ Unit" curriculum and materials including Germ models and Glo Germ	"Healthy Hands" magnet provided to parents and guardians. "Hand Checks on Wednesdays" to identify adverse effects of gel	ers responsible for encouraging use of gel and reinforcing protocol School nurse assisted in monitoring and hand checks for adverse effects.			ure 3 in paper)	for each grade level.			
Nicholson 2014	Handwashing with soap	Households with 5-year-olds and	Targeted 5-year-old children	Initial supply of 5 bars of free soap (90-gram Lifebuoy bars) replenished on submission of	Provision of soap and social marketing programme (Sidibe 2009) (Lifebuoy branding) to educate, motivate, and	Dedicated team of "promot-	Face-to-face in groups	"Classrooms" held in community	41 weeks Weekly "classrooms"	Mothers were asked to provide	Technical difficulties with "soap	Registers for "classrooms" and home	Soap consumption:

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	their mothers	and their mothers as change agents to reduce incidence of respiratory infections (and diarrhoeal disease) through handwashing using behaviour change principles (Claessen 2008), including social norms for child and mother (Perkins 2003), using fear of contamination,	empty wrappers. Environmental cue reminders (wall hangers, danglers) Rewards (e.g. stickers, coins, toy animals)	reward children for HWWS at key times Weeks 1 to 17: handwashing occasions, germ education, soap's importance in germ removal Week 18 onward: encouragement of HWWS on 5 key occasions supported by environmental cues "Classrooms" for children Home visits for mothers Parents' evenings to boost morale, build networks, and run competition for adherence, assignment completion, and folder decoration Establishment of a "Good Mums" club for sharing HWWS tips	ers" delivered education and home visits. Mothers provided supplied rewards.	Individually by mother to child	buildings Home visits of households in Mumbai, India	after school and home visits HWWS encouraged 5 key occasions: after defecation, before each of 3 meals, and during bathing. Week 18 onward: handwashing on 5 occasions for 10 consecutive days 6 weekly parents' meetings	and share handwashing tips with other mothers, competitions held for mothers.	acceleration sensors" to measure HWWS behaviours prevented successful use.	visits where 3-week gaps in attendance triggered supervisors to ask participants to resume or be withdrawn Monitoring of soap resale on open market by use of unique identifiers on soap wrappers and twice weekly checks in local shops Collection of used soap wrappers as	IG versus CG: 235 g versus 45 g

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			ami-nation and disgust (Curtis 2001), peer pres-sure (Sidibe 2003), morale boost-ing, and net-work-ing sup-port		Rewards provided by mothers. Children encouraged to advocate HWWS within families be-fore meals. Establishment of so-cial norms for child and mother with pledges in front of peers							soap con-sump-tion measure	
Pande-jpong 2012	3 ac-tive in-ter-ven-tions (no con-trol) differ-ent time-inter-val ap-plica-tions of al-cohol hand gel A. Every 60 min	Preschool class-es (stu-dents and teach-ers) and their par-ents	Tar-geted preschool chil-dren who can have high infec-tion rates in ILI; have close inter-action so at risk of air-borne, droplet, and	1 container of alcohol hand gel per class-room (active in-gredients: eth-yl alcohol, 70%; chlorhexidine gluconate,1%; Irgasan (tri-closan), 0.3%) Cost of hand gel every 60 minutes was USD 6.39 per child per 12-week period	Teachers instructed to: assist each child with dispensing hand gel at required time interval, store hand gel prop-erly, and refill gel as needed. Monitoring of hand gel use at specified times	Teach-ers su-per-vised, stored, and re-filled hand gel. In-struc-tions to teach-ers pre-sum-ably pro-vided	Face-to-face to schools, teach-ers and chil-dren Indi-vidual assis-tance to chil-dren with hand gel	Kinder-garten school in Bangkok, Thai-land	12 weeks overall 1 pump of gel per child per dis-infection round at 1 of 3 time in-tervals of school day: A. every 60 min B. every 120 min	None de-scribed.	Stu-dents whose fami-lies de-clined to par-ti-cipate were not asked to use alcohol hand gel. These stu-dents re-	2 re-search assis-tants moni-tored hand gel use every 60 or 120 minutes for the duration of study. Class-room teachers were re-quired to co-	Report-ed that adher-ence was ensured for each interven-tion group Cost of hand gel every 60 minutes was USD 6.39 per child per 12-week period.

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Table 1. Description of interventions in included studies, using the items from the Template for Intervention Description and Replication (TIDieR) checklist *(Continued)*

	B. Every 120 min C. Once before lunch		contact transmission; and are of increasingly younger ages through hand gel as a single strategy of convenient and effective disinfection	Leaflet describing risk factors for ILI for each family		by researchers. Leaflets distributed through school. Monitoring of use by 2 research assistants	Leaflets given to each family.		C. once only before lunch, the school standard for hand hygiene		mained in their classrooms and continued to follow the school standard for hand hygiene.	sign after each disinfection round.	
Priest 2014	Hand sanitiser provision (in addition to hand hygiene education session also provided to control group)	Primary schools and their students, teachers, and administrative staff	Reduce person-to-person community transmission of infectious disease by targeting improved	''No touch'' dispensers (> 60% ethanol) for each classroom that dispensed dose when hands were placed under an infrared sensor Supply of top-up sanitiser as needed	Dispensers installed into each classroom. Teachers asked to ensure that the children used sanitiser at particular times and to oversee general use (McKenzie 2010). Weekly classroom visits to top-up of	School liaison research assistants topped-up sanitiser. Teachers	Installation of dispensers to classrooms Supervision of children by teachers delivered	City schools in New Zealand	20 weeks (2 school terms) Sanitiser to be used by students at least after coughing/sneezing, blowing their nose,	Children were able to use the sanitiser at any time they wished as well as at key times (McKenzie 2010).	Change of sanitiser after week 10 to flavourless type of the same % ethanol in 41 of 396 classrooms	Weekly classroom visits by school liaison research assistants who recorded quantity of sanitiser used	100% dispensing 45 mL per child Average hand sanitiser dispensed/child for 34 schools: 94 mL

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Table 1. Description of interventions in included studies, using the items from the Template for Intervention Description and Replication (TIDieR) checklist *(Continued)*

			and additional hand hygiene of school children through supervised hand sanitiser provision as an alternative to improving and maintaining bathroom facilities		sanitiser and measure quantity used 30-minute in-class hand hygiene education session provided (also to control group) plus instruction in hand sanitiser use.		face-to-face individually and as a class.	and as they leave for morning break and for lunch break. Approximately 0.45 mL of sanitiser dispensed per wash. Weekly top-up of sanitiser		(10%) (in 9 of 34 schools) due to children tasting it when eating, affecting use.	Total amount of sanitiser per classroom was measured. adherence defined as dispensing a volume equivalent to at least 45 mL per child of hand sanitiser solution over the trial period.	Median classroom difference in sanitiser usage between first 10 weeks and second 10 weeks amongst classes that switched products was 220 mL.
Ram 2015	Soap and intensive handwashing promotion	Household compounds and its householders (adults and children) that	Reduce household transmission of ILI and influenza by promoting hand-	Hand-washing station in central location of each compound using: large water container with a tap; plastic case for soap;	Hand-washing station in each compound Didactic and interactive group-level education and skills training describing influenza symptoms, transmission, and prevention, promot-	Intervention staff arranged provision of handwashing station and pre-	All elements delivered face-to-face but at compound (facilities), group (ed-	Household compounds in a rural area of Bangladesh consisting of several house-	Initiation of intervention within 18 hours of study enrolment, then daily visits until 10 days follow-	Daily surveillance included observation of individual handwashing rein-	None described.	Daily surveillance of facilities and reinforcement and modelling of handwashing be-	Soap present for at least 7 days in all compounds and on all 10 days in 133 compounds (74%).

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Table 1. Description of interventions in included studies, using the items from the Template for Intervention Description and Replication (TIDieR) checklist *(Continued)*

	had a householder with ILI	washing in households with householder with ILI as other householders who are well are at highest risk of exposure due to crowded and poorly ventilated homes. Followed constructs of Social Cognitive Theory and the Health Belief Model (Glanz 2008)	bar of soap. Cue cards depicting critical times for hand-washing: after coughing or sneezing; after cleaning one's nose or child's nose, after defecation; after clearing a child who has defecated; before food preparation or serving; before eating.	ing health and non-health benefits of hand-washing with soap and identification of barriers and proposed solutions to hand-washing with soap Daily surveillance including weighing of soap and replacing if ≥ 20 g and resupply of water in container if needed Posting of cue cards Asking householders to demonstrate hand-washing with soap technique	sumably provided education. Intervention staff conducted daily surveillance and reinforcement visits.	ucation), and individual levels (reinforcement).	holds with common courtyard, shared latrine, water source, and cooking facilities	ing resolution of index case patient's symptoms Day 1 set up of hand-washing station	forcement and modelling as needed.	haviours including observed hand-washing Cue cards in common areas of courtyard Presence or absence of soap during each of first 10 days of surveillance from 180 household compounds Patterns and amount of soap use measured.[20]	Soap and water together were present 7 or more of first 10 days in 99% of compounds, with water and soap observed together on all 10 days in 99 compounds (55%) Soap consumption per capita: median: 2.3 g maximal: 5 g (on Day 7)

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Table 1. Description of interventions in included studies, using the items from the Template for Intervention Description and Replication (TIDieR) checklist *(Continued)*

			and behaviour change communication using social marketing concepts										
Roberts 2000	Education about infection control measures, handwashing, and aseptic nose wiping	Childcare centres and their staff and children	Reduce transmission of respiratory infections in childcare centres through improved infection control procedures	GloGerm (GloGerm, Moab, UT, USA) Newsletters to staff Songs and rhymes on hand-washing Plastic bags (sandwich bags available at supermarkets) to cover hand for nose wiping	Staff training in good health (developed by Kendrick 1994) and practical exercise of hand-washing with GloGerm Fortnightly visits and newsletter to reinforce training and to communicate techniques Recommended hand-washing technique as per guidelines of the time[21] and after toileting, before eating, after changing diaper (staff and child), and after wiping nose unless barrier used Teaching of technique to children and	Training and reinforcement activities provided by 1 of the researchers. Teachers delivered training to children based on their training.	Face-to-face in groups for training and classes and individually as needed to children or staff	Childcare centres in Canberra, Australia	8 months overall 3-hour training in evening or 1-hour during lunch for new staff after study start Duration of hand-washing: "count to 10" to wash and "count to 10" to rinse	Training for new staff provided as needed.	None described.	6-weekly adherence measured by recorded observation of recommended practice for 3 hours in the morning in each centre, graded by quantiles of frequency of recommended hand-washing by children.	Adherence was reported only in relation to analysis of outcomes. High adherence reported for nose wiping and child hand-washing.

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Table 1. Description of interventions in included studies, using the items from the Template for Intervention Description and Replication (TIDieR) checklist *(Continued)*

					wash hands for infants								
Sandora 2005	Healthy Hands Healthy Families	Families with an index child in out-of-home childcare	Reduce illness transmission in the home through multifactorial campaign centred on hand hygiene education and hand sanitiser	Alcohol-based hand sanitiser: active ingredient: 62% ethyl alcohol (PURELL Instant Hand Sanitiser; GOJO Industries, Inc, Akron, OH, USA) Hand hygiene educational materials at home (fact sheets, toys, games)	Supply of hand sanitiser and hand hygiene materials Biweekly telephone calls Biweekly educational materials	Study investigator	Not stated whether materials mailed or delivered in person	Homes in USA Sanitiser use in home	5 months overall Biweekly educational materials Sanitiser dispensed 1 mL each pump.	None described.	None described.	Recorded amount of hand sanitiser used (as reported by the primary caregiver)	Median frequency of reported times of hand sanitiser use: 5.2 per day 38% used > 2 ounces of hand sanitiser per fortnight = 4 to 5 uses per day
Savolainen-Kopra 2012 further details from Savolainen-Kopra 2010	STOPFLU Enhanced hygiene 2 active interventions IR1. Soap and	Office workers of office work units	Prevent transmission of respiratory infections in workplaces through enhanced hand hy-	IR1: Liquid hand soap ("Erisan Nonsid" by Farmos Inc., Turku, Finland) IR2: in addition: Alcohol-based hand rub, 80% ethanol ("LV" by Berner Inc.,	Toilets equipped with liquid hand soap (all groups) or alcohol-based hand rub (IR2). Guidance on other ways to limit transmission of infections, e.g. frequent handwashing in office and at home, coughing, sneezing into disposable handkerchief	In collaboration with occupational health clinics servicing the corporation	In-person provision of soap or hand rub Guidance and written instructions	Office work units in corporations in Helsinki, Finland	15 to 16 months overall Monthly visits by nurse throughout	Nurses assisted with any practical problems with intervention as they arose.	None described.	Adherence assessed by an electronic self-report survey of transmission-limiting habits 3 times (more	Avoiding handshaking became more common and remained high in both groups. Recorded use for per-

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	water wash IR2. Alcohol-based hand rub	giene with behavioural recommendations to reduce transmission by droplets during coughing or sneezing	Helsinki, Finland) Bottles of hand hygiene product (free of charge) to be used at home and in the office (IR2). Written instructions on hygiene for further reference	or sleeve, avoiding hand-shaking Visits to work clusters and monitoring of materials availability Monthly electronic "information spot" about viral diseases for motivation to maintain hygiene habits Adherence activities	Specially trained research nurse provided guidance and visited worker clusters throughout intervention period.	given personally. Face-to-face visits by study nurse				New employees received guidance on hand hygiene and habits.		details in protocol). Use of soap (IR1) and alcohol-based disinfectant (IR2) for personal use was recorded. Study nurse checked availability of soap and alcohol rub.	sonal use smaller than predicted use based on hand hygiene instructions. Soap or disinfectant usage per participant: IR1: 6.1 IR2: 6.9
Stebbins 2011	"WHACK the Flu" (hand sanitiser and training in hand and respirato-	Elementary schools and their students and homeroom teachers	Targeted school-aged children as important sources of influenza transmission	Hand sanitiser dispensers with 62% alcohol-based hand sanitiser from PURELL (GOJO Industries, Inc, Akron, OH, USA) automatically dispensing 1 dose	Delivery of grade-specific presentations on "WHACK the Flu" concepts and proper hand-washing technique and sanitiser use: (W)ash or sanitise your hands often; (H)ome is where you stay when you are sick; (A)void touching your eyes, nose	Project staff provided education. Home room teachers rein-	Face-to-face at schools, presumably as a group in classes	Elementary schools (Pittsburgh, USA) Dispensers installed	Whole intervention over 1 influenza season One-off installation of hand	Encouraged to wash hands or use additional doses of hand sanitiser, or	None reported.	Monthly teacher surveys of observed NPI-related behaviour in their students before, during, and after influen-	Teacher surveys of observed classroom NPI behaviour indicated successful adoption and mainte-

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	ry hygiene)		through improved cough etiquette and hand hygiene in schools including sanitiser as potential inexpensive non-pharmaceutical interventions		and mouth; (C)over your coughs and sneezes; and (Keep your distance from sick people (provided URL no longer active) Desired frequency of hand wash use taught to student (see When and how much) Installation of hand sanitiser dispensers Refresher training at each school Reinforcement of message and monitoring of sanitiser	forced message and monitored proper use of sanitiser.		in each classroom and all major common areas.	sanitiser dispensers One-off 45-minute education presentation and one-off refresher training at onset of influenza season Goal of use of 1 dose (0.6 mL) of sanitiser 4 times per day[22]	both, as needed		za season Measurement of hand sanitiser use at 2-week intervals throughout the intervention period	nance of behaviours throughout influenza season. Average sanitiser use: 2.4 times per day
Talaat 2011	Intensive hand hygiene campaign	Schools and their students, teachers, and parents	Reduce or prevent transmission of influenza viruses amongst children	Soap supplied as needed. Grade-specific student booklets each including a set of 12 games and fun activities that promoted hand-washing	Establishment of a hand hygiene team in each school Provision of hand hygiene activities: weekly exercises (e.g. games, aerobics, songs, experiments); school activities, (e.g. obliga-	Hand hygiene team (3 teachers from social studies, arts, and	Delivered face-to-face in groups and individually	Elementary schools (grades 1 to 3) in Cairo, Egypt In school	12 weeks overall Weekly hand hygiene campaign activities	Soap and hand-drying material provided by school administration if chil-	None described.	Observation by social workers of hand hygiene activities, availability of soap and drying material,	About 93% of the students had soap and drying material available.

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	through intensive hand hygiene intervention campaign	Hand hygiene activities materials including: games (e.g. how to escape from the germs); puzzles; soap activities (e.g. soap drawing); song specially developed to promote hand hygiene Teachers' guidebook including detailed description of the students' activities and methods to encourage students to practice these activities. Posters with messages to wash hands with soap and water upon arriving at school, before and after meals, after using the bath-	tory hand-washing under supervision, morning broadcast, parent meetings, students-parents information transfer); specific school initiatives: (e.g. competitions and awards, hand-washing committee, school trips to soap factory and water purification plant) More details in Table 1 of paper Song played regularly. Social worker weekly visits Distribution of flyers to parents	sports and the school nurse) ensured that all pre-designed activities for the hand hygiene campaign were implemented. 6 independent social workers visited the schools.	environment and classrooms Poster near sinks in classrooms and on playground	Weekly visits by social workers Twice-daily obligatory supervised hand-washing required by students for about 45 seconds, followed by proper rinsing and drying with a clean cloth towel.	dren did not bring their own as was the custom or families could not afford it. Schools could create own motivating activities such as selecting a weekly hand hygiene champion, developing theatre plays, and launching school contests for	and students' hand-washing during the day Schools created own activities to improve adherence.	All but 2 intervention schools "had a rigorous system of ensuring that school-children were washing their hands at least twice daily".

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				room, and after coughing or sneezing. Informational flyers for parents reinforcing the messages delivered at the schools.						drawings and songs.			
Teesing 2021 (additional sources: Teesing 2020a and Teesing 2020b)	HANDSOME multimodal nursing home HH adherence intervention	HH management staff and nurses and nursing students (with or of 3 or 4-year nursing degree) and residents	Change hygiene policy and individual HH behaviour of nurses through multimodal intervention designed specifically for nursing homes based on literature, interviews at nurs-	Materials for lessons about WHO-defined 5 moments for HH[23] using HANDSOME novel method: 'Room In' (moment 1), 'Room Out' (moments 4 and 5 combined), 'Before Clean' (moment 2), and 'After Dirty' (moment 3)[24] Nurse's watches and certificates earned on completion of e-learning Paint for washing hands exercise	See Table 1 of Teesing 2020a and Teesing 2020b for more details 1. Policy change: - management meeting (with senior nursing home manager, infection prevention specialist, and facilities manager), - personal hygiene rules - HH materials audit 2. Nursing staff interventions (The New Way of Working) i) 3 live lessons: a. introduction of HANDSOME/WHO HH moments; teaching and discussion re HH when handling medication, food,	Meeting and materials provided by researcher Study team member delivered 3 live lessons with involvement of senior NH manager Senior NH man-	Face to face in groups (management and nursing staff) Lessons in groups of maximums of 18/ session Online individual e-learning	In residents' rooms or other areas of 2 units each of 33 Dutch nursing homes with ≥ 3 nurses providing intense psychogeriatric and/ or somatic care to geriatric residents	4 months (Jan to Apr 2017) Management meeting (45 to 60 min) Personal hygiene policy presentation (10 min) Live lessons: 1 (20 min) 2 (30 min)	Persuasive communication used to encourage continuing when NH wanted to stop When < 3 nurses working at the unit, either the observers continued obser-	None described, except that the process was iterative in response to feedback from individual nursing homes	Unobtrusive HH direct observation disguised as registering of frequency of health care activities recorded on computer tablet (see Figure 2 in Teesing 2020a and Table 3 of Teesing 2020b) Compliance registered if	HH compliance (12 m f/ u) IG: 36% CG: 21% (OR 2.28, CI 1.67 to 3.11) HH compliance increased more for IG than CG for each WHO-defined moment, except for moment 2

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	ing homes and intervention mapping principles, the principle of repetition and informal discussions with members of over 20 nursing home organisations in an iterative process See protocol for more details of intervention mapping process using	28 stickers representing barriers to HH in 4 themes (facilities, forgetting, choosing not to do HH, and the telephone) E-learning materials including videos modelling knowledge, guided practice and promotion of active learning 10 posters (multiple copies, new one each month) Prize for photo competition NH certificate of good HH Small bottle of hand sanitiser for lesson participants	laundry; when to use hand sanitiser/soap/gloves. Team HH goal-setting; b. make inventory and solutions for barriers to HH adherence; and c. exercise washing hands with paint to see where missed; teaching how to disinfect hands ii) e-learning: introduction and 7 lessons showing: - correct/incorrect HH behaviour - common HH actions - when to use gloves - food and medication preparation Quizzes: iii) reminder posters hung throughout NH showing large picture of hands and text: “Did you remember to wash your hands?” (in Dutch’) iv) photo competition: prize for best photo of hands	agers involved in delivery of aspects, including a lesson on NH personal hygiene policy between lessons 1 and 2 Nurses and doctors in training provided adherence observation and assessment	Meetings on-site Lessons on-site and online Posters throughout NH	3 (40 min) given multiple times on 1 day E-learning: 5 to 10 min each Adherence observer training: 2 to 3 days Adherence observation: during observation hours (8 am to 1.30 pm, weekdays)	vations at an additional ward (who also received the intervention) or they stopped observing HH needed to happen in the same room as action occurred, except if a nurse brought a resident to another room, they carried something soiled or no door	HH occurred immediately before (moments 1 and 2) or after (moments 3, 4 and 5) a HH opportunity without touching another object (e.g. door handle) and only if hand sanitiser or soap, water and paper towel used Hand-related personal hygiene[28] for each nurse according to Dutch guidelines[29] 1 / every	Estimated attendance at lessons: varied per unit: 23% had < 50% attending at least 1 lesson, 18% had 50% to 74% attendance at at least 1 lesson and 59% had > 75% attendance at least 1 lesson (n = 22).

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	determinants and methods to develop strategies for intervention components	See website (www.zorgvoorbeter.nl/hygiene/hand-hygiene-verbeteren-verpleeghuis) for materials (in Dutch) used for intervention:[25] - Manual (84p) - E-learning module - PowerPoint presentation and script - Assignments - Awareness activities - Audit materials - Policy materials - Posters Adherence recording application and computer table Adherence observer training materials using method adapt-	3. Arts and craft project for residents involving hands that NH displays Adherence recording procedures Provision of hand sanitiser to lesson participants Provision of good HH certificate to NH if higher than average adherence Provision of nurse's watch on completion of e-learning Provision of adherence observers training	needed to be opened before leaving the room; for these instances, HH should take place at the end of action	nurse / day Attendance at live lessons and e-learning was recorded Participants asked if HH policy information received and if posters seen	

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											ed from a study in Dutch hospital[26]: videos and case studies and examination using videos from Hand Hygiene Australia[27]
											[1] World Health Organization. (2012). Hand hygiene in outpatient and home-based care and long-term care facilities: a guide to the application of the WHO multimodal hand hygiene improvement strategy and the "My Five Moments For Hand Hygiene" approach. World Health Organization. apps.who.int/iris/handle/10665/78060 (accessed 15 June 2022)
											[2] Moment 1 (before touching a resident) = Room In; Moment 4 (after touching a resident) and Mo-

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ment 5 (after touching a resident's surroundings) = Room Out; Moment 2 (before a clean/antiseptic procedure) = Before Clean; Moment 3 (after body fluid exposure risk) – After Dirty

[3] Handsome: handhygiëne in verpleeghuizen.: Zorg voor beter; 2019 May 03. URL: www.zorgvoorbeter.nl/handsome (accessed 7 June 2022)

[4] Veiligheid en Kwaliteit: Project Handen uit de Mouwen.: Stichting Samenwerkende Rijnmond Ziekenhuizen

[5] Auditor training.: Hand Hygiene Australia URL: www.hha.org.au/audits/auditor-training (accessed 7 June 2022)

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Temime 2018	Multifaceted hand hygiene programme (including alcohol-based hand rub)	Nursing home staff, residents, visitors, and outside care providers	Nursing homes and their residents, staff, and visitors and external providers have an increased risk of person-to-person transmission of pathogens, and HH is a simple and cost-effective tool for infection control; however, compliance with HH is poor in nurs-	Dispensers and pocket-sized containers of hand rub solution Posters promoting hand hygiene Developed local HH guidelines eLearning module on infection control and HH training with online quizzes requiring sufficient performance	Facilitated access to hand rub solution Campaign to promote HH with posters and event organisation Formation of local work groups in each NH Development of local HH guidelines Staff education using eLearning Monitoring of quantity of hand rub solution used	Same nurse provided HH training for all NHs. Provision of hand rub by NH Local work group developed guideline. eLearning module and posters presumably developed by research team.	Provision of materials face-to-face Education and quizzes via eLearning	Nursing homes in France	1 year overall One-off provision of hand rub One-off eLearning repeated if unsatisfactory performance.	If staff did not score sufficiently on online quiz, they were invited to repeat the eLearning.	None described.	Estimated mean amount of hand rub solution used per resident per day assessed as proxy for HH frequency, based on quantity of hand rub solution bought by NH (which was routinely monitored in all the NHs).	Hand rub solution used: baseline quantity of consumed hand rub solution was 4.5 mL per resident per day. Over the 1 year, mean quantity consumed was significantly higher in intervention NH (7.9 mL per resident per day) than control (5.7 per resident per day).

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Table 1. Description of interventions in included studies, using the items from the Template for Intervention Description and Replication (TIDieR) checklist *(Continued)*

			ing homes.										
Turner 2004a Clinical trial 1	3 active interventions (no control) Product: A. Ethanol B. Salicylic acid C. Salicylic acid with pyroglutamic acid	Healthy volunteers	Assess the residual virucidal activity of organic acids used in currently available over-the-counter skin products for the prevention of experimental rhinovirus colds	1.7 mL of hand products: A. 62% ethanol, 1% ammonium lauryl sulphate, and 1% Klucel) B. 3.5% salicylic acid, or vehicle containing C. 1% salicylic acid and 3.5% pyroglutamic acid	Disinfection of hands then application of test product then allowed to dry. 15 min later, fingertips of each hand contaminated with 155 $TCID_{50}$ of rhinovirus type 39 in a volume of 100 µL. Hands air-dried for 10 min. Intentional attempted inoculation with virus by contact with fingers, conjunctiva, and nasal mucosa with fingers of right hand. Left hand eluted in 2 mL of virus-collecting broth.	Researchers	Face-to-face individually	Communities in Manitoba, Canada	1.7 mL of product applied. See What for timing	Not described	Not described	Not described	Not described
Turner 2004b Clinical trial 2	2 active interventions (no control)	Healthy volunteers	Assess the residual virucidal activity of organic acids	Skin cleanser wipe containing: A. 4% pyroglutamic acid formulated with 0.1% benzalkonium chloride B. 62% ethanol	Application of product to hands with towelette then allowed to dry. 15 min later, fingertips of each hand contaminated with 106 $TCID_{50}$	Researchers	Face-to-face individually	Communities in Manitoba, Canada	Dose not reported; see What for timing Additional group	Not described	Not described	Not described	Not described

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	Skin cleaner wipe product: A. Pyroglutamic acid B. Ethanol	used in currently available over-the-counter skin products for the prevention of experimental rhinovirus colds		of rhinovirus type 39 in a volume of 100 µL. Intentional attempted inoculation with virus by contact with fingers, conjunctiva, and nasal mucosa with fingers of right hand. Left hand eluted in 2 mL of virus-collecting broth.				chal-lenged 1 h after application; final group challenged 3 h after application (remained at study site and not allowed to use or wash hands between).				
Turner 2012	Antiviral hand lotion	Healthy adults	Reduce rhinovirus infection and illness through hand disinfection with ethanol and organic acid sanitiser	Lotion containing 62% ethanol, 2% citric acid, and 2% malic acid Daily diary	Provision of lotion and instructions for use Meetings with participants to check compliance	Staff of study site presumably supplied lotion. Study site staff met with participants.	Face-to-face and presumably individually, but not specified	Study site at university community in the USA	9 weeks Every 3 hours whilst awake and after handwashing for 9 weeks Compliance meetings	None reported.	None reported.	Self-reported daily diary of time of each product application Twice weekly for 5 weeks then weekly meetings with	"All subjects … applied at least 90% of the expected amount of hand treatment" (p. 1424)

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									twice weekly for first 5 weeks then weekly meetings with participants			participants to reinforce compliance with treatment	
Yeung 2011	Multifaceted hand hygiene programme (including alcohol-based hand rub)	Long-term care facilities and their healthcare workers	Promote use of alcohol-based hand rub by staff in LTCFs as an effective, timely, and low-irritant method of hand hygiene in a high-risk environment	Free supply of pocket-sized containers of alcohol-based antiseptic hand rub (either WHO formulation I (80% ethanol) or II (80% propanol) carried by each HCW (supplier: Vickmans Laboratories) Replacement hand rub as required Hand hygiene seminar content Reminder materials (3 to 5 posters and specially designed ballpoint pens)	Provision of materials Provision of hand hygiene seminars to HCWs covering: indications, proper method, and importance of antiseptic hand rubbing and washing according to WHO 2006a) guidelines Provision of feedback session Direct, unobtrusive observation of hand hygiene adherence Training of observation staff	Study team delivered the materials, seminars, and observer training. Administrative staff of LTCF provided replacement hand rub and communicated with HCWs.	Delivered face-to-face and individually for hand rub and pens; not described if education was individually or by group, but seminar implies as a group	LTCFs in Hong Kong Posters posted in common areas. Adherence observations occurred in common rooms and resident rooms but not bathing or toi-	7 months overall Initial 2-week intervention period, then 7 months of hand rub provision and reminders 3 identical seminars at start of intervention; each staff member to attend once	Replacement of hand rub as required	As adherence dropped off in the middle months, the feedback session was delivered.	Direct observation of HCW adherence to handwashing and antiseptic hand rubbing (recorded separately and anonymously) during bedside procedures or physical contact with residents 3300 hand hygiene opportunities during	90% attendance of seminars Hand rubbing with gel increased significantly from 1.5% to 15.9%. Handwashing decreased significantly from 24.3% to 17.4%. Control: 30%

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						6 registered nurses conducted direct observation of adherence after 2-hour training (100% inter-rater reliability).		let areas.	Feedback session 3 months after start of intervention 2-hour training of observers Adherence observations either 9 am to 12 pm or 3 pm to 6 pm, 1 LTCF at a time			248.5 hours of observation on 92 days	Overall handwashing adherence increased from 25.8% to 33.3%.
Zomer 2015	Hand hygiene products and training	Day-care centres and their caregivers (staff)	Reduce infections in children attending DCCs through improved access	HH products: dispensers for paper towels, soap, alcohol-based hand sanitiser, and hand cream, with refills for 6 months	Provision of free HH products sponsored by SCA Hygiene Products, Sweden. Provision of posters and stickers for children and staff	Study team arranged supply of HH products and presumably provided	Products provided to DCCs in person for staff use. Mode of	DCCs in regions of the Netherlands	6 months overall Initial one-off supply of products	Replacement hand hygiene provided as required.	None described.	6-month follow-up observation of whether intervention dispensers and posters/stickers in use	2 DCCs did not use any HH products. Sanitiser products used in at least 1 of 2 groups

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Table 1. Description of interventions in included studies, using the items from the Template for Intervention Description and Replication (TIDieR) checklist *(Continued)*

	to HH materials (Zomer 2013a) and compliance of their DCC caregivers to hand hygiene guidelines based on socio-cognitive and environmental determinants of caregivers' HH behaviour[30] (Zomer 2013b)	Reminder posters and stickers for children and DCC caregivers Training materials including booklet	Provision of training about RIVM 2011 for mandatory HH[31] Distribution of training booklet Team training sessions aimed at goal-setting and formulating HH improvement activities (Erasmus 2011; Huis 2013)	training.	training not specified.	3 training sessions with 1-month interval 2 team training sessions	Survey of DCC caregivers HH guidelines compliance observed at 1, 3, and 6 months' follow-up: no. of HH actions/no. of opportunities	in 94%, 89%, 86%, and 45% of intervention DCCs. Posters used in 86%, stickers in 74%. DCC survey results: 79% attended at least 1 training session; 77% received HH guidelines booklet. HH compliance at 6 months: IG: 59% vs CG: 44% (Zomer TP, et al,

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													unpublished data) All intervention DCCs received guidelines training; all but 2 received at least 1 team training.
Hand hygiene and masks													
Aelami 2015	Hygienic education and package	Religious pilgrims	Prevent influenza-like illness by reduced infection transmission through personal hygiene measures	Hygiene package of: alcohol-based hand rub (gel or spray) surgical masks soap paper handkerchiefs user instructions	Not clearly described, but it appears that packages may have been distributed by trained physicians before departure to or on site of country of pilgrimage	Not specifically described	Not described, but it appears that packages were distributed face-to-face and individually	Not described if before departure (from Iran) or on site (in Saudi Arabia)	One-off during Hajj season	Not described	Not described	Not described	None described
Aiello 2010	2 active in-	Students living	Reduce the	7 face masks (standard medical procedure	Weekly supply of masks through student mailboxes	Not described, except	Education via email	University resi-	One-off education, 6	Mask wearing	University spring	Weekly web-based	Average mask use

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terventions: A. Face mask (FM) B. Face mask and hand hygiene (FM + HH)	in university residences	incidence of and mitigate ILI by use of non-pharmaceutical interventions of personal protection measures	masks with ear loops TECNOL procedure masks; Kimberly-Clark) 7 re-sealable plastic bags for mask storage when not in use (e.g. eating) and for disposal Alcohol-based hand sanitiser (62% ethyl alcohol in a gel base, portable 2-ounce squeeze bottle, 8-ounce pump) Hand hygiene education (proper hand hygiene practices and cough etiquette) via emailed video, study website, written materials detailing appropriate hand sanitiser and mask use	Provision of basic hand hygiene education through an email video link, the study website, and written materials; instruction to wear mask as much as possible; education in correct mask use, change of masks daily, use of provided re-sealable bags for mask storage and disposal Provision of replacement supplies which students signed for upon receipt	education provided via study website (URL not provided) "Trained staff" for compliance monitoring Study-affiliated residence hall staff provided replacement supplies.	and study website; provision of masks and sanitiser in person to residences	dence halls in the USA	weeks (excluding spring break) of face mask and/or hand hygiene measures which commenced at "the beginning of the influenza season just after identification of the first case of influenza on campus" (p.496). Replacement supplies provided as needed.	during sleep optional and encouraged outside of residence.	break occurred during weeks 4 and 5 of the study, with most students leaving campus and travelling; they were not required to continue protective measures at that time.	student survey included: self-reported average number of times hands washed/day and average duration of handwashing to obtain composite "optimal handwashing" score (at least 20 s ≥ 5/day); average no. of mask hours/day/week; average hand sanitiser use/day/week and amount used. Trained staff	hours/day: FM + HH 2.99 versus FM 3.92 Average handwashing times/day: FM + HH 6.11 versus FM 8.18 vs control group 8.75 Daily washing seconds/day: FM + HH 20.65 versus FM 23.15 vs control 22.35 Hand sanitiser use times/day:

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Table 1. Description of interventions in included studies, using the items from the Template for Intervention Description and Replication (TIDieR) checklist *(Continued)*

											in residence hall common areas observed silently and anonymously improper mask use, instances of hand sanitiser use.	FM + HH: 5.2 versus FM 2.31 vs control 2.02 No. of proper mask wearing participants/hour of observation: FM + HH 2.26 versus FM 1.94
Aiello 2012	2 interventions: A. Face mask (FM) B. Face mask and hand sanitiser (FM + HH)	Students living in university residences	Prevent ILI and laboratory-confirmed influenza by use of non-pharmaceutical interventions of personal protection	Packets of 7 standard medical procedure masks with ear loops (TECNOL procedure masks, Kimberly-Clark, Roswell, GA, USA) and plastic bags for storage during interruptions in mask use (e.g. whilst eating, sleeping) and for daily disposal	Intervention materials and educational video provided. Supply of masks and instructions on wearing Provision of replacement masks or sanitisers as needed on site	Trained study staff available at tables in each residence hall for surplus masks and sanitiser and for observing compliance	Hygiene packs delivered to student mailboxes; face-to-face supply also available	University residence halls in the USA	One-off educational video at start Weekly supply of hygiene packs Masks to be worn at least 6 hours/day	Students encouraged but not obliged to wear masks outside of residence hall.	1-week university spring break during the study when majority of students left campus	Weekly student survey including compliance (e.g. masks hours/day, frequency and amount of sanitiser use, number of hand washes/day, duration of hand-	Self-reported mask wearing: no significant difference Sanitiser use: significantly more in FM + HH than FM or control groups

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			measures (e.g. face masks and hand hygiene)	Hand sanitiser (2-ounce squeeze bottle, 8-ounce pump bottle with 62% ethyl alcohol in a gel base) Replacement face masks and hand sanitiser Educational video: proper hand hygiene and use of standard medical procedure face masks					Study staff available onsite with replacement supplies as needed for duration of intervention (6 weeks, excluding spring break)			washing (seconds) Observed compliance completed by trained study staff who daily and anonymously observed mask wearing in public areas of residences.	More results in S1 of paper. Staff observed an average of 0.0007 participants properly wearing a mask for each hour of observation.
Cowling 2009	2 active interventions in addition to control of lifestyle education: A. Enhanced hand hy-	Householders with index patient with influenza	Reduce transmission of influenza in households through personal protective measures	A. and B. Liquid soap for each kitchen and bathroom: 221 mL Ivory liquid hand soap (Proctor & Gamble, Cincinnati, OH, USA) Alcohol hand rub in individual small bottles (100 mL) WHO recom-	Home visits Provision of soap, hand rub, and masks as applicable and when to use them HH: education about efficacy of hand hygiene Demonstration of proper hand-wash-	Trained study nurse provided interventions.	Face-to-face to householders	Households in Hong Kong	Initial home visit scheduled within 2 days (ideally 12 h) of index case identification. Further home	Not described	Not described	Monitoring of adherence during home visits Evaluation of adherence on final visit by interview or self-	Most initial visits completed within 12 h. Intervention groups "reported higher adherence … than the

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	giene (HH) B. Face masks and enhanced hygiene (FM + HH)	mended formulation I, 80% ethanol, 1.45% glycerol, and 0.125% hydrogen peroxide (Vickmans Laboratories, Hong Kong, China) B. Adults: box of 50 surgical face masks (Tecnol–The Lite One (Kimberly-Clark, Roswell, GA, USA) to each household member or C. Children 3 to 7: box of 75 paediatric masks	ing and antisepsis techniques + FM: education about efficacy of surgical face masks in reducing disease spread to household contacts if all parties wear masks Demonstration of proper wearing and hygienic disposal All groups: provision of education about the importance of a healthy diet and lifestyle, both in terms of illness prevention (for household contacts) and symptom alleviation (for the index case)	visits day 3 and 6, 7-day follow-up HH: use of liquid soap after every washroom visit, sneezing or coughing, when their hands were soiled. Use rub when first returning home and immediately after touching any potentially contaminated surfaces FM: masks worn as often as	reported practices and counting of amount of soap and rub left in bottles and remaining masks for FM group	control group. Self-reported data were consistent with measurements of amount of soap, alcohol hand rub, and face masks used" (p.443) (see Table 6 in paper). "Adherence to the hand hygiene intervention was slightly higher in the hand hygiene group than the face mask plus hand hygiene group."	

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									possible at home (except eating or sleeping) and when the index patient was with the household members outside of the household				Median masks used: Index: 9 Contact: 4 More details in paper and Appendices
Larson 2010	2 active interventions in addition to control of URI education: A. Alcohol-based hand sanitiser (HS) B. Face masks and hand	Hispanic householders with at least 1 preschool or elementary school child	Reduce incidence and secondary transmission of URIs and influenza through non-pharmaceutical household level inter-	A. and B. 2-month supply of hand sanitiser in 8-, 4-, and 1-ounce containers: PURELL (Johnson & Johnson, Morris Plains, NJ, USA) B. 2-month supply of masks: Procedure Face Masks for adults and children (Kimberly-Clark,	Provision of materials and instructions for when to use including demonstration of use and observation of return demonstration by householder A. Mask worn when householder had: "temperature of ≥37.8°C and cough and/or sore throat in the absence of a known cause other than influenza" (CDC definition of influenza-like illness at the time).	4 trained bilingual research assistants (RAs) with minimum baccalaureate degree and experience in community-based research;	Face-to-face to householders	Households in New York, USA	19-month follow-up Initial home visit, then at least every 2 months Sanitiser for use at home, work, and school	Change masks between interactions with person with ILL Householders' questions and misconceptions addressed	None described.	RA home visits for adherence with random accompaniment by project manager, who also made random calls to householders Telephone calls to reinforce	Sanitiser use (mean ounces/month) HH: 12.1 FM + HH: 11.6 Mask compliance was "poor": 22/44 (50%) used within 48 hours of onset.

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	sanitiser (FM + HS)		ventions	Roswell, GA, USA) Replacement supplies at least once every 2 months Disposable thermometers Educational materials about URI prevention, treatment, and vaccination (written in Spanish or English language)	Home visits to reinforce adherence, replenish supplies and record use, answer questions B. Telephone calls to reinforce mask use All groups received URI educational materials.	procedures were practised with each other until demonstrated proficiency			B. Telephone calls days 1, 3, 6 Masks worn for 7 days when within 3 feet of person with ILL or no symptoms.	on home visits.		mask use Used bottles or face masks, or both, monitored for usage.	Mask users reported mean mask use of 2.
Simmerman 2011	2 active interventions: A. Handwashing education and handwashing kit (HW)	Households with a febrile, influenza-positive child	Decrease influenza virus transmission in household with a febrile influenza-positive child through promoted	A. and B. Hand-washing kit per household including graduated dispenser with standard unscented liquid hand soap (Teepol brand. Active ingredients: linear alkyl benzene sulfonate, potassium salt, and sodium lauryl ether sulphate)	A. and B. Provision of intensive hand-washing education on initial home visit to household members with 5 approaches: discussion, individual hand-washing training, self-monitoring diary, provision of soap, and provision of written materials (Kaewchana 2012) Individual hand-washing training	Study nurse conducted home visits, provided education and monitoring activities.	Education provided face-to-face as a group to household member and individually for hand-washing	In homes (in Bangkok, Thailand)	One-off provision of kits at initial home visit conducted within 24 hours of enrolment Subsequent home visits on	B. No face masks whilst eating or sleeping as impractical and could hinder breathing in ill child	None described.	Self-monitoring diary recording hand-washing frequency > 20 s and face mask use for that group Reinforcement	Reported average hand-washing episodes/day: HW: 4.7 HW + FM: 4.9 Parents had highest frequency (5.7), others (4.8),

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	B. Handwashing education, handwashing kit, and face masks (HW + FM)	use of handwashing or handwashing with face mask use	Replacement soap as needed Written materials from education including pamphlets and posters attached near sinks in household. B. Box of 50 standard paper surgical face masks and 20 paediatric face masks (Med-con company, Thailand #14IN-20AM-B-30IN)	("why to wash", "when to wash", and "how to wash" in 7 hand-washing steps described in Thailand Ministry of Public Health guidelines) B. Provision of education of benefits of and appropriate face mask wearing Soap replaced as needed. More details (Kaewchana 2012)	training.	days 3, 7, and 21 90-day supply of handwashing supplies 30-minute education provided at initial home visit	Impromptu education and training provided by nurses as questions arose.	of messages by nurses on subsequent home visits Amount of household liquid soap and number of face masks used	siblings (4.3), index cases (4.1). Average soap used/week: HW: 54 mL/person HW + FM: 58.1 mL/person B. Mask use: 12/person/week Mask wearing median minutes/day: 211 Parents 153, other relations 59, index patients 35, siblings 17

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Suess 2012	2 active interventions in addition to written information: A. Mask/hygiene (MH) B. Mask (M)	Households with an influenza-positive index case in the absence of further respiratory illness within the preceding 14 days	Prevent influenza transmission in households through easily applicable and accessible non-pharmaceutical interventions such as face masks or hand hygiene measures	A. Alcohol-based hand rub (Sterilium, Bode Chemie, Germany) A. and B. Surgical face masks in 2 different sizes: children < 14 years (Child's Face Mask, Kimberly-Clark, USA) and adults (Aérokyn Masques, LCH Medical Products, France) Written information provided on correct use of intervention and on infection prevention (Suess 2011) (tips and information on the new flu A/H1N1) (URL provided is no longer active) Digital tympanic thermometer	A. Provision of hand rub and masks A. and B. Provision of masks only Provision of thermometer and how to use it Mask fit assessed (at first household visit) Information provided by telephone and written instructions at home visit on proper use of interventions and recommendations to sleep in a different room than the index patient, not to take meals with the index patient, etc. (Suess 2011) In-person demonstration of interventions at first home visit All participating households received general written infor-	Study personnel arranged provision of materials, rang the participants, visited the homes, demonstrated and assessed fit of masks.	Provision of materials in person to households Initial telephone delivery of information Face-to-face home visits	Households in Berlin, Germany	Over 2 consecutive flu seasons Day 1 households received all necessary material instructions. Household visits no later than 2 days after symptom onset of the index case, then days 2, 3, 4, 6, 8 (5 times) or on days 3, 4, 6, 8 (4 times) depending on the day of recruitment	Adult masks worn if masks for under 14-year-olds did not fit properly. If other household members developed fever (> 38.0 °C), cough, or sore throat, they were asked to adopt the same preventive behaviour as the index patient.	In the season 2010/11 participants also recorded number of masks used per day.	Self-reported daily adherence with face masks, i.e. if they wore masks "always", "mostly", "sometimes", or "never" as instructed. Participants of the MH households additionally noted the number of hand disinfections per day. Exit questionnaire about (preventive) behaviour during	Face mask use (median/individual): MH: 12.6 M: 12.9 Daily adherence was good, reaching a plateau of over 50% in nearly all groups from the third day on. MH hand rub use (median): 87 mL (Suess 2011) MH mean frequency of daily hand

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			mation on infection prevention.					
		General written information on infection prevention		Hand rub use: after direct contact with the index patient (or other symptomatic household members), after at-risk activities or contact[31]		the past 8 days, general attitudes towards NPI, the actual amount of used intervention materials, and, if applicable, problems with wearing face masks.	disinfection: 7.6 (SD 6.4) times per day	See paper and Suess 2011 for more results.
				Mask use: at all times when index patient and/or any other household member with respiratory symptoms were together in 1 room		Used intervention material per household member was calculated by dividing the amount used per household by the number of household members.		

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									Regular change of face masks, not worn during the night or outside the household			See paper and Suess 2011 for more details.	
Hand hygiene and surface/object disinfection													
Ban 2015	Hand hygiene and surface cleaning or disinfection	Kindergartens and the families of their students	Reduce transmission of infection in young children from contaminated surfaces or hands through hand hygiene and surface cleaning or disinfection	Antibacterial products for hand hygiene and surface cleaning or disinfection: liquid antimicrobial soap for hand-washing (0.2% to 0.3% parachlorometaxylenol). Instant hand sanitiser for hand disinfecting (72% to 75% ethanol), antiseptic germicide (4.5% to 5.5% parachlorometaxylenol diluting before use). Bleach (4.5% to 5.0% sodium hypochlorite, diluting before	Provision of products to kindergartens and families Instruction of parents or guardians and teachers in hand hygiene techniques and use of antibacterial products Daily cleaning of kindergartens with products At least twice/week cleaning of homes and weekly cleaning or disinfecting of items such as children's toys, house furnishings, frequently touched objects (doorknobs,	Research team provided products and instructions and monitoring.	Materials provided to kindergartens and families in person and presumably instructions in person to families and staff.	In kindergartens (hard surfaces) and families' homes (Xiantao, China)	1 year overall Daily handwashing with soap before eating, after using bathroom, nose blowing, and outdoor activities Hand sanitiser carried daily.	Families and teachers could contact study management at any time as needed. Exchange of empty bottles for new ones at any time	Not described	Close contact with teachers and families for monitoring, e.g. unscheduled parents' meetings, quarterly home visits, phone interviews, and monthly cell phone messages	Consumption of products by person (mL/person/day). Liquid soap: 7.7 Sanitiser: 1.4 Bleach: 25.0 Antiseptic-germicide: 12.5

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				use) for surface disinfecting. Produced by Whealthfields Lohmann (Guangzhou) Company Ltd.	tables or desks), kitchen surfaces (utensils, cutlery, countertops, chopping boards, sinks, floors, etc.), bathroom surfaces (toilet, sink, floor, etc.) Monitoring activities				Kindergarten cleaning daily Home cleaning at least twice/week			Monthly survey of consumption of products by volume, total usage, person usage	
Carabin 1999	Hygiene programme	Daycare centres and their staff and children	Reduce infections in at-risk children (under 3 years old) in DCCs with inexpensive, easily implementable and practical interventions	Hygiene materials and documents, e.g. colouring books, hand-washing posters, hygiene videotapes Materials for training Reimbursement of equivalent of 1 full-time educator's salary Bleach (diluted 1:10) for toy and play area cleaning	Provision of comprehensive hygiene training session to entire DCC staff, especially the educators of participating classrooms Training in recommendations for hygiene practices: i. toy cleaning ii. hand-washing technique and schedule iii. use of creative reminder cues for hand-washing iv. open window for daily period v. sandbox and play area cleaning	Training appears to have been provided by study team.	Appears staff trained as a group, i.e. "entire DCC staff"	Daycare centres in Canada Location of training not described, except may have been off-site from DCCs since 1 DCC did not "send" staff to training.	15-month trial One-off 1-day training Toy cleaning at least every 2 days Handwashing at least after DCC arrival, after outside play, after bathroom, before lunch	Teachers to use creative reminder cues for handwashing with children	Not described	Follow-up telephone questionnaire for DCC directors about following training recommendations	Use of materials: colouring book: 22/24 poster: 23/24 videotapes: 18/24 staff meetings: 19/24 Increased frequency of toy cleaning: 6/24 Use of rake and shovel for

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					Payment of salary of educator for the day to encourage participation DCC meetings to discuss training session with all staff				Open windows at least 30 min/day Biweekly cleaning of sandbox/play area				sandpit: 17/24 Frequency of cleaning sandbox: 14/24
Kotch 1994	Hygiene	Caregivers at child day-care centres (CDCCs)	Develop feasible, multicomponent hygienic intervention to reduce infections in children at CDCCs who are at increased risk	Hygiene curriculum for caregivers Availability of soap, running water, and disposable towels Waterless disinfectant scrub (Cal Stat) used only if alternative was not washing at all. Handouts posted in CDCC.	Delivery of hygiene curriculum to caregivers through initial training session which required demonstration of participants' handwashing and diapering skills Local procedures: Hand-washing of children and staff Disinfection of toilet and diapering areas Physical separation of diapering areas from food preparation and serving areas Hygienic diaper disposal Daily washing and disinfection of toys,	Research team delivered training. Scrub donated by Calgon Vetal Laboratories.	Face-to-face training and follow-up group and individually	Classrooms of child day-care centres in the USA	8 months overall 3-hour initial training session Cleaning schedules as described in column What (procedures) On-site follow-up training	Follow-up sessions addressed questions and local adaptations to procedures. As-required induction training	During intervention, research team encouraged directors to address physical barrier to hygiene practice, such as distance between sink and diaper-	Follow-up sessions reinforced training. Meeting with directors 5 weekly unobtrusive recorded observation by training staff	Rate of compliance to barrier modification was better in younger centres, which were more likely to have written guidelines.

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					sinks, kitchen and bathroom floors Daily laundering of blankets, sheets, dress-up clothes Hygienic preparation, serving, and clean up of food Separate training of food handlers As-required induction training for new staff Onsite follow-up training reinforcing adaptations, demonstrations and discussion of hygiene techniques, responding to questions, and review of handouts Monthly meeting with centre directors to encourage leadership and support				1 week and 5 weeks later		ing areas and sink access in rooms.		
McConeghy 2017	Multifaceted handwashing and sur-	Nursing homes and their staff	Reduce exposure to pathogens	Education and launch materials	Pre-intervention: NH administrators required to:	Study personnel equipped staff with knowl-	Face-to-face interaction with staff for	Nursing homes in the USA	6 months overall: training period: 3 months	Sites could use existing comparable	2 sites retrained due to low training	Cloud-based audit and feedback system via	Online training participation rates:

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face-cleaning intervention	and person-person transmission in high-risk facility of close environment and potentially contaminated surfaces through multifaceted intervention equipping staff to protect residents from infection within the "culture" of care	Online module for certified nursing assistants about: infection prevention, product, and monitoring "Essential bundle" of hygiene products supplied at no cost: - hand sanitiser gel and foam - antiviral facial tissues - disinfecting spray - hand and face wipes Plus additional: - 4 skin cream and wipe products iPads for compliance audits Newsletters for support during intervention	- identify a "Heroes In Prevention" champion and team - allow all staff participation in education - iPad use for staff in each floor or community - ask staff to incorporate intervention into workflow Delivery of 3 components: - education - cleaning products - compliance audit and feedback Education: Launch event for all staff to publicise programme and explain roles Intensive training of "hygiene monitors" for data collection and compliance audit and feedback tool Training of site champion Training of select group of certified	edge and tools and support. NH staff (e.g. champion, hygiene monitors, nursing assistants) delivered aspects of interventions after specific training.	planning and some aspects and delivery of products Some aspects delivered online (e.g. nursing modules, compliance auditing)	Onsite and at unit/team levels Online training	1-hour launch event 1 or 2 hygiene monitors/site 1 champion/site 1-hour online module for selected nursing assistants iPads for each community or floor Weekly teleconferences initially de-	products from another vendor and fill in any gaps with study products. New staff provided with education, as needed and came onboard. Retraining of sites with low training participation rates	participation rate.	secure login to web browsers on NHs' existing computers or via iPads included weekly product consumption to get measure: weekly count of product units consumed x no. of hand hygiene occasions	> 90% for 3/5 sites, 13% and 23% for 2/5 Administrators demonstrated high fidelity in reporting measures of handwashing (> 80% of time). Handwashing rates in Figure 1B in paper reported as "relatively constant" and "not ideal in the first few months", but improved

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					nursing assistants (online module) Audit and feedback activities Ongoing support during intervention: - newsletter with best practices - teleconferences with each NH - "onboarding" education of new staff				creased in frequency over time. Weekly measurement of product consumption				significantly over time.
Sandora 2008	Multifactorial intervention, including alcohol-based hand sanitiser and surface disinfection	Elementary school and its students	Reduce transmission of infections in school-children through improved hand hygiene and environmental disinfection	1 container of disinfecting wipes (Clorox Disinfecting Wipes (The Clorox Company, Oakland, CA, USA); active ingredient, 0.29% quaternary ammonium chloride compound) Pre-labeled 1.7-ounce containers of alcohol-based hand sanitiser (AeroFirst non-aerosol alcohol-based	Sanitiser and wipes provided to classroom/teacher with instructions for use. Teachers disinfected desks once daily. Hand sanitiser to be used: before and after lunch, after use of the restroom (on return to the classroom; hand hygiene with soap and water occurred in the restroom, because sanitisers were not placed there), after	Research team arranged supply of materials and instructed teachers on use. Teachers instructed in use of materials and in col-	Products provided to schools. Instruction provided face-to-face to teachers and children.	Elementary schools and their classrooms in the USA	8-week period Desks disinfected once a day.	Products replenished as needed.	None described.	Individually labelled containers collected every 3 weeks from the classroom to assess adherence.	Product usage: average wipes used/ week: 897 (128 wipes/ classroom/week) Average bottles of hand sanitiser used per week: 8.75 (1.25 bottles/classroom/week)

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				foaming hand sanitiser (DEB SBS Inc, Stanley, NC, USA, for The Clorox Company); active ingredient, 70% ethyl alcohol) Receptacle in classrooms for empty containers	any contact with potentially infectious secretions (e.g. after exposure to other ill children or shared toys that had been mouthed)	lecting empty containers and distributing new product.							
Quarantine/Physical distancing														
Helsingen 2021	Rapid-Cycle Re-Implementation of TRAining Facilities in Norway (TRAiN) hygiene and physical distancing measures	Members of health and fitness training facilities aged 18 to 64 years not at increased risk for severe COVID-19	Enable safe reopening of fitness training facilities to maintain health and fitness by reducing the risk of SARS-CoV2 transmission	Infection mitigation measures described by "Norwegian guidelines for Hygiene and Social Distancing in Training Facilities during the COVID-19 Pandemic" (in Norwegian t-i.no/wp-content/uploads/2020/04/Bransjestandard-for-sentre.pdf) See Supplementary Appendix for "Standard for COVID-19 infection preven-	Implementation of the following during regular floor training facilities and group classes: - avoidance of body contact - 1 metre distance between individuals, - 2 metre distance for high intensity activities Provision of disinfectants at all workstations Requirement of HW and cleaning of all equipment by mem-	Facility employees controlled access and enforced implementation of guidelines and procedures at all times Staff present dur-	Face-to-face individually and as a group	5 health and fitness training facilities in Oslo, Norway	3 weeks May 22nd to June 15th, 2020 Hours of access not reported; presumably the participants had unlimited access to training facility within the procedures	Masks not required, so were optional Change rooms available Access controlled to avoid overcrowding	None described	Staff monitored access and distancing No apparent measures of fidelity	None described

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Table 1. Description of interventions in included studies, using the items from the Template for Intervention Description and Replication (TIDieR) checklist *(Continued)*

tion measures in fitness centers during the TRAiN-study"	bers before and after use with utensils provided	ing all opening hours	for distancing	Staff monitored that distance measures were ensured
	No physical contact between participants or participants and instructors			
Disinfectant readily available at workstations and strategic places (reception, booking station, changing rooms, toilets, water taps used for drinking or refilling bottles)	Regular cleaning of facilities by facility employees	Not reported if training needed for facility staff		
	Create lists of what should be cleaned and how often			Number of people attending depended on size of gym and associated changing rooms, showers and toilets. Facility to calculate the maximum number who could train at the
Rubbish cans without lids				
	Disinfection of instructor microphones			
Washbasin with soap or hand disinfection				
	Extra cleaning of frequently touched surfaces (e.g. door handles, card readers, washbasin batteries)			
Personal microphones for instructors (i.e. not shared)				
	Frequent refilling at all hygiene stations			
Infection preventive measures reminders online and via posters in facilities				
	Avoid queuing by making sure group classes do not start and stop at same			

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						time and keep 15 min minimum between group classes	same time while maintaining 1 to 2 m distance, as well as toilet, shower and change room capacity
						Access control by facility employees	
						Closure of showers and sauna but changing rooms open	
						Staff presence during all opening hours	
						Removal of lids on trash cans	
						Reminders of infection preventive measures	
						Communication to members about changes to training for social distancing	
						Advice to members to stay home if any COVID-19 related symptoms	

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					Advice to members to avoid touching eyes, nose and mouth Closure of childcare facilities								
Miyaki 2011	Quarantine from work (stay-at-home order)	Employees	Prevent spread of influenza in workplaces by quarantining workers who had a cohabiting family member with an ILI	Full wages to employee	Non-compulsory asking of workers whose family members developed an ILI to stay at home voluntarily on full wages. Daily measuring of temperature before leaving work. Where symptoms were doubtful, industrial physician made judgement. Company doctors provided input on cancelling of stay-at-home orders as required.	Health management department oversaw the procedures and decisions.	Mode of advice to employees not described.	Car industries in Japan	Stay-at-home order for 5 days after resolution of ILI symptoms or 2 days after alleviation of fever over 7.5 months	Strict standard for cancelling of stay-at-home orders described.	None described.	Recording of compliance with stay-at-home request	100% compliance to stay at home reported.
Young 2021 (additional source: Denford 2022)	Daily contact testing (DCT) with Lateral Flow Device (LFD)	Students and staff from secondary schools and further	Provide a quicker, more convenient and alternative	SARS-CoV-2 Lateral Flow Device (LFD) (Orient Gene, Huzhou, China)[47]	In addition to twice weekly asymptomatic testing with LFD according to national policy: students and staff who were close contacts[48] of students or staff members	A study worker was funded at each school but role not	Individually and face to face	172 secondary government funded, residential,	March to May 2021 Daily contact testing was performed at arrival	When testing could not start immediately following iden-	None reported	Daily participation rates in IG measured per day and per participant	Testing did not occur on 15.8% of person-school-days due to school or public health

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Table 1. Description of interventions in included studies, using the items from the Template for Intervention Description and Replication (TIDieR) checklist *(Continued)*

for contacts of COVID-19 cases	education colleges	testing option and policy for COVID-19 close contact testing in schools, as an alternative to self-isolation	who had a positive LFD or PCR were identified and offered daily LFD testing on arrival at school or college each morning (if asymptomatic and no household member isolating due to testing positive for COVID-19) Participants swabbed own nose (anterior nares), supervised by trained staff. Swabs tested by school staff using LFC Contacts with negative LFC attended education but were asked to self-isolate at home after school and on weekends/holidays Contacts with 5 negative tests (tests done over 7 consecutive days) including one on or after the 7th day of testing were released from self-isolation Contacts with positive test were required to self-isolate for 10 days, along with their contacts. Their school-based contacts were identified and process repeated	specified School staff tested the swabs that were taken by students Study staff trained according to national NHS Test and Trace standard process supervised LFD testing	special and independent day schools and further education colleges in England	at school each morning Day 1 of testing began the day after a case was identified Testing was done over 7 consecutive days (allowing for no testing on weekends) Schools actively participate between 19 April 2021 to 27 June 2021 (considered periods of low to moderate COVID-19 incidence)	tification of a case (e.g. due to a weekend), testing could start within 3 days of case identification	Compliance was calculated / school / week, and participant type, (= sum of all study school days of individuals eligible for DCT returning a test result or already having completed follow up each day, divided by the sum of individuals eligible for DCT. Qualitative interviews conducted to understand reasons for participation and	agency directives IG participation rate: 42.4% with marked variation between schools (range 0% to 100%). See Figure 2 for non-participation reasons breakdown (e.g. testing kit unavailable, whole cohort moved to isolation). Staff more likely to participate than students.

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Table 1. Description of interventions in included studies, using the items from the Template for Intervention Description and Replication (TIDieR) checklist *(Continued)*

									not (reported separately in Denford 2022)	See Figure 2 for participation by school type breakdown	
										"Although contacts at government-funded schools with students 11–16 years old with a low proportion of free school meals were most likely to participate, other school types were similar, such that differences in participation related to fac-	

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													tors other than school type." (p. 1227) Qualitative analysis of interviews indicated daily testing may be feasible and acceptable but needs improved communication to students and parents about rationale, test interpretation and actions (Denford 2022)
Other (miscellaneous/multimodal) interventions													
Ashraf 2020 (additional	6 active interventions of Wa-	Residents of households	Improve environmental	Free technologies and supplies:	Provision and delivery of supplies or installations as described in Materials column according to	540 CHW or 'promoters'	Mostly face to face in groups and in-	Households and compounds	2 years from May 2012	CHWs identified and ad-	S: latrine pits adapted	Measured by a separate trained	CHWs visited more than planned

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Table 1. Description of interventions in included studies, using the items from the Template for Intervention Description and Replication (TIDieR) checklist *(Continued)*

sources: Arnold 2013, Luby 2018, Parvez 2018, Rahman 2018, Unicomb 2018)	ter, sanitation, hygiene (WASH) and nutrition components: A. Water (W) B. Sanitation (S) C. Handwashing (H) D. Water + sanitation + handwashing (WSH) E. Nutrition F. Nutrition + WSH (WSHN	of village compounds and for some interventions, particularly pregnant women and their infants and children < 5 years	conditions to interrupt transmission of respiratory pathogens and improve child malnutrition thereby reducing childhood respiratory illness and improving childhood morbidity based on the Integrated Behavioural Model for Water Sanitation and Hy-	W: chlorine (sodium dichloroisocyanurate) tablets (Aquatabs, Medentech, Wexford, Ireland) - 10 L insulated safe storage vessel (Li-on Star Plastics, Sri Lanka) with a lid and tap for drinking water per household S: Dual-pit pour flush latrines with water seals for all compound households. Each pit had 5 concrete rings 0.3 m high; - Potties[34] (RFL, Bangladesh) - Sanisco ops[35] (locally developed hand-tool made for the trial for removal of faeces from compound) for households with index children	intervention type or combination. Interventions deployed so that they were in place before index children were born In combined intervention arms, the sanitation measures were delivered first, followed by handwashing, then water treatment. Household visits and community discussions based on behaviour change strategy by CHWs (paid a monthly stipend), including interactive sessions for developing solutions to improve practice. Key recommendations per IG: W: children drink treated, safely stored water from vessel (filled vessel with added 1 33 mg tablet, wait 30 min before drinking)	who were local women and residents of study villages recruited through transparent merit-based selection methods and consultation with community leaders CHWs had completed minimum of 8 years formal education, lived within	dividually with some activities by phone	(n = 5551) of rural villages in Gazipur, Kishoreganj, Mymensingh and Tangail Districts in Bangladesh Households spread across 0.2 to 2.2 km radius	6 to 8 households / CHW 1:12 supervisor to CHW ratio CHWs visited households 1 / week for first 6 months, then at least 1 / fortnight Promoter training: Initial: W, S, HW: 4 days; N, WSH: 5 days; WSHN: 9 days	dressed any barriers that arose through ongoing dialogue with caregivers CHWs met with supervisors monthly to adapt technology and behaviour-change approaches to meet evolving conditions CHW supervisors available	when insufficient space (2% of cases) Functional water seals count was low (< 80% benchmark) in initial months which triggered a rapid response which improved uptake (Rahman 2018); households were using own latrines with broken water seals in	team (university graduates) at regular intervals using a priori benchmarks: a) surveys and spot checks in 30 to 35 households / IG / per month, over 20-month period; b) 5-hours of structured observations in 324 IG and 108 control households, approximately 15 months after interventions	(5 to 7 / month) which researchers suggest may have affected uptake Reported "high adherence to all interventions" with "marked differences in promoted behaviors from the control group at both year 1 and year 2," with over 75% adherence in the single IG and combined IGs.

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giene[33] and 2 years of iterative testing and revision. Intervention specific behavioural objectives: W: drink treated and safely stored water S: safe faeces disposal H: HW with soap at key times N: age-appropriate nutrition birth	H: 2 HW stations, 1 water reservoir near kitchen (16 L) and 1 near latrine (40 L), each with basins for rinsing with a soapy water bottle (RFL, Bangladesh) and detergent sachets for index households[36] N: supply of lipid-based nutrient supplements (LNS, Nutriset; Malaunay, France) (for 6 to 24 months olds) 2 10g sachets per day per child; (118 kcal, 9.6g fat, 2.6g protein, 12 vitamins and 10 minerals) Cost: USD 0.08/day 18-month shelf life Stipends for CHWs (USD 20/month for 24	S: family use double pit latrines, potty train children and how to safely dispose of faeces and clean and maintain latrines H: family wash hands with soap after defecation, after cleaning a child who has defecated, before eating or before feeding a child, and before food preparation N: recommendations for exclusive breastfeeding up to 180 days and maternal and infant nutrition to mothers and index children; introduce diverse complementary food at 6 months; feed LNS from 6 to 24 months, mixed into the child's food (not intended as a replacement for breastfeeding or complementary foods). Messages adapted from the Alive & Thrive programme[37]	walking distance of IG cluster and passed a written and oral examination. They attended multiple training sessions and quarterly refreshers. Training covered active listening, strategies for developing collaborative solutions and techni-	Refresher training: 1 day each 21 day training of adherence team Monthly CHW supervisor meetings	by cell phone as needed Training of promoter varied in content and length depending on intervention type Potties provided if children < 3 years	parallel with trial latrines so pre-existing latrines were closed, visits by CHWs were increased and water-seal removal or breakage was discouraged Initial professional trainer for CHW training did not engage trainees enough so replaced with inter-	commenced. Measured: W: Presence of stored drinking water with detectable free chlorine (> 0.1 mg/L) S: a latrine with functional water seal, sani-scoop accessibility H: presence of soap at primary HW stations N: reported consumption of LNS sachets	Similar adherence in single W, S, H and N IGs compared with WSH and WSHN S: observed use of latrines: 94% to 97%; child sanitation practices (37% to 54%) H: HW with soap in IG more common after toilet use (67% to 74%) versus 18% to 40% in non-IGs and after cleaning child's anus (61% to 72%) but

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Table 1. Description of interventions in included studies, using the items from the Template for Intervention Description and Replication (TIDieR) checklist *(Continued)*

	to 24 months	months) delivered through mobile phone network to ensure timely payments Promoter's guide for visits for each relevant intervention including: - visit objective, - target audience - steps and materials to be used CHW ID badges Cell phones for CHW supervisors Training Plan and Manual for CHW supervisors covering: i) basic training - introduction of project, CHW roles and responsibilities, introduc-	On household visits, following a structured plan, CHWs greeted targeted household members, checked presence and functionality of relevant hardware and signs of use, observed recommended practice using a guide. CHWs used discussions, video dramas, storytelling, games and songs and provided training on hardware maintenance, where applicable Adherence observed and measured by separate team Supervision meetings of CHWs and periodic internal monitoring of their performance Intervention Delivery Team managed delivery through regular team phone calls, field meetings, field reports and liaison with relevant government and other stakeholders. It co-	cal aspects of interventions (see Table 1 of Luby 2018 for more details) CHWs were trained by 47 CHW supervisors who received direct training on intervention delivery Hardware installation team (n = 18)	nal training resource group Due to observation of intervention fatigue reported by CHWs and suboptimal practices observed, new behaviour change activities were developed (e.g. further technology use, increasing self-efficacy and	See Rahman 2018 for more details (Table 1) Continuous oversight and periodic monitoring of CHWs performance (CHW replaced within 1 month of attrition or critically low performance	low before food handling W: > 65% mothers and children observed drinking chlorine-treated water from safe container N: LNS feeding > 80% 33 low performing CHWs discontinued See Luby 2018, Parvez 2018, Arnold 2013, Unicomb 2018 for more details	

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	tion to behaviour-change principles based on the IBM-WASH theoretical framework and interpersonal and counselling communication skills. ii) Intervention-specific training iii) classroom practice / role playing	ensure rapid identification of issues with delivery. Including a dedicated training officer, it also trained the CHW supervisors who then trained the CHWs under their supervision ("train the trainer" approach)	9 field research officers The Intervention Delivery Team[38] co-ordinated delivery including CHWs, overseen by Principal Investigators with consultation from Technical Advisory Group (see Unicomb, 2018) Dedicated			roles for men)

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						Training Officer and Communication Development officer Adherence observed by separate team who received formal 21 day training							
Farr 1988a trial 1	2 active interventions in addition to control of no tissues: A. Virucidal	Families	Reduce transmission of viruses from hand contamination via hand-to-hand contact or	3-ply tissues with: A. 5.1 mg/inch^2 (2.54 cm^2) of the virucidal mixture (58.8% citric acid, 29.4% malic acid, 11.8% sodium lauryl sulphate) B. 3 mg/inch^2 (2.54 cm^2) of saccharin ap-	Family visits to distribute tissues Weekly contact of mother Families instructed to only use supplied tissues.	Nurse epidemiologist visited families.	Face-to-face visits to families and individuals in families (especially mothers)	Communities in the USA	6 months overall Monthly family visits Weekly contact with mother	Not described	Not described	Family visits and weekly contact with mother to encourage compliance	Not described

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	nasal tissues B. Placebo tissues		large-particle aerosol through tissues for nose blowing and coughs and sneezes	plied uniformly to all 3 plies of the tissue Tissues prepared by Kimberly-Clark Corporation, Neenah, WI, USA.									
Farr 1988b trial 2	2 active interventions (no control): A. Virucidal nasal tissues B. Placebo tissues	Families	Reduce transmission of viruses from hand contamination via hand-to-hand contact or large-particle aerosol through tissues for nose blowing and coughs and sneezes	2-ply tissues containing: A. 4.0 mg/inch^2 (2.54 cm^2) of antiviral mixture (53.3% citric acid, 26.7% malic acid, 20% sodium lauryl sulphate) B. 3 mg/inch^2 (2.54 cm^2) of succinic acid, malic acid, sodium hydroxide, and polyethylene glycol Tissues prepared by Kimberly-Clark Corporation, Neenah, WI, USA.	Family visits to distribute tissues and encourage compliance Weekly contact of mother Families instructed to only use supplied tissues.	Nurse epidemiologist visited families monthly. Study monitor visited bimonthly.	Face-to-face visits to families and individuals in families (especially mothers)	Communities in the USA	6 months overall Monthly family visits Weekly contact with mother Bimonthly study monitor visit	None described.	None described.	Bimonthly study monitor visits to encourage compliance as well as monthly and weekly contact by nurse	In 124/222 families, 1 or more family members reported not using the tissues regularly and/or reported having side effects from the tissues.

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Fretheim 2022a (additional source: Fretheim 2022b (protocol)	GLASSY (GLasses Against transmission of SARS-CoV-2 in the communitY	Adult members of the public who did not regularly wear glasses and who owned or could borrow glasses to use (e.g. sunglasses)	Provide a simple, readily available, environmentally friendly, safe and sustainable means of personal protection from infection with respiratory viruses including SARS-CoV-2	Instructions via online portal Regular eyewear, e.g. sunglasses owned by participant or that could be borrowed by participant	Request to wear sunglasses or other types of glasses when outside home and close to others in public spaces for 14 days	Research team	Individually Instructions provided via email and online portal (Nettskjema-platform)accessed via webpage hosted by the Norwegian Institute of Public Health	Outside the home, e.g. on public transport, in shopping malls (in Norway)	14 days when outside and close to others in public spaces Over 11 to 12 week period (February – April 2022)	Could borrow glasses if did not own any	None reported.	No contact was made with participants between enrolment and data collection.	Reported use of glasses often, almost always, or always: IG: 71% CG: 11% Negative experiences (especially fogging with mask use): IG: 21/76
Longini 1988	2 active interventions (no control):	Households and their families	Prevent intrafamilial transmission of viral agents in a com-	Treated tissues of 3-ply material identified with no specific identifiers (Kimberly-Clark Corporation) with inside layer containing:	Tissues delivered to households with specific instructions on use (all purposes, when blowing nose, coughing or sneezing) and to discard after use and to help young children use tissues if develop a cold.	Tissues assigned by study sponsor (Kimberly-Clark	Supply of tissues throughout 5-month trial period	Households in the USA	5 months' overall supply	Resupply of tissues as required	None described.	Reported use of tissues "not at all, some of the time, most of the time, or	Reported use "all of the time": A. versus B. 82% versus 71%

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	A. Virucidal nasal tissues B. Placebo tissues		munity setting	A. citric and malic acid plus sodium lauryl sulphate; B. succinic acid.			Corporation).						all of the time"	
Chard 2019 (additional details from- Chard 2018)	Water, Sanitation, and Hygiene for Health and Education in Laotian Primary Schools (WASH HELPS)	Primary schools and their students	Prevent the spread of pathogens within schools through improved water supply and hygiene facilities and improved WASH habits in children at home and throughout the life course	For each school: Water supply for school compound: (borehole, protected dug well with pump, or gravity-fed system) Water tank to supply toilet and hand-washing station School sanitation facilities (3 toilet compartments) Hand-washing facilities: 2 sinks with tapped water and supply of soap available	Provision of school: Water supply, sanitation facilities, hand-washing facilities (individual and group), drinking water filters Behaviour change education and promotion including daily group hygiene activities Daily hand-washing and cleaning schedules	UNICEF paid for materials. School and teachers conducted daily hand-washing activities with children. Students participated in daily group cleaning activities.	Facilities provided within schools. Children participated in group hand-washing and cleaning.	Primary schools and their classrooms (in Laos)	One-off provision of water and hygiene facilities Daily hand-washing activities and cleaning for 1 school year Cleaning schedules posted in at least 1 classroom near toilet.	Water supply tailored to the school requirements/environment. Sanitation facilities provided as needed and designated for boys, girls, and students with disabilities.	Rain water tank provision affected by rain water supply, so changed to tanks with motorised hand pumps or gravity-fed water supply systems. Theft and animal consump-	Unannounced visits every 6 to 8 weeks for structured observations to measure fidelity and adherence Fidelity Index score (0 to 20): for hardware provided see Table 1 in paper and protocol Adherence in-	Fidelity: 30.9% across all schools and visits Adherence: 29.4% Hardware provision: 87.8% of schools School-level adherence: 61.4% Group compound cleaning: 94.8%, toilet use: 75.5%, group toilet

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				(1 bar of soap/ pupil) 3 group hand-washing tables with soap and water At least 1 drinking water filter per classroom Schedules of daily group hand-washing, compound and toilet cleaning Cost per school: USD 13,000 to 17,500							tion of supplied soap reduced supply.	dex: student report of behavioural outcomes index score (0 to 4)	cleaning: 68.3%, group hand-washing: 48.7%, individual hand-washing with soap after toilet use: 23.9%. Further details (Chard 2018)
Hartinger 2016	Integrated environmental home-based intervention package (IHIP)	Households and their household-ers including children	Reduce infections and improve child growth in households in rural communities	Per household: "OPTIMA-improved stove": improved ventilated solid-fuel stove Kitchen sink with in-kitchen water connection providing piped water	Community engagement with local and regional stakeholders in design and development Provision of stoves, kitchen sinks, and plastic bottles for solar water treatment, and hygiene education	Health promoters hired local elementary school teachers and implemented and promoted	Face-to-face and to individual households; mode of delivery of training as individual or	Households in rural communities in Peru	Stoves and sinks installed over initial 3 months. Monthly reinforcement over 12 months of	Tailored to particular household facilities and environments as needed and to local	Not described	Weekly spot-check observations of household hygiene and environmental health conditions (e.g. presence	SODIS use: 60% initially and 10% at end of study Self-reported use by mothers: 90% with

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	with limited facilities through a multi component, low-cost environmental intervention to improve drinking water, sanitation, personal hygiene, and household air quality developed in pilot (Hartinger 2011; Hartinger 2012) using a participatory approach	Point-of-use water quality intervention applying solar disinfection to drinking water	Training of mothers/caretakers in: - solar drinking-water disinfection (SODIS)[39] according to standard procedures - hand hygiene (washing own and children's hands with soap at critical times[40]) - advice to separate animals and their excreta from the kitchen environment Project-initiated repairs	the interventions. 4 teams of field staff conducted spot-check observations.	group not described	SODIS, child and kitchen hygiene Weekly spot checks of compliance Repairs after 9 months Environmental samples test middle and end of 12-month surveillance.	beliefs and cultural customs Repairs to stoves as needed and checked at 9 months	of SODIS bottles on the roof or kitchen) using a checklist Monthly self-report by mothers of stove and sink use	slight decrease at end Self-reported stove use: 90% daily Sink use: 66% daily 35% of stoves needed minor repairs, 1% needed major repairs. Best-functioning stoves achieved mean 45% and 27% reduction of $PM_{2.5}$ and CO, respectively, in

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			that addressed local beliefs and cultural views										mothers' personal exposure.
Huda 2012	Sanitation Hygiene Education and Water Supply in Bangladesh (SHEWA-B)	Villages and their households with a child < 5 years old	Reduce illness in children < 5 years by improving hygiene practices, sanitation and water supply and treatment in their household	Materials for training of community hygiene promoters and promotion activities including flip charts and flash cards with messages alerting participants to presence of unobservable "germs" and practices to minimise germs See Box 1 in paper for 11 key messages.[41]	Engaging local residents under guidance of local NGOs to develop community action plans addressing: Latrine coverage and usage Access to and use of arsenic-free water Improved hygiene practices, especially hand-washing with soap Recruitment and appointment of community hygiene promoters Household visits, courtyard meetings, and social mobilisation activities (e.g. water, sanitation and hygiene fairs, village theatre, group discussions in tea stalls (the social meet-	Community hygiene promoters (local residents with at least 10 years' schooling trained for 10 days on behaviour change communication in water, sanitation, and hygiene)	Face-to-face delivery to groups (villages and households) and individuals	Villages and households in districts of Bangladesh Community activities held in villages. Meetings held in courtyards of groups of households.	18 months overall Expected household visit and courtyard meeting every 2 months Handwashing opportunities: after own or child's defecation, prior to preparing and serving food, prior to eat-	Community action plans developed for and by local residents.	Not described	Structured observation of handwashing and child faeces disposal behaviour in households and spot checks of type of household water and sanitation facilities	HW: Food-related: No significant difference from baseline to 18 months; IG versus CG After anus cleaning: 36% versus 27% Defecation: 30% versus 23% No access to latrine decreased from

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Table 1. Description of interventions in included studies, using the items from the Template for Intervention Description and Replication (TIDieR) checklist *(Continued)*

					ing point for village men)) by community promoters Structured observation in households			House-hold visits	ing and feeding a child				10.3% to 6.8%. No significant improvement in access to improved latrines, solid waste disposal, drainage systems, and covered containers for water storage
Ibfelt 2015	Disinfection of toys	Day-care nurseries	Reduce transmission of pathogens via shared toys in day-care environment through regular disinfection	Disinfectants: Turbo Oxysan (Ecolab, Valby, Denmark) for washing machines Sirafan M, Ecolab (1% to 3% benzalkonium chloride, 1% to 3% didecyldimethylammonium chloride, and 5% to 7% alcohol ethoxylates) for immersion or wiping	Collection and commercial cleaning of toys from nurseries: - linen and toys suitable for washing machines were washed at 46 °C and subsequently disinfected - toys not suitable for washing machines immersed in disinfectant or wiped with microfibre cloth	Commercial cleaning company: Berendsen A/S, Søborg, Denmark	Cleaning companies collected the toys and linen and cleaned them offsite, then returned them.	Day-care nurseries in Denmark Commercial industrial cleaning facility	2 to 3 months overall Cleaning every 2 weeks	Staggered cleaning to ensure children had toys to play with whilst others were being cleaned	None described.	None described.	None described.

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Table 1. Description of interventions in included studies, using the items from the Template for Intervention Description and Replication (TIDieR) checklist *(Continued)*

			treatment										
Najnin 2019 (see also- Qadri 2015 for further details)	2 active interventions: A. Combined cholera vaccine and 'behaviour change communication' intervention B. Cholera vaccine-alone group	Low-income households and compounds	Prevent or reduce transmission of respiratory illness based on the Integrated Behavioural Model for Water Sanitation and Hygiene (IBM-WASH) theoretical framework (Dreibelbis 2013; Hulland 2013)	A. and B. Cholera vaccine ShanChol™ (Shantha Biotechnics-Sanofi, India) A. Following hardware per compound: a. Hand-washing hardware: (i) Bucket with a tap (provided free of charge) (ii) Soapy water bottle (mixture of a commercially available sachet of powdered detergent (~USD 0.03) with 1.5 L of water in a plastic bottle with a hole punched in the cap) supplied by participating compounds	A. and B. Provision of cholera vaccine (2 doses at least 14 days apart) Provision of handwashing hardware and behaviour change communication activities Encouragement of hand-washing after defecation, after cleaning child's anus, and before preparing food Encouragement to add chlorine to own water vessels Benefits were again explained. Follow-up visits by health promoters	Dushtha Shasthya Kendra (DSK), an NGO, delivered the hardware and behavioural intervention (through community health promoters). Separate data collectors observed soap availability.	Handwashing and water treatment hardware mostly delivered at the compound level in person. Behaviour change communication messages were delivered both at compound and household levels.	Households and compounds (where several households share a common water source, kitchen, and toilets) in Bangladesh	Behaviour change communication messages delivered first (within 3 months of cholera vaccination). Point-of-use water hardware provided 3 months later. Follow-up health promoter visits 3 times in 2 months after hardware installation,	Hardware-related problems (breakage/leakage) were addressed on health promoter follow-up visits.	None described.	Unannounced home visits by data collectors who observed presence of soap/ soapy water and water in most convenient place for handwashing (either reserved in a container or available at the tap) Residual chlorine was measured indicating uptake of chlorine dispenser.	Presence of soap / soapy water and water: A. Handwashing group compounds: 45% (1729 / 3886); B. Vaccine-only group compound: 22% (438 / 1965); C. Control: 28% (556 / 1991) Residual chlorine present in stored drinking water of 4% (160/3886) of house-

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Table 1. Description of interventions in included studies, using the items from the Template for Intervention Description and Replication (TIDieR) checklist *(Continued)*

				(iii) Bowl to collect rinse water after washing hands (see photo in text or in Najnin 2017 doi.org/10.1093/ije/dyx187) b. Water treatment hardware: Dispenser containing liquid sodium hypochlorite See Figure 2 in Najnin 2017 for photos of both doi.org/10.1093/ije/dyx187 and more details. Participants own water vessels for water treatment Print materials for behaviour change to compounds and households						then 2 times/ month (over nearly 2 years).			holds in the vaccine-plus-behaviour-change compound and none in the other 2 compounds.
Swarthout 2020 (addi-	6 active interven-	Residents of	Improve envi-	Free technologies as appropriate to IG:	Provision and delivery of supplies or installations as de-	Community-based	Face to face in groups	8246 households	Installation and supply	Training tailored	None described	Participant reports	All interventions de-

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Table 1. Description of interventions in included studies, using the items from the Template for Intervention Description and Replication (TIDieR) checklist *(Continued)*

tional sources: Arnold 2013, Christensen 2015, Dentz 2017, Null 2018, Pickering 2019)	tions of water, sanitation, and handwashing (WASH), and nutrition components: A. Water (W) B. Sanitation (S) C. Handwashing (H) D. Combined (WSH) E. Nutrition (N) F. Combined (WSHN)	households of villages and for some interventions, particularly pregnant women (Mamas) and their infants and children < 5 years; Landowners of communal water sources and compound heads for latrine upgrades and construction	ronmental conditions to interrupt transmission of respiratory pathogens and improve child malnutrition thereby reducing childhood respiratory illness and improving childhood morbidity based on a literature review, a theory-based approach (health belief,	W: water treated with sodium hypochlorite (1.25% solution / 2 mg/L) using chlorine dispensers installed at communal water source collection points or bottled chlorine (1L for 333 20-l jerry-cans worth)[45] provided to households in compounds Chlorine strips to test chlorine levels S: installation of new or improvement of existing latrines with plastic slab latrines with tight-fitting lids; plastic potties and sani-scoops H: 2 HW stations (2-foot pedal-operated jerry-cans that dispensed soapy and rinse	scribed in Materials column according to intervention type or combination Provision of study materials to promoters Community meetings Household and community visits by promoters who: - delivered intervention-specific behaviour change messaging focusing on themes of nurture, aspiration and self-efficacy, considering convenience and cultural norms to improve adherence using scripts and visual aids; - provided instructions on hardware use and consumable supplies where applicable - advocated: W: drinking water treatment with sodium hypochlorite	health promoters nominated by their local communities and trained in the relevant intervention to be implemented Field enumerators assessed adherence in compounds Study staff trained promoters, provided pe-	(e.g. households or compounds) or individuals (mothers and their children)	and 7960 compounds of rural villages in Bungoma, Kakamega, and Vihiga counties in western Kenya	of materials before community meetings Community meeting 6 weeks after enrolment Monthly visits (45 to 60 min in 1st year) by promoters over 2 years (2012 to 2014) Timing of visits detailed in procedures provided at osf.io/7j9sk/ W: 1 L bottle of chlo-	for different interventions Troubleshooting of solutions to barriers to adherence by promoter and participants as needed Nutrition messaging was tailored to be age-appropriate Materials provided in both in	of visits by promoters in past month Unannounced visits by staff to a random sample of at least 20% of participants in IGs at 2, 6, 10, and 19 months after the interventions began to confirm delivery of materials and monitor availability of intervention materials and recommended behaviours after the interventions be-	livered within 3 months of enrolment Increased adherence indicators of ≥ 30% higher in all IGs relative to the control in the first year Adherence was comparable between the Individual IGs compared with combined IGs. W: 5 chlorine dispensers installed / cluster

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Table 1. Description of interventions in included studies, using the items from the Template for Intervention Description and Replication (TIDieR) checklist *(Continued)*

	social cognitive theory and persuasion theory),[42],[43],[44] formative research and the WASH Benefits pilot RCT (Christensen 2015)	water), 1 near food preparation, 1 near latrine. Rinse water provided by households; bar soap for soapy water container N: 2 x 10 g sachets / day / child of lipid-based nutrient supplementation (LNS) "Mwanzobora", (Nutriset, Malaunay, France) (118 kcal/day and 12 essential vitamins and 10 minerals) See Figure 2 of Christensen 2015 for photos of examples of some of the materials Community meeting and household visit summary sheets (in Kiswahili and English) and	S: use of improved latrines for defecation and safe disposal of children's and animals' faeces and use of plastic potties by children < 3 years and sani-scoops for faeces removal H: HW with soap before food preparation and after defecating (including assisting child); helped participants identify compound members to refill taps and manage barriers to use such as running out of soap N: early initiation of breastfeeding, exclusive breastfeeding 0 to 6 months and continued till 24 months; at 6 months, introduction of appropriate and diverse complementary foods; feeding frequency and during illness; supply of LNS to children 6 to 24 months and instruction to mix it was foods twice/day Promoters used visual aids to promote messages: - cue cards provided to Mamas at ini-	riodic observation and supervision and monthly phone calls	rine / 6 months H: bar soap provided every 3 months N: LNS introduced at 6 months of age of child Promoter training: 6 days single IGs. 7 days combined IGs. Refresher training at 6, 12 and 18 months after initial training	Kiswahili and English Chlorine dispensers located based on list of sources participants reported (at baseline) using for water collection Sani-scoops and potties were to be washed by caregivers with soap and water after use	gan (Null 2018) W: monthly tests of chlorine concentration in stored water; negative results prompted discussions to address chlorination barriers S: participant report of access to improved latrine; field enumerators observed if latrine had plastic or cement slab or ventilation pipe;	Year 1: 74% Year 2: 37% households were visited by a promoter in previous month W: Year 1: 42% Year 2: 21% had detectable total chlorine CG: 3% S: Year 1 and 2: > 80% had latrine access CG: 20%		

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Table 1. Description of interventions in included studies, using the items from the Template for Intervention Description and Replication (TIDieR) checklist *(Continued)*

	list of materials provided as PDFs at osf.io/7j9sk/ Key messages and visual aids provided at osf.io/7j9sk/ Including ~6 primary key messages per intervention, each with a series of specific topics, visual aids, and engagement activities (e.g. storytelling, mottos, etc.). Visual aids included: - cue card reminders - picture sheets for use by promoters - calendars for households with key messages - stickers for LNS box depicting appropriate feeding and storage	tial visits to hang on walls for reminders - picture sheets used by promoter to explain key concepts or messages - calendars provided to households during first compound visit - stickers attached to LNS box Adherence checking unannounced visits Initial training on intervention-specific behaviour change messages and materials Refresher training Periodic observation and supportive supervision by study staff	Supervision and observation of promoter by study staff at 2, 4, 9, 14 and 21 months and monthly phone calls	and tools kept out of reach of children (see the visual aids provided to participants: osf.io/9r4kg/ for potties and osf.io/mz2c6/ for sani-scoops)	caregiver report that child faeces safely disposed H: field enumerator observed if water and soap available N: report of LNS sachets consumed by child in last week / 14	HW: Year 1: 77% Year 2: 21% had HW materials CG: 9% N: Year 1: 95% Year 2: 115% of expected sachets consumed See Null 2018 for more details		

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											Promoter Training Materials for trainers and trainees for each intervention for initial training and for refresher training including detailed PDF training manuals available at osf.io/7j9sk/ focusing on key hygiene messages, visitation scripts and visual aids and hardware for each intervention[46]
											Promoters' supplies: Branded t-shirt, mobile phone, job aids and intervention materials, payment ($US15/month for first 6 months, then $9/month thereafter), detailed plans for every visit (key messages, scripts for visual aids, instructions for activities)

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Table 1. Description of interventions in included studies, using the items from the Template for Intervention Description and Replication (TIDieR) checklist *(Continued)*

Oral and/or nasal applications												
Almanza-Reyes 2021	Mouthwash and nose rinse with ARGOVIT silver nanoparticles (AgNPs)	Healthcare personnel (doctors, nurses, administrative staff) of a metropolitan hospital caring for patients diagnosed with atypical pneumonia and/or COVID-19	Reduce morbidity in healthcare professionals exposed to SARS-Co V-2 by inhibiting virus replication	Per participant: - 50 ml bottle of RGOVIT® AgNPs mouthwash and nasal rinse [Investigation and Production Center Vector-Vita Ltd., Novosibirsk, Russia] (metallic silver 0.06%, polyvinylpyrrolidone 0.63%, hydrolyzed collagen 0.31%, distilled water 99% wt.) - water - cotton swabs	Individuals provided with spray bottle containing AgNPs solution with 1 wt% concentration (0.6 mg/mL metallic silver) and instructed to do 1 of the following or a combination: a) mix 4 to 6 spray shots (~ 0.5 mL) with 20 mL of water and gargle solution for 15 to 30 seconds at least 3 times/day (gargle) or b) do not dilute with water and cover the oral cavity evenly with 1 to 2 direct spray shots (spray) c) apply the same solution to the inner part of the nasal alae and nasal passage with cotton swab twice a day (nasal rinse)	Researchers supplied materials and instructions Participants self-applied the mouthwash and nasal rinse materials	Individually and face to face	General hospital in Tijuana, Mexico	Over a 9 week period (April to June 2020) 4 to 6 spray shots of AgNP solution (0.5 mL) with 20 mL of water or 1 to 2 spray shots of solution without water for 15 to 30 seconds ≥ 3 times / day and 1 nasal lavage 2 times / day	Participants could choose application method	None described	Weekly self-report of number of: daily gargles; mouthwashes with spray; mouthwashes by gargle + spray; and nasal rinses	Mean applications/day: Gargle only: IG: 2 (n = 28) CG: 2.14 Spray only: IG: 2 (n = 34). Both gargle and spray: IG: 2 gargles, 4 sprays (n = 52) Nasal rinse: IG: 0.70 (n = 64) CG: 0.25
Gutiérrez-García 2022	Nasopharyngeal and oropha-	COVID-19 frontline medical	Reduce risk of COVID-19 in	SES (pH 6.5 to 7.5; REDOX potential 750 - 950 mV;	Written instructions provided to follow a prophylactic rinse protocol with SES 3 times/day for 4 weeks with advice	Not clearly specified; leaders of	Individually and face to face	Mexican COVID-19 hospital	4 nasal sprays (~ 0.4 mL) and 10 mL mouth-	None described	None described	None described	None described

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Table 1. Description of interventions in included studies, using the items from the Template for Intervention Description and Replication (TIDieR) checklist *(Continued)*

	ryngeal rinses with a neutral electrolyzed water (SES)	staff (nurses and physicians, males or females)	frontline unvaccinated medical staff	0.0015% of active species of chlorine and oxygen) provided by Esteripharma S.A. de C.V Per participant: - 4 plastic flasks of 240 mL oral SES (ESTERICIDE® Bucofaríngeo, COFEPRIS registration no. 1003C2013 SSA) with a graduated cap and - 4 plastic flasks of 30 mL nasal rinse (Esteri-Flu®, COFEPRIS registration no. 308C2015 SSA), with a valve for spraying	on correct way to use the mouthwashes and sprays and the need to report possible side effects immediately: a) nasal cavity: 4 vertical sprays in each nostril, inhaled deeply at the time of each spray b) oral cavity: mouthwash and gargle 10 mL for 60 seconds, then spit out In addition to standard COVID-19 safety protocols requiring wearing of adequate personal protection equipment at all times,[49] frequent handwashing[50] and disinfection of secondary uniform and footwear[51] and bath at end of working day	nursing and other relevant healthcare department distributed the study information and were the point of contact and monitored the protocol so they may have distributed intervention materials				wash gargle for 60 seconds 3 times / day for 4 weeks (September to November 2020)			
Goodall 2014	2 active interventions:	University students	Decrease the incidence	A. Vitamin D_3: container of 8 capsules of 10,000 IU (pur-	A. Vitamin D: instructed to take 1 pill weekly	Not specified, presum-	Vitamin D_3 supplied indi-	In university student hous-	2 months overall	None described.	None described.	None described.	None described.

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Table 1. Description of interventions in included studies, using the items from the Template for Intervention Description and Replication (TIDieR) checklist *(Continued)*

	A. Vitamin D_3 supplementation B. Gargling water		of URTI through increased vitamin D levels (associated with greater frequency and severity of URTI) and gargling (as preventative measure against URTI)	chased from Euro-Pharm International Canada Inc.) Weekly email reminder B. Gargling: 30 mL of tap water 2/day	B. Gargling: instructed to gargle twice daily for 30 seconds All participants received general lifestyle and health advice on sleep, nutrition, hand hygiene, and exercise.	ably the researchers, including a study pharmacist	vidually, but no further details. Method of lifestyle and health advice provision also not described.	ing (in residences or off-campus) in Canada	Vitamin D_3: weekly supplementation and email reminder Gargling: 30 mL of water for 30 seconds twice daily				
Ide 2014	2 active interventions (no control): A. Green tea gargling B. Water gargling	High school students	Prevent influenza spread and infection in high school students who are at increased	A. Bottled green tea (500 mL) containing a catechin concentration of 37 ± 0.2 mg/dL, including approximately 18% (-)-epigallocatechin gallate (manufactured by the Kakegawa Tea Merchants Association).	A. Provision of green tea B. Advice to gargle with tap water and not to gargle green tea during study A. and B. Advice to gargle at least 3 times/day (after arriving at school, after lunch, and after school) Consumption of green tea and other	Materials supplied by researchers. High schools' vice principals and head teachers as-	Green tea supplied individually to students. Mode of gargling advice not described.	High schools in Japan	Gargling 3 times/day for 90 days	None described.	None described.	Daily questionnaire included questions about daily adherence to gargling regimen. Adherence rate of	Gargling adherence rate: green tea group: 73.7%; water group: 67.2%

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Table 1. Description of interventions in included studies, using the items from the Template for Intervention Description and Replication (TIDieR) checklist *(Continued)*

			risk from close interaction through gargling as a non-pharmaceutical intervention, specifically green tea containing highly bioactive catechin (-)-epigallocatechin gallate, with possible anti-influenza virus properties	Concentration measured by high-performance liquid chromatography based on the average concentration in 10 bottles from the same production lot (September 2011) used for gargling in the study. B. Tap water	tea was not restricted for either group. Safety monitoring carried out throughout the study (not further described).	sisted with safety monitoring.						gargling at or above 75%, and absence of green tea gargling when in the water gargling group.	
Satomura 2005	2 active in-	Healthy adults	Prevent URTIs	A. Water B. 15 to 30 times dilut-	Local administrators instructed participants to:	Local project admin-	Not specified,	18 healthcare	60 days overall	If diluted povi-	3 participants	Completion of gargling	9 participants did not

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terventions: A. Water gargling B. Povidone-iodine gargling	through gargling water alone, which may wash out pathogens from the pharynx and oral cavity through whirling water or through chlorine, or povidone-iodine for its perceived virucidal properties	ed 7% povidone-iodine (as indicated by manufacturer)	- gargle dose of water or povidone-iodine 3 times/day; - maintain handwashing routine; - not change other hygiene habits; - not take any cold remedies; - complete gargling diary. Weekly monitoring of hygienic actions and encouragement to keep up assigned intervention every week	istrators (18 healthcare professionals) provided instructions and monitoring and encouragement.	but likely to have been face-to-face and individually, at least initially for instructions	sites in Japan (4 in northern region, 9 in central region, 5 in western region)	1. Water gargling: 20 mL for 15 s at least 3 times/day 2. Povidone-iodine gargling: 20 mL of dilution 3 times/day	done-iodine caused serious discomfort or was not available, participants were allowed to gargle with water instead.	assigned to povidone-iodine gargled with water instead as the povidone-iodine "did not agree with them".	diary: frequency of gargling and handwashing Weekly monitoring and encouragement by local administrators	complete diary. Average frequency of gargling / person / day: With water: A: 3.6 B: 0.8 Control: 0.9 With povidone-iodine: A.: < 0.1 B: 2.9 Control: 0.2

ABH: alcohol-based rub
AGNPs: ARGOVIT silver nanoparticles
ARI: acute respiratory infection
CDC: Centers for Disease Control and Prevention
CG: control group
CHG: chlorhexidine gluconate
CHW: community health worker
CO: carbon monoxide
DCCs: daycare centres

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DCT: daily contact testing
FM: face masks
H: handwashing
HCP: healthcare personnel
HCW: healthcare worker
HH: hand hygiene
HSG: hand sanitiser group
HSW: hand-washing with soap and water
HW: hand-washing
HWWS: hand-washing with soap
IG: intervention group
IHIP: integrated environmental home-based intervention package
ILI: influenza-like illness
IU: international units
LFD: lateral flow device
LNS: lipid-based nutrient supplements
LTCFs: long-term care facilities
m: metre
min: minute
N: nutrition
NGOs: non-governmental organisations
NH: nursing home
NHS: National Health Service
no.: number
NPIs: non-pharmaceutical interventions
PCR: polymerase chain reaction
PM2.5: particulate matter of less than 2.5 microns
RAs: research assistants
RIs: respiratory infections
RTIs: respiratory tract infections
S: sanitation
SD: standard deviation
SES: electrolysed water
SSTI: skin and soft-tissue infection
SWG: soap-and-water group
TCID: tissue-culture infectious dose
URTI: upper respiratory tract infection
W: water
WHO: World Health Organization
wk: week
WSH: combined water, sanitation and handwashing
WSHN: combined water, sanitation, handwashing and nutrition
w/w: weight for weight

[1] Filtration efficiency testing was conducted using a Fluke 985 particle counter (volumetric sampling rate of 2.83 litres/ minute. The measurement was taken of particles 0.3–0.5 µm in diameter flowing through the material with a face velocity of 8.5 cm/s. Internal testing found that cloth masks with an external layer made of Pellon 931 polyester fusible

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interface ironed onto interlocking knit with a middle layer of interlocking knit could achieve a 60% filtration efficiency. Upon discussions with the manufacturers, the researchers learned that those materials could not be procured. Using materials that were available, the highest filtration efficiency possible was 37%.
[2] "the exterior and interiors were spunbond and the middle layer was meltblown"
[3] 10 times with bar soap and water
[4] Featured the Honorable Prime Minister of Bangladesh Sheikh Hasina, the head of the Imam Training Academy, and the national cricket star Shakib Al Hasan.
[5] A grassroots organization with a network of volunteers across the country
[6] "consistent with the WHO guideline that defines physical distancing as one meter of separation." www.who.int/westernpacific/emergencies/covid-19/information/physical-distancing (accessed 13 June 2022).
[7] Occupational Safety and Health Administration (OSHA). OSHA technical manual: section VIII: chapter 2: respiratory protection. US Department of Labor. www.osha.gov/dts/osta/otm/otm_viii/otm_viii_2.html (accessed 21 April 2020).
[8] Ministry of Health and Long-Term Care, Public Health Division, Provincial Infectious Diseases Advisory Committee. Preventing respiratory illnesses: protecting patient and staff: infection control and surveillance standards for febrile respiratory illness (FRI) in non-outbreak conditions in acute care hospitals [September 2005] http://www.health.gov.on.ca/english/providers/program/infectious/diseases/best_prac/bp_fri_080406.pdf (accessed September 11 2009). [URL inactive]
[9] Before eating, after sneezing, coughing, handling money, using restroom, returning to desk and interacting with others who may be sick
[10] after coming into classroom, before and after lunch, after break, after physical education, when they went home and after coughing, sneezing or blowing their noses
[11] after toileting and when visibly dirty plus a protocol for particular circumstances: after coming into the classroom; before and after lunch; after playing outside; when they went home; after coughing, sneezing, or blowing their noses; and after diapering
[12] 1) when entering into the classroom; 2) after sneezing, coughing, or blowing their nose; 3) after using the toilet/washroom; 4) before eating any food; and 5) when leaving the school at the end of the day
[13] what to do if hands were dirty, why students should wash their hands, benefits of washing hands and using hand sanitiser, procedure for washing hands using hand sanitiser, to cover mouth and nose with upper part of sleeve while coughing and/or sneezing
[14] Boyce JM, Pittet D, Healthcare Infection Control Practices Advisory Committee, HICPAC/ SHEA/APIC/IDSA Hand Hygiene Task Force. Guideline for hand hygiene in healthcare settings. Recommendations of the Healthcare Infection Control Practices Advisory Committee and the HICPAC/SHEA/APIC/ IDSA Hand Hygiene Task Force. MMWR Recommendations and Reports 2002;51(RR-16):1–45. www.cdc.gov/mmwr/preview/mmwrhtml/rr5116a1.htm (accessed 21 April 2020). International Bank for Reconstruction and Development/ World Bank, Bank-Netherlands Water Partnership, Water and Sanitation Program. Hand washing manual: a guide for developing a hygiene promotion program to increase handwashing with soap. http://go.worldbank.org/PJTS4A53C0 (Accessed 16 May 2007). *[URL inactive]* California State Department of Education. *Techniques for Preventing the Spread of Infectious Diseases*. Sacramento (CA): California State Department of Education, 1983. Geiger BF, Artz L, Petri CJ, Winnail SD, Mason JW. *Fun with Handwashing Education*. Birmingham (AL): University of Alabama, 2000. Roberts A, Pareja R, Shaw W, Boyd B, Booth E, Mata JI. A tool box for building health communication capacity. www.globalhealthcommunication.org/tools/29 (Accessed 10 October 2007). *[URL inactive]* Stark P. *Handwashing Technique. Instructor's Packet. Learning Activity Package*. Sacramento (CA): California State Department of Education, 1982.
[15] DIN EN 1500: Chemische Desinfektionsmittel und Antiseptika, Hygienische Händedesinfektion, Prüfverfahren und Anforderungen (Phase 2/Stufe 2). Brüssel (Belgium): CEN, European Comittee for Standardization 1997;1-20.
[16] DIN EN 12791: Chemische Desinfektionsmittel und Antiseptika, Chirugische Händedesinfektionsmittel - Prüfverfahren und Anforderungen (Phase 2/Stufe 2). Brüssel (Belgium): CEN, European Comittee for Standardization 2005;1-31.
[17] after defaecation, after cleaning an infant who had defaecated, before preparing food, before eating, and before feeding infants
[18] non-governmental organisation that supports community-based health and development initiatives
[19] "Healthy Hands" Rules (from Figure 3 in paper): Do use "special soap" when arrive to school, before lunch, after go to bathroom (only if soap and water not available), if rub nose or eyes or if fingers in mouth, if teacher asks. Do not: use "special soap" if hand dirt on them, put "special soap" on another student, play with 'special soap", put hands near eyes after using "special soap".
[20] Calculated by subtracting each day's soap weight from the previous day's weight. Maximum number of grams of soap consumed for each compound was identified and the day on which the maximum soap consumption was recorded. A per capita estimate of daily soap consumption was calculated
[21] National Health and Medical Research Council. Staying Healthy in Child Care. Canberra (Australia): Australian Government Publishing Service, 1994
[22] upon arrival, before and after lunch, and prior to departure
[23] World Health Organization. (2012). Hand hygiene in outpatient and home-based care and long-term care facilities: a guide to the application of the WHO multimodal hand hygiene improvement strategy and the "My Five Moments For Hand Hygiene" approach. World Health Organization. apps.who.int/iris/handle/10665/78060 (accessed 15 June 2022)

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[24] Moment 1 (before touching a resident) = Room In; Moment 4 (after touching a resident) and Moment 5 (after touching a resident's surroundings) = Room Out; Moment 2 (before a clean/antiseptic procedure) = Before Clean; Moment 3 (after body fluid exposure risk) – After Dirty
[25] Handsome: handhygiëne in verpleeghuizen.: Zorg voor beter; 2019 May 03. URL: www.zorgvoorbeter.nl/handsome (accessed 7 June 2022)
[26] Veiligheid en Kwaliteit: Project Handen uit de Mouwen.: Stichting Samenwerkende Rijnmond Ziekenhuizen
[27] Auditor training.: Hand Hygiene Australia URL: www.hha.org.au/audits/auditor-training (accessed 7 June 2022)
[28] no long nails, acrylic nails, or polished nails and not wearing a ring, bracelet, wristwatch, brace, or long sleeves.
[29] Persoonlijke hygiëne: Verpleeghuizen, woonzorgcentra, voorzieningen voor kleinschalig wonen voor ouderen.: Werkgroep Infectie Preventie; 2014. URL: tinyurl.com/wpfqr8p (accessed 7 June 2022)
[30] knowledge and awareness of HH guidelines, perceived importance of performing HH, perceived behavioural control (i.e. perceived ease or difficulty of performing the behaviour), and habit
[31] "According to the Dutch national guidelines, HH is mandatory for caregivers before touching/preparing food, before caregivers themselves ate or assisted children with eating, and before wound care; and after diapering, after toilet use/wiping buttocks, after caregivers themselves coughed/sneezed/wiped their own nose, after contact with body fluids (e.g. saliva, vomit, urine, blood, or mucus when wiping children's noses), after wound care, and after hands were visibly soiled." (p. 2495)
[32] Having touched household items being used by the index patients and/or other symptomatic household contacts, and after coughing/sneezing, before meals, before preparing meals and when returning home
[33] Which addresses "contextual, psychosocial, and technological factors at the societal, community, interpersonal, individual, and habitual levels". (Luby 2018)
[34] Hussain F, Luby SP, Unicomb L, Leontsini E, Naushin T, Buckland AJ, et al. Assessment of the acceptability and feasibility of child potties for safe child feces disposal in rural Bangladesh. The American Journal of Tropical Medicine and Hygiene. 2017;97: 469–76.
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[37] Menon P, Nguyen PH, Saha KK, Khaled A, Sanghvi T, Baker J, et al. Combining intensive counseling by frontline workers with a nationwide mass media campaign has large differential impacts on complementary feeding practices but not on child growth: results of a cluster-randomized program evaluation in Bangladesh. The Journal of Nutrition 2016;146:2075–84.
[38] comprised of: senior program manager-intervention delivery, senior program manager-operations, Sanitation Intervention Team leader, senior field research officer, training officer, field research officers, CHW supervisors and CHWs
[39] SODIS: www.sodis.ch/index_EN.html
[40] after defecation, after changing diapers, before food preparation and before eating
[41] 1. Wash both hands with water and soap before eating/ handling food 2. Wash both hands with water and soap/ash after defecation 3. Wash both hands with water and soap/ash after cleaning baby's bottom 4. Use hygienic latrine by all family members including Children 5. Dispose of children's faeces into hygienic latrines 6. Clean and maintain latrine 7. Construct a new latrine if the existing one is full and fill the pit with soil/ash. 8. Safe collection and storage of drinking water 9. Draw drinking water from arsenic safe water point 10. Wash raw fruits and vegetables with safe water before eating and cover food properly 11. Manage menstruation period safely (p.605)
[42] Rosenstock IM, Strecher VJ, Becker MH. Social learning theory and the Health Belief Model. Health Education Quarterly 1988;15:175–83.
[43] Glanz K, Rimer BK, 2005. Theory at a Glance: A Guide for Health Promotion Practice. Washington, DC:US Department of Health and Human Services, Public Health Service, National Institutes of Health, National Cancer Institute.
[44] Hovland CI, Janis IL, Kelley HH, 1953. Communication and Persuasion; Psychological Studies of Opinion Change. New Haven, CT: Yale University Press.
[45] Based on family of five, consuming 2L of water per person per day, the bottle would last almost a year
[46] W: key concepts for water treatment and contamination, procedures for refilling dispenser and distributing bottled chlorine, chlorine testing and reporting; H: HW with soap at critical times and creating supportive environment; S: contamination pathways; N: early initiation and exclusive breastfeeding, complementary and supplementary feeding, LNS procedures for collection from health facility and delivery tracking, teaching mamas how to feed Mwanzobora to the child, cooking demonstration, age-specific messaging about nutrition
[47] Department of Health and Social Care. Lateral flow device performance data. July 7, 2021. www.gov.uk/government/publications/lateral-flow-device-performance-data (accessed 15 June 2022).
[48] "applicable to schools as defined in national guidelines were, face to face contact (within 1 metre for any length of time) or skin to skin contact or someone the case coughed on; or within 1 metre for ≥1 minute; or within 1-2 metres for >15 minutes." P.2 of Supplementary appendix

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Trusted evidence.
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[49] i.e., surgical uniform, N95 mask, eye-sealing glasses and plastic wallet, disposable cap, latex gloves, rubber footwear for hospital use and disposable shoe covers, while working. Additionally, third level care health professionals wore a full protective mask, Dermacare®, overalls with zipper, and an integrated hood with elastic hand and ankle cuffs, double disposable boot covers and double latex gloves.
[50] With liquid soap (2% chlorhexidine gluconate) and hand disinfection (0.05% chlorhexidine gluconate and 60-80% ethyl alcohol).
[51] With 80% ethyl alcohol

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Table 2. Results from trials of hand hygiene compared to control

Study	Comparison (see Table 1 for details of interventions)	Reported outcomes	Results
Alzaher 2018 cluster-RCT Saudi Arabia	Hand-washing workshop and posters versus usual practice	% absence days due to URI	0.39% and 0.72% in intervention group schools; 0.86% and 1.39% in control schools
Arbogast 2016 cluster-RCT USA	Hand sanitiser + wipes + hand foam versus none Both groups received education + signage about hand-washing	1. Health insurance claims for preventable illnesses per employee 2. Absences per employee	1. 0.30 claims in intervention; 0.37 in control (27% relative reduction; P = 0.03) 2. 1.45 in intervention; 1.53 in control (5.0% relative reduction in intervention; P = 0.30)
Ashraf 2020 cluster-RCT Bangladesh	6 intervention arms: water quality, sanitation, hand washing, combined WSH, nutrition, nutrition + WSH	7-day prevalence of acute respiratory illness (ARI).	Hand washing reduced ARI cases by 32% (RR 0.68, 95% CI 0.52 to 0.88)
Azor-Martinez 2016 RCT Spain	Hand-washing with soap and-water plus hand sanitiser versus usual hand-washing practices	% absence days due to URI	1.15% in intervention; 1.68% in control. Significantly lower in intervention (P < 0.001)
Azor-Martinez 2018 cluster-RCT Spain	Education and hand hygiene with soap and water versus hand hygiene with sanitiser versus usual hand-washing procedures	1. URI incidence rate ratio (primary) 2. Percentage difference in absenteeism days	1. HH soap versus control 0.94 (95% CI 0.82 to 1.08); HH sanitiser versus control 0.77 (95% CI 0.68 to 0.88); HH soap versus HH sanitiser 1.21 (95% CI 1.06 to 1.39) 2. HH soap 3.9% versus control 4.2% (P < 0.001); HH sanitiser 3.25% versus control 4.2% (P = 0.026); HH soap 3.9% versus HH sanitiser 3.25% (P < 0.001)
Biswas 2019 cluster-RCT Bangladesh	Hand sanitiser and respiratory hygiene education and cough/sneeze hygiene versus no intervention	1. ILI incidence rate (at least 1 episode) 2. Laboratory-confirmed influenza	1. 22 per 1000 student-weeks in intervention; 27 per 1000 student-weeks in control, not statistically significantly different 2. 3 per 1000 student-weeks in intervention; 6 per 1000 student-weeks in control, P = 0.01
Correa 2012 cluster-RCT Colombia	Alcohol-based hand sanitiser in addition to hand-washing versus usual hand-washing practice	ARIs in 3rd trimester of follow-up	Hazard ratio for intervention to control 0.69 (95% CI 0.57 to 0.83)
Cowling 2008 cluster-RCT Hong Kong	Hand hygiene (36 households) versus face mask (mask) versus education (control)	Secondary attack rate for: 1. laboratory-confirmed influenza; 2. ILI definition 1; 3. ILI definition 2;	1. HH 0.06; mask 0.07; control 0.06 2. HH 0.18; mask 0.18; control 0.18 3. HH 0.11; mask 0.10; control 0.11 4. HH 0.04; mask 0.08; control 0.04

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Table 2. Results from trials of hand hygiene compared to control *(Continued)*

		4. ILI definition 3.	
Cowling 2009 cluster-RCT Hong Kong	Hand hygiene (HH) versus face mask + hand hygiene (HH + mask) versus education (control)	Secondary attack rate for: 1. laboratory-confirmed influenza; 2. ILI definition 1; 3. ILI definition 2.	1. HH 5; HH + mask 7; control 10 2. HH 16; HH + mask 21; control 19 3. HH 4; HH + mask 7; control 5
DiVita 2011 (conference abstract) RCT Bangladesh	Hand-washing stations with soap and motivation vs none	1. SAR for laboratory-confirmed influenza 2. SAR for ILI	1. SAR higher in intervention group (11.0% versus 7.5%) 2. SAR higher in intervention group (14.2% versus 11.9%)
Feldman 2016 cluster-RCT Israel	Hand disinfection + soap and water installed versus none	1. Number of respiratory infections 2. Number of off-duty days	1. 11 in each group 2. 112 in intervention; 104 in control
Gwaltney 1980 RCT USA	Virucidal hand wash versus placebo	1. Number with illness after immediate exposure 2. Number with illness after 2-hour delay in exposure	1. 0 of 8 in intervention; 7 of 7 in control 2. 1 of 10 in intervention; 6 of 10 in control
Hubner 2010 RCT Germany	Hand disinfection provided versus none	Odds ratios (95% CI) (intervention:control) 1. Influenza 2. Common cold 3. Sinusitis 4. Sore throat 5. Fever 6. Cough	1. 1.02 (0.20 to 5.23) 2. 0.35 (0.17 to 0.71) 3. 1.87 (0.52 to 6.74) 4. 0.62 (0.31 to 1.25) 5. 0.38 (0.14 to 0.99) 6. 0.45 (0.22 to 0.91)
Ladegaard 1999 RCT Denmark	Hand hygiene and education versus none	Sick days during the "effect period"	22 days/child in the intervention group versus 36 days/child in the control group
Larson 2010 cluster-RCT USA	Education versus education with alcohol-based hand sanitiser versus education with hand sanitiser and face masks	Incidence rate ratios (episodes per 1000 person-weeks) for: 1. URI; 2. ILI; 3. influenza. Secondary attack rates for: 4. URI/ILI/influenza; 5. ILI/influenza.	1. HS 29; HS + masks 39; control 35 2. HS 1.9; HS + masks 1.6; control 2.3 3. HS 0.6; HS + masks 0.5; control 2.3 4. HS 0.14; HS + masks 0.12; control 0.14 5. HS 0.02; HS + masks 0.02; control 0.02

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Table 2. Results from trials of hand hygiene compared to control *(Continued)*

Little 2015 RCT England	Bespoke automated web-based hand hygiene motivational intervention with tailored feedback versus none	Number of participants with 1 or more episodes of URI	Risk ratio for intervention to control 0.86 (95% CI 0.83 to 0.89; P < 0.001)
Luby 2005 RCT Pakistan	Antibacterial soap and education about hand-washing versus plain soap and education versus none	1. Cough or difficulty breathing in children < 15 yrs (episodes/100 person-weeks) 2. Congestion or coryza in children < 15 yrs (episodes/100 person-weeks) 3. Pneumonia in children < 5 yrs (episodes/100 person-weeks)	All outcomes significantly lower than control 1. 4.21 in antibacterial soap group; 4.16 in plain soap group; 8.50 in control group 2. 7.32 in antibacterial soap group; 6.87 in plain soap group; 14.78 in control group 3. 2.42 in antibacterial soap group; 2.20 in plain soap group; 4.40 in control group
Millar 2016 cluster-RCT USA	Standard educational promotion of hand-washing versus enhanced promotion versus promotion plus a once-weekly application of chlorhexidine-based body wash	Incidence rates of ARI over 20 months	37.7 enhanced + body wash; 29.3 enhanced; 35.3 standard; RR for enhanced + body wash to standard 1.07 (95% CI 1.03 to 1.11); RR for enhanced to enhanced + body wash 0.78 (95% CI 0.75 to 0.81)
Morton 2004 cluster-RCT cross-over study USA	Alcohol gel plus education versus regular hand-washing	Absence due to infectious illness	Results not stated numerically
Nicholson 2014 cluster-RCT India	Combination hand-washing promotion with provision of free soap versus none	Target children: 1. Episodes of ARI (per 100 person-weeks) 2. School absence episodes (per 100 person-days) Families: 3. Episodes of ARI	1. 16 in intervention; 19 in control 2. 1.2 in intervention; 1.7 in control 3. 10 in intervention; 11 in control
Priest 2014 cluster-RCT New Zealand	Hand hygiene education and hand sanitiser versus education alone	1. % absence days due to respiratory illness 2. % absence days due to any illness	1. 0.84% in intervention group; 0.80% in control (P = 0.44) 2. 1.21% in intervention group; 1.16% in control (P = 0.35)
Ram 2015 RCT Bangladesh	Education to promote intensive hand-washing in households plus soap provision versus none	1. Secondary attack ratio for intervention to control for ILI 2. Laboratory-confirmed influenza	1. 1.24 (95% CI 0.93 to 1.65) 2. 2.40 (95% CI 0.68 to 8.47)
Roberts 2000 cluster-RCT	Hand-washing programme with training for staff and children versus none	Incidence rate ratio for ARI	IRR 0.92 for intervention to control (95% CI 0.86 to 0.99)

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Table 2. Results from trials of hand hygiene compared to control *(Continued)*

Australia			
Sandora 2008 cluster-RCT USA	Hand sanitiser and education versus none	Incidence rates for ARI (episodes per person-month)	0.43 in intervention; 0.42 in control
Savolainen-Kopra 2012 cluster-RCT Finland	Hand hygiene with soap and water (IR1 group) versus with alcohol-based hand rub (IR2 group) versus control (none); intervention groups also received education	1. Number of respiratory infection episodes/week 2. Number of reported infection episodes/week 3. Number of reported sick leave episodes/week	1. 0.076 in IR1; 0.085 in IR2; 0.080 in control, NS 2. 0.097 in IR1; 0.107 in IR2; 0.104 in control, NS 3. 0.042 in IR1; 0.035 in IR2; 0.035 in control. Significantly higher in IR1 compared with control
Simmerman 2011 cluster-RCT Thailand	Hand-washing (HW) versus hand-washing plus paper surgical face masks (HW + FM) versus control (none)	Odds ratios for secondary attack rates for influenza	OR for HW: control 1.20 (95% CI 0.76 to 1.88) OR for HW + masks: control 1.16 (95% CI 0.74 to 1.82) OR for HW + masks: HW 0.72 (95% CI 0.21 to 2.48)
Stebbins 2011 cluster-RCT USA	Training in hand and respiratory (cough) hygiene + hand sanitiser versus none	Incidence rate ratios for intervention to control for: 1. laboratory-confirmed influenza (RT-PCR); 2. influenza-A; 3. absence.	1. IRR 0.81 (95% CI 0.54 to 1.23) 2. IRR 0.48 (95% CI 0.26 to 0.87) 3. IRR 0.74 (95% CI 0.56 to 0.97)
Swarthout 2020 cluster-RCT Kenya	There were 6 intervention groups: chlorinated drinking water (W), improved sanitation (S), handwashing with soap (H), combined WSH, improved nutrition (N) through counselling lipid based nutrient supplementation (LNS) combined WSHN There were 2 control groups passive control (no promotional visits), a double-sized active control (monthly visits to measure mid–upper arm circumference)	Prevalence of ARIs in children	No evidence of an effect: RR 0.97, 95% CI 0.90 to 1.04.
Talaat 2011 cluster-RCT Egypt	Mandatory hand-washing intervention + education versus none	1. Number of absence days due to ILI 2. Number of absence days	1. 917 in intervention; 1671 in control (P < 0.001) 2. 13,247 in intervention; 19,094 in control (P < 0.001)
Teesing 2021 cluster-RCT Netherlands	Hand hygiene enhancement activities versus no activities.	Incidence of gastroenteritis, influenza-like illness (ILI), assumed pneumonia, urinary tract infections (UTIs), and infections caused MRSA in residents	Hand hygiene reduced risk of ILI (RR 0.51, 95% CI 0.31 to 0.83)

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Table 2. Results from trials of hand hygiene compared to control *(Continued)*

Temime 2018 cluster-RCT France	Hand hygiene with alcohol-based hand rub, promotion, staff education, and local work groups versus none	Incidence rate of ARI clusters (5 or more people in same nursing home)	2 ARI clusters in intervention; 1 in control
Turner 2012 RCT USA	Antiviral hand treatment versus no treatment	1. Number of rhinovirus infections 2. Common cold infections 3. Rhinovirus-associated illnesses	1. 49 in intervention; 49 in control, NS 2. 56 in intervention; 72 in control, NS 3. 26 in intervention; 24 in control, NS
White 2001 DB-RCT USA	Hand rub with benzalkonium chloride (hand sanitiser) versus placebo	ARI symptoms Laboratory: testing of virucidal and bactericidal activity of the product	30% to 38% decrease of illness and absenteeism (RR for illness absence incidence 0.69; RR for absence duration 0.71)
Yeung 2011 cluster-RCT Hong Kong	Alcohol-based hand gel + materials + education versus control (basic life support workshop)	Difference between pre-study period and post study in pneumonia infections recorded in residents	0.63/1000 reduction in intervention group; 0.16/1000 increase in control
Zomer 2015 cluster-RCT Netherlands	4 components: 1. Hand hygiene products, paper towel dispensers, soap, alcohol-based hand sanitiser, and hand cream provided for 6 months 2. Training and booklet 3. 2 team training sessions aimed at hand hygiene improvement 4. Posters and stickers for caregivers and children as reminders. Combination versus usual practice	Incidence rate ratio for intervention to control for common cold	IRR 1.07 (95% CI 0.97 to 1.19) 8.2 episodes per child-year in intervention; 7.4 episodes per child-year in control

ARI: acute respiratory infection
CI: confidence interval
cluster-RCT: cluster-randomised controlled trial
DB-RCT: double-blind randomised controlled trial
HH: hand hygiene
HS: hand sanitiser
HW: hand-washing
ILI: influenza-like illness
IRR: incidence rate ratio
NS: non-significant
OR: odds ratio
RCT: randomised controlled trial
RR: risk ratio
RT-PCR: reverse-transcriptase polymerase chain reaction
SAR: secondary attack rate

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URI: upper respiratory infection
yrs: years

Table 3. Results from trials of hand hygiene + medical/surgical masks compared to control

Study	Comparison (see Table 1 for details of interventions)	Reported outcomes	Results
Aelami 2015 (conference abstract) RCT Saudi Arabia	Hand hygiene education + alcohol-based hand rub + soap + surgical masks vs none	Proportion with ILI (defined as presence of ≥ 2 of the following during their stay: fever, cough, and sore throat)	52% in intervention; 55.3% in control (P < 0.001)
Aiello 2010 cluster-RCT USA	Face mask use (FM) vs face masks + hand hygiene (FM + HH) vs control Note that this study is not included in meta-analysis as each treatment group included only 1 cluster.	1. ILI 2. Laboratory-confirmed influenza A or B	Significant reduction in ILI cases in both intervention groups compared with control over weeks 3 to 6 No significant differences between FM and FM + HH
Aiello 2012 cluster-RCT USA	Face mask use (FM) vs face masks + hand hygiene (FM + HH) vs control	1. Clinical ILI 2. Laboratory-confirmed influenza A or B	1. Non-significant reductions in FM group compared with control over all weeks. Significant reduction in FM + HH group compared with control in weeks 3 to 6 2. Non-significant reductions in both intervention groups compared with control
Cowling 2009 cluster-RCT Hong Kong	Hand hygiene (HH) vs hand hygiene plus face masks (HH + mask) vs control	Secondary attack ratio for: 1. laboratory-confirmed influenza; 2. ILI definition 1; 3. ILI definition 2.	1. HH 5; HH + mask 7; control 10 2. HH 16; HH + mask 21; control 19 3. HH 4; HH + mask 7; control 5
Larson 2010 cluster-RCT USA	Education (control) vs education with alcohol-based hand sanitiser (HS) vs education + HS + face masks (HS + mask)	Incidence rate ratios (episodes per 1000 person-weeks) for: 1. URI; 2. ILI; 3. influenza. Secondary attack rates for: 4. URI/ILI/influenza; 5. ILI/influenza.	1. HS 29; HS + mask 39; control 35 2. HS 1.9; HS + mask 1.6; control 2.3 3. HS 0.6; HS + mask 0.5; control 2.3 4. HS 0.14; HS + mask 0.12; control 0.14 5. HS 0.02; HS + mask 0.02; control 0.02
Simmerman 2011 cluster-RCT Thailand	Control vs hand-washing (HW) vs hand-washing + paper surgical face masks (HW + mask)	Odds ratio for secondary attack rates for influenza	OR for HW: control 1.20 (95% CI 0.76 to 1.88) OR for HW + mask: control 1.16 (95% CI 0.74 to 1.82) OR for HW + mask: HW 0.72 (95% CI 0.21 to 2.48)
Suess 2012 cluster-RCT Germany	Face mask + hand hygiene (mask + HH) vs face masks only (mask) vs none (control)	Secondary attack rates in household contacts: 1. Laboratory-confirmed influenza 2. ILI	1. Mask 9; mask + HH 15; control 23 2. Mask 9; mask + HH 9; control 17

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CI: confidence interval
cluster-RCT: cluster-randomised controlled trial
FM: face mask
HH: hand hygiene
HS: hand sanitiser
HW: hand-washing
ILI: influenza-like illness
OR: odds ratio
RCT: randomised controlled trial
URI: upper respiratory infection
vs: versus

Table 4. Results from trials of soap + water compared to hand sanitisers

Study	Comparison (see Table 1 for details of interventions)	Reported outcomes	Results
Azor-Martinez 2018 cluster-RCT Spain	Education and hand hygiene with soap and water (HH soap) vs hand hygiene with sanitiser (HH sanitiser) vs usual hand-washing procedures	1. URI incidence rate ratio (primary) 2. Percentage difference in absenteeism days	1: HH soap vs control 0.94 (95% CI 0.82 to 1.08); HH sanitiser vs control 0.77 (95% CI 0.68 to 0.88); HH soap vs HH sanitiser 1.21 (95% CI 1.06 to 1.39) 2: HH soap 3.9% vs control 4.2% (P < 0.001); HH sanitiser 3.25% vs control 4.2% (P = 0.026); HH soap 3.9% vs HH sanitiser 3.25% (P < 0.001)
Pandejpong 2012 cluster-RCT Thailand	Alcohol hand gel applied every 60 minutes vs every 120 minutes vs once before lunch (3 groups).	Absent days due to confirmed ILI/ present days	0.017 in every hour group; 0.025 in every 2 hours group; 0.026 in before lunch group. Statistically significant difference between every hour group and before lunch group, and between every hour and every 2 hours groups
Savolainen-Kopra 2012 cluster-RCT Finland	Hand hygiene with soap and water (IR1 group) vs with alcohol-based hand rub (IR2 group) vs control (none); intervention groups also received education	1. Number of respiratory infection episodes/week 2. Number of reported infection episodes/week 3. Number of reported sick leave episodes/week	1. 0.076 in IR1; 0.085 in IR2; 0.080 in control, NS 2: 0.097 in IR1; 0.107 in IR2; 0.104 in control, NS 3: 0.042 in IR1; 0.035 in IR2; 0.035 in control. Significantly higher in IR1 compared with control
Turner 2004a and- Turner 2004b RCT Canada	Study 1. Ethanol vs salicylic acid 3.5% vs salicylic acid 1% and pyroglutamic acid 3.5% Study 2. Skin cleanser wipe vs ethanol (control)	% of volunteers infected with rhinovirus	7% in each intervention group; 32% in control (study 1) 22% in intervention, 30% in control (study 2)

CI: confidence interval
cluster-RCT: cluster-randomised controlled trial
HH: hand hygiene
ILI: influenza-like illness
NS: non-significant
RCT: randomised controlled trial
URI: upper respiratory infection
vs: versus

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Table 5. Results from trials of surface/object disinfection (with or without hand hygiene) compared to control

Study	Comparison (see Table 1 for details of interventions)	Reported outcomes	Results
Ban 2015 cluster-RCT China	Hand hygiene products, surface cleaning and disinfection provided to families and kindergartens vs none	1. Respiratory illness 2. Cough and expectoration	1. OR 0.47 for intervention to control (95% CI 0.38 to 0.59) 2. OR 0.56 (95% CI 0.48 to 0.65)
Carabin 1999 cluster-RCT Canada	One-off hygiene education and disinfection of toys with bleach vs none	Difference in incidence rate for URTI (cluster-level result)	0.28 episodes per 100 child-days lower in intervention group (95% CI 1.65 lower to 1.08 higher); URTI incidence rate IRR 0.80 (95% CI 0.68 to 0.93)
Ibfelt 2015 cluster-RCT Denmark	Disinfectant washing of linen and toys by commercial company every 2 weeks vs usual care	Presence of respiratory viruses on surfaces	Statistically significant reduction in intervention group in adenovirus, rhinovirus, RSV, metapneumovirus, but not other viruses including coronavirus
Kotch 1994 RCT USA	Training in hand-washing and diapering and disinfection of surfaces vs none	Respiratory illness incidence rate in: 1. children < 24 months; 2. children >= 24 months.	1. 14.78 episodes per child-year in intervention; 15.66 in control 2. 12.87 in intervention; 11.77 in control
McConeghy 2017 RCT USA	Staff education, cleaning products, and audit of compliance and feedback vs none	Infection rates	Upper respiratory infections not reliably recorded or reported.
Sandora 2008 cluster-RCT USA	Hand sanitiser and disinfection of classroom surfaces vs materials about good nutrition (control)	Absence due to respiratory illness (multivariable analysis)	Rate ratio 1.10 for intervention to control (95% CI 0.97 to 1.24)

CI: confidence interval
cluster-RCT: cluster-randomised controlled trial
IRR: incident rate ratio
OR: odds ratio
RCT: randomised controlled trial
RSV: respiratory syncytial virus
URTI: upper respiratory tract infection
vs: versus

Table 6. Results from trials of complex interventions compared to control

Study	Comparison (see Table 1 for details of interventions)	Reported outcomes	Results
Complex hygiene and sanitation interventions compared to control			
Chard 2019 cluster-RCT	Complex sanitation intervention and education vs none	Pupil-reported symptoms of res-	NS difference between groups. 29% of intervention group; 32% control group; adjusted risk ratio 1.08 (95% CI 0.95 to 1.23)

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Table 6. Results from trials of complex interventions compared to control *(Continued)*

Laos		piratory infection over 1 week	
Hartinger 2016 cluster-RCT Peru	Cooking and sanitation provision and education vs none	Number of ARI episodes per child-year	NS difference between groups. Risk ratio for intervention to control 0.95 (95% CI 0.82 to 1.10)
Huda 2012 cluster-RCT Bangladesh	Sanitation provision and education vs none	Respiratory illness	12.6% in intervention group; 13.0% in control group. Not adjusted for multiple outcome measurements. No CIs reported.
Najnin 2019 cluster-RCT Bangladesh	Sanitation and behaviour change intervention (plus cholera vaccine) vs none	Respiratory illness in past 2 days	2.8% in intervention group; 2.9% in control group

ARI: acute respiratory infection
CI: confidence interval
cluster-RCT: cluster-randomised controlled trial
NS: non-significant
RCT: randomised controlled trial
vs: versus

Table 7. Results from trials of virucidal tissues compared to control

Study	Comparison	Reported outcomes	Results
Virucidal tissues compared with placebo or no tissues			
Farr 1988a and Farr 1988b cluster-RCT USA Trial 1 and Trial 2	Trial 1. Virucidal nasal tissues vs placebo vs none Trial 2. Virucidal nasal tissues vs placebo	Respiratory illnesses per person over 24 weeks Trial 1 Trial 2	Trial 1: 3.4 in tissues group; 3.9 in placebo group; 3.6 in no-tissues group Trial 2: 3.4 in tissues group; 3.6 in placebo group NS
Longini 1988 DB-PC RCT USA	Virucidal nasal tissues vs placebo	Secondary attack rate of viral infections (number of infections in household members of index case)	10.0 in intervention; 14.3 in placebo; NS

cluster-RCT: cluster-randomised controlled trial
DB-PC: double-blind, placebo-controlled
NS: non-significant
RCT: randomised controlled trial
vs: versus

Table 8. Summary of main results of the review for the primary outcomes

Interventions	RCT/cluster-RCT (N = 78)
Medical/surgical masks	**Masks (medical/surgical) compared to no masks**

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Table 8. Summary of main results of the review for the primary outcomes *(Continued)*

	9 trials in the community showed no effect on ILI (RR 0.95, 0.84 to 1.09) (Abaluck 2022; Aiello 2010; Alfelali 2020; Barasheed 2014; Canini 2010; Cowling 2008;; MacIntyre 2009;; MacIntyre 2016; Suess 2012); and 6 trials in the community showed no effect on laboratory-confirmed influenza 95% CI RR 1.01 (0.72 to 1.42) (Aiello 2012; Alfelali 2020; Bundgaard 2021; Cowling 2008; MacIntyre 2009; Suess 2012). Two trials in health care workers where the control group wore masks if they were required provided inconclusive results with very wide confidence intervals (Jacobs 2009; MacIntyre 2015). **Medical/surgical masks versus other (non-N95) masks:** 1 trial showed more ILI with cloth mask (RR 13.25, 1.74 to 100.97) (MacIntyre 2015); 1 trial showed no effect of catechin-treated masks on influenza (adjusted OR 2.35, 0.40 to 13.72) (Ide 2016).
N95 respirator	**N95 respirators compared to medical/surgical masks** 3 trials showed no difference for clinical respiratory illness (RR 0.70, 0.45 to 1.10) (MacIntyre 2011; MacIntyre 2013; Radonovich 2019); 4 trials showed no difference for ILI (95% CI RR 0.81, 0.62 to 1.05) (Loeb 2009; MacIntyre 2009; MacIntyre 2011; Radonovich 2019); and 4 trials showed no difference for laboratory-confirmed influenza (95% CI RR 1.06, 0.81 to 1.38) (Loeb 2009; MacIntyre 2009; MacIntyre 2011; Radonovich 2019). 4 trials conducted in HCWs: 3 trials showed no difference for clinical respiratory illness (RR 0.70, 0.45 to 1.10) (MacIntyre 2011; MacIntyre 2013; Radonovich 2019); 3 trials showed no difference for ILI (RR 0.64, 0.32 to 1.31) (Loeb 2009; MacIntyre 2011; Radonovich 2019); and 3 trials showed no difference for laboratory-confirmed ILI (RR 1.02, 0.73 to 1.43) (Loeb 2009; MacIntyre 2011; Radonovich 2019).
Hand hygiene	**Hand hygiene compared to control** 19 trials found an effect on combined outcome (ARI or ILI or influenza) (RR 0.89, 0.83 to 0.94) (Ashraf 2020; Azor-Martinez 2018; Biswas 2019; Correa 2012; Cowling 2008; Cowling 2009; Hubner 2010; Larson 2010; Little 2015; Millar 2016; Nicholson 2014; Ram 2015; Roberts 2000; Sandora 2005; Simmerman 2011; Stebbins 2011; Swarthout 2020; Teesing 2021; Zomer 2015); 9 trials showed an effect on ARI (RR 0.86, 0.81 to 0.90) (Ashraf 2020; Azor-Martinez 2018; Correa 2012; Larson 2010; Little 2015; Millar 2016; Nicholson 2014; Sandora 2005; Swarthout 2020); 11 trials showed no effect on ILI (RR 0.94, 0.81 to 1.09) (Biswas 2019; Cowling 2008; Cowling 2009; Hubner 2010; Larson 2010; Little 2015; Ram 2015; Roberts 2000; Simmerman 2011; Teesing 2021; Zomer 2015); and 8 trials no effect on laboratory-confirmed influenza (RR 0.91, 95% CI 0.63 to 1.30) (Biswas 2019; Cowling 2008; Cowling 2009; Hubner 2010; Larson 2010; Ram 2015; Simmerman 2011; Stebbins 2011).
Hand hygiene + medical/surgical masks	**Hand hygiene + medical/surgical masks compared to control** 7 trials showed no effect on ILI (95% CI RR 0.97, 0.80 to 1.19) (Aelami 2015; Aiello 2010; Aiello 2012; Cowling 2009; Larson 2010; Simmerman 2011; Suess 2012); and 4 trials showed no effect on laboratory-confirmed influenza (RR 0.97, 0.69 to 1.36) (Cowling 2009; Larson 2010; Simmerman 2011; Suess 2012). **Hand hygiene + medical/surgical masks compared to hand hygiene** 3 trials showed no effect on ILI (RR 1.03, 0.69 to 1.53) or laboratory-confirmed influenza (RR 0.99, 0.69 to 1.44) (Cowling 2009; Larson 2010; Simmerman 2011).
Soap + water compared to sanitiser, and comparisons of different types of sanitiser	**Soap + water compared to sanitiser, and comparisons of different types of sanitiser** 1 trial hand sanitiser was more effective than soap and water (Azor-Martinez 2018); 1 trial there was no difference (Savolainen-Kopra 2012). 2 trials in children antiseptic was more effective (Morton 2004; White 2001); 1 trial in children antiseptic = soap (Luby 2005). 1 trial hand sanitisers were better than placebo, but no difference between sanitisers (Turner 2004a); 1 trial no difference between different wipes (Turner 2004b).

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Table 8. Summary of main results of the review for the primary outcomes *(Continued)*

Surface/object disinfection (with or without hand hygiene) compared to control	**Surface/object disinfection compared to control** 2 trials were effective on ARI (Ban 2015; Carabin 1999); 1 trial was effective for viruses detected on surfaces (Ibfelt 2015); 2 trials showed no difference in ARIs (Kotch 1994; McConeghy 2017).
Disinfection of living quarters	-
Complex interventions	**Complex interventions compared to control** 4 trials in low-income countries found no effect on respiratory viral illness (Chard 2019; Hartinger 2016; Huda 2012; Najnin 2019).
Physical interventions (masks, gloves, gowns combined)	-
Gloves	-
Gowns	-
Physical distancing	**Physical distancing compared to self-isolation** 1 trial reported 1 positive SARS-CoV-2 case in the fitness centre access arm versus 0 in the no access arm (risk difference 0.05%, 95% CI − 0.05 to 0.16%) (Helsingen 2021)
Quarantine in the community	**Quarantine compared to control** 1 trial effective for influenza (Cox hazard ratio 0.799, 95% CI 0.66 to 0.97) (Miyaki 2011). **Daily contact testing compared to self-isolation** 1 trial showed non-inferiority of daily contact testing of school-based contacts compared to self-isolation for SARS-CoV-2 (RR 0.96, 95% CI 0.75 to 1.22) (Young 2021)
Eye protection	**Glasses compared to no glasses** 1 pragmatic RCT conducted in Norway wearing any type of eyeglasses when close to other people outside their home (on public transport, in shopping malls etc.), over a 14-day period. Positive COVID-19 tests based on self-reporting were 9.6% and 11.5% (RR 0.83, 95% CI 0.69 to 1.00) (Fretheim 2022a).
Gargling	**Gargling compared to control** 1 trial gargling with tap water was effective, povidone-iodine was not effective (Satomura 2005); 1 trial gargling with green tea was not more effective than tap water (Ide 2014); 1 trial gargling with water was not effective (Goodall 2014); pooling of 2 trials showed no effect of gargling (RR 0.91, 95% CI 0.63 to 1.31) (Goodall 2014; Satomura 2005). **Mouth/nose rinse compared to control** 2 trials found a large protective effect on SARS-CoV-2 (RR 0.07, 0.01 to 0.23) (Almanza-Reyes 2021; Gutiérrez-García 2022).
Virucidal tissues	**Virucidal tissues compared to control** 1 trial had a small effect (Farr 1988a) ("The study authors conclude that virucidal tissues have only a small impact upon the overall rate of natural acute respiratory illnesses"); 2 trials showed a non-significant difference (Farr 1988b; Longini 1988).
Nose wash	-

ARI: acute respiratory infection
CI: confidence interval

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HCW: healthcare worker
ILI: influenza-like illness
OR: odds ratio
RCT: randomised controlled trial
RR: risk ratio

Table 9. Trial authors' outcome definitions

Study	Outcome definitions
Masks (n = 16)	
Abaluck 2022 cluster-RCT Bangladesh	COVID-19 symptoms as per the WHO case definition of probable COVID-19 given epidemiological risk factors: (i) fever and cough; (ii) 3 or more of the following symptoms (fever, cough, general weakness and/or fatigue, headache, myalgia, sore throat, coryza, dyspnoea, anorexia, nausea, and/or vomiting, diarrhoea, and altered mental status); or (iii) loss of taste or smell. The owner of the household's primary phone completed surveys by phone or in-person at weeks 5 and 9 after the start of the intervention. They were asked to report symptoms experienced by any household member consistent with the WHO. COVID-19 case definition. Laboratory: seropositivity was defined by having detectable IgG antibodies in blood samples against SARS-CoV-2, using the SCoV-2 Detect™ IgG ELISA kit (InBios, Seattle, Washington). This assay detects IgG antibodies against the spike protein subunit (S1) of SARS-CoV-2. Safety: harms were not directly assessed in this study, but it is stated no adverse events were reported.
Alfelali 2020 cluster-RCT Haj in Makkah, Saudi Arabia	Laboratory: swabs were placed it into UTM™ (COPAN) viral transport media. Swabs labelled with the participant's unique barcode number were stored in an icebox at –20 ˚C before being re-stored by day's end in a –80 ˚C freezer at the laboratory of the Hajj Research Center at Umm Al-Qura University, Makkah. After Hajj, these swabs were shipped in refrigerated or cold containers to the Centre for Infectious Disease and Microbiology Laboratory Services, Westmead Hospital, NSW, Australia. There, nucleic acid was extracted with the Qiagen bioROBOT EZ instrument (Qiagen, Valencia, CA), and amplification was performed using the Roche LC 480 (Roche Diagnostics GmbH, Mannheim, Germany) instrument. Respiratory viruses were detected using a real-time, multiplex reverse transcription polymerase chain reaction assay targeting human coronaviruses (OC43, 229E and NL63), influenza A and B viruses, respiratory syncytial virus (RSV), parainfluenza viruses 1 to 3, human metapneumovirus, rhinovirus, enterovirus and adenovirus. Middle East respiratory syndrome coronavirus (MERS-CoV) assay targeting the upstream region of the E gene (upE) was also performed. Safety: harms of using face masks were difficulty in breathing (26.2%); discomfort (22%); and a small minority (3%) reported feeling hot, sweating, a bad smell or blurred vision with eyeglasses.
Bundgaard 2021 RCT Denmark	Laboratory: viral RNA was extracted from swab samples in DNA/RNA Shield (Zymo Research) using Quick-RNA Microprep Kit (Zymo Research) with the below modifications. 200 µl samples were incubated for 1 min with proteinase K (Qiagen) in a final concentration of 0.2 µg/µl prior to treatment with lysis buffer (Quick-RNA Microprep Kit). Only a single washing step using 400 µl RNA Wash Buffer (Quick-RNA Microprep Kit) was performed before elution in 15µl RNase free water. Participants tested for SARS-CoV-2 IgM and IgG antibodies in whole blood using a point-of-care test (Lateral Flow test [Zhuhai Livzon Diagnostics]) according to the manufacturer's recommendations. After puncturing a fingertip with a lancet, they withdrew blood into a capillary tube and placed 1 drop of blood followed by 2 drops of saline in the test chamber in each of the 2 test plates (IgM and IgG). Safety: harms were not mentioned as an outcome in the methods, but psychological adverse effects were mentioned, and 14% reported adverse reactions from other people regarding wearing a face mask.

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Table 9. Trial authors' outcome definitions *(Continued)*

Cowling 2008 cluster-RCT Hong Kong	Laboratory: QuickVue Influenza A+B rapid test Viral culture on MDCK (Madin-Darby canine kidney cells) Samples were harvested using NTS, but the text refers to a second procedure from June 2007 onwards with testing for influenza viruses on index participants with a negative QuickVue result but a fever ≥ 38 °C who were also randomised and further followed up. Data on clinical signs and symptoms were collected for all participants, and an additional NTS was collected for later confirmation of influenza infection by viral culture. It is noteworthy that dropout was higher in households of index participants who had a negative result on the rapid influenza test (25/44, 57%) compared to those who had a positive result (45/154, 29%). Effectiveness: secondary attack ratios (SAR): SAR is the proportion of household contacts of an index case who subsequently were ill with influenza (symptomatic contact individuals with at least 1 NTS positive for influenza by viral culture or PCR) 3 clinical definitions were used for secondary analysis: 1. fever ≥ 38 °C or at least 2 of the following symptoms: headache, coryza, sore throat, muscle aches and pains; 2. at least 2 of the following S/S: fever ≥ 37.8 °C, cough, headache, sore throat and muscle aches and pains; and 3. fever of ≥ 37.8 °C plus cough or sore throat. Safety: harms were not mentioned as an outcome in the methods, but it was reported in the results that there were no adverse events.
Jacobs 2009 RCT Japan	Laboratory-confirmation not reported. Effectiveness: URTI is defined on the basis of a symptom score with a score > 14 being a URTI according to Jackson's 1958 criteria ("Jackson score"). These are not explained in text, although the symptoms are listed in Table 3 (any, sore throat, runny nose, stuffy nose, sneeze, cough, headache, earache, feel bad) together with their mean and scores (SD) by intervention arm. Safety: the text does not mention or report harms. These appear to be indistinguishable from URTI symptoms (e.g. headache, which is reported as of significantly longer duration in the intervention arm). Compliance is self-reported as high (84.3% of participants).
Loeb 2009 cluster-RCT HCW Canada	Clinical respiratory illness, influenza-like illness, and laboratory-confirmed respiratory virus infection. 1. Clinical respiratory illness, defined as 2 or more respiratory symptoms or 1 respiratory symptom and a systemic symptom. 2. Influenza-like illness, defined as fever ≥ 38 °C plus 1 respiratory symptom. 3. Laboratory-confirmed viral respiratory infection. Laboratory confirmation was by nucleic acid detection using multiplex RT-PCR for 17 respiratory viruses. Safety: harms were not mentioned as an outcome in the methods, but it is stated in the results that no adverse events were reported by participants.
MacIntyre 2009 cluster-RCT Australia	Eligibility criteria were stipulated as follows: 1. the household contained > 2 adults > 16 years of age and 1 child 0 to 15 years of age; 2. the index child had fever (temperature > 37.8 °C) and either a cough or sore throat; 3. the child was the first and only person to become ill in the family in the previous 2 weeks; 4. adult caregivers consented to participate in the study; and 5. the index child was not admitted to the hospital. Definitions used for outcomes:

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Table 9. Trial authors' outcome definitions *(Continued)*

	1. ILI defined by the presence of fever (temperature > 37.8 °C), feeling feverish or a history of fever, > 2 symptoms (sore throat, cough, sneezing, runny nose, nasal congestion, headache), or 1 of the symptoms listed plus laboratory confirmation of respiratory viral infection. 2. Laboratory confirmation: multiplex RT-PCR tests to detect influenza A and B and RSV, PIV types 1 to 3, picornaviruses (enteroviruses or rhinoviruses), adenoviruses, coronaviruses 229E and OC43, and hMPV plus ≥ 1 symptom Effectiveness: presence of ILI or a laboratory diagnosis of respiratory virus infection within 1 week of enrolment. Safety: harms not mentioned as an outcome in the methods, but it is reported in the results that more than 50% of participants reported concerns with mask wearing, mainly that wearing a face mask was uncomfortable, but there were no significant differences between the P2 (N95) and surgical mask groups. Other concerns were that the child did not want the parent wearing a mask.
Aiello 2010 cluster-RCT USA	Laboratory details are described in appendix. Effectiveness: ILI, defined as cough and at least 1 constitutional symptom (fever/feverishness, chills, headache, myalgia). ILI cases were given contact nurses phone numbers to record the illness and paid USD 25 to provide a throat swab. 368 participants had ILI, 94 of which had a throat swab analysed by PCR. 10 of these were positive for influenza (7 for A and 3 for B), respectively by arm 2, 5 and 3 using PCR, 7 using cell culture. Safety: no outcomes on harms planned or reported.
Canini 2010 cluster-RCT USA	The primary endpoint was the proportion of household contacts who developed an ILI during the 7 days following inclusion. Exploratory cluster-level efficacy outcome, the proportion of households with 1 or more secondary illness in household contacts. A temperature over 37.8 °C with cough or sore throat was used as primary clinical case definition. The authors also used a more sensitive case definition based on a temperature over 37.8 °C or at least 2 of the following: sore throat, cough, runny nose, or fatigue. Safety: adverse reactions due to mask wearing were reported, with 38 (75%) participants in the intervention arm experiencing discomfort with mask use due to warmth (45%), respiratory difficulties (33%), and humidity (33%). Children wearing children face masks reported feeling pain more frequently than other participants wearing adult face masks (P = 0.036).
Aiello 2012 cluster-RCT in halls of residence in the USA	Clinically verified ILI - case definition (presence of cough and at least 1 or more of fever/feverishness, chills, or body aches) Laboratory-confirmed influenza A or B. Throat swab specimens were tested for influenza A or B using real-time PCR. Safety: no outcomes on harms planned or reported.
Barasheed 2014 cluster-RCT Saudi Arabia	Laboratory: 2 nasal swabs from all ILI cases and contacts. 1 for influenza POCT using the QuickVue Influenza (A+B) assay (Quidel Corporation, San Diego, USA) and 1 for later NAT for influenza and other respiratory viruses. However, there was a problem with getting POCT on time during Hajj. Effectiveness: to assess the effectiveness of face masks in the prevention of transmission of ILI. ILI was defined as subjective (or proven) fever plus 1 respiratory symptom (e.g. dry or productive cough, runny nose, sore throat, shortness of breath). Safety: no outcomes on harms planned or reported.
MacIntyre 2011 cluster-RCT China	Clinical respiratory illness Influenza-like illness Laboratory-confirmed viral respiratory infection

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Table 9. Trial authors' outcome definitions *(Continued)*

	Laboratory-confirmed influenza A or B 1. Clinical respiratory illness, defined as 2 or more respiratory or 1 respiratory symptom and a systemic symptom. 2. Influenza-like illness, defined as fever ≥ 38 °C plus 1 respiratory symptom (i.e. cough, runny nose, etc.). 3. Laboratory-confirmed viral respiratory infection (detection of adenoviruses, human metapneumovirus, coronavirus 229E/NL63, parainfluenza viruses 1, 2, and 3, influenza viruses A and B, respiratory syncytial virus A and B, rhinovirus A/B and coronavirus OC43/HKU1 by multiplex PCR). 4. Laboratory-confirmed influenza A or B. 5. Adherence with mask/respirator use. Safety: adherence and adverse effects of mask wearing were collected at exit interviews 4 weeks' post study. Significantly higher adverse events with N95 respirator compared to medical mask for discomfort, headache, difficulty breathing, nose pressure, trouble communicating, not wearing, and unspecified "other" side effects. Over 50% of those wearing N95 respirators reported adverse events. Of those wearing medical masks versus N95 respirators, 85.5% (420/491) versus 47.4% (447/943) reported no adverse events (P < 0.001), respectively.
MacIntyre 2013 cluster-RCT China	Laboratory: 1. Laboratory-confirmed viral respiratory infection in symptomatic participants, defined as detection of adenoviruses; human metapneumovirus; coronaviruses 229E/NL63 and OC43/HKU1; parainfluenza viruses 1, 2, and 3; influenza viruses A and B; respiratory syncytial viruses A and B; or rhinoviruses A/B by NAT using a commercial multiplex PCR (Seegen, Inc., Seoul, Korea). 2. Laboratory-confirmed influenza A or B in symptomatic participants. 3. Laboratory-confirmed bacterial colonisation in symptomatic participants, defined as detection of *Streptococcus pneumoniae*, *Legionella*, *Bordetella pertussis*, *Chlamydia*, *Mycoplasma pneumoniae*, *or Haemophilus influenzae* type B by multiplex PCR (Seegen, Inc.). Effectiveness: clinical respiratory illness defined as 2 or more respiratory symptoms or 1 respiratory symptom and a systemic symptom. ILI defined as fever (38 °C) plus 1 respiratory symptom. Safety: adverse effects measured using a semi-structured questionnaire. Investigators stated that there was higher reported adverse effects and discomfort of N95 respirators compared with the other 2 arms. In terms of comfort, 52% (297 of 571) of the medical mask arm reported no problems, compared with 62% (317 of 512) of the targeted arm and 38% (217 of 574) of the N95 arm (P < 0.001).
MacIntyre 2015 cluster-RCT Vietnam	Clinical respiratory illness, influenza-like illness, and laboratory-confirmed respiratory virus infection. 1. Clinical respiratory illness, defined as 2 or more respiratory symptoms or 1 respiratory symptom and a systemic symptom. 2. Influenza-like illness, defined as fever ≥ 38 °C plus 1 respiratory symptom. 3. Laboratory-confirmed viral respiratory infection. Laboratory confirmation was by nucleic acid detection using multiplex RT-PCR for 17 respiratory viruses. Safety: adverse events associated with face mask use were reported in 40.4% (227/562) of HCWs in the medical/surgical mask arm and 42.6% (242/568) in the cloth mask arm (P = 0.45). The most frequently reported adverse events were: general discomfort (35.1%; 397/1130) and breathing problems (18.3%; 207/1130). The rate of ILI was higher in the cloth mask arm compared to medical/surgical masks (RR 13.25, 95% CI 1.74 to 100.97).
MacIntyre 2016 cluster-RCT China	Clinical respiratory illness, influenza-like illness, and laboratory-confirmed viral respiratory infection. 1. Clinical respiratory illness, defined as 2 or more respiratory symptoms (cough, nasal congestion, runny nose, sore throat, or sneezes) or 1 respiratory symptom and a systemic symptom (chill, lethargy, loss of appetite, abdominal pain, muscle or joint aches).

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Table 9. Trial authors' outcome definitions *(Continued)*

	2. Influenza-like illness, defined as fever ≥ 38 °C plus 1 respiratory symptom. 3. Laboratory-confirmed viral respiratory infection, defined as detection of adenoviruses, human metapneumovirus, coronaviruses 229E/NL63 and OC43/HKU1, parainfluenza viruses 1, 2, and 3, influenza viruses A and B, respiratory syncytial virus A and B, or rhinovirus A/B by NAT using a commercial multiplex PCR. Safety: no outcomes on harms planned or reported.
Radonovich 2019 cluster-RCT USA	Laboratory. Primary outcome: incidence of laboratory-confirmed influenza, defined as: 1. detection of influenza A or B virus by RT-PCR in an upper respiratory specimen collected within 7 days of symptom onset; 2. detection of influenza from a randomly obtained swab from an asymptomatic participant; and 3. influenza seroconversion (symptomatic or asymptomatic), defined as at least a 4-fold rise in haemagglutination inhibition antibody titres to influenza A or B virus between pre-season and postseason serological samples deemed not attributable to vaccination. Effectiveness. Secondary outcomes: incidence of 4 measures of viral respiratory illness or infection as follows: 1. acute respiratory illness with or without laboratory confirmation; 2. laboratory-detected respiratory infection, defined as detection of a respiratory pathogen by PCR or serological evidence of infection with a respiratory pathogen during the study surveillance period(s), which was added to the protocol prior to data analysis; and 3. laboratory-confirmed respiratory illness, identified as previously described (defined as self-reported acute respiratory illness plus the presence of at least PCR–confirmed viral pathogen in a specimen collected from the upper respiratory tract within 7 days of the reported symptoms and/or at least a 4-fold rise from pre-intervention to postintervention serum antibody titres to influenza A or B virus). Influenza-like illness, defined as temperature of at least 100 °F (37.8 °C) plus cough and/or a sore throat, with or without laboratory confirmation. Safety: 19 participants reported skin irritation or worsening acne during years 3 and 4 at 1 site in the N95 respirator group.
Hand and hygiene (n = 35)	
Alzaher 2018 cluster-RCT Saudi Arabia	Episode of URI was defined as having 2 of the following symptoms for a day or 1 of the symptoms for 2 or more consecutive days: 1) a runny nose, 2) a stuffy or blocked nose or noisy breathing, 3) sneezing, 4) a cough, 5) a sore throat, and 6) feeling hot, having a fever or a chill.
Arbogast 2016 cluster-RCT USA	ICD-9 used: 46611: acute bronchiolitis due to respiratory syncytial virus, 46619: acute bronchiolitis due to other infectious organisms, 4800: pneumonia due to adenovirus, 4809: viral pneumonia, unspecified, 4870: influenza with pneumonia, 07999: unspecified viral infection, 4658: acute upper respiratory infections of other multiple sites, 4659: acute upper respiratory infections of unspecified site, 4871: influenza with other respiratory manifestations.
Ashraf 2020 cluster-RCT Bangladesh	Main outcome: 7-day prevalence of acute respiratory infection (ARI), defined as caregiver-reported symptoms of persistent cough or panting, wheezing, or difficulty breathing (1 or 2) in the 7 days before the interview.
Azor-Martinez 2016 RCT Spain	Upper respiratory illness was defined as 2 of the following symptoms during 1 day, or 1 of the symptoms for 2 consecutive days: (1) runny nose; (2) stuffy or blocked nose or noisy breathing; (3) cough; (4) feeling hot or feverish or having chills; (5) sore throat; or (6) sneezing.

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Table 9. Trial authors' outcome definitions *(Continued)*

Azor-Martinez 2018 RCT Spain	Respiratory illness (RI) was defined as the presence of 2 of the following symptoms during 1 day or the presence of 1 of the symptoms for 2 consecutive days: (1) runny nose, (2) stuffy or blocked nose or noisy breathing, (3) cough, (4) feeling hot or feverish or having chills, (5) sore throat, or (6) sneezing. ICD-10 and ICD-9 diagnosis codes used: nonspecific upper respiratory tract infection (465.9), otitis media (382.9), pharyngotonsillitis (463), lower respiratory tract infections (485 and 486), acute bronchitis (490), and bronchiolitis (466.19). Study authors combined the bronchopneumonia code (485) and pneumonia code (486) under the label "lower respiratory tract infections." If > 1 antibiotic was prescribed during an episode, they used the first prescription for analysis. The final diagnosis was done by the medical researchers on the basis of the symptoms described above and a review of the medical history of children with RIs.
Biswas 2019 cluster-RCT Bangladesh	Influenza-like illness: an ILI episode was defined as measured fever > 38 °C or subjective fever and cough. Laboratory-confirmed influenza Nasal swabs for real-time RT-PCR.
Correa 2012 cluster-RCT Colombia	Acute respiratory infection was defined as 2 or more of the following symptoms for at least 24 hours, lasting at least 2 days: runny, stuffy, or blocked nose or noisy breathing; cough; fever, hot sensation, or chills; and/or sore throat. Ear pain alone was considered ARI alternately.
Cowling 2009 cluster-RCT Hong Kong	Laboratory-confirmed of influenza virus infection by RT-PCR for influenza A and B virus. Clinical influenza-like illness: used 2 clinical definitions of influenza based on self-reported data from the symptom diaries as secondary analyses. The first definition of clinical influenza was at least 2 of the following signs and symptoms: temperature 37.8 °C or greater, cough, headache, sore throat, and myalgia; the second definition was temperature 37.8 °C or greater plus cough or sore throat.
DiVita 2011 (conference abstract) RCT Bangladesh	Influenza-like illness was defined as fever in children < 5 years old and fever with cough or sore throat in individuals > 5 years old.
Feldman 2016 cluster-RCT Israel	Infectious diseases grouped into diarrhoeal, respiratory, and skin infection. Based on ICD-9, but no supplementary material was accessible for further definition (Supplementary Material C lists all ICD-9 diagnoses tallied in this "outcome").
Gwaltney 1980 RCT USA	Viral cultures and serology if rhinovirus in laboratory-inoculation
Hubner 2010 RCT Germany	Assessing illness rates due to common cold and diarrhoea. Collecting data on illness symptoms (common cold, sinusitis, sore throat, fever, cough, bronchitis, pneumonia, influenza, diarrhoea) and associated absenteeism at the end of every month. Definitions of symptoms were given to the participants as part of the individual information at the beginning of the study. Whilst most symptoms are quite self-explanatory, "influenza" and "pneumonia" are specific diagnoses that were confirmed by professional diagnosis only. Similarly, (self-) diagnosis of "fever" required objective measurement with a thermometer.
Ladegaard 1999	Laboratory: serological evidence

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Table 9. Trial authors' outcome definitions *(Continued)*

RCT Denmark	Effectiveness: influenza-like illness (described as fever, history of fever or feeling feverish in the past week, myalgia, arthralgia, sore throat, cough, sneezing, runny nose, nasal congestion, headache). However, a positive laboratory finding for influenza converts the ILI definition into one of influenza.
Larson 2010 cluster-RCT USA	Study goals: rates of symptoms and secondary transmission of URIs, incidence of virologically confirmed influenza, knowledge of prevention and treatment strategies for influenza and URIs, and rates of influenza vaccination. 1. Laboratory-confirmed influenza: nasal swabs to test for influenza types A and B as well as other common respiratory viruses by rapid culture (R-Mix, Diagnostic Hybrids, Inc., Athens, OH, USA). PCR and subtyping of the samples was done during the second half of the second year of the study. 2. Influenza-like illness: CDC definition of ILI from the Sentinel Physicians' Network was used to determine when masks should be worn: "temperature of ≥37.8°C and cough and/or sore throat in the absence of a known cause other than influenza". 3. Episodes of URI = upper respiratory infection: not clear, no explicitly stated definition, reported that the most commonly reported URI symptoms are cough or rhinorrhoea.
Little 2015 RCT England	Respiratory tract infections defined as 2 symptoms of an RTI for at least 1 day or 1 symptom for 2 consecutive days. For reported ILI, study authors did not use WHO or CDC definitions because these definitions require measured temperature, and thus were not appropriate (participants were not included after a clinical examination), and they did not use the European Centre for Disease Prevention and Control definition (1 systemic and 1 respiratory symptom) because, according to the international influenza collaboration, this definition does not necessarily differentiate ILI from a common cold. Influenzanet suggests making high temperature a separate element. Their pragmatic definition of ILI therefore required a high temperature (feeling very hot or very cold; or measured temperature > 37.5 °C), a respiratory symptom (sore throat, cough, or runny nose), and a systemic symptom (headache, severe fatigue, severe muscle aches, or severe malaise).
Luby 2005 RCT Pakistan	Defined pneumonia in children according to the WHO clinical case definition: cough or difficulty breathing with a raised respiratory rate (> 60 per minute in individuals younger than 60 days old, > 50 per minute for those aged 60 to 364 days, and > 40 per minute for those aged 1 to 5 years)
Millar 2016 cluster-RCT USA	Medically attended, outpatient cases of acute respiratory infection in the study population. The case definition was any occurrence of the following International Classification of Disease, 9 Revision, Clinical Modification (ICD-9) symptom or disease-specific codes: 460 to 466, 480 to 488, and specifically 465.9, 482.9, 486, and 487.1. **Acute respiratory infections (460 to 466)** 460 Acute nasopharyngitis (common cold) 461 Acute sinusitis 462 Acute pharyngitis 463 Acute tonsillitis 464 Acute laryngitis and tracheitis 465 Acute upper respiratory infections of multiple or unspecified sites 466 Acute bronchitis and bronchiolitis **Pneumonia and influenza (480 to 488)** 480 Viral pneumonia 481 Pneumococcal pneumonia (*Streptococcus pneumoniae* pneumonia) 482 Other bacterial pneumonia

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Table 9. Trial authors' outcome definitions *(Continued)*

	483 Pneumonia due to other specified organism 484 Pneumonia in infectious diseases classified elsewhere 485 Bronchopneumonia, organism unspecified 486 Pneumonia, organism unspecified 487 Influenza 488 Influenza due to identified avian influenza virus 465.9 Acute upper respiratory infections of unspecified site 482.9 Bacterial pneumonia NOS 487.1 Diagnosis of influenza with other respiratory manifestations
Morton 2004 cluster-RCT Cross-over study USA	Respiratory illnesses defined by symptoms of upper respiratory infections such as nasal congestion, cough, or sore throat, in any combination, with or without fever
Nicholson 2014 cluster-RCT India	Acute respiratory infections Operational definitions for all the illnesses were taken from Black's Medical Dictionary. ARIs defined as "Pneumonia, cough, fever, chest pain and shortness of breath, cold, inflammation of any or all of the airways, that is, nose, sinuses, throat, larynx, trachea and bronchi".
Pandejpong 2012 cluster-RCT Thailand	Influenza-like illness defined if 2 or more symptoms of stuffy nose, cough, fever or chills, sore throat, headache, diarrhoea, presence of hand, foot, or mouth ulcers.
Priest 2014 cluster-RCT New Zealand	Respiratory illness was defined as an episode of illness that included at least 2 of the following caregiver-reported symptoms for 1 day, or 1 of these symptoms for 2 days (but not fever alone): runny nose, stuffy or blocked nose or noisy breathing, cough, fever, sore throat, or sneezing.
Ram 2015 RCT Bangladesh	Influenza-like illness Age-specific definitions of ILI. For individuals ≥ 5 years old, ILI was defined as history of fever with cough or sore throat. For children < 5 years old, ILI was defined as fever; study authors used this relatively liberal case definition in order to include influenza cases with atypical presentations in children. Laboratory-confirmed influenza infection Oropharyngeal swabs from index case patients for laboratory testing for influenza. All swabs were tested by PCR for influenza A and B, with further subtyping of influenza A isolates.
Roberts 2000 cluster-RCT Australia	The symptoms of acute upper respiratory illness elicited from parents were: a runny nose, a blocked nose, and cough. Study authors used a definition of colds based on a community intervention trial of virucidal impregnated tissues. A cold was defined as either 2 symptoms for 1 day or 1 of the respiratory symptoms for at least 2 consecutive days, but not including 2 consecutive days of cough alone. Study authors defined a

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Table 9. Trial authors' outcome definitions *(Continued)*

	new episode of a cold as the occurrence of respiratory symptoms after a period of 3 symptom-free days.
Sandora 2005 cluster-RCT USA	The overall rates of secondary respiratory and GI illness. Respiratory illness was defined as 2 of the following symptoms for 1 day or 1 of the symptoms for 2 consecutive days: (1) runny nose; (2) stuffy or blocked nose or noisy breathing; (3) cough; (4) fever, feels hot, or has chills; (5) sore throat; and (6) sneezing. An illness was considered new or separate when a period of at least 2 symptom-free days had elapsed since the previous illness. An illness was defined as a secondary case when it began 2 to 7 days after the onset of the same illness type (respiratory or GI) in another household member.
Savolainen-Kopra 2012 cluster-RCT Finland	Nasal and pharyngeal stick samples from participants with respiratory symptoms
Simmerman 2011 cluster-RCT Thailand	Influenza-like illness defined by WHO as fever plus cough or sore throat, based on self-reported symptoms. Laboratory-confirmed secondary influenza virus infections amongst household members described as the secondary attack rate. The secondary influenza virus infection was defined as a positive rRT-PCR result on days 3 or 7 or a four-fold rise in influenza HI antibody titres with the virus type and subtype matching the index case.
Stebbins 2011 cluster-RCT USA	The primary outcome was an absence episode associated with an influenza-like illness that was subsequently laboratory-confirmed as influenza A or B. The following CDC definition for ILI was used: fever ≥ 38 °C with sore throat or cough.
Swarthout 2020 cluster-RCT Kenya	The primary outcome in this study is ARI symptoms - defined as having caregiver-reported cough or difficulty breathing, including panting or wheezing, within 7 days before the interview - in children younger than 3 years. Prespecified secondary outcomes in this study include difficulty breathing, including panting or wheezing, in the past 7 days (a more specific indicator of respiratory infection than a cough alone); ARI symptoms presenting with fever in the past 7 days (a potentially more severe infection); and enumerator-observed runny nose (an objective outcome).
Talaat 2011 cluster-RCT Egypt	Nasal swab for QuickVue test for influenza A and B viruses. Influenza-like illness (defined as fever > 38 °C and either cough or sore throat).
Teesing 2021 cluster-RCT The Netherlands	Incidence of gastroenteritis, ILI, assumed pneumonia, UTIs using the McGeer criteria, and infections caused by MRSA.
Temime 2018 cluster-RCT France	ARIs were defined as the combination of at least 1 respiratory symptom and 1 symptom of systemic infection.
Turner 2004b RCT Canada	Virologic assays

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Table 9. Trial authors' outcome definitions *(Continued)*

Turner 2012 RCT USA	Laboratory-confirmed rhinovirus infection by PCR assay. Common cold illness was defined as the presence of any of the symptoms of nasal obstruction, rhinorrhoea, sore throat, or cough on at least 3 consecutive days. Illnesses separated by at least 3 symptom-free days were considered as separate illnesses.
Yeung 2011 cluster-RCT Hong Kong	Pneumonia
Zomer 2015 cluster-RCT Netherlands	Incidence of gastrointestinal and respiratory infections in children monitored by parents. The common cold was defined as a blocked or runny nose with at least 1 of the following symptoms: coughing, sneezing, fever, sore throat, or earache.
Hand hygiene and masks (n = 6)	
Aelami 2015 (conference abstract) RCT Saudi Arabia	Influenza-like illness was defined as the presence of at least 2 of the following during their stay: fever, cough, and sore throat. Safety: no outcomes on harms planned or reported.
Aiello 2010 cluster-RCT USA	Influenza-like illness case definition (presence of cough and at least 1 constitutional symptom (fever/feverishness, chills, or body aches). Safety: no outcomes on harms planned or reported.
Cowling 2009 cluster-RCT Hong Kong	2 clinical definitions of influenza. First definition was at least 2 of the following signs and symptoms: temperature 37.8 °C or greater, cough, headache, sore throat, and myalgia. The second was temperature 37.8 °C or greater plus cough or sore throat. Safety: no outcomes on harms planned or reported.
Larson 2010 cluster-RCT USA	Study goals: rates of symptoms and secondary transmission of URIs, incidence of virologically-confirmed influenza, knowledge of prevention and treatment strategies for influenza and URIs, and rates of influenza vaccination. 1. Laboratory-confirmed influenza: nasal swabs to test for influenza types A and B as well as other common respiratory viruses by rapid culture (R-Mix, Diagnostic Hybrids, Inc., Athens, OH, USA). PCR and subtyping of the samples was done during the second half of the second year of the study. 2. Influenza-like illness: CDC definition of ILI from the Sentinel Physicians' Network was used to determine when masks should be worn: "temperature of ≥37.8°C and cough and/or sore throat in the absence of a known cause other than influenza". 3. Episodes of URI = upper respiratory infection: not clear, no explicitly stated definition, reported that the most commonly reported URI symptoms are cough or rhinorrhoea. Safety: no outcomes on harms planned or reported.
Simmerman 2011 cluster-RCT Thailand	Laboratory-confirmed secondary influenza virus infections amongst household members described as the secondary attack rate. The secondary influenza virus infection was defined as a positive rRT-PCR result on days 3 or 7 or a four-fold rise in influenza HI antibody titres with the virus type and subtype matching the index case. Influenza-like illness defined by WHO as fever plus cough or sore throat, based on self-reported symptoms.

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Table 9. Trial authors' outcome definitions *(Continued)*

	Safety: no outcomes on harms planned or reported.
Suess 2012 cluster-RCT Germany	Quantitative RT-PCR for samples of nasal wash. Influenza virus infection as a laboratory-confirmed influenza infection in a household member who developed fever (> 38.0 °C), cough, or sore throat during the observation period. Also secondary outcome measure of the occurrence of ILI as defined by WHO as fever plus cough or sore throat. Safety: the study reported that the majority of participants (107/172, 62%) did not report any problems with mask wearing. This proportion was significantly higher in the group of adults (71/100, 71%) compared to the group of children (36/72, 50%) (P = 0.005). The main problem stated by participants (adults and children) was "heat/humidity" (18/34, 53% of children; 10/29, 35% of adults) (P = 0.1), followed by "pain" and "shortness of breath" when wearing a face mask.
Surface/object disinfection (with or without hand hygiene)(n = 8)	
Ban 2015 cluster-RCT China	Acute respiratory illness classified as the appearance of 2 or more of the following symptoms: fever, cough and expectoration, runny nose and nasal congestion.
Carabin 1999 cluster-RCT Canada	The presence of nasal discharge (runny nose) accompanied by 1 or several of the following symptoms: fever, sneezing, cough, sore throat, ear pain, malaise, irritability. A URTI was defined as a cold for 2 consecutive days.
Chard 2019 cluster-RCT Laos	Pupils were considered to have symptoms of respiratory infection if they reported cough, runny nose, stuffy nose, or sore throat.
Ibfelt 2015 cluster-RCT Denmark	Laboratory confirmation of 16 respiratory viruses: influenza A; influenza B; coronavirus NL63229E, OC43 and HKU1; parainfluenza virus 1, 2, 3, and 4; rhinovirus; RSV A/B; adenovirus; enterovirus; parechovirus; and bocavirus using quantitative PCR
Kotch 1994 RCT USA	Respiratory symptoms include coughing, runny nose, wheezing or rattling in the chest, sore throat, or earache.
McConeghy 2017 RCT USA	Classified infections as lower respiratory tract infections (i.e. pneumonia, bronchitis, or chronic obstructive pulmonary disease exacerbation) or other.
Sandora 2008 cluster-RCT USA	RI was defined as an acute illness that included > 1 of the following symptoms: runny nose, stuffy or blocked nose, cough, fever or chills, sore throat, or sneezing.
White 2001 DB-RCT USA	RI was defined as: cough, sneezing, sinus trouble, bronchitis, fever alone, pink-eye, headache, mononucleosis, and acute exacerbation of asthma.

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Table 9. Trial authors' outcome definitions *(Continued)*

Other (miscellaneous) interventions (n = 5)	
Fretheim 2022a pragmatic RCT Norway	Respiratory infection was defined as having 1 respiratory symptom (stuffed or runny nose, sore throat, cough, sneezing, heavy breathing) and fever, or 1 respiratory symptom and at least 2 more symptoms (body ache, muscular pain, fatigue, reduced appetite, stomach pain, headache, loss of smell.
Hartinger 2016 cluster-RCT Peru	ARI was defined as a child presenting cough or difficulty breathing, or both. ALRI was defined as a child presenting cough or difficulty breathing, with a raised respiratory rate > 50 per minute in children aged 6 to 11 months and > 40 per minute in children aged > 12 months on 2 consecutive measurements. An episode was defined as beginning on the first day of cough or difficulty breathing and ending with the last day of the same combination, followed by at least 7 days without those symptoms.
Huda 2012 cluster-RCT Bangladesh	Study authors classified acute respiratory illness as having cough and fever or difficulty breathing and fever within 48 h prior to interview.
Najnin 2019 cluster-RCT Bangladesh	Classified participants as having respiratory illness if they reported having fever plus either cough or nasal congestion or fever plus breathing difficult.
Satomura 2005 RCT Japan	Upper respiratory tract infection defined as all of the following conditions: 1. both nasal and pharyngeal symptoms; 2. severity of at least 1 symptom increased by 2 grades or more; and 3. worsening of a symptom of 1 increment or more for > 3 days. Because of the difference in the mode of transmission, study authors excluded influenza-like diseases featured by moderate or severe fever; anti-influenza vaccination in the preseason and arthralgia, and treated them separately. The incidence was determined by 1 study physician who was blinded to group assignment.
Virucidal tissues (n = 2)	
Farr 1988a cluster-RCT USA trial 1 and trial 2	RI defined as: occurrence of at least 2 respiratory symptoms on the same day or the occurrence of a single respiratory symptom on 2 consecutive days (except for sneezing). The respiratory symptoms were as follows: sneezing, nasal congestion, nasal discharge, sore throat, scratchy throat, hoarseness, coughing, malaise, headache, feverishness, chilliness and myalgia.
Longini 1988 DB-PC RCT USA	Respiratory illness defined as 1 or more of the following symptoms occurring during the course of acute episode: coryza, sore throat or hoarseness, earache, cough, pain on respiration, wheezy breathing or phlegm from the chest.

ALRI: acute lower respiratory infection
ARIs: acute respiratory infections
CDC: Centers for Disease Control and Prevention
CI: confidence interval
cluster-RCT: cluster-randomised controlled trial
CRI: clinical respiratory illness
DB-PC: double-blind, placebo-controlled
DB-RCT: double-blind randomised controlled trial
DNA: deoxyribonucleic acid

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ELISA: enzyme-linked immunosorbent assay
GI: gastrointestinal
h: hours
HCW: healthcare workers
HI: haemagglutinin
hMPV: human metapneumo virus
ICD-9: International Classification of Disease, 9th Revision, Clinical Modification
ICD-10: International Classification of Disease, 10th Revision, Clinical Modification
IgG: immunoglobulin G
IgM: immunoglobulin M
ILI: influenza-like illness
min: minutes
MRSA: methicillin-resistant Staphylococcus aureus
NAT: nucleic acid testing
NOS: not otherwise specified
NTS: nasal and throat swab
PCR: polymerase chain reaction
PIV: parainfluenza virus
POCT: point-of-care testing
RCT: randomised controlled trial
RI: respiratory infection
RNA: ribonucleic acid
RR: risk ratio
rRT-PCR: real-time reverse transcriptase polymerase chain reaction
RSV: respiratory syncytial virus
RTI: respiratory tract infection
RT-PCR: reverse transcriptase polymerase chain reaction
SAR: secondary attack ratios
SD: standard deviation
S/S: signs and symptoms
URI: upper respiratory infection
URTI: upper respiratory tract infection
UTI: urinary tract infection
WHO: World Health Organization

APPENDICES

Appendix 1. Cochrane Central Register of Controlled Trials (CENTRAL) search string

([mh "Influenza, Human"] OR [mh "Influenzavirus A"] OR [mh "Influenzavirus B"] OR [mh "Influenzavirus C"] OR Influenza:ti,ab OR [mh "Respiratory Tract Diseases"] OR Influenzas:ti,ab OR “Influenza-like”:ti,ab OR ILI:ti,ab OR Flu:ti,ab OR Flus:ti,ab OR [mh ^"Common Cold"] OR "common cold":ti,ab OR colds:ti,ab OR coryza:ti,ab OR [mh coronavirus] OR [mh "sars virus"] OR coronavirus:ti,ab OR Coronaviruses:ti,ab OR [mh "coronavirus infections"] OR [mh "severe acute respiratory syndrome"] OR "severe acute respiratory syndrome":ti,ab OR "severe acute respiratory syndromes":ti,ab OR sars:ti,ab OR [mh "respiratory syncytial viruses"] OR [mh "respiratory syncytial virus, human"] OR [mh "Respiratory Syncytial Virus Infections"] OR "respiratory syncytial virus":ti,ab OR "respiratory syncytial viruses":ti,ab OR rsv:ti,ab OR parainfluenza:ti,ab OR “Respiratory illness”:ti,ab OR ((Transmission) AND (Coughing OR Sneezing)) OR ((respiratory:ti,ab AND Tract) AND (infection:ti,ab OR Infections:ti,ab OR illness:ti,ab)))
AND
([mh "Hand Hygiene"] OR handwashing:ti,ab OR “hand-washing”:ti,ab OR ((Hand:ti,ab OR Alcohol:ti,ab) AND (wash:ti,ab OR Washing:ti,ab OR Cleansing:ti,ab OR Rinses:ti,ab OR hygiene:ti,ab OR rub:ti,ab OR Rubbing:ti,ab OR sanitizer:ti,ab OR sanitiser:ti,ab OR cleanser:ti,ab OR disinfected:ti,ab OR Disinfectant:ti,ab OR Disinfect:ti,ab OR antiseptic:ti,ab OR virucid:ti,ab)) OR [mh "gloves, protective"] OR Glove:ti,ab OR Gloves:ti,ab OR [mh Masks] OR [mh "respiratory protective devices"] OR facemask:ti,ab OR Facemasks:ti,ab OR mask:ti,ab OR Masks:ti,ab OR respirator:ti,ab OR respirators:ti,ab OR [mh ^"Protective Clothing"] OR [mh "Protective Devices"] OR "patient isolation":ti,ab OR ((school:ti,ab OR Schools:ti,ab) AND (Closure:ti,ab OR Closures:ti,ab OR Closed:ti,ab)) OR [mh Quarantine] OR quarantine:ti,ab OR "Hygiene intervention":ti,ab OR [mh Mouthwashes] OR gargling:ti,ab OR "nasal tissues":ti,ab OR [mh "Eye Protective Devices"] OR Glasses:ti,ab OR Goggle:ti,ab OR "Eye protection":ti,ab OR Faceshield:ti,ab OR Faceshields:ti,ab OR Goggles:ti,ab OR "Face shield":ti,ab OR "Face shields":ti,ab OR Visors:ti,ab)
AND

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([mh "Communicable Disease Control"] OR [mh "Disease Outbreaks"] OR [mh "Disease Transmission, Infectious"] OR [mh "Infection Control"] OR "Communicable Disease Control":ti,ab OR "Secondary transmission":ti,ab OR ((Reduced:ti,ab OR Reduce:ti,ab OR Reduction:ti,ab OR Reducing:ti,ab OR Lower:ti,ab) AND (Incidence:ti,ab OR Occurrence:ti,ab OR Transmission:ti,ab OR Secondary:ti,ab))

Appendix 2. PubMed search string

("Influenza, Human"[Mesh] OR "Influenzavirus A"[Mesh] OR "Influenzavirus B"[Mesh] OR "Influenzavirus C"[Mesh] OR Influenza[tiab] OR "Respiratory Tract Diseases"[Mesh] OR "Bacterial Infections/transmission"[Mesh] OR Influenzas[tiab] OR “Influenza-like”[tiab] OR ILI[tiab] OR Flu[tiab] OR Flus[tiab] OR "Common Cold"[Mesh:NoExp] OR "common cold"[tiab] OR colds[tiab] OR coryza[tiab] OR coronavirus[Mesh] OR "sars virus"[Mesh] OR coronavirus[tiab] OR Coronaviruses[tiab] OR "coronavirus infections"[Mesh] OR "severe acute respiratory syndrome"[Mesh] OR "severe acute respiratory syndrome"[tiab] OR "severe acute respiratory syndromes"[tiab] OR sars[tiab] OR "respiratory syncytial viruses"[Mesh] OR "respiratory syncytial virus, human"[Mesh] OR "Respiratory Syncytial Virus Infections"[Mesh] OR "respiratory syncytial virus"[tiab] OR "respiratory syncytial viruses"[tiab] OR rsv[tiab] OR parainfluenza[tiab] OR “Respiratory illness”[tiab] OR ((Transmission[tiab]) AND (Coughing[tiab] OR Sneezing[tiab])) OR ((respiratory[tiab] AND Tract[tiab]) AND (infection[tiab] OR Infections[tiab] OR illness[tiab])))
AND
("Hand Hygiene"[Mesh] OR handwashing[tiab] OR hand-washing[tiab] OR ((Hand[tiab] OR Alcohol[tiab]) AND (wash[tiab] OR Washing[tiab] OR Cleansing[tiab] OR Rinses[tiab] OR hygiene[tiab] OR rub[tiab] OR Rubbing[tiab] OR sanitizer[tiab] OR sanitiser[tiab] OR cleanser[tiab] OR disinfected[tiab] OR Disinfectant[tiab] OR Disinfect[tiab] OR antiseptic[tiab] OR virucid[tiab])) OR "gloves, protective"[Mesh] OR Glove[tiab] OR Gloves[tiab] OR Masks[Mesh] OR "respiratory protective devices"[Mesh] OR facemask[tiab] OR Facemasks[tiab] OR mask[tiab] OR Masks[tiab] OR respirator[tiab] OR respirators[tiab] OR "Protective Clothing"[Mesh:NoExp] OR "Protective Devices"[Mesh] OR "patient isolation"[tiab] OR ((school[tiab] OR Schools[tiab]) AND (Closure[tiab] OR Closures[tiab] OR Closed[tiab])) OR Quarantine[Mesh] OR quarantine[tiab] OR “Hygiene intervention”[tiab] OR "Mouthwashes"[Mesh] OR gargling[tiab] OR “nasal tissues”[tiab] OR "Eye Protective Devices"[Mesh] OR Glasses[tiab] OR Goggle[tiab] OR “Eye protection”[tiab] OR Faceshield[tiab] OR Faceshields[tiab] OR Goggles[tiab] OR “Face shield”[tiab] OR “Face shields”[tiab] OR Visors[tiab])
AND
("Communicable Disease Control"[Mesh] OR "Disease Outbreaks"[Mesh] OR "Disease Transmission, Infectious"[Mesh] OR "Infection Control"[Mesh] OR Transmission[sh] OR “Prevention and control”[sh] OR "Communicable Disease Control"[tiab] OR “Secondary transmission”[tiab] OR ((Reduced[tiab] OR Reduce[tiab] OR Reduction[tiab] OR Reducing[tiab] OR Lower[tiab]) AND (Incidence[tiab] OR Occurrence[tiab] OR Transmission[tiab] OR Secondary[tiab])))
AND
(Randomized controlled trial[pt] OR controlled clinical trial[pt] OR randomized[tiab] OR randomised[tiab] OR placebo[tiab] OR "drug therapy"[sh] OR randomly[tiab] OR trial[tiab] OR groups[tiab])
NOT
(Animals[Mesh] not (Animals[Mesh] and Humans[Mesh]))
NOT
(“Case Reports”[pt] OR Editorial[pt] OR Letter[pt] OR Meta-Analysis[pt] OR “Observational Study”[pt] OR “Systematic Review”[pt] OR “Case Report”[ti] OR “Case series”[ti] OR Meta-Analysis[ti] OR “Meta Analysis”[ti] OR “Systematic Review”[ti])

Appendix 3. Embase (Elsevier) search string

('influenza'/exp OR Influenza:ti,ab OR 'Respiratory Tract Disease'/exp OR Influenzas:ti,ab OR Influenza-like:ti,ab OR ILI:ti,ab OR Flu:ti,ab OR Flus:ti,ab OR 'Common Cold'/de OR "common cold":ti,ab OR colds:ti,ab OR coryza:ti,ab OR 'coronavirus'/exp OR 'SARS coronavirus'/exp OR coronavirus:ti,ab OR Coronaviruses:ti,ab OR 'coronavirus infection'/exp OR 'severe acute respiratory syndrome'/exp OR "severe acute respiratory syndrome":ti,ab OR "severe acute respiratory syndromes":ti,ab OR sars:ti,ab OR 'Pneumovirus'/exp OR 'Human respiratory syncytial virus'/exp OR "respiratory syncytial virus":ti,ab OR "respiratory syncytial viruses":ti,ab OR rsv:ti,ab OR parainfluenza:ti,ab OR “Respiratory illness”:ti,ab OR ((Transmission) AND (Coughing OR Sneezing)) OR ((respiratory:ti,ab AND Tract) AND (infection:ti,ab OR Infections:ti,ab OR illness:ti,ab)))
AND
('hand washing'/exp OR handwashing:ti,ab OR hand-washing:ti,ab OR ((Hand:ti,ab OR Alcohol:ti,ab) AND (wash:ti,ab OR Washing:ti,ab OR Cleansing:ti,ab OR Rinses:ti,ab OR hygiene:ti,ab OR rub:ti,ab OR Rubbing:ti,ab OR sanitizer:ti,ab OR sanitiser:ti,ab OR cleanser:ti,ab OR disinfected:ti,ab OR Disinfectant:ti,ab OR Disinfect:ti,ab OR antiseptic:ti,ab OR virucid:ti,ab)) OR 'protective glove'/exp OR Glove:ti,ab OR Gloves:ti,ab OR 'mask'/exp OR 'gas mask'/exp OR facemask:ti,ab OR Facemasks:ti,ab OR mask:ti,ab OR Masks:ti,ab OR respirator:ti,ab OR respirators:ti,ab OR 'protective clothing'/de OR 'protective equipment'/exp OR "patient isolation":ti,ab OR ((school:ti,ab OR Schools:ti,ab) AND (Closure:ti,ab OR Closures:ti,ab OR Closed:ti,ab)) OR 'Quarantine'/exp OR quarantine:ti,ab OR "Hygiene intervention":ti,ab OR 'mouthwash'/exp OR gargling:ti,ab OR "nasal tissues":ti,ab OR ‘eye protective device'/exp OR Glasses:ti,ab OR Goggle:ti,ab OR "Eye protection":ti,ab OR Faceshield:ti,ab OR Faceshields:ti,ab OR Goggles:ti,ab OR "Face shield":ti,ab OR "Face shields":ti,ab OR Visors:ti,ab)
AND
('Communicable Disease Control'/exp OR 'epidemic'/exp OR 'disease transmission'/exp OR 'Infection Control'/exp OR "Communicable Disease Control":ti,ab OR "Secondary transmission":ti,ab OR ((Reduced:ti,ab OR Reduce:ti,ab OR Reduction:ti,ab OR Reducing:ti,ab OR Lower:ti,ab) AND (Incidence:ti,ab OR Occurrence:ti,ab OR Transmission:ti,ab OR Secondary:ti,ab)))
AND

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(random* OR factorial OR crossover OR placebo OR blind OR blinded OR assign OR assigned OR allocate OR allocated OR 'crossover procedure'/exp OR 'double-blind procedure'/exp OR 'randomized controlled trial'/exp OR 'single-blind procedure'/exp NOT ('animal'/exp NOT ('animal'/exp AND 'human'/exp)))

Appendix 4. CINAHL (EBSCO) search string

((MH "Influenza, Human+") OR (MH "Orthomyxoviridae+") OR TI Influenza OR AB Influenza OR (MH "Respiratory Tract Diseases+") OR TI Influenzas OR AB Influenzas OR TI Influenza-like OR AB Influenza-like OR TI ILI OR AB ILI OR TI Flu OR AB Flu OR TI Flus OR AB Flus OR (MH "Common Cold+") OR TI "common cold" OR AB "common cold" OR TI colds OR AB colds OR TI coryza OR AB coryza OR (MH "coronavirus+") OR (MH "sars virus+") OR TI coronavirus OR AB coronavirus OR TI Coronaviruses OR AB Coronaviruses OR (MH "coronavirus infections+") OR (MH "severe acute respiratory syndrome+") OR TI "severe acute respiratory syndrome" OR AB "severe acute respiratory syndrome" OR TI "severe acute respiratory syndromes" OR AB "severe acute respiratory syndromes" OR TI sars OR AB sars OR (MH "respiratory syncytial viruses+") OR TI "respiratory syncytial virus" OR AB "respiratory syncytial virus" OR TI "respiratory syncytial viruses" OR AB "respiratory syncytial viruses" OR TI rsv OR AB rsv OR TI parainfluenza OR AB parainfluenza OR TI “Respiratory illness” OR AB “Respiratory illness” OR ((Transmission) AND (Coughing OR Sneezing)) OR ((TI respiratory OR AB respiratory AND Tract) AND (TI infection OR AB infection OR TI Infections OR AB Infections OR TI illness OR AB illness)))
AND
((MH "Handwashing+") OR TI handwashing OR AB handwashing OR TI hand-washing OR AB hand-washing OR ((TI Hand OR AB Hand OR TI Alcohol OR AB Alcohol) AND (TI wash OR AB wash OR TI Washing OR AB Washing OR TI Cleansing OR AB Cleansing OR TI Rinses OR AB Rinses OR TI hygiene OR AB hygiene OR TI rub OR AB rub OR TI Rubbing OR AB Rubbing OR TI sanitizer OR AB sanitiser OR TI sanitizer OR AB sanitiser OR TI cleanser OR AB cleanser OR TI disinfected OR AB disinfected OR TI Disinfectant OR AB Disinfectant OR TI Disinfect OR AB Disinfect OR TI antiseptic OR AB antiseptic OR TI virucid OR AB virucid)) OR (MH "gloves+") OR TI Glove OR AB Glove OR Gloves OR (MH "Masks+") OR (MH "respiratory protective devices+") OR TI facemask OR AB facemask OR TI Facemasks OR AB Facemasks OR TI mask OR AB mask OR TI Masks OR AB Masks OR TI respirator OR AB respirator OR TI respirators OR AB respirators OR (MH "Protective Clothing") OR (MH "Protective Devices+") OR TI "patient isolation" OR AB "patient isolation" OR ((TI school OR AB school OR TI Schools OR AB Schools) AND (TI Closure OR AB Closure OR TI Closures OR AB Closures OR TI Closed OR AB Closed)) OR (MH "Quarantine+") OR TI quarantine OR AB quarantine OR TI "Hygiene intervention" OR AB "Hygiene intervention" OR (MH "Mouthwashes+") OR TI gargling OR AB gargling OR TI "nasal tissues" OR AB "nasal tissues" OR (MH "Eye Protective Devices+") OR TI Glasses OR AB Glasses OR TI Goggle OR AB Goggle OR TI "Eye protection" OR AB "Eye protection" OR TI Faceshield OR AB Faceshield OR TI Faceshields OR AB Faceshields OR TI Goggles OR AB Goggles OR TI "Face shield" OR AB "Face shield" OR TI "Face shields" OR AB "Face shields" OR TI Visors OR AB Visors)
AND
((MH "Infection Control+") OR (MH "Disease Outbreaks+") OR (MH "Infection Control+") OR TI "Communicable Disease Control" OR AB "Communicable Disease Control" OR TI "Secondary transmission" OR AB "Secondary transmission" OR ((TI Reduced OR AB Reduced OR TI Reduce OR AB Reduce OR TI Reduction OR AB Reduction OR TI Reducing OR AB Reducing OR TI Lower OR AB Lower) AND (TI Incidence OR AB Incidence OR TI Occurrence OR AB Occurrence OR TI Transmission OR AB Transmission OR TI Secondary OR AB Secondary)))
AND
((MH "Clinical Trials+") OR (MH "Quantitative Studies") OR TI placebo* OR AB placebo* OR (MH "Placebos") OR (MH "Random Assignment") OR TI random* OR AB random* OR TI ((singl* or doubl* or tripl* or trebl*) W1 (blind* or mask*)) OR AB ((singl* or doubl* or tripl* or trebl*) W1 (blind* or mask*)) OR TI clinic* trial* OR AB clinic* trial* OR PT clinical trial)

Appendix 5. Previous search strategies (pre-2010)

Details of the 2010 update and the search strategy used in the original review and the 2009 search strategy updates for MEDLINE, CENTRAL, EMBASE and CINAHL

In the 2010 update we searched, as we have done previously, the Cochrane Central Register of Controlled Trials (CENTRAL) 2010, Issue 3, which includes the Acute Respiratory Infections Group's Specialised Register, MEDLINE (April 2009 to October week 2, 2010), EMBASE (April 2009 to October 2010) and CINAHL (January 2009 to October 2010). Details of previous searches are in Appendix 1. In addition, to include more of the literature of low-income countries in this update, we ran searches in LILACS (2008 to October 2010), Indian MEDLARS (2008 to October 2010) and IMSEAR (2008 to October 2010).

We used the following search strategy (updated to include new and emerging respiratory viruses) to search MEDLINE and CENTRAL. We combined the MEDLINE search strategy with the Cochrane Highly Sensitive Search Strategy for identifying randomised trials in MEDLINE: sensitivity- and precision-maximising version (2008 revision) (Ovid format) (Lefebvre 2011). We also included an additional search strategy based on the work of Fraser, Murray and Burr (Fraser 2006) to identify observational studies.

1 Influenza, Human/
2 exp Influenzavirus A/
3 exp Influenzavirus B/
4 Influenzavirus C/
5 (influenza* or flu).tw.
6 Common Cold/
7 common cold*.tw.

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8 Rhinovirus/
9 rhinovir*.tw.
10 adenoviridae/ or mastadenovirus/ or adenoviruses, human/
11 adenoviridae infections/ or adenovirus infections, human/
12 adenovir*.tw.
13 coronavirus/ or coronavirus 229e, human/ or coronavirus oc43, human/ or infectious bronchitis virus/ or sars virus/
14 coronavir*.tw.
15 coronavirus infections/ or severe acute respiratory syndrome/
16 (severe acute respiratory syndrome* or sars).tw.
17 respiratory syncytial viruses/ or respiratory syncytial virus, human/
18 Respiratory Syncytial Virus Infections/
19 (respiratory syncytial virus* or rsv).tw.
20 Pneumovirus Infections/
21 parainfluenza virus 1, human/ or parainfluenza virus 3, human/
22 parainfluenza virus 2, human/ or parainfluenza virus 4, human/
23 (parainfluenza* or para-influenza* or para influenza).tw.
24 enterovirus a, human/ or exp enterovirus b, human/ or enterovirus c, human/ or enterovirus d, human/
25 Enterovirus Infections/
26 enterovir*.tw.
27 Human bocavirus/
28 bocavirus*.tw.
29 Metapneumovirus/
30 metapneumovir*.tw.
31 Parvovirus B19, Human/
32 parvoviridae infections/ or erythema infectiosum/
33 parvovirus*.tw.
34 Parechovirus/
35 parechovirus*.tw.
36 acute respiratory tract infection*.tw.
37 acute respiratory infection*.tw.
38 or/1-37
39 Handwashing/
40 (handwashing or hand washing or hand-washing).tw.
41 hand hygiene.tw.
42 (sanitizer* or sanitiser*).tw.
43 (cleanser* or disinfectant*).tw.
44 gloves, protective/ or gloves, surgical/
45 glov*.tw.
46 masks/ or respiratory protective devices/
47 (mask or masks or respirator or respirators).tw.
48 Protective Clothing/
49 Protective Devices/
50 Patient Isolators/
51 Patient Isolation/
52 patient isolat*.tw.
53 (barrier* or curtain* or partition*).tw.
54 negative pressure room*.tw.
55 ((reverse barrier or reverse-barrier) adj3 (nurs* or unit or isolation)).tw.
56 Cross Infection/pc [Prevention & Control]
57 (cross infection* adj2 prevent*).tw.
58 Communicable Disease Control/
59 Infection Control/
60 (school* adj3 (clos* or dismissal*)).tw.
61 temporary closur*.tw.
62 mass gathering*.tw.
63 (public adj2 (gathering* or event*)).tw.
64 (bans or banning or banned or ban).tw.
65 (outbreak adj3 control*).tw.
66 distancing*.tw.
67 Quarantine/
68 quarantine*.tw.
69 (protective adj2 (cloth* or garment* or device* or equipment)).tw.

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70 ((protective or preventive) adj2 (procedure* or behaviour* or behavior*)).tw.
71 personal protect*.tw.
72 (isolation room* or isolation strateg*).tw.
73 (distance adj2 patient*).tw.
74 ((spatial or patient) adj separation).tw.
75 cohorting.tw.
76 or/39-75
77 38 and 76
78 (animals not (animals and humans)).sh.
79 77 not 78

Ovid MEDLINE

1 Influenza, Human/
2 exp Influenzavirus A/
3 exp Influenzavirus B/
4 Influenzavirus C/
5 (influenza* or flu).tw.
6 Common Cold/
7 common cold*.tw.
8 Rhinovirus/
9 rhinovir*.tw.
10 adenoviridae/ or mastadenovirus/ or adenoviruses, human/
11 adenoviridae infections/ or adenovirus infections, human/
12 adenovir*.tw.
13 coronavirus/ or coronavirus 229e, human/ or coronavirus oc43, human/ or infectious bronchitis virus/ or sars virus/
14 coronavir*.tw.
15 coronavirus infections/ or severe acute respiratory syndrome/
16 (severe acute respiratory syndrome* or sars).tw.
17 respiratory syncytial viruses/ or respiratory syncytial virus, human/
18 Respiratory Syncytial Virus Infections/
19 (respiratory syncytial virus* or rsv).tw.
20 Pneumovirus Infections/
21 parainfluenza virus 1, human/ or parainfluenza virus 3, human/
22 parainfluenza virus 2, human/ or parainfluenza virus 4, human/
23 (parainfluenza* or para-influenza* or para influenza).tw.
24 enterovirus a, human/ or exp enterovirus b, human/ or enterovirus c, human/ or enterovirus d, human/
25 Enterovirus Infections/
26 enterovir*.tw.
27 Human bocavirus/
28 bocavirus*.tw.
29 Metapneumovirus/
30 metapneumovir*.tw.
31 Parvovirus B19, Human/
32 parvoviridae infections/ or erythema infectiosum/
33 parvovirus*.tw.
34 Parechovirus/
35 parechovirus*.tw.
36 acute respiratory tract infection*.tw.
37 acute respiratory infection*.tw.
38 or/1-37
39 Handwashing/
40 (handwashing or hand washing or hand-washing).tw.
41 hand hygiene.tw.
42 (sanitizer* or sanitiser*).tw.
43 (cleanser* or disinfectant*).tw.
44 gloves, protective/ or gloves, surgical/
45 glov*.tw.
46 masks/ or respiratory protective devices/
47 (mask or masks or respirator or respirators).tw.
48 Protective Clothing/
49 Protective Devices/

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50 Patient Isolators/
51 Patient Isolation/
52 patient isolat*.tw.
53 (barrier* or curtain* or partition*).tw.
54 negative pressure room*.tw.
55 ((reverse barrier or reverse-barrier) adj3 (nurs* or unit or isolation)).tw.
56 Cross Infection/pc [Prevention & Control]
57 (cross infection* adj2 prevent*).tw.
58 Communicable Disease Control/
59 Infection Control/
60 (school* adj3 (clos* or dismissal*)).tw.
61 temporary closur*.tw.
62 mass gathering*.tw.
63 (public adj2 (gathering* or event*)).tw.
64 (bans or banning or banned or ban).tw.
65 (outbreak adj3 control*).tw.
66 distancing*.tw.
67 Quarantine/
68 quarantine*.tw.
69 (protective adj2 (cloth* or garment* or device* or equipment)).tw.
70 ((protective or preventive) adj2 (procedure* or behaviour* or behavior*)).tw.
71 personal protect*.tw.
72 (isolation room* or isolation strateg*).tw.
73 (distance adj2 patient*).tw.
74 ((spatial or patient) adj separation).tw.
75 cohorting.tw.
76 or/39-75
77 38 and 76
78 (animals not (animals and humans)).sh.
79 77 not 78

Embase.com search strategy, October 2010
The search strategy was broadened in 2010 to be more inclusive of new and emerging viruses.

#3 #1 AND #25899
#2 766172
#2.8 #2.3 NOT #2.7766172
#2.7 #2.4 NOT #2.6
#2.6 #2.4 AND #2.5
#2.5 'human'/de AND [embase]/lim
#2.4 'animal'/de OR 'nonhuman'/de OR 'animal experiment'/de AND [embase]/lim
#2.3 #2.1 OR #2.2
#2.2 random*:ab,ti OR placebo*:ab,ti OR crossover*:ab,ti OR 'cross over':ab,ti OR allocat*:ab,ti OR trial:ti OR (doubl* NEXT/1 blind*):ab,ti AND [embase]/lim
#2.1 'randomized controlled trial'/exp OR 'single blind procedure'/exp OR 'double blind procedure'/exp OR 'crossover procedure'/exp AND [embase]/lim

#1 74545
#1.65 #1.28 AND #1.6474545
#1.64 #1.29 OR #1.30 OR #1.31 OR #1.32 OR #1.33 OR #1.34 OR #1.35 OR #1.36 OR #1.37 OR #1.38 OR #1.39 OR #1.40 OR #1.41 OR #1.42 OR #1.43 OR #1.44 OR #1.45 OR #1.46 OR #1.47 OR #1.48 OR #1.49 OR #1.50 OR #1.51 OR #1.52 OR #1.53 OR #1.54 OR #1.55 OR #1.56 OR #1.57 OR #1.58 OR #1.59 OR #1.60 OR #1.61 OR #1.62 OR #1.63
#1.63 cohorting:ab,ti OR 'cohort isolation':ab,ti AND [embase]/lim
#1.62 ((spatial OR patient*) NEAR/2 separation):ab,ti AND [embase]/lim
#1.61 (distance NEAR/2 patient*):ab,ti AND [embase]/lim
#1.60 (isolation NEXT/1 (room* OR strateg*)):ab,ti AND [embase]/lim
#1.59 'personal protection':ab,ti AND [embase]/lim
#1.58 ((protective OR preventive) NEAR/2 (procedure* OR behaviour* OR behavior*)):ab,ti AND [embase]/lim
#1.57 (protective NEAR/2 (cloth* OR garment* OR device* OR equipment)):ab,ti AND [embase]/lim
#1.56 quarantin*:ab,ti AND [embase]/lim

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#1.55 distancing:ab,ti AND [embase]/lim
#1.54 ((outbreak* OR transmission OR infection*) NEAR/2 control):ab,ti AND [embase]/lim
#1.53 bans:ab,ti OR banning:ab,ti OR banned:ab,ti OR ban:ab,ti AND [embase]/lim
#1.52 (public NEAR/2 (gathering* OR event*)):ab,ti AND [embase]/lim
#1.51 'mass gathering':ab,ti OR 'mass gatherings':ab,ti AND [embase]/lim
#1.50 (temporar* NEAR/2 closur*):ab,ti AND [embase]/lim
#1.49 (school* NEAR/3 (clos* OR dismissal*)):ab,ti AND [embase]/lim
#1.48 'infection control'/de AND [embase]/lim
#1.47 'epidemic'/dm_pc AND [embase]/lim
#1.46 (('cross infection' OR 'cross infections') NEAR/2 prevent*):ab,ti AND [embase]/lim
#1.45 'cross infection'/dm_pc AND [embase]/lim
#1.44 (('reverse barrier' OR 'reverse-barrier') NEAR/3 (nurs* OR unit OR isolat*)):ab,ti AND [embase]/lim
#1.43 'negative pressure room':ab,ti OR 'negative pressure rooms':ab,ti AND [embase]/lim
#1.42 barrier*:ab,ti OR curtain*:ab,ti OR partition*:ab,ti AND [embase]/lim
#1.41 (patient* NEAR/2 isolat*):ab,ti AND [embase]/lim
#1.40 'patient isolator'/de AND [embase]/lim
#1.39 'protective equipment'/de AND [embase]/lim
#1.38 'protective clothing'/de AND [embase]/lim
#1.37 facemask*:ab,ti OR mask:ab,ti OR masks:ab,ti OR goggles:ab,ti
OR respirator*:ab,ti OR respirators:ab,ti AND [embase]/lim
#1.36 'face mask'/exp OR 'mask'/de OR 'surgical mask'/de AND [embase]/lim
#1.35 glov*:ab,ti AND [embase]/lim
#1.34 'surgical glove'/de AND [embase]/lim
#1.33 cleanser*:ab,ti OR disinfect*:ab,ti OR antiseptic*:ab,ti OR virucid*:ab,ti AND [embase]/lim
#1.32 sanitizer*:ab,ti OR sanitiser*:ab,ti AND [embase]/lim
#1.31 (alcohol NEAR/2 rub*):ab,ti AND [embase]/lim
#1.30 handwash*:ab,ti OR (hand* NEAR/2 (wash* OR cleans* OR hygiene)):ab,ti AND [embase]/lim
#1.29 'hand washing'/de AND [embase]/lim
#1.28 #1.1 OR #1.2 OR #1.3 OR #1.4 OR #1.5 OR #1.6 OR #1.7 OR #1.8 OR #1.9 OR #1.10 OR #1.11 OR #1.12 OR #1.13 OR #1.14 OR #1.15 OR
#1.16 OR #1.17 OR #1.18 OR #1.19 OR #1.20 OR #1.21 OR #1.22 OR #1.23
OR #1.24 OR #1.25 OR #1.26 OR #1.27
#1.27 (respiratory NEAR/2 (infect* OR illness* OR virus* OR pathogen* OR acute)):ab,ti AND [embase]/lim
#1.26 parechovirus*:ab,ti AND [embase]/lim
#1.25 'parechovirus'/de AND [embase]/lim
#1.24 parvovirus*:ab,ti AND [embase]/lim
#1.23 'parvovirus infection'/de OR 'erythema infectiosum'/exp AND [embase]/lim
#1.22 'parvovirus'/de OR 'human parvovirus b19'/de AND [embase]/lim
#1.21 'human metapneumovirus'/de OR 'human metapneumovirus infection'/de AND [embase]/lim
#1.20 'bocavirus'/de OR 'bocavirus infection'/de AND [embase]/lim
#1.19 enterovir*:ab,ti AND [embase]/lim
#1.18 'enterovirus infection'/de OR 'coxsackie virus infection'/de OR 'echovirus infection'/de AND [embase]/lim
#1.17 'enterovirus'/de OR 'coxsackie virus'/exp OR 'echo virus'/de AND [embase]/lim
#1.16 parainfluenza:ab,ti OR 'para influenza':ab,ti OR 'para-influenza':ab,ti AND [embase]/lim
#1.15 'parainfluenza virus'/exp AND [embase]/lim
#1.14 'pneumovirus infection'/de AND [embase]/lim
#1.13 'respiratory syncytial virus':ab,ti OR 'respiratory syncytial viruses':ab,ti OR rsv:ab,ti AND [embase]/lim
#1.12 'respiratory syncytial pneumovirus'/de OR 'respiratory syncytial virus infection'/exp AND [embase]/lim
#1.11 coronavir*:ab,ti OR sars:ab,ti OR 'severe acute respiratory syndrome':ab,ti AND [embase]/lim
#1.10 'coronavirus infection'/de OR 'severe acute respiratory syndrome'/de AND [embase]/lim
#1.9 'coronavirus'/de OR 'human coronavirus nl63'/de OR 'sars coronavirus'/de OR 'transmissible gastroenteritis virus'/de
#1.8 adenovir*:ab,ti AND [embase]/lim
#1.7 'adenovirus infection'/de OR 'human adenovirus infection'/de OR 'human adenovirus'/exp AND [embase]/lim
#1.6 rhinovir*:ab,ti AND [embase]/lim
#1.5 'rhinovirus infection'/de OR 'human rhinovirus'/de AND [embase]/lim
#1.4 'common cold':ab,ti OR 'common colds':ab,ti OR coryza:ab,ti OR colds:ab,ti AND [embase]/lim
#1.3 'common cold'/de OR 'common cold symptom'/de AND [embase]/lim
#1.2 influenza*:ab,ti OR flu:ab,ti AND [embase]/lim
#1.1 'influenza'/exp AND [embase]/lim

CINAHL (EBSCO) search strategy, October 2010
The search strategy was broadened in 2010 to be more inclusive of new and emerging viruses.

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S54 S32 and S53
S53 S44 or S52
S52 S45 or S46 or S47 or S48 or S49 or S50 or S51
S51 TI observational stud* or AB observational stud*
S50 TI cohort stud* or AB cohort stud*
S49 (MH "Cross Sectional Studies")
S48 (MH "Nonconcurrent Prospective Studies")
S47 (MH "Correlational Studies")
S46 (MH "Case Control Studies+")
S45 (MH "Prospective Studies")
S44 S33 or S34 or S35 or S36 or S37 or S38 or S39 or S40 or S41 or S42 or S43
S43 TI allocat* N1 random* or AB allocat* N1 random*
S42 (MH "Quantitative Studies")
S41 TI placebo* or AB placebo*
S40 (MH "Placebos")
S39 TI random* allocation* or AB random* allocation*
S38 (MH "Random Assignment")
S37 TI (randomised control* trial* or randomized control* trial*) or AB (randomised control* trial* or randomized control* trial)
S36 TI ((singl* W1 blind*) or (singl* W1 mask*) or (doubl* W1 blind*) or (doubl* W1 mask*) or (trebl* W1 blind*) or (trebl* W1 mask*) or (tripl* W1 blind*) or (tripl* W1 mask*)) or AB ((singl* W1 blind*) or (singl* W1 mask*) or (doubl* W1 blind*) or (doubl* W1 mask*) or (trebl* W1 blind*) or (trebl* W1 mask*) or (tripl* W1 blind*) or (tripl* W1 mask*))
S35 TI clinic* W1 trial* or AB clinic* W1 trial*
S34 PT clinical trial
S33 (MH "Clinical Trials+")
S32 S15 and S31
S31 S16 or S17 or S18 or S19 or S20 or S21 or S22 or S23 or S24 or S25 or S26 or S27 or S28 or S29 or S30
S30 TI (bans or banning or banned or ban or "outbreak control" or "outbreak controls" or distancing* or quarantine* or "protective clothing" or "protective garment" or "protective garments" or "protective gown" or "protective gowns" or "protective device" or "protective devices" or "protective equipment" or "protective behaviour" or "protective behavior" or "protective behaviours" or "protective behaviors" or "protective procedure" or "protective procedures" or "preventive behaviours" or "preventive behaviour" or "preventive behavior" or "preventive behaviors" or "preventive procedure" or "preventive procedures" or "personal protective" or "isolation room" or "isolation rooms" or "isolation strategy" or "isolation strategies" or "patient distance" or "patient distancing" or "patient separation" or "spatial separation") or AB (handwashing or "hand washing" or hand-washing or "hand hygiene" or sanitizer or sanitiser or cleanser* or disinfectant* or glov* or mask or masks or respirator or respirators or "patient isolation" or "patient isolators" or barrier* or curtain* or partition* or "negative pressure room" or "negative pressure rooms" or "reverse barrier nursing" or "reverse barrier unit" or "reverse barrier isolation" or "cross infection" or "infection control" or "disease control" or "school closure" or "school closures" or "school dismissal" or "school dismissals" or "temporary closure" or "temporary closures" or "mass gathering" or "mass gatherings" or "public gathering" or "public gatherings" or "public event" or "public events")
S29 TI (handwashing or "hand washing" or hand-washing or "hand hygiene" or sanitizer or sanitiser or cleanser* or disinfectant* or glov* or mask or masks or respirator or respirators or "patient isolation" or "patient isolators" or barrier* or curtain* or partition* or "negative pressure room" or "negative pressure rooms" or "reverse barrier nursing" or "reverse barrier unit" or "reverse barrier isolation" or "cross infection" or "infection control" or "disease control" or "school closure" or "school closures" or "school dismissal" or "school dismissals" or "temporary closure" or "temporary closures" or "mass gathering" or "mass gatherings" or "public gathering" or "public gatherings" or "public event" or "public events") or AB (handwashing or "hand washing" or hand-washing or "hand hygiene" or sanitizer or sanitiser or cleanser* or disinfectant* or glov* or mask or masks or respirator or respirators or "patient isolation" or "patient isolators" or barrier* or curtain* or partition* or "negative pressure room" or "negative pressure rooms" or "reverse barrier nursing" or "reverse barrier unit" or "reverse barrier isolation" or "cross infection" or "infection control" or "disease control" or "school closure" or "school closures" or "school dismissal" or "school dismissals" or "temporary closure" or "temporary closures" or "mass gathering" or "mass gatherings" or "public gathering" or "public gatherings" or "public event" or "public events")
S28 (MH "Sterilization and Disinfection")
S27 (MH "Quarantine")
S26 (MH "Area Restriction (Iowa NIC)") OR (MH "Infection Protection (IowaNIC)")
S25 (MH "Infection Control")
S24 (MH "Cross Infection/PC")
S23 (MH "Isolation, Reverse")
S22 (MH "Patient Isolation")
S21 (MH "Protective Devices")
S20 (MH "Protective Clothing")
S19 (MH "Respiratory Protective Devices")
S18 (MH "Masks")
S17 (MH "Gloves")
S16 (MH "Handwashing+")

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S15 S1 or S2 or S3 or S4 or S5 or S6 or S7 or S8 or S9 or S10 or S11 or S12 or S13 or S14
S14 TI ("acute respiratory tract infection" or "acute respiratory tract infections" or "acute respiratory infection" or "acute respiratory infections") or AB (influenza* or flu or "common cold" or "common colds" or rhinovir* or adenovir* or coronavir* or sars or "severe acute respiratory syndrome" or "respiratory syncytial virus" or "respiratory syncytial viruses" or rsv or pneumovir* or parainfluenza* or "para influenza" or para-influenza or enterovir* or bocavir* or metapneumovir* or parvovir* or parechovir*)
S13 TI (influenza* or flu or "common cold" or "common colds" or rhinovir* or adenovir* or coronavir* or sars or "severe acute respiratory syndrome" or "respiratory syncytial virus" or "respiratory syncytial viruses" or rsv or pneumovir* or parainfluenza* or "para influenza" or para-influenza or enterovir* or bocavir* or metapneumovir* or parvovir* or parechovir*) or AB (influenza* or flu or "common cold" or "common colds" or rhinovir* or adenovir* or coronavir* or sars or "severe acute respiratory syndrome" or "respiratory syncytial virus" or "respiratory syncytial viruses" or rsv or pneumovir* or parainfluenza* or "para influenza" or para-influenza or enterovir* or bocavir* or metapneumovir* or parvovir* or parechovir*)
S12 (MH "Respiratory Tract Infections+")
S11 (MH "Parvovirus Infections+")
S10 (MH "Enterovirus Infections+")
S9 (MH "Enteroviruses+")
S8 (MH "Respiratory Syncytial Virus Infections")
S7 (MH "Respiratory Syncytial Viruses")
S6 (MH "SARS Virus")
S5 (MH "Severe Acute Respiratory Syndrome")
S4 (MH "Coronavirus Infections+")
S3 (MH "Coronavirus+") OR (MH "Coronavirus Infections")
S2 (MH "Common Cold")
S1 (MH "Influenza+") OR (MH "Influenza A H5N1") OR (MH "Influenza A

LILACS (Latin America and Caribbean) search strategy
(mh:"Influenza, Human" OR "Gripe Humana" OR "Influenza Humana" OR influenza* OR flu OR grippe OR gripe OR mh:"Influenzavirus A" OR mh:b04.820.545.405* OR mh:b04.909.777.545.405* OR mh:"Influenzavirus B" OR mh:b04.820.545.407* OR mh:b04.909.777.545.407* OR "influenzavirus B" OR mh:"Influenzavirus C" OR "Influenzavirus C" OR mh:"Common Cold" OR "common cold" OR "common colds" OR "Resfriado Común" OR "Resfriado Comum" OR coryza OR "Coriza Aguda") AND (mh:handwashing OR "Lavado de Manos" OR "Lavagem de Mãos" OR "Desinfección de Manos" OR "Desinfecção de Mãos" OR "Higienização de Mãos Pré-Cirúrgica" OR handwash* OR "hand washing" OR "hand hygiene" OR "hand cleaning" OR "hand cleanse" OR "hand cleansing" OR higiene OR sanitizer* OR sanitiser* OR cleanser* OR disinfect* OR esteriliza* OR desinfectar* OR virucid* OR antiseptic* OR mh:"Gloves, Protective" OR "protective glove" OR "protective gloves" OR "Guantes Protectores" OR "Luvas Protetoras" OR mh:e07.700.600.400* OR mh:j01.637.215.600.400* OR mh:j01.637.708.600.400* OR glov* OR guantes OR luvas OR mh:masks OR mask* OR máscaras OR mascarillas OR facemask* OR goggles OR respirator* OR mh:"Respiratory Protective Devices" OR "Dispositivos de Protección Respiratoria" OR "Dispositivos de Proteção Respiratória" OR mh:"Protective Clothing" OR "Ropa de Protección" OR "Roupa de Proteção" OR mh:e07.700.600* OR mh:j01.637.215.600* OR mh:j01.637.708.600* OR mh:"Protective Devices" OR "Equipos de Seguridad" OR "Equipamentos de Proteção" OR mh:e07.700* OR mh:j01.637.708* OR mh:vs2.006.001.001* OR mh:vs4.002.001.001.007.002.002* OR mh:"Patient Isolation" OR "patient isolation" OR "Aislamiento de Pacientes" OR "Isolamento de Pacientes" OR mh:"Patient Isolators" OR "patient isolators" OR "Aisladores de Pacientes" OR "Isoladores de Pacientes" OR barrier* OR curtain* OR partition* OR barrera OR barreira OR cortina OR tabique OR mh:"Cross Infection" OR "cross infection" OR "Infección Hospitalaria" OR "Infecção Hospitalar" OR "Infecciones en Hospitales" OR "Infecciones Nosocomiales" OR "Infecções Nosocomiais" OR mh:"Infection Control" OR mh:n06.850.780.200.450* OR "Control de Infecciones" OR "Controle de Infecções" OR mh:"Communicable Disease Control" OR "Control de Enfermedades Transmisibles" OR "Controle de Doenças Transmissíveis" OR mh:n06.850.780.200* OR mh:sp8.946.819.811* OR mh:"Disease Outbreaks/prevention & control" OR mh:quarantine OR cuarentena OR quarentena OR "personal protection" OR "isolation room" OR "sala de aislamiento" OR "quarto de isolamento" OR "patient distance" OR "distancia del paciente" OR "spatial separation" OR cohort* OR ban OR bans OR banning OR banned OR prohibici* OR proibi* OR "outbreak control" OR distanc* OR "school closure" OR "school closures" OR "temporary closure" OR "temporary closures" OR "cierre de la escuela" OR "fechamento da escola" OR "public gathering" OR "public gatherings" OR "reunion publica" OR "reverse barrier nursing" OR "reverse barrier unit" OR "reverse barrier isolation" OR "negative pressure room" OR "negative pressure rooms" OR "patient separation") AND db:("LILACS") AND type_of_study:("clinical_trials" OR "cohort" OR "case_control")

Indian MEDLARS search strategy
(influenza$ or flu or common cold$ or rhinovir$ or coronavir$ or adenovir$ or severe acute respiratory syndrome$ or sars or respiratory syncytial virus$ or rsv or parainfluenza$ or enterovir$ or metapneumovir$ or parvovir$ or bocavir$ or parechovir$) and (handwashing or hand washing or mask$ or glov$ or protect$ or isolat$ or barrier$ or curtain$ or partition$ or cross infection$ or infection control$ or disease control$ or school$ or quarantine$ or ban$ or cohort$ or distanc$ or spatial separation$)
IMSEAR (Index Medicus for the South East Asia Region) search strategy
(influenza or flu or common cold or rhinovirus or coronavirus or adenovirus or severe acute respiratory syndrome or sars or respiratory syncytial virus or rsv or parainfluenza or enterovirus or bocavirus or metapneumovirus or parvovirus or parechovirus) and (handwashing or hand washing or hand hygiene or sanitizer or sanitiser or cleanser or disinfectant or gloves or masks or mask or protective clothing or protective devices or patient isolation or barrier or curtain or partition or cross infection or disease control or infection control or school or schools or bans or banning or banned or ban or distancing or quarantine or isolation or spatial separation or cohorting or cohort isolation)

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In the first publication of this review we searched the Cochrane Central Register of Controlled Trials (CENTRAL) (The Cochrane Library 2006, issue 4); MEDLINE (1966 to November 2006); OLDMEDLINE (1950 to 1965); EMBASE (1990 to November 2006) and CINAHL (1982 to November 2006). The MEDLINE search terms were modified for OLDMEDLINE, EMBASE and CINAHL.

In this 2009 update we searched the Cochrane Central Register of Controlled Trials (CENTRAL) (The Cochrane Library 2009, issue 2); Ovid MEDLINE (2006 to May Week 1 2009); OLDMEDLINE (1950 to 1965); Ovid EMBASE (2006 to Week 18, 2009) and Ovid CINAHL (2006 to May Week 1 2009).

Ovid MEDLINE
1 exp Influenza/
2 influenza.tw.
3 flu.tw.
4 exp Common Cold/
5 common cold.tw.
6 exp Rhinovirus/
7 rhinovirus*.tw.
8 exp Adenoviridae/
9 adenovirus*.tw.
10 exp Coronavirus/
11 exp Coronavirus Infections/
12 coronavirus*.tw.
13 exp Respiratory Syncytial Viruses/
14 exp Respiratory Syncytial Virus Infections/
15 respiratory syncytial virus*.tw.
16 respiratory syncythial virus.tw.
17 exp Parainfluenza Virus 1, Human/
18 exp Parainfluenza Virus 2, Human/
19 exp Parainfluenza Virus 3, Human/
20 exp Parainfluenza Virus 4, Human/
21 (parainfluenza or para-influenza or para influenza).tw.
22 exp Severe Acute Respiratory Syndrome/
23 (severe acute respiratory syndrome or SARS).tw.
24 acute respiratory infection*.tw.
25 acute respiratory tract infection*.tw.
26 or/1-25 (59810)
27 exp Hand Washing/
28 (handwashing or hand washing or hand-washing).tw.
29 hand hygiene.tw.
30 (sanitizer* or sanitiser*).tw.
31 (cleanser* or disinfectant*).tw.
32 exp Gloves, Protective/
33 exp Gloves, Surgical/
34 glov*.tw.
35 exp Masks/
36 mask*1.tw.
37 exp Patient Isolators/
38 exp Patient Isolation/
39 patient isolat*.tw.
40 (barrier* or curtain* or partition*).tw.
41 negative pressure room*.tw.
42 reverse barrier nursing.tw.
43 Cross Infection/pc [Prevention]
44 school closure*.tw.
45 (clos* adj3 school*).tw.
46 mass gathering*.tw.
47 public gathering*.tw.
48 (ban or bans or banned or banning).tw.
49 (outbreak* adj3 control*).tw.
50 distancing.tw.
51 exp Quarantine/
52 quarantine*.tw.
53 or/27-49

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54 26 and 53
55 (animals not (humans and animals)).sh.
56 54 not 55

CENTRAL search strategy

#1 MeSH descriptor Influenza, Human explode all trees
#2 influenza:ti,ab,kw
#3 flu:ti,ab,kw
#4 MeSH descriptor Common Cold explode all trees
#5 "common cold":ti,ab,kw
#6 MeSH descriptor Rhinovirus explode all trees
#7 rhinovirus*:ti,ab,kw
#8 MeSH descriptor Adenoviridae explode all trees
#9 adenovirus*:ti,ab,kw
#10 MeSH descriptor Coronavirus explode all trees
#11 MeSH descriptor Coronavirus Infections explode all trees
#12 coronavirus*:ti,ab,kw
#13 MeSH descriptor Respiratory Syncytial Viruses explode all trees
#14 MeSH descriptor Respiratory Syncytial Virus Infections explode all trees
#15 respiratory syncytial virus*:ti,ab,kw
#16 respiratory syncythial virus*:ti,ab,kw
#17 MeSH descriptor Parainfluenza Virus 1, Human explode all trees
#18 MeSH descriptor Parainfluenza Virus 2, Human explode all trees
#19 MeSH descriptor Parainfluenza Virus 3, Human explode all trees
#20 MeSH descriptor Parainfluenza Virus 4, Human explode all trees
#21 (parainfluenza or para-influenza or para influenza):ti,ab,kw
#22 MeSH descriptor Severe Acute Respiratory Syndrome explode all trees
#23 (severe acute respiratory syndrome or SARS):ti,ab,kw
#24 acute respiratory infection*:ti,ab,kw
#25 acute respiratory tract infection*:ti,ab,kw
#26 (#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25)
#27 MeSH descriptor Handwashing explode all trees
#28 (handwashing or hand washing or hand-washing):ti,ab,kw
#29 hand hygiene:ti,ab,kw
#30 (sanitizer* or sanitiser*):ti,ab,kw
#31 (cleanser* or disinfectant*):ti,ab,kw
#32 MeSH descriptor Gloves, Protective explode all trees
#33 MeSH descriptor Gloves, Surgical explode all trees
#34 glov*:ti,ab,kw
#35 MeSH descriptor Masks explode all trees
#36 mask*:ti,ab,kw
#37 MeSH descriptor Patient Isolators explode all trees
#38 MeSH descriptor Patient Isolation explode all trees
#39 (barrier* or curtain* or partition*):ti,ab,kw
#40 negative NEXT pressure NEXT room*:ti,ab,kw
#41 "reverse barrier nursing":ti,ab,kw
#42 MeSH descriptor Cross Infection explode all trees with qualifier: PC
#43 school NEXT closure*:ti,ab,kw
#44 (clos* NEAR/3 school*):ti,ab,kw
#45 mass NEXT gathering*:ti,ab,kw
#46 public NEXT gathering*:ti,ab,kw
#47 ("ban" or "bans" or banned or banning):ti,ab,kw
#48 (outbreak* NEAR/3 control*):ti,ab,kw
#49 distancing:ti,ab,kw
#50 MeSH descriptor Quarantine explode all trees
#51 quarantine*:ti,ab,kw
#52 (#27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35 OR #36 OR #37 OR #38 OR #39 OR #40 OR #41 OR #42 OR #43 OR #44 OR #45 OR #46 OR #47 OR #48 OR #49 OR #50 OR #51)
#53 (#26 AND #52)

Ovid Embase search strategy

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1 exp Influenza/
2 influenza.tw.
3 flu.tw.
4 exp Common Cold/
5 common cold.tw.
6 exp Human Rhinovirus/
7 rhinovirus*.tw.
8 exp Adenovirus/
9 adenovirus*.tw.
10 exp Coronavirus/
11 coronavirus*.tw.
12 exp Respiratory Syncytial Pneumovirus/
13 respiratory syncytial virus*.tw.
14 respiratory syncythial virus.tw.
15 (parainfluenza or para-influenza or para influenza).tw.
16 exp Severe Acute Respiratory Syndrome/
17 (severe acute respiratory syndrome or SARS).tw.
18 acute respiratory infection*.tw.
19 acute respiratory tract infection*.tw.
20 or/1-19
21 exp Hand Washing/
22 (handwashing or hand washing or hand-washing).tw.
23 hand hygiene.tw.
24 (sanitizer$ or sanitiser$).tw.
25 (cleanser$ or disinfectant$).tw.
26 exp Glove/
27 exp Surgical Glove/
28 glov*.tw.
29 exp Mask/
30 mask*1.tw.
31 patient isolat*.tw.
32 (barrier* or curtain* or partition*).tw.
33 negative pressure room*.tw.
34 reverse barrier nursing.tw.
35 Cross Infection/pc [Prevention]
36 school closure*.tw.
37 (clos* adj3 school*).tw.
38 mass gathering*.tw.
39 public gathering*.tw. (5)
40 (ban or bans or banned or banning).tw.
41 (outbreak* adj3 control*).tw.
42 distancing.tw.
43 quarantine*.tw.
44 or/21-43
45 20 and 44

EBSCO CINAHL search strategy

S26 S10 and S24
S25 S10 and S24
S24 S11 or S12 or S13 or S14 or S15 or S16 or S17 or S18 or S19 or S20 or S21 or S22 or 23 or S24
S23 TI outbreak* N3 control* or AB outbreak* N3 control*
S22 TI (school closure* or mass gathering* or public gathering* or ban or bans or banned or banning or distancing or quarantine*) or AB (school closure* or mass gathering* or public gathering* or ban or bans or banned or banning or distancing or quarantine*)
S21 TI (patient isolat* or barrier* or curtain* or partition* or negative pressure room* or reverse barrier nursing) or AB (patient isolat* or barrier* or curtain* or partition* or negative pressure room* or reverse barrier nursing)
S20 TI (glov* or mask*) or AB (glov* or mask*)
S19 TI (handwashing or hand washing or hand-washing or hand hygiene) or AB (handwashing or hand washing or hand-washing or hand hygiene)
S18 (MH "Quarantine")
S17 (MM "Cross Infection")
S16 (MH "Isolation, Reverse")
S15 (MH "Patient Isolation+")

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S14 (MH "Respiratory Protective Devices")
S13 (MH "Masks")
S12 (MH "Gloves")
S11 (MH "Handwashing+")
S10 S1 or S2 or S3 or S4 or S5 or S6 or S7 or S8 or S9
S9 TI (influenza or flu or rhinovirus* or adenovirus* or coronavirus* or respiratory syncytial virus* or respiratory syncythial virus* or parainfluenza or para-influenza or para influenza or severe acute respiratory syndrome or SARS or respiratory viral infection* or viral respiratory infection*) or AB (influenza or flu or rhinovirus* or adenovirus* or coronavirus* or respiratory syncytial virus* or respiratory syncythial virus* or parainfluenza or para-influenza or para influenza or severe acute respiratory syndrome or SARS or respiratory viral infection* or viral respiratory
infection*)TI (influenza or flu or rhinovirus* or adenovirus* or coronavirus* or respiratory syncytial virus* or respiratory syncythial virus* or parainfluenza or para-influenza or para influenza or severe acute respiratory (syndrome or SARS or respiratory viral infection* or viral respiratory infection*) or AB (influenza or flu or rhinovirus* or adenovirus* or coronavirus* or respiratory syncytial virus* or respiratory syncythial virus* or parainfluenza or para-influenza or para influenza or severe acute respiratory syndrome or SARS or respiratory viral infection* or viral
respiratory infection*)
S8 (MH "SARS Virus")
S7 (MH "Severe Acute Respiratory Syndrome")
S6 (MH "Respiratory Syncytial Virus Infections")
S5 (MH "Respiratory Syncytial Viruses")
S4 (MH "Coronavirus+")
S3 (MH "Coronavirus Infections+")
S2 (MH "Common Cold")
S1 (MH "Influenza+")

WHAT'S NEW

Date	Event	Description
4 April 2023	Amended	John Conly's declaration of interest statement has been clarified in response to a feedback comment.

HISTORY

Protocol first published: Issue 4, 2006
Review first published: Issue 4, 2007

Date	Event	Description
27 January 2023	New citation required but conclusions have not changed	Our conclusions remain unchanged.
27 January 2023	New search has been performed	Searches updated. We included 11 new trials (Abaluck 2022; Alfelali 2020; Almanza-Reyes 2021; Ashraf 2020; Bundgaard 2021; Fretheim 2022a; Gutiérrez-García 2022; Helsingen 2021; Swarthout 2020; Teesing 2021; Young 2021), and excluded 20 new trials (Ahmadian 2022; Chen 2022; Costa 2021; Cyril Vitug 2021; Dalakoti 2022; Egger 2022; Ferrer 2021; Gharebaghi 2020; Giuliano 2021; Karakaya 2021; Kawyannejad 2020; Lim 2022; Malaczek 2022; Meister 2022; Mo 2022; Montero-Vilchez 2022; Munoz-Basagoiti 2022; Sanchez Barrueco 2022; Seneviratne 2021; Sevinc Gul 2022). We identified two new ongoing trials (Brass 2021; NCT04471766), and five trials awaiting classification (Contreras 2022; Croke 2022; Delaguerre 2022; Loeb 2022; Varela 2022).

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Date	Event	Description
1 April 2020	New search has been performed	Searches updated. In this 2020 update we only searched for RCTs and cluster-RCTs. We included 44 new trials (Aelami 2015; Aiello 2012; Alzaher 2018; Arbogast 2016; Azor-Martinez 2016; Azor-Martinez 2018; Ban 2015; Barasheed 2014; Biswas 2019; Canini 2010; Chard 2019; Correa 2012; DiVita 2011; Feldman 2016; Goodall 2014; Hartinger 2016; Hubner 2010; Huda 2012; Ibfelt 2015; Ide 2014; Ide 2016; Little 2015; MacIntyre 2011; MacIntyre 2013; MacIntyre 2015; MacIntyre 2016; McConeghy 2017; Millar 2016; Miyaki 2011; Najnin 2019; Nicholson 2014; Pandejpong 2012; Priest 2014; Radonovich 2019; Ram 2015; Savolainen-Kopra 2012; Simmerman 2011; Stebbins 2011; Suess 2012; Talaat 2011; Temime 2018; Turner 2012; Yeung 2011; Zomer 2015). We excluded 12 new trials (Azor-Martinez 2014; Bowen 2007; Chami 2012; Denbak 2018; Lennell 2008; Nandrup-Bus 2009; Patel 2012; Rosen 2006; Slayton 2016; Stedman-Smith 2015; Uhari 1999; Vessey 2007). We identified 5 new ongoing trials (NCT03454009; NCT04267952; NCT04296643; NCT04337541; Wang 2015) one of which – NCT04337541 - published as this review was going to press. We focused on RCTs and cluster-RCTs only and removed observational studies from this update.
1 April 2020	New citation required and conclusions have changed	There is now sufficient randomised controlled trial (RCT) evidence to show that hand hygiene is likely to provide a modest- benefit. Uncertainty remains for the other interventions. Further RCT evidence is needed.
22 October 2010	New citation required but conclusions have not changed	We updated the review again at the behest of the World Health Organization (WHO). External sources of support amended. External support from the WHO. The WHO interim guidelines document on 'Infection Prevention and Control of Epidemic and Pandemic Prone Acute Respiratory Diseases in Health Care' was published in 2007 to provide infection control guidance to help prevent the transmission of acute respiratory diseases in health care. The update of these guidelines will be evidence-based, and an update of this review was requested to assist in informing the evidence base for the revision of the WHO guidelines. Dr John Conly, Dr Mark Jones, and Sarah Thorning joined the review team.
22 October 2010	New search has been performed	Searches conducted. We included 7 new trials: 4 randomised controlled trials and 3 non-randomised comparative studies. We excluded 36 new trials.
7 May 2009	New search has been performed	For the 2009 update, we included 3 cluster-randomised controlled trials, Cowling 2009; MacIntyre 2009; Sandora 2008, and 1 individual randomised controlled trial (Satomura 2005, with its linked publication Kitamura 2007). We also included 1 retrospective cohort study (Foo 2006), 1 case-control study (Yu 2007), and 2 prospective cohort studies (Wang 2007; Broderick 2008). The content and conclusions of the 2007 review changed little, but the additional 8 studies add more information and certainty. Our meta-analysis remains unchanged as there were no new studies for pooling.

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Date	Event	Description
30 April 2009	New citation required but conclusions have not changed	New author joined the review team.
8 July 2008	Amended	Converted to new review format.
20 August 2007	Amended	Review first published Issue 4, 2007.

CONTRIBUTIONS OF AUTHORS

For this 2022 update:
Co-ordinated the update: LD
Updated Background section: LD, MJ, LA
Updated searches: JC
Excluded irrelevant citations and disputed resolutions for trial registry searches: GB, LA
Screened titles and abstracts: EB, GB, LA, TJ
Selected studies: PG, GB, JMC
Extracted study data: MJ, TH, GB, JMC, EF, TJ
Adjudicated data extraction: PG, JMC
Assessed of risk of bias: MJ, GB, EF
Analysed data: MJ
Contributed to writing the update: PG, MJ, LD, TH, GB, JMC, JC, EF, MVD, LA, TJ
Approved final draft: EB, LD, PG, MJ, TH, GB, JMC, JC, EF, MVD, LA, TJ

DECLARATIONS OF INTEREST

LAA: has declared that they have no conflict of interest.
GAB: reports working at King Saud University, Medical City, Riyadh, Saudi Arabia as clinical faculty in the College of Pharmacy, collaborating with pharmacy services to provide clinical pharmacy services in primary care clinics (non-paid).
EMB: has declared that they have no conflict of interest.
JC: is an Information Specialist at the Cochrane Acute Respiratory Infections Group but was not involved in the editorial process for this review.
JMC: has held or holds peer reviewed grants from the Canadian Institutes for Health Research (CIHR) on acute and primary care preparedness for COVID-19 in Alberta, Canada and has received components of funding from a CIHR funded study via McMaster University for a randomised trial of medical masks versus N95 respirators for preventing COVID-19 amongst healthcare workers. He has also been engaged in WHO funded studies using integrated human factors and ethnography approaches to identify and scale innovative IPC guidance implementation supports in primary care with a focus on low-resource settings and using drone aerial systems to deliver medical supplies and PPE to remote First Nations communities during the COVID-19 pandemic and was the primary local Investigator for a *Staphylococcus aureus* vaccine study funded by Pfizer for which all funding was provided only to the University of Calgary. He has received travel support from the Centers for Disease Control and Prevention (CDC) to attend an Infection Control Think Tank Meeting and from bioMerieux Canada to speak at a symposium on antimicrobial resistance co-hosted by the University of Toronto and bioMerieux Canada. He also reports being a member and Chair of the WHO Infection Prevention and Control Research and Development Expert Group for COVID-19 and reports being a member of the WHO Health Emergencies Programme (WHE) Ad-hoc COVID-19 IPC Guidance Development Group, both of which provide multidisciplinary advice to the WHO, for which no funding is received and from which no funding recommendations are made for any WHO contracts or grants. He reports declaring an opinion on topics in this review in *Clinical Microbiology and Infection* and *Antimicrobial Resistance and Infection Control*; reports being engaged as a co-author on a randomised trial of medical masks versus N95 respirators for preventing COVID-19 amongst healthcare workers published in the *Annals of Internal Medicine* in 2022 and mentioned in this current Cochrane Review, but no extraction or risk of bias assessment or data pooling or other assessment was undertaken by him nor will it be in any future updates. He has also been a member of the W21C since 2004 and served as its Medical Director from 2012-2022. W21C is a not-for-profit healthcare systems research and innovation initiative based in the University of Calgary's O'Brien Institute for Public Health and the Calgary Zone of Alberta Health Services. He reports working as an Infectious Diseases Consultant at Alberta Health Services, Calgary, Canada.
LD: is a Managing Editor at the Cochrane Acute Respiratory Infections Group but was not involved in the editorial process for this review.
EF: has declared that they have no conflict of interest.
PG: reports a grant from the National Health and Medical Research Council, Australia.
TH: is a member of the Cochrane Stroke Group Editorial Board but was not involved in the editorial process for this review.

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TJ: reports declaring an opinion on the topic of the review in articles for popular media. TJ is an Editor at the Cochrane Acute Respiratory Infections Group but was not involved in the editorial process for this review. See full statement here: https://restoringtrials.org/competing-interests-tom-jefferson/
MAJ: reports a grant from the National Institute for Health Research, UK. MAJ is Co-ordinating Editor at the Cochrane Acute Respiratory Infections Group but was not involved in the editorial process for this review.
MLvD: reports being a primary care panel member for the National COVID-19 Clinical Evidence Taskforce, Australia. MLvD is Deputy Co-ordinating Editor at the Cochrane Acute Respiratory Infections Group but was not involved in the editorial process for this review.

SOURCES OF SUPPORT

Internal sources

- No sources of support provided

External sources

- National Institute of Health Research (NIHR), UK

  Competitive grant awarded through The Cochrane Collaboration, 2009
- National Health and Medical Research Council (NHMRC), Australia

  Competitive grant to Chris Del Mar and Tom Jefferson, 2009
- World Health Organization, Geneva, Switzerland

  Requested and provided support to The Cochrane Collaboration for the 2011 update
- Sabbatical year (2010 to 2011) for John Conly while at the World Health Organization in Geneva, Switzerland was supported by the University of Calgary, Calgary, Canada

  2020/1011941
- National Institute of Health Research (NIHR), UK

  This Cochrane Review update is funded by the NIHR Incentive Scheme Award Reference 130721. The views expressed are those of the authors and not necessarily those of the NIHR or the Department of Health and Social Care.
- World Health Organization, Geneva, Switzerland

  Provided financial support for the 2020 update of this review. Reference number 2020/1011941
- National Institute of Health Research (NIHR), UK

  This 2022 Cochrane Review update is funded by the NIHR Incentive Scheme Award Reference NIHR150879. The views expressed are those of the authors and not necessarily those of the NIHR or the Department of Health and Social Care.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

We changed the title of the review in 2010 (see Published notes below).
For the 2020 update, we added one additional outcome: adverse events related to the intervention, and we split the outcomes into primary and secondary outcomes. We also focused only on randomised controlled trials (RCTs) and cluster-RCTs and removed observational studies.

NOTES

In Issue 1, 2010, the title of the review was changed from 'Interventions for the interruption or reduction of the spread of respiratory viruses' to 'Physical interventions to interrupt or reduce the spread of respiratory viruses'.

The original review was subsequently published as Jefferson T, Foxlee R, Del Mar C, Dooley L, Ferroni E, Hewak B, Prabhala A, Nair S, Rivetti A. Physical interventions to interrupt or reduce the spread of respiratory viruses: systematic review. BMJ 2008;336:77-80 and Jefferson T, Del Mar C, Dooley L, Ferroni E, Al-Ansary LA, Bawazeer GA, van Driel ML, Foxlee R, Rivetti A. Physical interventions to interrupt or reduce the spread of respiratory viruses: systematic review. BMJ 2009;339:b3675. DOI: 10.1136/bmj.b3675.

INDEX TERMS

Medical Subject Headings (MeSH)

*Communicable Disease Control [methods]; COVID-19 [epidemiology] [prevention & control]; Global Health [statistics & numerical data]; Influenza A Virus, H1N1 Subtype; Influenza, Human [epidemiology] [prevention & control]; Randomized Controlled Trials as Topic; *Respiratory Tract Infections [epidemiology] [prevention & control]; SARS-CoV-2

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MeSH check words

Aged; Child, Preschool; Humans

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Essay

Why Most Published Research Findings Are False

John P. A. Ioannidis

Summary

There is increasing concern that most current published research findings are false. The probability that a research claim is true may depend on study power and bias, the number of other studies on the same question, and, importantly, the ratio of true to no relationships among the relationships probed in each scientific field. In this framework, a research finding is less likely to be true when the studies conducted in a field are smaller; when effect sizes are smaller; when there is a greater number and lesser preselection of tested relationships; where there is greater flexibility in designs, definitions, outcomes, and analytical modes; when there is greater financial and other interest and prejudice; and when more teams are involved in a scientific field in chase of statistical significance. Simulations show that for most study designs and settings, it is more likely for a research claim to be false than true. Moreover, for many current scientific fields, claimed research findings may often be simply accurate measures of the prevailing bias. In this essay, I discuss the implications of these problems for the conduct and interpretation of research.

Published research findings are sometimes refuted by subsequent evidence, with ensuing confusion and disappointment. Refutation and controversy is seen across the range of research designs, from clinical trials and traditional epidemiological studies [1–3] to the most modern molecular research [4,5]. There is increasing concern that in modern research, false findings may be the majority or even the vast majority of published research claims [6–8]. However, this should not be surprising. It can be proven that most claimed research findings are false. Here I will examine the key factors that influence this problem and some corollaries thereof.

The Essay section contains opinion pieces on topics of broad interest to a general medical audience.

Modeling the Framework for False Positive Findings

Several methodologists have pointed out [9–11] that the high rate of nonreplication (lack of confirmation) of research discoveries is a consequence of the convenient, yet ill-founded strategy of claiming conclusive research findings solely on the basis of a single study assessed by formal statistical significance, typically for a *p*-value less than 0.05. Research is not most appropriately represented and summarized by *p*-values, but, unfortunately, there is a widespread notion that medical research articles

It can be proven that most claimed research findings are false.

should be interpreted based only on *p*-values. Research findings are defined here as any relationship reaching formal statistical significance, e.g., effective interventions, informative predictors, risk factors, or associations. "Negative" research is also very useful. "Negative" is actually a misnomer, and the misinterpretation is widespread. However, here we will target relationships that investigators claim exist, rather than null findings.

As has been shown previously, the probability that a research finding is indeed true depends on the prior probability of it being true (before doing the study), the statistical power of the study, and the level of statistical significance [10,11]. Consider a 2 × 2 table in which research findings are compared against the gold standard of true relationships in a scientific field. In a research field both true and false hypotheses can be made about the presence of relationships. Let R be the ratio of the number of "true relationships" to "no relationships" among those tested in the field. R is characteristic of the field and can vary a lot depending on whether the field targets highly likely relationships or searches for only one or a few true relationships among thousands and millions of hypotheses that may be postulated. Let us also consider, for computational simplicity, circumscribed fields where either there is only one true relationship (among many that can be hypothesized) or the power is similar to find any of the several existing true relationships. The pre-study probability of a relationship being true is $R/(R + 1)$. The probability of a study finding a true relationship reflects the power $1 - \beta$ (one minus the Type II error rate). The probability of claiming a relationship when none truly exists reflects the Type I error rate, α. Assuming that c relationships are being probed in the field, the expected values of the 2 × 2 table are given in Table 1. After a research finding has been claimed based on achieving formal statistical significance, the post-study probability that it is true is the positive predictive value, PPV. The PPV is also the complementary probability of what Wacholder et al. have called the false positive report probability [10]. According to the 2 × 2 table, one gets PPV = $(1 - \beta)R/(R - \beta R + \alpha)$. A research finding is thus

Citation: Ioannidis JPA (2005) Why most published research findings are false. PLoS Med 2(8): e124.

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Abbreviation: PPV, positive predictive value

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Competing Interests: The author has declared that no competing interests exist.

DOI: 10.1371/journal.pmed.0020124

Table 1. Research Findings and True Relationships

Research Finding	True Relationship		
	Yes	No	Total
Yes	$c(1-\beta)R/(R+1)$	$c\alpha/(R+1)$	$c(R+\alpha-\beta R)/(R+1)$
No	$c\beta R/(R+1)$	$c(1-\alpha)/(R+1)$	$c(1-\alpha+\beta R)/(R+1)$
Total	$cR/(R+1)$	$c/(R+1)$	c

DOI: 10.1371/journal.pmed.0020124.t001

more likely true than false if $(1-\beta)R > \alpha$. Since usually the vast majority of investigators depend on $\alpha = 0.05$, this means that a research finding is more likely true than false if $(1-\beta)R > 0.05$.

What is less well appreciated is that bias and the extent of repeated independent testing by different teams of investigators around the globe may further distort this picture and may lead to even smaller probabilities of the research findings being indeed true. We will try to model these two factors in the context of similar 2 × 2 tables.

Bias

First, let us define bias as the combination of various design, data, analysis, and presentation factors that tend to produce research findings when they should not be produced. Let u be the proportion of probed analyses that would not have been "research findings," but nevertheless end up presented and reported as such, because of bias. Bias should not be confused with chance variability that causes some findings to be false by chance even though the study design, data, analysis, and presentation are perfect. Bias can entail manipulation in the analysis or reporting of findings. Selective or distorted reporting is a typical form of such bias. We may assume that u does not depend on whether a true relationship exists or not. This is not an unreasonable assumption, since typically it is impossible to know which relationships are indeed true. In the presence of bias (Table 2), one gets PPV = $([1-\beta]R + u\beta R)/(R + \alpha - \beta R + u - u\alpha + u\beta R)$, and PPV decreases with increasing u, unless $1-\beta \leq \alpha$, i.e., $1-\beta \leq 0.05$ for most situations. Thus, with increasing bias, the chances that a research finding is true diminish considerably. This is shown for different levels of power and for different pre-study odds in Figure 1.

Conversely, true research findings may occasionally be annulled because of reverse bias. For example, with large measurement errors relationships are lost in noise [12], or investigators use data inefficiently or fail to notice statistically significant relationships, or there may be conflicts of interest that tend to "bury" significant findings [13]. There is no good large-scale empirical evidence on how frequently such reverse bias may occur across diverse research fields. However, it is probably fair to say that reverse bias is not as common. Moreover measurement errors and inefficient use of data are probably becoming less frequent problems, since measurement error has decreased with technological advances in the molecular era and investigators are becoming increasingly sophisticated about their data. Regardless, reverse bias may be modeled in the same way as bias above. Also reverse bias should not be confused with chance variability that may lead to missing a true relationship because of chance.

Testing by Several Independent Teams

Several independent teams may be addressing the same sets of research questions. As research efforts are globalized, it is practically the rule that several research teams, often dozens of them, may probe the same or similar questions. Unfortunately, in some areas, the prevailing mentality until now has been to focus on isolated discoveries by single teams and interpret research experiments in isolation. An increasing number of questions have at least one study claiming a research finding, and this receives unilateral attention. The probability that at least one study, among several done on the same question, claims a statistically significant research finding is easy to estimate. For n independent studies of equal power, the 2 × 2 table is shown in Table 3: PPV = $R(1-\beta^n)/(R+1-[1-\alpha]^n - R\beta^n)$ (not considering bias). With increasing number of independent studies, PPV tends to decrease, unless $1-\beta < \alpha$, i.e., typically $1-\beta < 0.05$. This is shown for different levels of power and for different pre-study odds in Figure 2. For n studies of different power, the term β^n is replaced by the product of the terms β_i for $i = 1$ to n, but inferences are similar.

Corollaries

A practical example is shown in Box 1. Based on the above considerations, one may deduce several interesting corollaries about the probability that a research finding is indeed true.

Corollary 1: The smaller the studies conducted in a scientific field, the less likely the research findings are to be true. Small sample size means smaller power and, for all functions above, the PPV for a true research finding decreases as power decreases towards $1-\beta = 0.05$. Thus, other factors being equal, research findings are more likely true in scientific fields that undertake large studies, such as randomized controlled trials in cardiology (several thousand subjects randomized) [14] than in scientific fields with small studies, such as most research of molecular predictors (sample sizes 100-fold smaller) [15].

Corollary 2: The smaller the effect sizes in a scientific field, the less likely the research findings are to be true. Power is also related to the effect size. Thus research findings are more likely true in scientific fields with large effects, such as the impact of smoking on cancer or cardiovascular disease (relative risks 3–20), than in scientific fields where postulated effects are small, such as genetic risk factors for multigenetic diseases (relative risks 1.1–1.5) [7]. Modern epidemiology is increasingly obliged to target smaller

Table 2. Research Findings and True Relationships in the Presence of Bias

Research Finding	True Relationship		
	Yes	No	Total
Yes	$(c[1-\beta]R + uc\beta R)/(R+1)$	$c\alpha + uc(1-\alpha)/(R+1)$	$c(R+\alpha-\beta R+u-u\alpha+u\beta R)/(R+1)$
No	$(1-u)c\beta R/(R+1)$	$(1-u)c(1-\alpha)/(R+1)$	$c(1-u)(1-\alpha+\beta R)/(R+1)$
Total	$cR/(R+1)$	$c/(R+1)$	c

DOI: 10.1371/journal.pmed.0020124.t002

effect sizes [16]. Consequently, the proportion of true research findings is expected to decrease. In the same line of thinking, if the true effect sizes are very small in a scientific field, this field is likely to be plagued by almost ubiquitous false positive claims. For example, if the majority of true genetic or nutritional determinants of complex diseases confer relative risks less than 1.05, genetic or nutritional epidemiology would be largely utopian endeavors.

Corollary 3: The greater the number and the lesser the selection of tested relationships in a scientific field, the less likely the research findings are to be true. As shown above, the post-study probability that a finding is true (PPV) depends a lot on the pre-study odds *(R)*. Thus, research findings are more likely true in confirmatory designs, such as large phase III randomized controlled trials, or meta-analyses thereof, than in hypothesis-generating experiments. Fields considered highly informative and creative given the wealth of the assembled and tested information, such as microarrays and other high-throughput discovery-oriented research [4,8,17], should have extremely low PPV.

Corollary 4: The greater the flexibility in designs, definitions, outcomes, and analytical modes in a scientific field, the less likely the research findings are to be true. Flexibility increases the potential for transforming what would be "negative" results into "positive" results, i.e., bias, *u*. For several research designs, e.g., randomized controlled trials [18–20] or meta-analyses [21,22], there have been efforts to standardize their conduct and reporting. Adherence to common standards is likely to increase the proportion of true findings. The same applies to outcomes. True findings may be more common when outcomes are unequivocal and universally agreed (e.g., death) rather than when multifarious outcomes are devised (e.g., scales for schizophrenia outcomes) [23]. Similarly, fields that use commonly agreed, stereotyped analytical methods (e.g., Kaplan-Meier plots and the log-rank test) [24] may yield a larger proportion of true findings than fields where analytical methods are still under experimentation (e.g., artificial intelligence methods) and only "best" results are reported. Regardless, even in the most stringent research designs, bias seems to be a major problem. For example, there is strong evidence that selective outcome reporting, with manipulation of the outcomes and analyses reported, is a common problem even for randomized trails [25]. Simply abolishing selective publication would not make this problem go away.

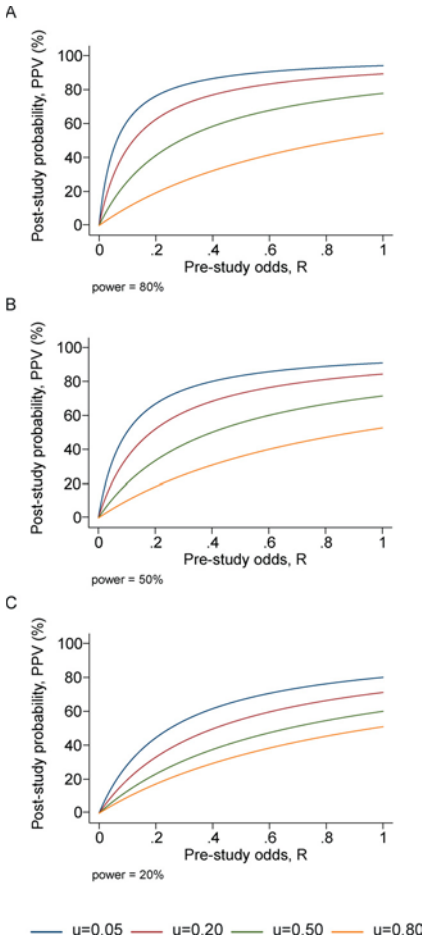
Corollary 5: The greater the financial and other interests and prejudices in a scientific field, the less likely the research findings are to be true. Conflicts of interest and prejudice may increase bias, *u*. Conflicts of interest are very common in biomedical research [26], and typically they are inadequately and sparsely reported [26,27]. Prejudice may not necessarily have financial roots. Scientists in a given field may be prejudiced purely because of their belief in a scientific theory or commitment to their own findings. Many otherwise seemingly independent, university-based studies may be conducted for no other reason than to give physicians and researchers qualifications for promotion or tenure. Such nonfinancial conflicts may also lead to distorted reported results and interpretations. Prestigious investigators may suppress via the peer review process the appearance and dissemination of findings that refute their findings, thus condemning their field to perpetuate false dogma. Empirical evidence on expert opinion shows that it is extremely unreliable [28].

Corollary 6: The hotter a scientific field (with more scientific teams involved), the less likely the research findings are to be true.

Table 3. Research Findings and True Relationships in the Presence of Multiple Studies

Research Finding	True Relationship		
	Yes	No	Total
Yes	$cR(1-\beta^n)/(R+1)$	$c(1-[1-\alpha]^n)/(R+1)$	$c(R+1-[1-\alpha]^n-R\beta^n)/(R+1)$
No	$cR\beta^n/(R+1)$	$c(1-\alpha)^n/(R+1)$	$c([1-\alpha]^n+R\beta^n)/(R+1)$
Total	$cR/(R+1)$	$c/(R+1)$	c

DOI: 10.1371/journal.pmed.0020124.t003

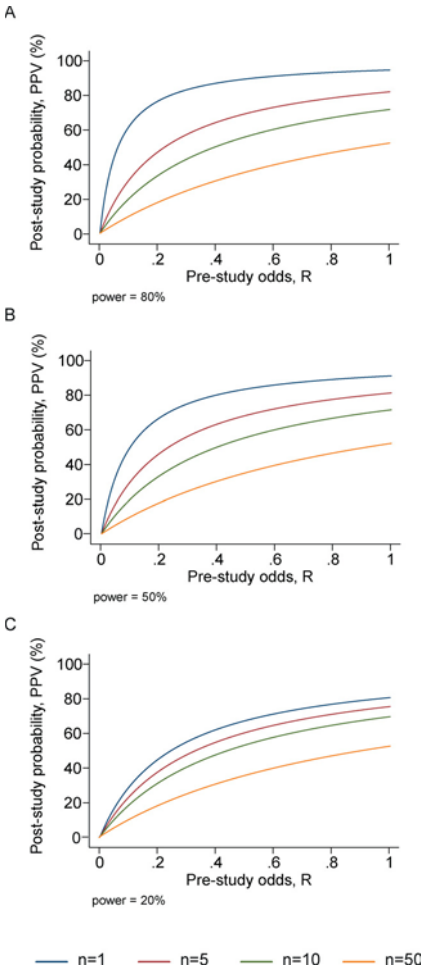


DOI: 10.1371/journal.pmed.0020124.g001

Figure 1. PPV (Probability That a Research Finding Is True) as a Function of the Pre-Study Odds for Various Levels of Bias, *u*

Panels correspond to power of 0.20, 0.50, and 0.80.

This seemingly paradoxical corollary follows because, as stated above, the PPV of isolated findings decreases when many teams of investigators are involved in the same field. This may explain why we occasionally see major excitement followed rapidly by severe disappointments in fields that draw wide attention. With many teams working on the same field and with massive experimental data being produced, timing is of the essence in beating competition. Thus, each team may prioritize on pursuing and disseminating its most impressive "positive" results. "Negative" results may become attractive for dissemination only if some other team has found a "positive" association on the same question. In that case, it may be attractive to refute a claim made in some prestigious journal. The term Proteus phenomenon has been coined to describe this phenomenon of rapidly



DOI: 10.1371/journal.pmed.0020124.g002

Figure 2. PPV (Probability That a Research Finding Is True) as a Function of the Pre-Study Odds for Various Numbers of Conducted Studies, *n*

Panels correspond to power of 0.20, 0.50, and 0.80.

alternating extreme research claims and extremely opposite refutations [29]. Empirical evidence suggests that this sequence of extreme opposites is very common in molecular genetics [29].

These corollaries consider each factor separately, but these factors often influence each other. For example, investigators working in fields where true effect sizes are perceived to be small may be more likely to perform large studies than investigators working in fields where true effect sizes are perceived to be large. Or prejudice may prevail in a hot scientific field, further undermining the predictive value of its research findings. Highly prejudiced stakeholders may even create a barrier that aborts efforts at obtaining and disseminating opposing results. Conversely, the fact that a field is hot or has strong invested interests may sometimes promote larger studies and improved standards of research, enhancing the predictive value of its research findings. Or massive discovery-oriented testing may result in such a large yield of significant relationships that investigators have enough to report and search further and thus refrain from data dredging and manipulation.

Box 1. An Example: Science at Low Pre-Study Odds

Let us assume that a team of investigators performs a whole genome association study to test whether any of 100,000 gene polymorphisms are associated with susceptibility to schizophrenia. Based on what we know about the extent of heritability of the disease, it is reasonable to expect that probably around ten gene polymorphisms among those tested would be truly associated with schizophrenia, with relatively similar odds ratios around 1.3 for the ten or so polymorphisms and with a fairly similar power to identify any of them. Then $R = 10/100{,}000 = 10^{-4}$, and the pre-study probability for any polymorphism to be associated with schizophrenia is also $R/(R + 1) = 10^{-4}$. Let us also suppose that the study has 60% power to find an association with an odds ratio of 1.3 at $\alpha = 0.05$. Then it can be estimated that if a statistically significant association is found with the *p*-value barely crossing the 0.05 threshold, the post-study probability that this is true increases about 12-fold compared with the pre-study probability, but it is still only 12×10^{-4}.

Now let us suppose that the investigators manipulate their design, analyses, and reporting so as to make more relationships cross the $p = 0.05$ threshold even though this would not have been crossed with a perfectly adhered to design and analysis and with perfect comprehensive reporting of the results, strictly according to the original study plan. Such manipulation could be done, for example, with serendipitous inclusion or exclusion of certain patients or controls, post hoc subgroup analyses, investigation of genetic contrasts that were not originally specified, changes in the disease or control definitions, and various combinations of selective or distorted reporting of the results. Commercially available "data mining" packages actually are proud of their ability to yield statistically significant results through data dredging. In the presence of bias with $u = 0.10$, the post-study probability that a research finding is true is only 4.4×10^{-4}. Furthermore, even in the absence of any bias, when ten independent research teams perform similar experiments around the world, if one of them finds a formally statistically significant association, the probability that the research finding is true is only 1.5×10^{-4}, hardly any higher than the probability we had before any of this extensive research was undertaken!

Most Research Findings Are False for Most Research Designs and for Most Fields

In the described framework, a PPV exceeding 50% is quite difficult to get. Table 4 provides the results of simulations using the formulas developed for the influence of power, ratio of true to non-true relationships, and bias, for various types of situations that may be characteristic of specific study designs and settings. A finding from a well-conducted, adequately powered randomized controlled trial starting with a 50% pre-study chance that the intervention is effective is eventually true about 85% of the time. A fairly similar performance is expected of a confirmatory meta-analysis of good-quality randomized trials: potential bias probably increases, but power and pre-test chances are higher compared to a single randomized trial. Conversely, a meta-analytic finding from inconclusive studies where pooling is used to "correct" the low power of single studies, is probably false if $R \leq 1{:}3$. Research findings from underpowered, early-phase clinical trials would be true about one in four times, or even less frequently if bias is present. Epidemiological studies of an exploratory nature perform even worse, especially when underpowered, but even well-powered epidemiological studies may have only a one in five chance being true, if $R = 1{:}10$. Finally, in discovery-oriented research with massive testing, where tested relationships exceed true ones 1,000-fold (e.g., 30,000 genes tested, of which 30 may be the true culprits) [30,31], PPV for each claimed relationship is extremely low, even with considerable

standardization of laboratory and statistical methods, outcomes, and reporting thereof to minimize bias.

Claimed Research Findings May Often Be Simply Accurate Measures of the Prevailing Bias

As shown, the majority of modern biomedical research is operating in areas with very low pre- and post-study probability for true findings. Let us suppose that in a research field there are no true findings at all to be discovered. History of science teaches us that scientific endeavor has often in the past wasted effort in fields with absolutely no yield of true scientific information, at least based on our current understanding. In such a "null field," one would ideally expect all observed effect sizes to vary by chance around the null in the absence of bias. The extent that observed findings deviate from what is expected by chance alone would be simply a pure measure of the prevailing bias.

For example, let us suppose that no nutrients or dietary patterns are actually important determinants for the risk of developing a specific tumor. Let us also suppose that the scientific literature has examined 60 nutrients and claims all of them to be related to the risk of developing this tumor with relative risks in the range of 1.2 to 1.4 for the comparison of the upper to lower intake tertiles. Then the claimed effect sizes are simply measuring nothing else but the net bias that has been involved in the generation of this scientific literature. Claimed effect sizes are in fact the most accurate estimates of the net bias. It even follows that between "null fields," the fields that claim stronger effects (often with accompanying claims of medical or public health importance) are simply those that have sustained the worst biases.

For fields with very low PPV, the few true relationships would not distort this overall picture much. Even if a few relationships are true, the shape of the distribution of the observed effects would still yield a clear measure of the biases involved in the field. This concept totally reverses the way we view scientific results. Traditionally, investigators have viewed large and highly significant effects with excitement, as signs of important discoveries. Too large and too highly significant effects may actually be more likely to be signs of large bias in most fields of modern research. They should lead investigators to careful critical thinking about what might have gone wrong with their data, analyses, and results.

Of course, investigators working in any field are likely to resist accepting that the whole field in which they have spent their careers is a "null field." However, other lines of evidence, or advances in technology and experimentation, may lead eventually to the dismantling of a scientific field. Obtaining measures of the net bias in one field may also be useful for obtaining insight into what might be the range of bias operating in other fields where similar analytical methods, technologies, and conflicts may be operating.

How Can We Improve the Situation?

Is it unavoidable that most research findings are false, or can we improve the situation? A major problem is that it is impossible to know with 100% certainty what the truth is in any research question. In this regard, the pure "gold" standard is unattainable. However, there are several approaches to improve the post-study probability.

Better powered evidence, e.g., large studies or low-bias meta-analyses, may help, as it comes closer to the unknown "gold" standard. However, large studies may still have biases and these should be acknowledged and avoided. Moreover, large-scale evidence is impossible to obtain for all of the millions and trillions of research questions posed in current research. Large-scale evidence should be targeted for research questions where the pre-study probability is already considerably high, so that a significant research finding will lead to a post-test probability that would be considered quite definitive. Large-scale evidence is also particularly indicated when it can test major concepts rather than narrow, specific questions. A negative finding can then refute not only a specific proposed claim, but a whole field or considerable portion thereof. Selecting the performance of large-scale studies based on narrow-minded criteria, such as the marketing promotion of a specific drug, is largely wasted research. Moreover, one should be cautious that extremely large studies may be more likely to find a formally statistical significant difference for a trivial effect that is not really meaningfully different from the null [32–34].

Second, most research questions are addressed by many teams, and it is misleading to emphasize the statistically significant findings of any single team. What matters is the

Table 4. PPV of Research Findings for Various Combinations of Power (1 − β), Ratio of True to Not-True Relationships *(R)*, and Bias *(u)*

1 − β	*R*	*u*	Practical Example	PPV
0.80	1:1	0.10	Adequately powered RCT with little bias and 1:1 pre-study odds	0.85
0.95	2:1	0.30	Confirmatory meta-analysis of good-quality RCTs	0.85
0.80	1:3	0.40	Meta-analysis of small inconclusive studies	0.41
0.20	1:5	0.20	Underpowered, but well-performed phase I/II RCT	0.23
0.20	1:5	0.80	Underpowered, poorly performed phase I/II RCT	0.17
0.80	1:10	0.30	Adequately powered exploratory epidemiological study	0.20
0.20	1:10	0.30	Underpowered exploratory epidemiological study	0.12
0.20	1:1,000	0.80	Discovery-oriented exploratory research with massive testing	0.0010
0.20	1:1,000	0.20	As in previous example, but with more limited bias (more standardized)	0.0015

The estimated PPVs (positive predictive values) are derived assuming $\alpha = 0.05$ for a single study.
RCT, randomized controlled trial.
DOI: 10.1371/journal.pmed.0020124.t004

totality of the evidence. Diminishing bias through enhanced research standards and curtailing of prejudices may also help. However, this may require a change in scientific mentality that might be difficult to achieve. In some research designs, efforts may also be more successful with upfront registration of studies, e.g., randomized trials [35]. Registration would pose a challenge for hypothesis-generating research. Some kind of registration or networking of data collections or investigators within fields may be more feasible than registration of each and every hypothesis-generating experiment. Regardless, even if we do not see a great deal of progress with registration of studies in other fields, the principles of developing and adhering to a protocol could be more widely borrowed from randomized controlled trials.

Finally, instead of chasing statistical significance, we should improve our understanding of the range of R values—the pre-study odds—where research efforts operate [10]. Before running an experiment, investigators should consider what they believe the chances are that they are testing a true rather than a non-true relationship. Speculated high R values may sometimes then be ascertained. As described above, whenever ethically acceptable, large studies with minimal bias should be performed on research findings that are considered relatively established, to see how often they are indeed confirmed. I suspect several established "classics" will fail the test [36].

Nevertheless, most new discoveries will continue to stem from hypothesis-generating research with low or very low pre-study odds. We should then acknowledge that statistical significance testing in the report of a single study gives only a partial picture, without knowing how much testing has been done outside the report and in the relevant field at large. Despite a large statistical literature for multiple testing corrections [37], usually it is impossible to decipher how much data dredging by the reporting authors or other research teams has preceded a reported research finding. Even if determining this were feasible, this would not inform us about the pre-study odds. Thus, it is unavoidable that one should make approximate assumptions on how many relationships are expected to be true among those probed across the relevant research fields and research designs. The wider field may yield some guidance for estimating this probability for the isolated research project. Experiences from biases detected in other neighboring fields would also be useful to draw upon. Even though these assumptions would be considerably subjective, they would still be very useful in interpreting research claims and putting them in context. ■

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Academics and competing interests in H1N1 influenza media reporting

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Received 17 July 2013
Revised 7 September 2013
Accepted 18 September 2013
Published Online First 11 November 2013

ABSTRACT

Background Concerns have been raised over competing interests (CoI) among academics during the 2009 to 2010 A/H1N1 pandemic. Media reporting can influence public anxiety and demand for pharmaceutical products. We assessed CoI of academics providing media commentary during the early stages of the pandemic.

Methods We performed a retrospective content analysis of UK newspaper articles on A/H1N1 influenza, examining quoted sources. We noted when academics made a risk assessment of the pandemic and compared this with official estimations. We also looked for promotion or rejection of the use of neuraminidase inhibitors or H1N1-specific vaccine. We independently searched for CoI for each academic.

Results Academics were the second most frequently quoted source after Ministers of Health. Where both academics and official agencies estimated the risk of H1N1, one in two academics assessed the risk as higher than official predictions. For academics with CoI, the odds of a higher risk assessment were 5.8 times greater than those made by academics without CoI (Wald p value=0.009). One in two academics commenting on the use of neuraminidase inhibitors or vaccine had CoI. The odds of CoI in academics promoting the use of neuraminidase inhibitors were 8.4 times greater than for academics not commenting on their use (Fisher's exact p=0.005).

Conclusions There is evidence of CoI among academics providing media commentary during the early H1N1 pandemic. Heightened risk assessments, combined with advocacy for pharmaceutical products to counter this risk, may lead to increased public anxiety and demand. Academics should declare, and journalists report, relevant CoI for media interviews.

INTRODUCTION

The UK spent an estimated one billion pounds on pharmaceutical products during the 2009 to 2010 A/H1N1 influenza pandemic, including neuraminidase inhibitors (NI) and H1N1-specific vaccine.[1] Pharmaceutical companies made profits of 4.5–6.5 billion pounds from H1N1 vaccines alone.[2] This was despite the evaluation of the pandemic as less severe than previous pandemics[3 4] and uncertainty over the effectiveness of neuraminidase inhibitors (a type of antiviral medication) in reducing transmission and complications of influenza.[5]

In the postpandemic period, there were significant concerns about competing interests (CoI) among experts on influential advisory committees, including the WHO Emergency Committee.[2 6 7] Members of these committees have been linked to manufacturers of both neuraminidase inhibitors and influenza vaccines.[7 8] There have been repeated calls for greater transparency around the potential influence of the pharmaceutical industry on the decisions made by these committees.[2 6 7 9]

Public health academics are often asked to provide commentary and analysis on emerging health risks by the media. Media coverage of health issues has been shown to influence the public's perception of risk, demand for new drugs and policy decisions.[10–13] In the UK, extensive media advocacy of the breast cancer drug trastuzumab (Herceptin) resulted in a 'fast-track' approval from the National Institute for Health and Clinical Excellence,[14] but there was subsequent debate over the cost-effectiveness of the drug.[15] It has been suggested that optimistic media portrayals may be more successful for pharmaceutical companies than explicit promotional campaigns as "the message is separated from an obvious marketing agenda and often includes a trusted voice, such as a university-based researcher. Paradoxically, this trust is based in part on a belief in the perceived independence of university researchers".[16] Like those on advisory committees, academics quoted in the media may also have possible CoI. Media commentaries, therefore, represent an alternative route to exert pressure on public demand and one in which CoI are not routinely declared.

We set out to examine media commentary on A/H1N1 influenza provided by academics during the period in which the UK government decided its policy on public provision of NI and H1N1-specific vaccine (NI/vaccine). We then independently searched for CoI for each academic to determine whether commentary from academics with and without CoI was significantly different.

METHODS

Design and setting

This study was a retrospective content analysis of UK newspaper reporting. We excluded television and radio coverage, as audiovisual reporting is often limited by time constraints and presents less divergent viewpoints and in-depth analysis compared with print media.[17 18]

Selection of newspaper articles

Figure 1 shows the flow of articles through the study. We used the Nexis-UK database, which provides full-text access to all UK national newspapers. Twelve UK national newspapers were included in the sample (January 2009 circulation figures are given in parentheses[19]): *Daily Mirror* (1 366 891), *Sunday Mirror* (1 244 007), *The Sun* (3 146 006), *News of the World* (3 031 025), *Daily Mail*

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To cite: Mandeville KL, O'Neill S, Brighouse A, *et al*. *J Epidemiol Community Health* 2014;**68**:197–203.

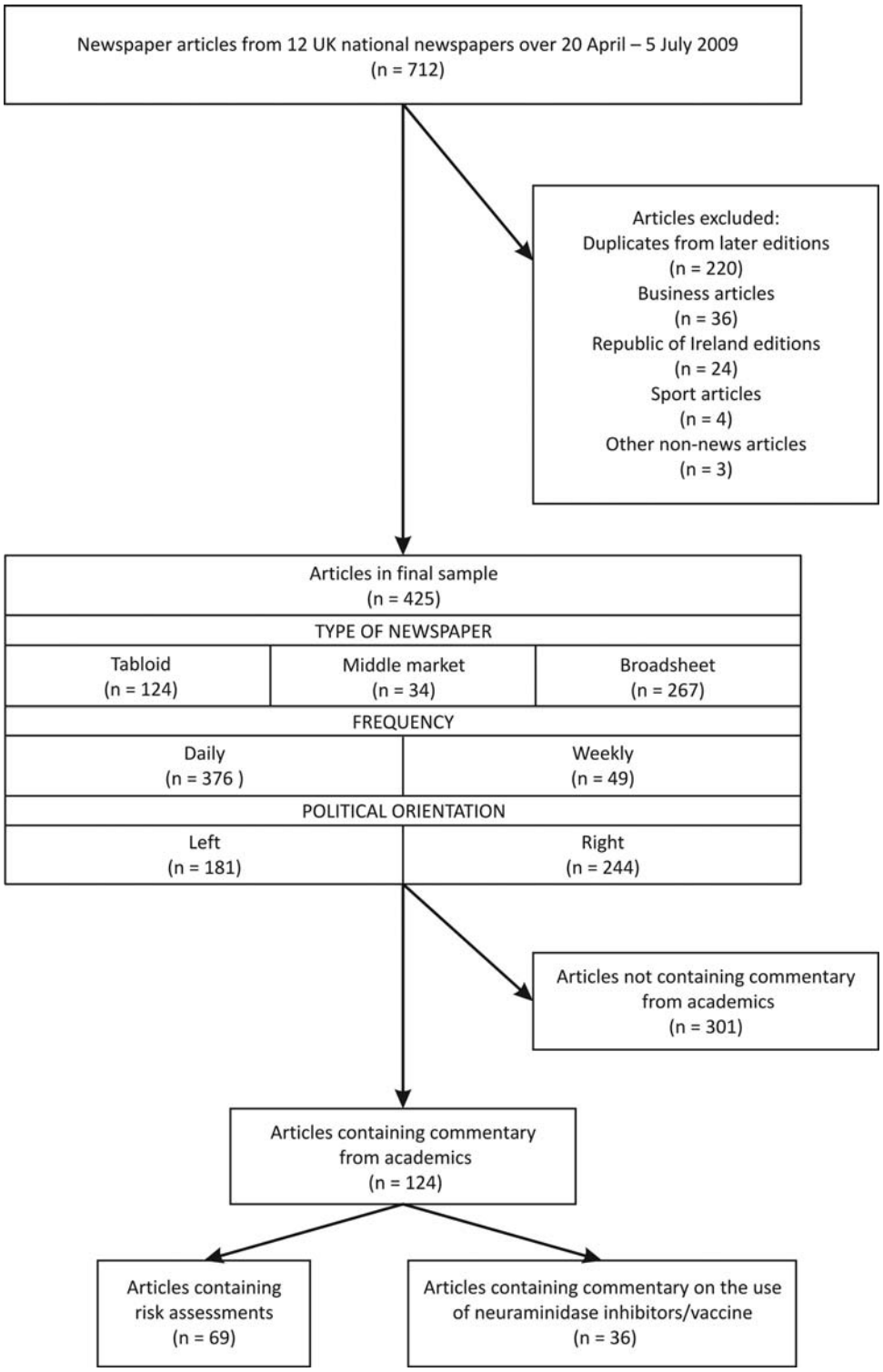

Figure 1 Flow of articles through study.

(2 200 398), *The Mail on Sunday* (2 134 809), *The Guardian* (358 844), *The Independent* (215 504), *The Observer* (427 867), *Daily Telegraph* (783 210), *The Times* (617 483) and *The Sunday Times* (1 198 984). These were selected in order to ensure coverage from tabloid, middle-market and broadsheet publications, daily and Sunday newspapers, and left and right political orientations so that a range of perspectives and reporting styles were represented. This typology has been used in previous content analyses.[20 21]

The database was searched using the following terms (an exclamation mark is used as a truncator in this database): H1N1, Influenza A, Swine !flu!, Pandemic !flu!, Pig !flu!. Only articles that contained at least three mentions of the search terms were eligible for inclusion in order to select articles where H1N1 influenza was the main theme. Articles with a different focus entirely, such as business, sports and non-news articles like obituaries, were excluded. Search dates were between 20 April and 5 July 2009, the period in which the major decisions on

pharmaceuticals as part of the pandemic response were taken by the UK government. Key events and policy decisions within this period are summarised in table 1.[1 22] News coverage dropped off considerably after this period.[20]

Using these criteria, 712 articles were eligible for inclusion. These were extracted into Microsoft Word and screened by one of the authors. Duplicate articles from later editions of the newspapers and any remaining articles as per exclusion criteria above were excluded, leaving 425 articles in the final sample. These provided a good coverage of formats, frequencies and political orientation, taking into account the circulation figures above (figure 1).

Coding framework

Each article was assessed independently by two authors using a standardised coding framework consisting of two sections.

The first section categorised the sources quoted in each article. The main categories consisted of Health Secretary/Minister (of England and the Devolved Administrations—Wales, Scotland and Northern Ireland); Department of Health (of England and the Devolved Administrations); Chief Medical Officer (of England and the Devolved Administrations); World Health Organization (WHO); the UK's Health Protection Agency (HPA), the Centers for Disease Prevention and Control (CDC); pharmaceutical company representative; and named academic (defined here as a researcher or academic clinician affiliated with a higher educational body or research institute in the article).

The second section looked in greater detail at those articles that quoted academic sources. First, we examined whether academics made a risk assessment of the emerging pandemic. For example, quotes such as "this is going to affect millions of people in England" or "thousands of people could die from this virus" would be a risk assessment. We then checked whether the academic cited official figures or whether there was a risk assessment made by an official body relevant to the UK population quoted within the same article (defined as WHO, Health Secretary/Minister(s), Chief Medical Officer(s), Department(s) of Health or HPA). Table 1 presents examples of risk assessments from these agencies during the study period. We used the official risk assessments as a benchmark to measure each academic risk assessment: judging whether it concurred with the official estimate, or was higher or lower (ie, implying more or less risk to the public).

All quotes by academics were then examined for reference to the use of NI or influenza vaccine. Those that made reference to NI/vaccine were further analysed as to whether they promoted or rejected the use of these products. The analysis was performed according to a pre-agreed consensus on terms. 'Promotion' was defined as advocacy of the effectiveness, need for or supply shortages of NI/vaccine. Conversely, 'rejection' referred to statements highlighting the adverse effects, ineffectiveness of or lack of need for NI/vaccine.

The coding framework was piloted on 20 articles by both coders, with subsequent minor modifications made to definitions before coding of the complete data set. Cohen's kappa was calculated to determine inter-rater agreement between the qualitative measures of risk assessment and promotion/rejection of pharmaceutical products.[23 24] Disagreements between coders were assessed by a third researcher for final arbitration. Microsoft Excel was used for all coding and calculations.

Evidence of CoI

For each named academic, we performed a comprehensive search for CoI based on the protocol from a recent study examining CoI in authors of clinical practice guidelines.[25] This was undertaken by two researchers who did not take part in the coding in order to minimise bias. We used the International Committee of Medical Journal Editors' definition that "Conflicts of interests exists when an author (…) has financial

Table 1 Key events, official risk assessments and UK policy decisions during study period

Date (2009)	Event/policy decision
Week of 20 April	First human cases of H1N1 confirmed in Mexico, the USA and Canada.
24 April	HPA press release: "The mild illness reported to date and the limited evidence of sustained human-to-human transmission suggest that the immediate level of threat to public health is very limited".
26 April	UK government agrees to containment measures as part of its emergency response, including treatment of suspected cases and their close contacts with neuraminidase inhibitors without waiting for diagnostic confirmation.
27 April	Confirmation of first UK cases. Minister of Health issues statement: "The range of symptoms in the people affected is similar to those of regular human seasonal influenza. It is important to note that, apart from in Mexico, all those infected with the virus have experienced mild symptoms and made a full recovery".
29 April	WHO states, "It is possible that the full clinical spectrum of this disease goes from mild illness to severe disease. We need to continue to monitor the evolution of the situation...". UK government decides to increase the national stockpile of neuraminidase inhibitors from 33.5 million to 50 million doses.
1 May	HPA confirms human-to-human transmission in UK, stating: "At this stage, we still only have two cases of human to human transmission in the UK. This does not yet represent sustained human to human transmission. The risk to the general public is still very low".
11 May	UK government takes decision to purchase sufficient H1N1-specific vaccine for 45% of the population.
11 June	WHO confirms start of a global pandemic, stating "we have good reason to believe that this pandemic, at least in its early days, will be of moderate severity. Worldwide, the number of deaths is small. [..]..we do not expect to see a sudden and dramatic jump in the number of severe or fatal infections".
15 June	DH statement: "The localised cases of swine flu found in the UK have so far been generally mild in most people, but are proving to be severe in a small minority of cases".
17 June	WHO welcomes donation by Sanofi-Aventis of 100 million doses of H1N1 vaccine for low-income countries.
26 June	GlaxoSmithKline and Baxter Healthcare contracted to provide a total of 132 million doses of H1N1-specific vaccine, sufficient for two doses for the whole UK population.
2 July	UK government changes to 'treatment' phase in its emergency response, where prophylaxis with neuraminidase inhibitors would be provided to those in high-risk groups only. HPA press release states: "Once the virus is widespread within the community, the value of antivirals in terms of slowing the spread of the disease or offering individual protection is greatly reduced".

DH, Department of Health (England); HPA, Health Protection Agency.

or personal relationships that inappropriately influence (bias) his or her actions)".[26] For each academic, we looked for associations with pharmaceutical or biotechnology companies, in the form of grants (including research), honorariums, speakers' fees, consultant/adviser/employee relationships and stock ownership.[25] These could be personal, indicating benefit to that individual (eg, honorariums), or non-personal, indicating benefit to a department or organisation for which an academic has managerial responsibility (eg, research grants).[16] We searched for CoI from the 4 years before the start of the pandemic, that is, March 2005 to March 2009. This is consistent with the WHO's standard that CoI should be declared if incurred in the 4 years before acting in an expert advisory role.[25 27]

For each academic, we made the following searches in a sequential manner, stopping after each stage if a CoI was identified:

- The CoI statements (where available) for four major scientific advisory committees relevant to this issue: Joint Committee on Vaccination and Immunisation (UK), Scientific Advisory Group on Emergencies (UK), WHO Emergency Committee and WHO Strategic Advisory Group of Experts.
- Funding sources detailed on the individual's profile page on the website of affiliated institution.
- A general internet search using Google linking "(name of academic)" with respectively "vaccine", "neuraminidase inhibitor", "antiviral", "Oseltamivir", "Zanamivir" and the name of the main pharmaceutical companies producing neuraminidase inhibitors (Roche, GlaxoSmithKline) and influenza vaccine (Novartis, GlaxoSmithKline, Baxter International, Sanofi-Pasteur). The list of manufacturers was obtained through the electronic Medicines Compendium (http://www.emc.medicines.org.uk).
- CoI and funding declarations on all publications in the past 4 years. These were identified through the PubMed/Medline database.

Two authors identified CoI, and a separate author verified the presence of CoI.

We calculated the likelihood of a risk assessment being higher than official estimates if it was made by an academic with CoI compared with those without CoI. As some academics made multiple risk assessments, we used a variant of the generalised linear model (generalised estimating equations, using a binary logistic link function, with an exchange correlation matrix) to take account of clustering.[28] We also calculated the likelihood of an academic who promoted or rejected the use of NI/vaccine having CoI compared with academics who provided general commentary, using Fisher's exact test. All statistics were calculated in SPSS V.19.

RESULTS

Quoted sources

Ministers of Health were the most frequently quoted sources (144/425, 33.9% of articles), while academics were the second most commonly quoted (29.7%, 126/425). Other common sources included WHO (27.8%, 118/425), Departments of Health (21.6%, 92/425), HPA (19.1%, 81/425), Chief Medical Officers (16.2%, 69/425) and CDC (5.6%, 24/425). Pharmaceutical companies were quoted in just eight articles (1.9%). A total of 61 named academics were quoted within the sample.

Risk assessments

Academics made 74 risk assessments, over half of which were higher than with those made by official agencies in the same article (59.5%, 44/74). In nearly a quarter, 23.0%, 17/74), academics concurred with official risk assessments and in 17.6% (13/74), academics estimated the risk as lower. Table 2 gives some examples of these different categories of risk assessments.

Use of NI/vaccine

Twenty academics commented specifically on the use of NI/vaccine in 36 articles (8.5% of total articles). Ten academics (50%) promoted the use of NI whereas four specifically rejected their use (20%). Nine academics (45%) promoted the use of a vaccine, while none rejected its use. Three academics (15%) promoted the use of both NI and vaccine. Examples of quotes for these categories are illustrated in table 3. Cohen's kappa for inter-rater agreement was 0.66 (values between 0.61 and 0.80 indicate substantial inter-rater agreement).[24]

Competing interests

A total of 61 named academics were quoted within the sample. We identified CoI in a third of these academics (29.5%, 18/61), through CoI declarations for scientific advisory committees (5), profile pages (2), internet searches (9) and publications (2). Most CoI were personal in nature (13/18, 72.2%), consisting of paid consultancies or advisory roles, directorships or stock in companies specialising in antiviral products. Seven CoI were non-personal (38.9%), relating to research grants or commercial

Table 2 Examples of risk assessments made by academics and official agencies, by category assigned to academic risk assessment

	Official risk assessment	Academic risk assessment
Higher than official agencies	"..between 400 000 and 800 000 people [become] ill in an average flu season, but [at the peak of a pandemic] you would probably be into several million cases" [Chief Medical Officer]	"The virus [is] likely to be two to three times more deadly than seasonal flu...the pandemic could mean that 25–35 per cent of the population would fall ill within three or four months, placing severe strain on the NHS".
Concurring with official agencies	Minister of Health: "There is no cause for anyone to feel there is going to be any danger to them at this stage... Pandemics come along every 20 years and the present outbreak [is] not inevitably going to move to level six", however [*the Minister of Health*] indicated that he thought it likely that the alert level might rise to pandemic."	"We haven't yet identified any features that give us cause for concern, or that indicate high virulence [...]. It is important that people keep a sense of perspective, because what we observe is what may lead to a pandemic. We don't know that it will lead to a pandemic, although many of us think that this is highly likely".
Lower than official agencies	"Even though the fatality rate is relatively low we will see a lot of people dying because of the large number of people being infected. As more and more cases are reported in the US, we are starting to see some hospitalisations and more severe cases. We may see the same pattern in the UK". [*World Health Organization*]	"This might not be any more virulent than normal seasonal flu infections. We feel reassured that if this develops into a pandemic it might not be a particularly severe one".

Table 3 Comments promoting or rejecting the use of neuraminidase inhibitors or vaccine

Type of comment	Example
Promoting the use of neuraminidase inhibitors	"There is no doubt Tamiflu [oseltamivir] will help". "There is an issue of Tamiflu resistance. All things being equal, it would be nice to get as much Relenza [zanamivir] as we can get our hands on".
Promoting the use of vaccine	"I think by far the safer option is to wait for the development of a vaccine which will almost certainly be around by the autumn". "Vaccines are our real hope".
Rejecting the use of neuraminidase inhibitors	"At present it [Tamiflu] should not be routinely prescribed". "No one really knows if Tamiflu will significantly reduce transmission; the expectation is it will, but we don't know for sure".

Table 4 Number of academics with competing interests by type of comment

Type of comment	Number of academics	Number with competing interests (%)
Promoting the use of NI	10	7 (70)
Rejecting the use of NI	4	1 (25)
Not commenting on the use of NI	47	10 (21.3)
Promoting the use of vaccine	9	5 (55.6)
Rejecting the use of vaccine	0	0 (0)
Not commenting on the use of vaccine	52	13 (25.5)

NI, neuraminidase inhibitors.

work funded by pharmaceutical companies. Two academics held both personal and non-personal CoI.

Out of the 44 risk assessments that were higher than official sources, 35 were made by academics with CoI. In contrast, 10 of the 30 risk assessments that concurred with or were lower than official sources were made by academics with CoI. As several academics made more than one risk assessment, data were fitted using generalised equalising equations. In this analysis, risk assessments were categorised as either being higher than official estimates or concurring with/lower than the official position, forming a binary dependent variable. The best-fitting model revealed that for risk assessments made by academics with CoI the odds of a higher risk assessment were 5.8 times greater compared with assessments made by academics without CoI (Wald p value=0.009).

Out of the 20 academics who commented on the use of NI/vaccine in the pandemic, one in two had CoI (10, 50%). This is a higher proportion than the one in three academics on the WHO's Emergency Committee advisory group who declared CoI.[8]

When we correlated CoI by type of comment, 7 out of 10 academics (70%) promoting the use of NI had CoI compared with 10 out of 47 (21.3%) of academics not commenting on their use (table 4). The odds of COI in academics promoting the use of NI were 8.4 times greater than for academics not commenting on the use of NI (Fisher's exact p=0.005). The odds of CoI in academics rejecting the use of NI were not significantly different to the odds in those not commenting their use (Fisher's exact p=1.0). Five out of nine academics (55.6%) promoting the use of a vaccine had a CoI compared with 13 out of 52 (25.0%) not commenting on its use, a non-significant trend (Fisher's exact p=0.11).

Only three articles in the entire sample noted that the quoted academics had a potential conflict of interest, with one columnist commenting that, "it would be helpful if newspapers informed us of these things".

DISCUSSION

During the period in which the UK government took its major decisions on pharmaceutical policy, one in two academics commenting on NI/vaccine use in UK national newspapers had CoI. The odds of CoI in academics promoting the use of NI were 8.4 times greater than for academics not commenting on the use of NI. If academics with CoI made an assessment of the risk of the pandemic, the odds of this risk assessment being higher than official sources were 5.8 times greater compared with assessments made by academics without CoI.

CoI among academics on influential advisory committees have led to intense debate worldwide.[2 6 7] This study estimates, for the first time, the prevalence of CoI among academics providing media commentary during the early H1N1 pandemic. We combined a rigorous search for CoI with a comprehensive sample of nationally prominent media during a critical policy-making period. Our findings are based on a small sample, however, and should be viewed as a scoping study. They are corroborated by a study by Moynihan *et al*[29] examining news coverage of three medications for non-communicable diseases, which found that out of 170 stories citing an expert or a scientific study, 50% (85) cited those with a financial tie to the drug manufacturer. Indeed, a study looking at UK newspapers' representations of the H1N1 pandemic found little discussion of the profits that pharmaceutical companies would make from the development of a H1N1-specific vaccine and few articles describing the potential side effects of vaccines.[20]

It is clear from our results that academics constitute an accessible and trusted source for journalists. Academics were the second most commonly quoted source after Ministers of Health, and therefore hold a unique and powerful position for communication on emerging public health issues. However, in a third of cases, academics estimated the risk of the emerging pandemic as higher than official sources. We recognise that academics may be involved in modelling outcomes based on early estimates and may therefore predict higher risks than is borne out by more comprehensive data. In addition, journalists may seek out divergent viewpoints in order to provide balance within a story or to increase its newsworthiness. However, consensus among risk assessors during public health emergencies is important to decrease public anxiety, increase the effectiveness of risk communication and promote adherence to personal protective measures.[30–32] We would suggest that this responsibility extends to the media as well, who may need to balance their investigative role with the need to provide a clear and consistent message during the early stages of a public health emergency. Indeed, content analyses of UK[20] and European media reporting on H1N1 influenza[33] found predominantly factual reporting with little evidence of sensationalism.

Our results provide some evidence that the provision of higher risk assessments and the promotion of NI are associated with CoI among academics. These add to the growing body of literature highlighting the potential influence of the pharmaceutical industry on policy decisions through multiple avenues, including advisory committees[6], drafting of guidelines[25] and

media commentary.[16] This type of influence may be stronger for more familiar health issues, such as cancer, as the public response to emerging health risks is usually one of scepticism.[30] Indeed, uptake of H1N1-specific vaccine during the pandemic among those in clinical risk groups was only 37.6%,[34] which suggests that both the official vaccination campaign and any media support for vaccination had limited impact.

There were several limitations to our study. Although this sample was drawn from a large number of articles, the number of academics actually commenting on the use of NI/vaccine was small. More quotes may have been obtained if the study period was extended to the end of the H1N1 pandemic in the UK, but any CoI would be less relevant after the main decisions on pharmaceutical products were taken. While newspaper articles provide a limited set of quotes, the actual interviews with academic sources were undoubtedly longer and may have contained more nuanced views than those represented by the quotes. The definitions and coding of promotion/rejection could be criticised as subjective, although similar definitions have been used in other content analyses.[35] Finally, we performed a comprehensive search for CoI, but there may be further conflicts (disclosed or undisclosed) that were not identified here.

Rather than trying to decrease commentary on public health issues from academics with CoI, a pragmatic approach would be to focus on the complete transparency of these interests[36] and allow readers in any capacity to judge comments from academics with these in mind. Indeed, there have been repeated calls for journalists to investigate CoI in their quoted sources in science articles.[16 37 38] In the study by Moynihan *et al*,[29] financial ties to drug manufacturers that were disclosed in the scientific literature were only reported in 39% of the news stories. In our analysis, disclosure was present in only 3% of articles, which may reflect the more fast-moving nature of the pandemic news coverage. In spite of potential logistical difficulties, we echo Caulfield[16] in his demand that all "reporters should always ask for and researchers should always offer information about [financial associations]".

There are, admittedly, limitations to disclosure. Kassirer points out that disclosure currently tells us nothing about the magnitude of CoI.[39] In addition, the interpretation of declared CoI can be subtle, as the emphasis is on complete disclosure of any CoI that may potentially influence an author outside of any judgement of their actual influence.[40] It is not known whether this distinction would be appreciated by those unversed in the particularities of scientific CoI declarations. Researchers may be understandably reluctant to put this to the test as news stories about scientific CoI are often high profile. In a 10-year analysis of news media coverage of scientific CoI, McCormas and Simone found that nearly 1 in 10 stories appeared on the front page, suggesting a high degree of newsworthiness.[40] Finally, journalists themselves may have undisclosed CoI that would impede truly impartial reporting.[16]

Despite these obstacles, we would argue that undisclosed CoI degrades public confidence in medical research, to the detriment of the whole scientific community. We would recommend that these principles are extended to more settings. We call on all academics to declare any potential CoI when providing commentary to the mass media. We encourage journalists to ask for and report any CoI in their interviewees, so that readers can judge their comments in full light of the facts. As Caulfield puts it,[16] complete transparency should now be the understood standard practice. Through these measures, the academic voice will retain its credibility in public health issues.

What is already known on this subject

- Considerable public funding was spent on vaccines and antiviral medication during the 2009 to 2010 A/H1N1 pandemic.
- Subsequently, there were concerns over competing interests of academics serving on scientific advisory committees during the pandemic.
- Many academics also provide media commentary on emerging health risks, and the media has been shown to influence public risk perception and demand for new drugs.

What this study adds

- Academics with competing interests were more likely to predict a higher risk to the public from the pandemic than official agencies compared with those without any competing interests.
- Academics promoting the use of antiviral medication were more likely to have a competing interest than those not commenting on its use.
- Given the evidence of competing interests among academics providing media commentary, these should be declared before media interviews in order for public health to retain its independent voice.

Correction notice The license of this article has also changed since publication to CC BY 4.0.

Contributors KM conceived and designed the study, and collected initial data. SON and KC performed the content analysis. AB and AW performed the search for competing interests. KM, KC, SON and KY analysed the data. KY performed the statistical analysis. KM wrote the first draft of the manuscript, and all authors contributed to and approved the final manuscript.

Funding KM is funded by the Wellcome Trust (grant number 09401). The funder had no role in study design, data collection and analysis, decision to publish or preparation of the manuscript.

Competing interests None.

Provenance and peer review Not commissioned; externally peer reviewed.

Data sharing statement Unpublished data from the content analysis are available from the authors.

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Coronavirus Vaccines

Summary of Yellow Card reporting

Published 1 December 2022

Data included: 9/12/2020 to 23/11/2022
This information is also available on the gov.uk website

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Update on publication frequency

The weekly summary of Yellow Card reporting has provided timely and relevant information to patients and healthcare professionals on the safety of the COVID-19 vaccines as they were deployed in the UK throughout the pandemic.

In line with the wider government's living with COVID-19 agenda, the updated summary is now published monthly. Robust safety monitoring and surveillance will continue to be carried out between publications and we will continue to communicate promptly on any updated safety advice when needed. We would ask anyone who suspects they have experienced a side effect linked with their COVID-19 vaccine to report via the Coronavirus Yellow Card website: https://coronavirus-yellowcard.mhra.gov.uk/.

The MHRA will be updating the format of summary of Yellow Card reporting in future publications to focus on the coronavirus vaccines being administered as part of the autumn booster campaign. Information on monovalent vaccines used in the previous primary and initial booster campaign will remain available as a record on the government website.

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Summary

Over the first 27 months of the pandemic over 178,397 people across the UK have died within 28 days of a positive test for coronavirus (COVID-19). Vaccination is the single most effective way to reduce deaths and severe illness from COVID-19. A national immunisation campaign has been underway since early December 2020.

Three COVID-19 vaccines - the monovalent COVID-19 Vaccine Pfizer/BioNTech, COVID-19 Vaccine AstraZeneca and monovalent COVID-19 Vaccine Moderna – were used in the primary and booster vaccination campaigns up to the end of August 2022. All have been authorised for supply by the Medicines and Healthcare products Regulatory Agency (MHRA) following a thorough review of safety, quality and efficacy information from clinical trials. In clinical trials, these vaccines showed very high levels of protection against symptomatic infections with COVID-19. Data are available on the impact of the vaccination campaign in reducing infections, illness and mortality in the UK.

The MHRA confirmed on 9 September 2021 that the COVID-19 vaccines made by Pfizer and AstraZeneca can be used as safe and effective booster doses. Following a review of the data for the COVID-19 Vaccine Moderna vaccine, the MHRA and Commission on Human Medicine (CHM) experts also concluded that this vaccine can be used as a safe and effective booster dose.

All vaccines and medicines have some side effects. These side effects need to be continuously balanced against the expected benefits in preventing illness.

On 15 August and 3 September 2022 respectively, the Moderna bivalent vaccine (Spikevax bivalent Original/Omicron) and the Pfizer/BioNTech bivalent vaccine (Comirnaty Original/Omicron BA.1) were approved by the MHRA as booster vaccines. Both bivalent vaccines are active against the original (Wuhan) strain of the SARS-CoV-2 virus and the Omicron BA.1 variant. They were found to meet the required standards of safety, quality and efficacy. COVID-19 vaccine Novavax (Nuvaxovid) is also being used as a booster dose in the small proportion of patients who are unable to receive mRNA vaccines. As part of the MHRA's responsibility to ensure that the benefits of the COVID-19 vaccines used in the UK continue to outweigh the risks, the MHRA is closely monitoring the bivalent mRNA vaccines and COVID-19 vaccine Novavax using the proactive pharmacovigilance surveillance strategy in place for the initial vaccine rollout. Our ongoing review of suspected adverse events following the launch of the National Autumn booster campaign has not revealed any new safety concerns. It should be noted that unless otherwise specified, the numbers of ADR reports for the mRNA COVID vaccines includes reports for both the mono- and bivalent COVID-19 mRNA vaccines.

The monovalent COVID-19 Vaccine Pfizer/BioNTech was evaluated in clinical trials involving more than 44,000 participants. The most frequent adverse reactions in these trials were pain at the injection site, fatigue, headache, myalgia (muscle pains), chills, arthralgia (joint pains), and fever; these were each reported in more than 1 in 10 people. These reactions were usually mild or moderate in intensity and resolved within a few days after vaccination. Adverse reactions were reported less frequently in older adults (over 55 years) than in younger people.

The COVID-19 Vaccine AstraZeneca was evaluated in clinical trials involving more than 23,000 participants. The most frequently reported adverse reactions in these trials were injection-site tenderness, injection-site pain, headache, fatigue, myalgia, malaise, pyrexia (fever), chills, and arthralgia, and nausea; these were each reported in more than 1 in 10 people. The majority of adverse reactions were mild to moderate in severity and usually resolved within a few days after vaccination. Adverse reactions were generally milder and reported less frequently in older adults (65 years and older) than in younger people.

The monovalent COVID-19 Vaccine Moderna was evaluated in clinical trials involving more than 30,000 participants. The most frequent adverse reactions in these trials were pain at the injection site, fatigue, headache, myalgia (muscle pains), arthralgia (joint pains), chills, nausea/vomiting, axillary swelling/tenderness (swelling/tenderness of glands in the armpit), fever, injection site swelling and redness; these were each reported in more than 1 in 10 people. These reactions were usually mild or moderate in intensity and resolved within a few days after vaccination. Adverse reactions were reported less frequently in older adults (over 65 years) than in younger people.

The COVID-19 Vaccine Novavax was evaluated in clinical trials involving more than 30,000 participants. The most frequently reported adverse reactions in these trials were headache, feeling sick (nausea) or getting sick (vomiting), muscle ache, joint pain, tenderness or pain where the injection is given, feeling very tired (fatigue) and generally feeling unwell; these were each reported in more than 1 in 10 people. These reactions were usually mild or moderate in intensity and resolved within a few days after vaccination. Adverse reactions were reported less frequently in older adults (over 65 years) than in younger people.

The MHRA continually monitors safety during widespread use of a vaccine. We have in place a proactive strategy to do this. We also work closely with our public health partners in reviewing the effectiveness and impact of the vaccines to ensure the benefits continue to outweigh any possible side effects.

Part of our monitoring role includes reviewing reports of suspected side effects. Any member of the public or health professional can submit suspected side effects through the Yellow Card scheme. The nature of Yellow Card reporting means that reported events are not always proven side effects. Some events may have happened anyway, regardless of

vaccination. This is particularly the case when millions of people are vaccinated, and especially when vaccines are being given to the most elderly people and people who have underlying illness.

As of 23 November 2022, for the UK, 177,925 Yellow Cards have been reported for the monovalent and bivalent COVID-19 Vaccine Pfizer/BioNTech, 246,866 have been reported for the COVID-19 Vaccine AstraZeneca, 47,045 for the monovalent and bivalent COVID-19 Vaccine Moderna, 52 for the COVID-19 Vaccine Novavax and 2,130 have been reported where the brand of the vaccine was not specified.

For the monovalent and bivalent COVID-19 Vaccine Pfizer/BioNTech, COVID-19 Vaccine AstraZeneca and monovalent and bivalent COVID-19 Vaccine Moderna the overall reporting rate is around 2 to 5 Yellow Cards per 1,000 doses administered.

In the 28 days since the previous summary for 26 October 2022 we have received a further 2,499 Yellow Cards for the monovalent and bivalent COVID-19 Vaccine Pfizer/BioNTech, 228 for the COVID-19 Vaccine AstraZeneca, 1,099 for the monovalent and bivalent COVID-19 Vaccine Moderna, 15 for the COVID-19 Vaccine Novavax and 154 where the brand was not specified. The increase in reports for Pfizer and Moderna COVID-19 vaccines is due to the bivalent vaccine use in the national autumn booster campaign. Our review to date of suspected adverse events since the launch of the campaign has not revealed any new safety concerns.

It is important to note that Yellow Card data cannot be used to derive side-effect rates or compare the safety profile of COVID-19 vaccines as many factors can influence ADR reporting. Additionally, it is important to consider that a Yellow Card report can include reference to more than one vaccine associated with a suspected reaction where different vaccines have been used as third or booster doses.

For all COVID-19 vaccines, the overwhelming majority of reports relate to injection-site reactions (sore arm for example) and generalised symptoms such as ‘flu-like’ illness, headache, chills, fatigue (tiredness), nausea (feeling sick), fever, dizziness, weakness, aching muscles, and rapid heartbeat. Generally, these happen shortly after the vaccination and are not associated with more serious or lasting illness.

These types of reactions reflect the normal immune response triggered by the body to the vaccines. They are typically seen with most types of vaccine and tend to resolve within a day or two. The nature of reported suspected side effects is broadly similar across age groups, although, as was seen in clinical trials and as is usually seen with other vaccines, they may be reported more frequently in younger adults.

A number of detailed assessments of safety topics have been undertaken and we have updated our advice on these topics accordingly. Overall, our advice remains that the benefits

of the vaccines outweigh the risks in the majority of people. Further comments on use in specific populations and details on the specific safety topics can be found within Section titled Analysis of data.

Conclusion

Vaccines are the best way to protect people from COVID-19 and have already saved tens of thousands of lives. Everyone should continue to get their vaccination when invited to do so unless specifically advised otherwise.

> As with all vaccines and medicines, the safety of COVID-19 vaccines is being continuously monitored.
>
> The benefits of the vaccines in preventing COVID-19 and serious complications associated with COVID-19 far outweigh any currently known side effects in the majority of patients.

Further information on the type of suspected adverse reactions (ADRs) reported for the monovalent and bivalent COVID-19 Vaccine Pfizer/BioNTech, the COVID-19 Vaccine AstraZeneca, the monovalent and bivalent COVID-19 Vaccine Moderna and the COVID-19 Vaccine Novavax is provided in Annex 1. It is important to read the attached guidance notes to ensure appropriate interpretation of the data.

Introduction

The Medicines and Healthcare products Regulatory Agency (MHRA) is the executive Agency of the Department of Health and Social Care that acts to protect and promote public health and patient safety, by ensuring that medicines and medical devices meet appropriate standards of safety, quality and efficacy.

The MHRA operates the Yellow Card scheme on behalf of the Commission on Human Medicines (CHM). The scheme collects and monitors information on suspected safety concerns or incidents involving vaccines, medicines, medical devices, and e-cigarettes. The scheme relies on voluntary reporting of suspected adverse incidents by healthcare professionals and members of the public (patients, users, or carers). The purpose of the scheme is to provide an early warning that the safety of a product may require further investigation. Further information about the Yellow Card scheme, including its contribution to identifying safety issues can be found on the Yellow Card website.

The MHRA is playing an active role in responding to the coronavirus pandemic. In relation to COVID-19 vaccines, the MHRA has authorised their supply following a rigorous review of their safety, quality and efficacy; however, as part of its statutory functions, the MHRA is responsible for monitoring all vaccines on an ongoing basis to ensure their benefits continue to outweigh any risks. This is a requirement for all authorised medicines and vaccines in the UK. This monitoring strategy is continuous, proactive and based on a wide range of information sources, with a dedicated team of scientists reviewing information daily to look for safety issues or unexpected, rare events.

This report summarises information received via the Yellow Card scheme and is published regularly to include other safety investigations carried out by the MHRA under the COVID-19 Vaccine Surveillance Strategy.

What is a Yellow Card?

The Yellow Card scheme is a mechanism by which anybody can voluntarily report any suspected adverse reactions or side effects to the vaccine. It is very important to note that a Yellow Card report does not necessarily mean the vaccine caused that reaction or event. We ask for any suspicions to be reported, even if the reporter isn’t sure if it was caused by the vaccine. Reports to the scheme are known as suspected adverse drug reactions (ADRs).

Many suspected ADRs reported on a Yellow Card do not have any relation to the vaccine or medicine and it is often coincidental that symptoms occurred around the same time as vaccination. The reports are continually reviewed to detect possible new side effects that may require regulatory action, and to differentiate these from things that would have

happened regardless of the vaccine or medicine being administered, for instance due to underlying or undiagnosed illness.

It is therefore important that the suspected ADRs described in this report are not interpreted as being proven side effects of COVID-19 vaccines. A list of the possible side effects of COVID-19 vaccines are provided in the product information document for healthcare professionals and the UK recipient information.

COVID-19 Vaccine Pfizer/BioNTech.

COVID-19 Pfizer/BioNTech bivalent (BA.1)

COVID-19 Vaccine AstraZeneca

COVID-19 Vaccine Moderna

COVID-19 Vaccine Moderna bivalent (BA.1)

COVID-19 Vaccine Novavax

These can also be found on the Coronavirus Yellow Card reporting site.

This public summary provides an overview of all UK suspected ADRs associated with the COVID-19 vaccines (the monovalent and bivalent COVID-19 Vaccine Pfizer/BioNTech, COVID-19 Vaccine AstraZeneca, monovalent and bivalent COVID-19 Vaccine Moderna and COVID-19 Vaccine Novavax), and the MHRA's analysis of the data, between 9 December 2020 and 23 November 2022 (inclusive). A glossary of key terms is provided in Annex 2.

If identified, information on new and emerging safety concerns will be provided in future editions of this report together with details of any resulting regulatory action or changes to advice on use of the vaccines.

Yellow Card reports

Vaccine doses administered

Official vaccination data from the UK Public Health agencies are no longer routinely published for all UK nations. Therefore, data for first and second doses will not be reported beyond 11 September 2022 as regional data is no longer available.[1] Data on the third doses and any booster doses will continue to be updated. From 23 November 2022 vaccine usage will be derived from individual nations' data projected according to the UK population estimates published by the Office for National Statistics (ONS).

Everyone aged 5 and over is eligible to receive a first and second dose of the COVID-19 vaccine. People aged 16 and over, and some children aged 12 to 15, are also eligible to receive a booster dose. People aged 5 and over who had a severely weakened immune system when they had their first 2 doses, will be offered a third dose before any booster doses. People aged 50 years and older, residents in care homes for older people, those aged 5 years and over in a clinical risk group and health and social care staff will be offered an autumn booster of COVID-19 vaccine.

Data from the UK Public Health agencies show that at least 53,813,491 people had received their first vaccination in the UK by 11 September 2022, with 50,762,968 people receiving a second dose.

Table 1: Number of people who have received the first dose of a vaccine for COVID-19 in the UK between 8 December 2020 and 11 September 2022.

Country	Number of people who have received a first dose
England	45,247,084
Wales	2,587,960
Northern Ireland	1,428,891
Scotland	4,549,556

Table 2: Number of people who have received the second dose of a vaccine for COVID-19 in the UK between 8 December 2020 and 11 September 2022.

Country	Number of people who have received a second dose
England	42,664,071
Wales	2,456,939
Northern Ireland	1,356,012

[1] First and second doses continue to be administered beyond this date, however, the number of doses is likely to be small and should not affect interpretation of the overall data.

Scotland	4,285,946

As of 11 September 2022, an estimated 27.2 million first doses of the monovalent COVID-19 Vaccine Pfizer/BioNTech and 24.9 million first doses of the COVID-19 Vaccine AstraZeneca had been administered, and around 25 and 24.2 million second doses each of the monovalent COVID-19 Vaccine Pfizer/BioNTech and COVID-19 Vaccine AstraZeneca respectively. An approximate 1.7 million first doses and approximately 1.6 million second doses of the monovalent COVID-19 Vaccine Moderna have also now been administered.

As of 23 November 2022, an estimated 40,528,279 people had received their third dose and/or at least one booster dose in the UK. Note that a patient may have received multiple booster doses, but they will only be counted once in this figure. People aged 16 and over, and some children aged 12 to 15, are eligible to receive a booster dose. An estimated 32.5 million third or booster doses of monovalent COVID-19 Vaccine Pfizer/BioNTech, 59,700 third or booster doses of COVID-19 Vaccine AstraZeneca and 13.1 million doses of monovalent COVID-19 Vaccine Moderna have been given. An approximate 9.7 million booster doses of bivalent COVID-19 Vaccine Pfizer/BioNTech and approximately 8.9 million booster doses of bivalent COVID-19 Vaccine Moderna had also been administered.

Data are not always reported weekly and can be updated for historical dates when vaccinations are recorded on the relevant system, therefore the data may be incomplete, and the resulting estimates are approximate. The estimated number of doses administered differs from the estimated number of people vaccinated due to the different data sources used.

Table 3: Number of people who have received at least one third or booster dose of a vaccine for COVID-19 in the UK between 8 December 2020 and 23 November 2022[2]

Country	Number of people who have received a third or any booster dose
England	33,804,868
Wales	2,081,755
Northern Ireland	1,046,821
Scotland	3,594,835

[2] As a result of changes to the publication schedules of vaccine usage data, Table 3 captures data from the date closest to our data lock point. This table includes data from England up to 20 November 2022, Scotland up to 11 September 2022, Wales up to 16 November 2022 and Northern Ireland up to the 23 November 2022. The estimated 40,528,279 people who had received a 3rd or any booster dose was derived from the numbers in Table 3.

Yellow Card reporting trends

A report of a suspected ADR to the Yellow Card scheme does not necessarily mean that it was caused by the vaccine, only that the reporter has a suspicion it may have been. Underlying or previously undiagnosed illness unrelated to vaccination can also be factors in such reports. **The relative number and nature of reports should therefore not be used to compare the safety of the different vaccines**. The MHRA may also refer to 'cases' as opposed to 'reports' within the analysis of the Yellow Card data; these typically refer to ADR reports that have undergone medical assessment and are considered to meet certain criteria for diagnosis of the reported event and have at least a plausible association with the vaccine. All cases and reports are kept under continual review in order to identify possible new risks.

Up to and including 23 November 2022, the MHRA received and analysed 177,925 UK Yellow Cards from people who have received the monovalent or bivalent COVID-19 Vaccine Pfizer/BioNTech. These reports include a total of 511,776 suspected reactions (i.e., a single report may contain more than one symptom). The first report was received on 9 December 2020.

Up to and including 23 November 2022, the MHRA received and analysed a total of 246,866 UK reports of suspected ADRs to the COVID-19 Vaccine AstraZeneca. These reports include a total of 874,912 suspected reactions (a single report may contain more than one symptom). The first report was received on 4 January 2021.

Up to and including 23 November 2022, the MHRA received and analysed a total of 47,045 UK reports of suspected ADRs to the monovalent and bivalent COVID-19 Vaccine Moderna. These include a total 151,628 suspected reactions (a single report may contain more than one symptom). The first report was received on 7 April 2021.

Up to and including 23 November 2022, the MHRA received and analysed a total of 52 UK reports of suspected ADRs to the COVID-19 Vaccine Novavax. These include a total of 106 suspected reactions (a single report may contain more than one symptom). The first report was received on 21 November 2021.

Additionally, up to and including 23 November 2022, the MHRA received 2,130 Yellow Card reports where the brand of vaccine was not specified by the reporter.

In the 28 days since the previous summary for 26 October 2022 we have received a further 2,499 Yellow Cards for the monovalent and bivalent COVID-19 Vaccine Pfizer/BioNTech, 228 for the COVID-19 Vaccine AstraZeneca, 1,099 for the monovalent and bivalent COVID-19 Vaccine Moderna, 15 for the COVID-19 Vaccine Novavax and 154 where the brand was not specified. Please note that a Yellow Card report can include more than one vaccine

suspected to have caused a reaction where different vaccines have been used as third or booster doses.

It is important to note that Yellow Card data cannot be used to derive side effect rates or compare the safety profile of COVID-19 vaccines as many factors can influence ADR reporting.

Table 4: Number of suspected ADR reports received in the UK up to and including 23 November 2022.

	Number of reports			
Country	**COVID-19 Vaccine Pfizer/ BioNTech (monovalent and bivalent)**	**COVID-19 Vaccine AstraZeneca**	**COVID-19 Vaccine Moderna (monovalent and bivalent)**	**Brand unspecified**
England	138,610	203,063	37,408	1,214
Wales	8,628	10,922	2,841	114
Northern Ireland	3,087	3,020	202	27
Scotland	13,254	17,608	3,891	239

The majority of COVID-19 Vaccine Novavax reports are from England.

The figures in Table 4 are based upon the postcode provided by the reporter. The sums of the reports in the table will not equal the total reports received for the vaccines as a postcode may not have always been provided or may have been entered incorrectly. It is important to note that the number of reports received for each country does not directly equate to the number of people who may have experienced adverse reactions and therefore cannot be used to determine the incidence of reactions. ADR reporting rates are influenced by many aspects, including the extent of use.

We are working with public health bodies and encouraging all healthcare professionals and patients alike to report any suspected ADRs to the Yellow Card scheme. As expected, reports gradually increase in line with an increase in doses administered.

The overall reporting rate for first, second and third or booster doses is in the order of 2 to 5 Yellow Cards per 1,000 doses administered for the monovalent and bivalent COVID-19 Vaccine Pfizer/BioNTech, COVID-19 Vaccine AstraZeneca and monovalent and bivalent

COVID-19 Vaccine Moderna. There is insufficient experience with COVID-19 Vaccine Novavax to be able to make similar estimates of reporting rates. It is known from the clinical trials that the more common side effects for all vaccines can occur at a rate of more than one in 10 doses (for example, local reactions or symptoms resembling transient flu-like symptoms).

Analysis of Data

One of the MHRA's main roles is to continually monitor the safety of medicines and vaccines during widespread use, and we have in place a proactive strategy to do this for COVID-19 vaccines. We also work closely with our public health partners in reviewing the effectiveness and impact that the vaccines are having to ensure benefits continue to outweigh any possible side effects. In addition, we work with our international counterparts to gather information on the safety of vaccines in other countries.

Given the huge scale of the COVID-19 immunisation programme, with many millions of doses of vaccines administered over a relatively short time period, vigilance needs to be continuous, proactive and as near real-time as is possible. The importance of this is two-fold. First, we need to rapidly detect, confirm, and quantify any new risks and weigh these against the expected benefits. We can then take any necessary action to minimise risks to individuals.

Secondly, we need to very quickly establish if any serious medical events which are temporally related to vaccination are merely a coincidental association. These associations are likely while we are still in the midst of a major national vaccination programme, and because many of the millions of people offered the vaccine in the early phase of a vaccination campaign were elderly and/or had underlying medical conditions, which increases the likelihood of unrelated illnesses occurring soon after vaccination. As mentioned above, the nature of Yellow Card reporting means that reported events are not always proven adverse reactions, and some may have happened regardless of vaccination.

Yellow Card reports of suspected ADRs are evaluated, together with additional sources of evidence, by a team of safety experts to identify any new safety issues or side effects. We apply statistical techniques that can tell us if we are seeing more events than we would expect to see, based on what is known about background rates of illness in the absence of vaccination. This aims to account for factors such as coincidental illness. We also look at the clinical characteristics to see if new patterns of illness are emerging that could indicate a new safety concern.

We supplement this form of safety monitoring with other epidemiology studies including analysis of data on national vaccine usage, anonymised GP-based electronic healthcare records and other healthcare data to proactively monitor safety. We also take into account the international experience based on data from other countries using the same vaccines. These combined safety data enables the MHRA to detect side effects or safety issues associated with COVID-19 vaccines. As well as confirming new risks, an equally important objective of monitoring will be to quickly rule out risks – in other words to confirm that the vaccine is not responsible for a suspected side effect and to provide reassurance on its safety.

Overall safety

As with any vaccine, COVID-19 vaccines will cause side effects in some people. The total number and the nature of the majority of Yellow Cards reports received so far is not unusual for a new vaccine for which members of the public and healthcare professionals are encouraged to report any suspected adverse reaction.

As highlighted above, it is known from the clinical trials that the most common side effects for all vaccines can occur at a rate of more than one per 10 doses (such as local reactions, symptoms resembling transient flu-like symptoms). Overall, Yellow Card reporting is therefore lower than the reporting rate of possible side effects from the clinical trials, although we generally do not expect all suspected side effects to be reported on Yellow Cards. The primary purpose of Yellow Card reporting is to detect new safety concerns.

For all of the original COVID-19 vaccines, detailed review of all reports has found that the overwhelming majority relate to injection-site reactions (sore arm for example) and generalised symptoms such as a ‘flu-like’ illness, headache, chills, fatigue (tiredness), nausea (feeling sick), fever, dizziness, weakness, aching muscles, and rapid heartbeat. Generally, these happen shortly after the vaccination and are not associated with more serious or lasting illness. These types of reaction reflect the acute immune response triggered by the body to the vaccines, are typically seen with most types of vaccine and tend to resolve within a day or two. The nature of reported suspected ADRs across all ages is broadly similar, although, as seen in the clinical trials and as is usually seen with other vaccines, they may be reported more frequently in younger adults.

As we receive more reports of these types of reactions with more exposure to the COVID-19 vaccines, we have built a picture of how individuals are experiencing them and the different ways that side effects may present in people. Some people have reported a sudden feeling of cold with shivering/shaking accompanied by a rise in temperature, often with sweating, headache (including migraine-like headaches), nausea, muscle aches and feeling unwell, starting within a day of having the vaccine. Similar to the flu like illness reported in clinical trials, these effects may last a day or two.

It is important to note that it is possible to have caught COVID-19 and not realise until after vaccination. If other COVID symptoms are experienced or fever is high and lasts longer than two or three days, vaccine recipients should stay at home and arrange to have a test.

A number of detailed assessments of safety topics have been undertaken and we have updated our advice on these topics accordingly. Overall, our advice remains that the benefits of the vaccines outweigh the risks in the majority of people. Further comments on use in specific populations and details on the following safety topics can be found below.

In addition to the specific safety topics summarised in this report, a range of other isolated events or series of reports of non-fatal, serious suspected ADRs have been reported. These all remain under continual review, including thorough analysis of expected rates in the absence of vaccine. There are currently no indications of specific patterns or rates of reporting that would suggest the vaccine has played a role.

Comments on safety in specific populations

Safety of COVID-19 vaccines in pregnancy

The MHRA closely monitors the safety of COVID-19 vaccine exposures in pregnancy, including published information as well as Yellow Card reports for COVID-19 vaccines used in pregnancy. These reports have been reviewed by the independent experts of the CHM's COVID-19 Vaccines Benefit Risk Expert Working Group and by the Medicines for Women's Health Expert Advisory Group (MWHEAG).

Pregnant women have the same risk of getting COVID-19 as non-pregnant women, but they may be at an increased risk of becoming severely ill, particularly if they get infected in the third trimester or if they also have underlying medical problems, compared to non-pregnant women. The current advice of the Joint Committee on Vaccination and Immunisation (JCVI) is that the COVID-19 vaccines, including booster doses, should be offered to those who are pregnant as a clinical risk group in the COVID-19 vaccination programme and can be given at any stage in pregnancy.

The number of Yellow Card reports for pregnant women are low in relation to the number of pregnant women who have received COVID-19 vaccines to date (about 135,000 women in England have given birth up to end of May 2022[3] after receiving at least 1 dose of COVID-19 vaccine during or shortly before pregnancy and about 47,000 women in Scotland and Wales have received at least 1 dose whilst pregnant up to end July 2022). Pregnant women have reported similar suspected reactions to the vaccines as people who are not pregnant. Reports of miscarriage and stillbirth are also low in comparison to how commonly these events occurred in the UK outside of the pandemic. A few reports of commonly occurring congenital anomalies and obstetric events have also been received. There is no pattern from the reports to suggest that any of the COVID-19 vaccines used in the UK, or any reactions to these vaccines, increase the risk of miscarriage, stillbirths, congenital anomalies or birth complications.

Sadly, miscarriage is estimated to occur in about 20 to 25 in 100 pregnancies in the UK and most occur in the first 12 to 13 weeks of pregnancy (the first trimester). Published studies

[3] Number of vaccinations during pregnancy are updated when data is made available by the UK Public Health bodies

from the USA[4] and Norway[5] have compared miscarriage rates for vaccinated and unvaccinated women who were pregnant over the same time periods. The studies included data from a large number of women (more than 15,000) who received the monovalent COVID-19 Vaccine Pfizer/BioNTech or monovalent COVID-19 Vaccine Moderna. Both studies found that the occurrence of miscarriage was equally likely amongst unvaccinated women as amongst women at the same stage of pregnancy who were vaccinated in the previous 3 to 5 weeks. Recent evidence from the COVID-19 in Pregnancy Scotland (COPS) study[6] compared rates of miscarriage amongst vaccinated and unvaccinated women in Scotland. The study found no differences in rates of miscarriage or ectopic pregnancy amongst women vaccinated with monovalent COVID-19 Vaccine Pfizer/BioNTech, monovalent COVID-19 Vaccine Moderna or COVID-19 Vaccine AstraZeneca, compared to rates for women of the same age and general health status who were either pregnant at a similar time of year prior to the pandemic or who became pregnant at around the same time (during the pandemic) and were unvaccinated. These studies provide strong evidence for no increased risk of miscarriage in association with the mRNA vaccines in current use.

Evidence for pregnancy outcomes other than miscarriage is accumulating as more pregnancies reach full term. Currently available evidence does not suggest any increased risks of pregnancy complications, stillbirths, preterm births or adverse neonatal outcomes following vaccination in later pregnancy.

Stillbirths are sadly estimated to occur in about 1 in 200 pregnancies in the UK. Information from surveillance by UKHSA (formerly Public Health England) has found similar rates of stillbirth amongst (more than 125,000) women who were vaccinated before or during pregnancy and those who gave birth over the same period and were unvaccinated. Likewise, surveillance by Public Health Scotland[7] and the COPS study[8] has found similar rates of perinatal mortality (including stillbirths) amongst (more than 15,700) women who were vaccinated during pregnancy and those who gave birth over the same period and who were unvaccinated and not infected with COVID-19.

[4] Kharbanda EO, et al. Spontaneous abortion following COVID-19 vaccination during pregnancy. JAMA. doi:10.1001/jama.2021.15494: https://jamanetwork.com/journals/jama/fullarticle/2784193

[5] Magnus, MC et al. Covid-19 Vaccination during Pregnancy and First-Trimester Miscarriage N Engl J Med 2021; 385:2008-2010 DOI: 10.1056/NEJMc2114466: https://www.nejm.org/doi/10.1056/NEJMc2114466

[6] Clavert, C et al A population-based matched cohort study of early pregnancy outcomes following COVID-19 vaccination and SARS-CoV-2 infection https://www.nature.com/articles/s41467-022-33937-y

[7] Public Health Scotland, COVID-19 Statistical report: https://publichealthscotland.scot/publications/covid-19-statistical-report/covid-19-statistical-report-11-may-2022/

[8] Stock SJ, et al SARS-CoV-2 infection and COVID-19 vaccination rates in pregnant women in Scotland Nature Medicine 2022 https://www.nature.com/articles/s41591-021-01666-2 .

Additional evidence on the safety of monovalent COVID-19 Vaccine Pfizer/BioNTech exposures in early pregnancy is available from a published study from Israel[9]. This study looked at live birth outcomes for more than 2,000 women who were vaccinated in their first trimester compared to more than 3,500 unvaccinated women who became pregnant around the same time. The study found no differences between vaccinated and unvaccinated women in rates of pre-term births, neonatal hospitalisation or mortality, or babies born with birth defects. This study provides further evidence for no increased risk of birth defects following monovalent COVID-19 Vaccine Pfizer/BioNTech.

Although, like most vaccines and medicines, clinical trials of COVID-19 vaccines in pregnant women were not carried out prior to use of the vaccines in the general population, there is now growing evidence from clinical use which provides reassurance on the safety of the vaccines in pregnancy. This adds to the evidence from non-clinical studies of the COVID-19 vaccines which have not raised any concerns about safety in pregnancy. The COVID-19 vaccines do not contain organisms that can multiply in the body, so they cannot infect an unborn baby in the womb.

The product information for monovalent and bivalent COVID-19 Vaccine Pfizer/BioNTech and COVID-19 Vaccine Moderna reflects that the available data are reassuring on safety and that the vaccines can be used during pregnancy.

The MHRA will continue to closely monitor safety data following use of the COVID-19 vaccines in pregnancy, including through evaluation of electronic healthcare record data.

Safety of COVID-19 vaccines in those breastfeeding

The MHRA closely monitors the safety of COVID-19 vaccines during breastfeeding, including evaluation of Yellow Card reports for COVID-19 vaccines from breastfeeding women. These reports have been reviewed by the independent experts of the CHM's COVID-19 Vaccines Benefit Risk Expert Working Group, by paediatric and breastfeeding experts.

There is no current evidence that COVID-19 vaccination while breastfeeding causes any harm to breastfed children or affects the ability to breastfeed.

COVID-19 vaccines do not contain live components and there is no known risk associated with being given a non-live vaccine whilst breastfeeding. The current advice of the Joint Committee on Vaccination and Immunisation (JCVI) is that breastfeeding parents may be offered any suitable COVID-19 vaccine depending on their age.

[9] Goldshtein et al Association of BNT162b2 COVID-19 Vaccination During Pregnancy With Neonatal and Early Infant Outcomes JAMA Pediatrics (2022) doi:10.1001/jamapediatrics.2022.0001

We have received about 4,000 Yellow Card reports from women breastfeeding at the time of vaccination. Most of these women reported only suspected reactions in themselves which were similar to reports for the general population, with no effects reported on their milk supply or in their breastfed children.

A small number of women have reported decreases in their milk supply, most of which were transient, or possible reactions in their breastfed child. A number of factors can affect milk supply and infant behaviour, including general maternal health, amount of sleep, and anxiety. The symptoms reported for the children (high temperature, rash, diarrhoea, vomiting and general irritability) are common conditions in children of this age, so some of the effects reported may have occurred by coincidence.

The product information for monovalent and bivalent COVID-19 Vaccine Pfizer/BioNTech and COVID-19 Vaccine Moderna reflects that the available data are reassuring on safety and that the vaccines can be used during breastfeeding.

A small number of women may experience a reduction in their breast milk production, and it may be helpful for breastfeeding women to know how to maintain their breast milk supply, particularly if they are feeling unwell. The NHS website has a good resource for this: https://www.nhs.uk/start4life/baby/breastfeeding/.

Suspected side effects reported in individuals under 18 years old

The MHRA closely monitors the safety of COVID-19 vaccine exposures in individuals under 18 years old, including Yellow Card reports for COVID-19 vaccines used in this age group.

Up to the 11 September 2022 there have been an estimated 4.2 million first doses, 2.9 million second doses of the monovalent COVID-19 Vaccine Pfizer/BioNTech given to under 18s; approximately 11,400 first doses and 8,500 second doses of the COVID-19 Vaccine AstraZeneca given to this population; and 2,100 first doses and 2,000 second doses of the monovalent COVID-19 Vaccine Moderna given to individuals under 18.

Up to 23 November 2022, there have been an estimated 0.4 million additional or booster doses of the monovalent COVID-19 Vaccine Pfizer/BioNTech and approximately 52,500 booster doses of the bivalent COVID-19 Vaccine Pfizer/BioNTech given to under 18s. An approximate 32,400 additional or booster doses of the monovalent COVID-19 Vaccine Moderna and less than 1,000 booster doses of the bivalent COVID-19 Vaccine Moderna were also administered in this age group. There has been extremely limited use of COVID-19 Vaccine AstraZeneca as boosters in those under 18 years.

The MHRA has received 4,205 UK reports of suspected ADRs for the monovalent or bivalent COVID-19 Vaccine Pfizer/BioNTech in which the individual was reported to be under 18

years old, 267 reports for the COVID-19 Vaccine AstraZeneca, 39 for the monovalent or bivalent COVID-19 Vaccine Moderna and 37 where the brand of vaccine was unspecified.

For the COVID-19 Vaccine Pfizer/BioNTech, which is currently the preferred COVID-19 vaccine for the under 18s age group in the UK vaccination programme for primary immunisation, the experience reported in under 18s is similar to that identified in the general population. A review of these reports does not raise any additional safety topics specific to this age group. This includes the different age subgroups (5-11, 12-15 and 16-17 year olds). Reporting rates for 5-11 year olds, 12-15 year olds and 16-17 year olds are all less than 1 per 1,000 doses. This is approximately half the reporting rate for the COVID-19 Vaccine Pfizer/BioNTech for those 18 years and over, which is around 2 per 1,000 doses.

As COVID-19 Vaccine AstraZeneca and monovalent COVID-19 Vaccine Moderna are not the preferred vaccines in under 18s there is insufficient experience in this age group to be able to make similar estimates.

There has been a small number of reports for myocarditis and pericarditis (inflammation of the heart) in individuals under 18 years both in the UK and internationally. This is a recognised potential risk with the monovalent and bivalent COVID-19 Vaccine Pfizer/BioNTech and monovalent and bivalent COVID-19 Vaccine Moderna and the MHRA continues to closely monitor these events. Further information surrounding these very rare reports of myocarditis and pericarditis within this population can be found within the specific section on this safety topic later in the summary. We will continue to closely monitor the safety of the COVID-19 vaccines in those under 18 years old.

Suspected side effects reported in individuals receiving a booster vaccination

Safety monitoring plans have been agreed to ensure action can be taken on any emerging safety concerns from supplementary or booster doses.

As of 23 November 2022, an estimated 64.3 million COVID-19 third doses and booster doses have been administered in the UK. This figure includes doses administered during the Autumn (2021) and Autumn (2022) booster programme. The monovalent COVID-19 Vaccine Pfizer/BioNTech and monovalent COVID-19 Vaccine Moderna were the preferred vaccines in the UK booster programme prior to Autumn 2022 and made up the vast majority of booster doses administered. The bivalent COVID-19 Vaccine Pfizer/BioNTech and bivalent COVID-19 Vaccine Moderna were the preferred vaccines for the Autumn (2022) booster programme. .

Up to the 23 November 2022 the MHRA has received 35,028 UK reports of suspected ADRs where the monovalent and bivalent COVID-19 Vaccine Pfizer/BioNTech was reported to be

the booster dose, 655 reports where the COVID-19 Vaccine AstraZeneca was reported to be the booster dose, 21,956 reports where the monovalent and bivalent COVID-19 Vaccine Moderna was reported to be the booster dose and 280 reports where the brand of vaccine booster was unspecified.

For the monovalent and bivalent COVID-19 Vaccine Pfizer/BioNTech combined this represents a reporting rate of 1 report per 1,000 third or booster doses and monovalent and bivalent for the COVID-19 Vaccine Moderna combined there is an estimated 1 reports per 1,000 third or booster doses. Both of these are lower than the reporting rate for all COVID-19 vaccine doses combined, which is between 2-5 reports per 1,000 doses. For the COVID-19 Vaccine AstraZeneca there has been very limited number of booster doses in the UK and a very small number of reports. There is insufficient experience with COVID-19 Vaccine AstraZeneca as a booster vaccine to be able to make similar estimates of reporting rates.

The nature of events reported with third and booster doses up to Autumn 2022 is similar to that reported for the first two doses of the COVID-19 vaccines, and the vast majority of reports relate to expected reactogenicity events. Review of third and booster dose reports does not raise any new safety concerns. As part of the MHRA’s booster safety monitoring strategy, reports of suspected adverse events following COVID-19 boosters given at the same time as seasonal flu vaccines have been closely monitored, and no new safety concerns have been identified in this data either.

There have been a small number of reports of suspected myocarditis and pericarditis (inflammation of the heart) following booster doses with monovalent Pfizer/BioNTech and Moderna COVID-19 vaccines. This is a recognised potential risk with the mRNA COVID-19 vaccines and the MHRA is closely monitoring these events. The reports after booster doses are extremely rare and there is no indication that these events are more serious after boosters. Further information surrounding these very rare reports of suspected myocarditis and pericarditis can be found within the specific section on this safety topic later in the summary.

For the Autumn 2022 COVID-19 vaccination booster campaign, the bivalent COVID-19 Pfizer/BioNTech booster vaccine (Comirnaty Original/Omicron BA.1) and the bivalent COVID-19 Moderna booster vaccine (Spikevax bivalent Original/Omicron) are mainly being used. The original monovalent Pfizer-BioNTech vaccine is recommended for eligible persons aged 5-11 years while the COVID-19 vaccine Novavax (Nuvaxovid) is recommended for those who cannot receive an mRNA vaccine. Review of the Yellow Card data received for these vaccines so far does not indicate any new safety concerns. We will continue to closely monitor the safety of all doses of the COVID-19 vaccines.

Comments on specific safety topics

The following reports reflect data up to 23 November 2022. The glossary provides an explanation of the clinical terms used.

Anaphylaxis (severe allergic reactions)

On 9 December 2020, the MHRA issued preliminary guidance on severe allergic reactions after administration of the monovalent COVID-19 Vaccine Pfizer/BioNTech due to early reports of anaphylaxis. Following further detailed review, this advice was amended on 30 December 2020 to the current advice. The advice is that people with a previous history of severe allergic reactions to any ingredients of the vaccine should not receive it. On 14 December 2021 it was announced that following a CHM review of the Yellow Card data on anaphylaxis after the primary course and boosters there would be a temporary suspension of the post vaccination 15-minute monitoring time for the majority of individuals. This helped to accelerate the public health response to the Omicron variant. On 5 May 2022 the 15-minute observation period after vaccination with the monovalent COVID-19 Pfizer/BioNTech or Moderna vaccines was removed for individuals aged 12 years and over and who have no history of a severe allergic reaction (as outlined in the Green Book[10] advice.) This followed careful review of the safety data by MHRA and advice from the CHM. A temporary suspension of the 15-minute observation period for children aged 5-11 years remains in place and this will be reviewed on a regular basis. The 15-minute observation period will remain in place for the small number of people who may have previously suffered anaphylaxis or other allergic reactions to a food, insect sting and most medicines or vaccines. The temporary suspension of the 15-minute observation time for children aged 5-11 years is under regular review by the CHM and the COVID-19 Vaccines Benefit Risk Expert Working Group.

Widespread use of the vaccine suggests that severe allergic reactions to the monovalent COVID-19 Vaccine Pfizer/BioNTech and monovalent COVID-19 Vaccine Moderna are very rare. Anaphylaxis can also be a very rare side effect associated with most other vaccines.

The MHRA continues to monitor reports of severe allergic reactions with the monovalent and bivalent COVID-19 Vaccine Pfizer/BioNTech and has received 687 UK spontaneous adverse reactions associated with anaphylaxis or anaphylactoid reactions. Severe allergic reactions to the monovalent COVID-19 Vaccine Pfizer/BioNTech remain very rare. The MHRA's guidance remains that those with a previous history of allergic reactions to the ingredients of the vaccine should not receive it.

[10] The Green Book has the latest information on vaccines and vaccination procedures, for vaccine preventable infectious diseases in the UK.

The MHRA is closely monitoring reports of anaphylaxis with the monovalent and bivalent COVID-19 Vaccine Moderna and has received 102 reports of anaphylaxis in association with the vaccines. Anaphylaxis is a potential side effect of the Moderna vaccines, and it is recommended that those with known hypersensitivity to the ingredients of these vaccines should not receive it.

Prior to Autumn 2022 the monovalent COVID-19 Vaccine Pfizer/BioNTech and monovalent COVID-19 Vaccine Moderna were the preferred vaccines in the UK booster programme. From September 2022, the bivalent original/Omicron BA.1 vaccines from Pfizer/BioNTech and Moderna are the main products being used in the Autumn 2022 booster program. Reports of anaphylaxis or anaphylactoid reactions remain very rare after booster doses. Analysis of the data shows that these events are about 5 times lower after booster doses compared to the first dose.

The MHRA also closely monitors reports of anaphylaxis or anaphylactoid reactions with the COVID-19 Vaccine AstraZeneca and has received 888 UK spontaneous adverse reactions associated with anaphylaxis or anaphylactoid reactions reported and such reports are very rare. The product information reflects the fact that reports of anaphylaxis have been received for the COVID-19 Vaccine AstraZeneca.

Bell’s palsy

Bell's palsy (BP) is temporary weakness or paralysis affecting one side of the face that develops gradually; most people recover from this condition within a few months. BP is known to be associated with a number of infectious diseases, including the SARS-CoV-2 virus. Reports of suspected BP following COVID-19 vaccination have been continuously reviewed by the MHRA. Whilst reporting of BP following COVID-19 vaccination is rare, evidence based on the latest available data shows that there may be an increased risk of BP following COVID-19 vaccination. To raise awareness of this potential adverse event amongst healthcare professionals and patients, facial paralysis has been included in the product information for COVID-19 Vaccine AstraZeneca, monovalent and bivalent COVID-19 Vaccine Pfizer/BioNTech and monovalent and bivalent COVID-19 Vaccine Moderna. We will continue to monitor these events following COVID-19 vaccination.

Transverse myelitis

Transverse myelitis (TM) is a rare acute neurological disorder where parts of the spinal cord are inflamed. TM is known to be associated with a number of viruses, such as the herpes and influenza virus. The MHRA has continually monitored reports of suspected transverse myelitis following COVID-19 vaccination since the start of the vaccination programme.

As of 26 October 2022, we have received 129 reports of suspected TM following administration of COVID-19 Vaccine AstraZeneca, 42 reports following administration of

monovalent COVID-19 Vaccine Pfizer/BioNTech and 8 reports following administration of monovalent COVID-19 Vaccine Moderna. There were no reports received with a fatal outcome following suspected TM. Whilst the incidence rate of this adverse event with any of the COVID-19 vaccines used in the UK remains extremely rare (less than 1 report per 100,000 doses of each vaccine), the available evidence reviewed by the MHRA suggests an association between TM and COVID-19 Vaccine AstraZeneca is possible.

Due to the serious nature of this adverse event and as a precaution, the product information has been updated to raise healthcare professionals' and patients' awareness of the signs and symptoms associated with TM which may include muscle weakness, localised or radiating back pain, bladder and bowel symptoms and changes in sensation. It is recommended that patients who had an episode of transverse myelitis following the first dose of COVID-19 Vaccine AstraZeneca should not receive a second dose of this vaccine.

Thrombo-embolic (blood clotting) events with concurrent low platelets

The MHRA has undertaken a thorough review into UK cases of an extremely rare and unlikely to occur specific type of blood clot in the brain, known as cerebral venous sinus thrombosis (CVST) occurring together with low levels of platelets (thrombocytopenia) following vaccination with the COVID-19 Vaccine AstraZeneca. It has also considered other blood clotting reports (thromboembolic events) alongside low platelet levels.

This scientific review concluded that the evidence of a link with COVID-19 Vaccine AstraZeneca is likely and an announcement was made on 7 April 2021 with a further statement on 7 May 2021. We have continued to publish the latest breakdown of all cases of these extremely rare side effects on a weekly and now monthly basis.

Anyone who experienced cerebral or other major blood clots occurring with low levels of platelets after their first vaccine dose of COVID-19 Vaccine AstraZeneca should not have further doses. Anyone who did not have these side effects should come forward for their second dose when invited.

Anyone who experiences any of the following from around 4 days after vaccination should seek medical advice urgently:

- a severe headache that is not relieved with simple painkillers or gets worse or feels worse when you lie down or bend over
- an unusual headache that may be accompanied by blurred vision, confusion, difficulty with speech, weakness, drowsiness or seizures (fits)
- rash that looks like small bruises or bleeding under the skin beyond the injection site

shortness of breath, chest pain, leg swelling or persistent abdominal (tummy) pain.

Up to 23 November 2022, the MHRA had received Yellow Card reports of 445 cases of major thromboembolic events (blood clots) with concurrent thrombocytopenia (low platelet counts) in the UK following vaccination with COVID-19 Vaccine AstraZeneca. Fifty-one of the 445 reports have been reported after a second dose. Of the 445 reports, 221 occurred in females, and 219 occurred in males aged from 18 to 93 years. The overall case fatality rate was 18% with 81 deaths, six of which occurred after the second dose.

Cerebral venous sinus thrombosis was reported in 161 cases (average age 46 years) and 284 had other major thromboembolic events (average age 54 years) with concurrent thrombocytopenia. The estimated number of first doses of COVID-19 Vaccine AstraZeneca administered in the UK by 23 November 2022 was 24.9 million and the estimated number of second doses was 24.1 million.

The overall incidence after first or unknown doses was 15.9 per million doses. Considering the different numbers of patients vaccinated with COVID-19 Vaccine AstraZeneca in different age groups, the data indicates that there is a higher reported incidence rate in the younger adult age groups following the first dose compared to the older groups (21.8 per million doses in those aged 18-49 years compared to 11.3 per million doses in those aged 50 years and over). The number of first doses given to those in the 18-49 years age group is estimated to be 8.5 million while an estimated 16.4 million first doses have been given to patients aged 50+ years. The MHRA advises that this evidence should be taken into account when considering the use of the vaccine. There is some evidence that the reported incidence rate is higher in females compared to men although this is not seen across all age groups and the difference remains small.

The overall incidence of thromboembolic events with concurrent low platelets after second doses was 2.1 cases per million doses. Taking into account the different numbers of patients vaccinated with COVID-19 Vaccine AstraZeneca in different age groups, the data indicates that there is a lower reported incidence rate in younger adult age groups following the second dose compared to the older groups (1.0 per million doses in those aged 18-49 years compared to 2.1 per million doses in those aged 50 years and over). The number of second doses given to those in the 18-49 years age group is estimated to be 8.0 million while an estimated 16.1 million second doses have been given to patients aged 50+ years. These rates after second doses should not be directly compared to the incidence rates reported after the first dose as the time for follow-up and identification of cases after second doses is more limited and differs across age groups. However, the data are reassuring, particularly regarding younger recipients where there is a significantly lower incidence after the second dose compared to the first, and there is overall no indication of an increased risk of these events after the second dose in any age group. Anyone who did not have these side effects should come forward for their second dose when invited.

These cases have also been analysed by the independent advisory body, the CHM's COVID-19 Vaccines Benefit Risk Expert Working Group, which includes lay representatives and advice from leading haematologists.

On the basis of this ongoing review, the advice remains that the benefits of the vaccine outweigh the risks in the majority of people.

Table 5: Number of suspected thrombo-embolic events with concurrent thrombocytopenia ADR cases received for the COVID-19 Vaccine AstraZeneca in the UK up to and including 23 November 2022.

Country	Number of cases
England	382
Wales	14
Northern Ireland	11
Scotland	36
Unknown	2

Table 6: Number of UK suspected thrombo-embolic events with concurrent thrombocytopenia ADR cases received for the COVID-19 Vaccine AstraZeneca by patient age up to and including 23 November 2022.

Age range (years)	Number of cases	Number of fatal cases
18-29	31	7
30-39	49	10
40-49	112	17
50-59	108	21
60-69	62	11
70-79	40	7
80-89	6	3

90-99	2	1
Unknown	35	4
Total	**445**	**81**

Table 7: Number of UK suspected thrombo-embolic events with concurrent thrombocytopenia ADR cases received for the COVID-19 Vaccine AstraZeneca by patient sex up to and including 23 November 2022.

Sex	Number of cases	Number of fatal cases
Male	219	36
Female	221	44
Unknown	5	1
Total	**445**	**81**

Up to 23 November 2022, the MHRA had received Yellow Card reports of 33 cases of major thromboembolic events (blood clots) with concurrent thrombocytopenia (low platelet counts) in the UK following use of the monovalent COVID-19 Vaccine Pfizer/BioNTech. These events occurred in 13 females, 19 males, and 1 unknown aged from 18 to 91 years, and the overall case fatality rate was 12% with four deaths reported.

Up to 23 November 2022, the MHRA had received Yellow Card reports of 8 cases of major thromboembolic events (blood clots) with concurrent thrombocytopenia (low platelet counts) in the UK following the use of monovalent COVID-19 Vaccine Moderna. These events occurred in 6 adult males and 2 adult females between the ages of 28-95. The overall case fatality rate was 13% with one death reported.

To note, direct comparison of the summary provided here, and the analysis prints is not possible. This review includes reports of CVST or other thrombo-embolic events with concurrent thrombocytopenia. Blood clotting events without lowered platelets are described below.

Yellow Card reports may contain more than one reported reaction and the analysis prints are listed by individual reactions rather than whole reports. Therefore, summing the reactions listed in the prints will not equate to the total cases included within this summary.

Thrombo-embolic (blood clotting) events without concurrent low platelets

The MHRA has conducted a thorough review of events of cerebral venous sinus thrombosis (CVST) without concurrent low platelet levels following vaccination with the COVID-19 Vaccine AstraZeneca and sought advice from the CHM's Vaccine Benefit Risk Expert Working Group. Blood clotting events with lowered platelets are described in a separate section (above). The scientific review concluded that there is a possible link between CVST without low platelets and COVID-19 Vaccine AstraZeneca. The product information for COVID-19 Vaccine AstraZeneca has been updated to include information that CVST events not associated with low levels of blood platelets occurred extremely rarely. The majority of the CVST events occurred within the first four weeks following vaccination. A potential cause has not been identified.

The MHRA has also confirmed that the evidence to date does not suggest that the COVID-19 Vaccine AstraZeneca increases the risk of venous thromboembolism (i.e., deep vein thrombosis/pulmonary embolism) in the absence of a low platelet count. The MHRA will continue to closely monitor reports of venous thromboembolism following COVID-19 vaccination.

Immune thrombocytopenia

Immune thrombocytopenia (ITP) is a condition where the immune system does not function correctly and becomes involved in destroying platelets, which can lead to bleeding; these events are usually short-lived and of minor severity. Reports of ITP following COVID-19 vaccination have been closely monitored by the MHRA. A recent thorough review of all the available evidence confirmed that this type of event is reported extremely rarely for COVID-19 Vaccine AstraZeneca in the UK, at approximately 5 reports per million doses. In approximately 10-20% of the reports, patients had a history of ITP, or an underlying condition known to be associated with ITP. Following the most recent review, the available data suggested a possible link between COVID-19 Vaccine AstraZeneca and ITP, and the product information for this vaccine has been updated to include information on the occurrence of ITP.

Capillary Leak Syndrome

The MHRA has received 18 reports of suspected capillary leak syndrome (a condition where fluid leaks from the small blood vessels into the body) in the context of more than 49 million doses of COVID-19 Vaccine AstraZeneca given. Of these reports, 3 people had a history of capillary leak syndrome. This is an extremely rare relapsing-remitting condition and triggers for relapses are not well understood. As a precautionary measure, the MHRA is advising that COVID-19 Vaccine AstraZeneca is not used in people who have previously experienced

episodes of capillary leak syndrome. The product information has been updated to reflect this advice.

The MHRA has also reviewed reports of capillary leak syndrome for the COVID-19 Moderna and Pfizer/BioNTech vaccines. For the monovalent COVID-19 Vaccine Moderna, while no association with new-onset of capillary leak syndrome was found, a potential risk of flare-up of existing capillary leak syndrome was identified following vaccination. The product information for the COVID-19 Vaccines Moderna highlights the potential risk of flare-up of capillary leak syndrome to healthcare professionals and patients. For the monovalent COVID-19 Vaccine Pfizer/BioNTech, no association between new-onset or flare-up of capillary leak syndrome was identified. The MHRA has received 2 reports of capillary leak syndrome following administration of the monovalent COVID-19 Vaccine Moderna and 2 reports following the administration of the monovalent COVID-19 Vaccine Pfizer/BioNTech.

Menstrual disorders (period problems) and unexpected vaginal bleeding

The MHRA has continued to review reports of suspected side effects of menstrual disorders (period problems) and unexpected vaginal bleeding following vaccination against COVID-19 in the UK. These reports are also being reviewed by the independent experts of the CHM's COVID-19 Vaccines Benefit Risk Expert Working Group and the Medicines for Women's Health Expert Advisory Group. Evidence from the most recent review suggested a possible association between the Pfizer and Moderna COVID-19 vaccines and heavy menstrual bleeding. The events were mostly not serious and were temporary in nature. The product information for the Pfizer and Moderna COVID-19 vaccines is therefore being updated to add heavy menstrual bleeding as a possible side effect. The rigorous evaluation completed to date does not support a link between COVID-19 vaccines and other changes to menstrual periods.

Up to 23 November 2022 a total of 51,695 suspected reactions relating to a variety of menstrual disorders have been reported after administration of COVID-19 vaccines including heavier than usual periods, delayed periods and unexpected vaginal bleeding. These suspected reactions have been reported in 40,327 individual Yellow Card reports (as each report may contain more than one suspected reaction). This is following approximately 88.1 million monovalent and bivalent COVID-19 vaccine doses administered to women up to 23 November 2022. The number of reports of menstrual disorders and vaginal bleeding is low in relation to both the number of people who have received COVID-19 vaccines to date and how common menstrual disorders are generally.

The menstrual changes reported are mostly transient in nature. There is no evidence to suggest that COVID-19 vaccines will affect fertility and your ability to have children.

Whilst uncomfortable or distressing, period problems are extremely common and stressful life events can disrupt menstrual periods. Changes to the menstrual cycle have also been reported following infection with COVID-19 and in people affected by long-COVID. General advice about period problems and/or unexpected vaginal bleeding is available from the NHS website. It is important that anyone experiencing changes to their periods that are unusual for them, persist over time, or has any new vaginal bleeding after the menopause, following COVID-19 vaccination, should contact their doctor. Anyone presenting with menstrual disorders and/or unexpected vaginal bleeding following COVID-19 vaccination should be treated according to clinical guidelines for these conditions, as usual.

The MHRA will continue to closely review reports of suspected side effects of menstrual disorders and unexpected vaginal bleeding.

Myocarditis and pericarditis (Inflammation of the heart)

The MHRA has undertaken a thorough review of both UK and international reports of suspected myocarditis and pericarditis following vaccination against COVID-19. There has been a consistent pattern of higher reporting of these suspected events with both the monovalent COVID-19 Vaccine Pfizer/BioNTech and COVID-19 Vaccine Moderna, and of these occurring more frequently in males. These reports have also been analysed by the government's independent advisory body, the CHM and its COVID-19 Vaccines Benefit Risk Expert Working Group. Following their advice, the product information for both monovalent COVID-19 Vaccine Moderna and COVID-19 Vaccine Pfizer/BioNTech was updated to inform healthcare professionals and patients of these reports and provide advice to be aware of important symptoms for myocarditis and pericarditis. This advice has also been included in the product information for the bivalent (original/Omicron BA.1) COVID-19 vaccines for Moderna and Pfizer/BioNTech.

These reports are very rare, and the events reported are typically mild with individuals usually recovering within a short time with standard treatment and rest.

People should come forward for their second and booster vaccination when invited to do so, unless advised otherwise.

It is important that anyone who experiences new onset of symptoms such as chest pain, shortness of breath or feelings of having a fast-beating, fluttering, or pounding heart seeks medical attention.

Up to and including 23 November 2022, we have received 851 reports of myocarditis and 579 reports of pericarditis following use of both COVID-19 Vaccine Pfizer/BioNTech, as well as ten reports of carditis, five reports each for viral myocarditis and endocarditis, four reports each for infective pericarditis and viral pericarditis, two reports each for myocarditis mycotic and myocarditis post infection, and one report each of infectious myocarditis, constrictive

pericarditis, pleuropericarditis, lupus pericarditis, non-infective endocarditis, eosinophilic myocarditis, hypersensitivity myocarditis, bacterial myocarditis, septic myocarditis and streptococcal endocarditis.

For COVID-19 Vaccine AstraZeneca there have been 241 reports of myocarditis and 226 reports of pericarditis following vaccination up to and including 23 November 2022 as well as nine reports for endocarditis, five reports for viral pericarditis, three reports each for viral myocarditis and carditis, two reports each for bacterial endocarditis and acute endocarditis, and one report each for infectious myocarditis, myocarditis post infection, autoimmune pericarditis and autoimmune myocarditis.

There have been 251 reports of myocarditis, 149 reports of pericarditis, three reports of carditis and one report each of hypersensitivity myocarditis, pleuropericarditis, viral myocarditis, gonococcal pericarditis and endocarditis following use of both COVID-19 Vaccines Moderna up to the same date.

Seven suspected myocarditis or pericarditis reports with a fatal outcome have been reported following the monovalent COVID-19 Vaccine Pfizer/BioNTech, six reports with a fatal outcome following the COVID-19 Vaccine AstraZeneca and two suspected myocarditis or pericarditis reports with a fatal outcome reported following the bivalent COVID-19 Vaccine Moderna to date. There have also been no myocarditis/pericarditis reports with a fatal outcome following the monovalent COVID-19 Vaccine Moderna and bivalent (original/Omicron BA.1) Pfizer/BioNTech COVID-19 vaccines to date. Reports with a fatal outcome are being monitored closely and are carefully followed up to gather relevant information. The majority of reports with a fatal outcome describe underlying illnesses in these patients that could provide alternative explanations for the events reported.

Based on reports of suspected ADRs in the UK, the overall reporting rate across all age groups for suspected myocarditis (including viral myocarditis), after first, second and booster or third doses, is 10 reports per million doses of monovalent COVID-19 Vaccine Pfizer/BioNTech and for suspected pericarditis (including viral pericarditis and infective pericarditis) the overall reporting rate is 6 reports per million doses. For monovalent COVID-19 Vaccine Moderna, the overall reporting rate for suspected myocarditis (including hypersensitivity myocarditis and viral myocarditis) is 14 per million doses and for suspected pericarditis (including pleuropericarditis and gonococcal pericarditis) is 8 per million doses. For COVID-19 Vaccine AstraZeneca the overall reporting rate for suspected myocarditis (including viral myocarditis and infectious myocarditis) is 5 per million doses and for suspected pericarditis (including viral pericarditis) is 5 per million doses. It should be noted that an individual report can contain more than one event and therefore the total number of reports will not be equal to the number of events.

When the reporting rate is calculated by age group (see Table 8) the reporting rate for suspected myocarditis and pericarditis is highest in the 18-29-year age group for the monovalent Pfizer/BioNTech and Moderna COVID-19 vaccines. A more even spread in reporting rates across the age groups is seen for AstraZeneca COVID-19 vaccine. For all vaccines there is a trend for decreased reporting in the older age groups.

The monovalent COVID-19 vaccine Pfizer/BioNTech was the preferred COVID-19 vaccine for the under 18s age group in the UK vaccination programme up to Autumn 2022. For the National Autumn booster campaign, the monovalent and bivalent (original/Omicron BA.1) Pfizer/BioNTech vaccines were recommended for eligible people aged 12-17 years and the monovalent Pfizer/BioNTech vaccine was recommended for those aged 5 to 11 years. For the monovalent Pfizer/BioNTech vaccine, which has been the most commonly used vaccine in the under 18s age group, there is no indication in the current data that there is an increased reporting rate of suspected myocarditis and pericarditis in this age group overall compared to young adults. Furthermore, the reporting rates for the 5-11 year, 12-15 year and 16-17 year age group are lower than that in the young adult 18-29 age group after the first and second doses.

Prior to Autumn 2022, both monovalent COVID-19 Vaccine Pfizer/BioNTech and COVID-19 Vaccine Moderna were the preferred vaccines in the UK booster programme, and the reporting rates for suspected myocarditis and pericarditis following booster or third doses of these vaccines are lower than those estimated for the first and second doses; these events are very rare after booster doses. There is no indication that these events are more severe after booster doses compared to first and second doses; most reports describe mild events with a rapid recovery and are similar to those experienced after the first and second doses. There is extremely limited usage of COVID-19 Vaccine AstraZeneca as a booster. Due to this limited usage and very small numbers of reports of suspected myocarditis and pericarditis after booster doses, it is not possible to calculate a reliable reporting rate for the COVID-19 Vaccine AstraZeneca when used as a booster; no association has been established between myocarditis or pericarditis and the COVID-19 Vaccine AstraZeneca.

It is important to note that Yellow Card data cannot be used to compare the safety profile of COVID-19 vaccines as many factors can influence ADR reporting.

These reporting rates may also be subject to change as more experience is gathered in the UK.

Table 8: Reporting rates per million doses for UK ADR reports of suspected myocarditis and pericarditis associated with COVID-19 Vaccines, by patient age and dose, up to and including 23 November 2022.

Age range (years)	COVID-19 vaccine Pfizer/ BioNTech (monovalent)			COVID-19 Vaccine Moderna (monovalent)			COVID-19 Vaccine AstraZeneca	
	1st or unknown dose	2nd Dose	3rd or booster dose	1st or unknown dose	2nd dose	3rd or booster dose	1st or unknown dose	2nd dose
Under 18	13	8	Not calculated*	Not applicable**	Not applicable**	Not applicable**	Not applicable**	Not applicable**
18-29	24	29	17	61	70	20	10	17
30-39	20	25	16	60	51	20	14	12
40-49	20	19	13	48	30	16	14	10
50-59	11	18	8	Not calculated*	Not calculated*	8	8	8
60-69	5	14	7	Not calculated*	Not applicable**	8	7	6
70+	4	5	4	Not calculated*	Not applicable**	1	4	5

*There is currently insufficient data to calculate a reliable estimate of the reporting rate in the UK due to the relatively limited exposure and small numbers of suspected reports in these individuals.

**There have been no reports of suspected heart inflammation events received for individuals in these age groups.

Table 9*: Number of UK ADR reports associated with suspected myocarditis, pericarditis and other related terms received for the COVID-19 Vaccines by patient age up to and including 23 November 2022.

Age range (years)	Number of reports		
	COVID-19 Vaccine Pfizer/BioNTech	COVID-19 Vaccine Moderna (monovalent)	COVID-19 Vaccine AstraZeneca

	(monovalent)		
Under 18	83	0	0
18-29	396	127	31
30-39	323	98	49
40-49	150	53	123
50-59	110	24	108
60+	168	23	109
Unknown	161	38	52
Total	**1391**	**363**	**472**

* Due to the dynamic nature of the Yellow Card data these figures may change both as new cases are received, and as duplicate cases are identified and managed.

Table 10*: Number of UK ADR reports associated with suspected myocarditis, pericarditis and other related terms received for the COVID-19 Vaccines by patient sex up to and including 23 November 2022.

Sex	Number of reports		
	COVID-19 Vaccine Pfizer/BioNTech (monovalent)	**COVID-19 Vaccine Moderna (monovalent)**	**COVID-19 Vaccine AstraZeneca**
Female	546	119	212
Male	799	234	250
Unknown	46	10	10
Total	**1391**	**363**	**472**

* Due to the dynamic nature of the Yellow Card data these figures may change both as new cases are received, and as duplicate cases are identified and managed.

Two large European epidemiological studies have estimated the excess risk of myocarditis following vaccination with both monovalent COVID-19 Vaccine Pfizer/BioNTech and COVID-19 Vaccine Moderna. One study showed that in a period of 7 days after the second dose of the monovalent COVID-19 Vaccine Pfizer/BioNTech there were about 27 (95% CI 26 - 28) extra cases of myocarditis in 12-29 year old males per million compared to unvaccinated

individuals, and for the monovalent COVID-19 Vaccine Moderna there were about 132 (95% CI 130 – 133) extra cases of myocarditis in 12-29 year old males per million. In another study, in a period of 28 days after the second dose of the monovalent COVID-19 Vaccine Pfizer/BioNTech there were 57 [95% CI 39 – 75] extra cases of myocarditis in 16-24 year old males per million compared to unvaccinated persons, and for the monovalent COVID-19 Vaccine Moderna there were 188 (95% CI 96 – 280) extra cases of myocarditis in 16-24 year old males per million individuals compared to unvaccinated individuals. These studies have shown that these events are very rare post vaccination with the mRNA vaccines, and that these events are more frequent in younger males. The findings of these studies are consistent with the trends seen in the Yellow Card data.

International data has shown that these suspected events have been observed to occur most frequently approximately 3 days after the first vaccine and 2 days after the second vaccine, and both UK and international data have identified that the large majority of suspected events occur within 7 days of vaccination. In the UK the body of evidence shows that there is similar frequency of reporting after the first and second dose.

Longer term follow-up in both the UK and US to at least 90 days following identification of cases of suspected myocarditis after both monovalent COVID-19 Vaccine Pfizer/BioNTech and Moderna found that the majority of individuals were fully recovered and back to normal activities.

Myocarditis and pericarditis happen very rarely in the general population, and it is estimated that in the UK there are about 60 new cases of myocarditis diagnosed per million patients per year and about 100 new cases of pericarditis diagnosed per million patients per year. Myocarditis is also known to be associated with COVID-19 infection, with an estimated 1,500 cases of myocarditis per million patients with COVID-19 during March 2020 to January 2021 in the US.

The MHRA will continue to closely monitor reports of suspected myocarditis and pericarditis with all currently authorised COVID-19 vaccines.

Delayed hypersensitivity reactions

The MHRA has been reviewing reports of skin reactions occurring around the vaccination site that appear a little while after vaccination. These reactions are suggestive of a delayed hypersensitivity reaction that occurs 4-11 days after vaccination. The reactions are characterized by a rash, swelling and tenderness that can cover the whole upper arm and may be itchy and/or painful and warm to the touch. The majority of the reports received have been with the monovalent COVID-19 Vaccine Moderna and the product information for this vaccine has been updated to highlight the possibility of delayed injection site reactions. This

information has also been included in the product information for the bivalent (original/Omicron BA.1) COVID-19 Vaccine Moderna.

The reactions are usually self-limiting and resolve within a day or two, although in some patients it can take slightly longer to disappear. Individuals who experience this reaction after their first dose may experience a similar reaction in shorter timeframe following the second dose, however, none of the reports received have been serious and people should still take their second dose when invited. Those who experience delayed skin reactions after their COVID-19 vaccination which do not resolve within a few days should seek medical advice.

Guillain-Barré Syndrome

Guillain-Barré Syndrome is a very rare condition which causes inflammation of the nerves and can lead to numbness, weakness and pain, usually in the feet, hands and limbs and can spread to the chest and face. Guillain-Barré Syndrome tends to affect both sides of the body at once. This condition is known to be associated with certain infectious diseases.

Up to and including the 23 November 2022, the MHRA has received 514 reports of suspected Guillain-Barré Syndrome with the COVID-19 Vaccine AstraZeneca and 29 reports of a related disease called Miller Fisher syndrome. Up to the same date, the MHRA has received 116 reports of Guillain-Barré Syndrome and 7 reports of Miller Fisher syndrome following use of the monovalent and bivalent COVID-19 Vaccine Pfizer/BioNTech. For the monovalent and bivalent COVID-19 Vaccine Moderna there have been 31 reports of Guillain-Barré Syndrome.

The MHRA has been closely monitoring and assessing reports of suspected Guillain-Barré Syndrome (GBS) received following administration of the COVID-19 vaccine. Following the most recent review of the available data the evidence of a possible association has strengthened. Therefore, following advice from the government’s independent advisory body, the CHM and its COVID-19 Vaccines Benefit Risk Expert Working Group, the product information for the COVID-19 Vaccine AstraZeneca was further updated to include GBS in the tabulated list of adverse reactions associated with the COVID-19 Vaccine AstraZeneca and to encourage healthcare professionals and the public to look out for signs of GBS.

The MHRA will continue to review reports of Guillain-Barré Syndrome received following vaccination with COVID-19 vaccines to further assess a possible association, with independent advice from its Vaccine Benefit-Risk Working Group.

Swelling of the vaccinated limb

There have been rare reports of extensive swelling of the vaccinated limb after receiving the monovalent COVID-19 Vaccine Pfizer/BioNTech. The product information has been updated to include “extensive swelling of the vaccinated limb” as a side effect of the vaccine. This

information has also been added to the product information for the bivalent (original/Omicron BA.1) COVID-19 Vaccine Pfizer/BioNTech. This type of swelling is also recognised to occur with other (non-COVID-19) vaccines.

Facial swelling in those with a history of facial dermal fillers

Rare reports of facial swelling occurring 1-2 days after vaccination in vaccine recipients with a history of injection of facial dermal fillers were observed in the clinical trials for the monovalent COVID-19 Vaccine Moderna. Information about this possible side effect has been included in the product information for the monovalent COVID-19 Vaccine Moderna since it was first authorised for use. It has also been added to the product information for the bivalent (original/Omicron BA.1) COVID-19 Vaccine Moderna.

The MHRA has also received Yellow Card reports of facial swelling in those with a history of injection of facial dermal fillers for the monovalent COVID-19 Vaccine Pfizer/BioNTech. A review of the world-wide ADR data for the monovalent COVID-19 Vaccine Pfizer/BioNTech found that, in most instances, the facial swelling was mild, transient and was localised to the site of the dermal filler. The product information for the monovalent COVID-19 Vaccine Pfizer/BioNTech has been updated to include facial swelling in those with a history of injection of facial dermatological fillers as a side effect of the vaccine. It has also been added to the product information for the bivalent (original/Omicron BA.1) COVID-19 Vaccine Pfizer/BioNTech.

Reports with a fatal outcome

Vaccination and surveillance of large populations means that, by chance, some people will experience and report a new illness or events in the days and weeks after vaccination. A high proportion of people vaccinated early in the vaccination campaign were very elderly, and/or had pre-existing medical conditions. Older age and chronic underlying illnesses make it more likely that coincidental adverse events including those with a fatal outcome will occur, especially given the millions of people vaccinated.

Part of our continuous analysis includes an evaluation of natural death rates over time, to determine if any specific trends or patterns are occurring that might indicate a vaccine safety concern. Based on age-stratified all-cause mortality in England and Wales taken from the Office for National Statistics (ONS) death registrations, several thousand deaths are expected to have occurred naturally, mostly in the elderly, within 7 days of the many millions of doses of vaccines administered so far.

For reference, weekly death registrations within England, Wales, Scotland and Northern Ireland are available from relevant statistical authorities. The most recent data during the preparation of the summary of Yellow Card reporting is summarised as follows:

- England and Wales (ONS): In the week ending 11 November 2022, 11,538 deaths were registered; of these deaths, 518 cited COVID-19, accounting for 4.5% of all deaths.

- Scotland (The National Records of Scotland): In the week ending 20 November 2022, 1,271 deaths were registered; of these deaths, 40 cited COVID-19, accounting for 3.1% of all deaths.

- Northern Ireland (The Northern Ireland Statistics and Research Agency): In the week ending 18 November 2022, 386 deaths were registered; of these deaths, 8 cited COVID-19, accounting for 2.1% of all deaths.

The MHRA takes all reports with a fatal outcome in patients who have received a COVID-19 vaccine very seriously and every report with a fatal outcome is reviewed carefully. All reports with a fatal outcome regardless of the time period between receiving the suspect vaccine and the reported death are reviewed. All available information is assessed to consider whether the vaccine may have caused the reported death. Cumulatively, the Yellow Card data is thoroughly analysed for patterns or evidence which might suggest a causal link between the vaccination and the reported death alongside data available from international sources. This is further considered by the Commission on Human Medicines and its Expert Advisory Groups.

The MHRA has received 857 UK reports of suspected ADRs to both COVID-19 Pfizer/BioNTech Vaccines in which the patient died after vaccination, 1,334 reports for the COVID-19 Vaccine AstraZeneca, 111 reports for both COVID-19 Vaccines Moderna and 60 reports where the brand of vaccine was unspecified. The MHRA has received no fatal UK reports for COVID-19 Vaccine Novavax.

A report with a fatal outcome to the Yellow Card scheme does not necessarily mean that it was caused by the vaccine, only that the reporter has a suspicion it may have been. Underlying or previously undiagnosed illness unrelated to vaccination can also be factors in such reports. The relative number and nature of UK reports with a fatal outcome are subject to many factors that influence ADR reporting. They should therefore not be used to directly compare the safety of the different vaccines.

The number of UK reports with a fatal outcome following a specific COVID-19 vaccine should not be directly compared with each other. Table 11 and Table 12 provide a breakdown by age and sex for all UK reports with a fatal outcome following COVID-19 vaccination received by the MHRA. Where there are than 5 reports for a given category, report numbers have been replaced with a ^ in order to prevent patient/reporter identification in line with our duty of confidentiality to patients and reporters.

Table 11*/: Number of UK reports with a fatal outcome received for COVID-19 Vaccines by patient age up to and including 23 November 2022.**

Age group (years)	COVID-19 Vaccine AstraZeneca	COVID-19 Vaccine Pfizer/Bio NTech	COVID-19 Vaccine Moderna	Brand unspecified	All vaccines
Under 18	^	6	-	^	9
18-29	29	19	^	-	49
30-39	49	34	6	^	90
40-49	97	32	6	^	138
50-59	158	45	^	10	218
60-69	205	78	13	9	305
70-79	267	179	19	6	471
80+	332	328	36	17	713
Unknown	195	136	25	13	369
Total	**1,334**	**857**	**111**	**60**	**2,362**

*Due to the dynamic nature of the Yellow Card data these figures may change both as new cases are received, and as duplicate cases are identified and managed. All reports with a fatal outcome regardless of the time period between receiving the suspect vaccine and the reported death are included.
** '-' denotes no reports received. '^' Where there are less than 5 reports , numbers have been replaced with a ^ in order to prevent patient/reporter identification in line with our duty of confidentiality to patients and reporters.

Table 12*/: Number of UK reports with a fatal outcome received for COVID-19 Vaccines by patient sex up to and including 23 November 2022.**

Sex	COVID-19 Vaccine AstraZeneca	COVID-19 Vaccine Pfizer/BioNTech	COVID-19 Vaccine Moderna	Brand unspecified	All vaccines
Female	619	356	44	25	1,044
Male	653	444	60	32	1,189
Unknown	62	57	7	^	129
Total	**1,334**	**857**	**111**	**60**	**2,362**

*Due to the dynamic nature of the Yellow Card data these figures may change both as new

cases are received, and as duplicate cases are identified and managed. All reports with a fatal outcome regardless of the time period between receiving the suspect vaccine and the reported death are included.
** Where there are less than 5 reports , numbers have been replaced with a ^ in order to prevent patient/reporter identification in line with our duty of confidentiality to patients and reporters.

As demonstrated in Table 11, reports with a fatal outcome are concentrated in older age groups with decreasing numbers in younger age groups. This finding is consistent with data from the ONS outlining weekly provisional figures on death registrations in England and Wales by sex and age group. As an example, in the week ending 12 February 2021 15,354 deaths were registered in England and Wales. In that week, 8,488 deaths (55.3%) occurred in those aged 80 years and older.

The pattern of reports with a fatal outcome following COVID-19 vaccination showed a peak in reporting for both COVID-19 Vaccine AstraZeneca and monovalent COVID-19 Pfizer/BioNTech Vaccine at the start of the UK rollouts of these vaccines when the JCVI prioritised COVID-19 vaccination for the elderly and those most at risk of morbidity and mortality from COVID-19. A second peak of reporting was also identified for COVID-19 Vaccine AstraZeneca which coincided with the UK's second wave of COVID-19 and the identification of the very rare risk of thrombo-embolic (blood clotting) events with concurrent low platelets. As outlined in the above safety summary of this risk the MHRA undertook a thorough review of UK cases including reports with a fatal outcome and provided updated guidance for healthcare professionals on how to minimise risks, as well as further advice on symptoms for vaccine recipients.

Reviews of reports with a fatal outcome associated with specific adverse events are provided in the summaries above. A possible link between thrombo-embolic (blood clotting) events with concurrent low platelets including reports with a fatal outcome and COVID-19 Vaccine AstraZeneca was identified in March 2021. The pattern of reporting for all other reports with a fatal outcome does not suggest the vaccines played a role in these deaths. The MHRA will continue to review relevant data whilst working alongside other regulatory bodies to promote and protect public health.

As the number of vaccine doses administered has increased, so has the number of reports with fatal outcomes following vaccination. However, this does not mean that there is a link between vaccination and the fatalities reported. The UK Health Security Agency has previously analysed the direct and indirect impact of the vaccination programme on infections and mortality. It has been estimated that up to 26 September 2021, the UK vaccination programme prevented between 23.9 and 24.3 million infections and between 123,600 and 131,300 deaths.

A study published by the ONS and the Office of Health Improvement and Disparities (OHID) analysed data on COVID-19 vaccination and mortality in young people during the coronavirus pandemic. The study found no indication of an increased risk of death from cardiac-related or other causes in those aged 12-29 years, in the six weeks following COVID-19 vaccination. This is consistent with findings from our rigorous safety monitoring activities. The study also suggested that the excess in death registrations in young people in 2021 was due to delays in the registration process and early indications of increased

numbers of deaths due to non-vaccine related external causes. The study data were reviewed by the independent experts of the CHM's COVID-19 Vaccines Benefit Risk Expert Working Group who agreed with the conclusion of the report that COVID-19 vaccines were not associated with an increased risk of death in young people.

The MHRA will continue to carefully review and monitor all reports submitted to us including those that cite a fatal outcome following COVID-19 vaccination. When a safety issue is confirmed the MHRA will act promptly to inform patients and healthcare professionals and take appropriate steps to mitigate any identified risk.

Conclusion

Over the first 27 months of the pandemic over 178,397 people across the UK have died within 28 days of a positive test for coronavirus.

Vaccination is the single most effective way to reduce deaths and severe illness from COVID-19. A national immunisation campaign has been underway since early December 2020.

In clinical trials, the monovalent COVID-19 Vaccine Pfizer/BioNTech, the COVID-19 Vaccine AstraZeneca and the monovalent COVID-19 Vaccine Moderna have demonstrated very high levels of protection against symptomatic infection. Data are available on the impact of the vaccination campaign in reducing infections and illness in the UK.

All vaccines and medicines have some side effects. These side effects need to be continuously balanced against the expected benefits in preventing illness.

Following widespread use of these vaccines across the UK, the vast majority of suspected adverse reaction reports confirm the safety profile seen in clinical trials. Most reports relate to injection-site reactions (sore arm for example) and generalised symptoms such as a ‘flu-like’ illness, headache, chills, fatigue, nausea, fever, dizziness, weakness, aching muscles, and rapid heartbeat. Generally, these reactions are not associated with more serious illness and likely reflect an expected, normal immune response to the vaccines.

The benefits of the vaccines in preventing COVID-19 and serious complications associated with COVID-19 far outweigh any currently known side effects. As with all vaccines and medicines, the safety of COVID-19 vaccines is continuously monitored, and benefits and possible risks remain under review.

We take every report of a suspected ADR seriously and encourage everyone to report through the Yellow Card scheme.

Annex 1 Vaccine Analysis Print

The attached Vaccine Analysis Prints contain a complete listing of all suspected adverse reactions that have been reported to the MHRA via the Yellow Card scheme for the monovalent and bivalent COVID-19 Vaccine Pfizer/BioNTech, the COVID-19 Vaccine AstraZeneca, the monovalent and bivalent COVID-19 Vaccine Moderna, the COVID-19 Novavax Vaccine and where the brand of the vaccine was not specified. This includes all reports received from healthcare professionals, members of the public, and pharmaceutical companies.

This information does not represent an overview of the potential side effects associated with the vaccines. A list of the recognised adverse effects of COVID-19 vaccines is provided in the information for healthcare professionals and the recipient information here. These can also be found on the Coronavirus Yellow Card reporting site. Conclusions on the safety and risks of the vaccines cannot be made on the data shown in the Print alone.

When viewing the vaccine analysis print you should remember that:

> Reporters are asked to submit Yellow Card reports even if they only have a suspicion that the medicine or vaccine may have caused the adverse reaction. The existence of an adverse reaction report in the print does not necessarily mean that the vaccine has caused the suspected reaction.
>
> It may be difficult to tell the difference between something that has occurred naturally and a suspected adverse reaction. Sometimes these events can be part of the condition being treated rather than being caused by the vaccine.
>
> Many factors have to be considered when assessing whether the vaccine has caused a reported adverse reaction. When monitoring the safety of vaccines and medicines, MHRA staff carry out careful analysis of these factors.

For a medicine or vaccine to be considered safe, the expected benefits will be greater than the risk of having harmful reactions. It is important to note that most people take medicines and vaccines without having any serious side effects.

Vaccine Analysis Print – COVID-19 Vaccine Pfizer/BioNTech

Vaccine Analysis Print - COVID-19 Vaccine AstraZeneca

Vaccine Analysis Print – COVID-19 Vaccine Moderna

Vaccine Analysis Print – COVID-19 Vaccine Novavax

Vaccine Analysis Print - Brand unspecified

Annex 2 Glossary

Anaphylaxis or anaphylactoid reactions

Anaphylaxis is a severe and potentially life-threatening allergic reaction. These reactions can occur after an exposure to a trigger, such as a certain ingredient in foods or medicines or an insect sting. Anaphylaxis and anaphylactoid reactions can be treated with adrenaline.

Bell's palsy

Bell's palsy is a condition that causes temporary weakness or paralysis (lack of movement) of the muscles in one side of the face. It is the most common cause of facial paralysis. For most people, the facial paralysis is temporary. Viral infections such as those with herpes viruses have been linked to Bell's palsy.

Bivalent vaccine

A vaccine which stimulates an immune response to two viral strains.

Booster dose/vaccination

A COVID-19 booster vaccine dose helps improve the protection obtained from the first two doses of the vaccine. It helps give longer-term protection against getting seriously ill from COVID-19.

Capillary Leak Syndrome (CLS)

Capillary Leak Syndrome (CLS) occurs when fluid leaks from the small blood vessels into the body.

Cerebral venous sinus thrombosis (CVST)

Cerebral venous sinus thrombosis occurs when the brain's venous sinuses or the smaller veins draining into them are partially or completely blocked by a blood clot. This prevents blood from draining out of the brain. As a result, the oxygen supply to nerve cells may be impaired and blood cells can leak into the brain tissue causing damage to the brain (haemorrhagic infarction).

Clinical Practice Research Datalink (CPRD)

Clinical Practice Research Datalink (CPRD) is a real-world research service to support public health and clinical studies. CPRD is jointly sponsored by the Medicines and Healthcare products Regulatory Agency and the National Institute for Health Research (NIHR), as part

of the Department of Health and Social Care. CPRD collects anonymised patient data from a network of GP practices across the UK.

Commission on Human Medicines (CHM)

The Commission on Human Medicines (CHM) advises ministers on the safety, efficacy and quality of medicinal products. For COVID-19 vaccines, the CHM has a COVID-19 Vaccines Safety Surveillance Methodologies Expert Working Group and a COVID-19 Vaccines Benefit Risk Expert Working Group.

Endocarditis

Endocarditis is inflammation of the inner lining of the heart (endocardium).

Epidemiology studies

Epidemiological studies include large numbers of people and are designed to compare the risk of a particular event in an exposed population, in this case those who have received a vaccine, to those who have not. They attempt to account for differences in the different groups to help us understand if any difference in risk is caused by the exposure. Epidemiological studies measure the risk of illness or death in an exposed population compared to that risk in an identical, unexposed population.

Guillain-Barré Syndrome

Guillain-Barré Syndrome is inflammation of the nerves and can lead to numbness, weakness and pain, usually in the feet, hands and limbs and can spread to the chest and face. This syndrome has been associated with viral infections such as the flu.

Immune thrombocytopenia Immune thrombocytopenia (ITP)

ITP is an auto-immune condition characterised by low blood platelet count (thrombocytopenia) and is associated with an increased risk in bleeding which often presents as bruising or petechia/purpura.

Miller-Fisher Syndrome

Miller-Fisher syndrome is a variation of Guillain-Barré Syndrome that affects the nervous system and can cause weakness in the face and a lack of balance and co-ordination. Similar to Guillain-Barré Syndrome, this syndrome has been associated with viral infections such as the flu.

Miscarriage

The loss of a pregnancy during the first 23 weeks.

Monovalent vaccine

A vaccine which stimulates an immune response to one viral strain.

Myocarditis

Myocarditis is the inflammation of the heart muscle (myocardium).

Non-clinical studies

Non-clinical studies refer to studies that are not performed on the human body. These are largely done before clinical trials in humans and can include animal safety and efficacy studies, human tissue sample studies or toxicology.

Pericarditis

Pericarditis is inflammation of the pericardium, the protective sac that surrounds your heart.

Regulation 174 authorisation

Temporary authorisation for supply of a medicine or vaccine by the UK Department of Health and Social Care and the Medicines and Healthcare products Regulatory Agency. This temporary authorisation grants permission for a medicine (vaccine) to be used for active immunisation to prevent COVID-19 disease caused by SARS-CoV-2 virus. Authorisation is subject to a number of conditions. These are available for each vaccine on the MHRA website.

Suspected adverse reactions

Also known as side effects. All medicines or vaccines can cause adverse reactions in some people. Adverse drug reactions reported to the MHRA are looked at and used to assess the balance of risks and benefits of medicines and vaccines.

Stillbirth

A stillbirth is when a baby is born dead after 24 completed weeks of pregnancy. If the baby dies before 24 completed weeks, it's known as a miscarriage.

Temporal Association

Events occurring following vaccination but may or may not be caused by the vaccine.

Third dose/vaccination

A COVID-19 third vaccine is being offered to those who had a weakened immune system when they had the first two doses of the COVID-19 vaccination. The third dose may help to improve immune response and give better protection.

Thrombocytopenia

Thrombocytopenia is where the blood contains a lower than normal number of platelets. Platelets are the smallest of the blood cells and are involved in the clotting process.

Transverse Myelitis

Transverse myelitis is a rare acute neurological disorder causing inflammation of the spinal cord, the part of the central nervous system that sends impulses from the brain to nerves in the body.

Yellow Card scheme

The MHRA's scheme for healthcare professionals and members of the public to report suspected adverse reactions for a medicine or vaccine, as well as medical devices and other products. The dedicated Coronavirus Yellow Card reporting site was launched in May 2020 specifically for medicines and medical devices used in COVID-19, as well as COVID-19 vaccines when authorised.

ORIGINAL ARTICLE

Safety and Efficacy of the BNT162b2 mRNA Covid-19 Vaccine

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ABSTRACT

BACKGROUND

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection and the resulting coronavirus disease 2019 (Covid-19) have afflicted tens of millions of people in a worldwide pandemic. Safe and effective vaccines are needed urgently.

METHODS

In an ongoing multinational, placebo-controlled, observer-blinded, pivotal efficacy trial, we randomly assigned persons 16 years of age or older in a 1:1 ratio to receive two doses, 21 days apart, of either placebo or the BNT162b2 vaccine candidate (30 μg per dose). BNT162b2 is a lipid nanoparticle–formulated, nucleoside-modified RNA vaccine that encodes a prefusion stabilized, membrane-anchored SARS-CoV-2 full-length spike protein. The primary end points were efficacy of the vaccine against laboratory-confirmed Covid-19 and safety.

RESULTS

A total of 43,548 participants underwent randomization, of whom 43,448 received injections: 21,720 with BNT162b2 and 21,728 with placebo. There were 8 cases of Covid-19 with onset at least 7 days after the second dose among participants assigned to receive BNT162b2 and 162 cases among those assigned to placebo; BNT162b2 was 95% effective in preventing Covid-19 (95% credible interval, 90.3 to 97.6). Similar vaccine efficacy (generally 90 to 100%) was observed across subgroups defined by age, sex, race, ethnicity, baseline body-mass index, and the presence of coexisting conditions. Among 10 cases of severe Covid-19 with onset after the first dose, 9 occurred in placebo recipients and 1 in a BNT162b2 recipient. The safety profile of BNT162b2 was characterized by short-term, mild-to-moderate pain at the injection site, fatigue, and headache. The incidence of serious adverse events was low and was similar in the vaccine and placebo groups.

CONCLUSIONS

A two-dose regimen of BNT162b2 conferred 95% protection against Covid-19 in persons 16 years of age or older. Safety over a median of 2 months was similar to that of other viral vaccines. (Funded by BioNTech and Pfizer; ClinicalTrials.gov number, NCT04368728.)

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*A complete list of investigators in the C4591001 Clinical Trial Group is provided in the Supplementary Appendix, available at NEJM.org.

Drs. Polack and Thomas contributed equally to this article.

This article was published on December 10, 2020, and updated on December 16, 2020, at NEJM.org.

DOI: 10.1056/NEJMoa2034577

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A Quick Take is available at NEJM.org

Coronavirus disease 2019 (Covid-19) has affected tens of millions of people globally[1] since it was declared a pandemic by the World Health Organization on March 11, 2020.[2] Older adults, persons with certain coexisting conditions, and front-line workers are at highest risk for Covid-19 and its complications. Recent data show increasing rates of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection and Covid-19 in other populations, including younger adults.[3] Safe and effective prophylactic vaccines are urgently needed to contain the pandemic, which has had devastating medical, economic, and social consequences.

We previously reported phase 1 safety and immunogenicity results from clinical trials of the vaccine candidate BNT162b2,[4] a lipid nanoparticle–formulated,[5] nucleoside-modified RNA (modRNA)[6] encoding the SARS-CoV-2 full-length spike, modified by two proline mutations to lock it in the prefusion conformation.[7] Findings from studies conducted in the United States and Germany among healthy men and women showed that two 30-μg doses of BNT162b2 elicited high SARS-CoV-2 neutralizing antibody titers and robust antigen-specific CD8+ and Th1-type CD4+ T-cell responses.[8] The 50% neutralizing geometric mean titers elicited by 30 μg of BNT162b2 in older and younger adults exceeded the geometric mean titer measured in a human convalescent serum panel, despite a lower neutralizing response in older adults than in younger adults. In addition, the reactogenicity profile of BNT162b2 represented mainly short-term local (i.e., injection site) and systemic responses. These findings supported progression of the BNT162b2 vaccine candidate into phase 3.

Here, we report safety and efficacy findings from the phase 2/3 part of a global phase 1/2/3 trial evaluating the safety, immunogenicity, and efficacy of 30 μg of BNT162b2 in preventing Covid-19 in persons 16 years of age or older. This data set and these trial results are the basis for an application for emergency use authorization.[9] Collection of phase 2/3 data on vaccine immunogenicity and the durability of the immune response to immunization is ongoing, and those data are not reported here.

Methods

Trial Objectives, Participants and Oversight

We assessed the safety and efficacy of two 30-μg doses of BNT162b2, administered intramuscularly 21 days apart, as compared with placebo. Adults 16 years of age or older who were healthy or had stable chronic medical conditions, including but not limited to human immunodeficiency virus (HIV), hepatitis B virus, or hepatitis C virus infection, were eligible for participation in the trial. Key exclusion criteria included a medical history of Covid-19, treatment with immunosuppressive therapy, or diagnosis with an immunocompromising condition.

Pfizer was responsible for the design and conduct of the trial, data collection, data analysis, data interpretation, and the writing of the manuscript. BioNTech was the sponsor of the trial, manufactured the BNT162b2 clinical trial material, and contributed to the interpretation of the data and the writing of the manuscript. All the trial data were available to all the authors, who vouch for its accuracy and completeness and for adherence of the trial to the protocol, which is available with the full text of this article at NEJM.org. An independent data and safety monitoring board reviewed efficacy and unblinded safety data.

Trial Procedures

With the use of an interactive Web-based system, participants in the trial were randomly assigned in a 1:1 ratio to receive 30 μg of BNT162b2 (0.3 ml volume per dose) or saline placebo. Participants received two injections, 21 days apart, of either BNT162b2 or placebo, delivered in the deltoid muscle. Site staff who were responsible for safety evaluation and were unaware of group assignments observed participants for 30 minutes after vaccination for any acute reactions.

Safety

The primary end points of this trial were solicited, specific local or systemic adverse events and use of antipyretic or pain medication within 7 days after the receipt of each dose of vaccine or placebo, as prompted by and recorded in an electronic diary in a subset of participants (the reactogenicity subset), and unsolicited adverse events (those reported by the participants without prompts from the electronic diary) through 1 month after the second dose and unsolicited serious adverse events through 6 months after the second dose. Adverse event data through approximately 14 weeks after the second dose are included in this report. In this report, safety

data are reported for all participants who provided informed consent and received at least one dose of vaccine or placebo. Per protocol, safety results for participants infected with HIV (196 patients) will be analyzed separately and are not included here.

During the phase 2/3 portion of the study, a stopping rule for the theoretical concern of vaccine-enhanced disease was to be triggered if the one-sided probability of observing the same or a more unfavorable adverse severe case split (a split with a greater proportion of severe cases in vaccine recipients) was 5% or less, given the same true incidence for vaccine and placebo recipients. Alert criteria were to be triggered if this probability was less than 11%.

EFFICACY

The first primary end point was the efficacy of BNT162b2 against confirmed Covid-19 with onset at least 7 days after the second dose in participants who had been without serologic or virologic evidence of SARS-CoV-2 infection up to 7 days after the second dose; the second primary end point was efficacy in participants with and participants without evidence of prior infection. Confirmed Covid-19 was defined according to the Food and Drug Administration (FDA) criteria as the presence of at least one of the following symptoms: fever, new or increased cough, new or increased shortness of breath, chills, new or increased muscle pain, new loss of taste or smell, sore throat, diarrhea, or vomiting, combined with a respiratory specimen obtained during the symptomatic period or within 4 days before or after it that was positive for SARS-CoV-2 by nucleic acid amplification–based testing, either at the central laboratory or at a local testing facility (using a protocol-defined acceptable test).

Major secondary end points included the efficacy of BNT162b2 against severe Covid-19. Severe Covid-19 is defined by the FDA as confirmed Covid-19 with one of the following additional features: clinical signs at rest that are indicative of severe systemic illness; respiratory failure; evidence of shock; significant acute renal, hepatic, or neurologic dysfunction; admission to an intensive care unit; or death. Details are provided in the protocol.

An explanation of the various denominator values for use in assessing the results of the trial is provided in Table S1 in the Supplementary Appendix, available at NEJM.org. In brief, the safety population includes persons 16 years of age or older; a total of 43,448 participants constituted the population of enrolled persons injected with the vaccine or placebo. The main safety subset as defined by the FDA, with a median of 2 months of follow-up as of October 9, 2020, consisted of 37,706 persons, and the reactogenicity subset consisted of 8183 persons. The modified intention-to-treat (mITT) efficacy population includes all age groups 12 years of age or older (43,355 persons; 100 participants who were 12 to 15 years of age contributed to person-time years but included no cases). The number of persons who could be evaluated for efficacy 7 days after the second dose and who had no evidence of prior infection was 36,523, and the number of persons who could be evaluated 7 days after the second dose with or without evidence of prior infection was 40,137.

STATISTICAL ANALYSIS

The safety analyses included all participants who received at least one dose of BNT162b2 or placebo. The findings are descriptive in nature and not based on formal statistical hypothesis testing. Safety analyses are presented as counts, percentages, and associated Clopper–Pearson 95% confidence intervals for local reactions, systemic events, and any adverse events after vaccination, according to terms in the *Medical Dictionary for Regulatory Activities* (MedDRA), version 23.1, for each vaccine group.

Analysis of the first primary efficacy end point included participants who received the vaccine or placebo as randomly assigned, had no evidence of infection within 7 days after the second dose, and had no major protocol deviations (the population that could be evaluated). Vaccine efficacy was estimated by $100 \times (1 - \mathrm{IRR})$, where IRR is the calculated ratio of confirmed cases of Covid-19 illness per 1000 person-years of follow-up in the active vaccine group to the corresponding illness rate in the placebo group. The 95.0% credible interval for vaccine efficacy and the probability of vaccine efficacy greater than 30% were calculated with the use of a Bayesian beta-binomial model. The final analysis uses a success boundary of 98.6% for probability of vaccine efficacy greater than 30% to compensate for the interim analysis and to control the overall type 1 error rate at 2.5%.

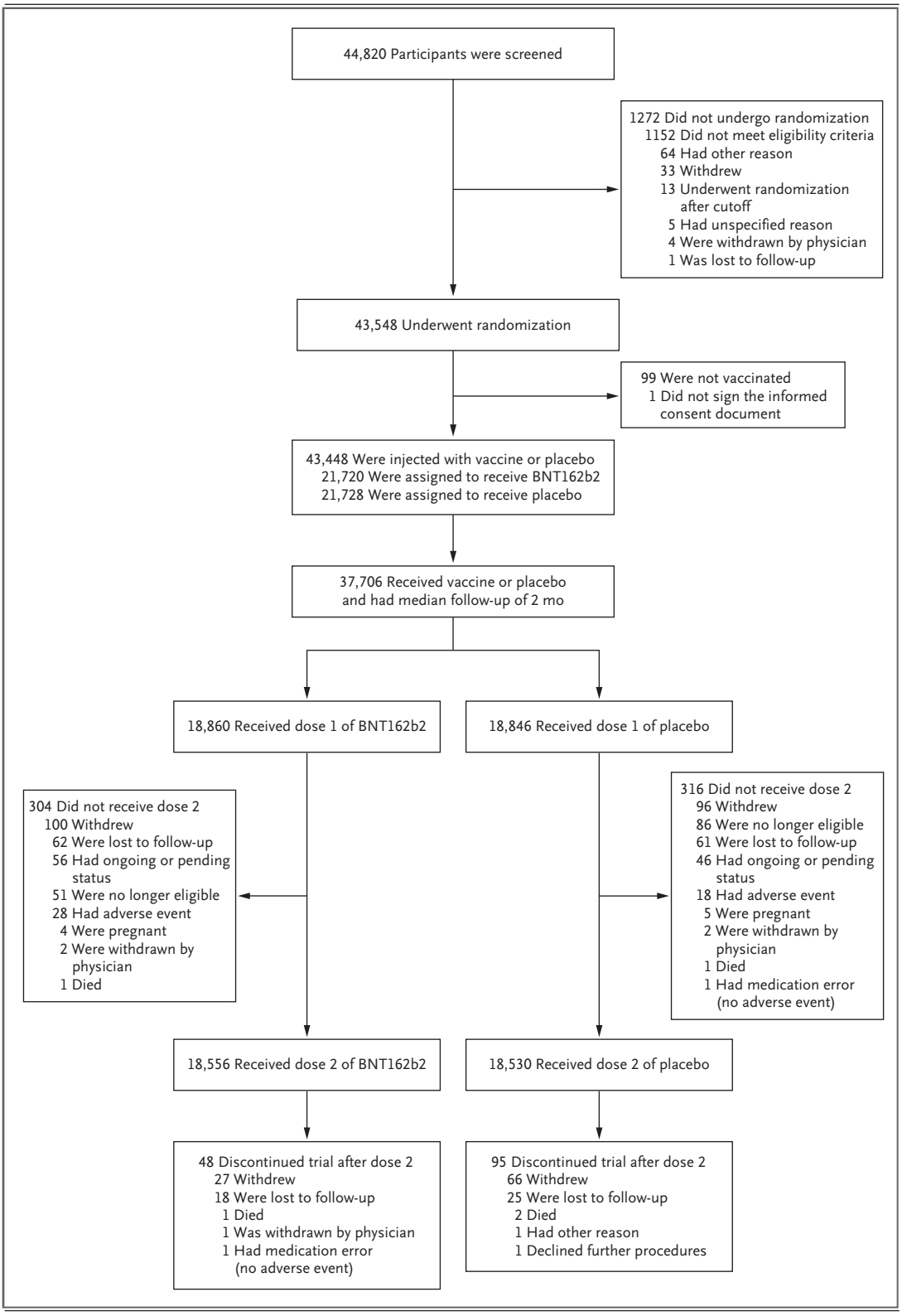

44,820 Participants were screened
1272 Did not undergo randomization
1152 Did not meet eligibility criteria
64 Had other reason
33 Withdrew
13 Underwent randomization after cutoff
5 Had unspecified reason
4 Were withdrawn by physician
1 Was lost to follow-up
43,548 Underwent randomization
99 Were not vaccinated
1 Did not sign the informed consent document
43,448 Were injected with vaccine or placebo
21,720 Were assigned to receive BNT162b2
21,728 Were assigned to receive placebo
37,706 Received vaccine or placebo and had median follow-up of 2 mo
18,860 Received dose 1 of BNT162b2
18,846 Received dose 1 of placebo
304 Did not receive dose 2
100 Withdrew
62 Were lost to follow-up
56 Had ongoing or pending status
51 Were no longer eligible
28 Had adverse event
4 Were pregnant
2 Were withdrawn by physician
1 Died
316 Did not receive dose 2
96 Withdrew
86 Were no longer eligible
61 Were lost to follow-up
46 Had ongoing or pending status
18 Had adverse event
5 Were pregnant
2 Were withdrawn by physician
1 Died
1 Had medication error (no adverse event)
18,556 Received dose 2 of BNT162b2
18,530 Received dose 2 of placebo
48 Discontinued trial after dose 2
27 Withdrew
18 Were lost to follow-up
1 Died
1 Was withdrawn by physician
1 Had medication error (no adverse event)
95 Discontinued trial after dose 2
66 Withdrew
25 Were lost to follow-up
2 Died
1 Had other reason
1 Declined further procedures

Figure 1 (facing page). Enrollment and Randomization.
The diagram represents all enrolled participants through November 14, 2020. The safety subset (those with a median of 2 months of follow-up, in accordance with application requirements for Emergency Use Authorization) is based on an October 9, 2020, data cutoff date. The further procedures that one participant in the placebo group declined after dose 2 (lower right corner of the diagram) were those involving collection of blood and nasal swab samples.

Moreover, primary and secondary efficacy end points are evaluated sequentially to control the familywise type 1 error rate at 2.5%. Descriptive analyses (estimates of vaccine efficacy and 95% confidence intervals) are provided for key subgroups.

RESULTS

PARTICIPANTS

Between July 27, 2020, and November 14, 2020, a total of 44,820 persons were screened, and 43,548 persons 16 years of age or older underwent randomization at 152 sites worldwide (United States, 130 sites; Argentina, 1; Brazil, 2; South Africa, 4; Germany, 6; and Turkey, 9) in the phase 2/3 portion of the trial. A total of

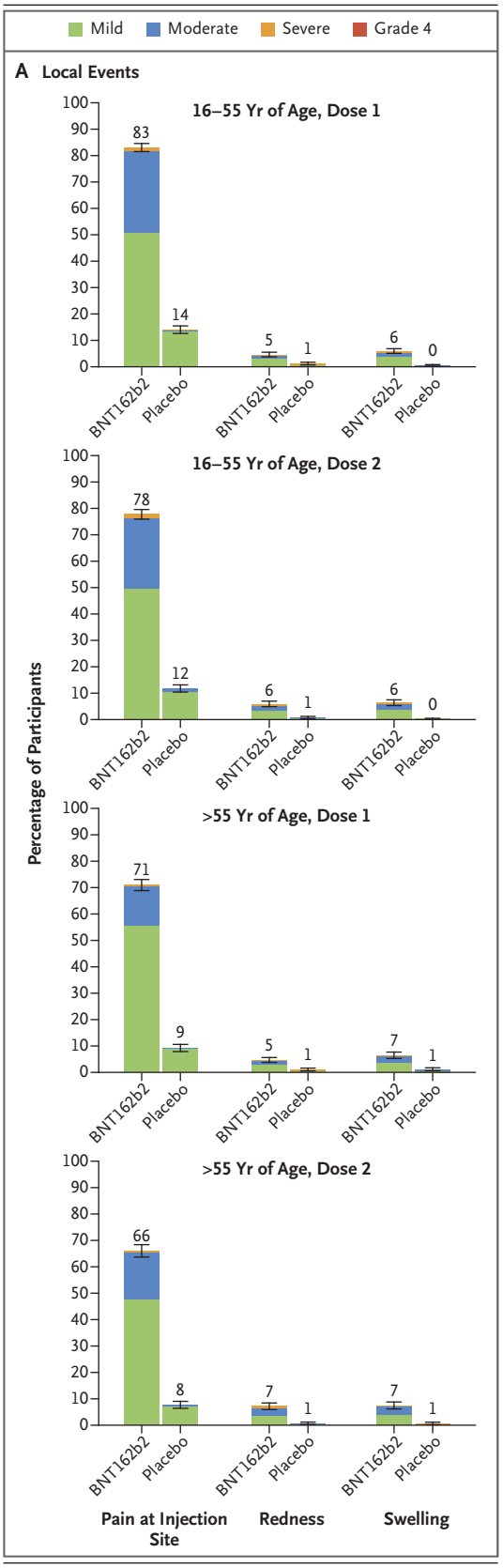
Table 1. Demographic Characteristics of the Participants in the Main Safety Population.*

Characteristic	BNT162b2 (N=18,860)	Placebo (N=18,846)	Total (N=37,706)
Sex — no. (%)			
Male	9,639 (51.1)	9,436 (50.1)	19,075 (50.6)
Female	9,221 (48.9)	9,410 (49.9)	18,631 (49.4)
Race or ethnic group — no. (%)†			
White	15,636 (82.9)	15,630 (82.9)	31,266 (82.9)
Black or African American	1,729 (9.2)	1,763 (9.4)	3,492 (9.3)
Asian	801 (4.2)	807 (4.3)	1,608 (4.3)
Native American or Alaska Native	102 (0.5)	99 (0.5)	201 (0.5)
Native Hawaiian or other Pacific Islander	50 (0.3)	26 (0.1)	76 (0.2)
Multiracial	449 (2.4)	406 (2.2)	855 (2.3)
Not reported	93 (0.5)	115 (0.6)	208 (0.6)
Hispanic or Latinx	5,266 (27.9)	5,277 (28.0)	10,543 (28.0)
Country — no. (%)			
Argentina	2,883 (15.3)	2,881 (15.3)	5,764 (15.3)
Brazil	1,145 (6.1)	1,139 (6.0)	2,284 (6.1)
South Africa	372 (2.0)	372 (2.0)	744 (2.0)
United States	14,460 (76.7)	14,454 (76.7)	28,914 (76.7)
Age group — no. (%)			
16–55 yr	10,889 (57.7)	10,896 (57.8)	21,785 (57.8)
>55 yr	7,971 (42.3)	7,950 (42.2)	15,921 (42.2)
Age at vaccination — yr			
Median	52.0	52.0	52.0
Range	16–89	16–91	16–91
Body-mass index‡			
≥30.0: obese	6,556 (34.8)	6,662 (35.3)	13,218 (35.1)

* Percentages may not total 100 because of rounding.
† Race or ethnic group was reported by the participants.
‡ The body-mass index is the weight in kilograms divided by the square of the height in meters.

Figure 2. Local and Systemic Reactions Reported within 7 Days after Injection of BNT162b2 or Placebo, According to Age Group.

Data on local and systemic reactions and use of medication were collected with electronic diaries from participants in the reactogenicity subset (8,183 participants) for 7 days after each vaccination. Solicited injection-site (local) reactions are shown in Panel A. Pain at the injection site was assessed according to the following scale: mild, does not interfere with activity; moderate, interferes with activity; severe, prevents daily activity; and grade 4, emergency department visit or hospitalization. Redness and swelling were measured according to the following scale: mild, 2.0 to 5.0 cm in diameter; moderate, >5.0 to 10.0 cm in diameter; severe, >10.0 cm in diameter; and grade 4, necrosis or exfoliative dermatitis (for redness) and necrosis (for swelling). Systemic events and medication use are shown in Panel B. Fever categories are designated in the key; medication use was not graded. Additional scales were as follows: fatigue, headache, chills, new or worsened muscle pain, new or worsened joint pain (mild: does not interfere with activity; moderate: some interference with activity; or severe: prevents daily activity), vomiting (mild: 1 to 2 times in 24 hours; moderate: >2 times in 24 hours; or severe: requires intravenous hydration), and diarrhea (mild: 2 to 3 loose stools in 24 hours; moderate: 4 to 5 loose stools in 24 hours; or severe: 6 or more loose stools in 24 hours); grade 4 for all events indicated an emergency department visit or hospitalization. I bars represent 95% confidence intervals, and numbers above the I bars are the percentage of participants who reported the specified reaction.

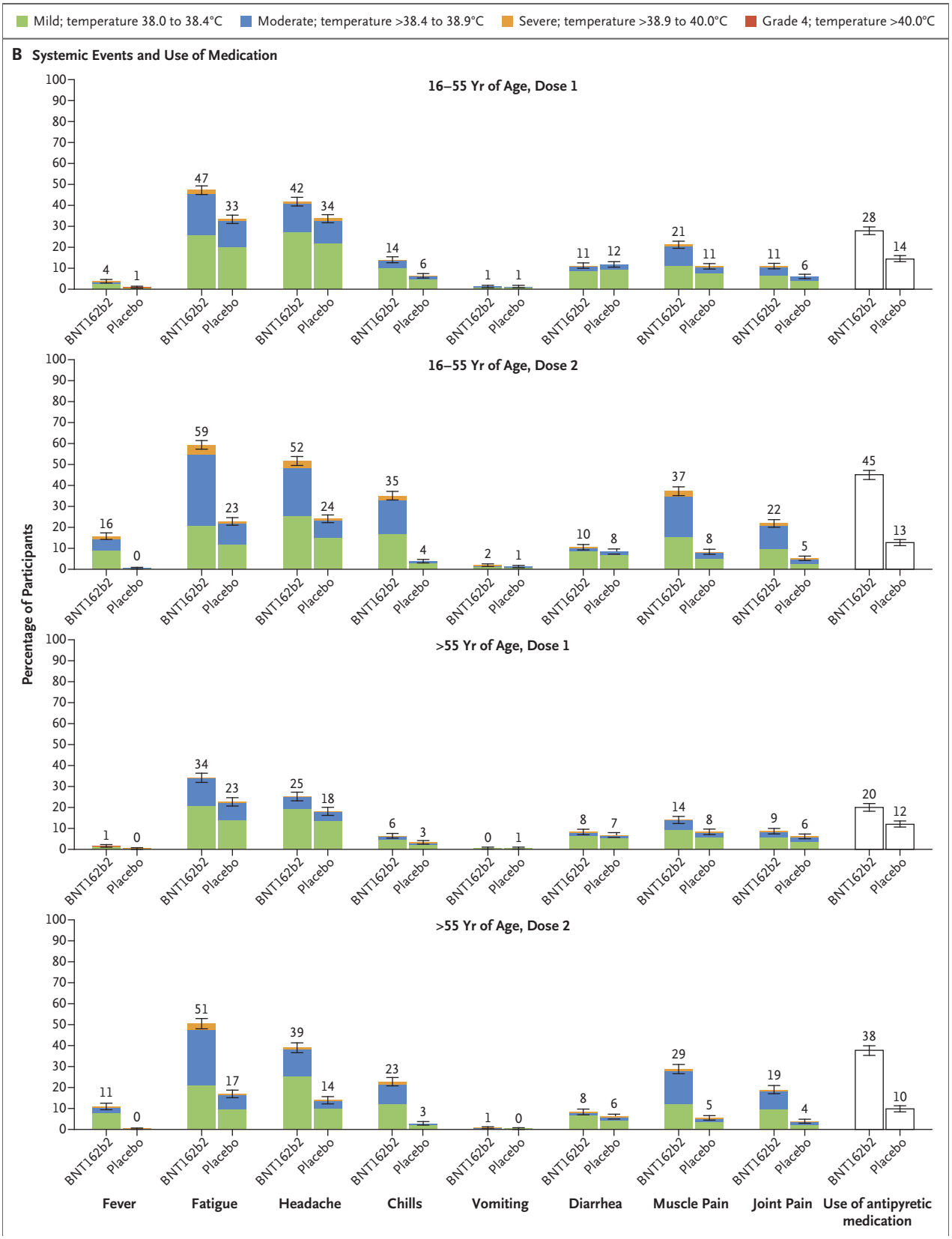


43,448 participants received injections: 21,720 received BNT162b2 and 21,728 received placebo (Fig. 1). At the data cut-off date of October 9, a total of 37,706 participants had a median of at least 2 months of safety data available after the second dose and contributed to the main safety data set. Among these 37,706 participants, 49% were female, 83% were White, 9% were Black or African American, 28% were Hispanic or Latinx, 35% were obese (body mass index [the weight in kilograms divided by the square of the height in meters] of at least 30.0), and 21% had at least one coexisting condition. The median age was 52 years, and 42% of participants were older than 55 years of age (Table 1 and Table S2).

SAFETY

Local Reactogenicity

The reactogenicity subset included 8183 participants. Overall, BNT162b2 recipients reported more local reactions than placebo recipients. Among BNT162b2 recipients, mild-to-moderate pain at


Mild; temperature 38.0 to 38.4°C
Moderate; temperature >38.4 to 38.9°C
Severe; temperature >38.9 to 40.0°C
Grade 4; temperature >40.0°C
B Systemic Events and Use of Medication
16–55 Yr of Age, Dose 1
16–55 Yr of Age, Dose 2
>55 Yr of Age, Dose 1
>55 Yr of Age, Dose 2
Percentage of Participants
BNT162b2
Placebo
Fever
Fatigue
Headache
Chills
Vomiting
Diarrhea
Muscle Pain
Joint Pain
Use of antipyretic medication

the injection site within 7 days after an injection was the most commonly reported local reaction, with less than 1% of participants across all age groups reporting severe pain (Fig. 2). Pain was reported less frequently among participants older than 55 years of age (71% reported pain after the first dose; 66% after the second dose) than among younger participants (83% after the first dose; 78% after the second dose). A noticeably lower percentage of participants reported injection-site redness or swelling. The proportion of participants reporting local reactions did not increase after the second dose (Fig. 2A), and no participant reported a grade 4 local reaction. In general, local reactions were mostly mild-to-moderate in severity and resolved within 1 to 2 days.

Systemic Reactogenicity

Systemic events were reported more often by younger vaccine recipients (16 to 55 years of age) than by older vaccine recipients (more than 55 years of age) in the reactogenicity subset and more often after dose 2 than dose 1 (Fig. 2B). The most commonly reported systemic events were fatigue and headache (59% and 52%, respectively, after the second dose, among younger vaccine recipients; 51% and 39% among older recipients), although fatigue and headache were also reported by many placebo recipients (23% and 24%, respectively, after the second dose, among younger vaccine recipients; 17% and 14% among older recipients). The frequency of any severe systemic event after the first dose was 0.9% or less. Severe systemic events were reported in less than 2% of vaccine recipients after either dose, except for fatigue (in 3.8%) and headache (in 2.0%) after the second dose.

Fever (temperature, ≥38°C) was reported after the second dose by 16% of younger vaccine recipients and by 11% of older recipients. Only 0.2% of vaccine recipients and 0.1% of placebo recipients reported fever (temperature, 38.9 to 40°C) after the first dose, as compared with 0.8% and 0.1%, respectively, after the second dose. Two participants each in the vaccine and placebo groups reported temperatures above 40.0°C. Younger vaccine recipients were more likely to use antipyretic or pain medication (28% after dose 1; 45% after dose 2) than older vaccine recipients (20% after dose 1; 38% after dose 2), and placebo recipients were less likely (10 to 14%) than vaccine recipients to use the medications, regardless of age or dose. Systemic events including fever and chills were observed within the first 1 to 2 days after vaccination and resolved shortly thereafter.

Daily use of the electronic diary ranged from 90 to 93% for each day after the first dose and from 75 to 83% for each day after the second dose. No difference was noted between the BNT162b2 group and the placebo group.

ADVERSE EVENTS

Adverse event analyses are provided for all enrolled 43,252 participants, with variable follow-up time after dose 1 (Table S3). More BNT162b2 recipients than placebo recipients reported any adverse event (27% and 12%, respectively) or a related adverse event (21% and 5%). This distribution largely reflects the inclusion of transient reactogenicity events, which were reported as adverse events more commonly by vaccine recipients than by placebo recipients. Sixty-four vaccine recipients (0.3%) and 6 placebo recipients (<0.1%) reported lymphadenopathy. Few participants in either group had severe adverse events, serious adverse events, or adverse events leading to withdrawal from the trial. Four related serious adverse events were reported among BNT162b2 recipients (shoulder injury related to vaccine administration, right axillary lymphadenopathy, paroxysmal ventricular arrhythmia, and right leg paresthesia). Two BNT162b2 recipients died (one from arteriosclerosis, one from cardiac arrest), as did four placebo recipients (two from unknown causes, one from hemorrhagic stroke, and one from myocardial infarction). No deaths were considered by the investigators to be related to the vaccine or placebo. No Covid-19–associated deaths were observed. No stopping rules were met during the reporting period. Safety monitoring will continue for 2 years after administration of the second dose of vaccine.

EFFICACY

Among 36,523 participants who had no evidence of existing or prior SARS-CoV-2 infection, 8 cases of Covid-19 with onset at least 7 days after the second dose were observed among vaccine recipients and 162 among placebo recipients. This case split corresponds to 95.0% vaccine efficacy (95% confidence interval [CI], 90.3 to 97.6; Ta-

Table 2. Vaccine Efficacy against Covid-19 at Least 7 days after the Second Dose.*

Efficacy End Point	BNT162b2		Placebo		Vaccine Efficacy, % (95% Credible Interval)‡	Posterior Probability (Vaccine Efficacy >30%)§
	No. of Cases	Surveillance Time (n)†	No. of Cases	Surveillance Time (n)†		
		(N=18,198)		(N=18,325)		
Covid-19 occurrence at least 7 days after the second dose in participants without evidence of infection	8	2.214 (17,411)	162	2.222 (17,511)	95.0 (90.3–97.6)	>0.9999
		(N=19,965)		(N=20,172)		
Covid-19 occurrence at least 7 days after the second dose in participants with and those without evidence of infection	9	2.332 (18,559)	169	2.345 (18,708)	94.6 (89.9–97.3)	>0.9999

* The total population without baseline infection was 36,523; total population including those with and those without prior evidence of infection was 40,137.
† The surveillance time is the total time in 1000 person-years for the given end point across all participants within each group at risk for the end point. The time period for Covid-19 case accrual is from 7 days after the second dose to the end of the surveillance period.
‡ The credible interval for vaccine efficacy was calculated with the use of a beta-binomial model with prior beta (0.700102, 1) adjusted for the surveillance time.
§ Posterior probability was calculated with the use of a beta-binomial model with prior beta (0.700102, 1) adjusted for the surveillance time.

ble 2). Among participants with and those without evidence of prior SARS CoV-2 infection, 9 cases of Covid-19 at least 7 days after the second dose were observed among vaccine recipients and 169 among placebo recipients, corresponding to 94.6% vaccine efficacy (95% CI, 89.9 to 97.3). Supplemental analyses indicated that vaccine efficacy among subgroups defined by age, sex, race, ethnicity, obesity, and presence of a coexisting condition was generally consistent with that observed in the overall population (Table 3 and Table S4). Vaccine efficacy among participants with hypertension was analyzed separately but was consistent with the other subgroup analyses (vaccine efficacy, 94.6%; 95% CI, 68.7 to 99.9; case split: BNT162b2, 2 cases; placebo, 44 cases). Figure 3 shows cases of Covid-19 or severe Covid-19 with onset at any time after the first dose (mITT population) (additional data on severe Covid-19 are available in Table S5). Between the first dose and the second dose, 39 cases in the BNT162b2 group and 82 cases in the placebo group were observed, resulting in a vaccine efficacy of 52% (95% CI, 29.5 to 68.4) during this interval and indicating early protection by the vaccine, starting as soon as 12 days after the first dose.

DISCUSSION

A two-dose regimen of BNT162b2 (30 μg per dose, given 21 days apart) was found to be safe and 95% effective against Covid-19. The vaccine met both primary efficacy end points, with more than a 99.99% probability of a true vaccine efficacy greater than 30%. These results met our prespecified success criteria, which were to establish a probability above 98.6% of true vaccine efficacy being greater than 30%, and greatly exceeded the minimum FDA criteria for authorization.[9] Although the study was not powered to definitively assess efficacy by subgroup, the point estimates of efficacy for subgroups based on age, sex, race, ethnicity, body-mass index, or the presence of an underlying condition associated with a high risk of Covid-19 complications are also high. For all analyzed subgroups in which more than 10 cases of Covid-19 occurred, the lower limit of the 95% confidence interval for efficacy was more than 30%.

The cumulative incidence of Covid-19 cases over time among placebo and vaccine recipients begins to diverge by 12 days after the first dose, 7 days after the estimated median viral incuba-

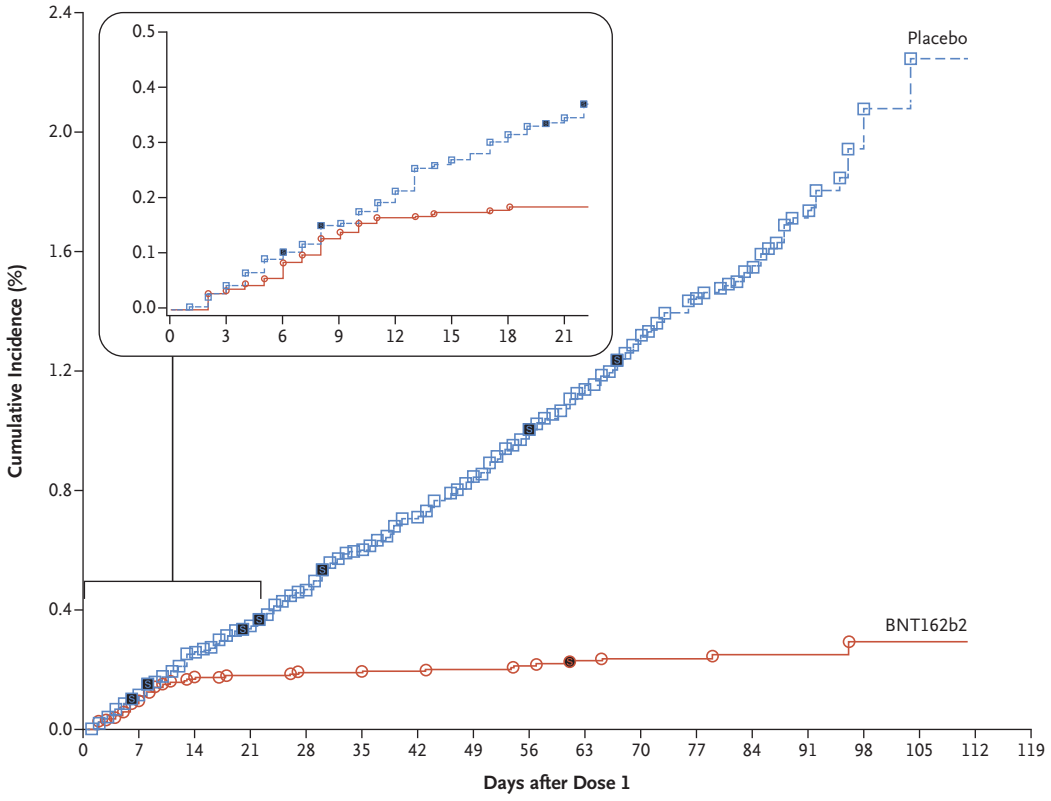
Table 3. Vaccine Efficacy Overall and by Subgroup in Participants without Evidence of Infection before 7 Days after Dose 2.

Efficacy End-Point Subgroup	BNT162b2 (N=18,198)		Placebo (N=18,325)		Vaccine Efficacy, % (95% CI)†
	No. of Cases	Surveillance Time (No. at Risk)*	No. of Cases	Surveillance Time (No. at Risk)*	
Overall	8	2.214 (17,411)	162	2.222 (17,511)	95.0 (90.0–97.9)
Age group					
16 to 55 yr	5	1.234 (9,897)	114	1.239 (9,955)	95.6 (89.4–98.6)
>55 yr	3	0.980 (7,500)	48	0.983 (7,543)	93.7 (80.6–98.8)
≥65 yr	1	0.508 (3,848)	19	0.511 (3,880)	94.7 (66.7–99.9)
≥75 yr	0	0.102 (774)	5	0.106 (785)	100.0 (–13.1–100.0)
Sex					
Male	3	1.124 (8,875)	81	1.108 (8762)	96.4 (88.9–99.3)
Female	5	1.090 (8,536)	81	1.114 (8,749)	93.7 (84.7–98.0)
Race or ethnic group‡					
White	7	1.889 (14,504)	146	1.903 (14,670)	95.2 (89.8–98.1)
Black or African American	0	0.165 (1,502)	7	0.164 (1,486)	100.0 (31.2–100.0)
All others	1	0.160 (1,405)	9	0.155 (1,355)	89.3 (22.6–99.8)
Hispanic or Latinx	3	0.605 (4,764)	53	0.600 (4,746)	94.4 (82.7–98.9)
Non-Hispanic, non-Latinx	5	1.596 (12,548)	109	1.608 (12,661)	95.4 (88.9–98.5)
Country					
Argentina	1	0.351 (2,545)	35	0.346 (2,521)	97.2 (83.3–99.9)
Brazil	1	0.119 (1,129)	8	0.117 (1,121)	87.7 (8.1–99.7)
United States	6	1.732 (13,359)	119	1.747 (13,506)	94.9 (88.6–98.2)

* Surveillance time is the total time in 1000 person-years for the given end point across all participants within each group at risk for the end point. The time period for Covid-19 case accrual is from 7 days after the second dose to the end of the surveillance period.
† The confidence interval (CI) for vaccine efficacy is derived according to the Clopper–Pearson method, adjusted for surveillance time.
‡ Race or ethnic group was reported by the participants. "All others" included the following categories: American Indian or Alaska Native, Asian, Native Hawaiian or other Pacific Islander, multiracial, and not reported.

tion period of 5 days,[10] indicating the early onset of a partially protective effect of immunization. The study was not designed to assess the efficacy of a single-dose regimen. Nevertheless, in the interval between the first and second doses, the observed vaccine efficacy against Covid-19 was 52%, and in the first 7 days after dose 2, it was 91%, reaching full efficacy against disease with onset at least 7 days after dose 2. Of the 10 cases of severe Covid-19 that were observed after the first dose, only 1 occurred in the vaccine group. This finding is consistent with overall high efficacy against all Covid-19 cases. The severe case split provides preliminary evidence of vaccine-mediated protection against severe disease, alleviating many of the theoretical concerns over vaccine-mediated disease enhancement.[11]

The favorable safety profile observed during phase 1 testing of BNT162b2[4,8] was confirmed in the phase 2/3 portion of the trial. As in phase 1, reactogenicity was generally mild or moderate, and reactions were less common and milder in older adults than in younger adults. Systemic reactogenicity was more common and severe after the second dose than after the first dose, although local reactogenicity was similar after the two doses. Severe fatigue was observed in approximately 4% of BNT162b2 recipients, which is higher than that observed in recipients of some vaccines recommended for older adults.[12] This rate of severe fatigue is also lower than that observed in recipients of another approved viral vaccine for older adults.[13] Overall, reactogenicity events were transient and resolved within a couple



Efficacy End-Point Subgroup	BNT162b2, 30 μg (N=21,669)		Placebo (N=21,686)		VE (95% CI)
	No. of participants	Surveillance time *person-yr (no. at risk)*	No. of participants	Surveillance time *person-yr (no. at risk)*	*percent*
Covid-19 occurrence					
After dose 1	50	4.015 (21,314)	275	3.982 (21,258)	82.0 (75.6–86.9)
After dose 1 to before dose 2	39		82		52.4 (29.5–68.4)
Dose 2 to 7 days after dose 2	2		21		90.5 (61.0–98.9)
≥7 Days after dose 2	9		172		94.8 (89.8–97.6)

Figure 3. Efficacy of BNT162b2 against Covid-19 after the First Dose.

Shown is the cumulative incidence of Covid-19 after the first dose (modified intention-to-treat population). Each symbol represents Covid-19 cases starting on a given day; filled symbols represent severe Covid-19 cases. Some symbols represent more than one case, owing to overlapping dates. The inset shows the same data on an enlarged y axis, through 21 days. Surveillance time is the total time in 1000 person-years for the given end point across all participants within each group at risk for the end point. The time period for Covid-19 case accrual is from the first dose to the end of the surveillance period. The confidence interval (CI) for vaccine efficacy (VE) is derived according to the Clopper–Pearson method.

of days after onset. Lymphadenopathy, which generally resolved within 10 days, is likely to have resulted from a robust vaccine-elicited immune response. The incidence of serious adverse events was similar in the vaccine and placebo groups (0.6% and 0.5%, respectively).

This trial and its preliminary report have several limitations. With approximately 19,000 participants per group in the subset of participants with a median follow-up time of 2 months after the second dose, the study has more than 83% probability of detecting at least one adverse event, if the true incidence is 0.01%, but it is not large enough to detect less common adverse events reliably. This report includes 2 months of follow-up after the second dose of vaccine for half the trial participants and up to 14 weeks' maximum follow-up for a smaller subset. Therefore, both

the occurrence of adverse events more than 2 to 3.5 months after the second dose and more comprehensive information on the duration of protection remain to be determined. Although the study was designed to follow participants for safety and efficacy for 2 years after the second dose, given the high vaccine efficacy, ethical and practical barriers prevent following placebo recipients for 2 years without offering active immunization, once the vaccine is approved by regulators and recommended by public health authorities. Assessment of long-term safety and efficacy for this vaccine will occur, but it cannot be in the context of maintaining a placebo group for the planned follow-up period of 2 years after the second dose. These data do not address whether vaccination prevents asymptomatic infection; a serologic end point that can detect a history of infection regardless of whether symptoms were present (SARS-CoV-2 N-binding antibody) will be reported later. Furthermore, given the high vaccine efficacy and the low number of vaccine breakthrough cases, potential establishment of a correlate of protection has not been feasible at the time of this report.

This report does not address the prevention of Covid-19 in other populations, such as younger adolescents, children, and pregnant women. Safety and immune response data from this trial after immunization of adolescents 12 to 15 years of age will be reported subsequently, and additional studies are planned to evaluate BNT162b2 in pregnant women, children younger than 12 years, and those in special risk groups, such as immunocompromised persons. Although the vaccine can be stored for up to 5 days at standard refrigerator temperatures once ready for use, very cold temperatures are required for shipping and longer storage. The current cold storage requirement may be alleviated by ongoing stability studies and formulation optimization, which may also be described in subsequent reports.

The data presented in this report have significance beyond the performance of this vaccine candidate. The results demonstrate that Covid-19 can be prevented by immunization, provide proof of concept that RNA-based vaccines are a promising new approach for protecting humans against infectious diseases, and demonstrate the speed with which an RNA-based vaccine can be developed with a sufficient investment of resources. The development of BNT162b2 was initiated on January 10, 2020, when the SARS-CoV-2 genetic sequence was released by the Chinese Center for Disease Control and Prevention and disseminated globally by the GISAID (Global Initiative on Sharing All Influenza Data) initiative. This rigorous demonstration of safety and efficacy less than 11 months later provides a practical demonstration that RNA-based vaccines, which require only viral genetic sequence information to initiate development, are a major new tool to combat pandemics and other infectious disease outbreaks. The continuous phase 1/2/3 trial design may provide a model to reduce the protracted development timelines that have delayed the availability of vaccines against other infectious diseases of medical importance. In the context of the current, still expanding pandemic, the BNT162b2 vaccine, if approved, can contribute, together with other public health measures, to reducing the devastating loss of health, life, and economic and social well-being that has resulted from the global spread of Covid-19.

Supported by BioNTech and Pfizer.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

A data sharing statement provided by the authors is available with the full text of this article at NEJM.org.

We thank all the participants who volunteered for this study; and the members of the C4591001 data and safety monitoring board for their dedication and their diligent review of the data. We also acknowledge the contributions of the C4591001 Clinical Trial Group (see the Supplementary Appendix); Tricia Newell and Emily Stackpole (ICON, North Wales, PA) for editorial support funded by Pfizer; and the following Pfizer staff: Greg Adams, Negar Aliabadi, Mohanish Anand, Fred Angulo, Ayman Ayoub, Melissa Bishop-Murphy, Mark Boaz, Christopher Bowen, Salim Bouguermouh, Donna Boyce, Sarah Burden, Andrea Cawein, Patrick Caubel, Darren Cowen, Kimberly Ann Cristall, Michael Cruz, Daniel Curcio, Gabriela Dávila, Carmel Devlin, Gokhan Duman, Niesha Foster, Maja Gacic, Luis Jodar, Stephen Kay, William Lam, Esther Ladipo, Joaquina Maria Lazaro, Marie-Pierre Hellio Le Graverand-Gastineau, Jacqueline Lowenberg, Rod MacKenzie, Robert Maroko, Jason McKinley, Tracey Mellelieu, Farheen Muzaffar, Brendan O'Neill, Jason Painter, Elizabeth Paulukonis, Allison Pfeffer, Katie Puig, Kimberly Rarrick, Balaji Prabu Raja, Christine Rainey, Kellie Lynn Richardson, Elizabeth Rogers, Melinda Rottas, Charulata Sabharwal, Vilas Satishchandran, Harpreet Seehra, Judy Sewards, Helen Smith, David Swerdlow, Elisa Harkins Tull, Sarah Tweedy, Erica Weaver, John Wegner, Jenah West, Christopher Webber, David C. Whritenour, Fae Wooding, Emily Worobetz, Xia Xu, Nita Zalavadia, Liping Zhang, the Vaccines Clinical Assay Team, the Vaccines Assay Development Team, and all the Pfizer colleagues not named here who contributed to the success of this trial. We also acknowledge the contributions of the following staff at BioNTech: Corinna Rosenbaum, Christian Miculka, Andreas Kuhn, Ferdia Bates, Paul Strecker, Ruben Rizzi, Martin Bexon, Eleni Lagkadinou, and Alexandra Kemmer-Brück; and the following staff at Polymun: Dietmar Katinger and Andreas Wagner.

APPENDIX

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Arterial events, venous thromboembolism, thrombocytopenia, and bleeding after vaccination with Oxford-AstraZeneca ChAdOx1-S in Denmark and Norway: population based cohort study

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Additional material is published online only. To view please visit the journal online.

Cite this as: *BMJ* 2021;373:n1114
http://dx.doi.org/10.1136/bmj.n1114

Accepted: 28 April 2021

ABSTRACT

OBJECTIVE

To assess rates of cardiovascular and haemostatic events in the first 28 days after vaccination with the Oxford-AstraZeneca vaccine ChAdOx1-S in Denmark and Norway and to compare them with rates observed in the general populations.

DESIGN

Population based cohort study.

SETTING

Nationwide healthcare registers in Denmark and Norway.

PARTICIPANTS

All people aged 18-65 years who received a first vaccination with ChAdOx1-S from 9 February 2021 to 11 March 2021. The general populations of Denmark (2016-18) and Norway (2018-19) served as comparator cohorts.

MAIN OUTCOME MEASURES

Observed 28 day rates of hospital contacts for incident arterial events, venous thromboembolism, thrombocytopenia/coagulation disorders, and bleeding among vaccinated people compared with expected rates, based on national age and sex specific background rates from the general populations of the two countries.

RESULTS

The vaccinated cohorts comprised 148 792 people in Denmark (median age 45 years, 80% women) and 132 472 in Norway (median age 44 years, 78% women), who received their first dose of ChAdOx1-S. Among 281 264 people who received ChAdOx1-S, the standardised morbidity ratio for arterial events was 0.97 (95% confidence interval 0.77 to 1.20). 59 venous thromboembolic events were observed in the vaccinated cohort compared with 30 expected based on the incidence rates in the general population, corresponding to a standardised morbidity ratio of 1.97 (1.50 to 2.54) and 11 (5.6 to 17.0) excess events per 100 000 vaccinations. A higher than expected rate of cerebral venous thrombosis was observed: standardised morbidity ratio 20.25 (8.14 to 41.73); an excess of 2.5 (0.9 to 5.2) events per 100 000 vaccinations. The standardised morbidity ratio for any thrombocytopenia/coagulation disorders was 1.52 (0.97 to 2.25) and for any bleeding was 1.23 (0.97 to 1.55). 15 deaths were observed in the vaccine cohort compared with 44 expected.

CONCLUSIONS

Among recipients of ChAdOx1-S, increased rates of venous thromboembolic events, including cerebral venous thrombosis, were observed. For the remaining safety outcomes, results were largely reassuring, with slightly higher rates of thrombocytopenia/coagulation disorders and bleeding, which could be influenced by increased surveillance of vaccine recipients. The absolute risks of venous thromboembolic events were, however, small, and the findings should be interpreted in the light of the proven beneficial effects of the vaccine, the context of the given country, and the limitations to the generalisability of the study findings.

WHAT IS ALREADY KNOWN ON THIS TOPIC

Spontaneous adverse event reports and clinical case series have described thrombocytopenia, bleeding, and arterial and venous thromboses occurring within days to weeks after vaccination with the Oxford-AstraZeneca covid-19 vaccine (ChAdOx1-S)

Whether these cases represent excess events above expected rates is unknown

WHAT THIS STUDY ADDS

Increased rates for venous thromboembolism were observed within 28 days of vaccination with ChAdOx1-S in Denmark and Norway, corresponding to 11 excess events per 100 000 vaccinations, including 2.5 excess cerebral venous thrombosis events per 100 000 vaccinations

Results were largely reassuring for arterial events, whereas slightly increased rates of thrombocytopenia or coagulation disorders and bleeding in the vaccinated group could be influenced by heightened surveillance

Absolute risks of events were small and should be interpreted in the context of the benefits of covid-19 vaccination at both the societal and the individual level

Introduction

As of early April 2021, the covid-19 pandemic has affected more than 130 million people worldwide and 2.8 million have died.[1] Vaccines represent the most powerful tool for controlling the pandemic.[2] Currently, four vaccines are approved for use against covid-19 in the European Union and these are manufactured by Pfizer-BioNTech (Comirnaty),[3] Moderna,[4] Oxford-AstraZeneca (Vaxzevria),[5 6] and, most recently, Janssen.[7] In large randomised controlled trials, these

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vaccines have shown 66% to 95% efficacy against symptomatic covid-19.[3-6]

During early to mid-March 2021, vaccination against covid-19 with the Oxford-AstraZeneca vaccine ChAdOx1-S was paused in several European countries because of spontaneous reports of severe and sometimes fatal thromboembolic events among vaccinated people.[8] According to a statement from the European Medicines Agency, 30 cases of predominantly venous thromboembolic events had been reported by 10 March 2021 among the approximately five million recipients of ChAdOx1-S in Europe at the time.[8]

The EMA subsequently stated that "The number of thromboembolic events in vaccinated people is no higher than the number seen in the general population."[9] Adverse events might, however, be substantially underestimated if based only on spontaneous adverse event reporting. Moreover, since early March 2021, an increasing number of case reports from Austria, Norway, Denmark, Germany, the United Kingdom, and other countries has suggested a potentially distinct thrombotic syndrome associated with ChAdOx1-S.[10-13] These reports have described severe thrombocytopenia, bleeding, arterial thrombosis, and venous thrombosis in unusual anatomical locations (cerebral venous sinus thrombosis, or thrombosis in the portal, splanchnic, or hepatic veins) but also lower limb venous thrombosis or pulmonary embolism in some patients, occurring within five to 24 days after vaccination.[14] Whether these cases represent an excess over the expected rate is yet to be established. The risk of such adverse effects also remains unknown, as rare events are not identified in even large clinical trials and adverse effects are often underreported during post-marketing surveillance. Given the ongoing covid-19 pandemic and the current shortage of vaccines, it is crucially important to assess risks with covid-19 vaccines in real world settings.

The objective of the current collaboration between scientific centres in Denmark and Norway was to assess nationwide rates of cardiovascular and haemostatic events after vaccination with ChAdOx1-S and to compare these rates with corresponding age and sex standardised rates in the general populations of the two countries.

Methods

Data sources

We obtained data from Danish healthcare registries through an accelerated process involving registry agencies and national health and data protection authorities. The emergency preparedness register for covid-19 (Beredt C19) in Norway supplied Norwegian data.[15] Beredt C19 includes information already collected by healthcare services, national health registries, and medical quality registers. Government funded healthcare systems in Scandinavian countries provide all legal residents with free access to healthcare.[16 17] The national health registries of these countries contain prospectively collected health information on all residents, with civil personal registration numbers, permitting individual level data linkage among national registries.[18]

The study was conducted according to the ethical and legal requirements of each country.[19] Owing to data privacy regulations, no cell counts below five could be reported.

Study cohorts

The vaccine cohorts consisted of all people aged 18-65 years in Denmark and Norway who received a first vaccination with ChAdOx1-S from 9 February 2021 to 11 March 2021 (the date the Danish and Norwegian vaccination programmes were halted owing to safety concerns). We excluded vaccine recipients younger than 18 years and older than 65 years and those who immigrated to the countries within 365 days before their first vaccination (ascertained from the civil registration systems in the two countries). The general populations aged 18-65 years in Denmark during 2016-18 and in Norway during 2018-19 served as prespecified comparator cohorts.

Vaccination against covid-19

The Danish vaccination register[20] and the corresponding Norwegian immunisation registry SYSVAK[21] provided the dates on which all members of the study cohorts received their first dose of ChAdOx1-S. The vaccine was authorised conditionally across the EU on 29 January 2021[22] and launched in Denmark, Norway, and other European countries shortly after. In Denmark, Norway, and many other European countries, ChAdOx1-S has been administered almost entirely to those younger than 65 years. In accordance with the Danish and Norwegian covid-19 vaccination strategies, the majority of ChAdOx1-S recipients were healthcare and social service workers.

Cardiovascular and haemostatic events

To obtain data on all inpatient stays and hospital outpatient clinic contacts (including emergency room visits), we accessed the national patient registers in Denmark and Norway (covering all hospitals). These registers contain doctor recorded diagnoses for each hospital contact according to ICD-10 (international classification of diseases, 10th revision).[16 17 23 24] We assessed rates of hospital contacts for a range of prespecified cardiovascular and haemostatic diagnoses, grouped as arterial events, venous thromboembolism, thrombocytopenia/coagulation disorders, and bleeding events (see supplementary file for ICD-10 codes).

In analyses of individual outcomes, we excluded people from the vaccinated cohorts who had a history of that specific outcome during the 365 days before their first vaccination. For the general population cohorts, we similarly excluded people with a history of a given outcome during a one year fixed washout period from calculations of rates of specific outcomes. Individual outcomes were considered independently—for example, those with a recent history of stroke were not excluded from estimates of the age and sex specific rate of pulmonary embolism.

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Statistical analyses

The observed number of incident events in the vaccinated cohorts was obtained by following the cohorts starting on the date of first vaccination for up to 28 days or until the date of death, emigration, the event of interest, or end of data availability (31 March 2021), whichever occurred first.

The expected number of events in the vaccinated cohorts was estimated based on the incidence rates of the given outcomes in the prespecified general population cohorts. These incidence rates were estimated from data for the general population aged 18-65 during 2016-18 in Denmark and during 2018-19 in Norway, with rates calculated stratified by sex and age in five year bands (18-24, 25-29, 30-34, 35-39, 40-44, 45-49, 50-54, 55-59, and 60-65, ascertained at the midpoints of the reference periods). The general population cohorts were followed for incident hospital contacts for the individual outcomes from 1 January 2016 to 31 December 2018 (Denmark) or 1 January 2018 to 31 December 2019 (Norway), emigration, death, or occurrence of the outcome in question, whichever came first. From these general population incidence rates, we estimated the expected number of events in the vaccinated cohort for each of the individual outcomes using indirect standardisation. Specifically, we multiplied the age, sex, and country specific general population incidence rate with the age, sex, and country specific follow-up time accumulated in the vaccinated cohorts for up to 28 days after vaccination. For each age, sex, and country specific stratum of the vaccine recipients, this yielded a count for the number of expected events, which we then summed across stratums. In this way, we obtained the expected number of outcomes that we would observe in the vaccinated cohort members if they had the same rate of outcomes as the general population, when taking into account age, sex, and country.

For each of the prespecified individual outcomes and for groups of outcomes, we calculated the Danish and Norwegian general population incidence rates, the observed and expected number of events, and the differences per 100 000 vaccine recipients followed for 28 days: excess events (standardised morbidity differences) per 100 000 vaccinations and standardised morbidity ratios. We obtained exact 95% confidence intervals for both from the Poisson distribution.[25]

Supplementary analyses

We conducted a range of prespecified supplementary analyses. Firstly, to investigate subgroup effects, we stratified the analyses by sex as well as by young versus middle aged adults (age categories 18-44 years and 45-65 years). Secondly, to focus specifically on early outcomes that could be more likely due to vaccination, we conducted an analysis with follow-up restricted to 14 days. Thirdly, to investigate the potential effect of heightened diagnostic awareness and thus inclusion of less serious events associated with brief hospital contacts among vaccine recipients, as well as the risk of incorrect coding or rule-out diagnoses from such brief contacts being counted as actual outcomes, we restricted the assessment of events to hospital contacts with a duration five hours or more. Finally, to assess whether use of a historical general population comparator cohort influenced the results, we used a general population cohort followed from 1 January 2020 to 15 March 2021 in both countries.

Public and patient involvement

No patients were involved in the design, execution, or interpretation of this study. Owing to both the urgency and the sensitivity of the study question, as well data privacy constraints, it was not possible to involve members of the public in the study.

Results

Among 282 572 people vaccinated against covid-19 with ChAdOx1-S in Denmark and Norway from February 2021 to 11 March 2021, 1308 (0.5%) were excluded owing to age (<18 years or >65 years) or recent immigration. The final vaccinated cohorts included 281 264 people: 148 792 in Denmark (median age 45 (interquartile range 33-55) years; 80.1% women), and 132 472 in Norway (44 (32-55); 77.6% women, table 1). Full 28 day follow-up was available for 206 894 people (73.6%) in the final cohorts. Among the remaining 74 370 people (26.4%) with fewer than 28 days of available follow-up, median available follow-up was 24 (interquartile range 23-26) days in Denmark and 23 (22-24) days in Norway.

Main analysis

Arterial events—83 arterial events were observed versus 86 expected, corresponding to a standardised morbidity ratio of 0.97 (95% confidence interval 0.77 to 1.20, fig 1). Within the arterial events group, the rate of intracerebral haemorrhage was increased, with a standardised morbidity ratio of 2.33 (1.01 to 4.59), corresponding to 1.7 (95% confidence interval 0.0 to 4.6) excess events per 100 000 vaccinations.

Venous thromboembolism—59 venous thromboembolic events were observed versus 30 expected, corresponding to a standardised morbidity ratio of 1.97 (1.50 to 2.54) and to 11 (5.6 to 17.0) excess events per 100 000 vaccinations (fig 1). An increase was also found for several subgroups, including pulmonary embolism (standardised morbidity ratio 1.79 (1.11 to 2.74); 3.4 (0.5 to 7.5) excess events per 100 000 vaccinations), lower limb venous thrombosis (1.47 (0.92 to 2.23); 2.6 (−0.4 to 6.8) excess events per 100 000 vaccinations), and other venous thrombosis (1.99 (1.03 to 3.48); 2.2 (0.1 to 5.5) excess events per 100 000 vaccinations). The standardised morbidity ratio for cerebral venous thrombosis was 20.25 (8.14 to 41.73) corresponding to 7 observed events versus 0.3 expected and an excess of 2.5 (0.9 to 5.2) events per 100 000 vaccinations.

Any thrombocytopenia/coagulation disorder—the standardised morbidity ratio for any thrombocytopenia/coagulation disorder was 1.52 (0.97 to 2.25), corresponding to 3.0 (−0.2 to 7.4)

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Table 1 | Baseline characteristics of 281 264 study participants aged 18-65 years who received the Oxford-AstraZeneca vaccine against covid-19 (ChAdOx1-S) in Denmark and Norway

Characteristics	Denmark (n=148 792)	Norway (n=132 472)
Women	119 119 (80.1)	102 848 (77.6)
Median (interquartile range) age (years):	45 (33-55)	44 (32-55)
18-24	13 731 (9.2)	13 092 (9.9)
25-29	13 784 (9.3)	12 704 (9.6)
30-34	12 774 (8.6)	13 002 (9.8)
35-39	13 968 (9.4)	13 199 (10.0)
40-44	17 134 (11.5)	14 365 (10.8)
45-49	19 827 (13.3)	15 582 (11.8)
50-54	19 629 (13.2)	15 916 (12.0)
55-59	21 027 (14.1)	17 630 (13.3)
60-65	16 918 (11.4)	16 982 (12.8)
Month vaccinated:		
February 2021	84 359 (56.7)	53 678 (40.5)
March 2021	64 433 (43.3)	78 794 (59.5)

excess events per 100 000 vaccinations (fig 2). This was driven by unspecified thrombocytopenia with a standardised morbidity ratio of 3.57 (1.78 to 6.38), corresponding to 2.9 (0.9 to 6.1) excess events per 100 000 vaccinations.

Any bleeding—the standardised morbidity ratio for any bleeding was 1.23 (0.97 to 1.55), corresponding to 5.1 (−0.7 to 12.2) excess events per 100 000 vaccinations (fig 2). This included a standardised morbidity ratio of 2.21 (1.54 to 3.08) for bleeding from the respiratory tract (eg, epistaxis and haemoptysis), corresponding to 7.1 (3.2 to 12.2) excess events per 100 000 vaccinations; and 3.30 (1.42 to 6.50) for unspecified bleeding, corresponding to 2.1 (0.4 to 4.9) excess events per 100 000 vaccinations.

Deaths—15 deaths were observed in the vaccinated cohort compared with 44 expected deaths based on the general population mortality rates, corresponding to a standardised morbidity ratio of 0.34 (0.19 to 0.57).

Supplementary analyses

Figure 3 presents the results from the prespecified supplementary analyses. Standardised morbidity ratio estimates were generally similar among those aged 18-44 years compared with those aged 45-65 years, with the exception of venous thromboembolism: 2.99 (1.94 to 4.42) among those aged 18-44 years versus 1.58 (1.09 to 2.20) among those aged 45-65 years, corresponding to a slightly higher absolute excess rate of events in the younger group (13 excess events per 100 000 vaccinations among those aged 18-44 years *v* 9 excess events per 100 000 vaccinations among those aged 45-65 years). When the analysis was restricted to women, no excess rate of thrombocytopenia/coagulation disorders was observed, whereas other estimates were largely unaltered. When restricting to men, no excess rate of venous thromboembolism was observed: standardised morbidity ratio 0.67 (0.22 to 1.56); the results were, however, imprecise. When the analysis was restricted to 14 day follow-up, the standardised morbidity ratio for thrombocytopenia/coagulation disorders increased to 1.93 (1.11 to 3.14), whereas no excess rate of bleeding was observed. When hospital contacts of less than five hours were excluded from the analysis, results for venous thromboembolism remained unchanged, whereas no excess bleeding events were observed, and the excess events of thrombocytopenia/coagulation disorders was diminished (to 1.3 (−0.8 to 4.6) excess events per 100 000 vaccinations). Using the more recent general population comparison cohort (2020-21), nearly identical general population rates were found for all outcomes, and as such effect estimates remained virtually unchanged (for full results see supplementary tables 1 and 2).

Post hoc analyses

Firstly, to investigate whether signals for venous thromboembolism or cerebral venous thrombosis could be explained by unmeasured confounding from use of systemic hormone therapy, the proportion of women were quantified in the Danish vaccinated cohort who redeemed a prescription for systemic hormone therapy (oral contraceptives or estradiol) during the year before cohort entry as well as in the general population comparator cohort. This showed that women who received ChAdOx1-S were on average using systemic hormone therapy slightly less often than the background population (see supplementary table 3). Secondly, E-values were calculated for the outcomes of venous thromboembolism and cerebral venous thrombosis—these represent the minimum magnitude of association that an unmeasured confounder needs to have with both the exposure and the outcome to move the estimate so that the lower boundary of the 95% confidence interval includes unity.[26] This yielded E-values of 2.37 for venous thromboembolism and 15.8 for cerebral venous thrombosis. Thirdly, to provide more clarity on the estimation of the expected counts and to investigate whether incidence rates in the background population were stable over time, yearly incidence rates were calculated for 2016-18 in Denmark, 2018-19 in Norway, and 2020-21 in both countries. This showed generally stable incidence rates over time in both countries for all outcomes (see supplementary tables 4-7). Fourthly, to investigate the potential influence from either previous or concomitant SARS-CoV-2 infection, the proportion of vaccine recipients with any positive test result for covid-19 before vaccination was identified (6.2% in Denmark and 1.4% in Norway). When these people were excluded from the analysis, the estimates for both overall venous thromboembolic events, and specifically cerebral venous thrombosis, remained virtually unchanged (data not shown owing to low counts conflicting with data privacy regulations). When the follow-up of vaccine recipients was further censored on a positive covid-19 test result after vaccination, which occurred for 0.24% (n=643) of the combined cohorts, results remained unchanged (data not shown). Finally, to contextualise the study findings of a cerebral venous thrombosis signal, the 28 day risk of cerebral venous thrombosis after a positive covid-19 test result was assessed for Denmark and Norway, using complete nationwide data on SARS-CoV-2 polymerase

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Outcome	Incidence rate* (Denmark /Norway)	Observed†	Expected	Standardised morbidity difference‡ /100 000 (95% CI)	Standardised morbidity ratio (95% CI)
Arterial events	4.52/4.71	83	86	-1.0 (-7.2 to 6.4)	0.97 (0.77 to 1.20)
Cardiac events	2.93/3.56	52	57	-1.9 (-6.8 to 4.1)	0.91 (0.68 to 1.19)
Acute myocardial infarction (AMI)	1.04/1.21	20	18	0.6 (-2.3 to 4.6)	1.09 (0.66 to 1.68)
Ischaemic heart disease without AMI	2.58/3.35	46	52	-2.2 (-6.8 to 3.5)	0.89 (0.65 to 1.18)
Cerebrovascular events	1.62/1.21	27	28	-0.5 (-3.9 to 4.0)	0.95 (0.63 to 1.38)
Cerebral infarction	1.03/0.75	16	17	-0.5 (-3.0 to 3.2)	0.92 (0.53 to 1.50)
Intracerebral haemorrhage	0.20/0.14	8	3	1.7 (0.0 to 4.6)	2.33 (1.01 to 4.59)
Occlusion and stenosis§	0.07/0.21	n<5	3	NR	NR
Stroke, unspecified	0.40/0.06	0	5	-1.8 (-1.8 to -0.4)	0.00 (0.00 to 0.78)
Subarachnoid haemorrhage	0.14/0.09	n<5	3	NR	NR
Transient ischaemic attack	0.07/0.09	0	2	-0.6 (-0.6 to 0.8)	0.00 (0.00 to 2.24)
Other arterial events¶	0.11/0.10	n<5	3	NR	NR
Venous thromboembolism	1.58/1.26	59	30	10.8 (5.6 to 17.1)	1.97 (1.50 to 2.54)
Cerebral venous thrombosis	0.02/0.01	7	0.3	2.5 (0.9 to 5.2)	20.25 (8.14 to 41.73)
Pulmonary embolism	0.57/0.57	21	12	3.4 (0.5 to 7.5)	1.79 (1.11 to 2.74)
Lower limb venous thrombosis	0.94/0.48	22	15	2.6 (-0.4 to 6.8)	1.47 (0.92 to 2.23)
Deep thrombophlebitis of veins in legs	0.35/0.38	10	7	0.9 (-1.0 to 4.0)	1.34 (0.64 to 2.46)
Unspecified deep thrombophlebitis in lower limbs	0.66/0.05	12	8	1.6 (-0.6 to 4.9)	1.54 (0.79 to 2.69)
Splanchnic thrombosis	0.04/0.06	n<5	1	NR	NR
Other venous thrombosis**	0.22/0.36	12	6	2.2 (0.1 to 5.5)	1.99 (1.03 to 3.48)
All cause mortality	2.54/1.84	15	44	-10.6 (-13.0 to -7.0)	0.34 (0.19 to 0.57)

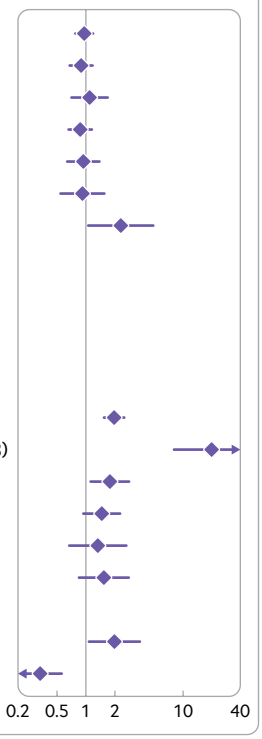

Fig 1 | General population incidence rates, observed and expected counts of events, excess events per 100 000 vaccinations, and standardised morbidity ratios of arterial events, venous thromboembolism, and all cause mortality within 28 days of vaccination in a cohort of 18-65 year old Danish and Norwegian people (n=281 264) receiving their first dose of the Oxford-AstraZeneca vaccine (ChAdOx1-S). NR=not reported owing to privacy regulations. *Per 1000 person years in the general population. †Observed events are not mutually exclusive (ie, one patient can contribute to two different third level outcomes. However, two different third level outcomes would only count once towards a common second level outcome, and similarly only once in a first level outcome). ‡Expected events based on incidence rates in the general population. §Full name: Occlusion and stenosis of precerebral or cerebral arteries, not resulting in cerebral infarction. ¶Including angiitis hypersensitiva, angiitis hypersensitiva with Schönlein-Henochs purpura, Buerger's syndrome, Goodpasture syndrome, microangiopathia thrombotica, other necrotising vasculitis, and thrombotic thrombocytopenic purpura. **Including embolism and thrombosis in non-specified veins, embolism and thrombosis in other specified veins, and embolism and thrombosis of caval vein

chain reaction results until 31 March 2021 from Danish and Norwegian microbiology databases.[27 28] Among all 162 222 people with a positive test result between ages 18 and 65 years in Denmark, fewer than five cerebral venous thrombosis events were observed over a 28 day period (precise count not shown owing to data privacy regulations), whereas among 66 721 people aged 18-65 years with a positive test result in Norway, zero cerebral venous thrombosis events were observed.

Discussion

In this large binational cohort study of recipients of the Oxford-AstraZeneca covid 19 vaccine (ChAdOx1 -S) aged 18-65 years, results were reassuring for most cardiovascular and haemostatic outcomes. We did, however, observe an increased rate of venous thromboembolic events, corresponding to 11 excess venous thromboembolic events per 100 000 vaccinations and including a clearly increased rate of cerebral venous thrombosis with 7 observed events versus 0.3 expected events among the 282 572 vaccine recipients (excess of 2.5 per 100 000 vaccinations, or one in 40 000 vaccine recipients). Conversely, we observed no increase in the rate of overall arterial events. We observed a slight increase in the rate of thrombocytopenia/coagulation disorders and bleeding, which was, however, attenuated after excluding brief hospital contacts (<5 hours) from the analysis.

Strengths and limitations of this study

The main strength of our study is its true population based approach, implemented in a setting with national health services providing free access to healthcare and with well defined and near complete follow-up based on computerised registries with full population coverage and daily updates.

The study also has potential weaknesses. The validity of our findings depends ultimately on the accurate coding of outcomes. The complex clinical syndrome

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Outcome	Incidence rate* (Denmark /Norway)	Observed†	Expected	Standardised morbidity difference‡ /100 000 (95% CI)	Standardised morbidity ratio (95% CI)
Thrombocytopenia/coagulation disorders	0.60/0.75	24	16	3.0 (-0.2 to 7.4)	1.52 (0.97 to 2.25)
Thrombocytopenia	0.15/0.38	17	6	4.2 (1.6 to 8.0)	3.02 (1.76 to 4.83)
Idiopathic thrombocytopenic purpura	0.07/0.06	n<5	1	NR	NR
Other primary thrombocytopenia	0.00/0.01	0	0.1	-0.0 (-0.0 to 1.3)	0.00 (0.00 to 35.70)
Secondary thrombocytopenia	0.01/0.18	NR	2	NR	NR
Thrombocytopenia unspecified	0.09/0.20	11	3	2.9 (0.9 to 6.1)	3.57 (1.78 to 6.38)
Coagulation disorders	0.45/0.38	7	10	-1.3 (-2.8 to 1.5)	0.67 (0.27 to 1.39)
Coagulation disorders, purpura	0.45/0.38	7	10	-1.3 (-2.8 to 1.5)	0.67 (0.27 to 1.39)
Disseminated intravascular coagulation	0.01/0.02	0	0.3	-0.1 (-0.1 to 1.3)	0.00 (0.00 to 12.20)
Bleeding events	2.75/3.04	74	60	5.1 (-0.7 to 12.2)	1.23 (0.97 to 1.55)
Bleeding	2.67/2.96	74	58	5.9 (0.0 to 12.9)	1.27 (1.00 to 1.60)
Anaemia from bleeding	0.11/0.60	n<5	8	NR	NR
Bleeding from respiratory tract	0.85/0.87	35	16	7.1 (3.2 to 12.2)	2.21 (1.54 to 3.08)
Bleeding, not specified	0.15/0.05	8	2	2.1 (0.4 to 4.9)	3.30 (1.42 to 6.50)
Haematuria	1.43/1.50	25	31	-2.1 (-5.4 to 2.3)	0.81 (0.53 to 1.20)
Intestinal bleeding	0.18/-§	n<5	2	NR	NR
Haemolytic anaemias¶	0.09/0.09	0	2	-0.8 (-0.8 to 0.5)	0.00 (0.00 to 1.66)

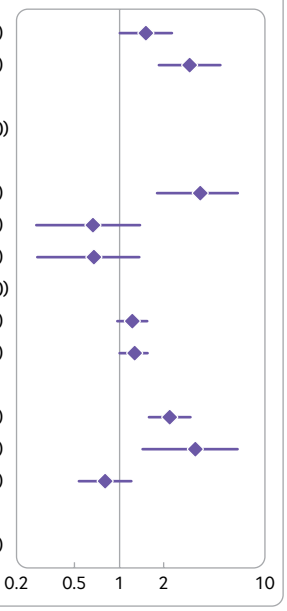

Fig 2 | General population incidence rates, observed and expected counts of events, excess events per 100 000 vaccinations, and standardised morbidity ratios of thrombocytopenia/coagulation disorders and bleeding events within 28 days of vaccination in a cohort of 18-65 year old Danish and Norwegian people (n=281 264) receiving their first dose of the Oxford-AstraZeneca covid-19 vaccine (ChAdOx1-S). NR=not reported owing to privacy regulations. *Per 1000 person years in the general population. †Observed events are not mutually exclusive (ie, one patient can contribute to two different third level outcomes. However, two different third level outcomes would only count once towards a common second level outcome, and similarly only once in a first level outcome). ‡Expected events based on incidence rates in the general population. §Not available in the Norwegian data source. ¶Including haemolytic anaemia, haemolytic uraemic syndrome, and paroxysmal nocturnal haemoglobinuria

reported with ChAdOx1-S is not captured completely by any single ICD-10 code. Instead, clinicians are likely to use the codes that reflect the dominant elements in individual patients' presentation. A general lack of specificity of the outcome diagnoses would reduce the strength of any potential associations. However, from early March the increased focus on the adverse events being examined might have heightened clinical awareness, and therefore the level of reported diagnoses, above those documented in our reference populations. This is probably mainly a concern for less serious adverse events (eg, epistaxis, mild thrombocytopenia) that otherwise could have gone undetected, as these do not necessarily lead to a hospital contact. This finding is supported by the results of the supplementary analysis excluding brief hospital contacts, in which the signal for bleeding events was removed, and the association for thrombocytopenia/coagulation disorders was diminished (on an absolute scale), whereas the observed signal for venous thromboembolic events, which are generally more serious, remained largely unchanged. Another limitation is that our expected counts of outcomes were based on the general population of each country. Active healthcare and social services workers—the primary recipients of ChAdOx1-S in Denmark and Norway—are likely to be healthier than the average population of the same age.[29] To the extent that better health decreases the risk of the studied outcomes, this will lead to falsely low estimated standardised morbidity ratios—that is, make the vaccine appear safer—and thus could not explain the safety signals observed in our study. A healthy vaccinee effect is expected to be particularly pronounced for all cause mortality,[30] as people with severe comorbidity or known terminal illness in Denmark and Norway will generally not have received ChAdOx1-S. Moreover, the vaccine is not administered to people who report acute illness on the planned vaccination date. These bias mechanisms are the most likely explanation for the observed low count for deaths in our study and hinders meaningful interpretation of the reported all cause mortality effects of receiving the vaccine. Furthermore, if known risk factors for venous thromboembolism were more prevalent among vaccine recipients than in the general population this might have led to falsely increased standardised morbidity ratios. This could include risk factors such as female sex, use of oral contraceptives, use of menopausal hormone therapy, and recent surgery or trauma or other immobilisation.[31] Our event rates were, however, standardised for any differences in sex and age, and use of systemic hormone therapy was not higher in our vaccine recipients than in the general population, and surgery or immobilisation is unlikely

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Outcome	Incidence rate* (Denmark /Norway)	Observed†	Expected	Standardised morbidity difference‡ /100 000 (95% CI)	Standardised morbidity ratio (95% CI)	Standardised morbidity ratio (95% CI)
Age 18-44 years						
Arterial events	0.90/0.77	6	8	-1.6 (-4.4 to 3.8)	0.74 (0.27 to 1.62)	
Venous thromboembolism	0.81/0.60	25	8	12.6 (5.9 to 21.5)	2.99 (1.94 to 4.42)	
Thrombocytopenia/coagulation disorders	0.61/0.52	11	8	2.6 (-1.6 to 9.1)	1.45 (0.73 to 2.60)	
Bleeding events	1.74/1.98	22	20	1.8 (-4.4 to 10.3)	1.12 (0.70 to 1.69)	
Age 45-65 years						
Arterial events	8.84/10.01	77	78	-0.4 (-12.3 to 13.7)	0.99 (0.78 to 1.24)	
Venous thromboembolism	2.48/2.12	34	22	9.1 (1.5 to 18.9)	1.58 (1.09 to 2.20)	
Thrombocytopenia/coagulation disorders	0.59/1.05	13	8	3.4 (-1.0 to 10.1)	1.57 (0.84 to 2.69)	
Bleeding events	3.94/4.44	52	40	3.4 (-1.0 to 10.1)	1.29 (0.96 to 1.69)	
Women only						
Arterial events	3.15/2.84	48	54	-2.9 (-8.8 to 4.4)	0.89 (0.65 to 1.17)	
Venous thromboembolism	1.49/1.08	54	22	14.8 (8.5 to 22.5)	2.41 (1.81 to 3.14)	
Thrombocytopenia/coagulation disorders	0.78/0.84	NR	13	NR	NR	
Bleeding events	2.47/2.95	56	46	4.8 (-1.6 to 12.7)	1.23 (0.93 to 1.59)	
Men only						
Arterial events	5.88/6.50	35	31	6.5 (-12.6 to 31.0)	1.11 (0.78 to 1.55)	
Venous thromboembolism	1.67/1.42	5	7	-4.4 (-10.4 to 7.4)	0.67 (0.22 to 1.56)	
Thrombocytopenia/coagulation disorders	0.95/0.66	n<5	3	NR	NR	
Bleeding events	3.03/3.13	18	14	6.3 (-6.7 to 24.9)	1.25 (0.74 to 1.97)	
14 day follow-up						
Arterial events	4.52/4.71	39	45	-4.3 (-12.3 to 6.0)	0.87 (0.62 to 1.19)	
Venous thromboembolism	1.58/1.26	27	16	8.1 (1.6 to 16.9)	1.73 (1.14 to 2.52)	
Thrombocytopenia/coagulation disorders	0.60/0.75	16	8	5.5 (0.6 to 12.6)	1.93 (1.11 to 3.14)	
Bleeding events	2.75/3.04	34	31	1.8 (-5.6 to 11.5)	1.08 (0.75 to 1.51)	
Excluding brief hospital contacts						
Arterial events	3.20/3.91	62	64	-0.7 (-6.0 to 5.8)	0.97 (0.75 to 1.25)	
Venous thromboembolism	0.88/0.81	40	18	8.3 (4.1 to 13.7)	2.28 (1.63 to 3.11)	
Thrombocytopenia/coagulation disorders	0.19/0.57	12	8	1.3 (-0.8 to 4.6)	1.42 (0.73 to 2.48)	
Bleeding events	0.63/1.28	14	20	-2.1 (-4.4 to 1.4)	0.71 (0.39 to 1.20)	
Using more recent general population comparison cohort§						
Arterial events	4.44/4.64	83	83	0.1 (-6.2 to 7.5)	1.00 (0.80 to 1.24)	
Venous thromboembolism	1.55/1.30	59	30	10.9 (5.6 to 17.2)	1.99 (1.51 to 2.57)	
Thrombocytopenia/coagulation disorders	0.49/0.75	24	14	3.5 (0.3 to 7.9)	1.66 (1.06 to 2.47)	
Bleeding events	2.47/2.62	74	52	8.1 (2.2 to 15.1)	1.42 (1.11 to 1.78)	

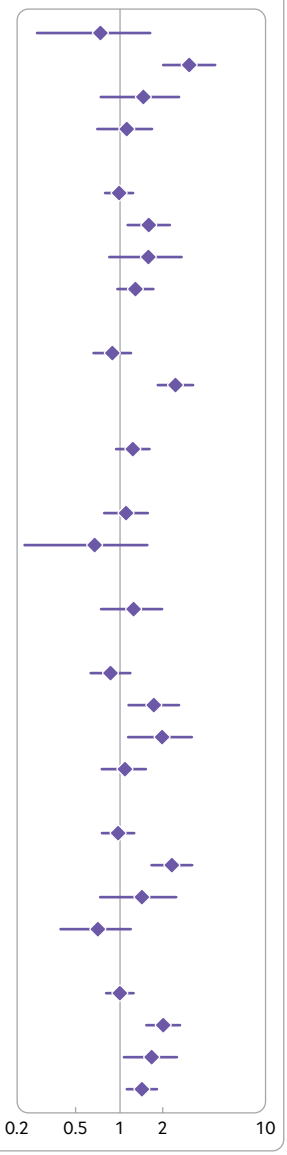

Fig 3 | Results from supplementary analyses restricted to subgroups of patients on sex, and age, shorter follow-up, and excluding brief hospital contacts. NR=not reported owing to privacy regulations. *Per 1000 person years in the general population. †Observed events are not mutually exclusive (ie, one patient can contribute to two different third level outcomes. However, two different third level outcomes would only count once towards a common second level outcome, and similarly only once in a first level outcome). ‡Expected events based on incidence rates in the general population. §The general population comparison cohort was followed from January 2020 through March 2021 in both countries

to be increased in members of the active work force. Similarly, as also observed in our post hoc analyses, any increase in observed venous thromboembolic events was unlikely to be explained by SARS-CoV-2 infections occurring in vaccinated people, as both the prevalence of covid-19 and the associated absolute risk of thromboembolic events was low in our setting.[32] Our post hoc confounder analysis (E-values) suggested that our findings were unlikely to be explained by unmeasured confounders. Nevertheless, residual confounding from other factors cannot be ruled out owing to the non-randomised observational design of our study. Lastly, important boundaries exist as to the generalisability of our study findings. Firstly, as our study was restricted to people aged 18-65 years, it cannot inform evaluations of the safety of ChAdOx1-S in older people. Similarly, data were only available for those who received their first dose of the vaccine, and as such do not provide information on the safety of the second dose. Finally, the study was conducted in two

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Scandinavian countries and therefore the results might not be generalisable to populations of predominantly non-white ethnicities.

Comparison with other studies

Specific immune mediated mechanisms might contribute to the increased risk of venous thromboembolism after vaccination with ChAdOx1-S. This is currently under investigation. Reports in the *New England Journal of Medicine* by now have described three detailed case series of 39 patients (5 in Norway,[10] 11 in Germany and Austria,[11] and 23 in the UK[12]) who presented with thrombocytopenia and thrombosis beginning five to 24 days after vaccination with ChAdOx1-S. Another case was reviewed in Denmark.[13] Among these 40 patients, 35 (88%) experienced any venous thrombosis, including a high proportion (26 patients, 65%) who experienced cerebral venous thrombosis, whereas 6 (15%) had splanchnic thrombosis and 7 (18%) pulmonary embolism, with multiple embolisms being common. This is now collectively referred to as vaccine induced thrombotic thrombocytopenia (VITT) or thrombosis with thrombocytopenia syndrome (TTS), with a suggested potential mechanism involving platelet activating antibodies directed against platelet factor 4, which are known to be triggered by heparin and sometimes other environmental factors.[33] As of yet, no individual level risk factors for vaccine induced thrombotic thrombocytopenia or thrombosis with thrombocytopenia syndrome have been confirmed,[14] with previously reported cases among both, for example, men and women and among users and non-users of hormone therapy.[10-13] To the extent that the excess rate of venous thrombosis events reported in this manuscript is associated with vaccine induced thrombotic thrombocytopenia or thrombosis with thrombocytopenia syndrome, our study has insufficient data, and it is not designed to identify subgroups at particular risk, which constitutes an important area for further research.[14] Importantly, whether this safety concern is specific to ChAdOx1-S or whether it is associated with either all adenovirus vector based covid-19 vaccines or even all covid-19 vaccines, is an important issue that remains to be elucidated. The European Medicines Agency recently raised "embolic and thrombotic events" as a new signal for the adenovirus vector based vaccine from Janssen,[34] and its use was put on temporary hold by the Centers for Disease Control and Prevention and the Food and Drug Administration in the United States while further investigations were ongoing.[14]

Policy implications

The regulatory implications of our study findings are complex. Given ChAdOx1-S's nearly 70% protection against a potentially lethal infection,[5 6] the risk to benefit ratio of the vaccine in a pandemic scenario and on a population level is likely to remain favourable. From a public health perspective, multiple factors should be considered, including regional availability of other vaccines, capacity of the local healthcare system, delays in reaching the desired level of herd immunity, regional control of the epidemic through other measures, and the importance of trust in authorities and confidence in the vaccination programme. Many of these factors directly influence the benefit of receiving a covid-19 vaccine, at both the societal and the individual level. Furthermore, the applicability of our findings to a given context needs to consider the limitations to the study's generalisability. Thus, vaccine recommendations must be context dependent and country specific. In any case, access to valid data on the magnitude of risk is essential. Such information must be made available and continuously updated for all covid-19 vaccines in the real world setting—ideally including studies that provide direct head-to-head comparisons of vaccines on both safety and efficacy, which constitutes an important area for further study.

Conclusions

Our study provides evidence of an excess rate of venous thromboembolism, including cerebral venous thrombosis, among recipients of the Oxford-AstraZeneca covid-19 vaccine ChAdOx1-S within 28 days of the first dose. The absolute risks of these events were, however, small. For the remaining safety outcomes, results were reassuring, with slightly higher rates of thrombocytopenia/coagulation disorders and bleeding, which could be influenced by heightened surveillance. The absolute risks described in this study are small in the context of the proven benefits of vaccination against covid-19, and the globally high incidence of serious cases of SARS-CoV-2 infection.

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Contributors: AP, LCL, MA, JH, ØL, AM, LP, HTS, RWT, and AH designed the study. AP, LCL, JD, ØK, GT, PLDR, and LP processed the collected data. AP and JH directed the analyses, which were carried out by LCL, GT, JD, ØK, and LP. All authors participated in the discussion and interpretation of the results. AP, JH, ØL, HTS, and RWT organised the writing and wrote the initial draft. All authors critically revised the manuscript for intellectual content and approved the final version. AP and AH are the guarantors. The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

Funding: None.

Competing interests: All authors have completed the ICMJE uniform disclosure form at http://www.icmje.org/coi_disclosure.pdf and declare: no support from any organisation for the submitted work. The authors report no personal conflicts of interest pertaining to this

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work. The Department of Clinical Epidemiology, Aarhus University Hospital, receives funding for other studies from the European Medicines Agency and companies in the form of research grants to (and administered by) Aarhus University. None of these studies have any relation to the present study. AP, JH, and LCL report participation in research projects funded by Alcon, Almirall, Astellas, AstraZeneca, Boehringer-Ingelheim, Novo Nordisk, Servier, Menarini Pharmaceuticals, and LEO Pharma, all regulator mandated phase IV studies, all with funds paid to their institution (no personal fees) and with no relation to the work reported in this paper. ØK reports participation in research projects funded by Novo Nordisk and LEO Pharma, all regulator mandated phase IV studies, all with funds paid to his institution (no personal fees) and with no relation to the work reported in this paper. HLG reports previous participation in research projects and clinical trials funded by Novo Nordisk, GSK, AstraZeneca, and Boheringer-Ingelheim, all paid to her previous institution Oslo University Hospital (no personal fees). MA has previously participated in research projects funded by Pfizer, Janssen, AstraZeneca, H Lundbeck & Mertz, and Novartis with grants received by Karolinska Institutet (no personal fees). MA has personally received fees for teaching from Atrium, the Danish Association of the Pharmaceutical Industry. The Pharmacovigilance Research Center is supported by a grant from the Novo Nordisk Foundation (NNF15SA0018404) to the University of Copenhagen.

Ethical approval: According to Danish law, studies based entirely on registry data do not require approval from an ethics review board. However, the Danish analysis was registered at the repository of the University of Southern Denmark (11.346), and data access was approved by the Danish Health Data Authority (FSEID-00005646). In Norway, the emergency preparedness register was established according to the Health Preparedness Act §2-4 and the study also was approved by the Norwegian Regional Committee for Research Ethics (REK Sør-Øst A, ref 122745).

Data sharing: No additional data available. For legal and ethical reasons, individual level patient data cannot be shared by the authors and are only accessible to authorised researchers after application to the Danish Health Data Authority, or in Norway after ethical approval and application to helsedata.no administered by the Directorate of eHealth.

The lead author (AP) affirms the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

Dissemination to participants and related patient and public communities: Dissemination to study participants is not possible. However, study findings will be disseminated to both Danish, Norwegian, and international regulators.

Provenance and peer review: Not commissioned; externally peer reviewed.

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Web appendix: Supplementary material

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Safety and immunogenicity of ChAdOx1 nCoV-19 vaccine administered in a prime-boost regimen in young and old adults (COV002): a single-blind, randomised, controlled, phase 2/3 trial

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Summary

Background Older adults (aged ≥70 years) are at increased risk of severe disease and death if they develop COVID-19 and are therefore a priority for immunisation should an efficacious vaccine be developed. Immunogenicity of vaccines is often worse in older adults as a result of immunosenescence. We have reported the immunogenicity of a novel chimpanzee adenovirus-vectored vaccine, ChAdOx1 nCoV-19 (AZD1222), in young adults, and now describe the safety and immunogenicity of this vaccine in a wider range of participants, including adults aged 70 years and older.

Methods In this report of the phase 2 component of a single-blind, randomised, controlled, phase 2/3 trial (COV002), healthy adults aged 18 years and older were enrolled at two UK clinical research facilities, in an age-escalation manner, into 18–55 years, 56–69 years, and 70 years and older immunogenicity subgroups. Participants were eligible if they did not have severe or uncontrolled medical comorbidities or a high frailty score (if aged ≥65 years). First, participants were recruited to a low-dose cohort, and within each age group, participants were randomly assigned to receive either intramuscular ChAdOx1 nCoV-19 ($2·2\times10^{10}$ virus particles) or a control vaccine, MenACWY, using block randomisation and stratified by age and dose group and study site, using the following ratios: in the 18–55 years group, 1:1 to either two doses of ChAdOx1 nCoV-19 or two doses of MenACWY; in the 56–69 years group, 3:1:3:1 to one dose of ChAdOx1 nCoV-19, one dose of MenACWY, two doses of ChAdOx1 nCoV-19, or two doses of MenACWY; and in the 70 years and older, 5:1:5:1 to one dose of ChAdOx1 nCoV-19, one dose of MenACWY, two doses of ChAdOx1 nCoV-19, or two doses of MenACWY. Prime-booster regimens were given 28 days apart. Participants were then recruited to the standard-dose cohort ($3·5–6·5\times10^{10}$ virus particles of ChAdOx1 nCoV-19) and the same randomisation procedures were followed, except the 18–55 years group was assigned in a 5:1 ratio to two doses of ChAdOx1 nCoV-19 or two doses of MenACWY. Participants and investigators, but not staff administering the vaccine, were masked to vaccine allocation. The specific objectives of this report were to assess the safety and humoral and cellular immunogenicity of a single-dose and two-dose schedule in adults older than 55 years. Humoral responses at baseline and after each vaccination until 1 year after the booster were assessed using an in-house standardised ELISA, a multiplex immunoassay, and a live severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) microneutralisation assay (MNA_{80}). Cellular responses were assessed using an ex-vivo IFN-γ enzyme-linked immunospot assay. The coprimary outcomes of the trial were efficacy, as measured by the number of cases of symptomatic, virologically confirmed COVID-19, and safety, as measured by the occurrence of serious adverse events. Analyses were by group allocation in participants who received the vaccine. Here, we report the preliminary findings on safety, reactogenicity, and cellular and humoral immune responses. This study is ongoing and is registered with ClinicalTrials.gov, NCT04400838, and ISRCTN, 15281137.

Findings Between May 30 and Aug 8, 2020, 560 participants were enrolled: 160 aged 18–55 years (100 assigned to ChAdOx1 nCoV-19, 60 assigned to MenACWY), 160 aged 56–69 years (120 assigned to ChAdOx1 nCoV-19: 40 assigned to MenACWY), and 240 aged 70 years and older (200 assigned to ChAdOx1 nCoV-19: 40 assigned to MenACWY). Seven participants did not receive the boost dose of their assigned two-dose regimen, one participant received the incorrect vaccine, and three were excluded from immunogenicity analyses due to incorrectly labelled samples. 280 (50%) of 552 analysable participants were female. Local and systemic reactions were more common in participants given ChAdOx1 nCoV-19 than in those given the control vaccine, and similar in nature to those previously reported

Lancet 2020; 396: 1979–93

Published **Online** November 19, 2020 https://doi.org/10.1016/S0140-6736(20)32466-1

This online publication has been corrected. The corrected version first appeared at thelancet.com on December 17, 2020, and further corrections have been made on April 8, 2021

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(injection-site pain, feeling feverish, muscle ache, headache), but were less common in older adults (aged ≥56 years) than younger adults. In those receiving two standard doses of ChAdOx1 nCoV-19, after the prime vaccination local reactions were reported in 43 (88%) of 49 participants in the 18–55 years group, 22 (73%) of 30 in the 56–69 years group, and 30 (61%) of 49 in the 70 years and older group, and systemic reactions in 42 (86%) participants in the 18–55 years group, 23 (77%) in the 56–69 years group, and 32 (65%) in the 70 years and older group. As of Oct 26, 2020, 13 serious adverse events occurred during the study period, none of which were considered to be related to either study vaccine. In participants who received two doses of vaccine, median anti-spike SARS-CoV-2 IgG responses 28 days after the boost dose were similar across the three age cohorts (standard-dose groups: 18–55 years, 20 713 arbitrary units [AU]/mL [IQR 13 898–33 550], n=39; 56–69 years, 16 170 AU/mL [10 233–40 353], n=26; and ≥70 years 17 561 AU/mL [9705–37 796], n=47; p=0·68). Neutralising antibody titres after a boost dose were similar across all age groups (median MNA_{80} at day 42 in the standard-dose groups: 18–55 years, 193 [IQR 113–238], n=39; 56–69 years, 144 [119–347], n=20; and ≥70 years, 161 [73–323], n=47; p=0·40). By 14 days after the boost dose, 208 (>99%) of 209 boosted participants had neutralising antibody responses. T-cell responses peaked at day 14 after a single standard dose of ChAdOx1 nCoV-19 (18–55 years: median 1187 spot-forming cells [SFCs] per million peripheral blood mononuclear cells [IQR 841–2428], n=24; 56–69 years: 797 SFCs [383–1817], n=29; and ≥70 years: 977 SFCs [458–1914], n=48).

Interpretation ChAdOx1 nCoV-19 appears to be better tolerated in older adults than in younger adults and has similar immunogenicity across all age groups after a boost dose. Further assessment of the efficacy of this vaccine is warranted in all age groups and individuals with comorbidities.

Funding UK Research and Innovation, National Institutes for Health Research (NIHR), Coalition for Epidemic Preparedness Innovations, NIHR Oxford Biomedical Research Centre, Thames Valley and South Midlands NIHR Clinical Research Network, and AstraZeneca.

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Introduction

As of Nov 13, 2020, over 52 million people have been diagnosed with COVID-19 worldwide, with over 1·2 million confirmed deaths.[1] Severe COVID-19 is more common in adults aged 70 years and older and in individuals with comorbidities such as hypertension, diabetes, cardiovascular disease, and chronic respiratory disease.[2] A safe and effective vaccine against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) will be an important tool in controlling the global COVID-19 pandemic. Although there are no licensed vaccines against COVID-19, 48 potential vaccine candidates based on a variety of platforms including lipid nanoparticle mRNA, DNA, adjuvanted protein, inactivated virus particles, and non-replicating viral vectors are in clinical trials (of which 11 candidates are in phase 3 trials) and a further 164 candidates are in preclinical testing.[3]

The WHO global target product profile of critical characteristics for prequalification of a COVID-19 vaccine requires candidates to be targeted at the most at-risk groups, including older adults; have a favourable safety profile; provide efficacy as measured by prevention of virologically confirmed disease or transmission, or both; and to provide at least 6 months of protection for individuals at ongoing risk of exposure to SARS-CoV-2.[4] On Sept 25, 2020, the UK Joint Committee on Vaccination and Immunisation (JCVI) gave interim recommendations for the national prioritisation of COVID-19 vaccines.[5] The following groups were provisionally prioritised: first, older adults living in residential care homes and residential care home workers; second, all adults aged 80 years or older and health-care and social-care workers; and third, all adults aged 75 years and older. However, the JCVI acknowledged that this priority ranking could change substantially if the first available vaccines were not considered safe or effective in older adults. Similar recommendations have also been made by the US Advisory Committee on Immunization Practices.[6]

Immunosenescence refers to the gradual deterioration and decline of the immune system brought on by ageing. Age-dependent differences in the functionality and availability of T-cell and B-cell populations are thought to have a key role in the decrease of immune response.[7] There has been a drive to develop vaccines and adjuvant formulations tailored for older adults to overcome this diminished immune response after vaccination. Assessment of immune responses in older adults is therefore essential in the development of COVID-19 vaccines that could protect this susceptible population.

The spike protein of SARS-CoV-2 binds to ACE2 receptors on target cells during viral entry. Analysis of convalescent patients suggests that the spike protein is an immunodominant antigen, eliciting both antibody and T-cell responses.[8] Most COVID-19 candidate vaccines have been developed to induce anti-spike protein immune responses. Clinical trials using several different vaccine platforms including mRNA,[9,10] adenoviral vectored vaccines,[11,12] inactivated virus,[13,14] and adjuvanted

Research in context

Evidence before this study

We searched PubMed for research articles published from database inception until Nov 13, 2020, with no language restrictions, using the terms "SARS-CoV-2", "vaccine", AND "clinical trial". We identified published clinical trial data on eight other vaccine candidates. Two recombinant viral vectored vaccines have been tested in clinical trials. A single dose adenovirus (Ad) 5 vector-based vaccine (CanSino Biological/Beijing Institute of Biotechnology, China) elicited neutralising antibodies and T-cell responses in a dose-dependent manner, but was less immunogenic in individuals older than 55 years. A heterologous prime-boost Ad5/Ad26-vectored vaccine schedule (Gamaleya Research Institute, Russia) generated neutralising antibody and cellular responses in adults younger than 60 years. Two nucleoside-modified mRNA vaccine candidates using a two-dose regimen were tested in adults aged 18–55 years and 65–85 years, and generated neutralising antibodies in both age groups in a dose-dependent manner, although immunogenicity decreased with age (Pfizer/BioNTech, USA). Another mRNA vaccine (Moderna, USA) was given to adults older than 56 years. The vaccine was tolerated, with neutralising antibodies induced in a dose-dependent manner, which increased after a second dose. Neutralising antibody responses with this mRNA vaccine appeared to be similar in adults older than 56 years to those aged 18–55 years who also received the vaccine. Two inactivated viral vaccines have also shown neutralising antibody responses in a dose-dependent manner in adults aged 18–59 years (Wuhan Institute Biological Products/SinoPharm, China) or adults aged 18–59 and 60 years and older (Beijing Institute Biological products/SinoPharm, China), with the second showing lower neutralising antibody titres in older adults after two doses. Finally, a clinical trial of a nanoparticle vaccine composed of adjuvanted trimeric severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) spike glycoproteins (Novavax, USA) reported results of a two-dose schedule given 3 weeks apart in healthy adults younger than 60 years. This vaccine was well tolerated and induced neutralisation responses that exceeded those measured in serum samples from convalescent symptomatic patients.

Added value of this study

This study is the fifth published clinical trial of a vaccine against SARS-CoV-2 tested in an older adult population (aged 18–55 years, 56–69 years, and ≥70 years). The vaccine was safe and well tolerated, with reduced reactogenicity in older adults. Antibody responses against the SARS-CoV-2 spike protein were induced in all age groups and were boosted and maintained at 28 days after booster vaccination, including in the 70 years and older group. Cellular immune responses were also induced in all age and dose groups, peaking at day 14 after vaccination.

Implications of all the available evidence

The populations at greatest risk of serious COVID-19 include people with coexisting health conditions and older adults. The immune correlates of protection against SARS-CoV-2 have not yet been determined, but neutralising antibodies are thought to be associated with protection, and in a COVID-19 non-human primate challenge model, neutralising antibody responses correlated with protection. These findings have led to the use of neutralisation assays to assess immune responses in recent human COVID-19 vaccine trials. Immunisation with ChAdOx1 nCoV-19 results in development of neutralising antibodies against SARS-CoV-2 in almost 100% of participants including older adults without severe comorbidities, with higher levels in boosted compared with non-boosted groups. Further assessment of the efficacy of this vaccine is warranted in all age groups and individuals with comorbidities.

spike glycoprotein[15] have shown neutralising antibody responses after immunisation.

Replication-deficient adenovirus vectors containing a pathogen-specific transgene have been used as novel vaccines because of their ability to induce strong humoral and cellular responses.[16] However, pre-existing immunity might reduce the immunogenicity of vectors derived from human viruses; hence, use of simian adenoviruses might be preferable. ChAdOx1 nCoV-19 (AZD1222) is a replication-defective chimpanzee adenovirus-vectored vaccine expressing the full-length SARS-CoV-2 spike glycoprotein gene (GenBank accession number MN908947). Vaccination of rhesus macaques with a single dose of ChAdOx1 nCoV-19 generates humoral and cellular immune responses and protects from lower respiratory infection after subsequent challenge with SARS-CoV-2.[17] Preliminary results of a phase 1/2 clinical trial of ChAdOx1 nCoV-19 in adults aged 18–55 years show that the vaccine is well tolerated and generates robust neutralising antibody and cellular immune responses against the spike glycoprotein.[18] Here we present the safety and immunogenicity results of a phase 2 component of a phase 2/3 multicentre study using ChAdOx1 nCoV-19 at two different doses, in adults including those aged 56–69 years and 70 years and older, and in a one-dose or two-dose regimen.

Methods

Study design and participants

In this continuing single-blind, multicentre, randomised, controlled, phase 2/3 trial, the safety and efficacy of the ChAdOx1 nCoV-19 vaccine is being assessed, with sequential age-escalation immunogenicity substudies being done in older age groups. The study is being run at 20 centres in the UK (listed in the appendix [pp 84–87]). Here we report selected results from the phase 2 component of the trial and for which participants were enrolled at two sites in the UK: the Oxford Vaccine Centre, Centre for Clinical Vaccinology and Tropical Medicine, University of Oxford (Oxford) and the NIHR

See Online for appendix

Southampton Clinical Research Facility, University Hospital Southampton NHS Foundation Trust (Southampton). Data on the participants from the phase 3 component will be published elsewhere.

We recruited participants in an age-escalation manner. We recruited adults aged 18–55 years, then adults aged 56–69 years, and then adults aged 70 years and older, without severe or uncontrolled medical comorbidities, as defined in the clinical study plan (appendix pp 48–54), through local advertisements. Participants aged 65 years and older with a Dalhousie Clinical Frailty Score of 4 or higher were excluded.[19]

Participants were enrolled into one of ten different groups. Recruitment was sequential with low-dose groups recruited first and standard-dose cohorts recruited after a protocol amendment was approved on June 5, 2020, that incorporated the new higher dose level. For the first stage of recruitment, participants aged 18–55 years were recruited to the low-dose group. Subsequently we recruited participants aged 56–69 years, and further extension to recruit those aged 70 years and older only occurred after safety review by the independent Data Safety Monitoring Board (DSMB). A minimum of 2 weeks of safety and immunogenicity data were reviewed by the DSMB before recruitment to each successive age cohort. The 18–55 years groups received two doses of vaccine and were randomly assigned to receive either the experimental vaccine or the control vaccine. The 56–69 years and 70 years and older groups were randomly assigned to receive either one dose or two doses of vaccine and were then randomly assigned to receive the experimental vaccine or the control vaccine. The same process was repeated with recruitment and randomisation for the standard-dose cohorts after review by the DSMB. All participants underwent a screening visit in which a full medical history, targeted examination, blood test for SARS-CoV-2 exposure, and a urinary pregnancy test in women of childbearing potential were done. Volunteers who were seropositive to SARS-CoV-2 before enrolment were excluded from participating in all groups, apart from those in the 18–55 years standard-dose cohort. Additionally, all participants included in this phase 2 component of the study, apart from those in the 18–55 years low-dose group, had additional safety tests (blood tests for HIV, hepatitis B and C serology, full blood count, and kidney and liver function tests). Full details of eligibility criteria are in the trial protocol (appendix pp 135–38).

Written informed consent was obtained from all participants, and the trial is being done in accordance with the principles of the Declaration of Helsinki and Good Clinical Practice. The study was sponsored by the University of Oxford (Oxford, UK) and approved in the UK by the Medicines and Healthcare products Regulatory Agency (reference 21584/0428/001-0001) and the South-Central Berkshire Research Ethics Committee (reference 20/SC/0179). Vaccine use was authorised by Genetically Modified Organisms Safety Committees at each participating site. An independent DSMB reviewed all interim safety reports. A copy of the protocol is included in the appendix (pp 83–212).

Randomisation and masking

Participants were randomly assigned to receive either the ChAdOx1 nCoV-19 vaccine or the quadrivalent MenACWY protein-polysaccharide conjugate vaccine. MenACWY was used as a comparator vaccine rather than a saline placebo to maintain masking of participants who had local or systemic reactions. Participants aged 18–55 years were randomly assigned (1:1) in the low-dose cohort and (5:1) in the standard-dose cohort to receive either ChAdOx1 nCoV-19 or MenACWY. For both 18–55 years cohorts, participants were given two doses of study vaccine. Participants aged 56–69 years were randomly assigned (3:1:3:1) to one dose of ChAdOx1 nCoV-19, one dose of MenACWY, two doses of ChAdOx1 nCoV-19, or two doses of MenACWY. Participants aged 70 years or older were randomly assigned (5:1:5:1) to one dose of ChAdOx1 nCoV-19, one dose of MenACWY, two doses of ChAdOx1 nCoV-19, or two doses of MenACWY.

Randomisation lists, using block randomisation stratified by age and dose group and study site, were generated by the study statistician (MV). Block sizes were chosen to align with the age group and dose group sizes. Computer randomisation was done with full allocation concealment within the secure web platform used for the study electronic case report form (REDCap version 9.5.22). The trial staff administering the vaccine prepared vaccines out of sight of the participants and syringes were covered with an opaque material until ready for administration to ensure masking of participants. Participants, clinical investigators, and the laboratory team remained masked to group allocation for the duration of the study. However, trial staff administering the vaccine were unmasked.

Procedures

In the previous phase 1/2 study,[18] a single standard dose of 5×10^{10} virus particles of ChAdOx1 nCoV-19 was used, based on previous experience with a ChAdOx1 Middle East respiratory syndrome (MERS) construct. In this study, we assessed a lower dose of $2\cdot2\times10^{10}$ virus particles and a standard dose of $3\cdot5–6\cdot5\times10^{10}$ virus particles in adults of different age cohorts. Due to the need to rapidly produce large numbers of doses of vaccine manufactured using Good Manufacturing Practice to allow timely enrolment into the phase 2/3 clinical trial, two different batches of vaccine were used in this study: one manufactured and vialed by Advent (Pomezia, Italy), and one manufactured by COBRA Biologics (Keele, UK) and vialed by Symbiosis (Stirling, UK). Both were manufactured according to Good Manufacturing Practice and approved by the regulatory agency in the UK, the Medicines and Healthcare

products Regulatory Agency. The 18–55 years standard-dose cohort received vaccine manufactured by COBRA Biologics for both first (ie, prime) and second (ie, boost) doses and all other cohorts received prime and boost doses, as randomised, manufactured by Advent. Analytical assessment of the batches indicates that the batches are comparable. Formal batch-to-batch comparison studies are ongoing and results will be reported when available.

ChAdOx1 nCoV-19 was administered as a single-dose or two-dose regimen (28 days apart) at either the low dose ($2·2\times10^{10}$ virus particles) or the standard dose ($3·5–6·5\times10^{10}$ virus particles). It was administered as a single intramuscular injection into the deltoid, according to specific study standard operating procedures. The MenACWY vaccine was provided by the UK Department of Health and Social Care and administered as per summary of product characteristics at the standard dose.[20] Depending on the batch used for vaccination, the injection volume for the low dose of ChAdOx1 nCoV-19 was either 0·22 mL or 0·5 mL. The injection volume used for the standard dose of ChAdOx1 nCoV-19 and MenACWY was 0·5 mL.

Safety data from animal studies and our previous phase 1/2 clinical trial[18] of ChAdOx1 nCoV-19 were reviewed before recruitment of participants. Volunteers were considered enrolled into the trial at the point of vaccination. Participants were observed in the clinic for a minimum of 15 min after the vaccination procedure in case of any immediate adverse events.

Participants from each group were instructed to complete a diary card to record solicited local and systemic adverse reactions for 7 days after each dose. Protocol-defined solicited local adverse events included injection-site pain, tenderness, warmth, redness, swelling, induration, and itch, and solicited systemic adverse events included malaise, muscle ache, joint pain, fatigue, nausea, headache, chills, feverishness (ie, a self-reported feeling of having a fever), and objective fever (defined as an oral temperature of 38°C or higher). All participants were given an emergency 24-h telephone number to contact the on-call study physician as required. Serious adverse events will be recorded throughout the follow-up period of 1 year after the last dose of vaccine.

Severity of adverse events was graded with the following criteria: mild (transient or mild discomfort for <48 h, no interference with activity, and no medical intervention or therapy required), moderate (mild-to-moderate limitation in activity, and no or minimal medical intervention or therapy required), severe (substantial limitation in activity and medical intervention or therapy required), or potentially life-threatening (requires assessment in emergency department or admission to hospital). All participants in the 56–69 years and 70 years and older groups and participants in the 18–55 years standard-dose group had clinical and immunogenicity assessments at 0, 7, 14, and 28 days after their prime and booster vaccinations. Participants in the 18–55 years low-dose group had clinical and immunogenicity assessments at baseline, immediately before the boost dose, and at 14 and 28 days after their booster vaccination.

Humoral responses at baseline and after vaccination were assessed using Meso Scale Discovery multiplexed immunoassay against spike and receptor binding domain [RBD], a standardised total IgG ELISA against trimeric SARS-CoV-2 spike protein, and a live SARS-CoV-2 microneutralisation assay MNA_{80}, which was done at Public Health England (Porton Down, UK), as described previously.[18] Cellular responses were assessed using an ex-vivo IFN-γ enzyme-linked immunospot (ELISpot) assay to enumerate antigen-specific T cells.[18] Neutralising antibodies to the ChAdOx1 vector were measured using a secreted embryonic alkaline phosphatase (SEAP)-reporter assay, which measures the reciprocal of the serum dilution required to reduce in-vitro expression of vector-expressed SEAP by 50%, 24 h after transduction.[21] Due to the labour-intensive nature of neutralisation assays, we prioritised analysis of samples from the ChAdOx1 nCoV-19 groups, randomly selecting more samples from ChAdOx1 nCoV-19 participants than control samples to be sent for blinded analysis.

Outcomes

The coprimary outcomes of the trial are to assess efficacy as measured by the number of cases of symptomatic, virologically confirmed COVID-19 and safety of the vaccine as measured by the occurrence of serious adverse events. Secondary outcomes include safety, reactogenicity, and immunogenicity profiles of ChAdOx1 nCoV-19 in older adults (aged 56–69 years and ≥70 years), efficacy against severe and non-severe COVID-19, death, and seroconversion against non-spike proteins. A full list of secondary and tertiary outcomes is in the protocol (pp 118–24).

Here we report preliminary results for selected secondary endpoints, comparing local and systemic reactogenicity and cellular and humoral immunogenicity of ChAdOx1 nCoV-19 between different age groups, after one or two doses and at low or standard dose. Efficacy analyses are not included in this report.

Statistical analysis

We present safety endpoints as frequencies (%) with 95% binomial exact CIs. We present immunological endpoints as medians and IQR. Analyses were by group allocation in participants who received the vaccine.

We did comparisons across the three age groups (aged 18–55 years, aged 56–69 years, and aged ≥70 years) using Kruskal-Wallis tests within each dose level of the vaccine (low dose or standard dose) for antibody responses or unadjusted analysis of variance applied to log-transformed values for neutralisation titres. We did comparisons between low-dose and standard-dose groups using Wilcoxon rank sum tests (antibody

response) or independent samples Student's *t* test applied to log-transformed values for neutralisation titres. We present unadjusted p values for a small number of statistical comparisons to avoid issues of multiplicity. To assess the association between responses on different assays, we used unadjusted linear regression to analyse log-transformed values after baseline.

Sample sizes were nominal for these immunogenicity subgroups and no power calculations were done.

We did all statistical analyses using SAS version 9.4 and R version 3.6.1 or later. This study is registered with ClinicalTrials.gov, NCT04400838, and with ISRCTN, 15281137.

Role of the funding source

AstraZeneca reviewed the data from the study and the final manuscript before submission, but the authors retained editorial control. All other funders of the study had no role in the study design, data collection, data analysis, data interpretation, or writing of the report. All authors had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

Between May 30 and Aug 8, 2020, 560 participants were enrolled in the study and randomly assigned to the experimental vaccine or control vaccine group: 160 participants aged 18–55 years (100 assigned to ChAdOx1 nCoV-19, 60 assigned to MenACWY), 160 aged 56–69 years (120 assigned to ChAdOx1 nCoV-19, 40 assigned to MenACWY), and 240 aged 70 years and older (200 assigned to ChAdOx1 nCoV-19, 40 assigned to MenACWY). Full details on randomisation are in figure 1. All participants randomly assigned to treatment were vaccinated. One participant (in the 18–55 years low-dose group) received the incorrect vaccine after randomisation and was excluded from analysis. Seven participants randomly assigned to receive two doses of vaccine chose not to continue with the boost dose and were excluded from further analyses. Three participants were excluded from immunology analyses due to incorrectly labelled samples (either incorrect participant identification numbers or incorrect timepoints noted on the label, or both; figure 1). The baseline characteristics of the participants eligible for inclusion in the analysis in each group are shown in the table. Participants 70 years and older were recruited from the NIHR Southampton Clinical Research Facility, University Hospital Southampton NHS Foundation Trust. All other participants were recruited at the Oxford Vaccine Centre, Centre for Clinical Vaccinology and Tropical Medicine, University of Oxford. Among the analysed population, 280 (50%) of 552 participants were female. 524 (95%) of 552 participants identified as white, and 540 (98%) were non-smokers. A large proportion of health-care workers who were predominantly female were enrolled in the 18–55 years and 56–69 years age groups. The median age in the 18–55 years group was 43·0 years (IQR 33·6–48·0), in the 56–69 years group was 60·0 years (57·5–63·0) and in the 70 years and older group was 73·0 years (71·0–76·0). The median age in the 70 years and older groups ranged from 73 years to 74 years across dosing groups, with the oldest participants aged 83 years.

The following results for local and systemic adverse reactions are all for participants who were randomly assigned to receive two doses of vaccine. Injection-site pain and tenderness were the most common solicited local adverse reactions and occurred most frequently in the first 48 h after vaccination (data for standard-dose regimen shown in figure 2; data for the low-dose groups and control groups are shown in the appendix [pp 7, 9, 19–21]). In those aged 56 years or older, a standard dose of ChAdOx1 nCoV-19, whether the prime or boost vaccination, elicited a greater number of local or systemic reactions than did MenACWY. The difference was less clear with the low-dose vaccine in the 56–69 years and 70 years and older groups, and the number of participants in the control groups was small (appendix p 30). At least one local symptom was reported after the prime vaccination with standard-dose ChAdOx1 nCoV-19 by 43 (88%) of 49 participants in the 18–55 years group, 22 (73%) of 30 in the 56–69 years group, and 30 (61%) of 49 in the 70 years and older group (appendix p 29). Similar proportions of local symptoms were reported after the boost vaccination with the standard dose of ChAdOx1 nCoV-19, with 37 (76%) of 49 participants in the 18–55 years group, 21 (72%) of 29 in the 56–69 years group, and 27 (55%) of 49 in the 70 years and older group reporting at least one local symptom. A similar pattern was seen across the age groups in participants after their prime vaccination with low-dose ChAdOx1 nCoV-19 and after the boost vaccination with the low-dose vaccine, but with fewer total adverse reactions than in the standard-dose groups (appendix pp 7, 9, 19–21). No severe local symptoms were reported by recipients of ChAdOx1 nCoV-19. In the two-dose control groups, across both the low-dose and standard-dose cohorts, local symptoms were reported by 33 (57%) of 58 participants in the 18–55 years group, five (25%) of 20 in the 56–69 years group, and seven (35%) of 20 in the 70 years and older group after the prime vaccination with MenACWY, and by 50 (86%) of 58 in the 18–55 years group, seven (37%) of 19 in the 56–69 years group, and four (20%) of 20 in the 70 years and older group after the boost vaccination with MenACWY (appendix p 29). Data for participants randomly assigned to receive only one dose of vaccine were similar to the data after a prime dose of vaccine in the two-dose groups (data not shown).

Fatigue, headache, feverishness, and myalgia were the most commonly solicited systemic adverse reactions (data for the standard-dose groups are shown in figure 3; data for the low-dose groups and control groups are shown in the appendix [pp 8, 10, 19–21]). At least one systemic symptom was reported after the prime

vaccination with the standard dose of ChAdOx1 nCoV-19 by 42 (86%) of 49 participants in the 18–55 years group, 23 (77%) of 30 in the 56–69 years group, and 32 (65%) of 49 in the 70 years and older group (appendix p 29). The severity of symptoms reported in the standard-dose groups was reduced after the boost vaccination, with only one (1%) of 127 participants reporting a severe reaction compared with seven (5%) of 128 participants after the prime vaccination. At least one systemic adverse reaction after the boost vaccination of standard dose of ChAdOx1

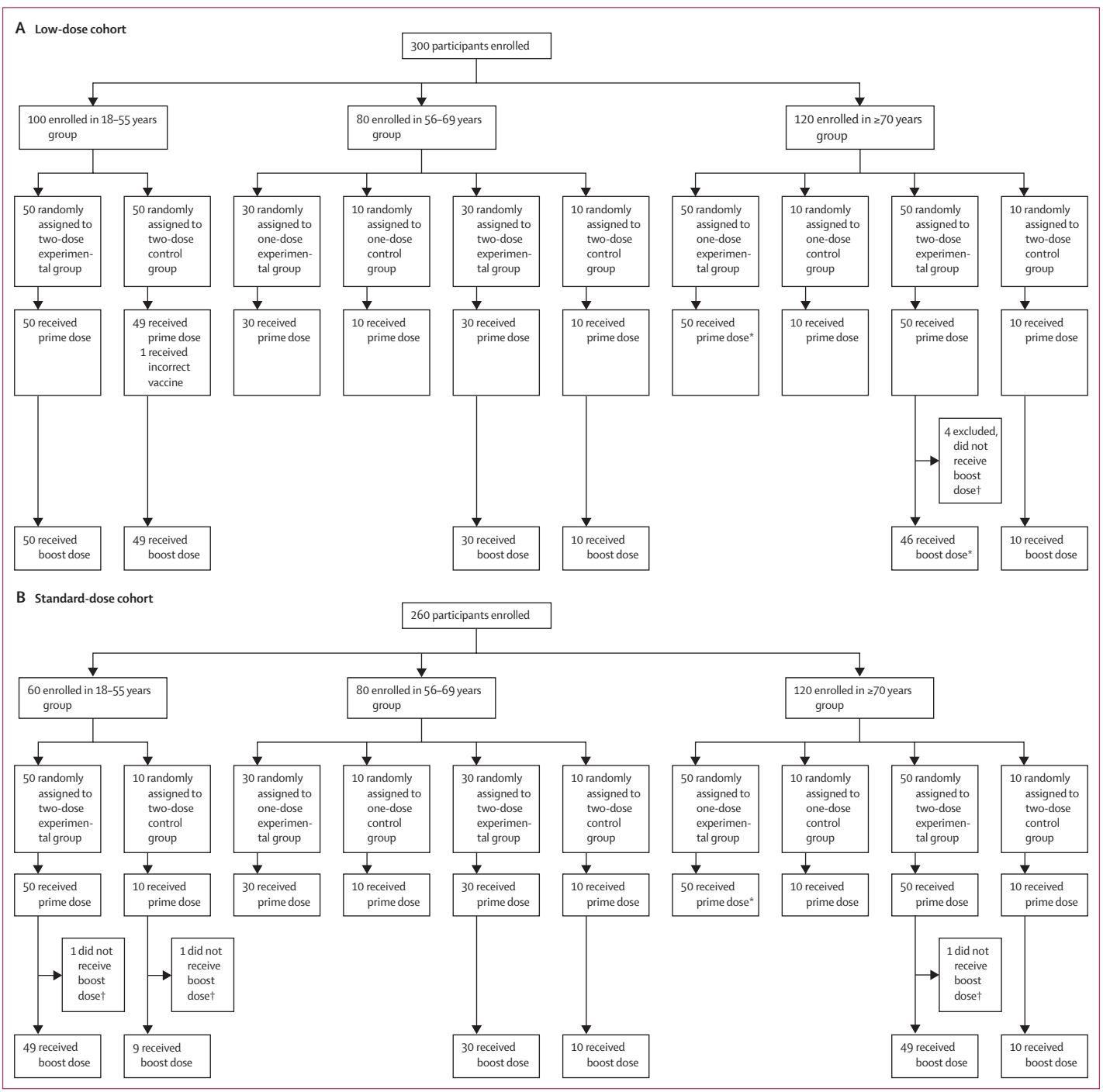

Figure 1: **Study profile for the low-dose (A) and standard-dose (B) cohorts**
*One participant excluded from immunogenicity analyses, due to mislabelling of laboratory sample. †Reasons for not receiving boost dose included that the participant moved away or was unavailable for visits, delay in receiving boost dose, or withdrawal of consent.

	Age 18–55 years		Age 56–69 years				Age ≥70 years			
	ChAdOx1 nCoV-19, two doses	MenACWY, two doses	ChAdOx1 nCoV-19, one dose	MenACWY, one dose	ChAdOx1 nCoV-19, two doses	MenACWY, two doses	ChAdOx1 nCoV-19, one dose	MenACWY, one dose	ChAdOx1 nCoV-19, two doses	MenACWY, two doses
Low dose										
Number enrolled	50	49	30	10	30	10	50	10	46	10
Sex										
Female	35 (70%)	28 (57%)	19 (63%)	4 (40%)	10 (33%)	8 (80%)	24 (48%)	6 (60%)	16 (35%)	6 (60%)
Male	15 (30%)	21 (43%)	11 (37%)	6 (60%)	20 (67%)	2 (20%)	26 (52%)	4 (40%)	30 (65%)	4 (40%)
Age, years, median (IQR, range)	44·5 (39·0–51·0, 22·0–54·0)	42·0 (32·0–48·0, 23·0–55·0)	60·0 (58·9–62·3, 56·0–69·0)	57·8 (56·3–60·8, 56·0–68·0)	60·4 (57·8–66·0, 56·0–69·4)	60·5 (58·3–63·9, 56·7–69·0)	73·5 (71·0–76·0, 69·0–83·0)	73·0 (70·0–74·0, 70·0–81·0)	73·0 (71·0–75·0, 70·0–82·0)	73·0 (71·2–74·0, 70·0–76·0)
BMI, kg/m², median (IQR, range)	24·6 (22·9–28·9, 19·4–45·1)	24·8 (21·6–27·7, 18·0–37·2)	25·0 (23·2–27·3, 20·2–37·6)	25·5 (22·5–27·3, 20·9–34·4)	25·9 (24·0–28·8, 21·3–36·6)	24·0 (23·2–26·0, 22·2–33·2)	26·0 (23·8–28·0, 20·0–36·0)	24·9 (22·3–26·9, 19·3–32·5)	26·0 (23·4–27·7, 19·4–42·1)	26·8 (24·3–29·5, 19·2–35·3)
Smoker	3 (6%)	1 (2%)	0	1 (10%)	2 (7%)	0	1 (2%)	0	1 (2%)	0
Alcohol drinker	44 (88%)	42 (86%)	28 (93%)	9 (90%)	26 (87%)	8 (80%)	43 (86%)	10 (100%)	43 (94%)	9 (90%)
Health-care worker	35 (70%)	26 (53%)	17 (57%)	7 (70%)	12 (40%)	4 (40%)	0	0	0	1 (10%)
Race or ethnicity										
White	48 (96%)	45 (92%)	30 (100%)	9 (90%)	27 (90%)	10 (100%)	50 (100%)	10 (100%)	45 (98%)	10 (100%)
Black or Black British	0	0	0	0	0	0	0	0	0	0
Asian or Asian British	2 (4%)	1 (2%)	0	0	2 (7%)	0	0	0	0	0
Mixed race or ethnicity	0	3 (6%)	0	0	0	0	0	0	1 (2%)	0
Other race or ethnicity*	0	0	0	1 (10%)	1 (3%)	0	0	0	0	0
Comorbidities										
Cardiovascular disease	4 (8%)	10 (20%)	5 (17%)	0	11 (37%)	0	14 (28%)	3 (30%)	16 (35%)	2 (20%)
Respiratory disease	12 (24%)	9 (18%)	7 (23%)	0	7 (23%)	0	6 (12%)	2 (20%)	6 (13%)	1 (10%)
Diabetes	0	0	0	0	0	1 (10%)	1 (2%)	0	2 (4%)	0
Standard dose										
Number enrolled	49	9	30	10	30	10	50	10	49	10
Sex										
Female	23 (47%)	7 (78%)	16 (53%)	3 (30%)	16 (53%)	5 (50%)	25 (50%)	1 (10%)	21 (43%)	2 (20%)
Male	26 (53%)	2 (22%)	14 (47%)	7 (70%)	14 (47%)	5 (50%)	25 (50%)	9 (90%)	28 (57%)	8 (80%)
Age, years, median (IQR, range)	39·0 (30·0–45·0, 19·0–55·0)	43·0 (35·8–50·0, 32·0–54·0)	59·0 (58·0–61·0, 56·0–69·0)	61·5 (57·5–63·8, 57·0–66·0)	59·5 (57·0–61·0, 56·0–67·0)	60·5 (57·9–61·0, 56·0–64·0)	74·0 (72·0–76·0, 70·0–80·0)	74·0 (71·0–75·5, 70·0–78·0)	73·0 (71·0–75·0, 70·0–83·0)	73·5 (72·2–74·8, 71·0–81·0)
BMI, kg/m², median (IQR, range)	26·9 (24·6–30·9, 20·2–39·7)	24·1 (23·8–25·6, 18·6–39·0)	26·7 (25·2–30·0, 18·6–36·8)	28·9 (25·6–30·2, 21·7–31·9)	24·0 (22·4–27·1, 19·9–33·5)	26·1 (23·6–27·7, 20·5–30·2)	25·1 (23·7–28·5, 17·5–32·6)	26·8 (25·8–28·5, 23·0–31·7)	27·1 (24·2–29·2, 20·3–40·2)	25·6 (24·1–29·3, 18·9–32·5)
Smoker	1 (2%)	0	0	0	0	1 (10%)	1 (2%)	0	0	0
Alcohol drinker	45 (92%)	6 (67%)	29 (97%)	10 (100%)	29 (97%)	10 (100%)	39 (78%)	9 (90%)	42 (86%)	9 (90·0%)
Health-care worker	13 (27%)	5 (56%)	10 (33%)	2 (20%)	12 (40%)	5 (50%)	2 (4%)	0	0	0
Race or ethnicity										
White	40 (82%)	7 (78%)	29 (97%)	10 (100%)	26 (87%)	9 (90%)	50 (100%)	10 (100%)	49 (100%)	10 (100%)
Black or Black British	1 (2%)	0	0	0	0	0	0	0	0	0
Asian or Asian British	7 (14%)	2 (22%)	0	0	4 (13%)	1 (10%)	0	0	0	0
Mixed race or ethnicity	0	0	0	0	0	0	0	0	0	0
Other race or ethnicity*	1 (2%)	0	1 (3%)	0	0	0	0	0	0	0
Comorbidities										
Cardiovascular disease	6 (12%)	0	4 (13%)	3 (30%)	4 (13%)	1 (10%)	20 (40%)	3 (30%)	13 (27%)	4 (40%)
Respiratory disease	10 (20%)	1 (11%)	4 (13%)	1 (10%)	3 (10%)	3 (30%)	3 (6%)	0	4 (8%)	0
Diabetes	2 (4%)	0	2 (7%)	2 (20%)	0	0	0	1 (10%)	3 (6%)	1 (10%)

Data are n (%) unless otherwise specified. BMI=body-mass index. *Included Hispanic-Columbian, Indian, Japanese, and White Irish/English.

Table: **Baseline characteristics of prime-boost participants included in the analysis**

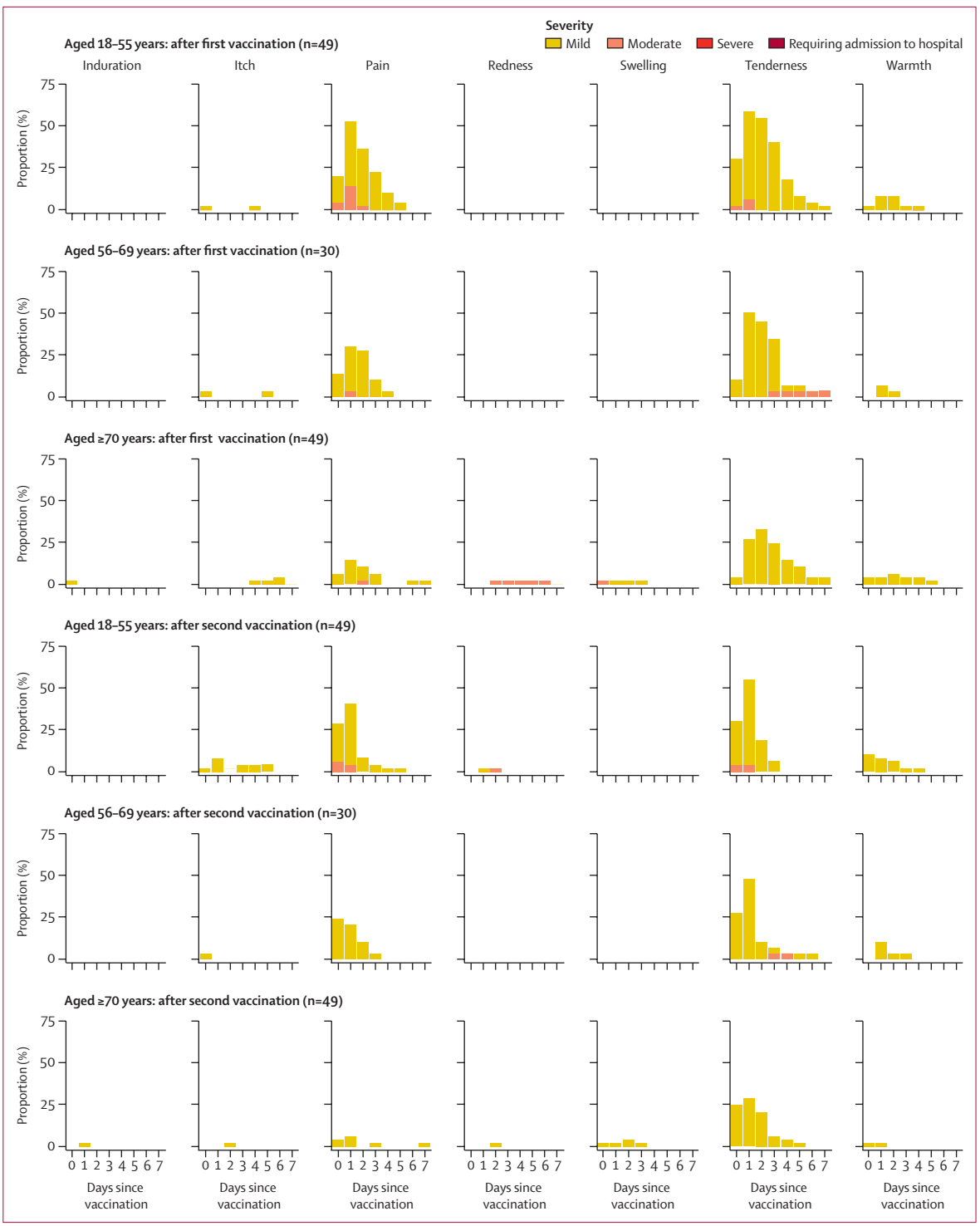

Figure 2: **Solicited local adverse reactions in the 7 days after prime and boost doses of standard-dose vaccine, by age**
Day 0 is the day of vaccination. Participants shown are those randomly assigned to receive two doses, and data are only shown for participants who received both doses of vaccine.

nCoV-19 was reported by 32 (65%) of 49 participants in the 18–55 years group, 21 (72%) of 29 in the 56–69 years group, and 21 (43%) of 49 in the 70 years and older group (appendix p 29). Within 7 days after the prime vaccination with ChAdOx1 nCoV-19, the incidence of objectively measured fever was low in the 18–55 years standard-dose

group (12 [24%] of 49), and no fevers were recorded in either the 56–69 years or 70 years and older standard-dose groups (appendix pp 16–18). No participants of any age who received the standard dose of ChAdOx1 nCoV-19 had objective fever after the boost vaccination. A similar pattern of decreasing reactogenicity with increasing age

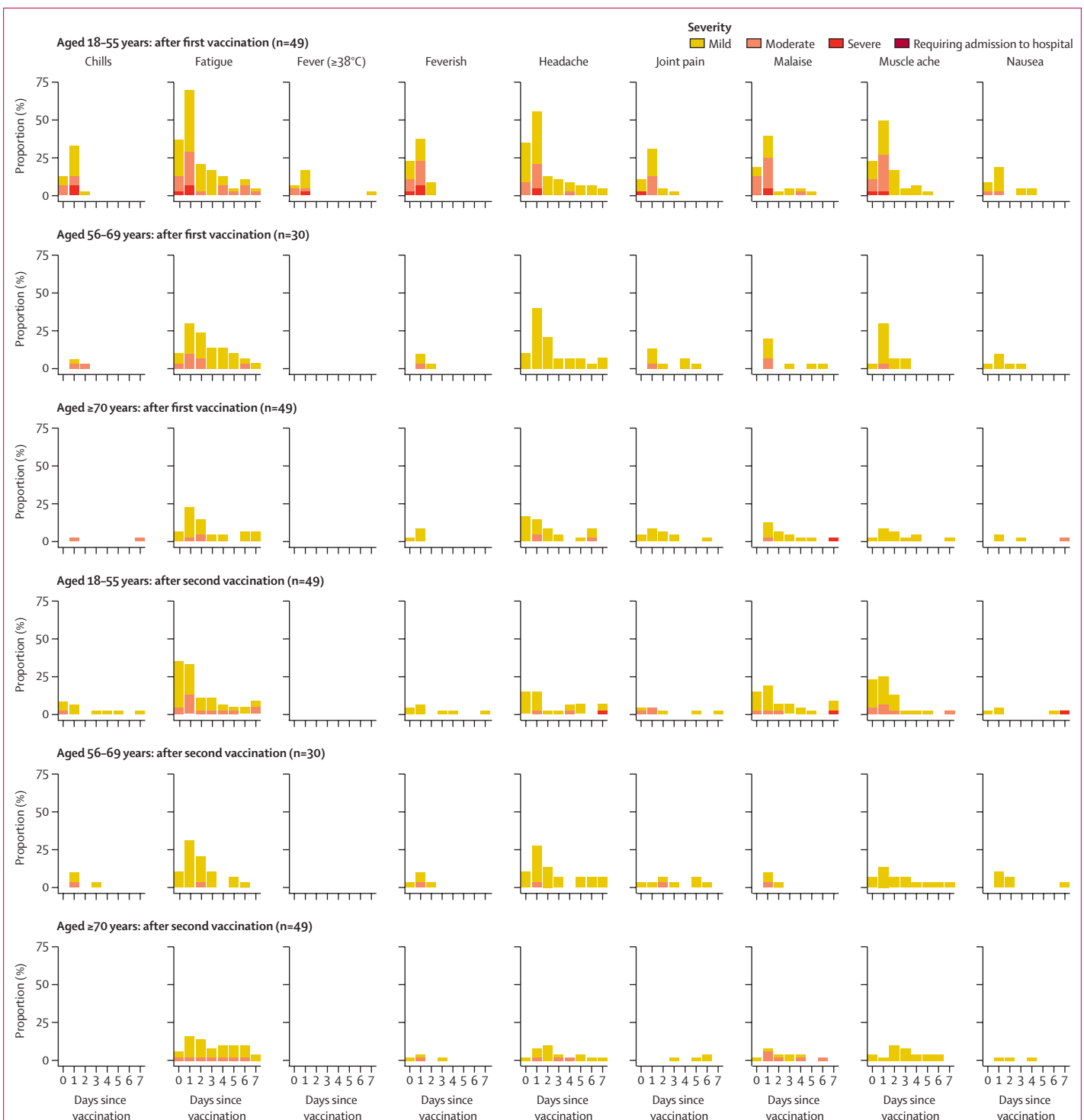

Figure 3: **Solicited systemic adverse reactions in the 7 days after prime and boost doses of standard-dose vaccine, by age**
Day 0 is the day of vaccination. Feverish is self-reported feeling of feverishness, whereas fever is an objective fever measurement (mild: 38·0 to <38·5°C, moderate: 38·5 to <39·0°C, severe: ≥39·0°C). Participants shown are those randomly assigned to receive two doses, and data are only shown for participants who received both doses of vaccine.

was seen in the low-dose groups (appendix pp 7, 8, 19–21). Similar results after the first dose were seen in those who were randomly assigned to receive only one dose of vaccine (data not shown). Data for the control groups are in the appendix (p 10).

As of Oct 26, 2020, 13 serious adverse events have occurred (across all age and vaccine groups), none of which are considered related to either study vaccine as assessed by the investigators (appendix p 31).

Using a multiplex immunoassay that detected total IgG against RBD and trimeric spike protein, we observed that participants who received the prime vaccination of standard-dose ChAdOx1 nCoV-19 had similar anti-spike antibody titres by day 28 after their prime vaccination as those who received a low dose (p=0·12 adjusted for age; figure 4; appendix p 12). At both dose levels, and for all dose groups combined, anti-spike IgG responses at day 28 decreased with increasing age (low-dose groups: 18–55 years, median 6439 arbitrary units [AU]/mL [IQR 4338–10 640], n=49; 56–69 years, 4553 AU/mL [2657–12 462], n=60; ≥70 years, 3565 AU/mL [1507–6345], n=93; p=0·0037; standard-dose groups: 18–55 years, median 9807 AU/mL [IQR 5847–17 220], n=43; 56–69 years, 5496 AU/mL [2548–12 061], n=55; ≥70 years, 4156 [2122–12 595], n=97; p=0·0044). By 28 days after the boost vaccination, similar antibody titres were seen across all two-dose groups, regardless of age or vaccine dose (eg, standard-dose groups: 18–55 years, median 20 713 AU/mL [IQR 13 898–33 550], n=39; 56–69 years, 16 170 AU/mL [10 233–40 353], n=26; and ≥70 years, 17 561 AU/mL [9705–37 796], n=47; p=0·68), and were higher than for those who did not receive a boost vaccination (appendix p 13). Similar results were seen with anti-RBD antibodies (figure 4; appendix p 12) and with an in-house standardised ELISA (appendix pp 12–13). Data for the control group are in the appendix (pp 12–13).

In a live SARS-CoV-2 microneutralisation assay (MNA_{80}), median titres peaked by day 42 in most groups that received two vaccinations (figure 5). There were no significant differences in normalised titres between age groups at day 42 (low-dose groups: 18–55 years, median 161 [IQR 99–233], n=41; 56–69 years, 143 [79–220], n=28; ≥70 years, 150 [103–255], n=34; p=0·90; standard-dose groups: 18–55 years, median 193 [IQR 113–238], n=39; 56–69 years, 144 [119–347], n=20; and ≥70 years, 161 [73–323], n=47; p=0·40). Within each age group, no significant differences were seen in neutralisation titres between low-dose and standard-dose vaccine recipients at the same timepoint (18–55 years p=0·33, 56–69 years p=0·12, ≥70 years p=0·62; figure 5; appendix p 14). Neutralising titres were achieved by 14 days after the boost vaccination in 208 (>99%) of 209 recipients of a boost vaccination. The one participant with a non-neutralising level was in the 70 years and older two-dose low-dose group.

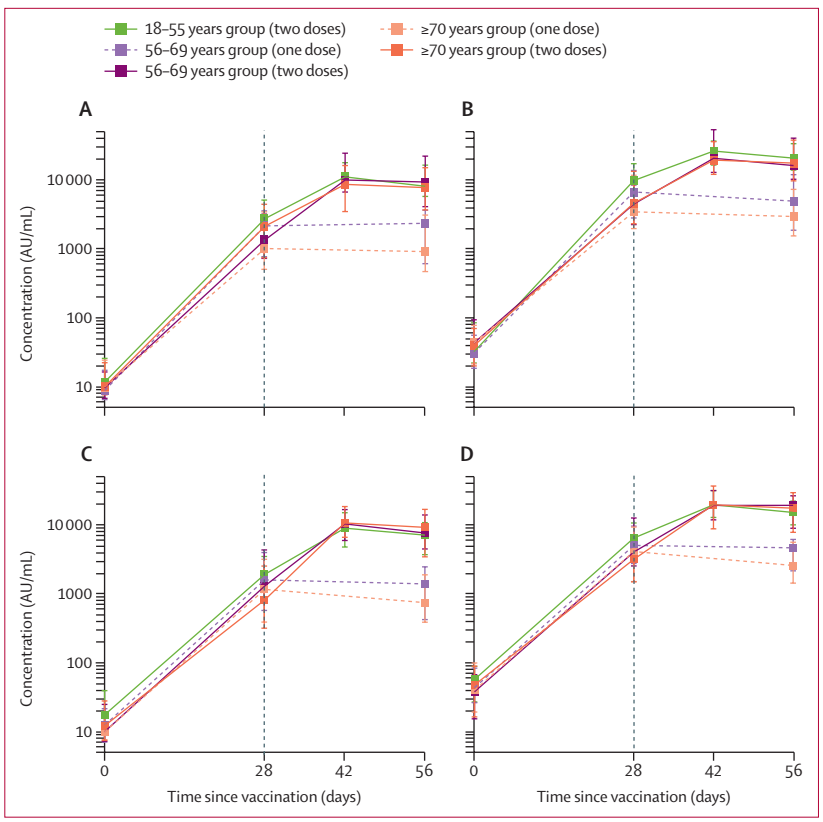

Figure 4: **SARS-CoV-2 IgG response to the receptor binding domain in the standard-dose groups (A) and low-dose groups (C) and the spike protein in the standard-dose groups (B) and the low-dose groups (D), by age**

Datapoints are medians, with whiskers showing the IQRs. Solid lines show participants who were randomly assigned to and received two doses of vaccine and dashed lines indicate participants who were randomly assigned to receive one dose. The vertical black line indicates when participants who received two doses received their boost dose. Data for the control groups are shown in the appendix (p 12). AU=arbitrary units. SARS-CoV-2=severe acute respiratory syndrome coronavirus 2.

Anti-spike IgG levels after vaccination across all timepoints in those who received two doses of vaccine were highly correlated with neutralising titres in all age groups and for both low-dose and standard-dose vaccines (r^2 from linear regression 0·42–0·75, all p<0·0001; appendix p 32).

IFN-γ ELISpot responses against SARS-CoV-2 spike protein peaked 14 days after the prime vaccination (standard-dose groups: 18–55 years, median 1187 spot-forming cells [SFCs] per million peripheral blood mononuclear cells [PBMCs; IQR 841–2428], n=24; 56–69 years, 797 SFCs [383–1817], n=29; and ≥70 years, 977 SFCs [458–1914], n=48; appendix p 16) and did not increase significantly after the boost vaccination (p=0·46 from paired Student's *t* test of day 28 *vs* day 42; figure 6). ELISpot data were unavailable for the 18–55 years low-dose group because PBMCs were not collected in this group. In those who received two standard doses of vaccine, a significant difference was seen across age groups with those aged 56–69 years having higher responses at day 42 than other age groups receiving the

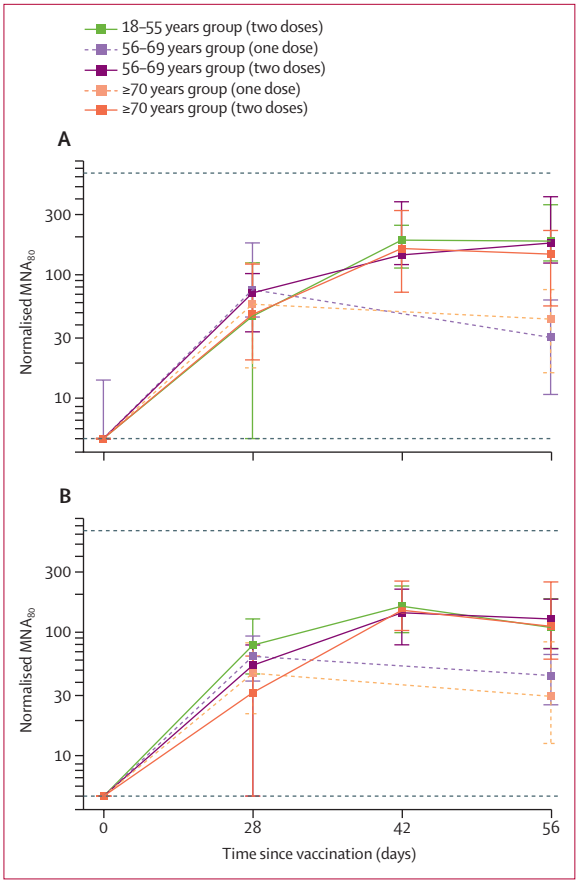

Figure 5: **Neutralising antibody titres measured using a live SARS-CoV-2 microneutralisation assay (MNA_{80}) after prime and boost doses of vaccine in standard-dose groups (A) and low-dose groups (B), by age**

Datapoints are medians, with whiskers showing the IQR. Solid lines show participants who were randomly assigned to and received two doses of vaccine and dashed lines indicate participants who were randomly assigned to receive one dose. Horizontal dotted lines show upper and lower limits of assay (values outside this range set to 640 beyond the upper limit and 5 beyond the lower limit). Data for the control groups are shown in the appendix (p 14).

To normalise data across assay runs, a reference sample was included in all assay runs and test samples normalised to this value by generating log_{10} ratios. SARS-CoV-2=severe acute respiratory syndrome coronavirus 2.

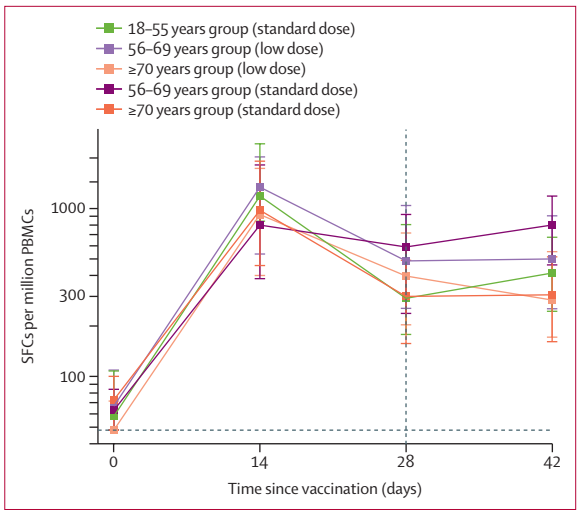

Figure 6: **IFN-γ ELISpot response to peptides spanning the SARS-CoV-2 spike insert after prime and boost doses of vaccine for all participants who were given two doses of vaccine, by age group and vaccine dose**

ELISpot data were unavailable for the 18–55 years low-dose group because PBMCs were not collected in this group. Datapoints are medians, with whiskers showing the IQR. The lower limit of detection is 48 SFCs per million PBMCs (horizontal dotted line). Day 42 samples are from participants who received the boost dose at day 28 (vertical dotted line). Data for both one-dose and two-dose groups, with numbers analysed at each timepoint, are in the appendix (p 15). ELISpot=enzyme-linked immunospot. PBMC=peripheral blood mononuclear cells. SARS-CoV-2=severe acute respiratory syndrome coronavirus 2. SFC=spot-forming cells.

same vaccine regimen (18–55 years, median 413 SFCs per million PBMCs [IQR 245–675], n=23; 56–69 years, 798 SFCs [462–1186], n=28; and ≥70 years, 307 SFCs [161–516], n=47; p<0·0001; appendix p 15).

Anti-ChAdOx1 neutralising antibody titres across different age and dose groups are shown in figure 7. Titres increased with the prime vaccination with ChAdOx1 nCoV-19 in all groups to similar levels, but were not increased further after a boost dose of vaccine at day 28. This observation was in contrast with the anti-SARS-CoV-2 spike protein antibody levels, which were increased 28 days after the boost vaccination (figure 4). Anti-ChAdOx1 neutralising titres immediately before the boost vaccination were negatively correlated with standardised ELISA values 28 days after the boost vaccination (p=0·037; figure 7), but no significant correlation was seen between anti-ChAdOx1 neutralising titres immediately before the boost vaccination and ELISpot responses 14 days after the boost vaccination (p=0·22; figure 7).

Discussion

Our findings show that the ChAdOx1 nCoV-19 vaccine was safe and well tolerated with a lower reactogenicity profile in older adults than in younger adults. Immunogenicity was similar across age groups after a boost vaccination. If these responses correlate with protection in humans, these findings are encouraging because older individuals are at disproportionate risk of severe COVID-19 and so any vaccine adopted for use against SARS-CoV-2 must be effective in older adults.

Most of the reported local and systemic adverse events were mild to moderate in severity, in line with our previous phase 1 study of the ChAdOx1 nCoV-19 vaccine[18] and previously reported studies of ChAdOx1-vectored vaccines.[22–24] Fewer adverse events were reported after the boost vaccination than after the prime vaccination and reactogenicity reduced with increasing age. The lower dose of vaccine was less reactogenic than the standard dose of vaccine across all age groups.

The serious adverse events observed during the trial in these study groups were judged to be unrelated to the study vaccines and occurred at frequencies expected for these conditions in the general population. None of the participants included in this report had any suspected

unexpected serious adverse reactions. In the phase 3 component of the trial, suspected unexpected serious adverse reactions occurred in other groups, and will be reported in detail in a subsequent publication. We carefully monitored suspected unexpected serious adverse reactions and other adverse events to ensure that no pattern of unexplained illnesses emerged that could indicate a safety concern. Independent assessments have led to the recommendation that the trial is safe to continue.

The ChAdOx1 nCoV-19 vaccine induced a specific antibody response to the SARS-CoV-2 spike glycoprotein and RBD at 28 days after a single dose across all age groups, including adults aged 70 years and older. A clear effect of a boost vaccination on antibody titres at day 56 was seen that was unrelated to dose regimen or age group. Similar patterns were observed with neutralising antibody responses, with no difference in the magnitude of the response at day 28 after the prime vaccine regardless of age or vaccine dose, but a booster effect was observed in individuals who received a second dose of vaccine.

Other clinical trials have also assessed safety, tolerability, and immunogenicity of SARS-CoV-2 vaccines in older adults. An adenovirus 5 vector-based vaccine also had reduced reactogenicity in adults aged 55 years and older compared with adults aged 18–54 years after a single dose of vaccine, although immunogenicity was concurrently reduced in this older age group.[11] A two-dose mRNA vaccine has also been shown to be immunogenic in adults older than 56 years with dose-dependent immune responses and similar neutralising antibody titres and cellular immune responses to younger adults.[9] Another two-dose mRNA vaccine has shown immunogenicity in older adults, but absolute neutralising antibody responses in adults aged 65–85 years were lower than in those aged 18–55 years.[10] By contrast with our observations, in both these studies, reactogenicity was more common after the second dose of an mRNA vaccine. A two-dose inactivated virus vaccine has also shown lower absolute neutralising antibody titres in adults aged 60 years and older than in adults aged 18–59 years, but reactogenicity was not formally compared between the first and second doses in this study.[13]

T-cell responses are important in controlling disease in natural infection[8] and therefore generation of a robust cellular immune response is a desirable attribute for a vaccine against SARS-CoV-2. Here, we found that spike-specific T-cell responses measured with ELISpot peaked at 14 days after the prime vaccination, consistent with previous studies of simian adenovirus-vectored vaccines,[25] and were similar in all groups regardless of age and vaccine dose. Spike protein T-cell responses measured with ELISpot have also been reported in studies with other adenovirus-vectored vaccines against SARS-CoV-2,[12] including in adults older than 55 years.[11] Theoretical concerns about vaccine-enhanced disease have led to a view that a type 1 T-helper (Th1)-biased CD4 response is a preferred coronavirus vaccine characteristic.[26] An adjuvanted nanoparticle vaccine has been shown to induce spike-specific CD4 T-cell cytokine responses with a predominantly Th1 profile,[15] as has an mRNA vaccine in small numbers of adults aged 56–70 years and 71 years and older.[9] More detailed investigations of antigen-specific T-cell responses in our study participants are ongoing.

The robust humoral and cellular immune responses obtained in our older adult population were encouraging given that a number of studies have shown that decreasing immune function with age leads to decreased immune responses to vaccines. This fact holds true for vaccines such as for influenza, for which pre-existing

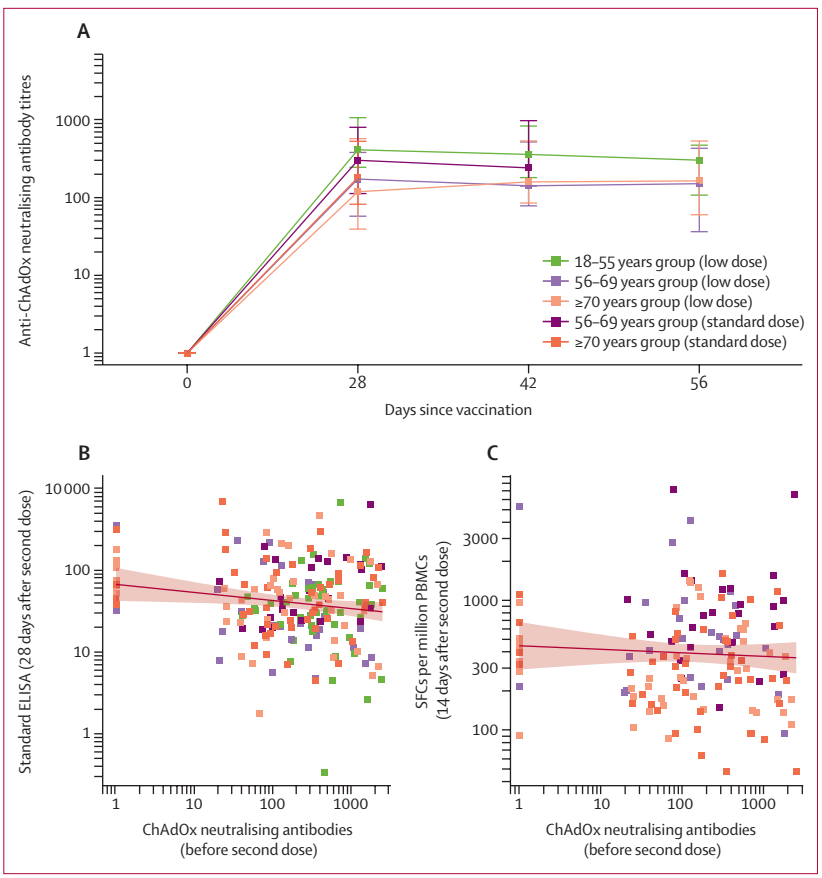

Figure 7: **Anti-ChAdOx1 vector neutralising titres after prime and boost doses of vaccine, by age and vaccine dose, and the correlation between pre-boost dose anti-ChAdOx1 neutralising antibodies and 28 days after boost dose antibody and T-cell responses**

(A) Anti-ChAdOx1 neutralising antibody titres in participants who received ChAdOx1 nCoV-19 vaccine by age and dose: datapoints are medians, with whiskers showing the IQR. Values below the limit of detection were assigned a value of 1. (B) Anti-ChAdOx1 neutralising antibody titre immediately before boost dose of vaccine versus standardised IgG ELISA against SARS-CoV-2 spike 28 days after the boost dose of vaccine with linear regression of logged values (p=0·037). (C) Anti-ChAdOx1 neutralising antibody titres immediately before boost dose of vaccine versus SARS-CoV-2 spike specific T cells measured by IFN-γ ELISpot on day 14 after the boost dose of vaccine with linear regression of logged values (p=0·22). In B and C, each datapoint is one participant and the solid line shows the linear regression, with the shaded area showing the 95% CI from an unadjusted linear regression of anti-vector neutralisation titres against logged ELISA (in B) or ELISpot (in C) response. Data were unavailable at day 56 for the 56–69 years standard-dose group. ELISpot=enzyme-linked immunospot. PBMC=peripheral blood mononuclear cells. SARS-CoV-2=severe acute respiratory syndrome coronavirus 2. SFC=spot-forming cells.

immune memory exists,[27] and vaccines that induce primary immune responses, such as hepatitis B.[28] Other adenovirus-vector platforms against SARS-CoV-2 have either shown reduced immunogenicity in an older age group[11] (although this study was of a single-dose regimen and so not directly comparable with our prime-boost regimen) or have not yet been tested in an older population.[12]

However, our results are consistent with previous studies of adenovirus-vector-based vaccines against respiratory pathogens that evoke humoral and T-cell responses in older adults, including a human adenovirus-vectored respiratory syncytial virus (RSV) vaccine[29] and a simian adenovirus-vectored RSV vaccine.[30] Our results with ChAdOx1 nCoV-19 are also consistent with those of a ChAdOx1-vectored vaccine against influenza that showed good immunogenicity in adults older than 50 years.[22]

Notably, the anti-spike antibody responses in our study increased after a boost vaccination at an interval of 1 month but the neutralising anti-vector antibody responses did not. There was also no difference in anti-vector immunity by age. We observed a small negative correlation between anti-vector antibody titres and anti-spike total IgG, but not T-cell ELISpot responses. Further work is needed to investigate if homologous boosting with adenovirus-vectored vaccines can be done without loss of immunogenicity to the pathogen-specific transgene.

In the absence of a clear serological correlate of protection against SARS-CoV-2, clinical studies have focused on measuring neutralising antibodies because these have been shown to confer protection from challenge in animal models.[9–15] Live virus neutralisation assays are labour intensive and can only be done in specialist laboratories under category 3 biological safety conditions. We found here that anti-spike IgG levels correlate with neutralising antibody titres for all age groups. This finding suggests that, should neutralising antibodies be shown to be protective in humans, routine serological assays could be used for the standardised evaluation of functional antibody by vaccine candidates in clinical trials.

A limitation of this study is its single-blind design. However, all laboratory analyses and clinical assessments reported in this manuscript were done in a blinded fashion. A further limitation is possible variation of severity of local reactions due to the difference in injection volumes between different batches of vaccine in the low-dose group. Ongoing studies in larger groups will investigate the reactogenicity of a booster dose in more detail. Finally, the selection of participants aged 70 years and older, with a median age of 73–74 years between dose groups and with few comorbidities, might not be representative of the general older population, including those living in residential care settings or older than 80 years. Early phase studies in older adults require healthy volunteers to be enrolled for safety assessments, and recruitment to the study occurred during a period of national lockdown when more susceptible individuals were advised by Public Health England to self-isolate. Therefore, we excluded volunteers with substantial comorbidities or clinical frailty. Larger studies are now underway to assess immunogenicity, safety, and efficacy in older adults with a wider range of comorbidities.

Ultimately, licensure of a vaccine relies on the demonstration of efficacy in preventing COVID-19 and safety. Phase 3 studies with ChAdOx1 nCoV-19 are ongoing in the UK, Brazil, and the USA to assess vaccine efficacy and safety. Here we found similar safety and immunogenicity of ChAdOx1 nCoV-19 in older adults compared with younger adults, which could support the use of this vaccine in this older age group, if it is shown to be protective in phase 3 trials.

Contributors

AJP and SCG conceived and designed the trial and AJP is the chief investigator. AJP, AMM, HR, MNR, MV, and PMF contributed to the protocol and design of the study. AVSH and SNF were the study site principal investigators. ALF, CD, EAC, KJE, RM, and TL were responsible for laboratory testing and assay development. MV and NGM did the statistical analysis. SCG and TL were responsible for vaccine development. ADD, CG, and RT were responsible for vaccine manufacture. AJP, AMM, MNR, MV, NGM, and TL contributed to the preparation of the report. AMM, DRO, HR, KJE, MNR, PKA, and PMF contributed to the implementation of the study. All other authors contributed to the implementation of the study and data collection. All authors critically reviewed and approved the final version.

Declaration of interests

Oxford University has entered into a partnership with AstraZeneca for further development of ChAdOx1 nCoV-19 (AZD1222). AstraZeneca reviewed the data from the study and the final manuscript before submission, but the authors retained editorial control. SCG is cofounder of Vaccitech (a collaborator in the early development of this vaccine candidate) and named as an inventor on a patent covering use of ChAdOx1-vectored vaccines (PCT/GB2012/000467) and a patent application covering this SARS-CoV-2 vaccine. TL is named as an inventor on a patent application covering this SARS-CoV-2 vaccine and was consultant to Vaccitech. PMF is a consultant to Vaccitech. AJP is Chair of the UK Department of Health and Social Care's JCVI, but does not participate in policy advice on coronavirus vaccines, and is a member of the WHO Strategic Advisory Group of Experts (SAGE). AVSH is a cofounder of and consultant to Vaccitech and is named as an inventor on a patent covering design and use of ChAdOx1-vectored vaccines (PCT/GB2012/000467). MDS reports grants from Janssen, GlaxoSmithKline, MedImmune, Novavax, and MCM Vaccine and grants and non-financial support from Pfizer outside of the submitted work. CG reports personal fees from the Duke Human Vaccine Institute outside of the submitted work. ADD reports grants and personal fees from AstraZeneca outside of the submitted work. All other authors declare no competing interests.

Data sharing

The study protocol and clinical study plan are provided in the appendix (pp 45–212). Anonymised participant data will be made available when the trial is complete, upon requests directed to the corresponding author. Proposals will be reviewed and approved by the sponsor, investigator, and collaborators on the basis of scientific merit. After approval of a proposal, data can be shared through a secure online platform after signing a data access agreement. All data will be made available for a minimum of 5 years from the end of the trial.

Acknowledgments

This Article reports independent research funded by UK Research and Innovation (MC_PC_19055), Engineering and Physical Sciences Research Council (EP/R013756/1), Coalition for Epidemic Preparedness

Innovations, and the National Institute for Health Research (NIHR). We acknowledge support from Thames Valley and South Midland's NIHR Clinical Research Network and the staff and resources of NIHR Southampton Clinical Research Facility, and the NIHR Oxford Health Biomedical Research Centre. PMF received funding from the Coordenacao de Aperfeicoamento de Pessoal de Nivel Superior, Brazil (finance code 001). ALF was supported by the Chinese Academy of Medical Sciences Innovation Fund for Medical Science, China (grant number: 2018-I2M-2-002). KJE is an NIHR Biomedical Research Centre Senior Research Fellow. AJP and SNF are NIHR senior investigators. The views expressed in this publication are those of the authors and not necessarily those of the NIHR or the UK Department of Health and Social Care. We thank the senior management at AstraZeneca for facilitating and funding the Mesoscale antibody assay included in this manuscript. We also thank the volunteers who participated in this study.

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ORIGINAL ARTICLE

Safety and Efficacy of Single-Dose Ad26.COV2.S Vaccine against Covid-19

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ABSTRACT

BACKGROUND

The Ad26.COV2.S vaccine is a recombinant, replication-incompetent human adenovirus type 26 vector encoding full-length severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) spike protein in a prefusion-stabilized conformation.

METHODS

In an international, randomized, double-blind, placebo-controlled, phase 3 trial, we randomly assigned adult participants in a 1:1 ratio to receive a single dose of Ad26.COV2.S (5×10^{10} viral particles) or placebo. The primary end points were vaccine efficacy against moderate to severe–critical coronavirus disease 2019 (Covid-19) with an onset at least 14 days and at least 28 days after administration among participants in the per-protocol population who had tested negative for SARS-CoV-2. Safety was also assessed.

RESULTS

The per-protocol population included 19,630 SARS-CoV-2–negative participants who received Ad26.COV2.S and 19,691 who received placebo. Ad26.COV2.S protected against moderate to severe–critical Covid-19 with onset at least 14 days after administration (116 cases in the vaccine group vs. 348 in the placebo group; efficacy, 66.9%; adjusted 95% confidence interval [CI], 59.0 to 73.4) and at least 28 days after administration (66 vs. 193 cases; efficacy, 66.1%; adjusted 95% CI, 55.0 to 74.8). Vaccine efficacy was higher against severe–critical Covid-19 (76.7% [adjusted 95% CI, 54.6 to 89.1] for onset at ≥14 days and 85.4% [adjusted 95% CI, 54.2 to 96.9] for onset at ≥28 days). Despite 86 of 91 cases (94.5%) in South Africa with sequenced virus having the 20H/501Y.V2 variant, vaccine efficacy was 52.0% and 64.0% against moderate to severe–critical Covid-19 with onset at least 14 days and at least 28 days after administration, respectively, and efficacy against severe–critical Covid-19 was 73.1% and 81.7%, respectively. Reactogenicity was higher with Ad26.COV2.S than with placebo but was generally mild to moderate and transient. The incidence of serious adverse events was balanced between the two groups. Three deaths occurred in the vaccine group (none were Covid-19–related), and 16 in the placebo group (5 were Covid-19–related).

CONCLUSIONS

A single dose of Ad26.COV2.S protected against symptomatic Covid-19 and asymptomatic SARS-CoV-2 infection and was effective against severe–critical disease, including hospitalization and death. Safety appeared to be similar to that in other phase 3 trials of Covid-19 vaccines. (Funded by Janssen Research and Development and others; ENSEMBLE ClinicalTrials.gov number, NCT04505722.)

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*The members of the ENSEMBLE Study Group are listed in the Supplementary Appendix, available at NEJM.org.

This article was published on April 21, 2021, at NEJM.org.

DOI: 10.1056/NEJMoa2101544

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Since emerging in December 2019, the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic has caused high morbidity and mortality, with new variants rapidly spreading.[1-4] Vaccines to prevent coronavirus disease 2019 (Covid-19) have been developed with unprecedented speed.[5,6]

The Ad26.COV2.S vaccine comprises a recombinant, replication-incompetent human adenovirus type 26 (Ad26) vector[7] encoding a full-length, membrane-bound SARS-CoV-2 spike protein in a prefusion-stabilized conformation.[8,9] Other Ad26-based vaccines, including an approved Ebola vaccine, are safe and have induced durable immune responses.[8,10-13] Ad26.COV2.S induced durable protection at low doses in preclinical SARS-CoV-2 challenge studies,[8,14] and initial clinical data showed that a single dose at 5×10^{10} viral particles was safe and induced excellent humoral and cellular immune responses.[9] Ad26.COV2.S can be stored for up to 2 years in a standard freezer and up to 3 months at refrigerator temperatures, which simplifies transport, storage, and use in a pandemic.

We are conducting an ongoing phase 3 trial (ENSEMBLE) to evaluate the safety and efficacy of a single dose of Ad26.COV2.S at 5×10^{10} viral particles for the prevention of Covid-19 and SARS-CoV-2 infection in adults. Here, we report the results of the primary analyses.

Methods

Trial Design and Oversight

We are conducting this ongoing, 2-year, multicenter, randomized, double-blind, placebo-controlled, phase 3, pivotal trial in Argentina, Brazil, Chile, Colombia, Mexico, Peru, South Africa, and the United States. All the participants provided written informed consent. The trial adheres to the principles of the Declaration of Helsinki and to the Good Clinical Practice guidelines of the International Council for Harmonisation. The protocol (available with the full text of this article at NEJM.org) and amendments were approved by institutional review boards according to local regulations. An unblinded independent data and safety monitoring board continuously monitors safety, including monitoring for vaccine-associated enhanced respiratory disease.

The trial is a collaboration between the sponsor, Janssen Research and Development, which is an affiliate of Janssen Vaccines and Prevention and part of the Janssen pharmaceutical companies of Johnson & Johnson, and the Operation Warp Speed Covid-19 Rapid Response Team (which includes the Biomedical Advanced Research and Development Authority, the National Institutes of Health, the Covid-19 Prevention Trials Network, and the Department of Defense). The trial was designed and conducted, and the data analysis and data interpretation were performed, by the sponsor and collaborators. Trial-site investigators collected and contributed to the interpretation of the data. All the data were available to the authors, who vouch for the accuracy and completeness of the data and for the fidelity of the trial to the protocol. Medical writers who were funded by the sponsor assisted in drafting the manuscript.

Trial Participants

Stages 1a and 2a of the trial were conducted in parallel and included 2000 adults 18 to 59 years of age and 60 years of age or older, respectively, who were in good or stable health and did not have coexisting conditions that have been associated with an increased risk of severe Covid-19. After a 3-day safety review by the data and safety monitoring board, stages 1b and 2b were initiated. Those stages additionally included adults of the same respective age ranges who had stable and well-controlled coexisting conditions. The eligibility criteria are provided in the Supplementary Methods section in the Supplementary Appendix, available at NEJM.org. Participants were not excluded on the basis of SARS-CoV-2 infection or serostatus.

Procedures

Details of the trial procedures are provided in the Supplementary Methods section. Participants were randomly assigned in a 1:1 ratio, with the use of randomly permuted blocks, to receive either Ad26.COV2.S or saline placebo. Randomization was conducted with an interactive Web-response system and stratified according to trial site, age group, and the presence or absence of coexisting conditions that have been associated with an increased risk of severe Covid-19.

Vaccine or placebo was administered on day 1. Ad26.COV2.S was supplied in single-use vials at a concentration of 1×10^{11} viral particles per milliliter and was administered at a dose of 5×10^{10}

viral particles as a single intramuscular injection (0.5 ml) by a health care worker who was unaware of the group assignment.

Participants reported Covid-19 symptoms electronically using the Symptoms of Infection with Coronavirus-19 questionnaire (methods described in Fig. S1 in the Supplementary Appendix). Participants and trial staff obtained nasal swabs, which were tested with the use of a Food and Drug Administration (FDA) Emergency Use Authorization reverse-transcriptase–polymerase-chain-reaction (RT-PCR) assay for SARS-CoV-2 at a local laboratory and subsequently confirmed centrally (m-2000 SARS-CoV-2 real-time RT-PCR, Abbott). Seropositivity for SARS-CoV-2 was evaluated by means of a SARS-CoV-2 nucleocapsid (N) immunoassay (Elecsys, Roche) at trial entry and on days 29 and 71. Assays were performed according to the manufacturers' protocols.

Primary and key secondary efficacy evaluations were based on centrally confirmed cases of Covid-19. Owing to the high incidence of Covid-19 and the time taken for central confirmation, not all cases had been centrally confirmed at the time of the primary analysis. A supplementary analysis of RT-PCR–positive cases from all sources, whether centrally confirmed or not, was therefore performed for subgroups, hospitalizations, and deaths.

SAFETY ASSESSMENTS

Serious adverse events and adverse events leading to withdrawal from the trial are being recorded throughout the trial. In a safety subpopulation comprising approximately 6000 participants (see below), data on solicited local and systemic adverse events were recorded in an electronic diary for 7 days after administration and unsolicited adverse events for 28 days after administration.

EFFICACY ASSESSMENTS

The two primary end points were the efficacy of the Ad26.COV2.S vaccine against the first occurrence of centrally confirmed moderate to severe–critical Covid-19 with an onset at least 14 days after administration and at least 28 days after administration in the per-protocol population (see below). All the potential cases of severe–critical Covid-19 and cases of moderate Covid-19 with at least three signs or symptoms were classified as being severe–critical by an independent Clinical Severity Adjudication Committee whose members were unaware of the group assignments. This committee adjudicated cases on the basis of clinical judgment (e.g., a single low oxygen-saturation measurement was not classified as indicating severe Covid-19 unless other clinical findings were consistent with a severe classification). The case definitions for Covid-19 and the protocol-defined secondary and exploratory end points are described in the Supplementary Appendix.

STATISTICAL ANALYSIS

The full analysis set included all the participants who underwent randomization and received a dose of trial vaccine or placebo. The per-protocol population comprised participants who received a dose of trial vaccine or placebo, were seronegative or had an unknown serostatus at the time that the vaccine or placebo was administered, and had no protocol deviations that were likely to affect vaccine efficacy. Participants who were RT-PCR–positive between days 1 and 14 or between days 1 and 28 were excluded from the analysis of cases with an onset at least 14 days after administration and at least 28 days after administration, respectively. The per-protocol population was the main population for the efficacy analyses. Safety analyses were conducted in the full analysis set, including the safety subpopulation.

The null hypothesis was that the efficacy of Ad26.COV2.S would be no higher than 30% for each primary end point, as evaluated with a truncated sequential probability ratio test[15,16] at a one-sided significance level of 0.025. The sample size was reduced from 60,000 to approximately 40,000 on the basis of the high incidence of Covid-19 during the trial. The primary analysis was triggered on a positive recommendation from the data and safety monitoring board, after the FDA-specified median 8-week follow-up was reached and prespecified data requirements were met.

If the null hypothesis was rejected for both primary end points, secondary objectives were evaluated against a null hypothesis that used a lower limit of vaccine efficacy of more than 0% with prespecified multiplicity adjustments for familywise type I error control (Fig. S2). Exact Poisson regression[17] was used for the analysis of vaccine efficacy and the associated confidence interval calculations, with accounting for follow-up time. The cumulative incidence over time was

estimated with the use of Kaplan–Meier methods to evaluate the onset of vaccine efficacy and vaccine efficacy over time. Participants had their data censored at the end of their follow-up.

The frequency of serious adverse events was tabulated in the full analysis set. The frequency and severity of solicited and unsolicited adverse events were tabulated in the safety subpopulation.

RESULTS

PARTICIPANTS

The trial began enrollment on September 21, 2020, and the data-cutoff date for the present analysis was January 22, 2021. A total of 44,325 participants underwent randomization, of whom 43,783 received vaccine or placebo; the per-protocol population included 39,321 SARS-CoV-2–negative participants, of whom 19,630 received Ad26.COV2.S and 19,691 received placebo (Fig. S3). The demographic characteristics and coexisting conditions of the participants at baseline were balanced across the two groups (Tables 1 and S4). A total of 9.6% of the participants were SARS-CoV-2–seropositive at baseline. The median follow-up was 58 days (range, 1 to 124), and 55% of participants had at least 8 weeks of follow-up; later and slower recruitment of participants 60 years of age or older with coexisting conditions resulted in a shorter duration of follow-up in this subgroup (Table S5).

SAFETY

The safety subpopulation included 3356 participants in the vaccine group and 3380 in the placebo group. During the 7-day period after the administration of vaccine or placebo, more solicited adverse events were reported by Ad26.COV2.S recipients than by placebo recipients and by participants 18 to 59 years of age than by those 60 years of age or older (Fig. 1). In the vaccine group, injection-site pain was the most common local reaction (in 48.6% of the participants); the most common systemic reactions were headache (in 38.9%), fatigue (in 38.2%), myalgia (in 33.2%), and nausea (in 14.2%).

The adverse events of at least grade 3 that were considered by the investigators to be possibly related to Ad26.COV2.S or placebo are listed in Table S6. Serious adverse events, excluding those related to Covid-19, were reported by 83 of 21,895 vaccine recipients (0.4%) and by 96 of 21,888 placebo recipients (0.4%). Seven serious adverse events were considered by the investigators to be related to vaccination in the Ad26.COV2.S group (Table S7).

A numeric imbalance was observed for venous thromboembolic events (11 in the vaccine group vs. 3 in the placebo group). Most of these participants had underlying medical conditions and predisposing factors that might have contributed to these events (Table S8). Imbalances were also observed with regard to seizure (which occurred in 4 participants in the vaccine group vs. 1 in the placebo group) and tinnitus (in 6 vs. 0). A causal relationship between these events and Ad26.COV2.S cannot be determined. These events will be monitored in the post-marketing setting.

Three deaths were reported in the vaccine group and 16 in the placebo group, all of which were considered by the investigators to be unrelated to the trial intervention (Table S7). No deaths related to Covid-19 were reported in the vaccine group, whereas 5 deaths related to Covid-19 were reported in the placebo group. Transverse sinus thrombosis with cerebral hemorrhage and a case of the Guillain–Barré syndrome were each seen in 1 vaccine recipient.

EFFICACY

In the per-protocol at-risk population, 468 centrally confirmed cases of symptomatic Covid-19 with an onset at least 14 days after administration were observed, of which 464 were moderate to severe–critical (116 cases in the vaccine group vs. 348 in the placebo group), which indicated vaccine efficacy of 66.9% (adjusted 95% confidence interval [CI], 59.0 to 73.4) (Table 2). In terms of the primary end point of disease onset at least 28 days after administration, 66 cases of moderate to severe–critical Covid-19 in the vaccine group and 193 cases in the placebo group were observed, which indicated vaccine efficacy of 66.1% (adjusted 95% CI, 55.0 to 74.8) (Table 2).

The cumulative incidence of the first occurrence of moderate to severe–critical Covid-19 diverged between the two trial groups at approximately 14 days after the administration of vaccine or placebo, which indicates an early onset of protection with the vaccine (Fig. 2A). Fewer cases in the vaccine group were observed after day 14 while cases continued to accrue in the placebo group, which led to increasing vaccine efficacy over time (Fig. S4A). Efficacy against

Table 1. Characteristics of the Trial Participants at Baseline (Full Analysis Set).*

Characteristic	Ad26.COV2.S (N = 21,895)	Placebo (N = 21,888)	Total (N = 43,783)
Age			
Median (range) — yr	52 (18–100)	52 (18–94)	52 (18–100)
Distribution — no. (%)			
18–59 yr	14,564 (66.5)	14,547 (66.5)	29,111 (66.5)
≥60 yr	7,331 (33.5)	7,341 (33.5)	14,672 (33.5)
Sex — no. (%)			
Female	9,820 (44.9)	9,902 (45.2)	19,722 (45.0)
Male	12,071 (55.1)	11,982 (54.7)	24,053 (54.9)
Nonbinary	2 (<0.1)	4 (<0.1)	6 (<0.1)
Unknown	2 (<0.1)	0	2 (<0.1)
Race or ethnic group — no. (%)†			
American Indian or Alaskan Native	92 (0.4)	95 (0.4)	187 (0.4)
Indigenous South American	1,991 (9.1)	1,965 (9.0)	3,956 (9.0)
Asian	743 (3.4)	687 (3.1)	1,430 (3.3)
Black	4,251 (19.4)	4,264 (19.5)	8,515 (19.4)
Native Hawaiian or other Pacific Islander	58 (0.3)	48 (0.2)	106 (0.2)
White	12,858 (58.7)	12,838 (58.7)	25,696 (58.7)
Multiracial	1,204 (5.5)	1,245 (5.7)	2,449 (5.6)
Not reported, unknown, or missing	698 (3.2)	746 (3.4)	1,444 (3.3)
Hispanic ethnic group — no. (%)†			
Hispanic	9,874 (45.1)	9,963 (45.5)	19,837 (45.3)
Non-Hispanic	11,472 (52.4)	11,362 (51.9)	22,834 (52.2)
Not reported, unknown, or missing	549 (2.5)	563 (2.6)	1,112 (2.5)
Country or region — no. (%)			
Latin America	8,954 (40.9)	8,951 (40.9)	17,905 (40.9)
Argentina	1,498 (6.8)	1,498 (6.8)	2,996 (6.8)
Brazil	3,644 (16.6)	3,634 (16.6)	7,278 (16.6)
Chile	563 (2.6)	570 (2.6)	1,133 (2.6)
Colombia	2,125 (9.7)	2,123 (9.7)	4,248 (9.7)
Mexico	238 (1.1)	241 (1.1)	479 (1.1)
Peru	886 (4.0)	885 (4.0)	1,771 (4.0)
South Africa	3,286 (15.0)	3,290 (15.0)	6,576 (15.0)
United States	9,655 (44.1)	9,647 (44.1)	19,302 (44.1)
SARS-CoV-2 serostatus — no. (%)			
Positive	2,151 (9.8)	2,066 (9.4)	4,217 (9.6)
Negative	19,104 (87.3)	19,191 (87.7)	38,295 (87.5)
Missing	640 (2.9)	631 (2.9)	1,271 (2.9)
Body-mass index‡			
Median	27.0	27.0	27.0
≥30 — no./total no. (%)	6264/21,871 (28.6)	6217/21,853 (28.4)	12,481/43,724 (28.5)
≥1 Coexisting condition — no. (%)	8,936 (40.8)	8,922 (40.8)	17,858 (40.8)

* The full analysis set included all the participants who underwent randomization and received a dose of Ad26.COV2.S vaccine or placebo. Percentages may not total 100 because of rounding. SARS-CoV-2 denotes severe acute respiratory coronavirus 2.

† Race and ethnic group were reported by the participants. American Indian or Alaskan Native was reported only by participants residing in the United States.

‡ The body-mass index (BMI) is the weight in kilograms divided by the square of the height in meters. A BMI of 30 or higher indicates obesity.

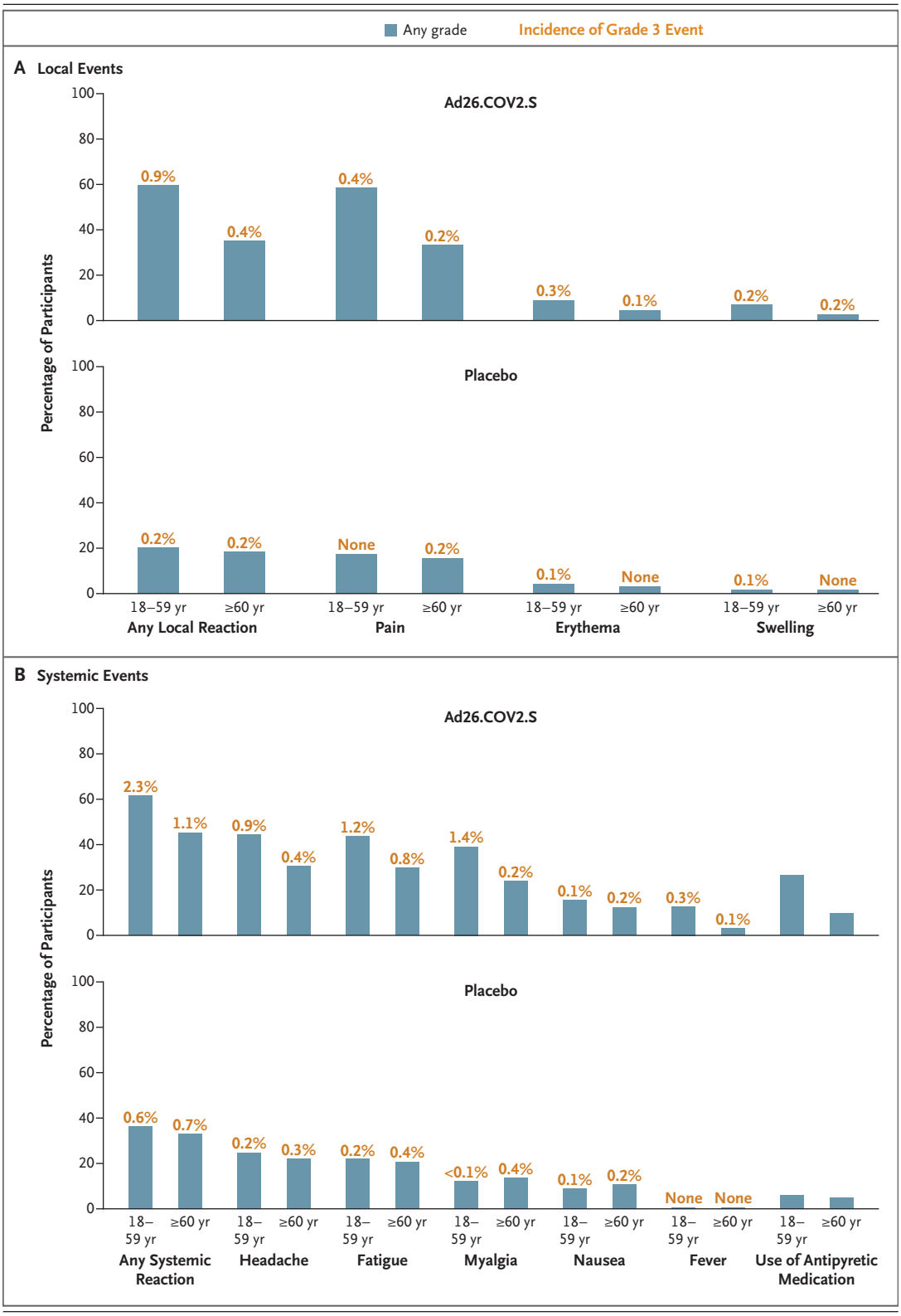

Any grade
Incidence of Grade 3 Event
A Local Events
Ad26.COV2.S
Placebo
Percentage of Participants
100
80
60
40
20
0
0.9%
0.4%
0.4%
0.2%
0.3%
0.1%
0.2%
0.2%
0.2%
0.2%
None
0.2%
0.1%
None
0.1%
None
18–59 yr
≥60 yr
Any Local Reaction
Pain
Erythema
Swelling
B Systemic Events
2.3%
1.1%
0.9%
0.4%
1.2%
0.8%
1.4%
0.2%
0.1%
0.2%
0.3%
0.1%
0.6%
0.7%
0.2%
0.3%
0.2%
0.4%
<0.1%
0.4%
0.1%
0.2%
None
None
18–59 yr
≥60 yr
Any Systemic Reaction
Headache
Fatigue
Myalgia
Nausea
Fever
Use of Antipyretic Medication

Figure 1 (facing page). Solicited Local and Systemic Adverse Events Reported within 7 days after the Administration of Vaccine or Placebo (Safety Subpopulation).

Most solicited local and systemic adverse events occurred within 1 to 2 days after the administration of vaccine or placebo and had a median duration of 1 to 2 days. No grade 4 local or systemic adverse events were reported. There were no local or systemic reactogenicity differences between participants who were seronegative at baseline and those who were seropositive (data not shown). Pain was categorized as grade 1 (mild; does not interfere with activity), grade 2 (moderate; requires modification of activity or involves discomfort with movement), grade 3 (severe; inability to perform usual activities), or grade 4 (potentially life-threatening; hospitalization or inability to perform basic self-care). Erythema and swelling were categorized as grade 1 (mild; 25 to 50 mm), grade 2 (moderate; 51 to 100 mm), grade 3 (severe; >100 mm), or grade 4 (potentially life-threatening; necrosis or leading to hospitalization). Systemic events were categorized as grade 1 (mild; minimal symptoms), grade 2 (moderate; notable symptoms not resulting in loss of work or school time), grade 3 (severe; incapacitating symptoms resulting in loss of work or school time), or grade 4 (life-threatening; hospitalization or inability to perform basic self-care). Fever was defined as grade 1 (mild; ≥38.0 to 38.4°C), grade 2 (moderate; ≥38.5 to 38.9°C), grade 3 (severe; ≥39.0 to 40.0°C), or grade 4 (potentially life-threatening; >40°C).

disease with an onset at least 28 days after administration was similar across age groups, but efficacy against disease with an onset 14 days after administration was higher among older participants than among younger participants (Table 2). This discrepancy probably resulted from differences in follow-up duration or from smaller sample sizes in subgroups. The number of primary end-point cases was similar to the number of cases of symptomatic Covid-19 as defined according to the FDA harmonized definition (Table 2); thus, the primary end-point analyses captured most of the cases of symptomatic Covid-19. Estimates of vaccine efficacy in the analyses of the two primary end points and the secondary end points of centrally confirmed cases differed by less than 2 percentage points from the estimates in analyses of positive cases from all sources, and the confidence intervals were similar (Tables 2 and 3). Vaccine-efficacy estimates in the full analysis set were generally lower than those in the per-protocol population because the estimates included cases that occurred at or after 1 day after administration, when immunity was building (Table S9).

With regard to severe–critical Covid-19, vaccine efficacy was 76.7% (adjusted 95% CI, 54.6 to 89.1) against disease with onset at least 14 days after administration and 85.4% (adjusted 95% CI, 54.2 to 96.9) against disease with onset at least 28 days after administration (Table 2). The cumulative-incidence curves began to separate approximately 7 days after administration; vaccine efficacy increased with longer follow-up and was 92.4% after day 42 (post hoc calculation) (Figs. 2B and S4B).

The analysis of vaccine efficacy against asymptomatic infection included all the participants with a newly positive N-immunoassay result at day 71 (i.e., those who had been seronegative or had no result available at day 29 and who were seropositive at day 71). Only 2650 participants had an N-immunoassay result available at day 71, and therefore only a preliminary analysis could be performed. A total of 18 asymptomatic infections were identified in the vaccine group and 50 in the placebo group (vaccine efficacy, 65.5%; 95% CI, 39.9 to 81.1).

Vaccine efficacy against Covid-19 involving medical intervention ranged from 75.0 to 100.0% (Table S10). Two cases of Covid-19 with onset at least 14 days after administration in the Ad26.COV2.S group and 29 such cases in the placebo group led to hospitalization (vaccine efficacy, 93.1%; 95% CI, 72.7 to 99.2) (Fig. S5). No hospitalizations for cases with an onset at least 28 days after administration occurred in the vaccine group, as compared with 16 hospitalizations in the placebo group (vaccine efficacy, 100%; 95% CI, 74.3 to 100.0).

Participants with moderate Covid-19 who had received Ad26.COV2.S most frequently reported 4 to 6 symptoms, as compared with 7 to 9 symptoms in participants who had received placebo (Fig. S6). The total mean symptom-severity score as reported on the Symptoms of Infection with Coronavirus-19 questionnaire was 24% (95% CI, –1 to 46) lower among vaccine recipients than among placebo recipients at day 1 after symptom onset, 47% (95% CI, 23 to 66) lower at day 7 after symptom onset, and 53% (95% CI, 0 to 81) lower at day 14 after symptom onset among partici-

Table 2. Vaccine Efficacy against Covid-19 with Onset at Least 14 Days and at Least 28 Days after the Administration of Vaccine or Placebo (Per-Protocol at-Risk Population).*

Variable	≥14 Days after Administration†					≥28 Days after Administration‡				
	Ad26.COV2.S (N=19,514)		Placebo (N=19,544)		Vaccine Efficacy (95% CI)	Ad26.COV2.S (N=19,306)		Placebo (N=19,178)		Vaccine Efficacy (95% CI)
	no. of cases	*person-yr*	*no. of cases*	*person-yr*	%	*no. of cases*	*person-yr*	*no of cases*	*person-yr*	%
Moderate to severe–critical Covid-19	116	3116.6	348	3096.1	66.9 (59.0–73.4)	66	3102.0	193	3070.7	66.1 (55.0–74.8)
18–59 yr	95	2106.8	260	2095.0	63.7 (53.9–71.6)	52	2097.6	152	2077.0	66.1 (53.3–75.8)
≥60 yr	21	1009.8	88	1001.2	76.3 (61.6–86.0)	14	1004.4	41	993.6	66.2 (36.7–83.0)
Symptomatic Covid-19 of any severity	117	3116.5	351	3095.9	66.9 (59.1–73.4)	66	3102.0	195	3070.5	66.5 (55.5–75.1)
Mild	1	3116.5	3	3095.9	NC§	0	3102.0	2	3070.5	NC§
Moderate	102	3116.6	288	3096.1	64.8 (55.8–72.2)	61	3102.0	159	3070.7	62.0 (48.7–72.2)
Severe–critical	14	3125.1	60	3122.0	76.7 (54.6–89.1)	5	3106.2	34	3082.6	85.4 (54.2–96.9)
Severity-adjusted symptomatic Covid-19¶	117	3116.5	351	3095.9	68.1 (60.3–74.3)	66	3102.0	195	3070.5	69.0 (56.7–77.6)
18–59 yr	95	2106.8	260	2095.0	65.8 (56.2–73.1)	52	2097.6	152	2077.0	69.3 (57.4–77.7)
≥60 yr	22	1009.6	91	1001.0	74.5 (57.9–84.3)	14	1004.4	43	993.5	67.9 (38.2–82.8)
Moderate to severe–critical Covid-19, including noncentrally confirmed cases	173	3113.9	509	3089.1	66.3 (59.9–71.8)	113	3100.3	324	3065.9	65.5 (57.2–72.4)
Covid-19, according to FDA harmonized definition‖	114	3116.6	345	3,096.3	67.2 (59.3–73.7)	65	3102.0	193	3070.6	66.7 (55.6–75.2)
Moderate to severe–critical Covid-19, according to Cox proportional-hazards model**	116	3116.6	348	3,096.1	66.9 (59.1–73.2)	66	3102.0	193	3070.7	66.2 (55.3–74.4)

* All cases of coronavirus disease 2019 (Covid-19) were centrally confirmed unless stated otherwise and occurred in participants who had been seronegative at baseline and negative on reverse-transcriptase–polymerase-chain-reaction (RT-PCR) testing before 14 or 28 days after the administration of vaccine or placebo, for the respective end points, and were therefore at risk for Covid-19. The follow-up time for each participant was defined as the time from the administration of vaccine or placebo to the onset of Covid-19 or the last available trial measurement (January 22, 2021). Adjusted 95% confidence intervals are shown for moderate and severe–critical Covid-19, severe–critical Covid-19, severity-adjusted Covid-19, and moderate to severe–critical Covid-19, including non–centrally confirmed cases; unadjusted 95% confidence intervals are shown for other end points. The adjusted confidence interval was calculated with implementation of type I error control for multiple testing. Adjusted confidence intervals are presented for the end points that were prespecified for inferential evaluation at the primary analysis and on reaching the associated minimal required number of cases for that end point. Mild cases of Covid-19 were defined as a positive result on RT-PCR testing and the presence of at least one of the following symptoms: fever (body temperature, ≥38.0°C), sore throat, malaise, headache, myalgia, gastrointestinal symptoms,

cough, chest congestion, runny nose, wheezing, skin rash, eye irritation or discharge, chills, loss of taste or smell, red or bruised looking feet or toes, or shaking chills or rigors. Moderate cases were defined as a positive RT-PCR test and either the presence of at least two of the following symptoms: fever (≥38.0°C), heart rate of at least 90 beats per minute, shaking chills or rigors, sore throat, cough, malaise, headache, myalgia, gastrointestinal symptoms, loss of taste or smell, or red or bruised-looking feet or toes; or the presence at least one of the following symptoms: respiratory rate of at least 20 breaths per minute, abnormal oxygen saturation (but >93% while the patient was breathing ambient air at sea level), clinical or radiologic evidence of pneumonia, radiologic evidence of deep-vein thrombosis, or shortness of breath or difficulty breathing. Severe–critical cases were defined as a positive RT-PCR test and the presence of at least one of the following features: clinical signs at rest that were indicative of severe systemic illness (respiratory rate of ≥30 breaths per minute, heart rate of ≥125 beats per minute, oxygen saturation of ≤93% while the patient was breathing ambient air at sea level, or partial pressure of oxygen divided by the fraction of inspired oxygen, <300 mm Hg); respiratory failure (defined as the use of high-flow oxygen, noninvasive ventilation, mechanical ventilation, or extracorporeal membrane oxygenation); shock; clinically meaningful acute renal, hepatic, or neurologic dysfunction; intensive care unit admission; or death.

† The at-risk population for this analysis excluded participants who were RT-PCR–positive between days 1 and 14 after the administration of vaccine or placebo.

‡ The at-risk population for this analysis excluded participants who were RT-PCR–positive between days 1 and 28 after the administration of vaccine or placebo.

§ The vaccine efficacy was not calculated (NC) if fewer than 6 cases were observed for an end point.

¶ Shown is the weighted version of the estimates of vaccine efficacy against mild, moderate, and severe–critical Covid-19.[18]

‖ The Food and Drug Administration (FDA) harmonized definition of Covid-19 was defined as a positive RT-PCR test and the presence of Covid-19 symptoms consistent with the FDA harmonized definition at the time that the protocol was written: fever or chills, cough, shortness of breath or difficulty breathing, fatigue, muscle or body aches, headache, new loss of taste or smell, sore throat, congestion or runny nose, nausea or vomiting, or diarrhea.

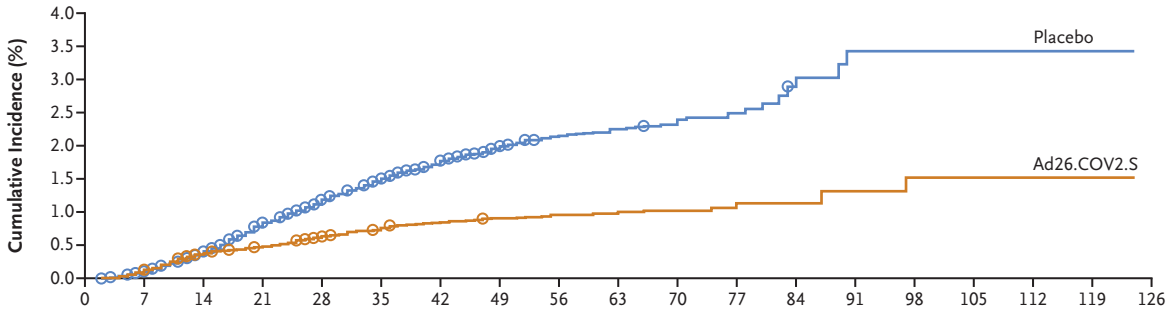
** A supportive analysis with the use of a Cox proportional-hazards regression model of the time to moderate to severe–critical Covid-19 was used to estimate vaccine efficacy.

pants with an onset of moderate illness at least 28 days after administration (Fig. S1).

The estimates of vaccine efficacy against severe–critical disease were consistently high across countries that had sufficient cases for analysis (Table 3). On the basis of interim sequencing data from 512 unique RT-PCR–positive samples obtained from 714 participants (71.7%) with SARS-CoV-2 infection, the reference sequence (Wuhan-Hu-1 including the D614G mutation) was detected predominantly in the United States (190 of 197 sequences [96.4%]) and the 20H/501Y.V2 variant (also called B.1.351) was detected predominantly in South Africa (86 of 91 sequences [94.5%]), whereas in Brazil, the reference sequence was detected in 38 of 124 sequences (30.6%) and the reference sequence with the E484K mutation (P.2 lineage) was detected in 86 of 124 sequences (69.4%). Despite the high prevalence of the 20H/501Y.V2 variant in South Africa and in Covid-19 cases in the trial, vaccine efficacy was maintained (52.0% against moderate to severe–critical disease and 73.1% against severe–critical disease with onset ≥14 days after administration; 64.0% against moderate to severe–critical disease and 81.7% against severe–critical disease with onset at ≥28 days after administration) (Fig. 2C and Table 3). In South Africa, no hospitalizations of participants with an onset of Covid-19 at least 28 days after administration occurred in the vaccine group, as compared with 6 hospitalizations in the placebo group. All five Covid-19–related deaths in the trial occurred in the placebo group in South Africa.

No meaningful differences in vaccine efficacy were observed among subgroups defined according to sex, race, or ethnic group (Fig. S7 and Table S11). A lower point estimate of vaccine efficacy was observed among participants 60 years of age or older with coexisting conditions in the analysis of cases with onset at least 28 days after administration (15 cases of moderate to severe–critical Covid-19 among vaccine recipients vs. 26 cases among placebo recipients) but not in the analysis of cases with onset at least 14 days after administration (22 vs. 63 cases) (Fig. S7). Estimates of efficacy over time that were based on Kaplan–Meier analysis were similar among participants 60 years of age or older with coexisting conditions and those without coexisting conditions (Figs. S4C and S8). Two participants 60 years of age or older with coexisting conditions in the

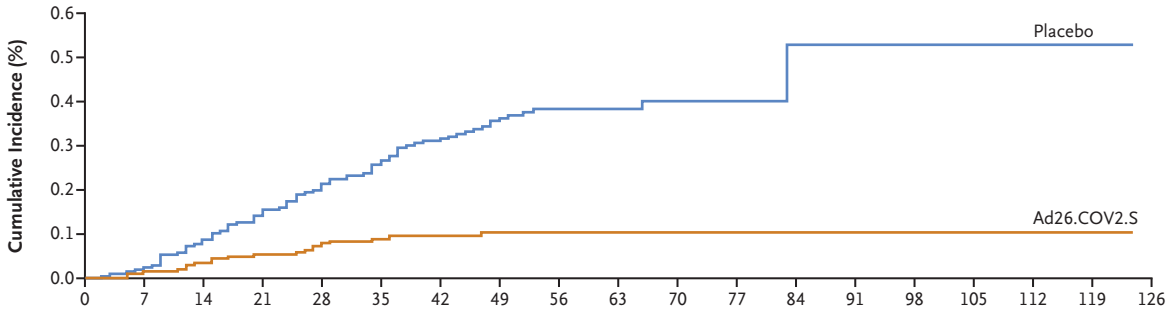
A Moderate to Severe–Critical Cases of Covid-19



No. at Risk																			
Placebo	19,822	19,804	19,745	19,652	19,579	19,488	18,411	14,814	10,823	7740	3876	1439	708	485	482	480	133	27	0
Ad26.COV2.S	19,744	19,725	19,669	19,642	19,612	19,578	18,541	14,909	10,930	7831	3998	1468	713	484	483	482	142	31	0

No. of Cases																			
Placebo	0	22	81	168	237	299	351	387	407	416	423	425	430	432	432	432	432	432	432
Ad26.COV2.S	0	27	76	96	126	151	168	178	184	188	189	191	191	192	193	193	193	193	193

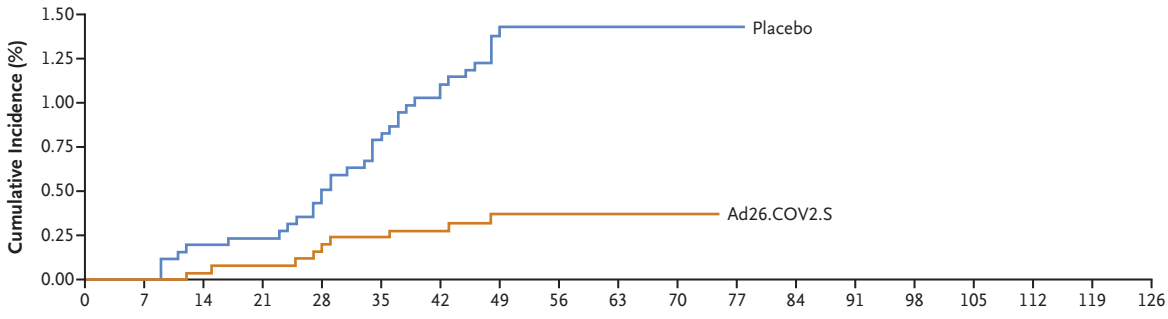
B Severe–Critical Cases of Covid-19



No. at Risk																			
Placebo	19,822	19,817	19,799	19,779	19,760	19,725	18,682	15,088	11,069	7939	3995	1485	732	500	497	495	137	29	0
Ad26.COV2.S	19,744	19,741	19,734	19,725	19,718	19,705	18,685	15,043	11,046	7919	4039	1481	720	490	490	489	146	31	0

No. of Cases																			
Placebo	0	5	18	32	44	55	65	73	76	76	77	77	78	78	78	78	78	78	78
Ad26.COV2.S	0	3	7	11	16	18	20	21	21	21	21	21	21	21	21	21	21	21	21

C Severe–Critical Cases of Covid-19 in South Africa



No. at Risk																			
Placebo	2536	2536	2531	2528	2521	2510	2502	1963	1283	712	143	2	0	0	0	0	0	0	0
Ad26.COV2.S	2504	2504	2503	2501	2497	2495	2494	1941	1284	694	157	0	0	0	0	0	0	0	0

No. of Cases																			
Placebo	0	0	5	6	13	21	28	35	35	35	35	35	35	35	35	35	35	35	35
Ad26.COV2.S	0	0	1	2	5	6	7	9	9	9	9	9	9	9	9	9	9	9	9

Figure 2 (facing page). Cumulative Incidence of Covid-19 with Onset at Least 1 Day after Vaccination and Vaccine Efficacy over Time.

Panel A shows the cumulative incidence of moderate to severe–critical cases of coronavirus disease 2019 (Covid-19); circles indicate severe–critical cases. Panel B shows the cumulative incidence of severe–critical cases. Cases included in the analyses in Panels A and B were centrally confirmed cases in the full analysis set among participants who were seronegative at baseline. Panel C shows the cumulative incidence of severe–critical cases in South Africa among participants who were seronegative at baseline; these cases were those that were positive on reverse-transcriptase–polymerase-chain-reaction (RT-PCR) testing from all sources, whether centrally confirmed or not.

vaccine group were hospitalized, as compared with 11 such participants in the placebo group (vaccine efficacy, 81.6%; 95% CI, 15.8 to 98.0).

DISCUSSION

This international, phase 3 ENSEMBLE trial showed the efficacy of a single dose of the Ad26.COV2.S vaccine in preventing Covid-19. Efficacy against moderate to severe–critical Covid-19 was 67% against disease with onset at least 14 days after administration and 66% against disease with onset 28 days after administration. Because the number of primary end-point cases was similar to the number of cases according to the FDA harmonized definition, this estimate essentially captures most of the cases of symptomatic Covid-19. Higher efficacy against severe–critical Covid-19 was observed, with vaccine efficacy of 77% against disease with onset at least 14 days after administration and 85% against disease with onset at least 28 days after administration.

The onset of efficacy was evident as of 14 days after administration for moderate to severe–critical disease and as of 7 days after administration for severe–critical disease. Efficacy continued to increase through approximately 8 weeks after administration, especially for severe–critical Covid-19. No evidence of waning efficacy was noted among the approximately 3000 participants who were followed for 11 weeks or among 1000 participants who were followed for 15 weeks, a finding that is consistent with the persistence of humoral immunity that was observed in a phase 1–2a trial.[9]

Efficacy against severe–critical Covid-19 was consistently high overall and in individual countries that had sufficient cases for analysis, which is particularly important because severe disease has the greatest effect on individual persons and health care systems.[19] Efficacy against Covid-19 involving hospitalization was 93% with regard to onset at least 14 days after administration (2 cases in the vaccine group and 29 in the placebo group) and 100% with regard to onset at least 28 days after administration (no hospitalizations in the vaccine group and 16 in the placebo group). Although hospitalization can be influenced by local practice and resource availability, all the hospitalizations that were reported were justified by clear clinical findings and were consistent across countries. Moreover, identical management practices would have applied to the Ad26.COV2.S group and the placebo group in each country. Five deaths that were related to Covid-19 occurred in the placebo group, but there were no such deaths in the vaccine group. The reduction in the incidence of death and the high efficacy against hospitalization are expected to substantially reduce the effect of this disease on individual persons and dramatically decrease the burden on health care systems.

Vaccine recipients with breakthrough Covid-19 reported fewer and less severe symptoms than did placebo recipients with Covid-19, which suggests that illness is milder after vaccination. The data are consistent with studies reporting higher efficacy of the influenza vaccine against more severe influenza[20-22] and the attenuation of influenza among vaccinees.[23-25] A preliminary analysis indicated that Ad26.COV2.S provided at least 66% protection against serologically confirmed asymptomatic infection with SARS-CoV-2. The effect on the incidence of symptomatic and asymptomatic SARS-CoV-2 infection by the vaccine suggests that it might be useful in reducing community-wide transmission.

New SARS-CoV-2 virus lineages have emerged, with mutations in the N-terminal and receptor-binding domains of the spike protein that are known targets for neutralizing antibodies; in particular, the E484K mutation is associated with reduced neutralization sensitivity.[26-31] Of main concern are variants that were first identified in Brazil, South Africa, and the United Kingdom.[2-4] In our trial, 95% of the Covid-19 cases in South Africa in which SARS-CoV-2 was sequenced were caused by the 20H/501Y.V2 variant, whereas a

Table 3. Vaccine Efficacy against Covid-19 with Onset at Least 14 Days and at Least 28 Days after Administration of Vaccine or Placebo, According to Country (Per-Protocol at-Risk Population).*

Variable	≥14 Days after Administration†					≥28 Days after Administration‡				
	Ad26.COV2.S		Placebo		Vaccine Efficacy (95% CI)	Ad26.COV2.S		Placebo		Vaccine Efficacy (95% CI)
	no.	*person-yr*	*no.*	*person-yr*	%	*no.*	*person-yr*	*no.*	*person-yr*	%
Worldwide										
No. of participants	19,514		19,544			19,306		19,178		
Moderate to severe–critical Covid-19	173	3113.9	509	3089.1	66.3 (59.9 to 71.8)	113	3100.3	324	3065.9	65.5 (57.2 to 72.4)
Severe–critical Covid-19	19	3124.7	80	3121.0	76.3 (57.9 to 87.5)	8	3106.0	48	3082.0	83.5 (54.2 to 96.9)
United States										
No. of participants	9,119		9,086			8,958		8,835		
Moderate to severe–critical Covid-19	51	1414.0	196	1391.3	74.4 (65.0 to 81.6)	32	1403.4	112	1375.6	72.0 (58.2 to 81.7)
Severe–critical Covid-19	4	1417.2	18	1404.8	78.0 (33.1 to 94.6)	1	1405.2	7	1382.2	85.9 (–9.4 to 99.7)
Brazil										
No. of participants	3,370		3,355			3,354		3,312		
Moderate to severe–critical Covid-19	39	555.7	114	548.8	66.2 (51.0 to 77.1)	24	554.8	74	546.1	68.1 (48.8 to 80.7)
Severe–critical Covid-19	2	558.9	11	556.8	81.9 (17.0 to 98.1)	1	556.2	8	549.8	87.6 (7.8 to 99.7)
South Africa										
No. of participants	2,473		2,496			2,449		2,463		
Moderate to severe–critical Covid-19	43	377.6	90	379.2	52.0 (30.3 to 67.4)	23	376.1	64	376.9	64.0 (41.2 to 78.7)
Severe–critical Covid-19	8	380.2	30	382.9	73.1 (40.0 to 89.4)	4	377.0	22	379.0	81.7 (46.2 to 95.4)

* All cases of Covid-19 occurred in participants who had been seronegative at baseline and RT-PCR–negative before 14 or 28 days after the administration of vaccine or placebo, for the respective end points, and were therefore at risk for Covid-19; these participants were positive on RT-PCR testing from all sources. Adjusted 95% confidence intervals are shown for Covid-19 cases worldwide; unadjusted 95% confidence intervals are shown for country-specific end points. The adjusted confidence interval implements type I error control for multiple testing.

† The at-risk population for this analysis excluded participants who were RT-PCR–positive between days 1 and 14 after the administration of vaccine or placebo.

‡ The at-risk population for this analysis excluded participants who were RT-PCR–positive between days 1 and 28 after the administration of vaccine or placebo.

variant from the P.2 lineage carrying the E484K mutation was identified in 69% of the cases in Brazil with a sequenced sample. However, despite the high prevalence of SARS-CoV-2 variants of concern, vaccine efficacy remained high. This finding shows that a Covid-19 vaccine that was based on the original Wuhan-Hu-1 strain can elicit cross-protective efficacy against new variants in South Africa and Brazil. Nonneutralizing antibodies against SARS-CoV-2 variants are probably preserved because they are not limited to the N-terminal or receptor-binding domains, where most mutations occur. Antibodies with Fc-mediated functions are induced by Ad26.COV2.S against SARS-CoV-2 in humans,[32] and these Fc functional antibodies show no decrease in potency against new variants (personal communication: G. Alter and D. Barouch). In addition, CD8+ T-cell responses to the SARS-CoV-2 spike protein were seen in a phase 1–2a trial.[9] T-cell epitopes were shown to be conserved between SARS-CoV-2 variants according to immunoinformatics analyses.[33-35] These factors might contribute to the high efficacy against severe–critical disease, hospitalization, and death in South Africa, where the relatively neutralization-resistant 20H/501Y.V2 variant predominates.[26,36]

Efficacy against symptomatic infection was similar among younger and older participants and among participants with coexisting conditions and those without coexisting conditions. A subgroup analysis involving participants 60 years of age or older showed that vaccine efficacy against symptomatic disease with onset at least 14 days after administration was similar in subgroups defined according to the presence or absence of coexisting conditions. With regard to onset at least 28 days after administration, vaccine efficacy appeared lower among participants with coexisting conditions than among those without coexisting conditions. This finding can be attributed to imprecision owing to fewer cases and shorter follow-up in this subgroup. Furthermore, Kaplan–Meier curves indicated that the cumulative incidence of cases among vaccine recipients 60 years of age or older with coexisting conditions was similar to that in the overall trial population, which suggests a similar vaccine efficacy. Vaccine efficacy against hospitalization among vaccine recipients 60 years of age or older with coexisting conditions was 82%, a finding consistent with this result.

This trial confirmed the findings from a phase 1–2a trial[9] showing that Ad26.COV2.S had an acceptable safety and reactogenicity profile. Reactogenicity to Ad26.COV2.S was transient, was lower in older participants than in younger participants, and resolved quickly. Severe reactogenicity (grade ≥3) was uncommon, and serious adverse events were rare. Data from the current trial are supported by long-term and robust safety data on the Ad26 platform.[10-12]

A key strength of this trial is that it showed vaccine efficacy in an ethnically and geographically diverse population, including participants in regions with emerging SARS-CoV-2 variants, as well as in participants with coexisting conditions that have been associated with an increased risk of severe Covid-19. A limitation of the trial is the relatively short follow-up, which was necessitated, as in other Covid-19 vaccine trials, by the urgent need for vaccine. The data do not suggest a waning of protection. Long-term unblinded follow-up is planned to compare results in initial Ad26.COV2.S recipients with those in placebo recipients who are expected to receive Ad26.COV2.S after a protocol amendment has been approved.

This trial was conducted during a time of an extraordinarily high incidence of SARS-CoV-2 infection. Lower vaccine efficacy has been associated with a higher incidence of disease.[37-39] This situation, combined with the emergence of viral variants, precludes the comparison of vaccine trials. In this trial, we robustly field-tested a simple regimen under high attack-rate conditions on three continents and consistently found early and increasing protection from severe disease.

In this trial, we found that a single dose of Ad26.COV2.S protected against symptomatic Covid-19 and was particularly efficacious against severe–critical disease (including hospitalization and death), including in countries where variants that are considered to be relatively resistant to antibody neutralization predominate. Safety appeared to be similar to that seen in previous phase 3 trials of Covid-19 vaccines. The single-dose schedule and favorable storage conditions of this vaccine provide major advantages in its deployment and effect worldwide.

Supported by Janssen Research and Development, an affiliate of Janssen Vaccines and Prevention and part of the Janssen pharmaceutical companies of Johnson & Johnson, and in whole or in part by federal funds from the Office of the Assistant Secretary for Preparedness and Response, Biomedical Advanced Research

and Development Authority, under Other Transaction Agreement HHSO100201700018C, and from the National Institute of Allergy and Infectious Diseases (NIAID), National Institutes of Health. The NIAID provides grant funding to the HIV Vaccine Trials Network (HVTN) Leadership and Operations Center (UM1 AI68614), the HVTN Statistics and Data Management Center (UM1 AI68635), the HVTN Laboratory Center (UM1 AI68618), the HIV Prevention Trials Network Leadership and Operations Center (UM1 AI68619), the AIDS Clinical Trials Group Leadership and Operations Center (UM1 AI68636), the Infectious Diseases Clinical Research Consortium Leadership Group (UM1 AI148684), and Vaccine and Therapeutic Evaluation Units (UM1 AI148576, UM1 AI148373, UM1 AI148685, and UM1 AI148452).

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

A data sharing statement provided by the authors is available with the full text of this article at NEJM.org.

We thank all the participants in this trial, the staff members at the trial locations, the members of the data and safety monitoring board, all the investigators at the clinical sites, the COV3001 study team (Richard Gorman, Carmen A. Paez, Edith Swann, James Kublin, Simbarashe G. Takuva, Alex Greninger, Pavitra Roychoudhury, Robert W. Coombs, Keith R. Jerome, Flora Castellino, Xiaomi Tong, Corrina Pavetto, Teletha Gipson, Tina Tong, Marina Lee, James Zhou, Michael Fay, Kelly McQuarrie, Chimeremma Nnadi, Obiageli Sogbetun, Nina Ahmad, Ian De Proost, Cyrus Hoseyni, Paul Coplan, Najat Khan, Peter Ronco, Dawn Furey, Jodi Meck, Johan Vingerhoets, Boerries Brandenburg, Jerome Custers, Jenny Hendriks, Jarek Juraszek, Marit de Groot, Griet Van Roey, Dirk Heerwegh, and Ilse Van Dromme), and Mary L. Greenacre (An Sgriobhadair) and Jill E. Kolesar and Kurt Kunz (Cello Health Communications–MedErgy) for writing and editorial assistance, funded by Janssen Global Services, with an earlier version of the manuscript.

APPENDIX

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ORIGINAL ARTICLE

Final Analysis of Efficacy and Safety of Single-Dose Ad26.COV2.S

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ABSTRACT

BACKGROUND

The Ad26.COV2.S vaccine was highly effective against severe–critical coronavirus disease 2019 (Covid-19), hospitalization, and death in the primary phase 3 efficacy analysis.

METHODS

We conducted the final analysis in the double-blind phase of our multinational, randomized, placebo-controlled trial, in which adults were assigned in a 1:1 ratio to receive single-dose Ad26.COV2.S (5×10^{10} viral particles) or placebo. The primary end points were vaccine efficacy against moderate to severe–critical Covid-19 with onset at least 14 days after administration and at least 28 days after administration in the per-protocol population. Safety and key secondary and exploratory end points were also assessed.

RESULTS

Median follow-up in this analysis was 4 months; 8940 participants had at least 6 months of follow-up. In the per-protocol population (39,185 participants), vaccine efficacy against moderate to severe–critical Covid-19 at least 14 days after administration was 56.3% (95% confidence interval [CI], 51.3 to 60.8; 484 cases in the vaccine group vs. 1067 in the placebo group); at least 28 days after administration, vaccine efficacy was 52.9% (95% CI, 47.1 to 58.1; 433 cases in the vaccine group vs. 883 in the placebo group). Efficacy in the United States, primarily against the reference strain (B.1.D614G) and the B.1.1.7 (alpha) variant, was 69.7% (95% CI, 60.7 to 76.9); efficacy was reduced elsewhere against the P.1 (gamma), C.37 (lambda), and B.1.621 (mu) variants. Efficacy was 74.6% (95% CI, 64.7 to 82.1) against severe–critical Covid-19 (with only 4 severe–critical cases caused by the B.1.617.2 [delta] variant), 75.6% (95% CI, 54.3 to 88.0) against Covid-19 leading to medical intervention (including hospitalization), and 82.8% (95% CI, 40.5 to 96.8) against Covid-19–related death, with protection lasting 6 months or longer. Efficacy against any severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection was 41.7% (95% CI, 36.3 to 46.7). Ad26.COV2.S was associated with mainly mild-to-moderate adverse events, and no new safety concerns were identified.

CONCLUSIONS

A single dose of Ad26.COV2.S provided 52.9% protection against moderate to severe–critical Covid-19. Protection varied according to variant; higher protection was observed against severe Covid-19, medical intervention, and death than against other end points and lasted for 6 months or longer. (Funded by Janssen Research and Development and others; ENSEMBLE ClinicalTrials.gov number, NCT04505722.)

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*The members of the ENSEMBLE Study Group are listed in the Supplementary Appendix, available at NEJM.org.

This article was published on February 9, 2022, at NEJM.org.

DOI: 10.1056/NEJMoa2117608

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The Ad26.COV2.S vaccine (Johnson & Johnson–Janssen) is a recombinant, replication-incompetent human adenovirus type 26 (Ad26) vector encoding a full-length, membrane-bound severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) spike protein in a prefusion stabilized conformation.[1,2] Primary analysis of the phase 3 ENSEMBLE trial, performed when preset criteria had been met and conducted during the early emergence of variants and for a median follow-up of 58 days, showed 66.9% efficacy against moderate to severe–critical (i.e., severe or critical) coronavirus disease 2019 (Covid-19) and greater than 85% efficacy against severe–critical disease.[3] Here, we report the final analysis of the double-blind phase of ENSEMBLE, which was conducted in accordance with the protocol when data for more than 90% of the participants had been unblinded.

Methods

Trial Design and Oversight

We have reached the stage in this ongoing multinational, randomized, double-blind, placebo-controlled, phase 3 trial at which crossover vaccination of the participants in the control group has occurred. The trial was designed and conducted and the data were analyzed and interpreted by the sponsor (Janssen Research and Development) and collaborators (see the Supplementary Methods section in the Supplementary Appendix, available with the full text of this article at NEJM.org). The trial-site investigators collected and contributed to the interpretation of the data. All the data were available to the authors, who vouch for the accuracy and completeness of the data and for the fidelity of the trial to the protocol, available at NEJM.org. Medical writers funded by the sponsor assisted in drafting the manuscript.

Trial Participants

Participants were adults who were 18 years of age or older and were in good or stable health, without coexisting conditions or with stable and well-controlled coexisting conditions. Key exclusion criteria were previous receipt of a Covid-19 vaccine or abnormal immune system function (see the Supplementary Methods section). After emergency use authorization, participants who received placebo during the double-blind phase became eligible for vaccination with Ad26.COV2.S (crossover vaccination), provided they had not received another Covid-19 vaccine outside the trial. This crossover shortened the follow-up time in the projected double-blind phase of the trial.

Procedures

Trial procedures are described in the Supplementary Methods section. Participants were randomly assigned in a 1:1 ratio with the use of randomly permuted blocks in an interactive Web-response system to receive Ad26.COV2.S (5×10^{10} viral particles) or saline placebo as an intramuscular injection (0.5 ml). The investigators at the trial sites and the participants remained unaware of the group assignments until the unblinding or crossover visit.

Primary and key secondary efficacy evaluations were based on centrally confirmed Covid-19 cases (confirmed molecularly with the use of m-2000 SARS-CoV-2 real-time reverse-transcriptase polymerase chain reaction [RT-PCR], Abbott); cases were clinically assessed independently by a clinical severity adjudication committee. Participants responded to a twice-weekly questionnaire assessing whether they had Covid-19 symptoms, which were reported with the use of the electronic Symptoms of Infection with Coronavirus-19 questionnaire. Additional details are provided in the Supplementary Methods section.

Efficacy Assessments

The two primary end points were vaccine efficacy against the first occurrence of centrally RT-PCR–confirmed moderate to severe–critical Covid-19 with onset at least 14 days after administration and at least 28 days after administration in the per-protocol population (Table S1 in the Supplementary Appendix). Covid-19 case definitions and protocol-defined secondary and exploratory end points (e.g., efficacy according to SARS-CoV-2 lineage) are provided in the Supplementary Methods.

Safety Assessments

Serious adverse events and suspected adverse events of special interest are recorded throughout the trial. During the double-blind phase of the trial, a safety subpopulation that included approximately 6000 participants recorded solicited local and systemic adverse events in an electronic diary for 7 days after administration and unso-

licited adverse events for 28 days after administration.

STATISTICAL ANALYSIS

The full analysis population included all the participants who underwent randomization and received a dose of trial vaccine or placebo. The at-risk population excluded participants who had a Covid-19 case with an onset before day 15 or before day 29 for the vaccine efficacy evaluations at least 14 days after administration or at least 28 days after administration, respectively. Efficacy analyses were conducted in the per-protocol population, which included participants who received vaccine or placebo in the double-blind phase; participants who were seropositive or RT-PCR–positive at baseline were excluded from the per-protocol population. Safety analyses were conducted with the full analysis population. Participant data were censored on unblinding or receipt of a Covid-19 vaccine outside the trial.

Statistical hypothesis testing was conducted in accordance with the prespecified scheme for the control of familywise type I error as indicated with adjusted 95% confidence intervals. End points that had already been inferentially evaluated in the primary analysis were summarized descriptively with 95% confidence intervals. Other prespecified end points not included in the prespecified scheme for familywise type I error control (such as exploratory end points) are summarized with descriptive 95% confidence intervals. Nonprespecified end points are designated as post hoc. Exact Poisson regression was used for analyses of efficacy and associated calculations of confidence intervals.[4] Cumulative incidence was estimated with Kaplan–Meier methods to evaluate time to the first occurrence of Covid-19 and vaccine efficacy over time.

The frequency of serious adverse events was tabulated for the full analysis population; the frequency and severity of solicited and unsolicited adverse events were tabulated in the safety subpopulation.

RESULTS

PARTICIPANTS

Trial enrollment began on September 21, 2020, and the data cutoff for the final analysis was July 9, 2021, with the end of the double-blind period varying among countries. Table S2 shows case numbers in each country according to viral lineage, and Figure 1 shows the detection of viral lineages over time according to country. Emergency use authorization for Ad26.COV2.S occurred on February 27, 2021; crossover began after approval of protocol amendment 4, with the first participant in the placebo group vaccinated on March 10, 2021. The characteristics of the participants at baseline were balanced between trial groups (Table S3) and were generally representative of the population at risk for Covid-19 in the United States (Table S4). Worldwide, 19.5% of the participants in the trial were 65 years of age or older, and 42.0% had coexisting conditions.

In total, 43,788 participants underwent randomization and received vaccine or placebo, and 39,185 participants who were seronegative for SARS-CoV-2 at baseline were included in the per-protocol analysis population for the double-blind phase (Fig. S1). At the time of the final analysis, 97% of the participants had completed the double-blind phase or had withdrawn prematurely. Median follow-up was 121 days (range, 1 to 284), and 35,788 (91.3%) and 8940 (22.8%) of the participants in the per-protocol population had follow-up of at least 2 months and at least 6 months, respectively, in the double-blind phase. Follow-up was nearly identical in the full analysis population (median, 123 days [range, 0 to 284]; 40,260 [91.9%] and 11,290 [25.8%] of the participants had follow-up of ≥2 months and ≥6 months, respectively).

EFFICACY AGAINST MODERATE TO SEVERE–CRITICAL COVID-19

In the per-protocol at-risk population, 484 moderate to severe–critical Covid-19 cases with onset at least 14 days after administration were noted in the vaccine group, as compared with 1067 in the placebo group (vaccine efficacy, 56.3%; 95% confidence interval [CI], 51.3 to 60.8) (Table 1). Vaccine efficacy against moderate to severe–critical Covid-19 with onset at least 28 days after administration was 52.9% (95% CI, 47.1 to 58.1). The primary end point captured most symptomatic disease with onset at least 28 days after administration, with only 10 cases of mild Covid-19 occurring in the vaccine group and 12 in the placebo group, resulting in efficacy of 52.4% (95% CI, 46.6 to 57.6) against any symptomatic infection.

The Kaplan–Meier cumulative incidence curves

for moderate to severe–critical Covid-19 separated after 14 days (Fig. 2A); vaccine efficacy persisted through approximately 6 to 7 months after administration with a modest decline, after which wide confidence intervals and low numbers of at-risk participants preclude interpretation (Fig. 2B). This apparent reduction in efficacy may be related to the emergence of more neutralization-resistant variants toward the end of the trial (Fig. 1), as evidenced by the absence of a decline in efficacy against minor, "other" viral sequences (i.e., SARS-CoV-2 with substitu-

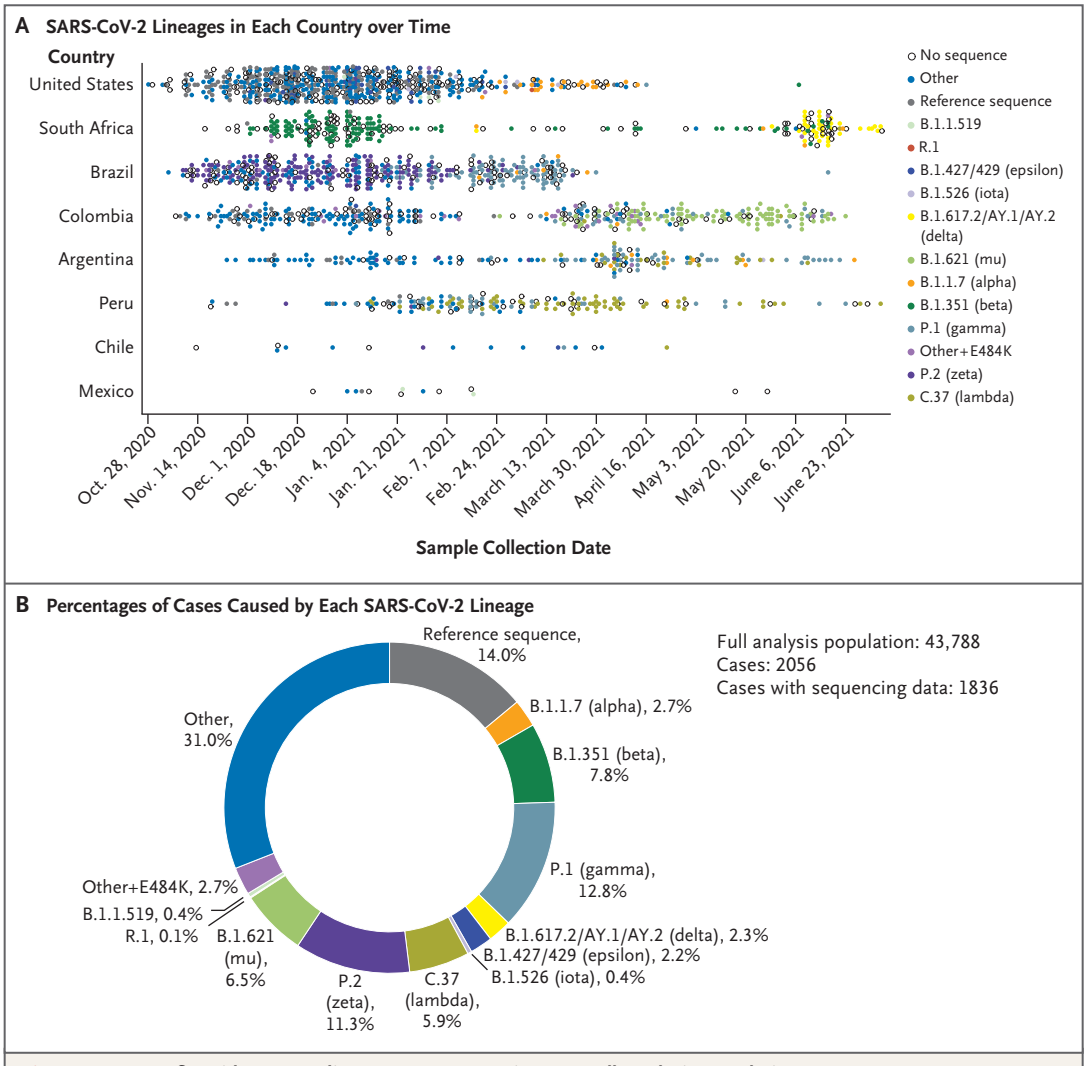


Figure 1. Cases of Covid-19 According to SARS-CoV-2 Lineage (Full Analysis Population).

The distribution of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) lineages among cases of coronavirus disease 2019 (Covid-19) is shown for each country in the trial over time during the double-blind phase of the trial. The reference sequence is defined as the SARS-CoV-2 Wuhan-Hu-1 sequence but with the D614G amino acid variation. At the time of the trial, sequences categorized as "other" were those with substitutions not resulting in another SARS-CoV-2 lineage or variant. "Other+E484K" refers to sequences with E484K but no other substitutions resulting in another SARS-CoV-2 lineage or variant. Next-generation sequencing was performed with the use of the Swift Biosciences SNAP Assay, version 2. Amino acid variants are defined as changes from the reference sequence. The last available visit date across countries was July 1 through 9, 2021, and the last available date of onset for a primary end-point case was June 26 (Argentina), March 24 (Brazil), April 22 (Chile), June 23 (Colombia), May 27 (Mexico), July 1 (Peru), July 5 (South Africa), and April 16 (United States). None of the cases were caused by the eta, kappa, theta, or C.36.3 variant. The alpha, beta, gamma, and delta variants were variants of concern according to World Health Organization definitions at the time of the analysis.

tions not considered to result in another lineage or variant) (Fig. S2). Because efficacy results for the primary end point were similar at 14 or more days and at 28 or more days after administration, only the latter results are shown for secondary and exploratory end points.

EFFICACY ACCORDING TO VIRAL LINEAGE

New viral lineages emerged and became dominant in most countries in the trial during the analysis period, with some variants occurring predominately in one country (e.g., B.1.351 [beta] in South Africa, C.37 [lambda] in Peru, and B.1.621 [mu] in Colombia) (Fig. 1). Vaccine efficacy was 70.2% (95% CI, 35.3 to 87.6) against moderate to severe–critical Covid-19 caused by the B.1.1.7 (alpha) variant; 69.0% (95% CI, 59.1 to 76.8) against moderate to severe–critical Covid-19 caused by SARS-CoV-2 classified as "other," with efficacy remaining stable through 195 days of follow-up; and 58.2% (95% CI, 35.0 to 73.7) against moderate to severe–critical Covid-19 caused by the reference strain (B.1.D614G). Overall efficacy was 44.4% (95% CI, 34.6 to 52.8) against SARS-CoV-2 lineages other than the reference strain (Fig. 3), including 51.9% (95% CI, 19.1 to 72.2) against the beta variant and 36.5% (95% CI, 14.1 to 53.3) against the P.1 (gamma) variant; at the end of the double-blind period, there was no observed difference between vaccine and placebo with respect to the 21 cases caused by the B.1.617.2 (delta) variant in South Africa (vaccine efficacy, –5.7%; 95% CI, –177.7 to 59.2). The Kaplan–Meier curves suggest that efficacy against the circulating reference strain and beta variant began 14 days and 25 days after immunization, respectively, and began immediately on exposure to the alpha variant, which emerged at least 2 months after vaccination of the participants in the vaccine group was completed (Fig. 1). Kaplan–Meier curves were plotted to the end of the double-blind phase, independent of whether cases were occurring in both groups. An additional variant analysis was conducted for cases that occurred during the double-blind period but were sequenced after database lock; results were consistent with those of the initial analysis (Fig. S3).

EFFICACY AGAINST SEVERE–CRITICAL COVID-19

For severe–critical Covid-19, overall vaccine efficacy was 74.6% (95% CI, 64.7 to 82.1) (Table 1). The cumulative incidence curves, which began to separate approximately 7 days after administration (Fig. 4), with no evidence of waning for approximately 6 to 7 months after administration.

Vaccine efficacy against severe–critical Covid-19 was 93.1% (95% CI, 54.4 to 99.8) for the reference strain; 71.8% (95% CI, 56.3 to 82.3) for non–reference strain SARS-CoV-2 lineages, including "other" sequences with the E484K mutation; 78.4% (95% CI, 34.5 to 94.7) for the beta variant; 63.6% (95% CI, 18.8 to 85.1) for the gamma variant; 67.6% (95% CI, –29.8 to 94.4) for the lambda variant; and 79.5% (95% CI, 38.5 to 94.9) for the mu variant. Only six cases of severe–critical Covid-19 caused by the alpha variant and four caused by the delta variant were reported (Fig. S4).

ADDITIONAL SECONDARY AND EXPLORATORY EFFICACY END POINTS

Vaccine efficacy against moderate to severe–critical Covid-19 with onset at least 28 days after administration in all participants regardless of serostatus at baseline, excluding participants in whom Covid-19 developed before day 29 (at-risk population), was 53.2% (95% CI, 47.5 to 58.4). Vaccine efficacy against moderate to severe–critical Covid-19 with onset 1 day after administration was 52.6% (95% CI, 47.6 to 57.2).

Vaccine efficacy against Covid-19 with onset at least 28 days after administration that led to medical intervention (including hospitalization) was 75.6% (adjusted 95% CI, 54.3 to 88.0) (Table 1) and lasted 6 to 7 months (Fig. S5). Efficacy against severe–critical Covid-19 leading to medical intervention (including hospitalization) was approximately 90% initially and tapered to 70% by approximately 6 weeks, remaining at that level for 5 to 6 months. On the basis of available sequences, 3 such cases were caused by the reference strain (all in the placebo group) and 44 were caused by variants (11 in the vaccine group and 33 in the placebo group; vaccine efficacy, 67.5%; 95% CI, 34.1 to 85.2) (Fig. S6). The severity and duration of symptoms, the effect on Covid-19 lasting longer than 28 days, and vaccine efficacy against any infection, including asymptomatic infection, are described in the Supplementary Results (Figs. S7 through S10).

Among the 2131 participants in the vaccine group who were seropositive for SARS-CoV-2 nucleocapsid (N) protein at baseline as compared with the 18,924 participants in the placebo group

Table 1. Vaccine Efficacy against Covid-19 with Onset at Least 14 Days and at Least 28 Days after the Administration of Vaccine or Placebo (Per-Protocol at-Risk Population).*

End Point	≥14 Days after Administration†					≥28 Days after Administration‡				
	Ad26.COV2.S (N=19,400)		Placebo (N=19,398)		Vaccine Efficacy (95% CI)	Ad26.COV2.S (N=19,113)		Placebo (N=18,924)		Vaccine Efficacy (95% CI)
	no. of cases	*person-yr*	*no. of cases*	*person-yr*	%	*no. of cases*	*person-yr*	*no. of cases*	*person-yr*	%
Moderate to severe–critical Covid-19§	484	6685.6	1067	6440.2	56.3 (51.3 to 60.8)	433	6658.4	883	6400.4	52.9 (47.1 to 58.1)
18–59 yr	381	4682.1	847	4514.2	56.6 (51.0 to 61.7)	340	4663.8	716	4486.7	54.3 (48.0 to 60.0)
≥60 yr	103	2003.5	220	1926.0	55.0 (42.9 to 64.7)	93	1994.6	167	1913.7	46.6 (30.7 to 59.0)
Symptomatic Covid-19 of any severity¶	495	6683.8	1082	6437.4	55.9 (51.0 to 60.5)	443	6656.8	895	6398.3	52.4 (46.6 to 57.6)
Mild‖	11	6683.8	15	6437.4	29.4 (–64.6 to 70.7)	10	6656.8	12	6398.3	19.9 (–102.3 to 69.0)
Moderate‖	429	6685.6	862	6440.2	52.1 (46.1 to 57.4)	388	6658.4	707	6400.4	47.2 (40.2 to 53.5)
Severe–critical¶	56	6774.6	205	6625.2	73.3 (63.9 to 80.5)	46	6733.8	176	6542.1	74.6 (64.7 to 82.1)
Any SARS-CoV-2 infection¶**††	—	—	—	—	—	1038	6560.8	1699	6257.5	41.7 (36.3 to 46.7)‡‡
Asymptomatic SARS-CoV-2 infection¶††	—	—	—	—	—	498	6581.0	669	6289.3	28.9 (20.0 to 36.8)‡‡
Covid-19 leading to medical intervention¶§§	18	6783.9	74	6656.7	76.1 (56.9 to 87.7)¶	16	6739.8	64	6567.1	75.6 (54.3 to 88.0)‡‡
Death from any cause¶¶	19	6787.0	45	6669.3	58.5 (27.6 to 77.1)	19	6742.4	37	6577.3	49.9 (10.6 to 72.8)
Covid-19–related death¶¶	3	6786.9	19	6668.4	84.5 (47.3 to 97.1)	3	6742.2	17	6576.4	82.8 (40.5 to 96.8)
Covid-19 according to FDA harmonized definition‖‖	492	6684.7	1067	6440.5	55.6 (50.5 to 60.2)	441	6657.3	884	6399.6	52.0 (46.2 to 57.3)

* All coronavirus disease 2019 (Covid-19) cases were centrally confirmed unless stated otherwise and occurred in participants who had been seronegative at baseline, had negative results on reverse-transcriptase–polymerase-chain-reaction (RT-PCR) testing before 14 or 28 days after administration of vaccine or placebo, and were considered to be at risk for Covid-19. The follow-up time for each participant was defined as the time from administration until onset of a Covid-19 episode or the end of the double-blind period (July 9, 2021). Mild Covid-19 cases were defined by a positive RT-PCR test result and at least one of the following signs or symptoms: fever (body temperature, ≥38.0°C), sore throat, malaise, headache, myalgia, gastrointestinal symptoms, cough, chest congestion, runny nose, wheezing, skin rash, eye irritation or discharge, chills, loss of taste or smell, red or bruised-looking feet or toes, and shaking chills or rigors. Moderate Covid-19 cases were defined by a positive RT-PCR test result and two or more of the following symptoms: fever (body temperature, ≥38.0°C), heart rate of at least 90 beats per minute, shaking chills or rigors, sore throat, cough, malaise, headache, myalgia, gastrointestinal symptoms, loss of taste or smell, and red or bruised-looking feet or toes; or one or more of the following symptoms: respiratory rate of at least 20 breaths per minute, abnormal oxygen saturation (but >93% while breathing room air at sea level), clinical or radiologic evidence of pneumonia, radiologic evidence of deep-vein thrombosis, and shortness of breath or difficulty breathing. Severe–critical Covid-19 cases were defined by a positive RT-PCR test result and one or more of the following features: signs of severe systemic illness (respiratory rate, ≥30 breaths per minute; heart rate, ≥125 beats per minute; oxygen saturation, ≤93% while breathing room air at sea level; or ratio of partial pressure of oxygen [in mm Hg] to fraction of inspired oxygen, <300); respiratory failure (leading to receipt of high-flow oxygen, noninvasive ventilation, mechanical ventilation, or extracorporeal membrane oxygenation [ECMO]); shock; significant acute renal, hepatic, or neurologic dysfunction; admission to an intensive care unit; or death.

† The at-risk population excluded participants who were RT-PCR–positive between day 1 and day 14.
‡ The at-risk population excluded participants who were RT-PCR–positive between day 1 and day 28.
§ The primary end points were the first occurrence of centrally RT-PCR–confirmed moderate to severe–critical Covid-19 with onset at least 14 days after administration and at least 28 days after administration. One participant had a moderate case of Covid-19 and later had a severe case; the adjudication committee considered these to be two separate infections.
¶ This end point was a confirmatory secondary end point.
‖ This end point was a supportive secondary end point.
** This category includes undetected cases that were subsequently detected through a positive serologic result (according to the clinical severity adjudication committee), which did not count as either symptomatic cases (because they were RT-PCR–negative) or asymptomatic cases.
†† Data on this end point were not obtained for cases in which onset occurred after 14 days after administration.
‡‡ The 95% confidence intervals for vaccine efficacy against any severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection, asymptomatic infections, and Covid-19 leading to medical intervention were adjusted for multiplicity on the basis of prespecified procedures for familywise type I error control. All other confidence intervals have not been adjusted for multiplicity and should not be used to infer statistical significance.
§§ Medical intervention included hospitalization as adjudicated by the clinical severity adjudication committee, admission to an intensive care unit, mechanical ventilation, and ECMO, linked to objective measures such as decreased oxygenation and findings on radiography or computed tomography.
¶¶ This end point was an exploratory end point.
‖‖ At the time the protocol was written, the Food and Drug Administration (FDA) harmonized Covid-19 definition was a positive RT-PCR test result plus any of the following symptoms: fever or chills, cough, shortness of breath or difficulty breathing, fatigue, muscle or body aches, headache, new loss of taste or smell, sore throat, congestion or runny nose, nausea or vomiting, and diarrhea.

who were seronegative at baseline, observed vaccine efficacy against moderate to severe–critical Covid-19 was 97.7% (post hoc 95% CI, 93.3 to 99.5) (Table S5); the small number of cases (3) in the vaccine group precludes analysis of this end point according to viral lineage. Previous infection alone, in an analysis involving seropositive and seronegative placebo recipients, was found to provide 90.4% (95% CI, 83.2 to 95.1) protection against moderate to severe–critical Covid-19.

Vaccine efficacy against Covid-19–related death was 82.8% (95% CI, 40.5 to 96.8) (Table 1), with protection sustained through at least 6 months after administration. At least 28 days after administration, 3 Covid-19–related deaths occurred in the vaccine group (all in participants who were ≥60 years of age), as compared with 17 in the placebo group.

EFFICACY IN SUBGROUPS

In subgroup analyses, vaccine efficacy against moderate to severe–critical Covid-19 in participants with human immunodeficiency virus (HIV) infection was found to be 23.5% (95% CI, –78.3 to 68.2). Vaccine efficacy against moderate to severe–critical disease varied according to country: 33.1 (95% CI, 6.3 to 52.5) in Peru, 45.3 (95% CI, 29.1 to 58.0) in Brazil, 49.3 (95% CI, 26.9 to 65.3) in South Africa, and 69.7 (95% CI, 60.7 to 76.9) in the United States. Data on additional subgroup analyses are provided in the Supplementary Results (Figs. S11 and S12 and Table S6).

SAFETY

The safety subpopulation included 3356 participants in the vaccine group and 3380 in the placebo group. Overall, more solicited adverse events occurred in the vaccine group than in the placebo group during the 7-day period after administration. Grade 3 local and systemic solicited adverse events during the 7-day period were similar to those reported in the primary analysis (Fig. S13). In general, lower reactogenicity was observed among older adults than among younger adults. Among the 155 participants in the vaccine group who were seropositive for SARS-CoV-2 at baseline (safety subpopulation), 60.0% and 52.9% reported a solicited local or systemic adverse event, respectively, similar to the percentages among the 3201 baseline-seronegative participants (54.5% and 60.6%, respectively). Grade

3 or higher solicited local adverse events were rare among vaccine recipients, regardless of their serostatus at baseline (occurring among 1.3% of those who were seropositive and 0.6% of those who were seronegative). Grade 3 or higher systemic adverse events occurred in 1.3% of seropositive vaccine recipients and 2.3% of seronegative vaccine recipients.

Unsolicited events of grade 3 or higher severity (safety subpopulation) and unsolicited events of grade 3 or higher that were considered by the investigators to be related to vaccine or placebo (full analysis population and safety subpopulation) are summarized in Tables S7 and S8. Serious adverse events that were not related to Covid-19 (full analysis population) occurred in 223 par-

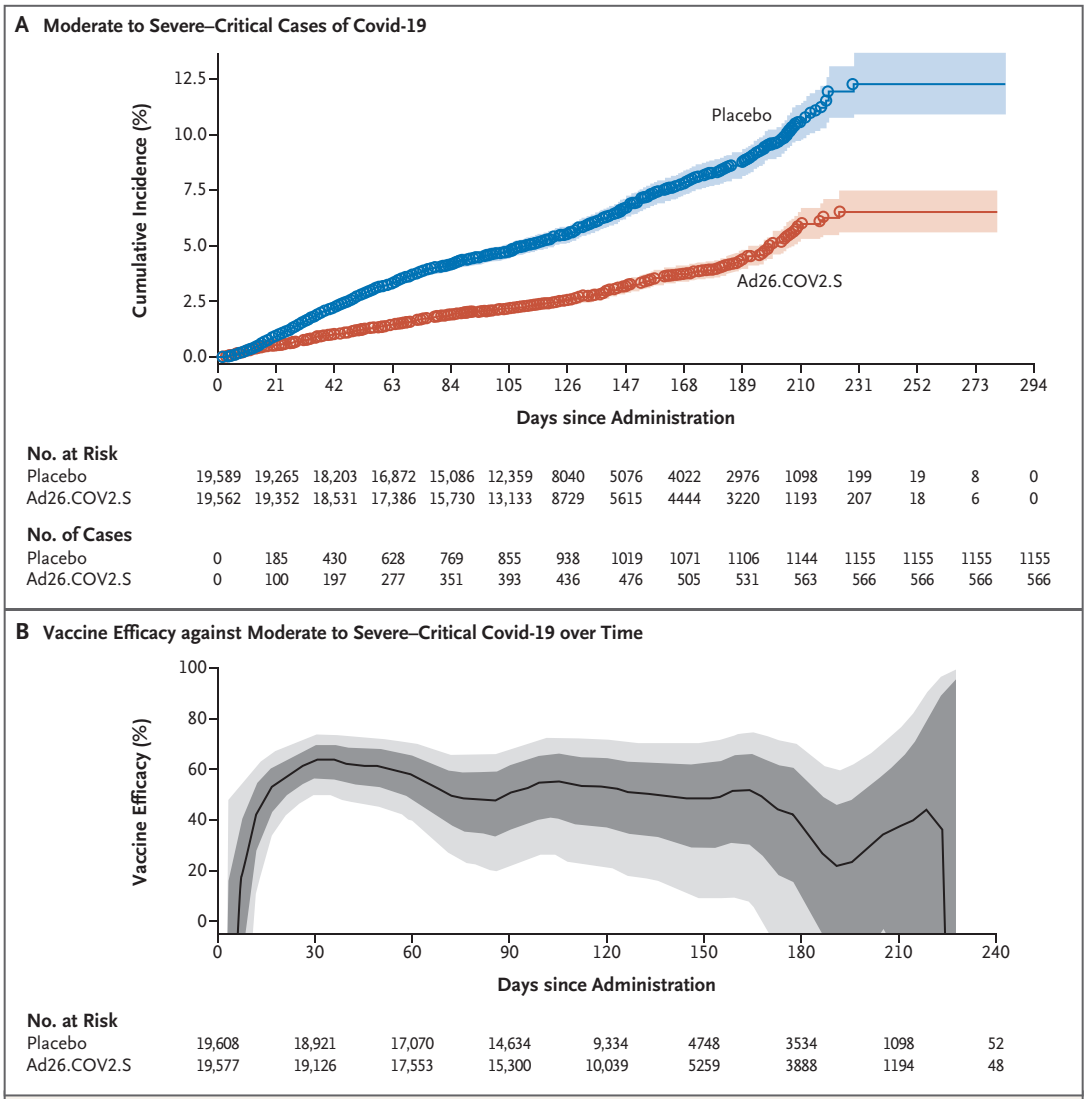


Figure 2. Cumulative Incidence of Moderate to Severe–Critical Covid-19 and Vaccine Efficacy over Time (Per-Protocol Population).

Panel A shows the Kaplan–Meier cumulative incidence of molecularly confirmed moderate to severe–critical Covid-19 with onset at least 1 day after administration of vaccine or placebo. Shading indicates the 95% confidence interval. Panel B shows vaccine efficacy against moderate to severe–critical Covid-19 over time; dark gray shading indicates the 95% pointwise confidence interval, and light gray shading the 95% simultaneous confidence interval. The graph includes 95% of the events that occurred before day 189, with the hazard smoothed over 21 days. Participants were seronegative at baseline, as determined by reverse-transcriptase–polymerase-chain-reaction (RT-PCR) and serologic tests.

ticipants (1.0%) in the vaccine group and in 265 participants (1.2%) in the placebo group. Additional information on serious adverse events is provided in Table S9.

Imbalances in adverse events that occurred during a 28-day risk window after administration are described in the Supplementary Results (Table S10). At the time of the final analysis with prolonged follow-up, imbalances were seen for tinnitus (15 cases in the vaccine group vs. 4 in the placebo group), urticaria (13 vs. 6), convulsion (9 vs. 4), pulmonary embolism (10 vs. 5), and deep-vein thrombosis (11 vs. 3); no imbalances were observed for the Guillain–Barré syndrome (1 case per group) or Bell's palsy (2 cases in the vaccine group and 1 in the placebo group) (Table S10). No cases of capillary leak syndrome, myocarditis, or encephalitis were reported. Thrombosis with thrombocytopenia was defined as an adverse event of special interest (Supplementary Methods). One event, which occurred in a 25-year-old man within 28 days after administration of Ad26.COV2.S, occurred in association with positivity for anti-PF4 antibodies and met the Centers for Disease Control and Prevention (CDC) tier 1–2 and Brighton Collaboration level 1 criteria for vaccine-induced immune thrombotic thrombocytopenia (VITT, also known as thrombosis with thrombocytopenia syndrome).

At the time of the final analysis, 83 deaths had been reported in the double-blind phase (28 in the vaccine group and 55 in the placebo group, with 5 and 22, respectively, related to Covid-19 in the full analysis population). All deaths were considered by the investigators to be unrelated to the vaccine or placebo.

DISCUSSION

In the final analysis of the double-blind portion of our phase 3 trial, median follow-up was 4 months, with 8940 participants having at least 6 months of follow-up. A single dose of the Ad26.COV2.S vaccine remained effective (52.9%) in preventing moderate to severe–critical Covid-19 and all symptomatic Covid-19 (52.4%), despite the emergence of variants during the trial. Efficacy against severe–critical disease remained higher (74.6%) than efficacy against moderate to severe–critical disease, with a lower point estimate for variants (93.1% efficacy against the reference strain and 71.8% efficacy against non–reference strain lineages, including "other" sequences with the E484K mutation), indicating that Ad26.COV2.S induces higher levels of protection in proportion to the severity of the disease and the nature of the viral mutation.

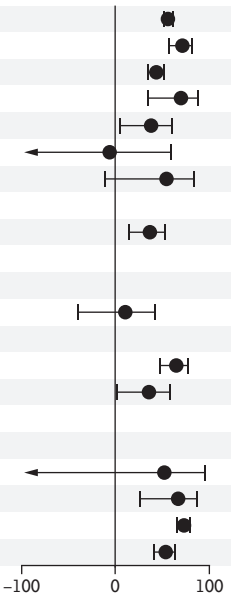
During the placebo-controlled period, which differed between countries on the basis of when the participants became aware of the trial-group assignments, the incidence of SARS-CoV-2 infection was highly variable geographically and over time as new viral variants emerged. The reduction in overall efficacy in the final analysis as compared with the primary analysis[3] (vaccine efficacy for the primary end point at least 28 days after administration, 66.1% in the primary analysis and 52.9% in the final analysis) was most likely due to lower vaccine efficacy against variants that appeared outside the United States (Latin America) in this multinational trial after the primary analysis — for example, 10.1% against the lambda variant and 36.5% against the gamma variant. Regional emergence of variants such as lambda and gamma contributed to the lower vaccine efficacy that was observed for some subgroups (e.g., Asian, Hispanic, and American Indian or Alaskan Native populations). In the United States, where the alpha variant emerged after the reference strain, vaccine efficacy against moderate to severe–critical Covid-19 was 69.7%.

The efficacy findings in this trial are consistent with durable immune responses being elicited by Ad26.COV2.S[5] and with immediate efficacy against the alpha variant occurring at least 60 days after vaccination. Furthermore, the onset of protection differed between the original strain (14 days) and the more neutralization-resistant beta variant (25 days). The higher vaccine efficacy observed against the more resistant beta variant[6] as compared with the lower efficacy against the less resistant lambda variant suggests that other factors also played a role in protection.

Conclusions about vaccine efficacy against symptomatic Covid-19 caused by the delta variant, including severe–critical Covid-19 (with only 4 cases among the participants), were not possible in this trial because of the wide confidence intervals. Real-world data from several studies[7-10] — some of which analyzed more severe symptomatic disease, against which this vaccine has higher efficacy — have shown varying degrees of efficacy of Ad26.COV2.S against symptomatic delta-variant infection. Effectiveness ranged from

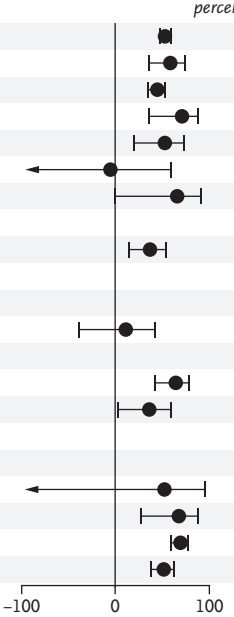
A Vaccine Efficacy against Moderate to Severe–Critical Covid-19 with Onset at least 14 Days after Administration

	Ad26.COV2.S (N=19,577)		Placebo (N=19,608)		Vaccine Efficacy (95% CI)
	no. of events/ no. of participants	*no. of person-yr*	*no. of events/ no. of participants*	*no. of person-yr*	*percent*
Any SARS-CoV-2	484/19,400	6685.60	1067/19,398	6440.18	56.3 (51.3 to 60.8)
Reference strain	32/19,400	6685.60	108/19,398	6440.18	71.5 (57.3 to 81.4)
Lineages other than reference strain	265/19,400	6685.60	454/19,398	6440.18	43.8 (34.4 to 51.9)
B.1.1.7 (alpha)	9/19,400	6685.60	29/19,398	6440.18	70.1 (35.1 to 87.6)
B.1.351 (beta)	36/19,400	6685.60	56/19,398	6440.18	38.1 (4.2 to 60.4)
B.1.617.2/AY.1/AY.2 (delta)	11/19,400	6685.60	10/19,398	6440.18	−6.0 (−178.3 to 59.2)
B.1.427/429 (epsilon)	8/19,400	6685.60	17/19,398	6440.18	54.7 (−10.8 to 83.1)
B.1.525 (eta)	0/19,400	6685.60	0/19,398	6440.18	
P.1 (gamma)	74/19,400	6685.60	112/19,398	6440.18	36.4 (13.9 to 53.2)
B.1.526 (iota)	0/19,400	6685.60	4/19,398	6440.18	
B.1.617.1 (kappa)	0/19,400	6685.60	0/19,398	6440.18	
C.37 (lambda)	43/19,400	6685.60	46/19,398	6440.18	10.0 (−39.5 to 42.0)
P.3 (theta)	0/19,400	6685.60	0/19,398	6440.18	
P.2 (zeta)	34/19,400	6685.60	93/19,398	6440.18	64.8 (47.3 to 77.0)
B.1.621 (mu)	38/19,400	6685.60	57/19,398	6440.18	35.8 (1.5 to 58.6)
C.36.3	0/19,400	6685.60	0/19,398	6440.18	
R.1	1/19,400	6685.60	0/19,398	6440.18	
B.1.1.519	2/19,400	6685.60	4/19,398	6440.18	51.8 (−236.1 to 95.6)
Other+E484K	9/19,400	6685.60	26/19,398	6440.18	66.7 (26.6 to 86.3)
Other	78/19,400	6685.60	280/19,398	6440.18	73.2 (65.4 to 79.4)
No sequencing data available	109/19,400	6685.60	225/19,398	6440.18	53.3 (41.1 to 63.2)



B Vaccine Efficacy against Moderate to Severe–Critical Covid-19 with Onset at least 28 Days after Administration

	Ad26.COV2.S (N=19,577)		Placebo (N=19,608)		Vaccine Efficacy (95% CI)
	no. of events/ no. of participants	*no. of person-yr*	*no. of events/ no. of participants*	*no. of person-yr*	*percent*
Any SARS-CoV-2	433/19,113	6658.36	883/18,924	6400.36	52.9 (47.1 to 58.1)
Reference strain	30/19,113	6658.36	69/18,924	6400.36	58.2 (35.0 to 73.7)
Lineages other than reference strain	239/19,113	6658.36	413/18,924	6400.36	44.4 (34.6 to 52.8)
B.1.1.7 (alpha)	9/19,113	6658.36	29/18,924	6400.36	70.2 (35.3 to 87.6)
B.1.351 (beta)	23/19,113	6658.36	46/18,924	6400.36	51.9 (19.1 to 72.2)
B.1.617.2/AY.1/AY.2 (delta)	11/19,113	6658.36	10/18,924	6400.36	−5.7 (−177.7 to 59.2)
B.1.427/429 (epsilon)	5/19,113	6658.36	14/18,924	6400.36	65.7 (−0.9 to 90.3)
B.1.525 (eta)	0/19,113	6658.36	0/18,924	6400.36	
P.1 (gamma)	74/19,113	6658.36	112/18,924	6400.36	36.5 (14.1 to 53.3)
B.1.526 (iota)	0/19,113	6658.36	4/18,924	6400.36	
B.1.617.1 (kappa)	0/19,113	6658.36	0/18,924	6400.36	
C.37 (lambda)	43/19,113	6658.36	46/18,924	6400.36	10.1 (−39.2 to 42.1)
P.3 (theta)	0/19,113	6658.36	0/18,924	6400.36	
P.2 (zeta)	25/19,113	6658.36	67/18,924	6400.36	64.1 (42.5 to 78.3)
B.1.621 (mu)	38/19,113	6658.36	57/18,924	6400.36	35.9 (1.7 to 58.7)
C.36.3	0/19,113	6658.36	0/18,924	6400.36	
R.1	1/19,113	6658.36	0/18,924	6400.36	
B.1.1.519	2/19,113	6658.36	4/18,924	6400.36	51.9 (−235.4 to 95.7)
Other+E484K	8/19,113	6658.36	24/18,924	6400.36	68.0 (26.3 to 87.6)
Other	68/19,113	6658.36	211/18,924	6400.36	69.0 (59.1 to 76.8)
No sequencing data available	96/19,113	6658.36	190/18,924	6400.36	51.4 (37.6 to 62.4)



60% to 94% against hospitalization,[7,8,10-12] 13% to 78% against SARS-CoV-2 infection,[8,9,12-14] and 52% to 82% against death after SARS-CoV-2 infection[9,10] during periods and in regions in which the delta variant was prominent.

Vaccine efficacy against symptomatic Covid-19

Figure 3 (facing page). Vaccine Efficacy against Moderate to Severe–Critical Covid-19 According to SARS-CoV-2 Lineage (Per-Protocol Population).

Shown is vaccine efficacy against moderate to severe–critical Covid-19 with onset at least 14 days after administration (Panel A) and at least 28 days after administration (Panel B). SARS-CoV-2 in the category of "Lineages other than the reference strain" were all variants of concern or interest, with "other" sequences excluded. At the time of the trial, sequences categorized as "other" were those with substitutions not resulting in another SARS-CoV-2 lineage or variant. "Other+E484K" refers to sequences with E484K but no other substitutions resulting in another SARS-CoV-2 lineage or variant. Vaccine efficacy was not calculated if fewer than 6 cases were observed for an end point. Confidence intervals have not been adjusted for multiplicity and should not be used to infer statistical significance.

in participants with HIV infection in our trial was low, at 23.5%, with wide confidence intervals. However, in a large phase 3B study involving 477,234 participants, vaccine effectiveness was 73% against hospitalization and 65% against death among the approximately 37,000 participants living with HIV infection.[10]

We observed that participants with previous asymptomatic infection (defined by serologic positivity for SARS-CoV-2 N protein and an absence of history of symptomatic Covid-19) can benefit from immunization with a Covid-19 vaccine. In a post hoc analysis, previous infection alone provided 90.4% protection against symptomatic infection, and after administration of Ad26.COV2.S in seropositive participants, 97.7% protection was observed in a comparison with seronegative placebo recipients; these findings extended observations from previous immunologic studies.[15-17]

When Covid-19 developed in participants who had received Ad26.COV2.S, they had lower severity of illness, shorter duration of illness, and lower viral loads than placebo recipients. In addition, vaccination with Ad26.COV2.S led to fewer medical interventions (including hospitalization) than placebo (vaccine efficacy against medical intervention ≥28 days after administration, 75.6%). Vaccine efficacy against Covid-19–related death was 82.8% with onset at least 28 days after administration, and the three Covid-19–related deaths among vaccine recipients occurred in participants 60 years of age or older who were seronegative at baseline and had coexisting conditions associated with an increased risk of severe Covid-19.

Serious adverse events were rare: serious adverse events not associated with Covid-19 occurred in approximately 1% of the participants in each group during the double-blind period. Tinnitus was observed in postauthorization surveillance and is classified as "very rare" in the fact sheet associated with the label.[18] Of the very rare events occurring after vaccination that were identified after marketing began,[18,19] no cases of anaphylaxis or capillary leak syndrome occurred, and one case of VITT[20-22] meeting the CDC and Brighton Collaboration criteria occurred in this trial. With 3 to 4 cases per million vaccinations being reported in the postmarketing period, we would not expect to see more than 1 case of VITT in a clinical trial involving more than 43,000 participants (21,898 of whom received Ad26.COV2.S).

Strengths of the current analysis included a longer follow-up period than in our primary analysis that extends our primary findings, as well as the analysis of vaccine efficacy across geographic regions, across diverse populations, and against infection with variants. A limitation of the trial was the premature discontinuation of follow-up in the placebo-controlled phase and variable follow-up times among countries, depending on when approval of the post–emergency use authorization amendment occurred (which permitted group assignments to be revealed to participants and those in the placebo group to be vaccinated). Therefore, for the delta and omicron variants, limited or no data were obtained in the double-blind phase of the study. Going forward, vaccine effectiveness for new variants will need to come from studies involving real-world evidence.

On the basis of the reported results at the end of the double-blind phase, the efficacy of Ad26.COV2.S against moderate to severe–critical disease and against severe–critical disease was lower than that observed in clinical trials assessing messenger RNA vaccines.[23,24] The recently noted incidence of breakthrough infections with the omicron variant in vaccine-primed persons,[25] regardless of the primary vaccine regimen, suggests that a booster may be required for all primary vaccine regimens. Recent data from a study involving South African health care workers conducted during the omicron wave indicate 85% efficacy

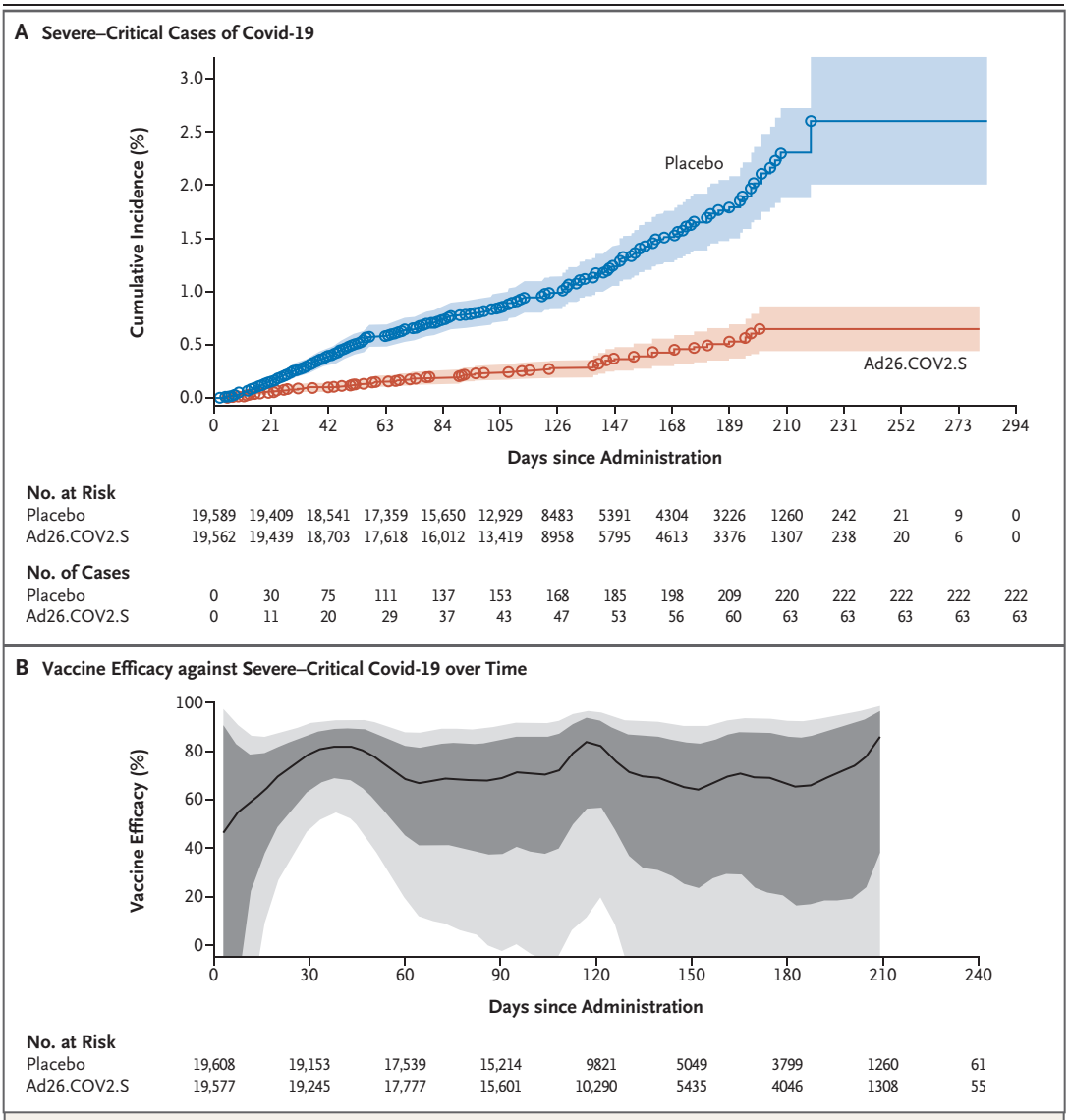


Figure 4. Cumulative Incidence of Severe–Critical Covid-19 and Vaccine Efficacy over Time (Per-Protocol Population).

Panel A shows the Kaplan–Meier cumulative incidence of molecularly confirmed severe–critical Covid-19 with onset at least 1 day after administration of vaccine or placebo. Shading indicates the 95% confidence interval. Panel B shows vaccine efficacy against severe–critical Covid-19 over time; dark gray shading indicates the 95% pointwise confidence interval, and light gray shading the 95% simultaneous confidence interval. The graph includes 95% of the events that occurred before day 189, with the hazard smoothed over 21 days. Participants were seronegative at baseline, as determined by RT-PCR and serologic tests.

of Ad26.COV2.S against hospitalization when given as a single priming dose followed by a booster 6 to 9 months later.[26]

Overall, our findings indicate that a single dose of Ad26.COV2.S provided protection against severe disease and hospitalization, which could be important in regions requiring mass vaccination or in populations with poor adherence to two-dose prime regimens, and support the use of Ad26.COV2.S in the ongoing effort against the global Covid-19 pandemic.

Supported by Janssen Research and Development, an affiliate of Janssen Vaccines and Prevention and part of the Janssen pharmaceutical companies of Johnson & Johnson, and in whole or in part by federal funds from the Biomedical Advanced Research and Development Authority, part of the Office of the Assistant Secretary for Preparedness and Response at the Department of

Health and Human Services, under Other Transaction Agreement HHSO100201700018C, and from the National Institute of Allergy and Infectious Diseases (NIAID), National Institutes of Health. The NIAID provides grant funding to the HIV Vaccine Trials Network (HVTN) Leadership and Operations Center (UM1 AI68614), the HVTN Statistics and Data Management Center (UM1 AI68635), the HVTN Laboratory Center (UM1 AI68618), the HIV Prevention Trials Network (HPTN) Leadership and Operations Center (UM1 AI68619), the AIDS Clinical Trials Group (ACTG) Leadership and Operations Center (UM1 AI68636), the Infectious Diseases Clinical Research Consortium Leadership Group (UM1 AI148684) and Vaccine and Therapeutic Evaluation Units (UM1 AI148576, UM1 AI148373, UM1 AI148685, UM1 AI148452).

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

A data sharing statement provided by the authors is available with the full text of this article at NEJM.org.

We thank all the participants in this trial, the staff members at the trial locations, the members of the data and safety monitoring board, all the investigators at the clinical sites, the members of the clinical severity adjudication committee (Janet S. Lee, Brian T. Garibaldi, Charles Shey Wiysonge, Anoma Nellore, Timothy E. Albertson, Christian Sandrock, and Victor F. Tapson), the COV3001 study team (Richard Gorman, Carmen A. Paez, James Kublin, Simbarashe G. Takuva, Alex Greninger, Pavitra Roychoudhury, Robert W. Coombs, Keith R. Jerome, Kimberly L. Taylor, Flora Castellino, Xiaomi Tong, Corrina Pavetto, Teletha Gipson, Tina Tong, Marina Lee, James Zhou, Michael Fay, Daniel Wolfe, Peter B. Gilbert, Ollivier Hyrien, Alex Luedtke, Hein Fennema, Kim Offergeld, Nancy Cauwenberghs, Tamzin Tanner, Kelly McQuarrie, Chimeremma Nnadi, Obiageli Sogbetun, Nina Ahmad, Ian De Proost, Cyrus Hoseyni, Paul Coplan, Najat Khan, Peter Ronco, Sanne Roels, Daniel Backenroth, Jennifer Bogert, Fei Chen, Pei-Ling Chu, Kimberly Cooper, Hilde Delanghe, John T. Jones, Monika Peeters, Willem Talloen, Jose Pinheiro, Ilse Scheys, Pallavi Shetti, Nathalie Vaissiere, Jose Salas, Molli Imola Sandor, Jiajun Xu, Dawn Furey, Jodi Meck, Boerries Brandenburg, Jenny Hendriks, Jarek Juraszek, Marit de Groot, Griet Van Roey, and Dirk Heerwegh), and Catherine DeBrosse and Jill E. Kolesar (Cello Health Communications–MedErgy) for writing and editorial assistance, funded by Janssen Global Services, with an earlier version of the manuscript.

APPENDIX

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VIEWPOINTS

Salicylates and Pandemic Influenza Mortality, 1918–1919 Pharmacology, Pathology, and Historic Evidence

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The high case-fatality rate—especially among young adults—during the 1918–1919 influenza pandemic is incompletely understood. Although late deaths showed bacterial pneumonia, early deaths exhibited extremely "wet," sometimes hemorrhagic lungs. The hypothesis presented herein is that aspirin contributed to the incidence and severity of viral pathology, bacterial infection, and death, because physicians of the day were unaware that the regimens (8.0–31.2 g per day) produce levels associated with hyperventilation and pulmonary edema in 33% and 3% of recipients, respectively. Recently, pulmonary edema was found at autopsy in 46% of 26 salicylate-intoxicated adults. Experimentally, salicylates increase lung fluid and protein levels and impair mucociliary clearance. In 1918, the US Surgeon General, the US Navy, and the *Journal of the American Medical Association* recommended use of aspirin just *before* the October death spike. If these recommendations were followed, and if pulmonary edema occurred in 3% of persons, a significant proportion of the deaths may be attributable to aspirin.

> In February 1919…Edward's fever kept getting higher and higher…aspirin…was given to him by the 1/2-handful over and over…Edward sweated through his mattress…Dr.…could not save his patient.
>
> —Clella B. Gregory, Pandemic Influenza Storybook, US Department of Health and Human Services [1]

The unprecedented overall mortality and the mortality rate among young adults during the 1918–1919 influenza pandemic are incompletely understood. Deaths in the United States peaked with a sudden spike in October 1918. Later, Wade Hampton Frost [2] studied surveys of 8 US cities and found that, for every 1000 persons aged 25–29 years, ~30% were infected with influenza virus, and 1% died of pneumonia or influenza. This 3% case-fatality rate has been called, "perhaps the most important unsolved mystery of the pandemic" [3, p 1022].

Mortality was driven by 2 overlapping clinical-pathologic syndromes: an early, severe acute respiratory distress (ARDS)–like condition, which was estimated to have caused 10%–15% of deaths (sequential autopsy series are lacking) [3)]; and a subsequent, aggressive bacterial pneumonia "superinfection," which was present in the majority of deaths [4, 5].

Factors that contributed to the severity of illness and death (eg, viral pathogenicity, bacterial colonization, immune response, smoking, preexisting conditions, and treatment) remain to be elucidated. Of most interest are

Received 29 March 2009; accepted 25 June 2009; electronically published 29 September 2009.

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Clinical Infectious Diseases 2009; 49:1405–10
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1058-4838/2009/4909-0020$15.00
DOI: 10.1086/606060

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those amenable to intervention, because fear of another 1918-like influenza pandemic drives pandemic planning today.

Recent studies suggest enhanced pathogenicity of certain influenza viruses as well as abnormal immune host responses. The 1918 influenza H1N1 virus, in contrast to a conventional human H1N1 influenza virus (A/Kawasaki/173/01), infected the lower respiratory tract, produced acute respiratory distress, and was associated with a dysregulated antiviral response in a cynomologous macaque model [6]. Also, the 1918 viral polymerase complex (PA, PB1, and PB2) promoted growth of the 1918 virus in the lower respiratory tract of ferrets [7]. Similarly, 2003 human H5N1 isolates, like 1997 human H5N1 isolates, induced overproduction of proinflammatory cytokines in human macrophages in vitro [8].

However, it is unlikely that the virus and immune responses alone were responsible for the 1918 deaths. As recently reviewed by Brundage and Shanks [4], most persons had self-limited disease with case-fatality rates of <2%, and mortality and case-fatality rates differed widely among populations. During the fall of 1918, death and influenza case-fatality rates ranged from 0.58% to 3.3% and 2.1% to 10%, respectively, in the 12 US Army camps with >10,000 cases of influenza or pneumonia each [9, 10]. Frost [2] noted that the wide variation in mortality rates between cities, some of which were close together, was not explained by climate, population density, preventive measures, or other environmental characteristics. These observations suggest the importance of factors related to location rather than the virus itself. Likewise, the unusual mortality rate among young adults remains unexplained. Salicylate has been suggested [3, 11, 12], and increased mortality rates have been found in ferrets exposed to influenza, aspirin, and an arginine-deficient diet, compared with each alone or in 2 combinations [13], yet mechanistic and epidemiologic evidence has not been fully explored.

The hypothesis presented herein is that salicylate therapy for influenza during the 1918–1919 pandemic resulted in toxicity and pulmonary edema, which contributed to the incidence and severity of early ARDS-like lungs, subsequent bacterial infection, and overall mortality. Pharmacokinetic data, which were unavailable in 1918, indicate that the aspirin regimens recommended for the "Spanish influenza" predispose to severe pulmonary toxicity.

A confluence of events created a "perfect storm" for widespread salicylate toxicity. The loss of Bayer's patent on aspirin in February 1917 allowed many manufacturers into the lucrative aspirin market. Official recommendations for aspirin therapy at toxic doses were preceded by ignorance of the unusual nonlinear kinetics of salicylate (unknown until the 1960s), which predispose to accumulation and toxicity; tins and bottles that contained no warnings and few instructions; and fear of "Spanish" influenza, an illness that had been spreading like wildfire.

More recently, influenza deaths have been attributed to salicylate. From the 1950s to the 1980s, thousands of deaths among children following influenza and other infections (eg, Reye syndrome) were unexplained until studies identified aspirin as the major contributor [14–16], and aspirin label warnings were followed by a disappearance of the condition [17]. Reye syndrome toxicity (vomiting, hyperventilation, delirium, and coma, with brain swelling and fat in the liver and proximal renal tubules) develops after ~4 days of salicylate therapy [14] with reported mean daily doses of 25 mg/kg [18]. (Adults with salicylate toxicity present mainly with abnormal consciousness and respiratory distress [19].) Also, a recent avian influenza A–associated fatality involved Reye syndrome and aspirin use [20], and several autopsies of persons who had avian influenza revealed hemorrhagic lungs, fatty liver changes, and swollen kidneys [21] consistent with salicylate intoxication.

Four lines of evidence support the role of salicylate intoxication in 1918 influenza mortality: pharmacokinetics, mechanism of action, pathology, and the spate of official recommendations for toxic regimens of aspirin immediately before the October 1918 death spike. (Grains of aspirin used in older texts are converted to milligrams as follows: 1 grain equals 65 mg).

ASPIRIN REGIMENS (DOSE AND SCHEDULE) RECOMMENDED IN 1918 ARE NOW KNOWN TO REGULARLY PRODUCE TOXICITY

In 1977, a US Food and Drug Administration panel [22] recommended that the maximum safe daily dose of aspirin for the general population was 4000 mg, with a mean hourly rate of 167 mg/h, and that "dosing regimens exceeding either this total daily dosage or mean hourly rate provide a significantly greater risk without a compensating therapeutic benefit" (p 35360). As an example of the unusual nonlinear kinetics of salicylate, the panel noted that simulations show that, after increasing the dose from 2 to 4 g daily (given every 6 h), "the total amount of drug in the body at steady state will increase from 1.3 grams to 5.3 grams, a 400% increase." In 2007, an evidence-based consensus guideline [23] recommended that anyone with an acute ingestion of 150 mg/kg or 6.5 g of aspirin equivalent, whichever is lower, warrants referral to an emergency department and recognized that, after multiple doses, it is difficult to generalize any dose associated with toxicity, because lower daily doses (2–3 g for several days) may lead to toxicity in some patients.

In the early 1900s, physicians treating serious conditions (eg, rheumatic fever) generally "pushed" salicylate until the appearance of toxicity and then backed off [24]. In 1918, dosing recommendations for pandemic influenza were similar to

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these high-dose, hospital-based regimens, except that the recommendations for influenza generally offered no instruction for dose adjustment if toxicity occurred.

French's historic 1920 report for the British Ministry of Health [25] on the pandemic states that the aspirin dose was "15 to 20 grains" (975–1300 mg). No frequency was given. One London doctor "drenched" his patient with salicin: 20 grains (1300 mg) hourly for 12 hours nonstop [26]. Others suggested sodium salicylate, 6 grains (390 mg) over 3 hours for several days [27]. Aspirin was recommended for pulmonary edema [28]. On 26 September 1918, the US Navy recommended a cathartic and 5 grains (325 mg) of aspirin, warning against large doses [29]. However, the Navy's *Materia Medica* stated that the maximum dose was 1300 mg [30]. On 5 October 1918, *The Journal of the American Medical Association* [31] recommended aspirin: "The acetylsalicylic acid may be given in a dosage of 1 gm. (15 grains) every three hours…or a smaller dose combined with 0.1 gm. (2 grains) acetophenetidin, until symptomatic relief is secured" (p 1137). These recommended doses (1000–1300 mg), with frequencies ranging from hourly to every 3 hours, resulting in daily doses of 8–31.2 grams, are above the maximum safe dose defined above and would lead to accumulation, as noted below.

Hints of unusual pharmacokinetics and individual variation were noted before the pandemic but largely ignored. In 1906, Langmeade [32] observed "great variation in the amount required" (p 1824) for toxicity and reported a hospitalized child (receiving 325 mg every 6 hours) who, on day 4, developed vomiting, fever, dyspnea, cyanosis, and coma and died. He recommended caution early in treatment so "the personal factor may be estimated." In 1913, Hanzlik [24] studied records of 400 hospitalized persons treated with a common regimen, 10–20 grains of a salicylate hourly with sodium bicarbonate until toxicity occurred (headache, nausea, tinnitus or deafness, delirium, or hallucinations). He found that the mean toxic dose of aspirin for male persons was 165 grains (10,725 mg), a probable overestimation, because sodium bicarbonate greatly enhances salicylate excretion. The toxic dose of synthetic salicylate in males ranged from 1300 to 31,200 mg.

The development of tests to measure salicylate in the blood in the 1940s allowed Alvin F. Coburn [33] of the US Navy, while studying rheumatic fever, to find that a dose of 10 g daily led to levels that averaged 36 mg/dL on day 3 in 9 adults. In 1948, Graham and Parker [34] were among the first to correlate the blood salicylate level with symptoms of toxicity. First, after studying 58 individuals, they found considerable variation in the level at which symptoms developed, such as vomiting (16.3–38.6 mg/dL), hyperventilation (21–44.2 mg/dL), pulmonary edema (49.4 mg/dL), and severe dyspnea (46–53.6 mg/dL). They also studied 33 patients who attained levels of 35 mg/dL during the first 7 days of therapy and found the following severe toxicities: hyperventilation (in 33%), vomiting (in 30%), marked sweating (in 12%), headache (in 12%) severe drowsiness (in 12%), confusion (in 6%), severe dyspnea (in 6%), excitement (in 6%), epistaxis (in 6%), vertigo (in 3%), pulmonary edema (in 3%), and hemorrhage (in 3%). The incidence of these toxicities may be higher, because administration was halted when hyperventilation occurred. A retrospective study [35] of 56 salicylate-intoxicated adults, with intoxication defined as a peak salicylate level $\geqslant$30 mg/dL, found 6 patients (11%) with noncardiogenic pulmonary edema. For adults aged >30 years, the incidence of noncardiogenic pulmonary edema was 35%. Interestingly, none of 55 consecutive intoxicated pediatric patients had pulmonary edema.

In the 1960s, scientists learned why toxicity occurs with intense aspirin therapy: salicylates have unusual and complex pharmacokinetic characteristics that predispose to accumulation, rendering both dose and schedule critically important. In 1965, Levy [36] showed that, when the amount of drug in the body reaches ~360 mg, the half-life increases as elimination changes from first order to zero order. Later, Bardare et al [37], who studied children, observed half-lives of ~5 h at a dosage of ~50 mg/kg per day (3500 mg in a 70-kg person), of ~15 h at dosages of 75–95 mg/kg per day, and of ~40 h at dosages >100 mg/kg per day. Dosing at intervals of the half-life or less will lead to accumulation.

In addition to the saturable metabolism described by Levy and colleagues [36, 38, 39], accumulation of salicylate can occur for other reasons, including individual variation in elimination rate [38], reduced renal excretion [40], and low urine pH [41]. Higher doses, as mentioned above, slow elimination [42] and enhance the volume of distribution [43]. Acidosis [44] and hypoproteinemia [45] increase brain uptake and toxicity. The salicylate level [42] and the level at which toxicity occurs [24, 34] vary among individuals. Therefore, it is likely that severe salicylate intoxication, including pulmonary edema, developed in some persons who followed the recommended 1918 dosing regimens.

SALICYLATES CAUSE IMMEDIATE LUNG TOXICITY AND MAY PREDISPOSE TO BACTERIAL INFECTION BY INCREASING LUNG FLUID AND PROTEIN LEVELS AND IMPAIRING MUCOCILIARY CLEARANCE

The occurrence of pulmonary edema in humans with salicylate intoxication is well documented [19, 35]. Increased pulmonary vascular bed permeability to fluid and protein, decreases in arterial pO2, and increases in postmortem extravascular lung water followed salicylate administration in sheep [46]. Salicylate also depresses the lung's mucociliary transport system [47].

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THE PATHOLOGY OF THE EARLY DEATHS IS CONSISTENT WITH ASPIRIN TOXICITY AND VIRUS-INDUCED PATHOLOGY

Autopsy reports by pathologists of the day describe extremely wet, sometimes hemorrhagic lungs in early deaths. On 23 September 1918 at Camp Devens in Massachusetts, 12,604 soldiers had influenza, and 727 had pneumonia; after examining the lungs of a dead soldier, Colonel Welch concluded, "This must be some new kind of infection or plague" [48, p 190]. What struck E. R. Le Count [49], consulting pathologist to the US Public Health Service, as most unusual was the amount of lung tissue actually "pneumonic" seemed "too little in many cases to explain death by pneumonia." He saw a thin, watery, bloody liquid in the lung tissue, "like the lungs of the drowned," as well as pleural exudates with small hemorrhages unlike those seen in "any other form of acute pneumonia of which I am familiar." Importantly, he also noted the brain was "quite regularly swollen," the kidneys were "regularly the seat of cloudy swelling," and the liver had "superficial fatty change," (changes noted in children with salicylate intoxication; see below). He concluded, "It is difficult to believe that a disease with so many distinctive features and…novelty…can fail to possess a correspondingly definite etiology." Brain weight was increased by 100–200 g in ~50% of persons, most likely indicating cerebral edema; cerebral bleeding was common [9, 10]. Wolbach [50], chief pathologist at the Peter Bent Brigham Hospital in Boston, Massachusetts, found bacterial infection in late deaths, yet a person dying on day 2 exhibited edema and congestion of the lung, a purpuric rash, and no bacterial growth. He surmised a natural progression from the early lesion to the bacterial lesions: "Two types of lungs stand out." In early deaths, the lungs were "dark red and wet…dripping wet." French [25] described the lesion as "albuminuous, non-cellular, coagulable.…One realized that this albuminous exudate…was the probable cause of the cyanosis." The exudates were "so entirely unlike what is met with in any ordinary forms of pneumonia that they seemed to be essential importance, the other changes—haemorrhages, broncho-pneumonia and so on—being super additions.…"

Although these pathology findings have been induced with the 1918 influenza virus in models [6], they are also consistent with aspirin toxicity. A study of 177 adults with aspirin toxicity (and a 15% mortality rate) found the most common presentations were depressed consciousness (61%) and respiratory failure (47%), even "at therapeutic levels" [19]. Autopsy findings for patients with the 26 fatal cases were pulmonary edema (46%), ulcers (46%), cerebral hemorrhage (23%), and cerebral edema (31%). Coagulation disturbance or thrombocytopenia was found in 38%. A detailed autopsy of an adult with aspirin poisoning revealed cyanosis, pulmonary congestion, alveolar hemorrhage, subpleural and subepicardial hemorrhages, petechiae, cloudy swelling of the kidneys, and fatty degeneration of the liver [51, 52]. ARDS-like disease has also been reported [53]. Children with aspirin toxicity (or Reye syndrome) are less likely than adults to present with pulmonary edema [35], although in addition to brain swelling, fatty liver, and cloudy swelling of the kidneys [54, 55], some have pulmonary edema [55, 56], "frothy, blood-tinged fluid" [57], and lung hemorrhages [54].

A report from Camp Dix noted, "The disease was a veritable plague. The extraordinary toxicity, the marked prostration, the extreme cyanosis and the rapidity of development stamp this disease as a distinct clinical entity heretofore not fully described.…Pneumonia is an important but somewhat secondary factor" [58, p 1817]. Salicylate toxicity is often overlooked [59] because another condition is present, the dose is thought to be trivial, and the symptoms (hyperventilation, vomiting, sweating, headache, drowsiness, confusion, dyspnea, excitement [salicylate jag], epistaxis, vertigo, pulmonary edema, and hemorrhage) are nonspecific [34]. In 1918, differentiating progressive salicylate intoxication from infection pathologically or clinically, "the dyspnea lasts from a few hours to a day…followed by respiratory failure, circulatory collapse, convulsions, and death" [40], was almost impossible.

ASPIRIN ADVERTISEMENTS IN AUGUST 1918 AND A SERIES OF OFFICIAL RECOMMENDATIONS FOR ASPIRIN IN SEPTEMBER AND EARLY OCTOBER PRECEDED THE DEATH SPIKE OF OCTOBER 1918

In May 1918, usual but highly contagious influenza was publicized in Spain (hence, "Spanish influenza") [48]. In June, after 6 weeks of usual influenza in Europe, serious pulmonary lesions and deaths increased in those "admitted to the special influenza centres," especially those with an "old-standing renal lesion" [60]. In July, increased mortality of young Londoners was documented [61].

Farbenfabriken Bayer's worldwide efforts had left few places lacking aspirin. In the United States, Bayer's giant factory produced aspirin under "American" management. After Bayer executives were charged with violating the Trading with the Enemies Act in August 1918, advertisements encouraged confidence in aspirin [62]. The "Spanish lady" came to the United States and struck 2000 Navy men in Boston in late August. The majority recovered, but oddly, 5%–10% developed a "very severe and massive bronchopneumonia," which, in many, lacked an accompanying leukocytosis [63]. Influenza spread.

Official recommendations for aspirin were issued on 13 September 1918 by the US Surgeon General [64], who stated aspirin had been used in foreign countries "apparently with much success in the relief of symptoms" (p 13), on 26 September 1918 by the US Navy [29], and on 5 October 1918 by *The*

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Journal of the American Medical Association [31]. Recommendations often suggested dose regimens that predispose to toxicity as noted above. At the US Army camp with the highest mortality rate, doctors followed Osler's treatment recommendations, which included aspirin [48], ordering 100,000 tablets [65]. Aspirin sales more than doubled between 1918 and 1920 [66].

The number of deaths in the United States increased steeply, peaking first in the Navy in late September, then in the Army in early October, and finally in the general population in late October [67]. Homeopaths, who thought aspirin was a poison, claimed few deaths [11, 48]. Others may have suspected that aspirin was responsible. On 23 November, 1918, Horder [68] wrote in *The Lancet* that, for "intensely toxic cases…aspirin and all so-called febrifuge drugs must be rigidly excluded from the treatment" (p 695)

In summary, just before the 1918 death spike, aspirin was recommended in regimens now known to be potentially toxic and to cause pulmonary edema and may therefore have contributed to overall pandemic mortality and several of its mysteries. Young adult mortality may be explained by willingness to use the new, recommended therapy and the presence of youth in regimented treatment settings (military). The lower mortality of children may be a result of less aspirin use. The major pediatric text [69] of 1918 recommended hydrotherapy for fever, not salicylate; its 1920 edition [70] condemned the practice of giving "coal tar products" in full doses for reduction of fever. The occurrence of Reye syndrome–like illness before the 1950s is debated and consistent with the fact that children's aspirin was not marketed until the late 1940s. Varying aspirin use may also contribute to the differences in mortality between cities and between military camps.

To determine the proportion of virus-induced pathology, subsequent bacterial infection, and overall 1918 pandemic mortality attributable to salicylate, experimental models and analysis of primary consecutive individual treatment and pathology records are needed. Prospectively, aspirin should be investigated in countries where aspirin is used for influenza.

Acknowledgments

Potential conflicts of interest: K.M.S.: no conflicts.

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ORIGINAL ARTICLE

Safety and Efficacy of the BNT162b2 mRNA Covid-19 Vaccine through 6 Months

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ABSTRACT

BACKGROUND

BNT162b2 is a lipid nanoparticle–formulated, nucleoside-modified RNA vaccine encoding a prefusion-stabilized, membrane-anchored severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) full-length spike protein. BNT162b2 is highly efficacious against coronavirus disease 2019 (Covid-19) and is currently approved, conditionally approved, or authorized for emergency use worldwide. At the time of initial authorization, data beyond 2 months after vaccination were unavailable.

METHODS

In an ongoing, placebo-controlled, observer-blinded, multinational, pivotal efficacy trial, we randomly assigned 44,165 participants 16 years of age or older and 2264 participants 12 to 15 years of age to receive two 30-μg doses, at 21 days apart, of BNT162b2 or placebo. The trial end points were vaccine efficacy against laboratory-confirmed Covid-19 and safety, which were both evaluated through 6 months after vaccination.

RESULTS

BNT162b2 continued to be safe and have an acceptable adverse-event profile. Few participants had adverse events leading to withdrawal from the trial. Vaccine efficacy against Covid-19 was 91.3% (95% confidence interval [CI], 89.0 to 93.2) through 6 months of follow-up among the participants without evidence of previous SARS-CoV-2 infection who could be evaluated. There was a gradual decline in vaccine efficacy. Vaccine efficacy of 86 to 100% was seen across countries and in populations with diverse ages, sexes, race or ethnic groups, and risk factors for Covid-19 among participants without evidence of previous infection with SARS-CoV-2. Vaccine efficacy against severe disease was 96.7% (95% CI, 80.3 to 99.9). In South Africa, where the SARS-CoV-2 variant of concern B.1.351 (or beta) was predominant, a vaccine efficacy of 100% (95% CI, 53.5 to 100) was observed.

CONCLUSIONS

Through 6 months of follow-up and despite a gradual decline in vaccine efficacy, BNT162b2 had a favorable safety profile and was highly efficacious in preventing Covid-19. (Funded by BioNTech and Pfizer; ClinicalTrials.gov number, NCT04368728.)

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*A list of the investigators in the C4591001 Clinical Trial Group is provided in the Supplementary Appendix, available at NEJM.org.

This article was published on September 15, 2021, at NEJM.org.

DOI: 10.1056/NEJMoa2110345

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The coronavirus disease 2019 (COVID-19) pandemic continues, with recent estimates of more than 187 million cases diagnosed and more than 4 million deaths.[1] Vaccines are currently available by means of full approval, conditional marketing approval, and emergency use authorization pathways.[2-5] BNT162b2 is a lipid nanoparticle–formulated,[6] nucleoside-modified RNA[7] encoding the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) full-length spike glycoprotein in a prefusion stabilized conformation.[8] To date, more than 1 billion doses of BNT162b2 have been distributed.

We previously reported safety and efficacy data obtained through a median of 2 months of postimmunization follow-up from a global phase 1–2–3 trial of BNT162b2 involving persons 16 years of age or older. Vaccine efficacy against Covid-19 was 95%. BNT162b2 had a favorable safety profile in diverse populations.[9] These data formed the basis for BNT162b2 emergency or conditional authorizations globally.[10] Safety, efficacy, and immunogenicity data from participants 12 to 15 years of age in this trial have been reported.[11] Here, we report safety and efficacy findings from a prespecified analysis of the phase 2–3 portion of the trial through approximately 6 months of follow-up. These additional data contributed to the full approval of BNT162b2 in the United States.

Methods

Objectives, Participants, and Oversight

This randomized, placebo-controlled, observer-blinded, phase 1–2–3 trial assessed the safety, efficacy, and immunogenicity of the BNT162b2 vaccine in adolescents and adults. The current report of the findings from the phase 2–3 portion of the trial focuses on safety assessments among participants 16 years of age or older and prespecified assessments of vaccine efficacy among participants 12 years of age or older through 6 months of follow-up after immunization. Because the enrollment of participants 12 to 15 years of age began on October 15, 2020, 6-month postimmunization data are currently unavailable for this age cohort. Shorter-duration safety, immunogenicity, and efficacy data for participants 12 to 15 years of age are reported separately[11]; however, data for this cohort are included in the analyses of vaccine efficacy in the overall population (all participants ≥12 years of age) reported here.

Participants who were healthy or had stable chronic medical conditions were eligible. An active immunocompromising condition or recent immunosuppressive therapy was an exclusion criterion. Participants with a history of Covid-19 were excluded, although evidence of current or previous SARS-CoV-2 infection on laboratory testing of trial-obtained samples was not an exclusion criterion. Trial-related responsibilities and ethical conduct are summarized in the Supplementary Appendix, available with the full text of this article at NEJM.org. The protocol contains additional details of the trial and is available at NEJM.org. The first draft of the manuscript was written by the fourth author. The authors had the opportunity to review the data included in this article and confirm the accuracy of the data presented through the specified data cutoff date. The authors vouch for the accuracy and completeness of the data and for the fidelity of the trial to the protocol.

Procedures

The participants were randomly assigned in a 1:1 ratio to receive two 30-μg intramuscular injections, 21 days apart, of BNT162b2 (0.3 ml volume per dose) or saline placebo. Randomization was performed with an interactive Web-based system. Starting in December 2020, after BNT162b2 became available under emergency or conditional use authorizations, participants 16 years of age or older who became eligible for Covid-19 vaccination according to national or local recommendations were given the option to learn their trial assignment. Those who had been randomly assigned to receive placebo were offered BNT162b2. After unblinding of the group assignments, participants were followed in an open-label trial period.

Safety

Safety end points included solicited, prespecified local reactions, systemic events, and antipyretic or pain medication use during the first 7 days after receipt of each vaccine or placebo dose, which were recorded in an electronic diary; unsolicited adverse events after receipt of the first dose through 1 month after the second dose; and serious adverse events after receipt of the first dose through 1 and 6 months after the second dose

was received. Safety data are presented for the blinded follow-up and open-label periods.

EFFICACY

BNT162b2 efficacy against laboratory-confirmed Covid-19 with an onset of 7 days or more after the second dose was assessed and summarized descriptively in participants without serologic or virologic evidence of SARS-CoV-2 infection within 7 days after the second dose and in participants with or without evidence of previous infection. Efficacy against severe Covid-19 was also assessed. Lineages of SARS-CoV-2 detected in midturbinate specimens are reported here for Covid-19 cases that occurred 7 days or more after the second dose in South African participants without evidence of previous infection. Methods for determining SARS-CoV-2 lineages and case definitions for confirmed and severe cases of Covid-19 are summarized in the Supplementary Appendix.

STATISTICAL ANALYSIS

The analysis populations are summarized in Table S1 in the Supplementary Appendix. Safety analyses included participants 16 years of age or older without known human immunodeficiency virus (HIV) infection who provided informed consent and received at least one BNT162b2 or placebo dose. The results of the safety analyses, which are descriptive and not based on formal hypothesis testing, are presented as counts, percentages, and associated Clopper–Pearson 95% confidence intervals for adverse events, according to terms in the *Medical Dictionary for Regulatory Activities*, version 23.1, and reactogenicity events for each trial group. Safety data that were reported up to March 13, 2021, are summarized here. The 95% confidence intervals in this report were not adjusted for multiplicity.

The analysis of vaccine efficacy during the blinded period of the trial included all participants 12 years of age or older without known HIV infection who received at least one BNT162b2 or placebo dose. Vaccine efficacy was calculated as $100 \times (1-\text{IRR})$, where IRR (incidence rate ratio) is the ratio of the rate (number per 1000 person-years of follow-up) of confirmed cases of Covid-19 in the BNT162b2 group to the corresponding rate in the placebo group. Descriptive analyses of vaccine efficacy were performed and associated 95% confidence intervals were calculated with the use of the Clopper–Pearson method, with adjustment for surveillance time, which accounts for potential differential follow-up between the two trial groups. As described in the statistical analysis plan, available with the protocol, hypothesis-testing analyses were performed with the use of a Bayesian approach, and the descriptive analyses presented here were performed with a frequentist approach for clarity of communication. Because the percentage of participants who reported symptoms but were missing a valid polymerase-chain-reaction test result was small and slightly higher in the placebo group, data for these participants were not imputed in the analysis.

The previously reported primary efficacy objective was achieved on the basis of an analysis of 170 accrued cases of Covid-19 that could be evaluated (data cutoff date, November 14, 2020).[9] The current report provides updated efficacy analyses that were performed with data from cases that had accrued up to March 13, 2021.

RESULTS

PARTICIPANTS

Between July 27, 2020, and October 29, 2020, a total of 45,441 participants 16 years of age or older underwent screening, and 44,165 underwent randomization at 152 sites (130 sites in the United States, 1 site in Argentina, 2 sites in Brazil, 4 sites in South Africa, 6 sites in Germany, and 9 sites in Turkey) in the phase 2–3 portion of the trial. Of these participants, 44,060 received at least one dose of BNT162b2 (22,030 participants) or placebo (22,030), and 98% (21,759 in the BNT162b2 group and 21,650 in the placebo group) received the second dose (Fig. 1). During the blinded period of the trial, 51% of the participants in each group had 4 to less than 6 months of follow-up after the second dose; 8% of the participants in the BNT162b2 group and 6% of those in the placebo group had 6 months of follow-up or more after the second dose. During the combined blinded and open-label periods, 55% of the participants in the BNT162b2 group had 6 months of follow-up or more after the second dose. A total of 49% of the participants were female, 82% were White, 10% were Black, and 26% were Hispanic or Latinx; the median age was 51 years. A total of 34% of the participants had a body-mass index (the weight in kilograms divided by the square of the height in meters) of

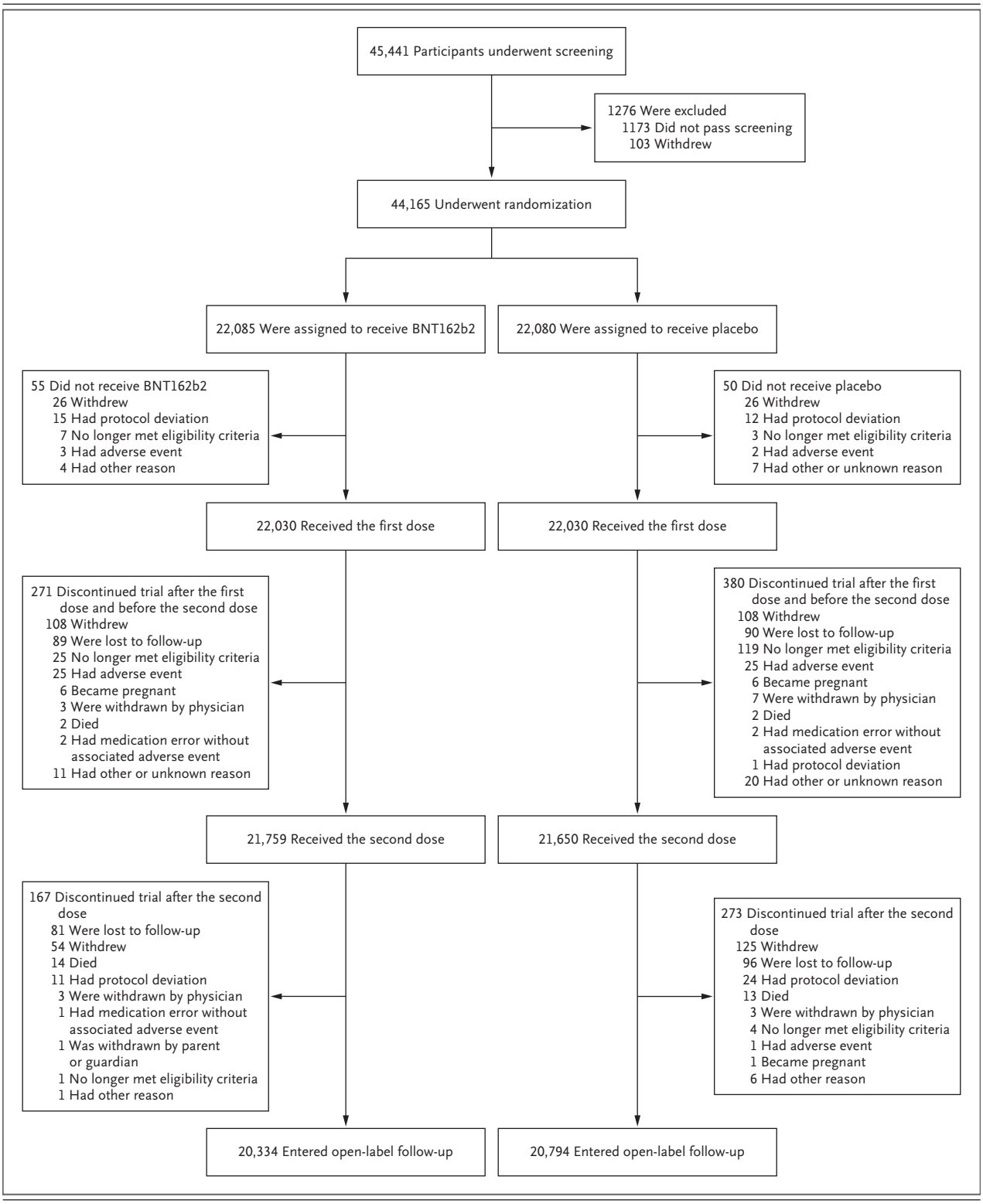

45,441 Participants underwent screening
1276 Were excluded
1173 Did not pass screening
103 Withdrew
44,165 Underwent randomization
22,085 Were assigned to receive BNT162b2
22,080 Were assigned to receive placebo
55 Did not receive BNT162b2
26 Withdrew
15 Had protocol deviation
7 No longer met eligibility criteria
3 Had adverse event
4 Had other reason
50 Did not receive placebo
26 Withdrew
12 Had protocol deviation
3 No longer met eligibility criteria
2 Had adverse event
7 Had other or unknown reason
22,030 Received the first dose
22,030 Received the first dose
271 Discontinued trial after the first dose and before the second dose
108 Withdrew
89 Were lost to follow-up
25 No longer met eligibility criteria
25 Had adverse event
6 Became pregnant
3 Were withdrawn by physician
2 Died
2 Had medication error without associated adverse event
11 Had other or unknown reason
380 Discontinued trial after the first dose and before the second dose
108 Withdrew
90 Were lost to follow-up
119 No longer met eligibility criteria
25 Had adverse event
6 Became pregnant
7 Were withdrawn by physician
2 Died
2 Had medication error without associated adverse event
1 Had protocol deviation
20 Had other or unknown reason
21,759 Received the second dose
21,650 Received the second dose
167 Discontinued trial after the second dose
81 Were lost to follow-up
54 Withdrew
14 Died
11 Had protocol deviation
3 Were withdrawn by physician
1 Had medication error without associated adverse event
1 Was withdrawn by parent or guardian
1 No longer met eligibility criteria
1 Had other reason
273 Discontinued trial after the second dose
125 Withdrew
96 Were lost to follow-up
24 Had protocol deviation
13 Died
3 Were withdrawn by physician
4 No longer met eligibility criteria
1 Had adverse event
1 Became pregnant
6 Had other reason
20,334 Entered open-label follow-up
20,794 Entered open-label follow-up

Figure 1 (facing page). Screening, Randomization, and Follow-up.

The diagram represents all enrolled participants 16 years of age or older through the data cutoff date (March 13, 2021). The diagram includes two deaths that occurred after the second dose in human immunodeficiency virus (HIV)–infected participants (one in the BNT162b2 group and one in the placebo group; these deaths were not reported in the Results section of this article because the analysis of HIV-infected participants is being conducted separately). Information on the screening, randomization, and follow-up of the participants 12 to 15 years of age has been reported previously.[11]

30.0 or more, 21% had at least one underlying medical condition, and 3% had baseline evidence of a previous or current SARS-CoV-2 infection (Table 1 and Table S2).

Between October 15, 2020, and January 12, 2021, a total of 2306 participants 12 to 15 years of age underwent screening, and 2264 underwent randomization at 29 U.S. sites. Of these participants, 2260 received at least one dose of BNT162b2 (1131 participants) or placebo (1129), and 99% (1124 in the BNT162b2 group and 1117 in the placebo group) received the second dose.[11] Among participants who received at least one dose of BNT162b2 or placebo, 58% had at least 2 months of follow-up after the second dose, 49% were female, 86% were White, 5% were Black, and 12% were Hispanic or Latinx. Full details of the demographic characteristics of the participants have been reported previously.[11]

SAFETY

Reactogenicity

The subgroup that was evaluated for reactogenicity in the current report, in which reactions were reported in an electronic diary, included 9839 participants 16 years of age or older. In this subgroup, 8183 participants had been included in the previous analysis, and 1656 were enrolled after the data cutoff for that analysis.[9] The reactogenicity profile of BNT162b2 in this expanded subgroup did not differ substantially from that described previously.[9] This subgroup included 364 participants who had evidence of previous SARS-CoV-2 infection, 9426 who did not have evidence, and 49 who lacked the data needed to determine previous infection status.

More participants in the BNT162b2 group than in the placebo group reported local reactions, the most common of which was mild-to-moderate pain at the injection site (Fig. S1A). Local reactions were reported with similar frequency among the participants with or without evidence of previous SARS-CoV-2 infection, and the reactions were of similar severity. No local reactions of grade 4 (according to the guidelines of the Center for Biologics Evaluation and Research[12]) were reported.

More participants in the BNT162b2 group than in the placebo group reported systemic events, the most common of which was fatigue (Fig. S1B). Systemic events were mostly mild to moderate in severity, but there were occasional severe events. Systemic reactogenicity was similar among those with or without evidence of previous SARS-CoV-2 infection, although BNT162b2 recipients with evidence of previous infection reported systemic events more often after receipt of the first dose, and those without evidence reported systemic events more often after receipt of the second dose. For example, 12% of recipients with evidence of previous SARS-CoV-2 infection and 3% of those without evidence reported fever after receipt of the first dose; 8% of those with evidence of previous infection and 15% of those without evidence reported fever after the second dose. The highest temperature reported was a transient fever of higher than 40.0°C on day 2 after the second dose in a BNT162b2 recipient without evidence of previous infection.

Adverse Events

Analyses of adverse events during the blinded period included 43,847 participants 16 years of age or older (Table S3). Reactogenicity events among the participants who were not in the reactogenicity subgroup were reported as adverse events, which resulted in imbalances between the BNT162b2 group and the placebo group with respect to adverse events (30% vs. 14%), related adverse events (24% vs. 6%), and severe adverse events (1.2% vs. 0.7%). New adverse events attributable to BNT162b2 that were not previously

Table 1. Demographic Characteristics of the Participants at Baseline.*

Characteristic	BNT162b2 (N = 22,026)	Placebo (N = 22,021)	Total (N = 44,047)
Sex — no. (%)			
Male	11,322 (51.4)	11,098 (50.4)	22,420 (50.9)
Female	10,704 (48.6)	10,923 (49.6)	21,627 (49.1)
Race or ethnic group — no. (%)†			
White	18,056 (82.0)	18,064 (82.0)	36,120 (82.0)
Black or African American	2,098 (9.5)	2,118 (9.6)	4,216 (9.6)
Asian	952 (4.3)	942 (4.3)	1,894 (4.3)
American Indian or Alaska Native	221 (1.0)	217 (1.0)	438 (1.0)
Native Hawaiian or other Pacific Islander	58 (0.3)	32 (0.1)	90 (0.2)
Multiracial	550 (2.5)	533 (2.4)	1,083 (2.5)
Not reported	91 (0.4)	115 (0.5)	206 (0.5)
Ethnicity†			
Hispanic or Latinx	5,704 (25.9)	5,695 (25.9)	11,399 (25.9)
Not reported	111 (0.5)	114 (0.5)	225 (0.5)
Country — no. (%)			
Argentina	2,883 (13.1)	2,881 (13.1)	5,764 (13.1)
Brazil	1,452 (6.6)	1,448 (6.6)	2,900 (6.6)
Germany	249 (1.1)	250 (1.1)	499 (1.1)
South Africa	401 (1.8)	399 (1.8)	800 (1.8)
Turkey	249 (1.1)	249 (1.1)	498 (1.1)
United States	16,792 (76.2)	16,794 (76.3)	33,586 (76.3)
Age group at vaccination — no. (%)			
16–55 yr	13,069 (59.3)	13,095 (59.5)	26,164 (59.4)
>55 yr	8,957 (40.7)	8,926 (40.5)	17,883 (40.6)
Age at vaccination — yr			
Median	51.0	51.0	51.0
Range	16–89	16–91	16–91
SARS-CoV-2 status — no. (%)‡			
Positive	689 (3.1)	716 (3.3)	1,405 (3.2)
Negative	21,185 (96.2)	21,180 (96.2)	42,365 (96.2)
Missing data	152 (0.7)	125 (0.6)	277 (0.6)
Body-mass index — no. (%)§			
≥30.0: obese	7,543 (34.2)	7,629 (34.6)	15,172 (34.4)
Missing data	7 (<1)	6 (<1)	13 (<1)

* Data are summarized for participants 16 years of age or older in the safety population. The demographic characteristics of participants 12 to 15 years of age were reported previously.[11] Percentages may not total 100 because of rounding. SARS-CoV-2 denotes severe acute respiratory syndrome coronavirus 2.
† Race and ethnicity were reported by the participants. The categories shown are those that were used to collect the data.
‡ Positive status was defined as a positive N-binding antibody result or a positive nucleic acid amplification test (NAAT) result at visit 1 or medical history of coronavirus disease 2019 (Covid-19). Negative status was defined as a negative N-binding antibody result or a negative NAAT result at visit 1 and no medical history of Covid-19.
§ The body-mass index is the weight in kilograms divided by the square of the height in meters.

Table 2. Vaccine Efficacy against Covid-19 from 7 Days after Receipt of the Second Dose during the Blinded, Placebo-Controlled Follow-up Period.*

Efficacy End Point	BNT162b2			Placebo			Vaccine Efficacy (95% CI)‡
	No. of Cases	Surveillance Time†	No. at Risk	No. of Cases	Surveillance Time†	No. at Risk	
		1000 person-yr			*1000 person-yr*		*percent*
		(N=20,998)			**(N=21,096)**		
First occurrence of Covid-19 from 7 days after receipt of the second dose among participants without evidence of previous infection	77	6.247	20,712	850	6.003	20,713	91.3 (89.0–93.2)
		(N=22,166)			**(N=22,320)**		
First occurrence of Covid-19 from 7 days after receipt of the second dose among participants with or without evidence of previous infection	81	6.509	21,642	873	6.274	21,689	91.1 (88.8–93.0)

* This analysis included participants who had no serologic or virologic evidence (within 7 days after receipt of the second dose) of previous SARS-CoV-2 infection (i.e., negative N-binding antibody [serum] test at visit 1 and SARS-CoV-2 not detected by NAAT [nasal swab] at visits 1 and 2) and had a negative NAAT at any unscheduled visit up to 7 days after receipt of the second dose.

† The surveillance time is the total time (in 1000 person-years) at risk for the given end point across all participants within each group. The time period for the accrual of Covid-19 cases was from 7 days after the second dose to the end of the surveillance period.

‡ Vaccine efficacy was calculated as 100×(1−IRR), where IRR (incidence rate ratio) is the ratio of the rate (number per 1000 person-years of follow-up) of confirmed cases of Covid-19 in the BNT162b2 group to the corresponding rate in the placebo group. The 95% confidence interval for vaccine efficacy was derived with the use of the Clopper–Pearson method, with adjustment for surveillance time.

identified in earlier reports included decreased appetite, lethargy, asthenia, malaise, night sweats, and hyperhidrosis. Few participants had serious adverse events or adverse events that led to trial withdrawal. No new serious adverse events were considered by the investigators to be related to BNT162b2 after the data cutoff date of the previous report.[9]

During the combined blinded and open-label periods, cumulative safety data during follow-up were available through 6 months after the second dose for 12,006 participants who were originally randomly assigned to the BNT162b2 group. No new safety signals relative to the previous report were observed during the longer follow-up period in the current report, which included open-label observation of the original BNT162b2 recipients and placebo recipients who received BNT162b2 after unblinding.[9]

During the blinded, placebo-controlled period, 15 participants in the BNT162b2 group and 14 in the placebo group died; during the open-label period, 3 participants in the BNT162b2 group and 2 in the original placebo group who received BNT162b2 after unblinding died. None of these deaths were considered to be related to BNT162b2 by the investigators. Causes of death were balanced between BNT162b2 and placebo groups (Table S4).

Safety monitoring will continue according to the protocol for 2 years after the second dose for participants who originally received BNT162b2 and for 18 months after the second BNT162b2 dose for placebo recipients who received BNT162b2 after unblinding.

EFFICACY

Among 42,094 participants 12 years of age or older who could be evaluated and had no evidence of previous SARS-CoV-2 infection, Covid-19 with an onset of 7 days or more after the second dose was observed in 77 vaccine recipients and in 850 placebo recipients up to the data cutoff date (March 13, 2021), corresponding to a vaccine efficacy of 91.3% (95% confidence interval [CI], 89.0 to 93.2) (Table 2). Among 44,486 participants

with or without evidence of previous infection who could be evaluated, cases of Covid-19 were observed in 81 vaccine recipients and in 873 placebo recipients, corresponding to a vaccine efficacy of 91.1% (95% CI, 88.8 to 93.0).

Among the participants with evidence of previous SARS-CoV-2 infection based on a positive baseline N-binding antibody test, Covid-19 was observed in 2 vaccine recipients after the first dose and in 7 placebo recipients. Among the participants with evidence of previous SARS-CoV-2 infection based on a positive nucleic acid amplification test at baseline, cases of Covid-19 were observed in 10 vaccine recipients and in 9 placebo recipients (Table S5). Covid-19 was less common among the placebo recipients with positive N-binding antibodies at trial entry (7 of 542 participants, for an incidence of 1.3%) than among those without evidence of infection at trial entry (1015 of 21,521, for an incidence of 4.7%); these findings indicate that previous infection conferred approximately 72.6% protection.

Among the participants with or without evidence of previous infection, cases of Covid-19 were observed in 46 vaccine recipients and in 110 placebo recipients from receipt of the first dose up to receipt of the second dose, corresponding to a vaccine efficacy of 58.4% (95% CI, 40.8 to 71.2) (Fig. 2). During the interval from the approximate start of observed protection at 11 days after receipt of the first dose up to receipt of the second dose, vaccine efficacy increased to 91.7% (95% CI, 79.6 to 97.4). From its peak after the second dose, observed vaccine efficacy declined. From 7 days to less than 2 months after the second dose, vaccine efficacy was 96.2% (95% CI, 93.3 to 98.1); from 2 months to less than 4 months after the second dose, vaccine efficacy was 90.1% (95% CI, 86.6 to 92.9); and from 4 months after the second dose to the data cutoff date, vaccine efficacy was 83.7% (95% CI, 74.7 to 89.9).

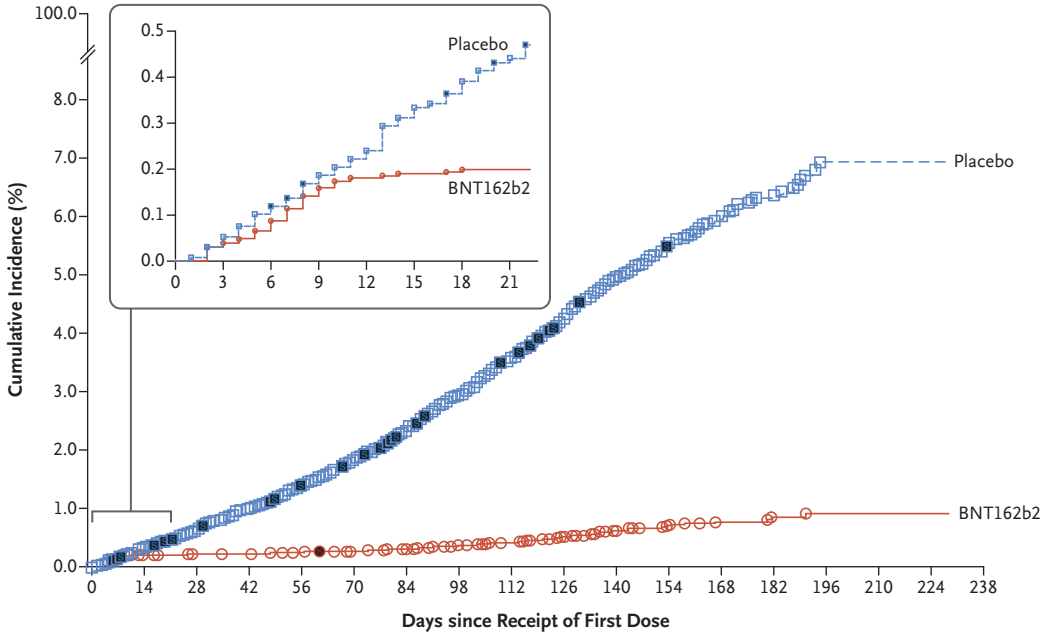
Severe Covid-19, as defined by the Food and Drug Administration,[13] with an onset after receipt of the first dose occurred in 31 participants, of whom 30 were placebo recipients; this finding corresponds with a vaccine efficacy of 96.7% (95% CI, 80.3 to 99.9) against severe Covid-19 (Fig. 2 and Table S6). Although the trial was not powered to definitively assess efficacy according to subgroup, supplemental analyses indicated that vaccine efficacy after the second dose in subgroups defined according to age, sex, race, ethnic group, presence or absence of coexisting medical conditions, and country was generally consistent with that observed in the overall population (Table 3 and Table S7).

Given the concern about the SARS-CoV-2 B.1.351 (or beta) variant, which appears to be neutralized less efficiently by BNT162b2-immune sera than many other lineages,[14] whole-viral-genome sequencing was performed on midturbinate samples from Covid-19 cases observed in South Africa, where this lineage was prevalent. Nine cases of Covid-19 were observed in South African participants without evidence of previous SARS-CoV-2 infection, all of whom were placebo recipients; this finding corresponds with a vaccine efficacy of 100% (95% CI, 53.5 to 100) (Table 3). Midturbinate specimens from 8 of 9 cases contained sufficient viral RNA for whole-genome sequencing. All viral genomes were the beta variant (Global Initiative on Sharing All Influenza Data accession codes are provided in the Supplementary Appendix).

DISCUSSION

In this update to the preliminary safety and efficacy report of two 30-μg doses, at 21 days apart, of BNT162b2, 91.1% vaccine efficacy against Covid-19 was observed from 7 days to 6 months after the second dose in participants 12 years of age or older. Vaccine efficacy against severe disease with an onset after receipt of the first dose was approximately 97%. This finding, combined with the totality of available evidence, including real-world effectiveness data,[15-18] alleviates theoretical concerns over potential enhancement of vaccine-mediated disease.[19]

The benefit of BNT162b2 immunization started approximately 11 days after receipt of the first dose, with 91.7% vaccine efficacy from 11 days after receipt of the first dose up to receipt of the second dose. The trial cannot provide information on persistence of protection after a single dose, because 99% of the participants received the second dose as scheduled during the blinded trial period. A recent trial showed that although nonneutralizing viral antigen–binding antibody levels rise between the first and second BNT162b2 dose, serum neutralizing titers are low or undetectable during this interval.[20] Early protection against Covid-19 without strong serum neutral-



Efficacy End Point	BNT162b2 (N=23,040)			Placebo (N=23,037)			Vaccine Efficacy
	No. of cases	Surveillance time	No. at risk	No. of cases	Surveillance time	No. at risk	
		1000 person-yr			*1000 person-yr*		*% (95% CI)*
Overall: first occurrence of Covid-19 after receipt of first dose	131	8.412	22,505	1034	8.124	22,434	87.8 (85.3 to 89.9)
After receipt of first dose up to receipt of second dose	46	1.339	22,505	110	1.331	22,434	58.4 (40.8 to 71.2)
<11 Days after receipt of first dose	41	0.677	22,505	50	0.675	22,434	18.2 (–26.1 to 47.3)
≥11 Days after receipt of first dose up to receipt of second dose	5	0.662	22,399	60	0.656	22,369	91.7 (79.6 to 97.4)
After receipt of second dose to <7 days after	3	0.424	22,163	35	0.422	22,057	91.5 (72.9 to 98.3)
≥7 Days after receipt of second dose	82	6.649	22,132	889	6.371	22,001	91.2 (88.9 to 93.0)
≥7 Days after receipt of second dose to <2 mo after	12	2.923	22,132	312	2.884	22,001	96.2 (93.3 to 98.1)
≥2 Mo after receipt of second dose to <4 mo after	46	2.696	20,814	449	2.593	20,344	90.1 (86.6 to 92.9)
≥4 Mo after receipt of second dose	24	1.030	12,670	128	0.895	11,802	83.7 (74.7 to 89.9)

Figure 2. Efficacy of BNT162b2 against Covid-19 after Receipt of the First Dose (Blinded Follow-up Period).

The top of the figure shows the cumulative incidence curves for the first occurrence of coronavirus disease 2019 (Covid-19) after receipt of the first dose (efficacy analysis population of participants ≥12 years of age who could be evaluated). Each symbol represents Covid-19 cases starting on a given day, and filled symbols represent severe Covid-19 cases. Because of overlapping dates, some symbols represent more than one case. The inset shows the same data on an enlarged y axis through 21 days. The bottom of the figure shows the time intervals for the first occurrence of Covid-19 in the efficacy analysis population, as well as the surveillance time, which is given as the total time (in 1000 person-years) at risk for the given end point across all participants within each group. The time period for the accrual of Covid-19 cases was from after receipt of the first dose to the end of the surveillance period for the overall row and from the start to the end of the range stated for each time interval. Vaccine efficacy was calculated as 100×(1−IRR), where IRR (incidence rate ratio) is the ratio of the rate (number per 1000 person-years of follow-up) of confirmed cases of Covid-19 in the BNT162b2 group to the corresponding rate in the placebo group. The 95% confidence interval for vaccine efficacy was derived with the use of the Clopper–Pearson method, with adjustment for surveillance time.

ization indicates that neutralizing titers alone do not appear to explain early BNT162b2-mediated protection from Covid-19. Other immune mechanisms (e.g., innate immune responses, CD4+ or CD8+ T-cell responses, B-cell memory responses, and antibody-dependent cytotoxicity) may contribute to protection.[21-26]

Efficacy peaked at 96.2% during the interval from 7 days to less than 2 months after the second dose and declined gradually to 83.7% from

Table 3. Vaccine Efficacy against Covid-19 up to 7 Days after Receipt of the Second Dose among Participants without Evidence of Infection.*

First Occurrence of Covid-19 after Receipt of the First Dose	BNT162b2 (N=20,998)			Placebo (N=21,096)			Vaccine Efficacy (95% CI)‡
	No. of Cases	Surveillance Time†	No. at Risk	No. of Cases	Surveillance Time†	No. at Risk	
		1000 person-yr			*1000 person-yr*		*percent*
Overall population	77	6.247	20,712	850	6.003	20,713	91.3 (89.0 to 93.2)
Age group — yr							
16 or 17	0	0.061	342	10	0.057	331	100 (58.2 to 100)
16 to 55	52	3.593	11,517	568	3.439	11,533	91.2 (88.3 to 93.5)
≥55	25	2.499	8,194	266	2.417	8,208	90.9 (86.3 to 94.2)
≥65	7	1.233	4,192	124	1.202	4,226	94.5 (88.3 to 97.8)
≥75	1	0.239	842	26	0.237	847	96.2 (76.9 to 99.9)
Sex							
Male	42	3.246	10,637	399	3.047	10,433	90.1 (86.4 to 93.0)
Female	35	3.001	10,075	451	2.956	10,280	92.4 (89.2 to 94.7)
Race or ethnic group§							
White	67	5.208	17,186	747	5.026	17,256	91.3 (88.9 to 93.4)
Black or African American	4	0.545	1,737	48	0.527	1,737	91.9 (78.0 to 97.9)
Asian	3	0.260	946	23	0.248	934	87.6 (58.9 to 97.6)
American Indian or Alaska Native	0	0.041	186	3	0.037	176	100 (–119.0 to 100)
Native Hawaiian or other Pacific Islander	0	0.015	54	1	0.008	30	100 (–1961.2 to 100)
Multiracial	3	0.151	518	22	0.128	476	88.5 (61.6 to 97.8)
Not reported	0	0.026	85	6	0.030	104	100 (2.8 to 100)
Ethnicity§							
Hispanic or Latinx	29	1.786	5,161	241	1.711	5,120	88.5 (83.0 to 92.4)
Non-Hispanic and non-Latinx	47	4.429	15,449	609	4.259	15,484	92.6 (90.0 to 94.6)
Not reported	1	0.032	102	0	0.033	109	NA
Country							
Argentina	15	1.012	2,600	108	0.986	2,586	86.5 (76.7 to 92.7)
Brazil	12	0.406	1,311	80	0.374	1,293	86.2 (74.5 to 93.1)
Germany	0	0.047	236	1	0.048	242	100 (–3874.2 to 100)
South Africa	0	0.080	291	9	0.074	276	100 (53.5 to 100)
Turkey	0	0.027	228	5	0.025	222	100 (–0.1 to 100)
United States	50	4.674	16,046	647	4.497	16,046	92.6 (90.1 to 94.5)

* This analysis of vaccine efficacy during the blinded, placebo-controlled follow-up period included all participants who had undergone randomization and were 12 years of age or older without baseline evidence of previous infection who had undergone randomization. NA denotes not applicable.

† Surveillance time is the total time (in 1000 person-years) at risk for the given end point across all participants within each group. The time period for the accrual of Covid-19 cases was from 7 days after the second dose to the end of the surveillance period.

‡ Vaccine efficacy was calculated as 100×(1−IRR). The 95% confidence interval for vaccine efficacy was derived with the use of the Clopper–Pearson method, with adjustment for surveillance time.

§ Race and ethnicity were reported by the participants. The categories shown are those that were used to collect the data.

4 months after the second dose to the data cutoff date — an average decline of approximately 6% every 2 months. Ongoing follow-up is needed to understand persistence of the vaccine effect over time, the need for booster dosing, and timing of such a dose. Most participants who initially received placebo have now been immunized with BNT162b2, ending the placebo-controlled period of the trial. Nevertheless, ongoing observation of participants through 2 years in this trial, together with real-world effectiveness data,[15-18] will determine whether a booster is likely to be beneficial after a longer interval. Booster trials to evaluate safety and immunogenicity of BNT162b2 are under way to prepare for this possibility.

From 7 days after the second dose, 86 to 100% efficacy was observed across diverse demographic profiles, including age, sex, race or ethnic group, and factors that increase the risk of Covid-19, such as high body-mass index and other coexisting medical conditions. BNT162b2 was also highly efficacious in various geographic regions including North America, Europe, South Africa, and Latin America. Although vaccine efficacy was slightly lower in Latin American countries, BNT162b2 had a high efficacy of approximately 86% in Argentina and Brazil. Circulation of SARS-CoV-2 variants — some of which are associated with more rapid transmission and potentially greater pathogenicity[27] — has raised concerns that such variants could evade vaccine-mediated protection. Our studies of in vitro neutralization of a variety of SARS-CoV-2 variants have, to date, showed that all tested BNT162b2-immune sera neutralize all tested variants.[14,28-32] The beta variant, which has shown the greatest reduction in neutralization and was the dominant strain in South Africa during the reported observation period, is still neutralized at serum titers higher than those observed at the onset of protection against Covid-19 after the first vaccine dose.[9,14,20] We found that BNT162b2 had an observed efficacy of 100% (95% CI, 53.5 to 100) against Covid-19 in South Africa (9 cases occurred in the placebo recipients and 0 cases in the BNT162b2 recipients), and 8 of 9 cases for which sequence information could be obtained involved the beta variant of SARS-CoV-2.

Safety data are now available for approximately 44,000 participants 16 years of age or older; 12,006 participants have at least 6 months of safety follow-up data after a second BNT162b2 dose. The safety profile observed at a median of 2 months after immunization was confirmed through 6 months after immunization in the current analysis. No cases of myocarditis were noted.

Before immunization, 3% of the participants 16 years of age or older had evidence of SARS-CoV-2 infection. Although this group had a slightly higher incidence of systemic reactogenicity events after receipt of the first dose than those without evidence of previous infection, the group had a slightly lower incidence of reactogenicity events after the second dose than those without previous infection. Thus, there was minimal observed difference in the overall reactogenicity profile on the basis of infection status at baseline. Nine cases of Covid-19 were observed among participants with previous serologically defined natural infection: two cases were observed among the vaccine recipients and seven among the placebo recipients. These data support the current practice of immunizing without screening for evidence of previous infection.

This report has several limitations. Duration of protection and safety data that could be collected in a blinded, placebo-controlled manner were limited by the ethical and practical need to immunize eligible initial placebo recipients under emergency use authorization and according to the recommendations of public health authorities. The data presented here do not address whether vaccination prevents asymptomatic infection; however, evaluation of that question is ongoing in this trial, and real-world data suggest that BNT162b2 prevents asymptomatic infection.[33,34] Preliminary analyses of breakthrough cases have not yet identified a correlate of protection, since vaccine protection rates remain high. This report does not address vaccine efficacy and safety in pregnant women and in children younger than 12 years of age. Studies evaluating BNT162b2 in these populations are ongoing.

The data in this report show that BNT162b2 prevents Covid-19 effectively for up to 6 months after the second dose across diverse populations, despite the emergence of SARS-CoV-2 variants, including the beta variant, and the vaccine continues to show a favorable safety profile.

Supported by BioNTech and Pfizer.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

A data sharing statement provided by the authors is available with the full text of this article at NEJM.org.

We thank all the participants who volunteered for this trial; the investigators in the C4591001 Clinical Trial Group for their contributions; the members of our data monitoring committee (Jonathan Zenilman [chair], Robert Belshe, Kathryn Edwards, Stephen Self, and Lawrence Stanberry) for their review of the data; Tricia Newell, Sheena Hunt, and Philippa Jack of ICON (North Wales, PA) for editorial support, which was funded by Pfizer; the following Pfizer staff: Greg Adams, Negar Aliabadi, Mohanish Anand, Fred Angulo, Ayman Ayoub, Melissa Bishop-Murphy, Mark Boaz, Christopher Bowen, Donna Boyce, Sarah Burden, Andrea Cawein, Patrick Caubel, Darren Cowen, Kimberly Ann Cristall, Michael Cruz, Daniel Curcio, Gabriela Dávila, Carmel Devlin, Gokhan Duman, Niesha Foster, Maja Gacic, Juleen Gayed, Ahmed Hassan, Luis Jodar, Stephen Kay, William Lam, Esther Ladipo, Joaquina Maria Lazaro, Marie-Pierre Hellio Le Graverand-Gastineau, Kwok Lee, Zhenghui Li, Jacqueline Lowenberg, Hua Ma, Rod MacKenzie, Robert Maroko, Jason McKinley, Tracey Mellelieu, Neda Aghajani Memar, Farheen Muzaffar, Brendan O'Neill, Jason Painter, Elizabeth Paulukonis, Allison Pfeffer, Katie Puig, Kimberly Rarrick, Balaji Prabu Raja, Christine Rainey, Kellie Lynn Richardson, Elizabeth Rogers, Melinda Rottas, Charulata Sabharwal, Uzma Sarwar, Vilas Satishchandran, Harpreet Seehra, Judy Sewards, Huiqing Si, Helen Smith, David Swerdlow, James Trammel, Elisa Harkins Tull, Sarah Tweedy, Erica Weaver, John Wegner, Jenah West, Christopher Webber, David C. Whritenour, Fae Wooding, Emily Worobetz, Nita Zalavadia, and Liping Zhang, as well as the Vaccines Clinical Assay Team, the Vaccines Assay Development Team, and all the Pfizer colleagues not named here who contributed to the success of this trial; the following BioNTech staff: Corinna Rosenbaum, Christian Miculka, Andreas Kuhn, Ferdia Bates, Paul Strecker, Ruben Rizzi, Martin Bexon, Eleni Lagkadinou, and Alexandra Kemmer-Brück; and Dietmar Katinger and Andreas Wagner at Polymun.

APPENDIX

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Evidence-Based Medicine

In the 1990s, **evidence-based medicine** emerged as a way to improve and evaluate patient care. It involves combining the best research evidence with the patient's values to make decisions about medical care. Looking at all available medical studies and literature that pertain to an individual patient or a group of patients helps doctors to properly diagnose illnesses, to choose the best testing plan, and to select the best treatments and methods of disease prevention. Using evidence-based medicine techniques for large groups of patients with the same illness, doctors can develop **practice guidelines** for evaluation and treatment of particular conditions. In addition to improving treatment, such guidelines can help individual physicians and institutions measure their performance and identify areas for further study and improvement. The February 25, 2009, issue of *JAMA* includes an article about the importance of using evidence-based medicine to develop practice guidelines. This Patient Page is based on one published in the September 6, 2006, issue of *JAMA*.

LOOKING FOR EVIDENCE IN MEDICAL LITERATURE

Systematic reviews of the medical literature, large **randomized controlled trials** (the best way to assess the efficacy of a treatment), and **large prospective studies** (followed up over time) are types of research published in the medical literature that can be helpful in providing evidence about tests and treatments. Reports of the experiences of individual patients or small groups usually provide less reliable evidence, although they may provide important clues about possible adverse effects of treatments.

USING EVIDENCE-BASED MEDICINE

Practice guidelines developed using evidence-based medicine have helped to reduce **mortality** (chance of dying) from heart attacks. Evidence-based medicine guidelines have also improved care for persons with diabetes and other common medical problems. Evidence-based medicine does not replace physicians' judgment based on clinical experience. Any recommendations taken from evidence-based medicine must be applied by a physician to the unique situation of an individual patient. Sometimes there is no reliable research evidence to guide decision making, and some conditions are rare enough that there is no way to do large studies.

IMPROVING YOUR HEALTH

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Sources: National Institutes of Health, The Cochrane Collaboration, Centre for Evidence-Based Medicine, American Heart Association, American Diabetes Association

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RESEARCH ARTICLE SUMMARY

CORONAVIRUS

Impact of community masking on COVID-19: A cluster-randomized trial in Bangladesh

Jason Abaluck*†, Laura H. Kwong†, Ashley Styczynski†, Ashraful Haque, Md. Alamgir Kabir, Ellen Bates-Jefferys, Emily Crawford, Jade Benjamin-Chung, Shabib Raihan, Shadman Rahman, Salim Benhachmi, Neeti Zaman Bintee, Peter J. Winch, Maqsud Hossain, Hasan Mahmud Reza, Abdullah All Jaber, Shawkee Gulshan Momen, Aura Rahman, Faika Laz Banti, Tahrima Saiha Huq, Stephen P. Luby‡, Ahmed Mushfiq Mobarak*‡

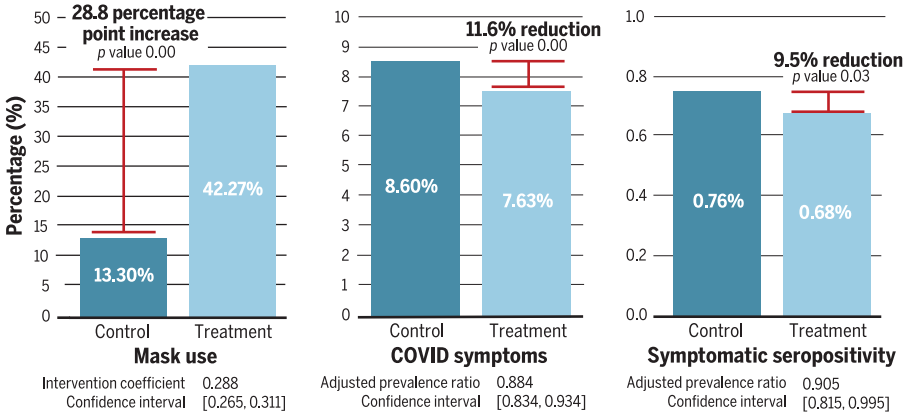
INTRODUCTION: Mask usage remains low across many parts of the world during the COVID-19 pandemic, and strategies to increase mask-wearing remain untested. Our objectives were to identify strategies that can persistently increase mask-wearing and assess the impact of increasing mask-wearing on symptomatic severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infections.

RATIONALE: We conducted a cluster-randomized trial of community-level mask promotion in rural Bangladesh from November 2020 to April 2021 (N = 600 villages, N = 342,183 adults). We cross-randomized mask promotion strategies at the village and household level, including cloth versus surgical masks. All intervention arms received free masks, information on the importance of masking, role modeling by community leaders, and in-person reminders for 8 weeks. The control group did not receive any interventions. Participants and surveillance staff were not informed of treatment assignments, but project materials were clearly visible. Outcomes included symptomatic SARS-CoV-2 seroprevalence (primary) and prevalence of proper mask-wearing, physical distancing, social distancing, and symptoms consistent with COVID-19 illness (secondary). Mask-wearing and distancing were assessed through direct observation at least weekly at mosques, markets, the main entrance roads to villages, and tea stalls. Individuals were coded as physically distanced if they were at least one arm's length from the nearest adult; social distancing was measured using the total number of adults observed in public areas. At 5- and 9-week follow-ups, we surveyed all reachable participants about COVID-19–related symptoms. Blood samples collected at 10- to 12-week follow-ups for symptomatic individuals were analyzed for SARS-CoV-2 immunoglobulin G (IgG) antibodies.

RESULTS: There were 178,322 individuals in the intervention group and 163,861 individuals in the control group. The intervention increased proper mask-wearing from 13.3% in control villages (N = 806,547 observations) to 42.3% in treatment villages (N = 797,715 observations) (adjusted percentage point difference = 0.29; 95% confidence interval = [0.26, 0.31]). This tripling of mask usage was sustained during the intervention period and for 2 weeks after. Physical distancing increased from 24.1% in control villages to 29.2% in treatment villages (adjusted percentage point difference = 0.05 [0.04, 0.06]). We saw no change in social distancing. After 5 months, the impact of the intervention on mask-wearing waned, but mask-wearing remained 10 percentage points higher in the intervention group. Beyond the core intervention of free distribution and promotion at households, mosques, and markets; leader endorsements; and periodic monitoring and reminders, several elements had no additional effect on mask-wearing, including text reminders, public signage commitments, monetary or nonmonetary incentives, and altruistic messaging or verbal commitments.

The proportion of individuals with COVID-19–like symptoms was 7.63% (N = 12,784) in the intervention arm and 8.60% (N = 13,287) in the control arm, an estimated 11.6% reduction after controlling for baseline covariates. Blood samples were collected from consenting, symptomatic adults (N = 10,790). Adjusting for baseline covariates, the intervention reduced symptomatic seroprevalence by 9.5% (adjusted prevalence ratio = 0.91 [0.82, 1.00]; control prevalence = 0.76%; treatment prevalence = 0.68%). We find that surgical masks are particularly effective in reducing symptomatic seroprevalence of SARS-CoV-2. In villages randomized to surgical masks (N = 200), the relative reduction was 11.1% overall (adjusted prevalence ratio = 0.89 [0.78, 1.00]). The effect of the intervention is most concentrated among the elderly population; in surgical mask villages, we observe a 35.3% reduction in symptomatic seroprevalence among individuals ≥60 years old (adjusted prevalence ratio = 0.65 [0.45, 0.85]). We see larger reductions in symptoms and symptomatic seropositivity in villages that experienced larger increases in mask use. No adverse events were reported.

CONCLUSION: A randomized-trial of community-level mask promotion in rural Bangladesh during the COVID-19 pandemic shows that the intervention increased mask usage and reduced symptomatic SARS-CoV-2 infections, demonstrating that promoting community mask-wearing can improve public health. ■



Impact of intervention on mask use and biological outcomes. The figure shows the raw means of mask-wearing (left), COVID-19 symptoms (middle), and symptomatic seropositivity (right) in the control and treatment arms. The estimated change in each outcome, confidence intervals, and p values adjust for preregistered covariates (and thus are not computable from the raw values). Individuals who were symptomatic but did not consent to blood collection were dropped from the sample; measured symptomatic seropositivity thus understates the true fraction of the population that was symptomatic seropositive.

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Cite this article as J. Abaluck *et al.*, *Science* **375**, eabi9069 (2022). DOI: 10.1126/science.abi9069

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RESEARCH ARTICLE

CORONAVIRUS

Impact of community masking on COVID-19: A cluster-randomized trial in Bangladesh

Jason Abaluck[1]*†, Laura H. Kwong[2,3]†, Ashley Styczynski[4]†, Ashraful Haque[5], Md. Alamgir Kabir[5], Ellen Bates-Jefferys[6], Emily Crawford[1], Jade Benjamin-Chung[7], Shabib Raihan[5], Shadman Rahman[5], Salim Benhachmi[8], Neeti Zaman Bintee[5], Peter J. Winch[9], Maqsud Hossain[10], Hasan Mahmud Reza[11], Abdullah All Jaber[10], Shawkee Gulshan Momen[10], Aura Rahman[10], Faika Laz Banti[10], Tahrima Saiha Huq[10], Stephen P. Luby[2,4]‡, Ahmed Mushfiq Mobarak[1,12]*‡

We conducted a cluster-randomized trial to measure the effect of community-level mask distribution and promotion on symptomatic severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infections in rural Bangladesh from November 2020 to April 2021 (*N* = 600 villages, *N* = 342,183 adults). We cross-randomized mask type (cloth versus surgical) and promotion strategies at the village and household level. Proper mask-wearing increased from 13.3% in the control group to 42.3% in the intervention arm (adjusted percentage point difference = 0.29; 95% confidence interval = [0.26, 0.31]). The intervention reduced symptomatic seroprevalence (adjusted prevalence ratio = 0.91 [0.82, 1.00]), especially among adults ≥60 years old in villages where surgical masks were distributed (adjusted prevalence ratio = 0.65 [0.45, 0.85]). Mask distribution with promotion was a scalable and effective method to reduce symptomatic SARS-CoV-2 infections.

As of September 2021, the COVID-19 pandemic has taken the lives of more than 4.7 million people. Inspired by the growing body of scientific evidence that face masks have the potential to slow the spread of the disease and save lives (*1*–*10*), we conducted a cluster-randomized controlled trial covering 342,183 adults in 600 villages in rural Bangladesh with the dual goals of (i) identifying strategies to increase community-wide mask-wearing and (ii) tracking changes in symptomatic severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infections as a result of our intervention. Although vaccines may constrain the spread of SARS-CoV-2 in the long-term, it is unlikely that a substantial fraction of the population in low- and middle-income countries will have access to vaccines before the end of 2021 (*11*). Developing scalable and effective means of combating COVID-19 is thus of first-order policy importance.

The World Health Organization (WHO) declined to recommend mask adoption until June 2020, citing the lack of evidence from community-based randomized-controlled trials as well as concerns that mask-wearing would create a false sense of security (*12*). Critics argued that those who wore masks would engage in compensating behaviors, such as failing to physically distance from others, resulting in a net increase in transmission (*13*). We directly test this hypothesis by measuring physical distancing.

We designed our trial to encourage universal mask-wearing at the community level, rather than mask-wearing among only those with symptoms. We encouraged even healthy individuals to wear masks because a substantial share of COVID-19 transmission stems from asymptomatic or presymptomatic individuals (*14*) and masks may protect healthy wearers by reducing the inhalation of aerosols or droplets (*15*–*17*).

After performing pilot studies, we settled on a core intervention package that combined household mask distribution with communication about the value of mask-wearing; mask promotion and in-person reminders at mosques, markets, and other public places; and role-modeling by public officials and community leaders. We also tested several other strategies in subsamples, such as asking people to make a verbal commitment, creating opportunities for social signaling, text messaging, and providing village-level incentives to increase mask-wearing. The selection of strategies to test was informed by both our pilot study results and research in public health, psychology (*18*–*20*), economics (*21*–*23*), marketing (*24*–*26*), and other social sciences (*27*) on product promotion and dissemination strategies. We tested many different strategies because it was difficult to predict in advance which ones would lead to persistent increases in mask-wearing. Prediction studies we conducted with policymakers and public health experts at the WHO, India's National Council of Applied Economic Research, and the World Bank suggested that even these experts with influence over policy design could not easily predict which specific strategies would prove most effective in our trial.

We powered our intervention around the primary outcome of symptomatic seroprevalence. During our study, we collected survey data on the prevalence of WHO-defined COVID-19 symptoms from all available study participants and then collected blood samples at endline from those who reported symptoms at any time during the 8-week study. Our trial is therefore designed to track the fraction of individuals who are both symptomatic and seropositive. We chose this as our primary outcome because (i) the goal of public health policy is ultimately to prevent symptomatic infections (even if preventing asymptomatic infections is instrumentally important in achieving that goal) and (ii) symptomatic individuals are far more likely to be seropositive so powering for this outcome required conducting an order of magnitude fewer costly blood tests. As secondary outcomes, we also report the effects of our intervention on WHO-defined symptoms for probable COVID-19 infection and mask-wearing.

Bangladesh is a densely populated country with 165 million inhabitants; reported infections reached 15,000 per day during our study period, but reported cases and deaths are likely underestimated by one to two orders of magnitude (*28*–*32*). The evolution of mask use over time in Bangladesh is discussed in greater detail in (*33*). In Bangladesh, the government strongly recommended mask use from early April 2020. In an April 2020 telephone survey, more than 80% of respondents self-reported wearing a mask and 97% self-reported owning a mask. The Bangladeshi government formally mandated mask use in late May 2020 and threatened to fine those who did not comply, although enforcement was weak to nonexistent, especially in rural areas. During in-person surveillance between 21 and 25 May 2020 in 1441 places in 52 districts, we observed 51% of about 152,000 individuals wearing a mask. Another wave of surveillance was conducted between 19 and 22 June 2020 in the same 1441 locations, and mask-wearing dropped to 26%, with 20% wearing masks that covered their mouth and

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nose and 6% wearing masks improperly. An August 2020 phone survey in rural Kenya found that although 88% of respondents claim to wear masks in public, direct observation revealed that only 10% actually did (*34*). These observations suggest that mask promotion interventions could be useful in rural areas of low- and middle-income countries, which are home to several billion people at risk for COVID-19.

Results

Our analysis followed our preregistered analysis plan (https://osf.io/vzdh6/) except where indicated. Our primary outcome was symptomatic seroprevalence for SARS-CoV-2. We also analyzed the impact of our intervention on mask-wearing, physical distancing, social distancing, and COVID-19–like symptoms. No adverse events were reported during the study period.

Sample selection

The unions where we conducted our intervention are geographically dispersed throughout rural Bangladesh, as shown in Fig. 1. (Appendix C discusses in more detail how these unions were selected.) Tables S1 and S2 summarize sample selection for our analysis. We initially approved 134,050 households, of which 125,053 provided baseline information. From these 125,053 households, we collected baseline information from 342,183 individuals. Of these, 336,010 (98%) provided symptom data at week 5 and/or 9. Of these, 27,160 (8.0%) reported COVID-19–like symptoms during the 9 weeks since the study began. We attempted to collect blood samples from all symptomatic individuals. Of these, 10,790 (39.7%) consented to have blood collected (40.2% in the treatment group and 39.3% in the control group; $p = 0.24$). We show in table S3 that consent rates are about 40% across men and women and among adults of different age groups in both treatment and control villages.

As such, the sample of individuals for whom we have symptom data is much larger than the sample for whom we have serology data. We tested 9512 (88.2%) of the collected blood samples to determine seroprevalence for SARS-CoV-2 immunoglobulin G (IgG) antibodies. Untested samples (<12%) either lacked sufficient quantity for our test or could not be matched to individuals from our sample because of a barcode scanning error. In our primary outcome analysis, we drop individuals for whom we are missing symptom data or who did not consent to blood sample collection. For the analyses where symptomatic status is the outcome, we report results using both this smaller sample as well as the larger sample of all individuals who provided symptom data. In the baseline, we collected blood samples from a random sample of individuals ($N = 10{,}085$), of whom 339 had COVID-19–like symptoms. We use these to check balance with respect to baseline symptomatic seropositivity (as well as baseline symptomatic status).

Of the 600 villages initially recruited for the study, the analysis sample excludes four villages where interventions could not be performed owing to a lack of local government cooperation. We exclude an additional 11 villages and their village-pairs (where a village and its village-pair are a control-treatment pair) because we did not observe them in the baseline period before the intervention and one village and its pair for lack of observational data throughout the intervention period, for a total analysis sample of 572 villages.

Primary analyses

Our primary outcomes are balanced at baseline

Although our stratification procedure should have achieved balance with respect to variables observed at the time of randomization, given the many possible opportunities for errors in implementation, we confirm in appendix L that our control and treatment villages are balanced with respect to our primary outcome variables. This assessment was not preregistered. We investigated several other covariates and found a few small imbalances. We checked whether these affect the main results that we report in this paper. For example, we found more 18- to 30-year-olds in the treatment group than in the control group, perhaps because households reported teenagers as 18 years old to receive more masks; our results are robust to dropping this age range.

Our intervention increased mask-wearing

The first column in the top panel of Table 1 reports coefficients from a regression of mask-wearing on a constant, an intervention indicator (based on the assigned groups), baseline mask-wearing, the baseline symptom rate, and indicators for each control-intervention pair. More details of our statistical methods and standard error construction are available in appendix K. Mask-wearing was 13.3% in control villages and 42.3% in treatment villages. Our regression adjusted estimate is an increase of 28.8 percentage points (95% confidence interval = [0.26, 0.31]; numbers in brackets represent 95% confidence intervals throughout the text and tables). If we omit all covariates (except fixed effects for the strata within which we randomized), our point estimate is identical (table S5). Considering only surveillance conducted when no mask distribution was taking place, mask-wearing increased 27.9 percentage points, from 13.4% in control villages to 41.3% in intervention villages (regression adjusted estimate = 0.28 [0.26, 0.30]). We also run our analysis separately in mosques, markets, and other locations such as tea stalls, the entrance of restaurants, and the main road in the village. The increase in mask-wearing was largest in mosques (37.0 percentage points), whereas in all other locations it was 25 to 29 percentage points.

Our intervention increased physical distancing

Contrary to concerns that mask-wearing would promote risk compensation, we did not find evidence that our intervention undermines distancing behavior. In the bottom panel of Table 1, we report identical specifications to the top panel but with physical distancing as the dependent variable. In control villages, 24.1% of observed individuals practiced physical distancing compared with 29.2% in intervention villages, an increase of 5.1% (regression adjusted estimate = 0.05 [0.04, 0.06]). Evidently, protective behaviors like mask-wearing and physical distancing are complements rather than substitutes: Endorsing mask-wearing and informing people about its importance encouraged rural Bangladeshis to take the pandemic more seriously and engage in another form of self-protection. The increases in physical distancing were similar in cloth and surgical mask villages.

Physical distancing increased 5.1 percentage points overall, but there was substantial heterogeneity across locations. In markets, individuals were 7.4 percentage points more likely to physically distance. By contrast, there was no physical distancing practiced in any mosque, in either treatment or control villages, probably as a result of the strong religious norm of standing shoulder-to-shoulder when praying.

Our intervention had no impact on social distancing

It is possible that physical distancing increases because our intervention results in fewer total people being present in public spaces. If socializing increased in the intervention group, but only among risk-conscious people, then we might see physical distancing increase despite people engaging in overall riskier behavior. To assess this, as well as to assess directly if the intervention increased socializing, we studied the effects of our intervention on the total number of people observed at public locations. Although surveillance staff were not able to count everyone in busy public areas, the total number of people they were able to observe gives some indication of the crowd size. We found no difference in the number of people observed in public areas between the treatment and control groups overall (table S6). The social distancing analysis was not preregistered, although the specification exactly parallels our analysis of physical distancing.

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Table 1. Mask-wearing and physical distancing, controlling for baseline variables. All regressions include an indicator for each control-intervention pair and baseline symptom rates. The analyses in the top panel control for baseline rates of proper mask-wearing, and the analyses in the bottom panel control for baseline rates of physical distancing. "Baseline symptom rate" is defined as the rate of surveyed individuals in a village who report symptoms coinciding with the WHO definition of a probable COVID-19 case. We assume that (i) all reported symptoms were acute onset, (ii) all people live or work in an area with a high risk of transmission of virus, and (iii) all people have been a contact of a probable or confirmed case of COVID-19 or are linked to a COVID-19 cluster. "No active promotion" refers to any time that surveillance was conducted while promotion was not actively occurring (regardless of the week of the intervention). This excludes surveillance during the Friday Jumma Prayers in the mosque, when promoters were present and actively encouraged mask-wearing. "Other locations" include tea stalls, at the entrance of the restaurant as patrons enter, and the main road to enter the village. "Surgical villages" refer to all treatment villages that received surgical masks as part of the intervention and their control pairs. "Cloth villages" refer to all treatment villages that received cloth masks as part of the intervention and their control pairs. The surgical and cloth subsamples include surveillance from all available locations, equivalent to the column labeled "Full" but run separately for each subgroup. Of the 572 villages included in the analysis sample, we exclude an additional village and its pair in the mosque and market subsamples and two villages and their pairs in the other location subsample because we did not observe them in the baseline period before the intervention. There are 190 treatment villages that received surgical masks as part of the intervention and 96 treatment villages that received cloth masks. Standard errors are in parentheses.

Parameter	Full	No active promotion	Mosques	Markets	Other locations	Surgical mask villages	Cloth mask villages
			Proper mask-wearing				
Intervention coefficient	0.288***	0.279***	0.370***	0.287***	0.251***	0.301***	0.256***
	(0.012)	(0.011)	(0.016)	(0.012)	(0.012)	(0.015)	(0.019)
			Physical distancing				
Intervention coefficient	0.051***	0.056***	0.000	0.074***	0.068***	0.054***	0.044***
	(0.005)	(0.005)	(0.000)	(0.007)	(0.006)	(0.006)	(0.011)
N villages	572	572	570	570	568	380	192

***Significant at the 1% level. **Significant at the 5% level. *Significant at the 10% level.

Our intervention reduced symptomatic seroprevalence

Among the 336,010 participants who completed symptom surveys, 27,160 (8.1%) reported experiencing COVID-19–like illnesses during the study period. More participants in the control villages reported incident COVID-19–like illnesses (N = 13,853; 8.6%) compared with participants in the intervention villages (N = 13,307; 7.6%). More than one-third (39.7%) of symptomatic participants agreed to blood collection. After omitting symptomatic participants who did not consent to blood collection, symptomatic seroprevalence was 0.76% in control villages and 0.68% in the intervention villages. Because the fractions we are reporting omit nonconsenters from the numerator but not the denominator, it is likely that the true rates of symptomatic seroprevalence are substantially higher (perhaps by 2.5 times, if nonconsenters have similar seroprevalence to consenters).

In Table 2 (and table S7), we report results from a regression of symptomatic seroprevalence on a treatment indicator, clustering at the village level and controlling for fixed effects for each pair of control and treatment villages. In the tables, we report results with and without additional controls for baseline symptoms and mask-wearing rates. In table S7, we report results from our prespecified linear model, and in Table 2, we report results from a generalized linear model with a Poisson family and log-link function. Here, we discuss the latter results (which are in units of relative risk); the linear model implies results of an almost identical magnitude. The prevalence ratios and accompanying confidence intervals reported in the text correspond to the specifications with baseline controls (hence, "adjusted" prevalence ratio).

The results in all specifications are the same: We estimate a roughly 9% decline in symptomatic seroprevalence in the treatment group (adjusted prevalence ratio = 0.91 [0.82, 1.00]) for a 29 percentage point increase in mask-wearing over 8 weeks. In the second column of Table 2 and table S7, we split our results by mask type (surgical versus cloth). We find clear evidence that surgical masks lead to a relative reduction in symptomatic seroprevalence of 11.1% (adjusted prevalence ratio = 0.89 [0.78, 1.00]; control prevalence = 0.81%; treatment prevalence = 0.72%). Although the point estimates for cloth masks suggests that they reduce risk, the confidence limits include both an effect size similar to surgical masks and no effect at all (adjusted prevalence ratio = 0.94 [0.78, 1.10]; control = 0.67%; treatment = 0.61%).

In appendix N, we investigate the robustness of these results to alternative methods of dealing with missing data from nonconsenters. In the main text, following our prespecified analysis plan, we drop nonconsenting symptomatic individuals. If we instead impute seropositivity for symptomatic nonconsenters based on the population average seropositivity among symptomatic individuals, our pooled estimate of the impact of masking becomes larger and more precise. Notably, with this alternative imputation, we find effects for both cloth and surgical masks on symptomatic seroprevalence.

Not all symptomatic seroprevalence is necessarily a result of infections occurring during our intervention; individuals may have had preexisting SARS-CoV-2 infections and then became symptomatic (perhaps caused by an infection other than SARS-CoV-2). In appendix I, we show that if either (i) masks have the same proportional impact on COVID and non-COVID symptoms or (ii) all symptomatic seropositivity is caused by infections during our intervention, then the percentage decline in symptomatic seroprevalence will exactly equal the decline in symptomatic seroconversions. More generally, the relationship between the two quantities depends on whether masks have a greater impact on COVID or non-COVID symptoms, as well as the proportion of symptomatic seropositivity that is a result of infections preexisting at baseline.

Our intervention reduced WHO COVID-19 symptoms

In Table 3 and table S8, we report results from the same specifications with WHO-defined COVID-19 symptomatic status as the outcome. This is defined as any of following:

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Table 2. Symptomatic seroprevalence, expressed in prevalence ratios. All regressions include an indicator for each control-intervention pair. The regressions "with baseline controls" include controls for baseline rates of proper mask-wearing and baseline symptom rates. "Baseline symptom rate" is defined as the rate of surveyed individuals in a village who report symptoms coinciding with the WHO definition of a probable COVID-19 case. We assume that (i) all reported symptoms were acute onset, (ii) all people live or work in an area with a high risk of transmission of virus, and (iii) all people have been a contact of a probable or confirmed case of COVID-19 or are linked to a COVID-19 cluster. The analysis includes all people surveyed in the baseline household visits, excluding individuals for whom we did not collect midline or endline symptoms, symptomatic individuals from whom we did not collect blood, and individuals from whom we drew blood but did not test their blood. The regressions exclude an additional 17,377 individuals in 34 villages because there are zero people who are symptomatic-seropositive in their village pairs. To check robustness to the type of clustering, in panels 2 and 3 of fig. S2, we show the histogram of effect sizes under "randomization inference" if we randomly reassign treatment within each pair of villages and then estimate our primary specification. We find that our estimated effect size is smaller than 7.0% of the simulated estimates with controls and 7.4% of the simulated estimates without controls (these are the corresponding *p* values of the randomization inference *t* test). Blank spaces indicate variables not included in the regression specification reported in each column.

Parameter	Intervention effect	Intervention effect by mask type
No baseline controls		
Intervention prevalence ratio	0.905** [0.815, 0.995]	
Intervention prevalence ratio for surgical mask villages		0.894* [0.782, 1.007]
Intervention prevalence ratio for cloth mask villages		0.925 [0.766, 1.083]
Average symptomatic-seroprevalence rate in paired control villages†	0.0076	0.0076
With baseline controls		
Intervention prevalence ratio	0.905** [0.815, 0.995]	
Intervention prevalence ratio for surgical mask villages		0.889** [0.780, 0.997]
Intervention prevalence ratio for cloth mask villages		0.942 [0.781, 1.103]
N individuals	304,726	304,726
N villages	572	572

***Significant at the 1% level. **Significant at the 5% level. *Significant at the 10% level. †We report the mean rate of symptomatic seroprevalence at endline. This is not equivalent to the coefficient on the constant due to the inclusion of the pair indicators as controls.

1) Fever and cough.

2) Any three of the following: fever; cough; general weakness and/or fatigue; headache; muscle aches; sore throat; coryza (nasal congestion or runny nose); dyspnoea (shortness of breath or difficulty breathing); anorexia (loss of appetite), nausea, and/or vomiting; diarrhea; or altered mental status.

3) Anosmia (loss of smell) and ageusia (loss of taste).

We find clear evidence that the intervention reduced symptoms: We estimate a reduction of 11.6% (adjusted prevalence ratio = 0.88 [0.83, 0.93]; control = 8.60%; treatment = 7.63%). Additionally, when we look separately by cloth and surgical masks, we find that the intervention led to a reduction in COVID-19–like symptoms under either mask type (p = 0.000 for surgical; p = 0.066 for cloth), but the effect size in surgical mask villages was 30 to 80% larger depending on the specification. In table S9, we run the same specifications using the smaller sample used in our symptomatic seroprevalence regression (i.e., those who consented to give blood). In this sample, we continue to find an effect overall and an effect for surgical masks but see no statistically significant effect for cloth masks.

In-person reinforcement is crucial to our intervention

Our core intervention package combined multiple distinct elements: We provided people with free masks and information about the importance of mask-wearing, we had mask promoters reinforce mask-wearing by stopping individuals in public places who were not wearing masks and reminding them to do so, and we partnered with local leaders to encourage mask-wearing at mosques and markets. Additionally, in some villages, we provided a variety of reminders, commitment devices, and incentives for village leaders. In appendix J, we attempt to disentangle the role played by these different elements in encouraging mask use.

We find no evidence that any of our village-level or household-level treatments, other than mask color, affected mask-wearing. For mask color, we see marginally significant differences that are small in magnitude. In surgical mask villages, blue masks were more likely to be observed than green masks (adjusted percentage point difference = 0.03 [−0.00, 0.06]), and in cloth mask villages, red masks were more likely to be observed than purple masks (adjusted percentage point difference = −0.02 [−0.04, −0.00]). Text message reminders, incentives for village-leaders, or explicit commitment signals explain little of the observed increase in mask-wearing. Compared with self-protection messaging alone, altruistic messaging had no greater impact on mask-wearing, and twice-weekly text messages and a verbal commitment had no significant effects. We saw no significant difference in the rates of mask-wearing in the village-level randomization of surgical versus cloth masks.

We do find nonexperimental evidence that in-person mask promotion and reinforcement is a crucial part of our intervention. Our first pilot study contained all elements of our intervention except in-person reinforcement. Our second pilot study (1 week later) and the full intervention (several months later) added in-person reinforcement. Under the assumption that treatment effects would otherwise be constant over time, we find that in-person reinforcement accounts for 19.2 percentage points of our effect (regression adjusted estimate = 0.19 [−0.33, −0.05]), or 65% of the total effect size. In table S10, we show that this difference is statistically significant whether or not we include baseline controls. This was not a prespecified analysis.

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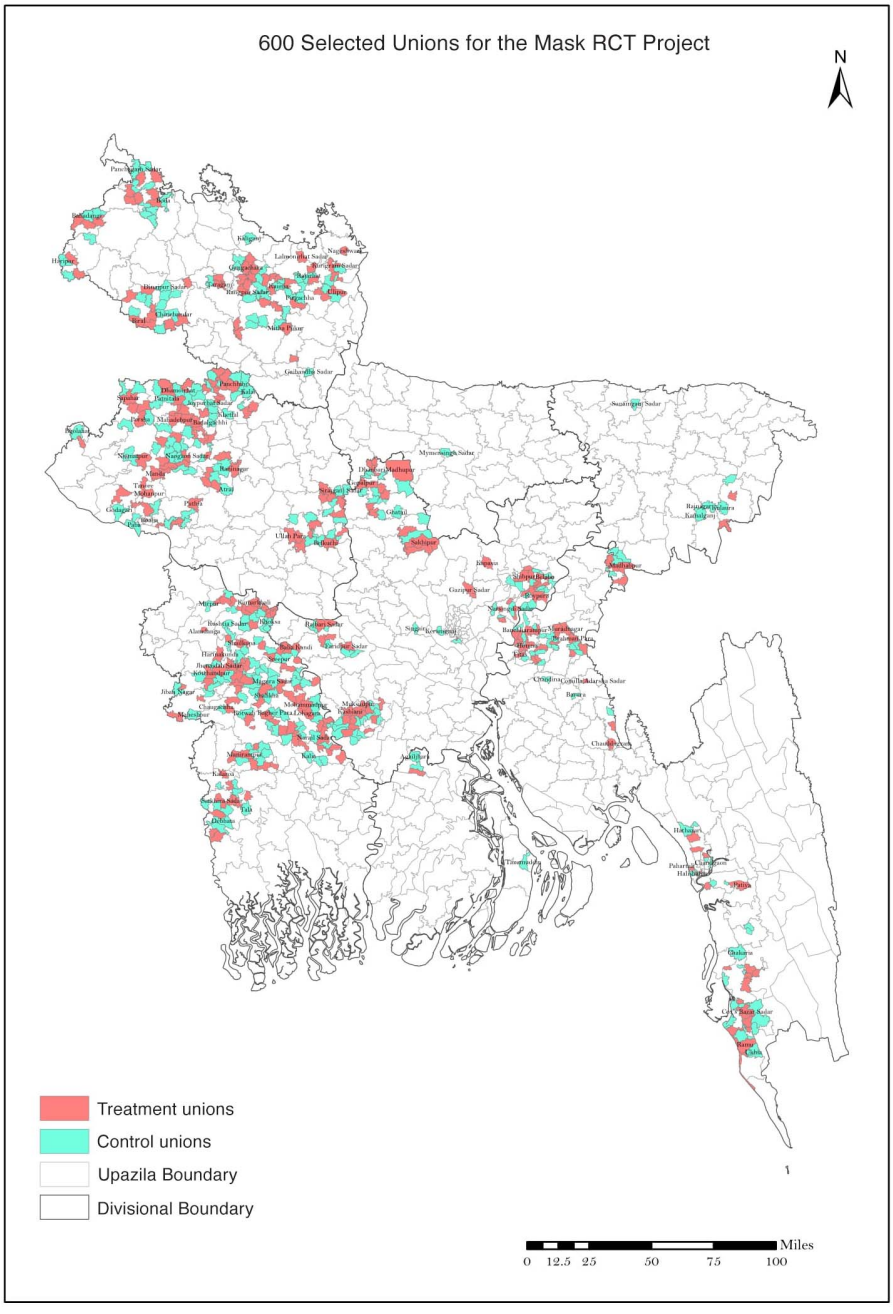

Fig. 1. Map of 600 treatment and control unions. The figure shows the location of the 600 treatment and control unions in the study. RCT, randomized controlled trial; 1 mile = 1.6 km.

Our intervention yields persistent increases in mask-wearing

In appendix M, we present results on mask-wearing after our intervention ended. Even though the door-to-door free mask distribution occurred in the first week only, there was almost no attenuation of mask-wearing over the initial 10 weeks of surveillance. Notably, mask-wearing remained comparably increased in the treatment group during the 2 weeks we continued surveillance after the end of all intervention activities in the village. Three to 4 months later, mask-wearing waned but remained 10 percentage points higher in treatment regions.

Subgroup analyses

Women wear masks more often, but men respond more to the intervention

In table S11, we analyze the impact of our intervention on mask-wearing and physical distancing separately by gender, as well as by whether baseline mask-wearing was above or below the median. Gender was recorded in 65% of observations; age was not recorded during the direct observation surveillance of mask-wearing in public places, and thus we do not conduct an age-stratified assessment. This observed sample is representative of the rural Bangladeshi population that is present in crowded public places during the day; this population is largely composed of men, who have more social contacts outside the home than women. In the gender results, we drop surveillance observations for mosques because in rural Bangladesh it is rare for women to attend mosque. We found that the intervention increased mask-wearing by 27.1 percentage points for men ([0.25, 0.30]) and 22.5 percentage points for women ([0.20, 0.25]). Although we do not have the variation to test this, the gendered difference in effect size may be because our mask promoters were predominantly men or because the mask-wearing rate in control villages was so much higher for women (31% for women versus 12% for men). We intentionally hired predominantly men because most staff interactions would be with men. Men constituted 88.2% of all observed adults. We also found a larger increase in mask-wearing in villages with below-median baseline mask-wearing (where mask-wearing increased from 8.7 to 41.9% at endline) than in those with above-median baseline mask-wearing (where the increase was from 17.5 to 42.6%).

The effect on symptomatic seroprevalence is especially large among the elderly

In Table 4 and table S12, we report results from our primary specification separately by age. Table S12 reports our preregistered specification, a linear model run separately for each decade of age, pooling cloth mask and surgical mask villages. Table 4 synthesizes these results, collapsing by categories of <40, 40 to 49, 50 to 59, and ≥60 years old, reporting results as a relative risk reduction, and showing results separately for surgical and cloth masks. We generally find that the impact of the intervention is concentrated among individuals over age 50. In surgical mask villages, we observe a 22.8% decline in symptomatic seroprevalence among individuals aged 50 to 59 years (adjusted prevalence ratio = 0.77 [0.60, 0.95]) and a 35.3% decline among individuals ≥60 years old in our baseline specification (p = 0.000) (adjusted prevalence ratio = 0.65 [0.45, 0.85]). For cloth masks, we find an insignificant (5%) reduction overall but some evidence of a reduction in symptomatic seroprevalence among 40- to 49-year-olds; we investigate more deeply in appendix N and find that the age gradient appears to be sensitive to how we deal with missing values. In the bottom panel of Table 4, we report results where we impute the population average seroprevalence among all nonconsenters rather than dropping them. This alternative approach

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Table 3. WHO-defined COVID-19 symptoms, expressed in prevalence ratios. All regressions include an indicator for each control-intervention pair. The regressions "with baseline controls" include controls for baseline rates of proper mask-wearing and baseline symptom rates. "Baseline symptom rate" is defined as the rate of surveyed individuals in a village who report symptoms coinciding with the WHO definition of a probable COVID-19 case. We assume that (i) all reported symptoms were acute onset, (ii) all people live or work in an area with a high risk of transmission of virus, and (iii) all people have been a contact of a probable or confirmed case of COVID-19 or are linked to a COVID-19 cluster. The analysis includes all people surveyed in the baseline household visits, excluding individuals for whom we did not collect midline or endline symptoms. Blank spaces indicate variables not included in the regression specification reported in each column.

Parameter	Intervention effect	Intervention effect by mask type
No baseline controls		
Intervention prevalence ratio	0.885*** [0.834, 0.934]	
Intervention prevalence ratio for surgical mask villages		0.865*** [0.803, 0.928]
Intervention prevalence ratio for cloth mask villages		0.922* [0.838, 1.005]
Average symptomatic rate in paired control villages†	0.0860	0.0860
With baseline controls		
Intervention prevalence ratio	0.884*** [0.834, 0.934]	
Intervention prevalence ratio for surgical mask villages		0.874*** [0.809, 0.939]
Intervention prevalence ratio for cloth mask villages		0.907** [0.823, 0.991]
N individuals	321,948	321,948
N villages	572	572

***Significant at the 1% level. **Significant at the 5% level. *Significant at the 10% level. †We report the mean rate of symptomatic status at endline. This is not equivalent to the coefficient on the constant due to the inclusion of the pair indicators as controls.

yields more precise overall estimates and suggests that both cloth and surgical masks have greater impacts on symptomatic seroprevalence at older ages, although the impact of surgical masks among those ≥60 years old is smaller than in our baseline specification. Ex ante, it is not obvious to us which imputation method should be preferred, although the second approach makes our results less sensitive to differential consent rates that we observe in some waves of our intervention, as discussed in appendix N.

The effect on WHO COVID-19 symptoms is larger among the elderly

In tables S13 and S14 (the latter being our preregistered specification), we perform the same analysis using the larger sample of individuals who reported symptom information. In this sample, we continue to find larger effects at older ages, although the differences are not as stark as those for the symptomatic seroprevalence outcome. In table S15, we show that the age gradient is steeper for surgical masks.

Men and women have similar reductions in symptoms and symptomatic seroprevalence

In appendix N and table S28, we show results for symptoms and symptomatic seropositivity by gender. We see a similar pattern to the cloth and surgical mask results: We see significant effects for both genders for symptoms and symptomatic seroposivity when we impute seropositivity at the average value for nonconsenters. If we instead drop nonconsenters, the symptomatic seropositivity estimates for men become less precise and are no longer significantly different from zero, whereas the estimates for women remain unchanged.

Additional preregistered specifications

In appendix P, we discuss additional preregistered specifications that are not reported in the text, either because they were substantially underpowered given the available data or because data on required variables were unavailable. We also discuss ways in which trial implementation deviated from our preregistered protocol, such as switching from exclusively phone surveys to household visits at weeks 5 and 9 to increase response rates.

Intervention cost and benefit estimates

In appendix Q, we assess the costs of implementing our intervention relative to the health benefits, specifically focusing on our ongoing efforts to implement this same intervention at scale in Bangladesh. We consider a range of possible estimates for excess deaths from COVID-19 from 1 May to 1 September 2021, and we assume that our age-specific impacts on symptomatic seroprevalence will lead to proportional reductions in mortality. We estimate that a scaled version of our intervention being implemented in Bangladesh will cost about $1.50 per person, and between $10,000 and $52,000 per life saved, depending on which estimate we use for excess deaths.

Discussion

We present results from a cluster-randomized controlled trial of a scalable intervention designed to increase mask-wearing and reduce COVID-19 symptomatic infections. Our estimates suggest that mask-wearing increased by 28.8 percentage points, corresponding to an estimated 51,357 additional adults wearing masks in intervention villages, and this effect was persistent even after active mask promotion was discontinued. The intervention led to a 9.5% reduction in symptomatic SARS-CoV-2 seroprevalence (which corresponds to 105 fewer symptomatic seropositives) and an 11.6% reduction in the prevalence of COVID-19–like symptoms, corresponding to 1541 fewer people reporting these symptoms. If we assume that nonconsenting symptomatic individuals were seropositive at the same rate as consenting symptomatic individuals, the total estimated symptomatic seropositives prevented would be 354. The effects were substantially larger (and more precisely estimated)

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Table 4. Symptomatic seroprevalence by age groups and mask type, expressed in prevalence ratios. All regressions include an indicator for each control-intervention pair. The regressions include controls for baseline rates of mask-wearing and baseline symptom rates. "Baseline symptom rate" is defined as the rate of surveyed individuals in a village who report symptoms coinciding with the WHO definition of a probable COVID-19 case. We assume that (i) all reported symptoms were acute onset, (ii) all people live or work in an area with a high risk of transmission of virus, and (iii) all people have been a contact of a probable or confirmed case of COVID-19 or are linked to a COVID-19 cluster. The analysis in the top panel uses the preregistered sample, equivalent to that in Table 2; it includes all people surveyed in the baseline household visits, excluding individuals for whom we did not collect midline or endline symptoms, symptomatic individuals from whom we did not collect blood, and individuals from whom we drew blood but did not test their blood. The analysis in the bottom panel replicates the regressions in the top panel but imputes the seropositivity of individuals from whom we did not draw blood. For symptomatic individuals from whom we did not draw blood, we simulate their symptomatic-seroprevalence status by using the average rate of conditional seropositivity among all symptomatic individuals. This analysis includes all people surveyed in the baseline household visits, excluding individuals for whom we did not collect midline or endline symptoms.

Parameter	All	<40 years old	40 to 49 years old	50 to 59 years old	≥60 years old
Preregistered sample: Drop individuals without blood draws					
Intervention prevalence ratio for surgical mask villages	0.889**	0.967	1.009	0.772**	0.647***
	[0.780, 0.997]	[0.834, 1.100]	[0.817, 1.200]	[0.595, 0.949]	[0.448, 0.845]
Intervention prevalence ratio for cloth mask villages	0.942	1.058	0.713**	0.838	1.084
	[0.781, 1.103]	[0.870, 1.247]	[0.459, 0.967]	[0.524, 1.153]	[0.769, 1.399]
Average symptomatic-seroprevalence in paired control villages†	0.0076	0.0055	0.0095	0.0108	0.0104
N individuals	287,349	146,306	35,839	24,086	27,943
N villages	538	480	384	348	360
Imputing symptomatic-seroprevalence for missing blood draws					
Intervention prevalence ratio for surgical mask villages	0.873***	0.917*	0.975	0.815***	0.701***
	[0.801, 0.945]	[0.829, 1.005]	[0.862, 1.088]	[0.688, 0.942]	[0.577, 0.824]
Intervention prevalence ratio for cloth mask villages	0.890**	0.861***	0.838**	1.153	0.792**
	[0.787, 0.993]	[0.758, 0.965]	[0.678, 0.998]	[0.970, 1.336]	[0.601, 0.983]
Average symptomatic-seroprevalence in paired control villages†	0.0189	0.0152	0.0226	0.0229	0.0251
N individuals	321,383	177,708	51,676	37,340	43,431
N villages	570	566	528	504	534

***Significant at the 1% level. **Significant at the 5% level. *Significant at the 10% level. †We report the mean rate of symptomatic seroprevalence at endline. This is not equivalent to the coefficient on the constant due to the inclusion of the pair indicators as controls.

in communities where we distributed surgical masks, consistent with their greater filtration efficiency as measured in the laboratory (manuscript forthcoming). In villages randomized to receive surgical masks, the relative reduction in symptomatic seroprevalence was 11% overall, 23% among individuals aged 50 to 59 years, and 35% among those ≥60 years of age in preferred specifications.

We found clear evidence that surgical masks are effective in reducing symptomatic seroprevalence of SARS-CoV-2. Although cloth masks clearly reduce symptoms, we find less clear evidence of their impact on symptomatic SARS-CoV-2 infections, with the statistical significance depending on whether we impute missing values for nonconsenting adults. The number of cloth mask villages (100) was half that for surgical masks (200), meaning that our results tend to be less precise. Additionally, we found evidence that surgical masks were no less likely to be adopted than cloth masks. Surgical masks have higher filtration efficiency, are cheaper, are consistently worn, and are better supported by our evidence as tools to reduce COVID-19 cases.

Our results should not be taken to imply that mask-wearing can prevent only 10% of COVID-19 cases, let alone 10% of COVID-19 mortality. Our intervention induced 29 more people out of every 100 to wear masks, with 42% of people wearing masks in total. The total impact with near-universal masking—perhaps achievable with alternative strategies or stricter enforcement—may be several times larger than our 10% estimate. Additionally, the intervention reduced symptomatic seroprevalence more when surgical masks were used and even more for the highest-risk individuals in our sample (23% for ages 50 to 59 years and 35% for ages ≥60 years). These numbers likely give a better sense of the impact of our intervention on severe morbidity and mortality, because most of the disease burden of the COVID-19 pandemic is borne by the elderly. Where achievable, universal mask adoption is likely to have still larger impacts.

There are several possible theories for why we might observe a larger reduction in COVID-19 cases for older adults. We did not directly measure age during surveillance, but mask-wearing could have increased more for older adults. A second theory is that older adults are more susceptible to infections at viral loads that are preventable by masks. A third theory is that older adults have fewer social connections, so that reducing transmission through any one connection is more likely to prevent infection by severing all transmissible routes. A fourth theory is that people exercised more care and were more likely to wear masks when proximate to the elderly.

We identified a combination of core intervention elements that were effective in increasing mask-wearing in rural Bangladesh: Mask distribution and role-modeling, combined with mask promotion, lead to large and sustained increases in mask use. Results from our pilot studies suggest that combining mask distribution, role-modeling, and active mask promotion—rather than mask distribution and role-modeling alone—seems critical to achieving the full effect. Our trial results also highlight many factors that appear inessential: We find no evidence that public commitments, village-level incentives, text messages, altruistic messaging, or verbal commitments change mask-wearing behavior. The null results on our cross-randomizations do not necessarily imply that these approaches are not worth trying in other contexts, but they teach us that large, persistent increases in mask-wearing are possible without these elements.

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Prediction studies that we conducted with policy-makers and public health experts at the WHO and the World Bank before presentations of the study results suggest that our results are informative for policy design. Most of the respondents in the prediction studies anticipated that text messages, verbal commitments, and incentives would increase mask-wearing, when in reality, we estimated fairly precise null effects, and poll respondents believed that in-person mask promotion would have no additional effect, whereas the evidence from our pilot studies suggests that it is essential (for additional details, see appendix R).

Our intervention design is immediately relevant for Bangladesh's plans for larger-scale distribution of masks across all rural areas. The Bangladesh Directorate General of Health has assigned the study team and the nongovernmental organization Bangladesh Rural Advancement Committee (BRAC) the responsibility to scale up the strategies that were proven most effective in this trial to reach 81 million people (*35*). At the time of writing, we are implementing this program in the 37 districts prioritized by the government based on SARS-CoV-2 test positivity rates. Our results are also relevant for mask dissemination and promotion campaigns planned in other countries and settings that face similar challenges in ensuring mask usage as a result of limited reach and enforcement capacity. The mask promotion model described in this paper was subsequently adopted by governments and other implementers in Pakistan (*36*), India (*37*), and Nepal (*38*). The intervention package would be feasible to implement in a similar fashion in other world regions as well. Beyond face masks, the conceptual underpinning of our strategies could be applied to encourage the adoption of other health behaviors and technologies, in particular, those easily observable by others outside the household, such as purchase and consumption of food, alcohol, and tobacco products in stores, restaurants, or other public spaces (*39*); hand washing and infection control in health care facilities (*40*–*42*); hygiene interventions in childcare and school settings (*43*, *44*); improved sanitation (*45*, *46*); or vaccination drives (*47*).

Although critics of mask mandates suggest that individuals who wear masks are more likely to engage in high-risk behaviors (*48*), we found no evidence of risk compensation as a result of increased mask-wearing. Indeed, we found that our intervention slightly increased the likelihood of physical distancing, presumably because individuals participating in the intervention took the threat of COVID-19 more seriously. These findings are consistent with other behaviors, including seat belt use (*49*) or immunization (*50*), where risk compensation, even if present, is not sufficient to outweigh direct effects.

The intervention may have influenced rates of COVID-19 by increasing mask use, physical distancing, and/or other risk prevention behaviors. Three factors suggest that the direct impact of masks is the most likely explanation for our documented health impacts. First, in appendix O, we analyze cross-sectionally the relationship between our biological outcomes and both mask-wearing and physical distancing. We find that symptoms and symptomatic seropositivity are negatively correlated with mask-wearing, but not with physical distancing, after controlling for mask-wearing. This analysis uses variation in observational data, rather than solely experimental data, and should therefore be interpreted with caution, as discussed in the appendix. Second, we see no change in physical distancing in the highest-risk environment in our study, typically crowded indoor mosques. However, women do not typically go to mosques in rural Bangladesh, and their symptomatic seropositivity decreased by just as much as that of men, so outdoor transmission or transmission in settings that we do not observe directly may be important. Third, our study complements a large body of laboratory and quasi-experimental evidence that masks have a direct effect on SARS-CoV-2 transmission (*1*).

We estimate that a scaled version of our intervention being implemented in Bangladesh will cost between $10,000 and $52,000 per life saved, depending on what fraction of excess deaths are attributable to COVID-19. This is considerably lower than the value of a statistical life in Bangladesh [$205,000 (*51*)] and, under severe outbreaks, is comparable to the most cost-efficient humanitarian programs at scale [e.g., distributing insecticide nets to prevent malaria costs $9200 per life saved (*52*)]. This estimate includes only mortality impacts and not morbidity, and greater cost-efficiency is possible if our intervention can be streamlined to further isolate the essential components. Most of our costs were the personnel costs for mask-promoters: If we consider only the costs of mask production, these numbers would be 20 times lower. Thus, the overall cost to save a life in countries where mask mandates can be enforced at minimal cost with existing infrastructure may be substantially lower than our estimates above.

Study limitations

Our study has several limitations. The distinct appearance of project-associated masks and increased mask-wearing in intervention villages made it impossible to blind surveillance staff to study-arm assignment. However, staff were not informed about the exact purpose of the study. Even though surveillance staff were plain-clothed and were instructed to remain discreet, community members could have recognized that they were being observed and changed their behavior. Additionally, survey respondents could have changed their likelihood of reporting symptoms in places where mask-wearing was more widespread. If respondents were more cognizant of symptoms in mask-wearing areas, this may bias us toward underestimating the impact of masks; if respondents in mask-wearing areas were less concerned with mild symptoms and thus were less likely to recall them, this might bias us toward overestimating the impact of masks. Although we confirm that blood consent rates are not significantly different in the treatment and control groups and are comparable across all demographic groups, we cannot rule out that the composition of consenters differed between the treatment and control groups. The slightly higher point estimate for consent in the treatment group biases us away from finding an effect, because it raises symptomatic seroprevalence in the treatment group. Although control villages were at least 2 km from intervention villages, adults from control villages may have come to intervention villages to receive masks, reducing the apparent impact of the intervention. Although we did not directly assess harms in this study, there could be costs resulting from discomfort with increased mask-wearing, adverse health effects such as dermatitis or headaches, or impaired communication.

Because the study was powered to detect differences in symptomatic seroprevalence, we cannot distinguish whether masks work by making symptoms less severe (through a reduced viral load at transmission) or by reducing new infections. We selected the WHO case definition of COVID-19 for its sensitivity, though its limited specificity may imply that the impact of masks on symptoms comes partly from non–SARS-CoV-2 respiratory infections. If masks reduce COVID-19 by reducing symptoms (for a given number of infections), they could help ease the morbidity and mortality resulting from a given number of SARS-CoV-2 infections. If masks reduce infections, they may reduce the total number of infections over the long-term by buying more time to increase the fraction of the population that is vaccinated. At the time of the study, the predominant circulating SARS-CoV-2 strain was B.1.1.7 (Alpha) (*53*). The impacts of the Delta variant on the number of infections prevented by a given mask-wearer are uncertain; the population-wide consequences of infections prevented by a given mask-wearer may be larger given a higher reproduction number.

We found that mask distribution, role modeling, and promotion in a low- and middle-income country setting increased mask-wearing and physical distancing, leading to lower illness, particularly in older adults. We find especially robust evidence that surgical masks prevent COVID-19. Whether people with respiratory symptoms should generally wear masks to

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prevent respiratory virus transmission, including for viruses other than SARS-CoV-2, is an important area for future research. Our findings suggest that such behavior may benefit public health.

Methods and materials

Sampling frame and timeline

The intervention protocol, prespecified analysis plan, and CONSORT checklist are available at https://osf.io/vzdh6/. We discuss our sample-size calculations in appendix B and discuss the selection and pairwise randomization in appendix C. In brief, we stratified villages based on geographic location and available case data, and then selected one treatment and one control village from each pair.

Village-level cluster randomization was important for three reasons. First, unlike technologies with primarily private benefits, mask adoption is likely to yield especially large benefits at the community level. Second, mask adoption by some may influence mask adoption by others because mask-wearing is immediately visible to other members of the community (*45*). Third, this design allows us to assess the full impact of masks on symptomatic infections, including through source control. Individual-level randomization would identify only whether masks protect wearers.

Our intervention was designed to last 8 weeks in each village. The intervention started in different villages at different times, rolling out over a 6-week period in seven waves. There were between 16 and 61 village-pairs grouped in each wave based on geographic proximity, and paired control and treatment villages were always included in the same wave. The first wave was rolled out on 17 and 18 November 2020 and the last wave was rolled out on 5 and 6 January 2021.

Innovations for Poverty Action (IPA) staff traveled to many villages that had low mask uptake in the first 5 weeks of the study and found that in these villages, local leaders were not very engaged in supporting mask promotion. Hence, we retrained mask-promotion staff partway through the intervention to work more closely with local leaders and set specific milestones for that partnership.

Outcomes

Our primary outcome was symptomatic seroprevalence of SARS-CoV-2. Our secondary outcomes were prevalence of proper mask-wearing, physical distancing, and symptoms consistent with COVID-19. For COVID-19 symptoms, we used the symptoms that correspond to the WHO case definition of probable COVID-19 given epidemiological risk factors: (i) fever and cough; (ii) three or more of the following symptoms (fever; cough; general weakness and/or fatigue; headache; myalgia; sore throat; coryza; dyspnea; anorexia, nausea, and/or vomiting; diarrhea; and altered mental status); or (iii) loss of taste or smell. Seropositivity was defined by having detectable IgG antibodies against SARS-CoV-2.

Intervention materials and activities

Our entire intervention was designed to be easily adopted by other nongovernmental organizations or government agencies and required minimal monitoring. We have made the materials public in multiple languages to ease widespread adoption and replication by other implementers (https://osf.io/23mws/).

We provide design specifications for our masks in appendix F. We used high-quality surgical masks that had a filtration efficiency of 95% [standard deviation (SD) = 1%]; this is substantially higher than the filtration efficiency of the cloth masks we designed, which had a filtration efficiency of 37% (SD = 6%). These cloth masks had substantially higher filtration than common commercial three-ply cotton masks but lower filtration than hybrid masks that use materials not commonly available for community members in low-resource settings (*54*). Although cloth masks have less leakage because they fit the face more closely (*55*) and can be sewn without specialized equipment, they are an order of magnitude more expensive than surgical masks. The filtration efficiency of the high-quality surgical masks used in this study was 76% after washing them with bar soap and water 10 times (manuscript forthcoming). Although surgical masks can break down into microplastics that can enter the environment if disposed of improperly, an analysis of waste generated in Bangladesh's first lockdown finds that the mass of surgical mask waste was one-third that of polyethylene bags, which also break down into macro- and microplastics (*56*–*58*).

Surgical masks were outfitted with a sticker that had a logo of a mask with an outline of the Bangladeshi flag and a phrase in Bengali that noted that the mask could be washed and reused (*59*). The relatively large scale of our bulk order allowed us to negotiate mask prices of $0.50 per cloth mask and $0.13 per surgical mask ($0.06 of which was the cost of a sticker reminding people that they could wash and reuse the surgical mask).

Adult household members were asked to wear masks whenever they were outside their house and around other people. To emphasize the importance of mask-wearing, we prepared a brief video of notable public figures discussing why, how, and when to wear a mask. The video was shown to each household during the mask distribution visit and featured the Honorable Prime Minister of Bangladesh Sheikh Hasina, the head of the Imam Training Academy, and the national cricket star Shakib Al Hasan. During the distribution visit, households also received a brochure based on WHO materials that depicted proper mask-wearing.

We implemented a basic set of interventions in all treatment villages and cross-randomized additional intervention elements in randomly chosen subsets of treatment villages to investigate whether those have any additional impact on mask-wearing. The basic intervention package consists of five main elements:

1) One-time mask distribution and information provision (about masks) at households.

2) Mask distribution in markets for 3 to 6 days per week during all 8 weeks of the intervention.

3) Mask distribution at mosques on three Fridays during the first 4 weeks of the intervention.

4) Mask promotion in public spaces and markets where non–mask wearers were encouraged to wear masks (weekly or biweekly).

5) Role modeling and advocacy by local leaders, including imams discussing the importance of mask-wearing at Friday prayers using a scripted speech provided by the research team.

Participants and mask surveillance staff were not told which villages were in which intervention arm, but the intervention materials were clearly visible. The prespecified analyses and sample exclusions were made by analysts blinded to the treatment assignment.

Cross-randomization of behavior change communication and incentives

Village-level cross-randomizations

Within the intervention arm, we cross-randomized villages to four village-level and four household-level treatments to test the impact of a range of social and behavior change communication strategies on mask-wearing. All intervention villages were assigned to either the treatment or the control group of each of these four randomizations. These village-level randomizations were as follows:

1) Randomization of treated villages to either cloth or surgical masks.

2. Randomization of treated villages to public commitment (providing households signage and asking them to place signage on doors that declares they are a mask-wearing household) or not. The signage was meant to encourage formation of social norms through public signaling.

3. Randomization of treated villages to no incentive, nonmonetary incentive, or monetary incentive of $190 given to the village leader for a project benefitting the public. We announced that the monetary reward or the certificate would be awarded if village-level mask-wearing among adults exceeded 75% at 8 weeks after the intervention started.

4. Randomization of treated villages to 0 or 100% of households receiving twice-weekly

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text message reminders about the importance of mask-wearing.

Household-level cross-randomizations

We had three household-level cross-randomizations. In any single village, only one of these household randomizations was operative. Because our data collection protocols relied on passive observation at the village level, we could not record the mask-wearing behavior of individual households. To infer the effect of the household-level treatments, we therefore varied the color of the masks distributed to the household based on its cross-randomization status and had surveillance staff record the mask color of observed individuals. In surgical mask villages, a household received blue or green masks and promoters distributed an equal number of blue and green masks in public settings. In cloth mask villages, households received violet or red masks and promoters distributed blue masks in public settings. To avoid conflating the effect of the household-specific treatment with the effect of the mask color, we randomized which color corresponded to which treatment status across villages (this way a specific color was not fully coincident with a specific treatment). The household-level randomizations, described in further detail in appendix D and visualized in fig. S1, were as follows:

1) Households were randomized to receive messages emphasizing either altruism or self-protection.

2) Households were randomized to making a verbal commitment to be a mask-wearing household (all adults in the household promise to wear a mask when they are outside and around other people) or not. This experiment was conducted in a third set of villages where there was no public signage commitment.

3) Households were randomized to receive twice-weekly text reminders or not. As mentioned above, the text message saturation was randomly varied to 0, 50, or 100% of all households receiving texts, and in the 50% villages, the specific households that received the texts was also random.

Conceptual basis for tested social and behavioral change communication

We selected intervention elements that had a reasonable chance of persuading rural Bangladeshis to wear masks by consulting literature in public health, development and behavioral economics, and marketing to identify some of the most promising strategies. An extensive literature identifies price and access as key deterrents to the adoption of welfare-improving products, and especially of technologies that produce positive health externalities, such as face masks (*21*, *60*). Household distribution of free face masks therefore formed the core part of our strategy. Inspired by large literature in marketing and economics on the role of opinion leaders in new product diffusion, we additionally emphasized a partnership with community leaders in mask distribution (*25*, *61*).

The additional village- and household-level treatments we experimented with were also motivated by insights from marketing, public health, development, and behavioral economics. For example, masks are a visible good where social norms are expected to be important, so we consulted the literature that documented peer effects in product adoption (*62*–*65*). We experimented with incentives because it is unclear whether extrinsic rewards crowd out intrinsic motivation (*66*–*68*). We tested whether soft commitment devices encourage targets to follow through with actual behavior change (*69*, *70*), whether public displays can promote social norms (*27*), whether an altruistic framing inspires people more or less than self-interest (*71*), whether social image concerns and signaling can lead to higher compliance (*22*, *72*), and whether regular reminders are a useful tool to ensure adoption (*23*).

Piloting interventions

IPA implemented two pilot studies: Pilot 1 from 22 to 31 July 2020 and Pilot 2 from 13 to 26 August 2020. The objective of the pilot studies was to mimic some of the major aspects of the main experiment to identify implementation challenges. Each pilot study was conducted in 10 unions that were not part of the main study area. We used the difference between the pilot studies to better understand which elements of our full intervention were essential. We also conducted focus group discussions and in-depth interviews with village residents, community leaders, religious leaders, and political leaders to elicit opinions on how to maximize the effectiveness of the intervention.

Surveillance strategies

Mask-wearing and physical distancing were measured through direct observation. Surveillance was conducted using a standard protocol that instructed staff to spend 1 hour at each of the following high-traffic locations in the village: market, restaurant entrances, main road, tea stalls, and mosque; the location and timing changed so that the mask-wearing and physical distancing practices of as many individuals as possible could be recorded. Although SARS-CoV-2 transmission is more likely in indoor locations with limited ventilation than outside, rural Bangladeshi villages have few nonresidential spaces where people gather, so observations were conducted outside except at the mosque, where surveillance was conducted inside.

Surveillance staff were distinct from intervention implementation staff and conducted surveillance in paired intervention and control villages. To minimize the likelihood that village residents would perceive that their mask-wearing behavior was being observed, surveillance staff were separate from mask promoters and wore no identifying apparel while passively observing mask-wearing and physical distancing practices in the communities. They recorded the mask-wearing behavior of all of the adults that they were able to observe during surveillance periods; observations were not limited to adults from enrolled households. Surveillance staff noted whether adults were wearing any mask or face covering, whether the mask was one distributed by our project (and, if so, the color), and how the mask was worn. We defined proper mask-wearing as wearing either a project mask or an alternative face-covering over the mouth and nose and improper mask-wearing as wearing a mask in any way that did not fully cover the mouth and nose. Surveillance staff observed a single individual and recorded that person as practicing physical distancing if he or she was at least one arm's length away from all other people. Additional details are available in appendix G.

Symptomatic SARS-CoV-2 testing

Symptom reporting

The owner of the household's primary phone completed surveys by phone or in-person at weeks 5 and 9 after the start of the intervention. They were asked to report symptoms experienced by any household member that occurred in the previous week and over the previous month. COVID-19–like symptoms were defined by whether they were consistent with the WHO COVID-19 case definition for suspected or probable cases with an epidemiological link (*73*).

Blood sample collection

We collected endline capillary blood samples from participants who reported COVID-19–like symptoms during the study period and consented to blood collection. We additionally collected samples on a subset of randomly selected participants at baseline, independent of symptoms, to assess overall seropositivity. For the purposes of blood collection, endline was defined as 10 to 12 weeks from the start of the intervention. Blood samples were obtained by puncture with a 20-gauge safety lancet to the third or fourth digit. Five hundred microliters of blood were collected into Microtainer capillary blood collection serum separator tubes (BD, Franklin Lakes, NJ). Blood samples were transported on ice and stored at −20°C until testing.

SARS-CoV-2 testing

Blood samples were tested for the presence of IgG antibodies against SARS-CoV-2 using the

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SCoV-2 Detect IgG ELISA kit (InBios, Seattle, WA). This assay detects IgG antibodies against the spike protein subunit (S1) of SARS-CoV-2. The assays were performed according to the manufacturer's instructions. Additional details are presented in appendix H.

Symptomatic seropositivity

Our primary outcome is symptomatic seropositivity. As noted above, individuals are symptomatic if they (i) meet the WHO surveillance definition of probable COVID-19 illness and (ii) are seropositive in our blood test at endline. If either of these conditions fail to hold, $Y_{ij} = 0$, where Y_{ij} is an indicator for whether individual i in village j is symptomatic seropositive. To assess seropositivity, we tested all individuals who were symptomatic in either our 5- or 9-week household survey.

Our goal is to estimate the impact of the intervention on symptomatic seropositivity, defined as $\psi_0 = E_x[E(Y_{ij}|T_j = 1, x_j) - E(Y_{ij}|T_j = 0, x_j)]$ where T_j is an indicator for whether a village was treated and x_j are village-level covariates, including baseline mask use in each village (constructed as described below) and baseline influenza-like illness and COVID-19 illness based on reported symptoms, as well as indicators for each pair of villages from our pairwise stratification method.

In our preregistered specification, we estimate this parameter by ordinary least squares, clustering at the village level using the approach in (*74*–*76*). The dependent variable is Y_{ij}, the independent variable of interest is T_j, and controls are included for the x_j covariates, including baseline mask use and baseline respiratory symptom rates in each village. We also report results from a generalized linear model with a Poisson family and log-link function to compute relative risk (*77*). More details of our statistical analyses are reported in appendix K.

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ACKNOWLEDGMENTS

Thanks to S. Flora, the additional director general of the Directorate General of Health Services in Bangladesh; J. Snowden; and K. Levy for ongoing support and encouragement. Thanks to WHO chief scientist S. Swaminathan for her encouragement to conduct this trial. Thanks to A. Chowdhury, policy advisor to the Bangladesh government, and S. El Arifeen of the International Centre for Diarrhoeal Disease Research, Bangladesh (icddr,b) for establishing connections with the Bangladesh Directorate General of Health Services in the Ministry of Health and Family Welfare. Thanks to M. Friedman and the CDC Bangladesh country office for assistance with antibody tests. Thanks to A. Saleh, the executive director of BRAC; M. Chowdhury; T. M. Drishti; I. A. Chowdhury; and hundreds of BRAC staff for help with implementation, especially in the scale-up phase of this project in Bangladesh. Similarly, R. Nanavaty, S. Hebbar, and other staff of SEWA India; Captain Usman and his team at the Lahore Commissioners office; the Nepal Rapid Action Taskforce (C19 RAT); Senator C. Sanguinetti; M. Sanchez; and F. L. Boo played crucial roles in replication and scale-ups in India, Pakistan, Nepal, and Uruguay. Thanks also to J. Chevalier, B. P. Kasina, and S. Daves-Ohlin for their advice and assistance; T. Schmidt for help in shipping; P. Hull for econometrics consulting; A. Bhattacharya of the Tata Institute of Fundamental Research and S. Kumar of Stanford University for conducting filtration efficiency testing of the study masks and evaluation of the impact of washing on surgical mask performance; Y. Choudhury from Katex for assistance with the surgical masks; A. Rahman from Standard Group for assistance with the cloth masks; GreenVoice; A. Gsellman for help with visualizations; and many employees at IPA Bangladesh for assistance throughout this project. Most importantly, our continued engagement in and scaling-up of mask promotion would not be possible without the tireless efforts of the Mask-NORM team, including N. Saldanha, H. McAnnally-Linz, M. Rehman, G. Patel, J. Pinilla, J. Rajashekar, P. Adhikary, S. Barnhardt, M. Ali, U. Wattal, I. Haque, A. Tamayo, L. Burke, J. Mosenkis, and many other staff of Yale University and IPA. **Funding:** This research was financially supported by a grant from GiveWell.org to IPA (grant GR-000000272). J.B.-C. was supported by the National Institute of Allergy and Infectious Diseases, National Institutes of Health (grant K01AI141616). **Research ethics approvals:** Our study protocols were reviewed and approved by the Yale University Institutional Review Board (protocol ID 2000028482) and by the Bangladesh Medical Research Council National Research Ethics Committee (IRB registration number 330 26 08 2020). We also received separate administrative approval from the Bangladesh Ministry of Health and Family Welfare. The Bangladesh Directorate General of Health Services under the Ministry of Health; Aspire to Innovate (a2i), an information and data-focused organization within the Bangladesh government; North-South University in Dhaka; and icddr,b partnered in the study design and discussions and reviewed protocols. We provide ethical justification for our decisions in our online ethics appendix (https://osf.io/m2bwq/). **Author contributions:** Conceptualization: J.A., L.H.K., A.S., S.P.L., A.M.M.; Methodology: J.A., L.H.K., A.S., J.B.-C., P.J.W., S.P.L., A.M.M.; Software: E.C.; Validation: E.C.; Formal analysis: J.A., E.C.; Investigation: L.H.K., A.S., M.H., H.M.R., A.A.J., S.G.M., A.R., F.L.B., T.S.H.; Resources: E.B.-J., S.B.; Data curation: S.Rah., E.C., N.Z.B.; Writing: J.A., L.H.K., A.S., E.C., S.P.L., A.M.M.; Visualization: E.C., N.Z.B.; Supervision: J.A., S.P.L., A.M.M.; Project administration: J.A., L.H.K., A.H., M.A.K., S.Rai., S.Rah.; Funding acquisition: J.A., A.M.M., L.H.K., A.S., S.P.L. **Competing interests:** The funder had no role in the study design, interpretation of results, or decision to publish. The authors declare no competing interests. **Data and materials availability:** This clinical trial has been registered at clinicaltrials.gov (identifier NCT04630054). All data and code are provided in our online repository (https://gitlab.com/emily-crawford/bd-mask-rct) (*78*). This work is licensed under a Creative Commons Attribution 4.0 International (CC BY 4.0) license, which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited. To view a copy of this license, visit https://creativecommons.org/licenses/by/4.0/. This license does not apply to figures/photos/artwork or other content included in the article that is credited to a third party; obtain authorization from the rights holder before using such material.

SUPPLEMENTARY MATERIALS

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8 April 2021; accepted 23 November 2021
Published online 2 December 2021
10.1126/science.abi9069

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Science
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Impact of community masking on COVID-19: A cluster-randomized trial in Bangladesh

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Science, **375** (6577), eabi9069.
DOI: 10.1126/science.abi9069

Persuading people to mask

Even in places where it is obligatory, people tend to optimistically overstate their compliance for mask wearing. How then can we persuade more of the population at large to act for the greater good? Abaluck *et al*. undertook a large, cluster-randomized trial in Bangladesh involving hundreds of thousands of people (although mostly men) over a 2-month period. Colored masks of various construction were handed out free of charge, accompanied by a range of mask-wearing promotional activities inspired by marketing research. Using a grassroots network of volunteers to help conduct the study and gather data, the authors discovered that mask wearing averaged 13.3% in villages where no interventions took place but increased to 42.3% in villages where in-person interventions were introduced. Villages where in-person reinforcement of mask wearing occurred also showed a reduction in reporting COVID-like illness, particularly in high-risk individuals. —CA

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Annals of Internal Medicine

ORIGINAL RESEARCH

Effectiveness of Adding a Mask Recommendation to Other Public Health Measures to Prevent SARS-CoV-2 Infection in Danish Mask Wearers

A Randomized Controlled Trial

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Background: Observational evidence suggests that mask wearing mitigates transmission of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). It is uncertain if this observed association arises through protection of uninfected wearers (protective effect), via reduced transmission from infected mask wearers (source control), or both.

Objective: To assess whether recommending surgical mask use outside the home reduces wearers' risk for SARS-CoV-2 infection in a setting where masks were uncommon and not among recommended public health measures.

Design: Randomized controlled trial (DANMASK-19 [Danish Study to Assess Face Masks for the Protection Against COVID-19 Infection]). (ClinicalTrials.gov: NCT04337541)

Setting: Denmark, April and May 2020.

Participants: Adults spending more than 3 hours per day outside the home without occupational mask use.

Intervention: Encouragement to follow social distancing measures for coronavirus disease 2019, plus either no mask recommendation or a recommendation to wear a mask when outside the home among other persons together with a supply of 50 surgical masks and instructions for proper use.

Measurements: The primary outcome was SARS-CoV-2 infection in the mask wearer at 1 month by antibody testing, polymerase chain reaction (PCR), or hospital diagnosis. The secondary outcome was PCR positivity for other respiratory viruses.

Results: A total of 3030 participants were randomly assigned to the recommendation to wear masks, and 2994 were assigned to control; 4862 completed the study. Infection with SARS-CoV-2 occurred in 42 participants recommended masks (1.8%) and 53 control participants (2.1%). The between-group difference was −0.3 percentage point (95% CI, −1.2 to 0.4 percentage point; $P = 0.38$) (odds ratio, 0.82 [CI, 0.54 to 1.23]; $P = 0.33$). Multiple imputation accounting for loss to follow-up yielded similar results. Although the difference observed was not statistically significant, the 95% CIs are compatible with a 46% reduction to a 23% increase in infection.

Limitation: Inconclusive results, missing data, variable adherence, patient-reported findings on home tests, no blinding, and no assessment of whether masks could decrease disease transmission from mask wearers to others.

Conclusion: The recommendation to wear surgical masks to supplement other public health measures did not reduce the SARS-CoV-2 infection rate among wearers by more than 50% in a community with modest infection rates, some degree of social distancing, and uncommon general mask use. The data were compatible with lesser degrees of self-protection.

Primary Funding Source: The Salling Foundations.

Ann Intern Med. 2021;174:335–343. doi:10.7326/M20-6817 **Annals.org**
For author, article, and disclosure information, see end of text.
This article was published at Annals.org on 18 November 2020.

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the cause of coronavirus disease 2019 (COVID-19), has infected more than 54 million persons (1, 2). Measures to impede transmission in health care and community settings are essential (3). The virus is transmitted person-to-person, primarily through the mouth, nose, or eyes via respiratory droplets, aerosols, or fomites (4, 5). It can survive on surfaces for up to 72 hours (6), and touching a contaminated surface followed by face touching is another possible route of transmission (7). Face masks are a plausible means to reduce transmission of respiratory viruses by minimizing the risk that respiratory droplets will reach wearers' nasal or oral mucosa. Face masks are also hypothesized to reduce face touching (8, 9), but frequent face and mask touching has been reported among health care personnel (10). Observational evidence supports the efficacy of face masks in health care settings (11, 12) and as source control in patients infected with SARS-CoV-2 or other coronaviruses (13).

An increasing number of localities recommend masks in community settings on the basis of this observational evidence, but recommendations vary and controversy

See also:

Editorial comments 419, 421

Web-Only
Supplement

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exists (14). The World Health Organization (WHO) and the U.S. Centers for Disease Control and Prevention (15) strongly recommend that persons with symptoms or known infection wear masks to prevent transmission of SARS-CoV-2 to others (source control) (16). However, WHO acknowledges that we lack evidence that wearing a mask protects healthy persons from SARS-CoV-2 (prevention) (17). A systematic review of observational studies reported that mask use reduced risk for SARS, Middle East respiratory syndrome, and COVID-19 by 66% overall, 70% in health care workers, and 44% in the community (12). However, surgical and cloth masks were grouped in preventive studies, and none of the 3 included non–health care studies related directly to COVID-19. Another systematic review (18) and American College of Physicians recommendations (19) concluded that evidence on mask effectiveness for respiratory infection prevention is stronger in health care than community settings.

Observational evidence suggests that mask wearing mitigates SARS-CoV-2 transmission, but whether this observed association arises because masks protect uninfected wearers (protective effect) or because transmission is reduced from infected mask wearers (source control) is uncertain. Here, we report a randomized controlled trial (20) that assessed whether a recommendation to wear a surgical mask when outside the home among others reduced wearers' risk for SARS-CoV-2 infection in a setting where public health measures were in effect but community mask wearing was uncommon and not recommended.

METHODS

Trial Design and Oversight

DANMASK-19 (Danish Study to Assess Face Masks for the Protection Against COVID-19 Infection) was an investigator-initiated, nationwide, unblinded, randomized controlled trial (ClinicalTrials.gov: NCT04337541). The trial protocol was registered with the Danish Data Protection Agency (P-2020-311) (Part 10 of the **Supplement**, available at Annals.org) and published (21). The researchers presented the protocol to the independent regional scientific ethics committee of the Capital Region of Denmark, which did not require ethics approval (H-20023709) in accordance with Danish legislation (Parts 11 and 12 of the **Supplement**). The trial was done in accordance with the principles of the Declaration of Helsinki.

Participants and Study Period

During the study period (3 April to 2 June 2020), Danish authorities did not recommend use of masks in the community and mask use was uncommon (<5%) outside hospitals (22). Recommended public health measures included quarantining persons with SARS-CoV-2 infection, social distancing (including in shops and public transportation, which remained open), limiting the number of persons seen, frequent hand hygiene and cleaning, and limiting visitors to hospitals and nursing homes (23, 24). Cafés and restaurants were closed during the study until 18 May 2020.

Eligible persons were community-dwelling adults aged 18 years or older without current or prior symptoms or diagnosis of COVID-19 who reported being outside the home among others for at least 3 hours per day and who did not wear masks during their daily work. Recruitment involved media advertisements and contacting private companies and public organizations. Interested citizens had internet access to detailed study information and to research staff for questions (Part 3 of the **Supplement**). At baseline, participants completed a demographic survey and provided consent for researchers to access their national registry data (Parts 4 and 5 of the **Supplement**). Recruitment occurred from 3 through 24 April 2020. Half of participants were randomly assigned to a group on 12 April and half on 24 April.

Intervention

Participants were enrolled and data registered using Research Electronic Data Capture (REDCap) software (25). Eligible participants were randomly assigned 1:1 to the mask or control group using a computer algorithm and were stratified by the 5 regions of Denmark (**Supplement Table 1**, available at Annals.org). Participants were notified of allocation by e-mail, and study packages were sent by courier (Part 7 of the **Supplement**). Participants in the mask group were instructed to wear a mask when outside the home during the next month. They received 50 three-layer, disposable, surgical face masks with ear loops (TYPE II EN 14683 [Abena]; filtration rate, 98%; made in China). Participants in both groups received materials and instructions for antibody testing on receipt and at 1 month. They also received materials and instructions for collecting an oropharyngeal/nasal swab sample for polymerase chain reaction (PCR) testing at 1 month and whenever symptoms compatible with COVID-19 occurred during follow-up. If symptomatic, participants were strongly encouraged to seek medical care. They registered symptoms and results of the antibody test in the online REDCap system. Participants returned the test material by prepaid express courier.

Written instructions and instructional videos guided antibody testing, oropharyngeal/nasal swabbing, and proper use of masks (Part 8 of the **Supplement**), and a help line was available to participants. In accordance with WHO recommendations for health care settings at that time, participants were instructed to change the mask if outside the home for more than 8 hours. At baseline and in weekly follow-up e-mails, participants in both groups were encouraged to follow current COVID-19 recommendations from the Danish authorities.

Antibody and Viral PCR Testing

Participants tested for SARS-CoV-2 IgM and IgG antibodies in whole blood using a point-of-care test (Lateral Flow test [Zhuhai Livzon Diagnostics]) according to the manufacturer's recommendations and as previously described (26). After puncturing a fingertip with a lancet, they withdrew blood into a capillary tube and placed 1 drop of blood followed by 2 drops of saline in the test chamber in each of the 2 test plates (IgM and IgG). Participants reported IgM and IgG results separately as

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"1 line present" (negative), "2 lines present" (positive), or "I am not sure, or I could not perform the test" (treated as a negative result). Participants were categorized as seropositive if they had developed IgM, IgG, or both. The manufacturer reported that sensitivity was 90.2% and specificity 99.2%. A previously reported internal validation using 651 samples from blood donors before November 2019 and 155 patients with PCR-confirmed SARS-CoV-2 infection estimated a sensitivity of 82.5% (95% CI, 75.3% to 88.4%) and specificity of 99.5% (CI, 98.7% to 99.9%) (26). We (27) and others (28) have reported that oropharyngeal/nasal swab sampling for SARS-CoV-2 by participants, as opposed to health care workers, is clinically useful. Descriptions of RNA extraction, primer and probe used, reverse transcription, preamplification, and microfluidic quantitative PCR are detailed in Part 6 of the Supplement.

Data Collection

Participants received 4 follow-up surveys (Parts 4 and 5 of the Supplement) by e-mail to collect information on antibody test results, adherence to recommendations on time spent outside the home among others, development of symptoms, COVID-19 diagnosis based on PCR testing done in public hospitals, and known COVID-19 exposures.

Outcomes

The primary outcome was SARS-CoV-2 infection, defined as a positive result on an oropharyngeal/nasal swab test for SARS-CoV-2, development of a positive SARS-CoV-2 antibody test result (IgM or IgG) during the study period, or a hospital-based diagnosis of SARS-CoV-2 infection or COVID-19. Secondary end points included PCR evidence of infection with other respiratory viruses (Supplement Table 2, available at Annals.org).

Sample Size Calculations

The sample size was determined to provide adequate power for assessment of the combined composite primary outcome in the intention-to-treat analysis. Authorities estimated an incidence of SARS-CoV-2 infection of at least 2% during the study period. Assuming that wearing a face mask halves risk for infection, we estimated that a sample of 4636 participants would provide the trial with 80% power at a significance level of 5% (2-sided α level). Anticipating 20% loss to follow-up in this community-based study, we aimed to assign at least 6000 participants.

Statistical Analysis

Participants with a positive result on an antibody test at baseline were excluded from the analyses. We calculated CIs of proportions assuming binomial distribution (Clopper–Pearson).

The primary composite outcome (intention-to-treat) was compared between groups using the χ^2 test. Odds ratios and confidence limits were calculated using logistic regression. We did a per protocol analysis that included only participants reporting complete or predominant use of face masks as instructed. A conservative sensitivity analysis assumed that participants with a positive result on an antibody test at the end of the study who had not provided antibody test results at study entrance had had a positive result at entrance. To further examine the uncertainty of loss to follow-up, we did (post hoc) 200 imputations using the R package smcfcs, version 1.4.1 (29), to impute missing values of outcome. We included sex, age, type of work, time out of home, and outcome in this calculation.

Prespecified subgroups were compared by logistic regression analysis. In a post hoc analysis, we explored whether there was a subgroup defined by a constellation of participant characteristics for which a recommendation to wear masks seemed to be effective. We included sex, age, type of work, time out of home, and outcome in this calculation.

Two-sided *P* values less than 0.05 were considered statistically significant. Analyses were done using R, version 3.6.1 (R Foundation).

Role of the Funding Source

An unrestricted grant from the Salling Foundations supported the study, and the BESTSELLER Foundation donated the Livzon tests. The funders did not influence study design, conduct, or reporting.

RESULTS

Participants

A total of 17 258 Danish citizens responded to recruitment, and 6024 completed the baseline survey and fulfilled eligibility criteria. The first participants (group 1; n = 2995) were randomly assigned on 12 April 2020 and were followed from 14 to 16 April through 15 May 2020. Remaining participants (group 2; n = 3029) were randomly assigned on 24 April 2020 and were followed from 2 to 4 May through 2 June 2020. A total of 3030 participants were randomly assigned to the recommendation to wear face masks, and 2994 were assigned not to wear face masks (Figure); 4862 participants (80.7%) completed the study. Table 1 shows baseline characteristics, which were well balanced between groups. Participants reported having spent a median of 4.5 hours per day outside the home.

Adherence

Based on the lowest adherence reported in the mask group during follow-up, 46% of participants wore the mask as recommended, 47% predominantly as recommended, and 7% not as recommended.

Primary Outcome

The primary outcome occurred in 42 participants (1.8%) in the mask group and 53 (2.1%) in the control group. In an intention-to-treat analysis, the between-group difference was −0.3 percentage point (CI, −1.2 to 0.4 percentage point; P = 0.38) (odds ratio [OR], 0.82 [CI, 0.54 to 1.23]; P = 0.33) in favor of the mask group (Supplement Figure 1, available at Annals.org). When this analysis was repeated with multiple imputation for missing data due to loss to follow-up, it yielded similar results (OR, 0.81 [CI, 0.53 to 1.23]; P = 0.32). Table 2

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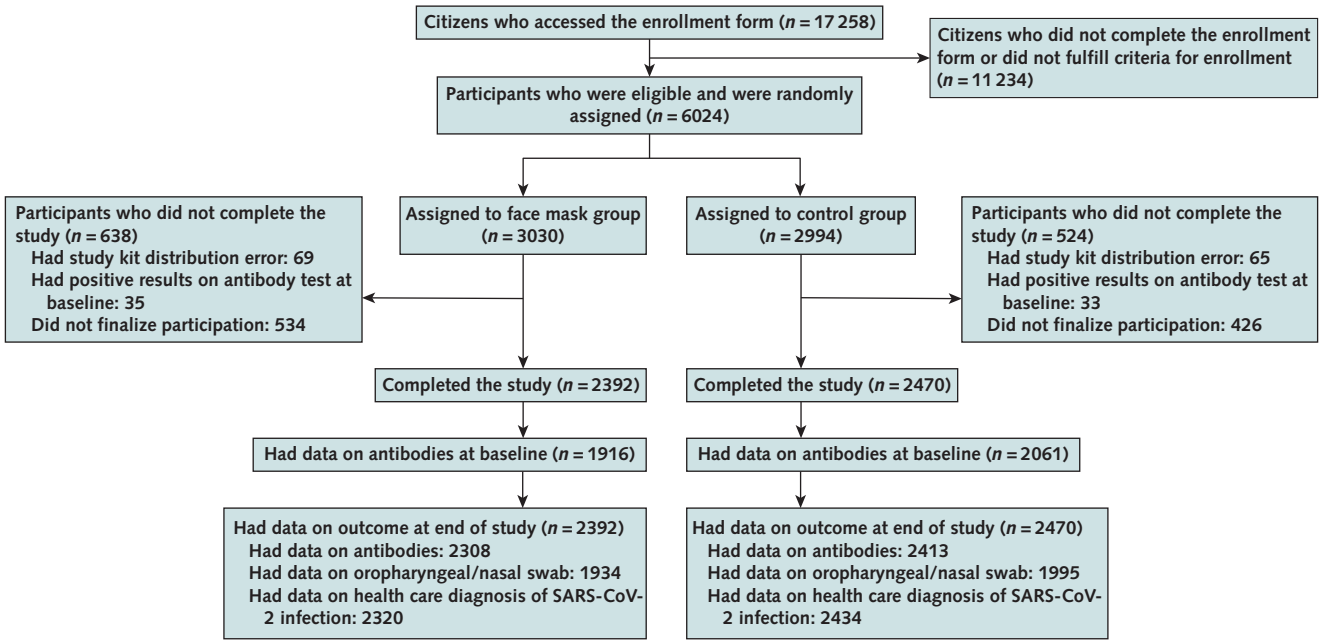
Figure. Study flow diagram.



Inclusion and exclusion criteria are described in the Methods section, and criteria for completion of the study are given in the **Supplement** (available at Annals.org). SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.

provides data on the components of the primary end point, which were similar between groups.

In a per protocol analysis that excluded participants in the mask group who reported nonadherence (7%), SARS-CoV-2 infection occurred in 40 participants (1.8%) in the mask group and 53 (2.1%) in the control group (between-group difference, −0.4 percentage point [CI, −1.2 to 0.5 percentage point]; $P = 0.40$) (OR, 0.84 [CI, 0.55 to 1.26]; $P = 0.40$). **Supplement Figure 2** (available at Annals.org) provides results of the prespecified subgroup analyses of the primary composite end point. No statistically significant interactions were identified.

In the preplanned sensitivity analysis, those who had a positive result on an antibody test at 1 month but had not provided antibody results at baseline were considered to have had positive results at baseline ($n = 18$)—that is, they were excluded from the analysis. In this analysis, the primary outcome occurred in 33 participants (1.4%) in the face mask group and 44 (1.8%) in the control group (between-group difference, −0.4 percentage point [CI, −1.1 to 0.4 percentage point]; $P = 0.22$) (OR, 0.77 [CI, 0.49 to 1.22]; $P = 0.26$).

Three post hoc (not preplanned) analyses were done. In the first, which included only participants reporting wearing face masks "exactly as instructed," infection (the primary outcome) occurred in 22 participants (2.0%) in the face mask group and 53 (2.1%) in the control group (between-group difference, −0.2 percentage point [CI, −1.3 to 0.9 percentage point]; $P = 0.82$) (OR, 0.93 [CI, 0.56 to 1.54]; $P = 0.78$). The second post hoc analysis excluded participants who did not provide antibody test results at baseline; infection occurred in 33 participants (1.7%) in the face mask group and 44 (2.1%) in the control group (between-group difference, −0.4 percentage point [CI, −1.4 to 0.4 percentage point]; $P = 0.33$) (OR, 0.80 [CI, 0.51 to 1.27]; $P = 0.35$). In the third post hoc analysis, which investigated constellations of patient characteristics, we did not find a subgroup where face masks were effective at conventional levels of statistical significance (data not shown).

A total of 52 participants in the mask group and 39 control participants reported COVID-19 in their household. Of these, 2 participants in the face mask group and 1 in the control group developed SARS-CoV-2 infection, suggesting that the source of most observed infections was outside the home. Reported symptoms did not differ between groups during the study period (**Supplement Table 3**, available at Annals.org).

Secondary Outcomes

In the mask group, 9 participants (0.5%) were positive for 1 or more of the 11 respiratory viruses other than SARS-CoV-2, compared with 11 participants (0.6%) in the control group (between-group difference, −0.1 percentage point [CI, −0.6 to 0.4 percentage point]; $P = 0.87$) (OR, 0.84 [CI, 0.35 to 2.04]; $P = 0.71$). Positivity for any

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virus, including SARS-CoV-2, occurred in 9 mask participants (0.5%) versus 16 control participants (0.8%) (between-group difference, −0.3 percentage point [CI, −0.9 to 0.2 percentage point]; $P = 0.26$) (OR, 0.58 [CI, 0.25 to 1.31]; $P = 0.19$).

Discussion

In this community-based, randomized controlled trial conducted in a setting where mask wearing was uncommon and was not among other recommended public health measures related to COVID-19, a recommendation to wear a surgical mask when outside the home among others did not reduce, at conventional levels of statistical significance, incident SARS-CoV-2 infection compared with no mask recommendation. We designed the study to detect a reduction in infection rate from 2% to 1%. Although no statistically significant difference in SARS-CoV-2 incidence was observed, the 95% CIs are compatible with a possible 46% reduction to 23% increase in infection among mask wearers. These findings do offer evidence about the degree of protection mask wearers can anticipate in a setting where others are not wearing masks and where other public health measures, including social distancing, are in effect. The findings, however, should not be used to conclude that a recommendation for everyone to wear masks in the community would not be effective in reducing SARS-CoV-2 infections, because the trial did not test the role of masks in source control of SARS-CoV-2 infection. During the study period, authorities did not recommend face mask use outside hospital settings and mask use was rare in community settings (22). This means that study participants' exposure was overwhelmingly to persons not wearing masks.

The observed infection rate was similar to that reported in other large Danish studies during the study period (26, 30). Of note, the observed incidence of SARS-CoV-2 infection was higher than we had estimated when planning a sample size that would ensure more than 80% power to detect a 50% decrease in infection. The intervention lasted only 1 month and was carried out during a period when Danish authorities recommended quarantine of diagnosed patients, physical distancing, and hand hygiene as general protective means against SARS-CoV-2 transmission (23). Cafés and restaurants were closed through 18 May, but follow-up of the second randomized group continued through 2 June.

The first randomized group was followed while the Danish society was under lockdown. Reopening occurred (18 May 2020) during follow-up of the second group of participants, but it was not reflected in the outcome because infection rates were similar between groups (Supplement Figure 2). The relative infection rate between mask wearers and those not wearing masks would most likely be affected by changes in applied protective means or in the virulence of SARS-CoV-2, whereas the rate difference between the 2 groups would probably not be affected solely by a higher–or lower–number of infected citizens.

Although we saw no statistically significant difference in presence of other respiratory viruses, the study was not sufficiently powered to draw definite conclusions about the protective effect of masks for other viral infections. Likewise, the study had limited power for any of the subgroup analyses.

The primary outcome was mainly defined by antibodies against SARS-CoV-2. This definition was chosen because the viral load of infected patients may be only transiently detectable (31, 32) and because approximately half of persons infected with SARS-CoV-2 are asymptomatic (26, 33). Masks have been hypothesized to reduce inoculum size (34) and could increase the likelihood that infected mask users are asymptomatic, but this hypothesis has been challenged (35). For these reasons, we did not

Table 1. Characteristics of Participants Completing the Study

Characteristic	Face Mask Group (*n* = 2392)	Control Group (*n* = 2470)
Mean age (SD), *y*	47.4 (14)	47.0 (13)
Female sex, *n (%)*	1545 (64.6)	1571 (63.6)
Smoker, *n (%)*	478 (20.0)	499 (20.2)
Wears eyeglasses daily, *n (%)*	956 (40.0)	929 (37.6)
Capital Region resident, *n (%)**	1220 (51.0)	1289 (52.2)
Provided antibody test results at baseline, *n (%)*	1916 (80.1)	2061 (83.4)
Occupation, *n (%)*		
Shop employee	108 (4.5)	85 (3.4)
Cashier	101 (4.2)	96 (3.9)
Craftsperson	110 (4.6)	103 (4.2)
Office employee	265 (11.1)	312 (12.6)
Manager	111 (4.6)	108 (4.4)
Transportation employee	617 (25.8)	625 (25.3)
Service employee	107 (4.5)	104 (4.2)
Home care/nursing home employee	197 (8.2)	229 (9.3)
Early childhood care staff	89 (3.7)	88 (3.6)
Salesperson	37 (1.5)	47 (1.9)
Other	650 (27.2)	673 (27.2)

* According to national authority data, the Capital Region had a higher frequency of coronavirus disease 2019 than other Danish regions; see subgroup analyses in Supplement Figure 2 (available at Annals.org).

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Table 2. Distribution of the Components of the Composite Primary Outcome

Outcome Component	Face Mask Group (*n* = 2392), *n (%)*	Control Group (*n* = 2470), *n (%)*	Odds Ratio (95% CI)*
Primary composite end point	42 (1.8)	53 (2.1)	0.82 (0.54–1.23)
Positive antibody test result†			
IgM	31 (1.3)	37 (1.5)	0.87 (0.54–1.41)
IgG	33 (1.4)	32 (1.3)	1.07 (0.66–1.75)
Positive SARS-CoV-2 RT-PCR	0 (0)	5 (0.2)	–
Health care–diagnosed SARS-CoV-2 or COVID-19	5 (0.2)	10 (0.4)	0.52 (0.18–1.53)

COVID-19 = coronavirus disease 2019; RT-PCR = reverse transcriptase polymerase chain reaction; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.

* Calculated using logistic regression. The between-group differences in frequencies of positive SARS-CoV-2 RT-PCR were not statistically significant ($P = 0.079$).

† 124 participants in the mask group and 140 in the control group registered "not done" or unclear results of the antibody test—i.e., they were included in the analysis because they sent an oropharyngeal swab for PCR.

rely solely on identification of SARS-CoV-2 in oropharyngeal/nasal swab samples. As mentioned in the Methods section, an internal validation study estimated that the point-of-care test has 82.5% sensitivity and 99.5% specificity (26).

The observed rate of incident SARS-CoV-2 infection was similar to what was estimated during trial design. These rates were based on thorough screening of all participants using antibody measurements combined with PCR, whereas the observed official infection rates relied solely on PCR test–based estimates during the period. In addition, authorities tested only a small subset of primarily symptomatic citizens of the entire population, yielding low incidence rates. On this basis, the infection rates we report here are not comparable with the official SARS-CoV-2 infection rates in the Danish population. The eligibility requirement of at least 3 hours of exposure to other persons outside the home would add to this difference. Between 6 April and 9 May 2020, we found a similar seroprevalence of SARS-CoV-2 of 1.9% (CI, 0.8% to 2.3%) in Danish blood donors using the Livzon point-of-care test and assessed by laboratory technicians (36). Testing at the end of follow-up, however, may not have captured any infections contracted during the last part of the study period, but this would have been true in both the mask and control groups and was not expected to influence the overall findings.

The face masks provided to participants were high-quality surgical masks with a filtration rate of 98% (37). A published meta-analysis found no statistically significant difference in preventing influenza in health care workers between respirators (N95 [American standard] or FFP2 [European standard]) and surgical face masks (38). Adherence to mask use may be higher than observed in this study in settings where mask use is common. Some mask group participants (14%) reported adverse reactions from other citizens (**Supplement Table 4**, available at Annals.org). Although adherence may influence the protective effect of masks, sensitivity analyses had similar results across reported adherence.

How SARS-CoV-2 is transmitted—via respiratory droplets, aerosols, or (to a lesser extent) fomites—is not firmly established. Droplets are larger and rapidly fall to the ground, whereas aerosols are smaller ($\leq$5 μm) and may evaporate and remain in the air for hours (39). Transmission of SARS-CoV-2 may take place through multiple routes. It has been argued that for the primary route of SARS-CoV-2 spread—that is, via droplets—face masks would be considered effective, whereas masks would not be effective against spread via aerosols, which might penetrate or circumnavigate a face mask (37, 39). Thus, spread of SARS-CoV-2 via aerosols would at least partially explain the present findings. Lack of eye protection may also have been of importance, and use of face shields also covering the eyes (rather than face masks only) has been advocated to halt the conjunctival route of transmission (40, 41). We observed no statistically significant interaction between wearers and nonwearers of eyeglasses (**Supplement Figure 2**). Recent reports indicate that transmission of SARS-CoV-2 via fomites is unusual (42), but masks may alter behavior and potentially affect fomite transmission.

The present findings are compatible with the findings of a review of randomized controlled trials of the efficacy of face masks for prevention (as personal protective equipment) against influenza virus (18). A recent meta-analysis that suggested a protective effect of face masks in the non–health care setting was based on 3 observational studies that included a total of 725 participants and focused on transmission of SARS-CoV-1 rather than SARS-CoV-2 (12). Of 725 participants, 138 (19%) were infected, so the transmission rate seems to be higher than for SARS-CoV-2. Further, these studies focused on prevention of infection in healthy mask wearers from patients with a known, diagnosed infection rather than prevention of transmission from persons in their surroundings in general. In addition, identified comparators (control participants) not wearing masks may also have missed other protective means. Recent observational studies that indicate a protective association between mandated mask use in the community and SARS-CoV-2 transmission are limited by study design and simultaneous introduction of other public health interventions (14, 43).

Several challenges regarding wearing disposable face masks in the community exist. These include practical aspects, such as potential incorrect wearing, reduced adherence, reduced durability of the mask depending on type of mask and occupation, and weather. Such circumstances may necessitate the use of multiple face masks during the day. In our study, participants used a mean of 1.7 masks per weekday and 1.3 per weekend day (**Supplement Table 4**). Wearing a face mask may be physically unpleasant, and psychological barriers and other side effects have been described (44). "Face mask

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policing" between citizens might reinforce use of masks but may be challenging. In addition, the wearer of a face mask may change to a less cautious behavior because of a false sense of security, as pointed out by WHO (17); accordingly, our face mask group seemed less worried (**Supplement Table 4**), which may explain their increased willingness to wear face masks in the future (**Supplement Table 5**, available at Annals.org). These challenges, including costs and availability, may reduce the efficacy of face masks to prevent SARS-CoV-2 infection.

The potential benefits of a community-wide recommendation to wear masks include combined prevention and source control for symptomatic and asymptomatic persons, improved attention, and reduced potential stigmatization of persons wearing masks to prevent infection of others (17). Although masks may also have served as source control in SARS-CoV-2–infected participants, the study was not designed to determine the effectiveness of source control.

The most important limitation is that the findings are inconclusive, with CIs compatible with a 46% decrease to a 23% increase in infection. Other limitations include the following. Participants may have been more cautious and focused on hygiene than the general population; however, the observed infection rate was similar to findings of other studies in Denmark (26, 30). Loss to follow-up was 19%, but results of multiple imputation accounting for missing data were similar to the main results. In addition, we relied on patient-reported findings on home antibody tests, and blinding to the intervention was not possible. Finally, a randomized controlled trial provides high-level evidence for treatment effects but can be prone to reduced external validity.

Our results suggest that the recommendation to wear a surgical mask when outside the home among others did not reduce, at conventional levels of statistical significance, the incidence of SARS-CoV-2 infection in mask wearers in a setting where social distancing and other public health measures were in effect, mask recommendations were not among those measures, and community use of masks was uncommon. Yet, the findings were inconclusive and cannot definitively exclude a 46% reduction to a 23% increase in infection of mask wearers in such a setting. It is important to emphasize that this trial did not address the effects of masks as source control or as protection in settings where social distancing and other public health measures are not in effect.

Reduction in release of virus from infected persons into the environment may be the mechanism for mitigation of transmission in communities where mask use is common or mandated, as noted in observational studies. Thus, these findings do not provide data on the effectiveness of widespread mask wearing in the community in reducing SARS-CoV-2 infections. They do, however, offer evidence about the degree of protection mask wearers can anticipate in a setting where others are not wearing masks and where other public health measures, including social distancing, are in effect. The findings also suggest that persons should not abandon other COVID-19 safety measures regardless of the use of masks. While we await additional data to inform mask recommendations, communities must balance the seriousness of COVID-19, uncertainty about the degree of source control and protective effect, and the absence of data suggesting serious adverse effects of masks (45).

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Acknowledgment: The authors thank Mrs. Kristine Sarah Hedegaard Andersen for valuable technical and logistic assistance and Mrs. Helena Aagaard Glud, Mr. Oscar Mejias Gomez, Mr. Andreas Visbech Madsen, Mr. Shoeib Moradi, Mrs. Louise Brogaard, Mrs. Maria Heinesen, Mrs. Karin Tarp, Mr. Weihua Tian, Mrs. Henriette Vorsholt, and Mrs. Shila Mortensen for valuable assistance in the laboratory work and analyses.

Grant Support: By the Salling Foundations.

Disclosures: Disclosures can be viewed at www.acponline.org/authors/icmje/ConflictOfInterestForms.do?msNum=M20-6817.

Data Sharing Statement: The authors have indicated that they will not be sharing data.

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