Efficacy and safety of COVID-19 vaccines

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Efficacy and safety of COVID-19 vaccines

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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.

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.

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?

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.

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)	**Vaccine efficacy** **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)	**Vaccine efficacy** **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			46,149 (3 RCTs)[j]	⊕⊕⊖⊖ **Low**[k]	—

	1.41; n = 2260; Walsh 2020 (≥ 18 years): RR 1.50, 95% CI 0.53 to 4.21; n = 42					
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 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; **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: 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]	112 per 100,000	**105 per 100,000** (54 to 209)	**RR 0.94** (0.48 to 1.86)	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.

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 14 days after dose 2 to 2.3 months (median) and 5.3 months.
[c]ModernaTX: 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%)
[f]Follow-up: 5.3 months
[g]ModernaTX: 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]	—
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 (studies)	Certainty of the evidence	Comments
	Risk with placebo	Risk with ChAdOx1				
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).

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					
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.

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
[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).

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: estimates could not be pooled due to asymmetry in the CIs)		—	19,852 (2 RCTs)[c]	⊕⊕⊖⊖ **Low**[d,g]	—
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, re-

						ceiving 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%).
[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]	—
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				
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.
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** (46.70 to 82.50)	6289 (1 RCT)[c]	⊕⊕⊕⊕ **High**[d]	—
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.

[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)

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]	—
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.

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.
[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]	—

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					

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.

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.

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.

- 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.

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.

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

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.

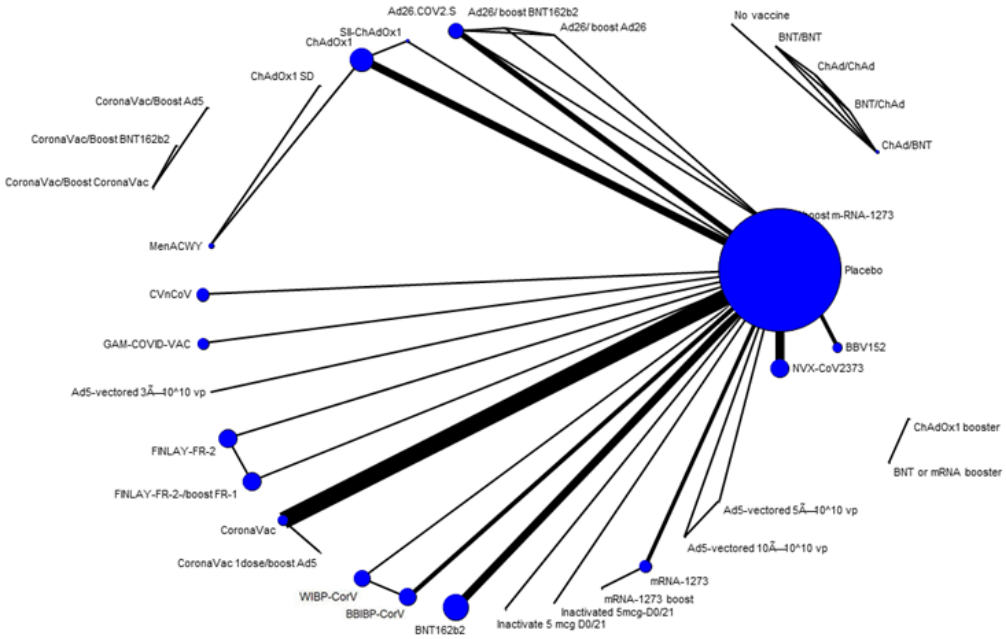
We performed a pairwise meta-analysis and presented summary effect estimates with 95% CIs for each direct comparison, with at least two studies providing data. We used the random-effects model to incorporate the anticipated clinical and methodological heterogeneity across studies. We presented trials 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.

- 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).

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

(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.

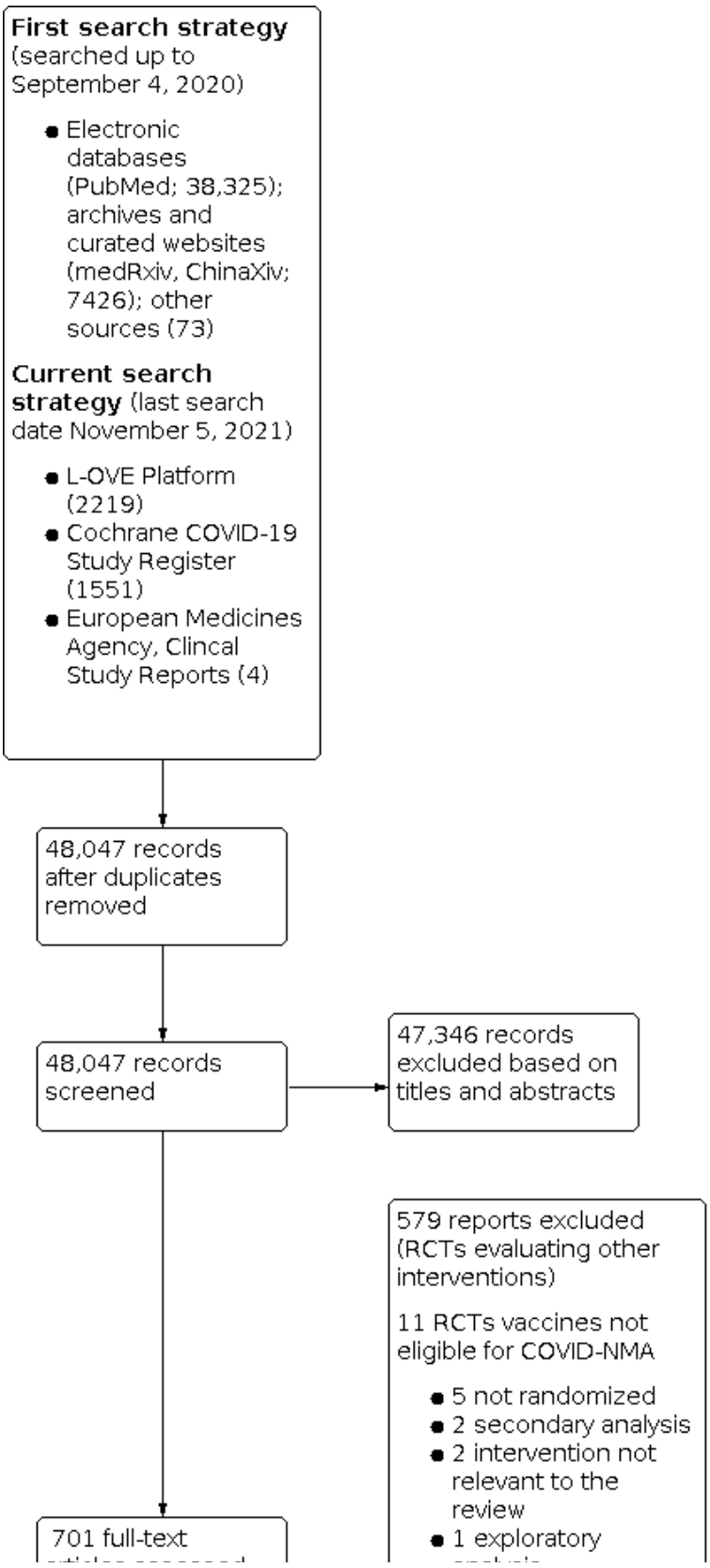
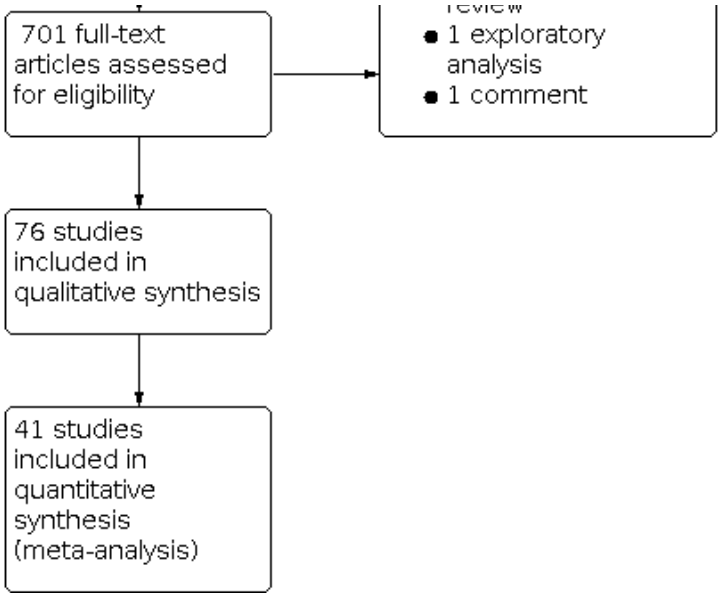


Figure 2. (Continued)



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 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 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 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.

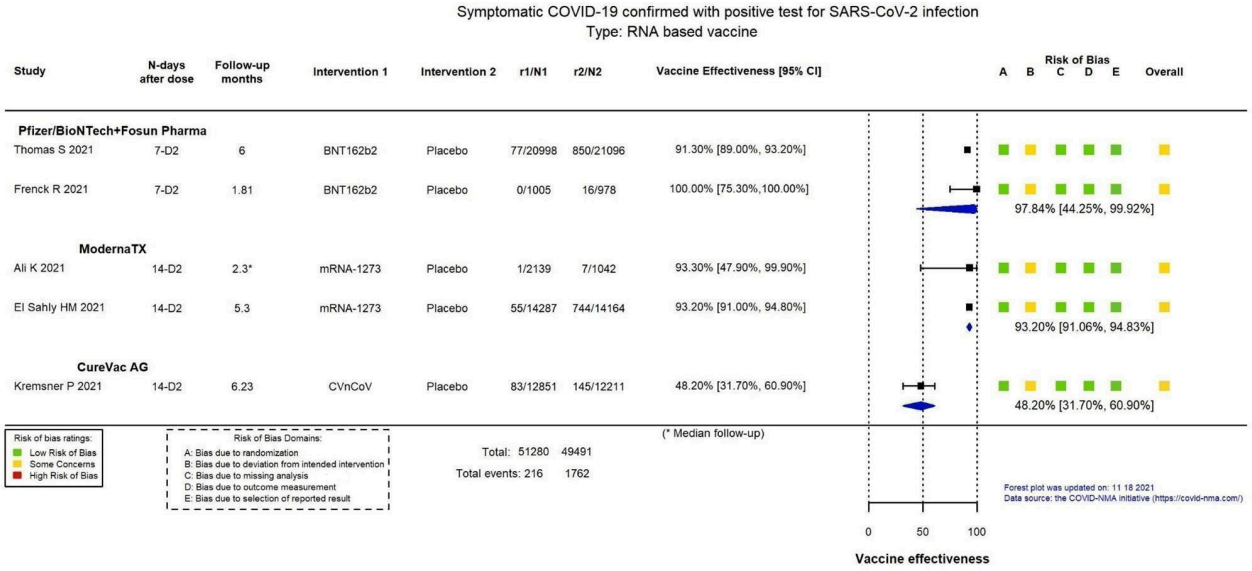
We identified and included three trials in the analysis assessing BNT162b2. The outcomes 'confirmed SARS-CoV-2 infection after complete vaccination', 'systemic reactogenicity events', 'GMT of specific antibodies against SARS-CoV-2' and 'cellular immune response' were not reported for this comparison.

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).

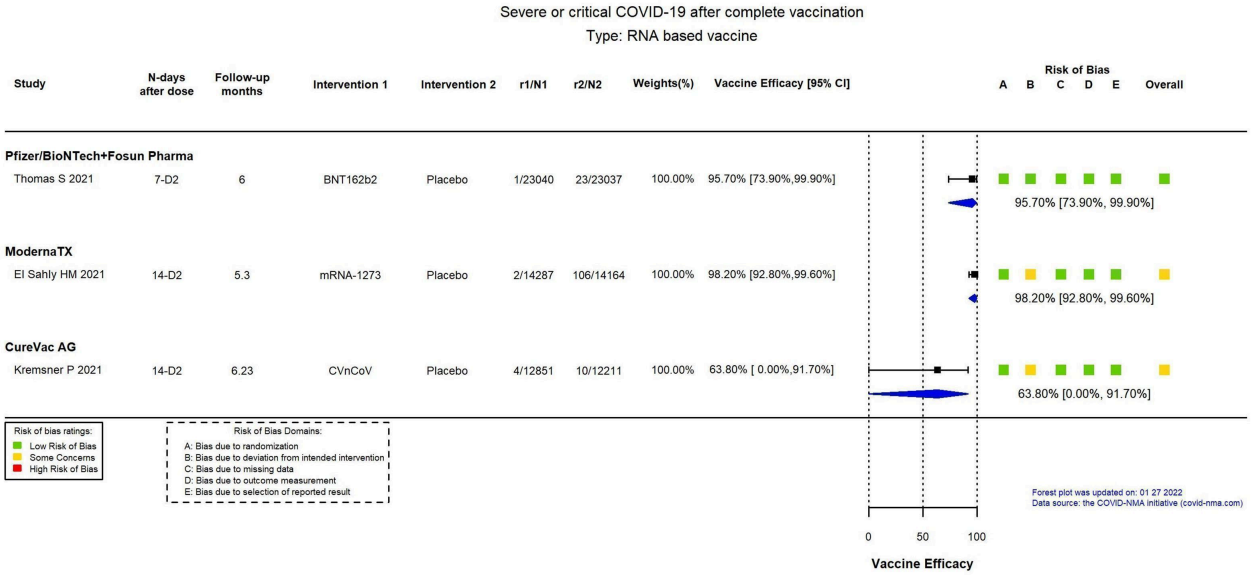
Figure 3. Analysis 1.1.2: RNA-based vaccine. Outcome: confirmed symptomatic COVID-19 after complete vaccination. Ali 2021 included only participants 3 to 17 years of age. Frenck 2021 included only participants 12 to 15 years of age.



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.

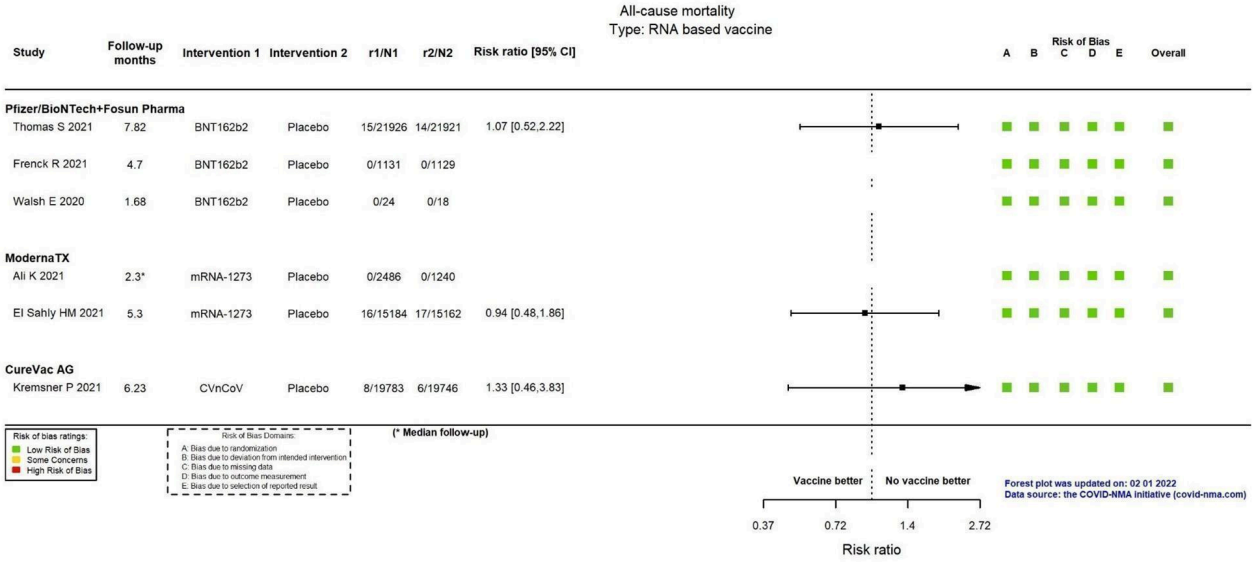


All-cause mortality

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).

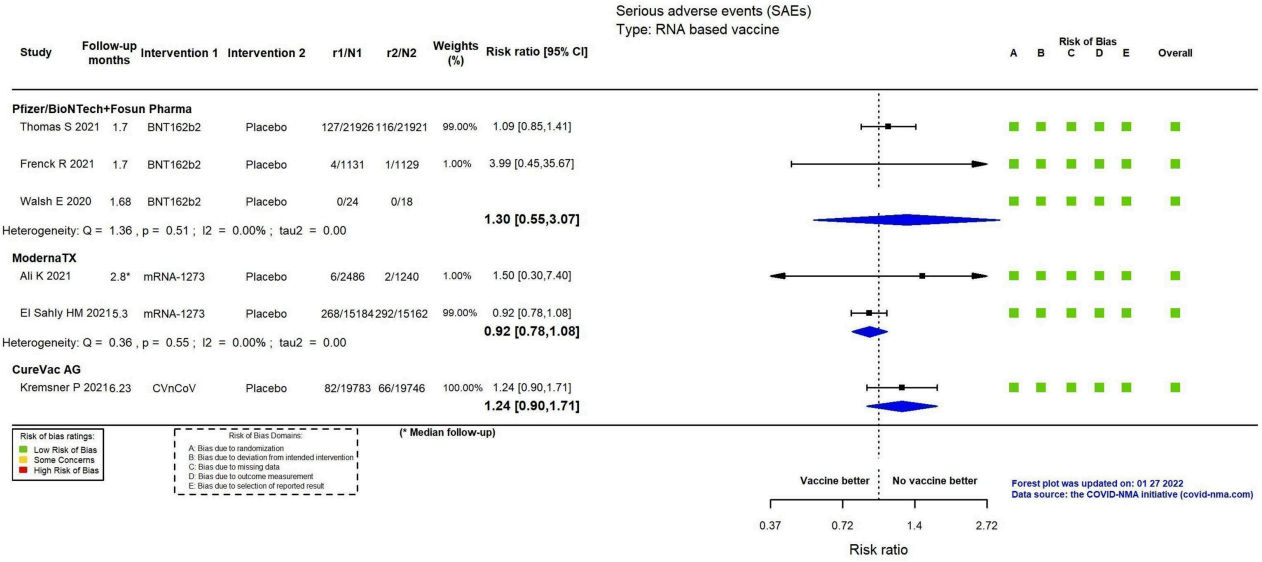
Figure 5. Analysis 1.1.4: RNA-based vaccine. Outcome: all-cause mortality. Ali 2021 included only participants 3 to 17 years of age. Frenck 2021 included only participants 12 to 15 years of age.



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).

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.

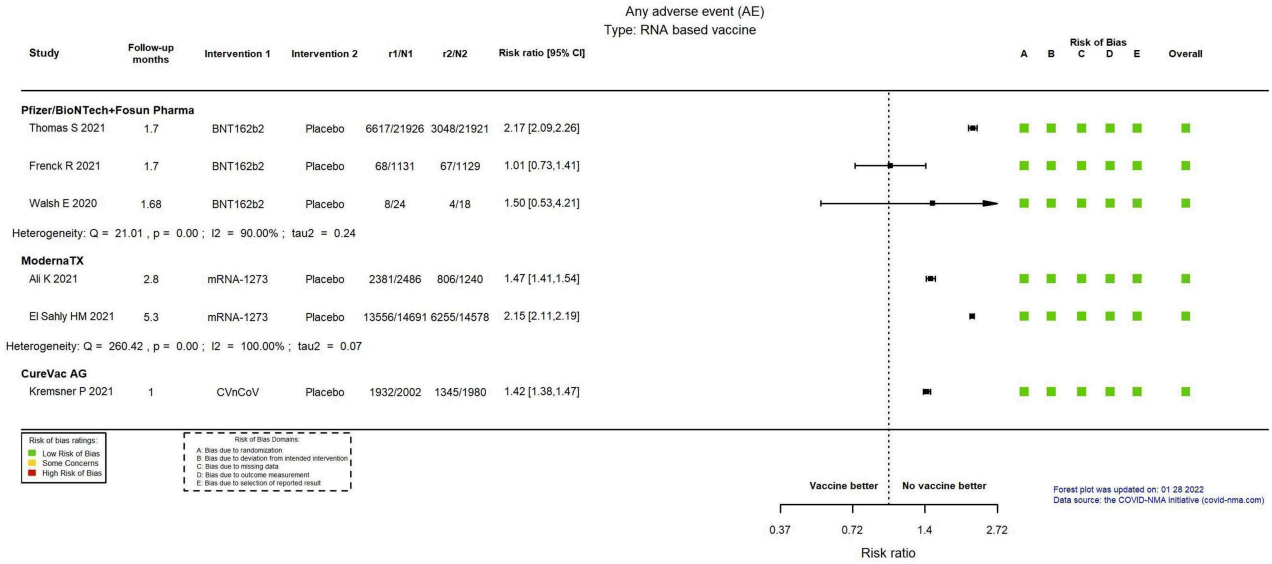


Any adverse event

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.



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.

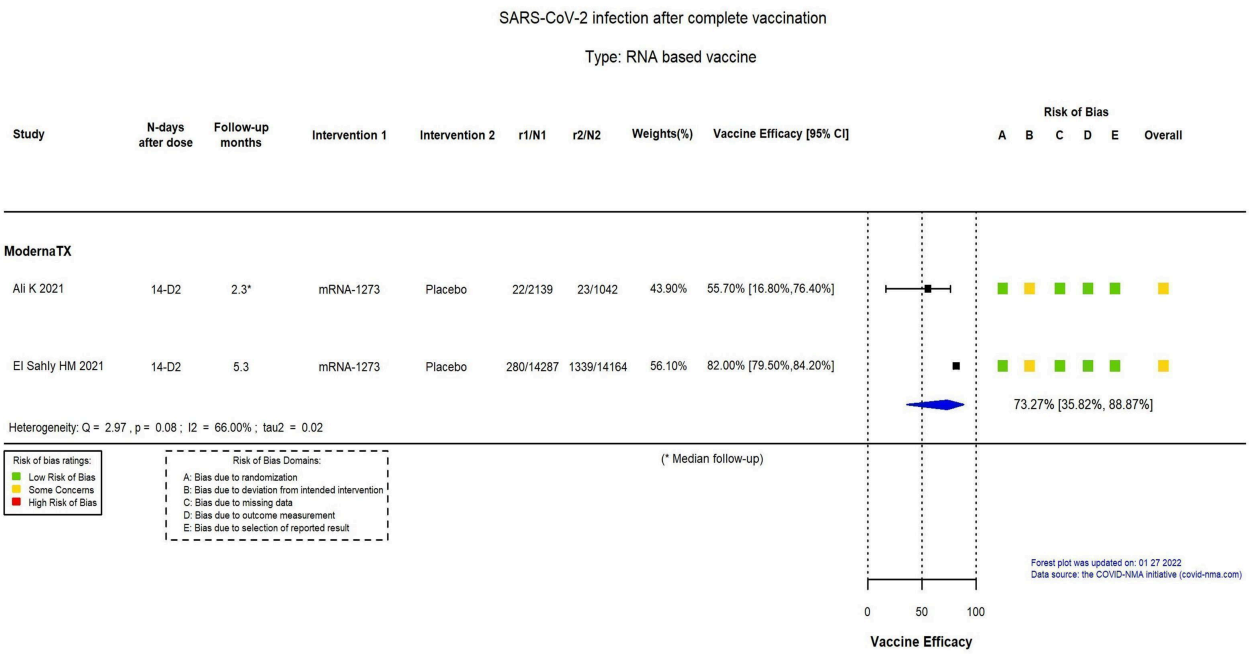
We identified and included two trials in the analysis assessing mRNA-1273. The outcomes 'GMT of specific antibodies against SARS-CoV-2', 'GMT of neutralizing antibodies against SARS-CoV-2' and 'cellular immune response' were not reported for this comparison.

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 0.94, 95% CI 0.48 to 1.86; 1 RCT, 30,346 participants; low-certainty evidence; Figure 5).

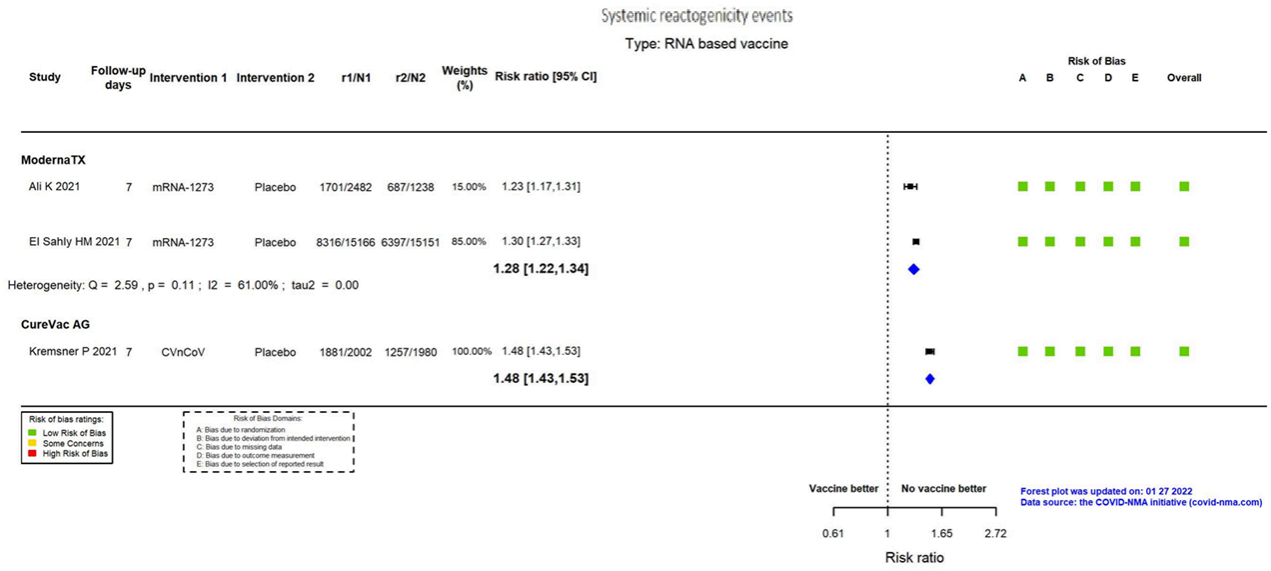
Serious adverse events

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

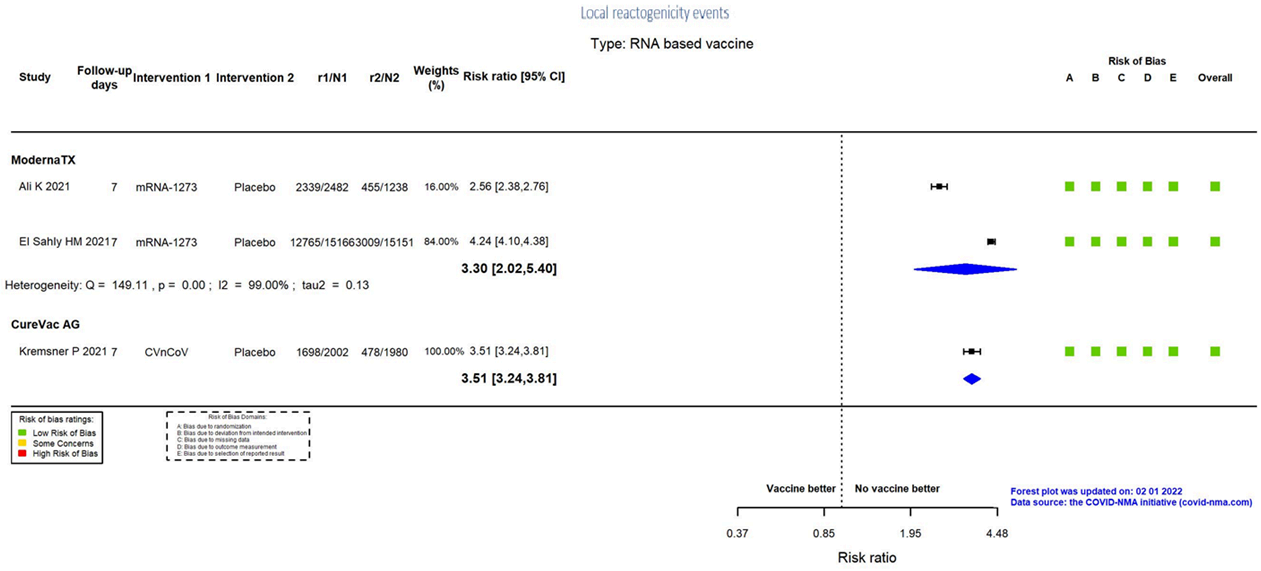
Two RCTs reported the outcome at 2.8 months (median) and 5.3 months' follow-up (Ali 2021; El Sahly 2021). We decided not to pool the results due to considerable heterogeneity (I^2 = 100%) probably caused by studies assessing participants in different age groups; Ali 2021 included participants aged three 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).

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

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.

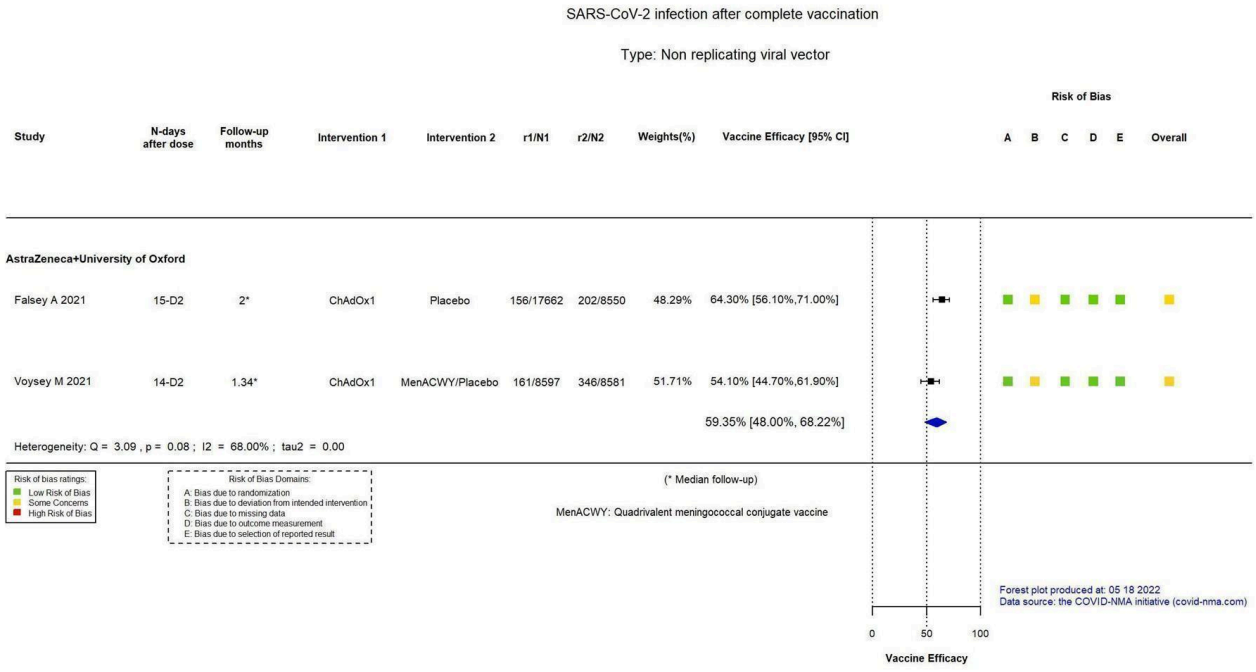
The outcomes 'severe or critical COVID-19 after complete vaccination', 'GMT of neutralizing antibodies against SARS-CoV-2' and 'cellular immune response' were not reported for this comparison.

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).

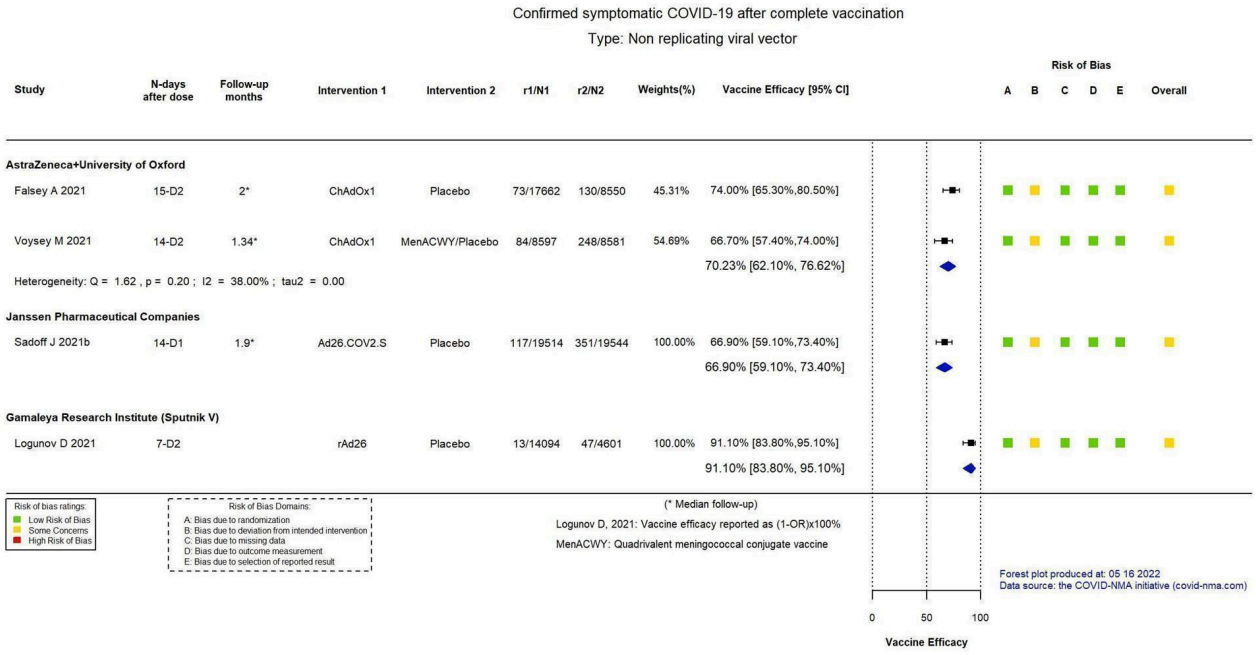
Figure 11. Analysis 2.1.1: Non-replicating viral vector vaccine. Outcome: confirmed SARS-CoV-2 infection after complete vaccination. Voysey 2021a: data pooled from four trials.



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).

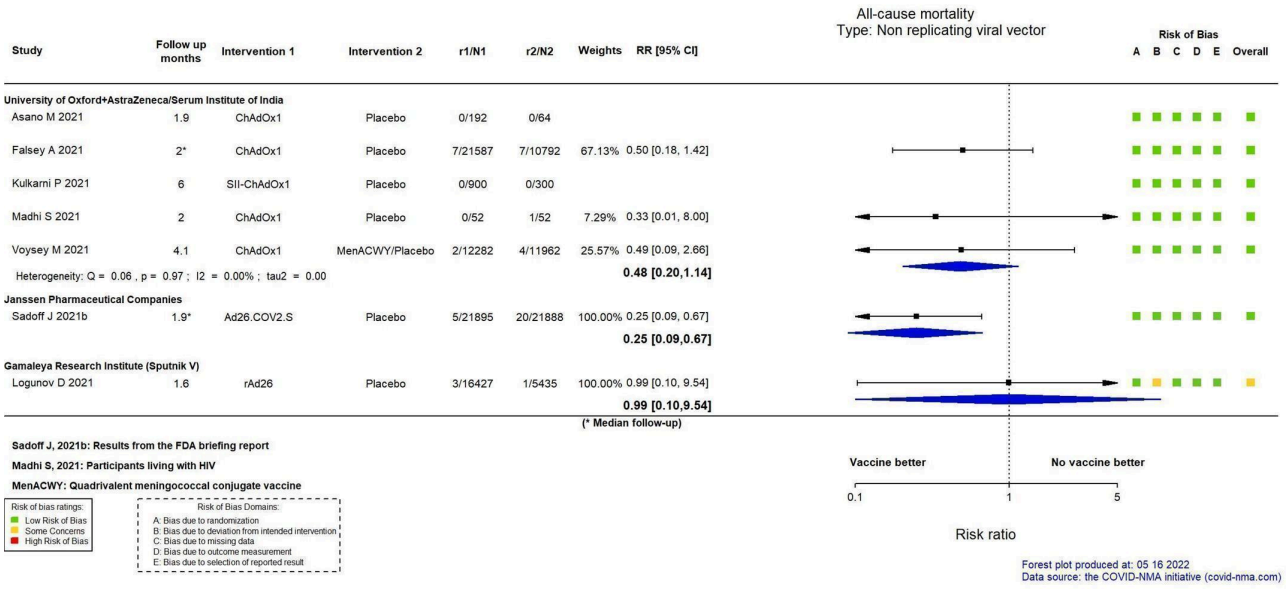
Figure 12. Analysis 2.1.2: non-replicating viral vector vaccine. Outcome: confirmed symptomatic COVID-19 after complete vaccination. Voysey 2021a: data pooled from four trials.



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).

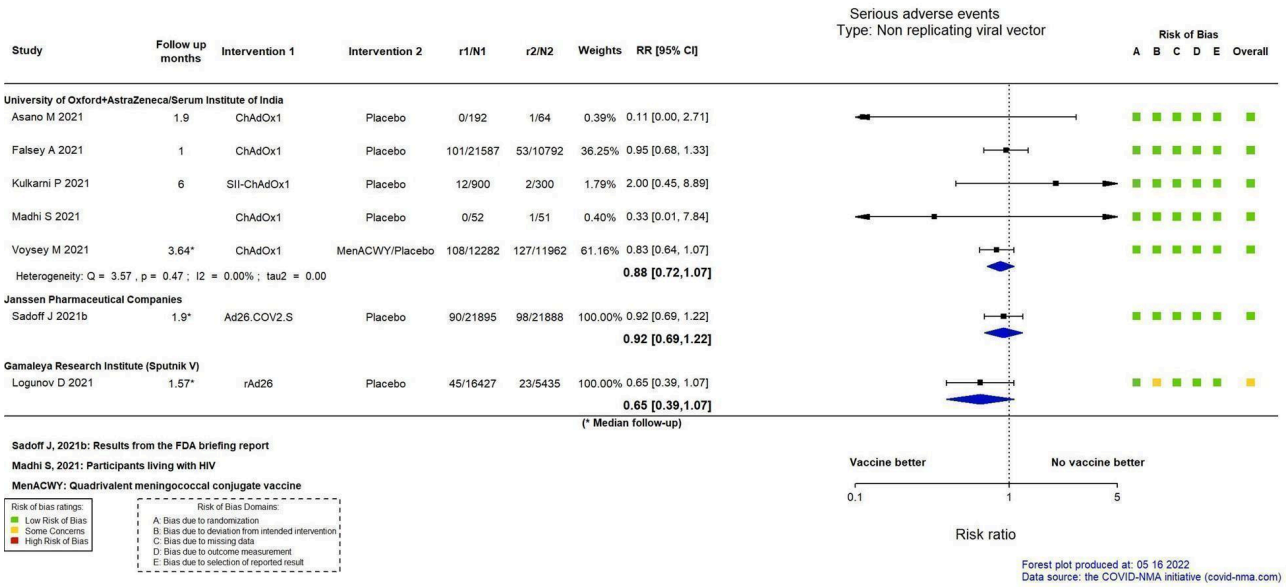
Figure 13. Analysis 2.1.4: non-replicating viral vector vaccine. Outcome: all-cause mortality. In Kulkarni 2021, the control arm received adjuvant. Voysey 2021a: data pooled from four trials.



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).

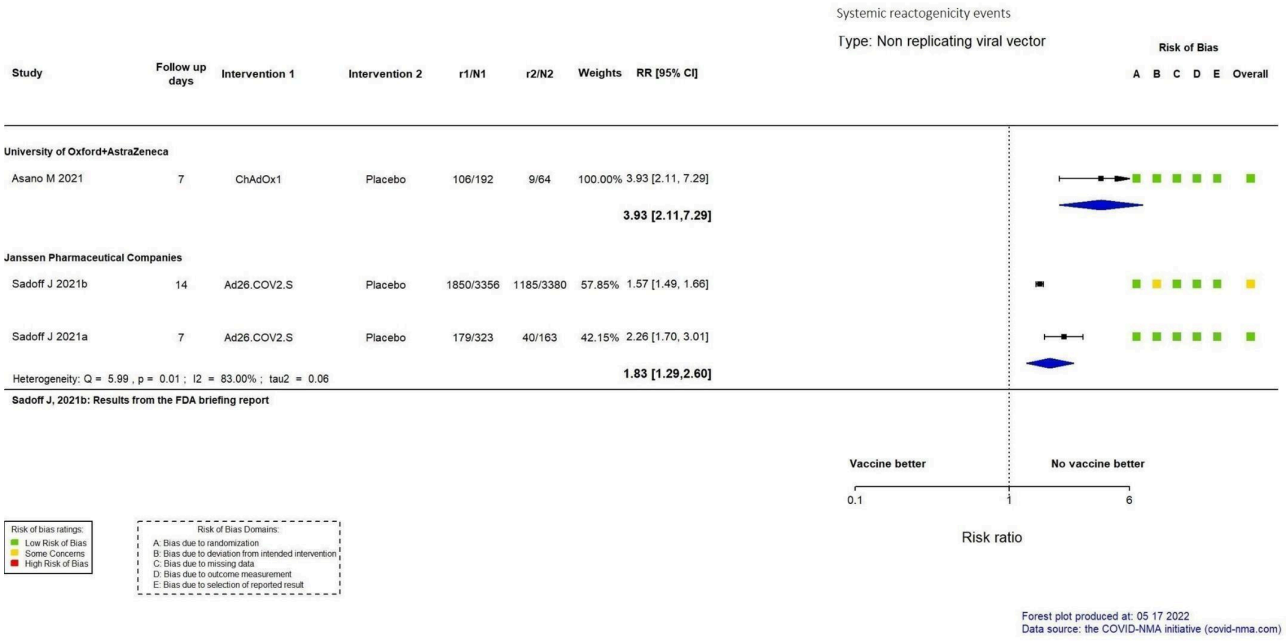
Figure 14. Analysis 2.1.5: non-replicating viral vector vaccine. Outcome: serious adverse events (SAEs). In Kulkarni 2021, the control arm received adjuvant. Voysey 2021a: data pooled from four trials.



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).

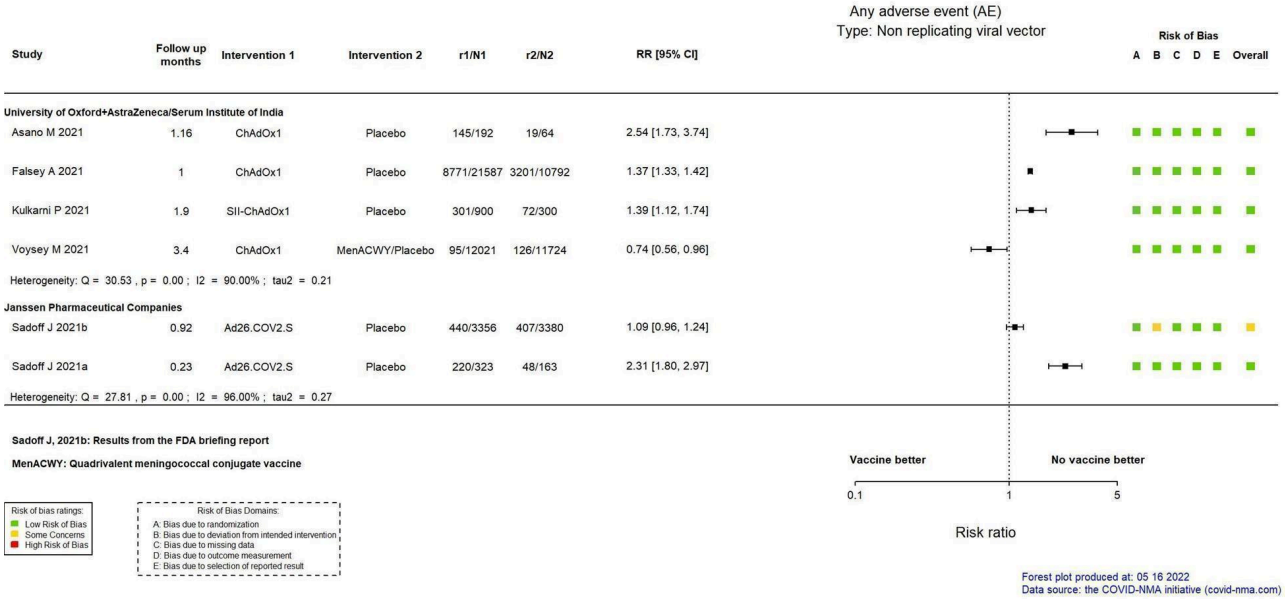
Figure 15. Analysis 2.1.6: non-replicating viral vector vaccine. Outcome: systemic reactogenicity events.



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

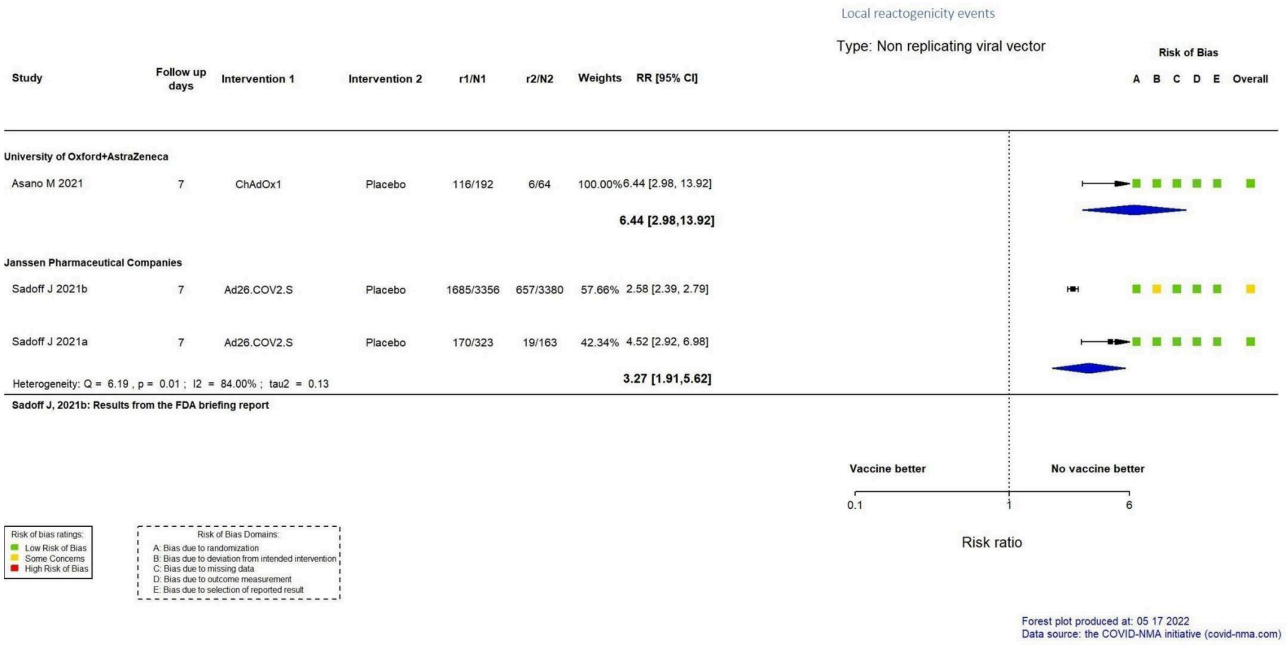
GMTs of a specific antibody against SARS-COV-2

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).

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.

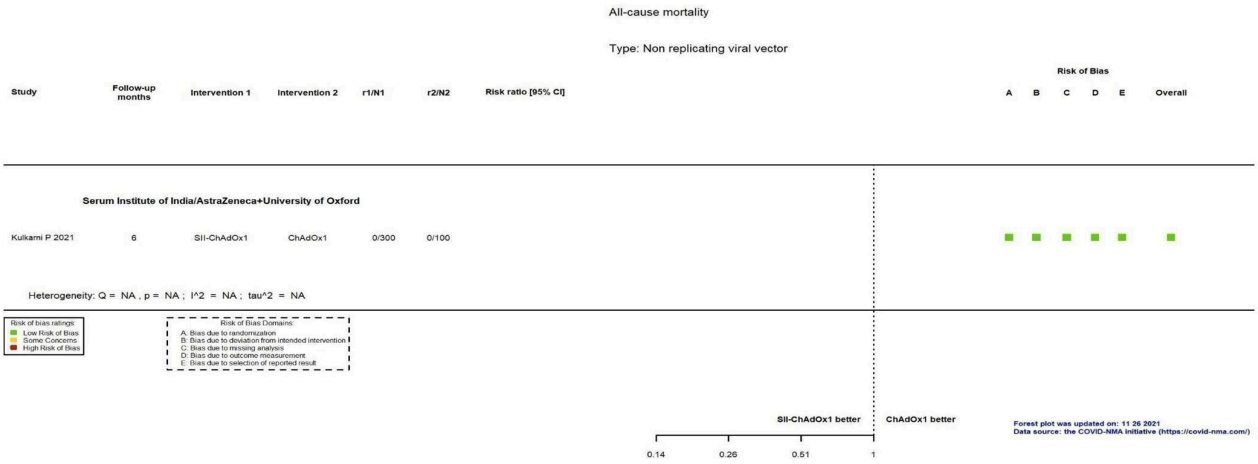
Kulkarni 2021 reported results on ChAdOx1 compared to SII-ChAdOx1 (the equivalent of ChAdOx1 manufactured in India at Serum Institute of India).

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).

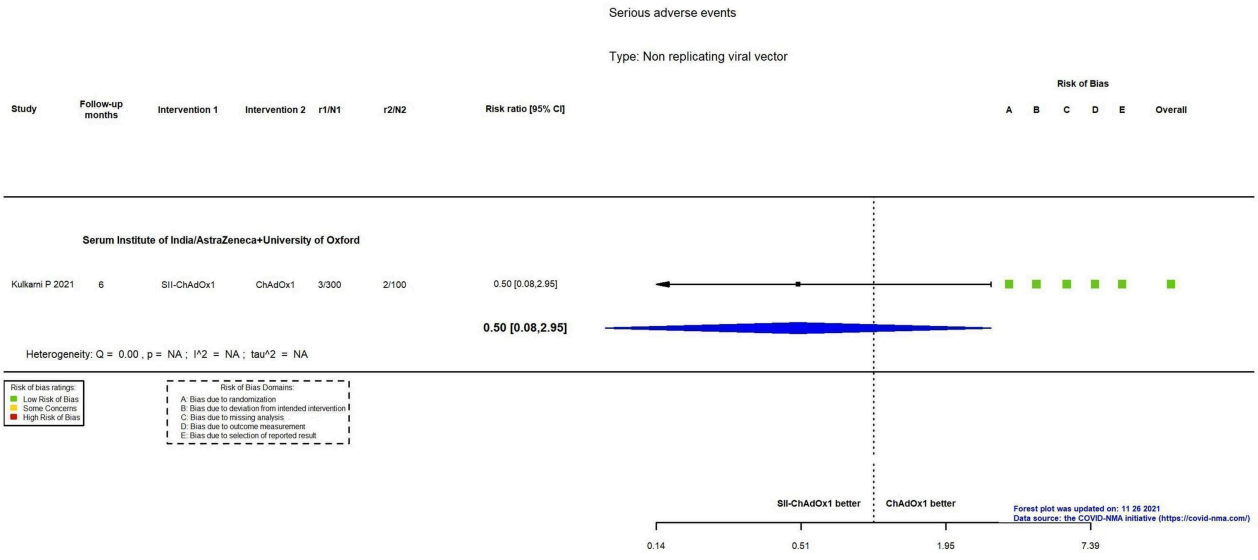
Figure 18. Analysis 2.2.1: serum Institute of India/Astra Zeneca+University of Oxford – SII-ChAdOx1 versus University of Oxford – ChAdOx1. Outcome: all-cause mortality.



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).

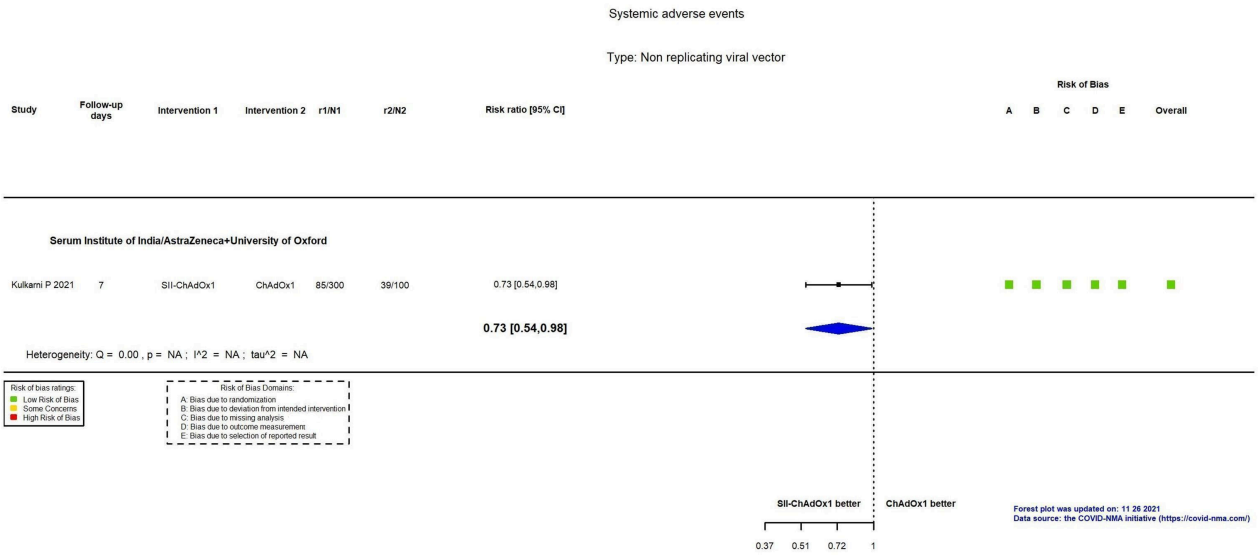
Figure 19. Analysis 2.2.2: SII-ChAdOx1 versus ChAdOx1. Outcome: serious adverse events (SAEs).



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).

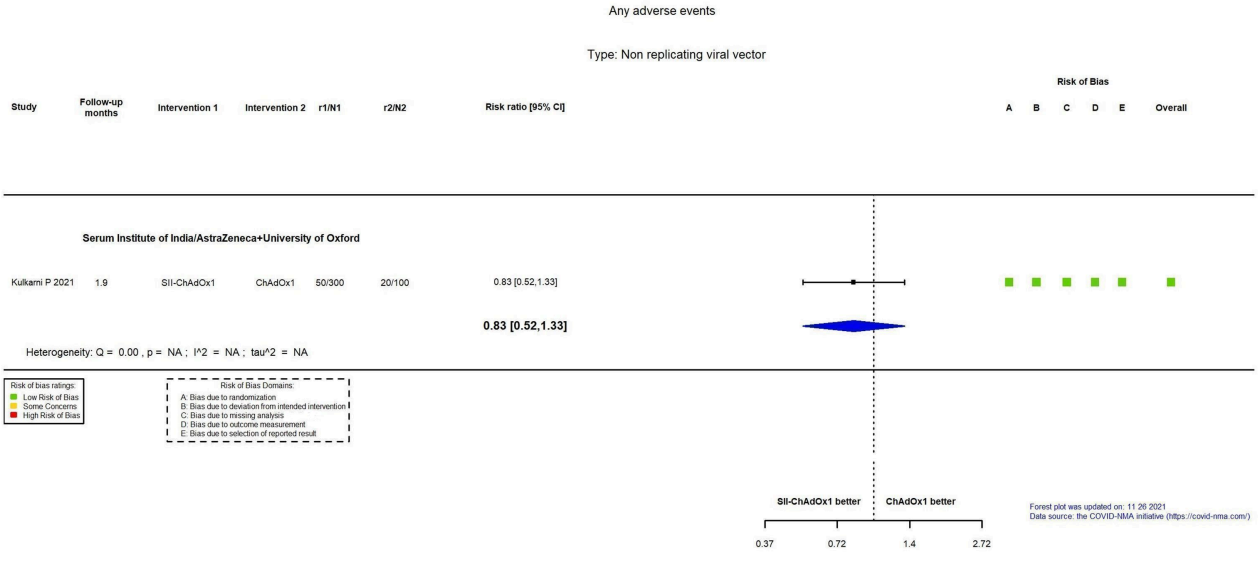
Figure 20. Analysis 2.2.3: SII-ChAdOx1 versus ChAdOx1. Outcome: systemic reactogenicity events.



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

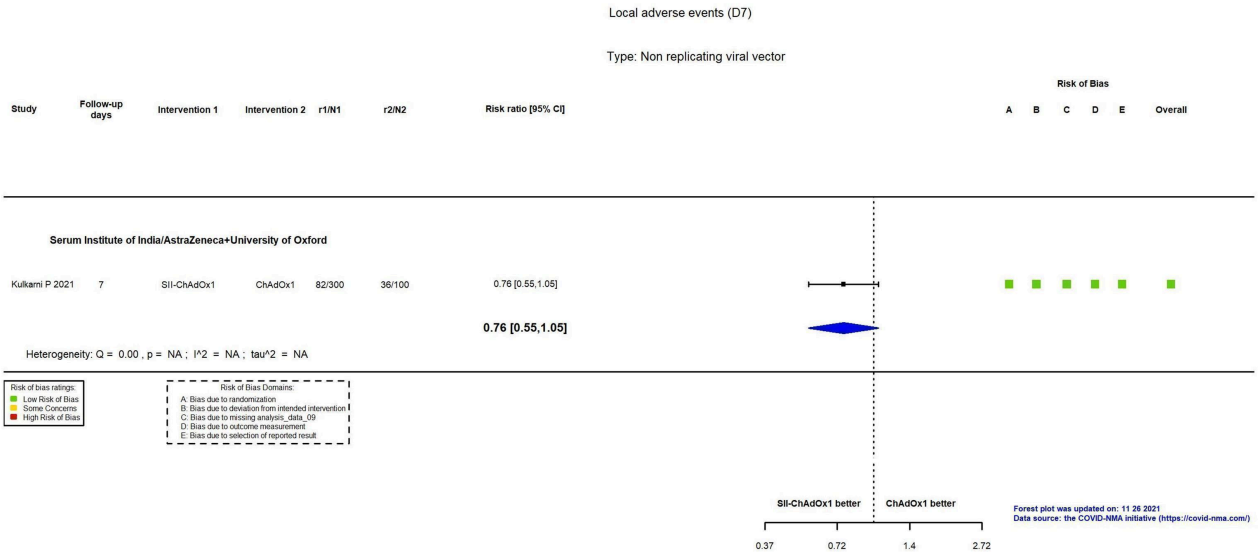
Kulkarni 2021 reported that SII-ChAdOx1 elicited slightly higher levels of specific antibodies against SARS-COV-2 (GMR 1.52, 95% CI 1.03 to 2.26) compared to ChAdOx1 (Appendix 16). Results for neutralizing antibodies against SARS-COV-2 were not conclusive because of imprecision (GMR 1.23, 95% CI 0.92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

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

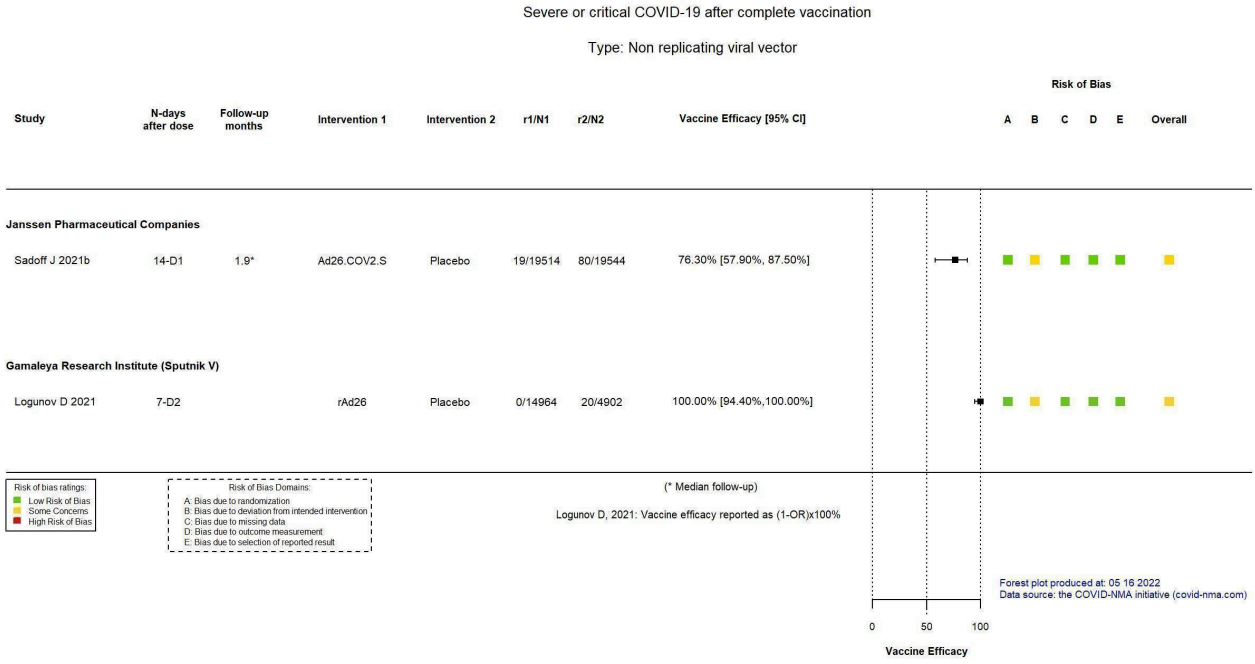
Confirmed symptomatic COVID-19 after complete vaccination

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).

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).

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.

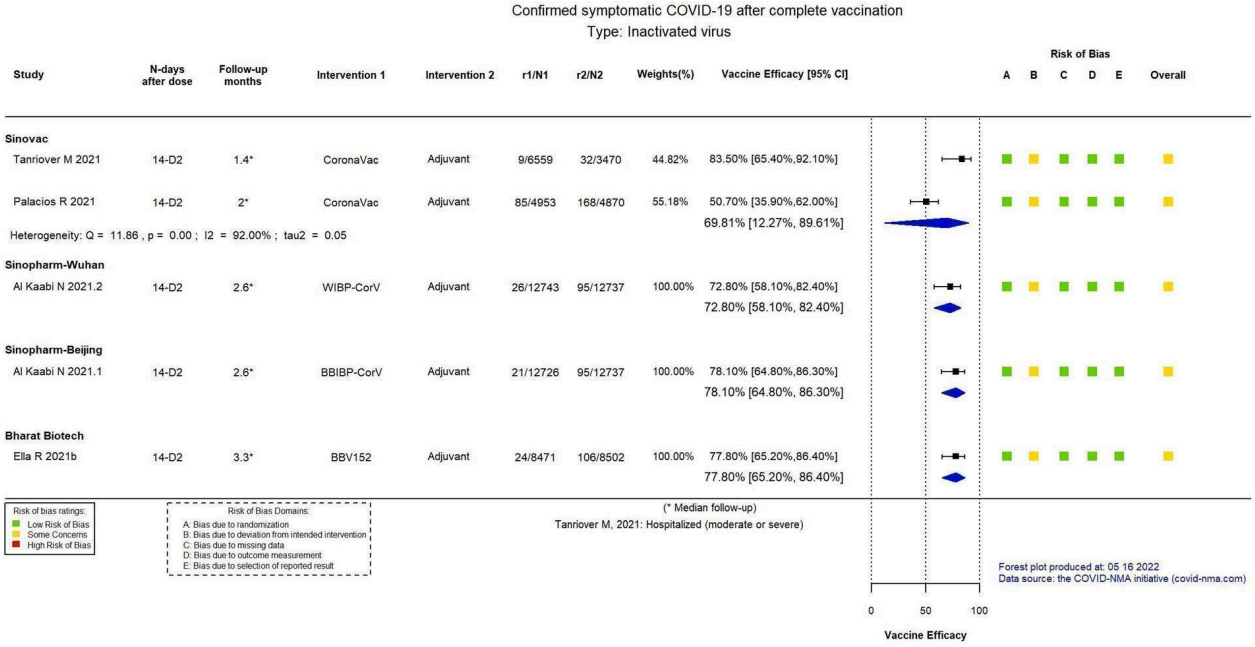
We identified and included in the analysis seven trials assessing CoronaVac – Sinovac. The outcome 'SARS-CoV-2 infection after complete vaccination' was not reported for this comparison.

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).

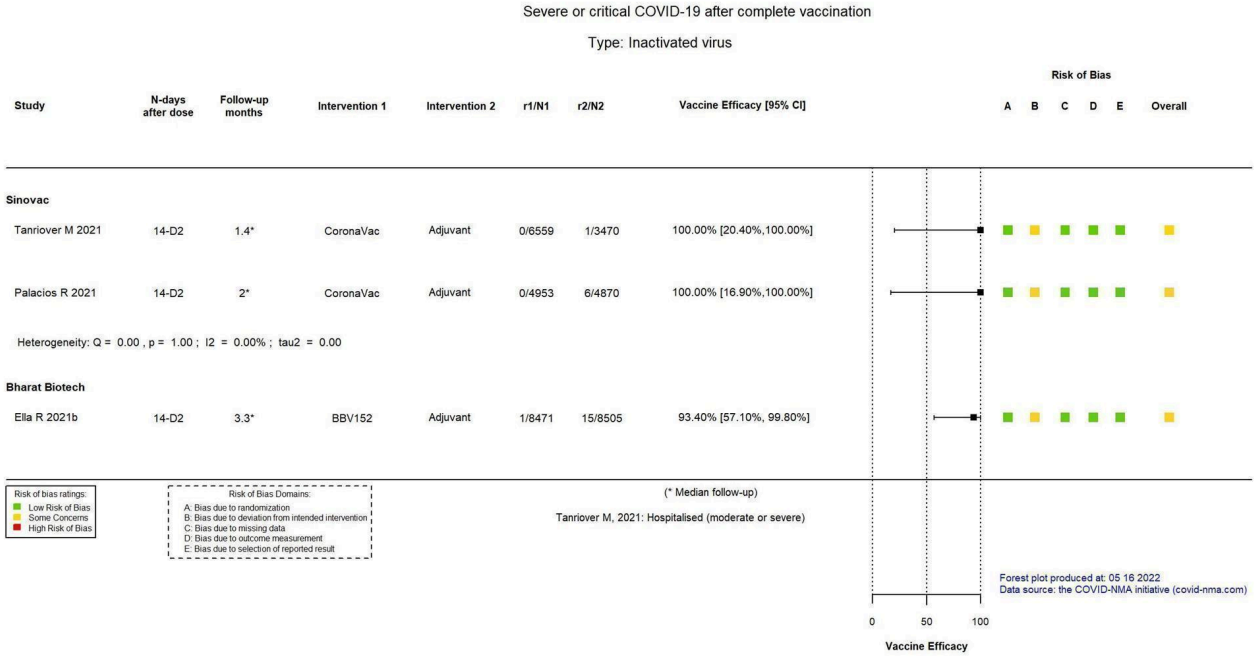
Figure 24. Analysis 3.1.2: inactivated virus vaccine. Outcome: confirmed symptomatic COVID-19 after complete vaccination. Al Kaabi 2021.1 and Al Kaabi N 2021.2 refers to two different comparisons from the same report (Al Kaabi 2021).



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).

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

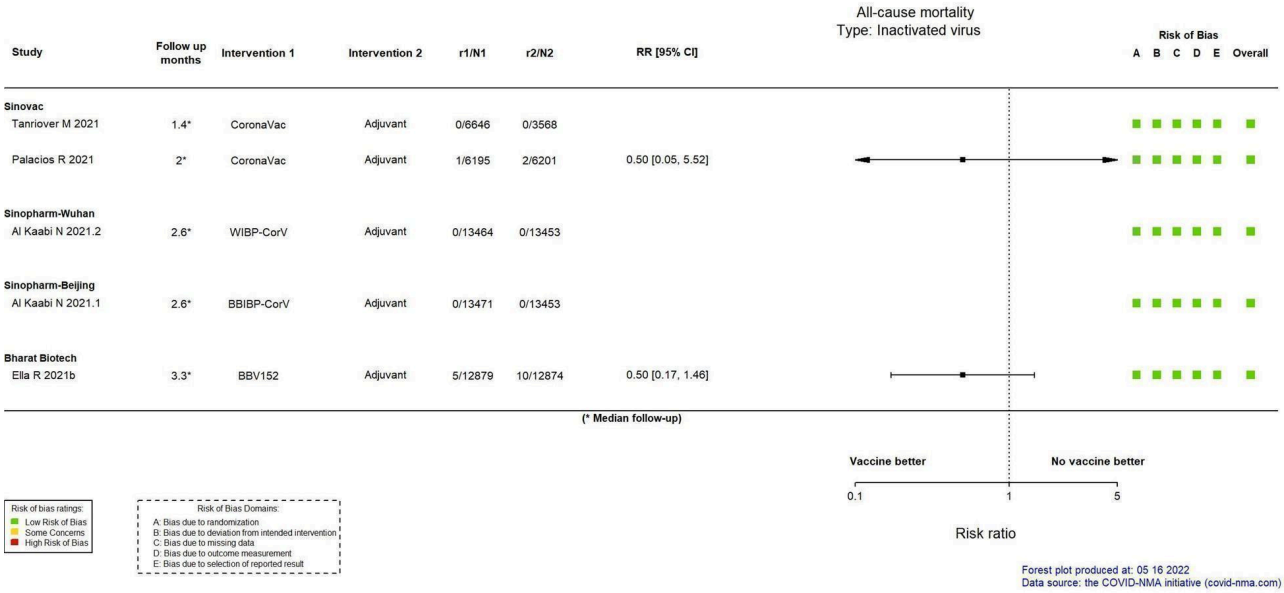


All-cause mortality

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).

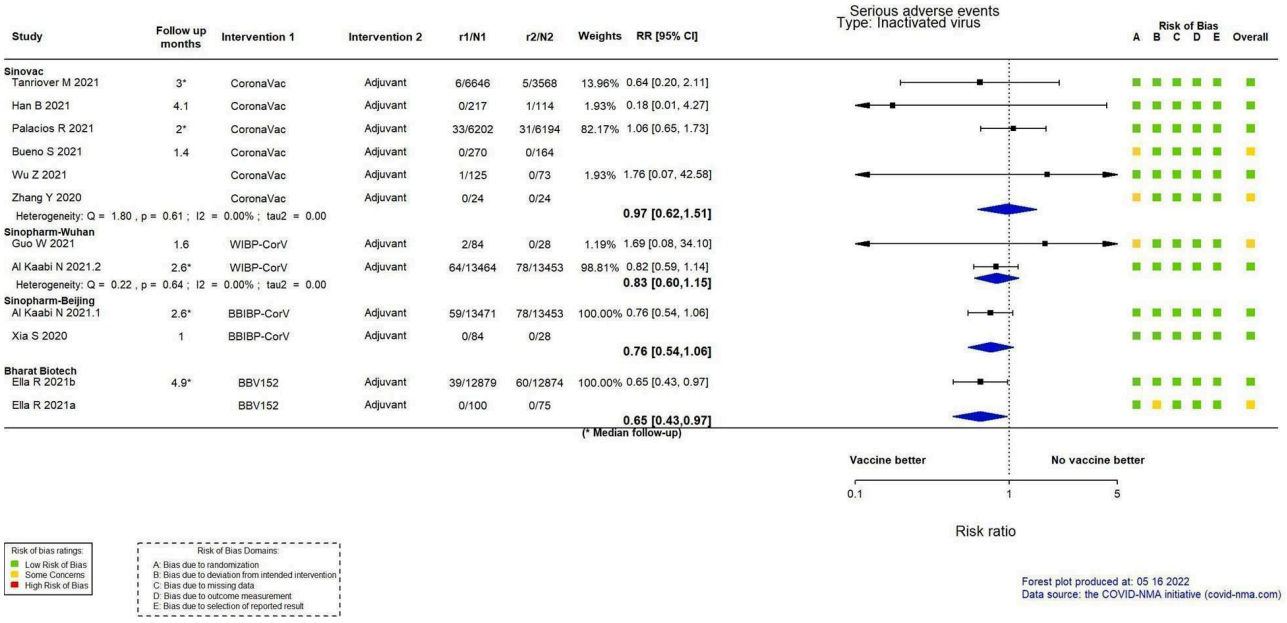
Figure 26. Analysis 3.1.4: inactivated virus vaccine. Outcome: all-cause mortality. Al Kaabi 2021.1 and Al Kaabi N 2021.2 refers to two different comparisons from the same report (Al Kaabi 2021).



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).

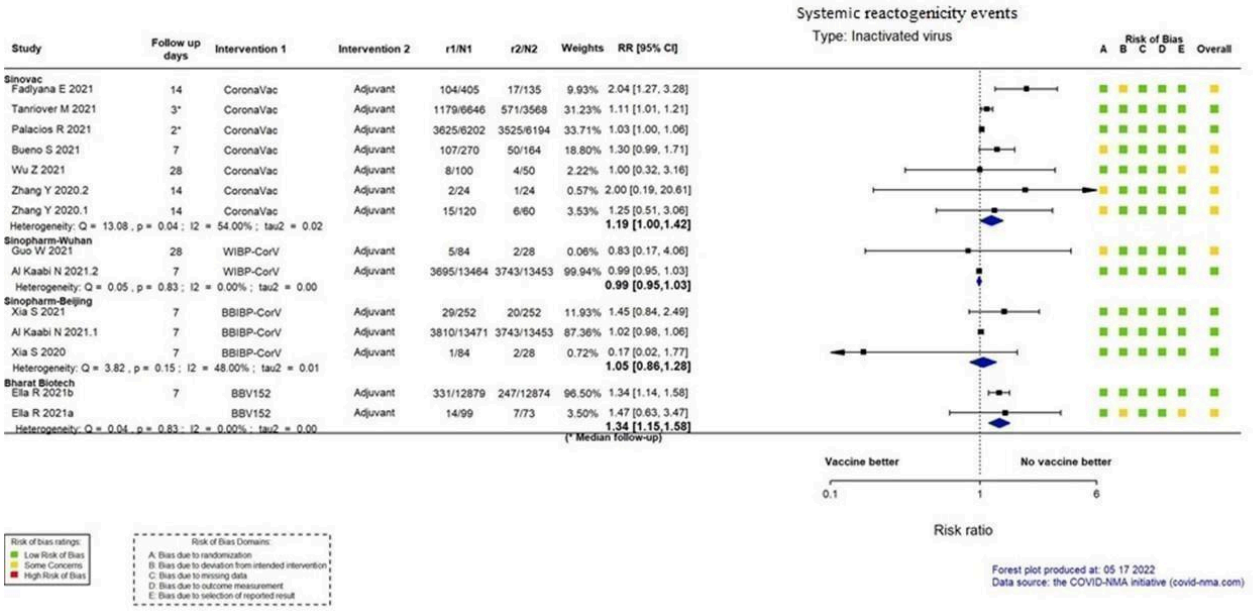
Figure 27. Analysis 3.1.5: inactivated virus vaccine. Outcome: serious adverse events (SAEs). Han 2021 included only participants 3 to 17 years of age. Wu 2021a included only participants 60 years of age and older. Wu 2021a reports data for phase 1 and 2. Al Kaabi 2021.1 and Al Kaabi N 2021.2 refer to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

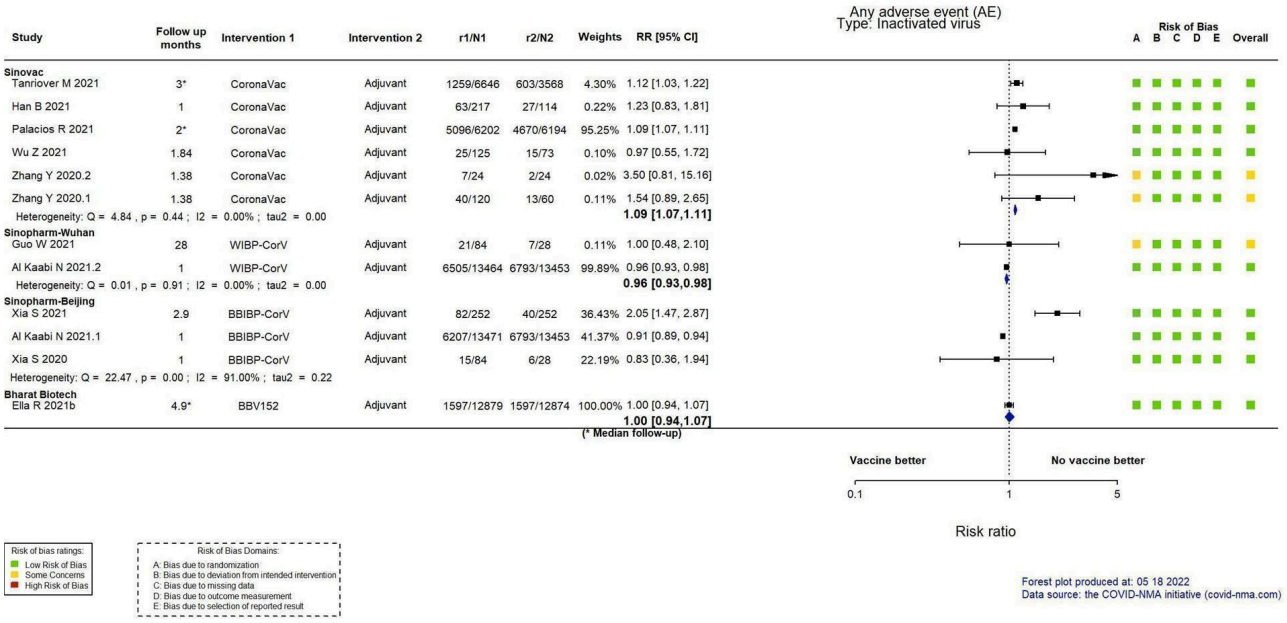
Figure 28. Analysis 3.1.6: inactivated virus vaccine. Outcome: systemic reactogenicity events. Xia S 2021 included only participants 3 to 17 years of age (Xia 2021). Wu Z 2021 included only participants 60 years of age and older (Wu 2021a). Wu Z 2021 reports data for phase 2 (Wu 2021a). Al Kaabi 2021.1 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).

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

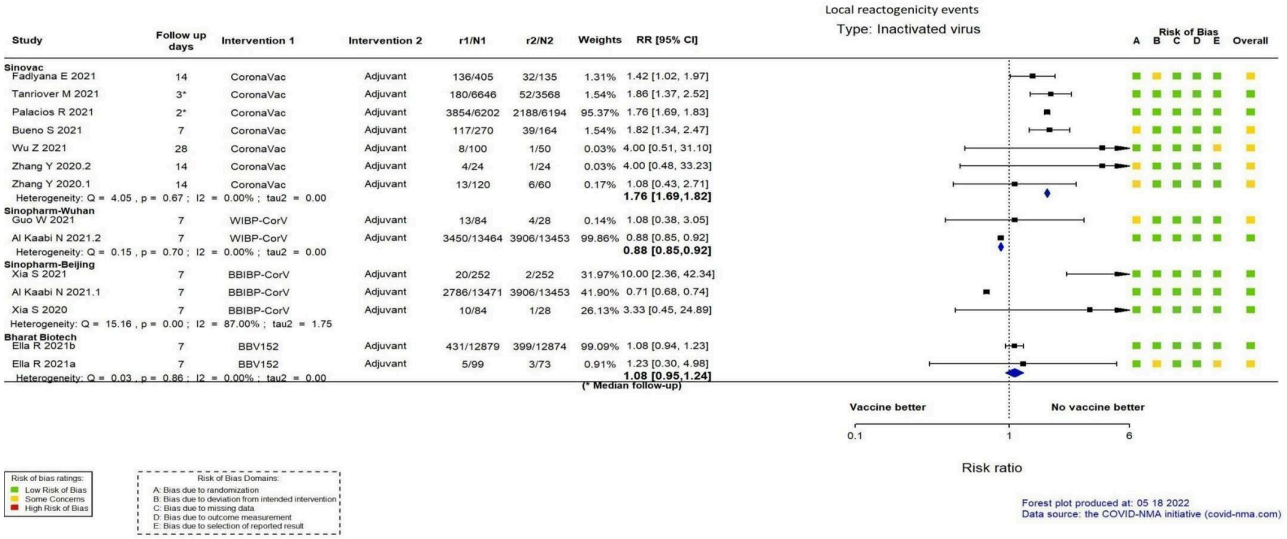
Immunogenicity outcomes

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).

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.

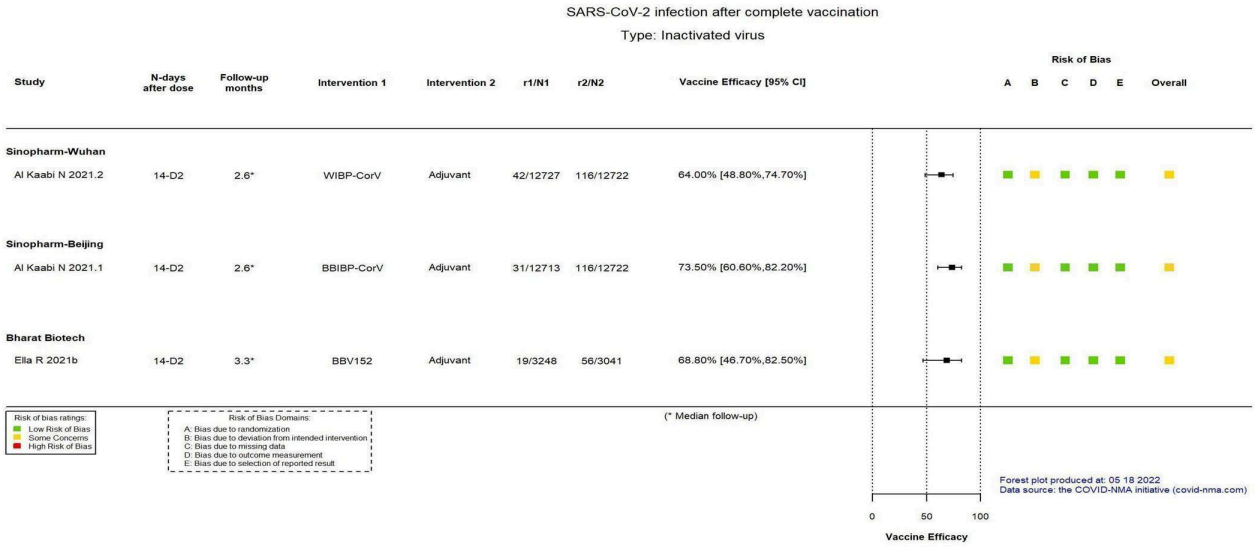
We identified and included two trials in the analysis assessing WIBP-CorV. The outcomes 'severe or critical COVID-19 after complete vaccination', 'cellular immune response' and 'incidence of specific safety outcomes' were not reported for this comparison.

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).

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

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).

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.

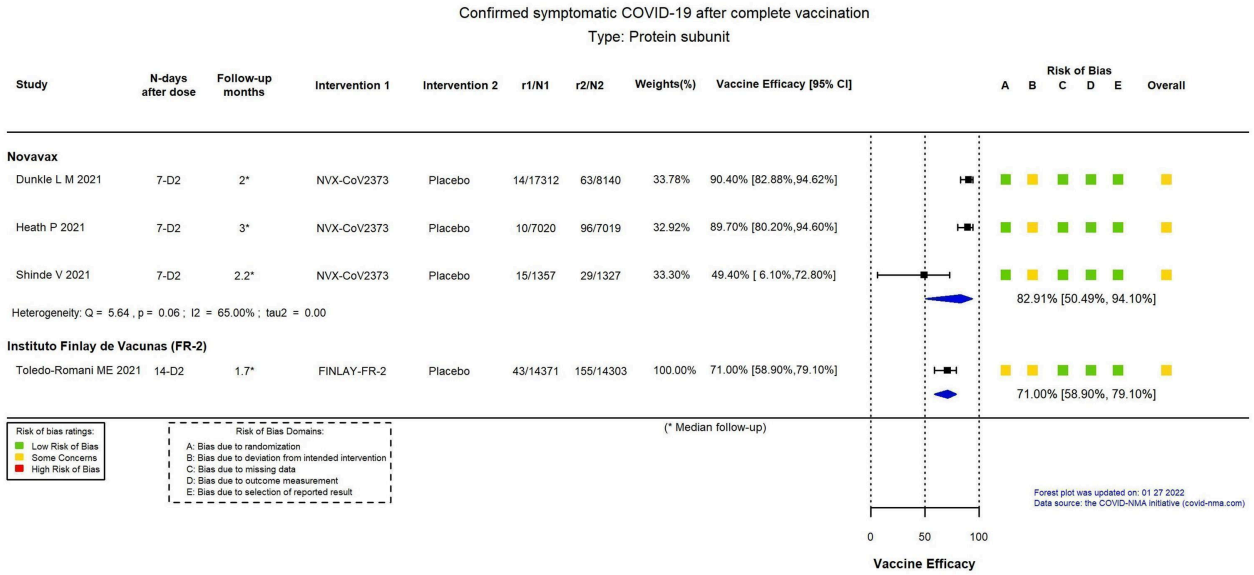
Low-certainty evidence for the efficacy outcomes might be explained by the inclusion of results from a trial conducted in South Africa during a period of high prevalence of the Beta variant (Shinde 2021). Vaccine efficacy against this variant was considerably lower than the efficacy reported in the primary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

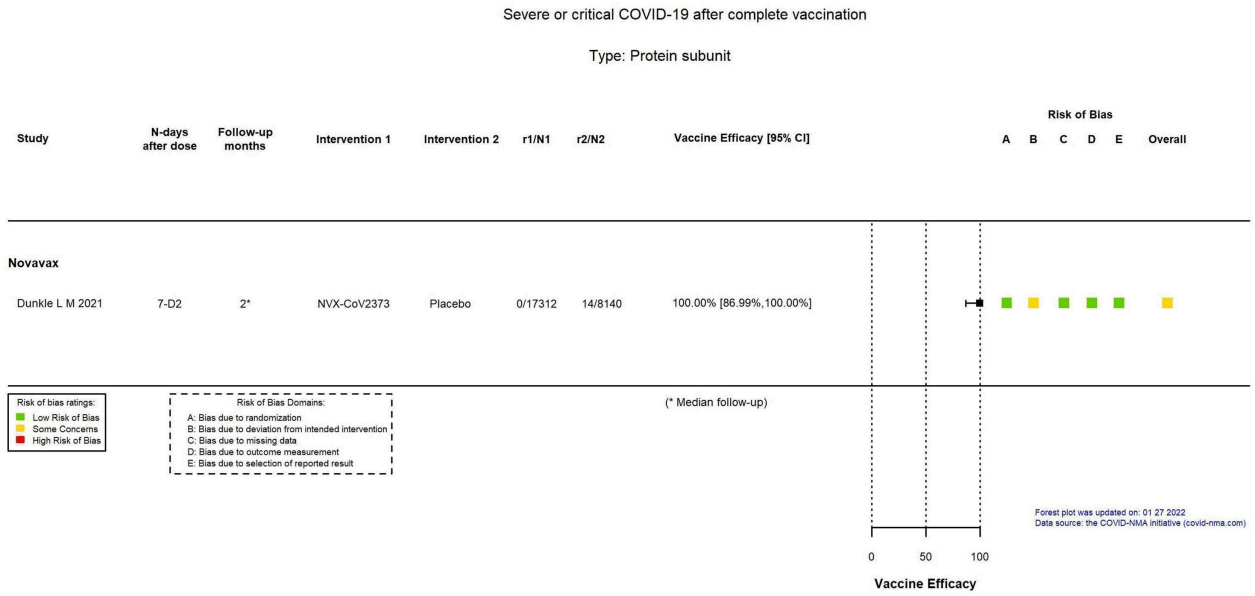
Figure 32. Analysis 4.1.1: protein subunit vaccine. Outcome: confirmed symptomatic COVID-19 after complete vaccination.



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).

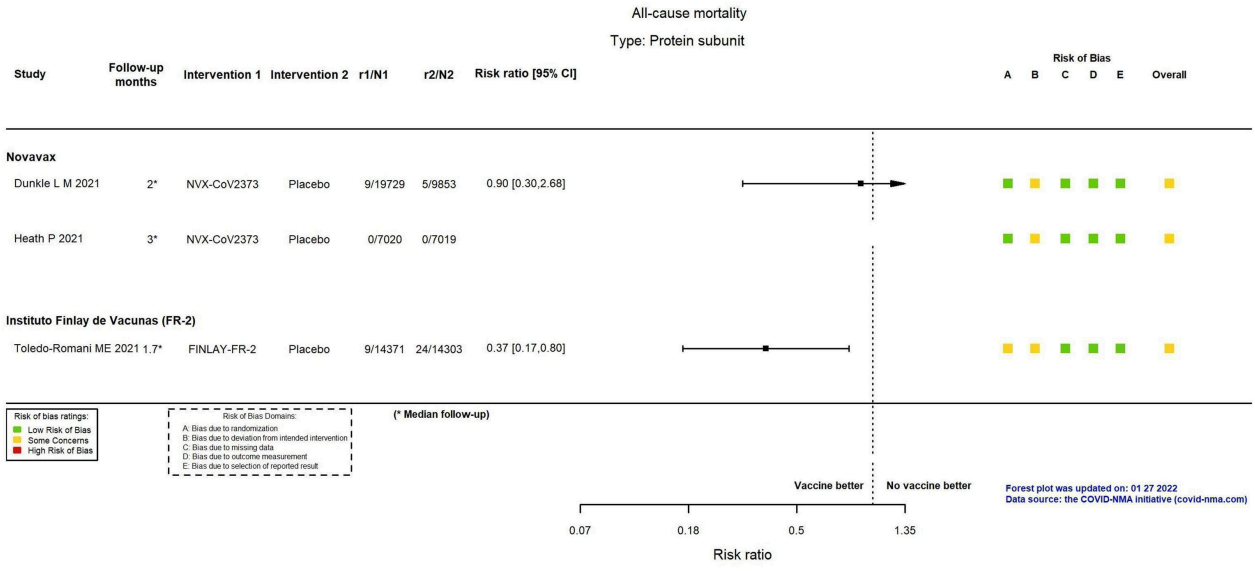
Figure 33. Analysis 4.1.2: protein subunit vaccine. Outcome: severe or critical COVID-19 after complete vaccination.



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).

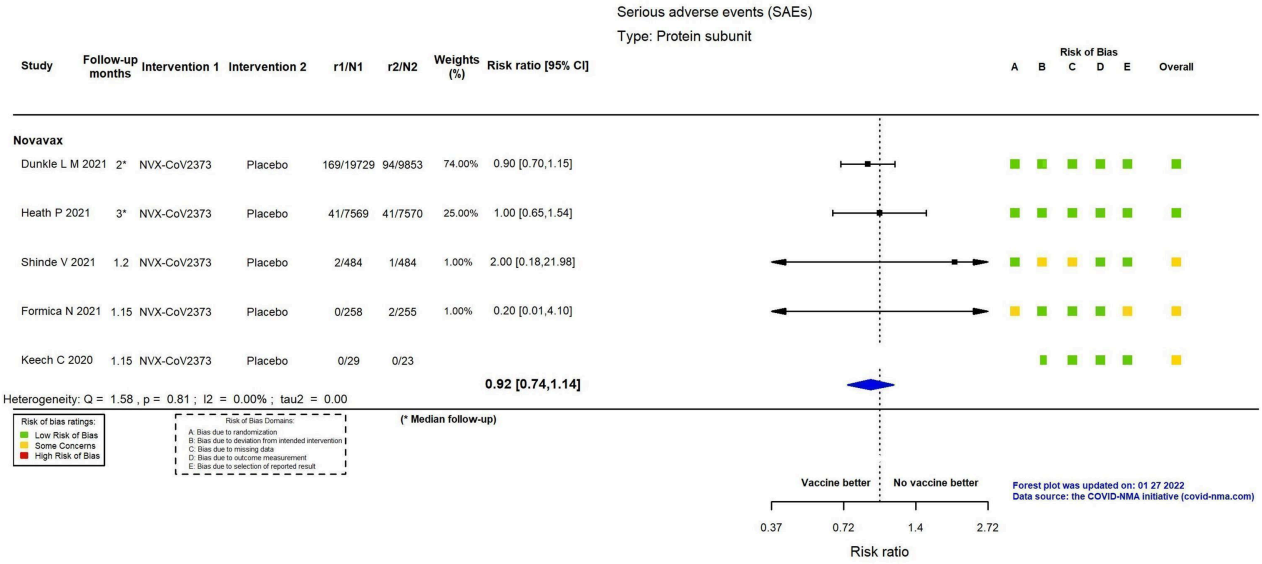
Figure 34. Analysis 4.1.3: protein subunit vaccine. Outcome: all-cause mortality.



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).

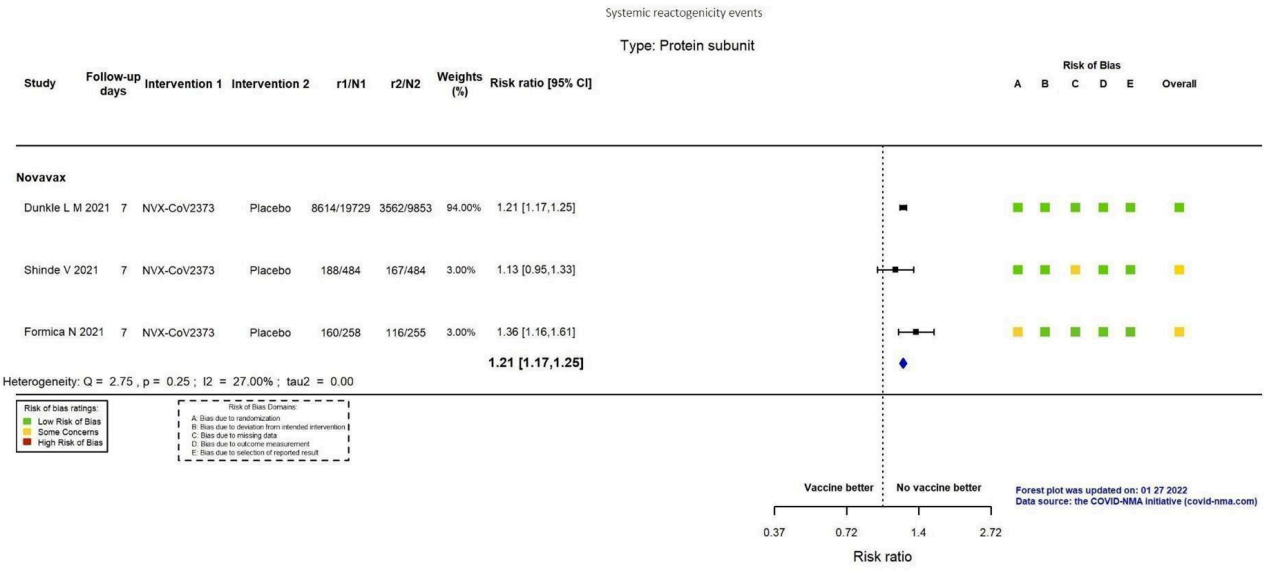
Figure 35. Analysis 4.1.4: protein subunit vaccine. Outcome: serious adverse events (SAEs).



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).

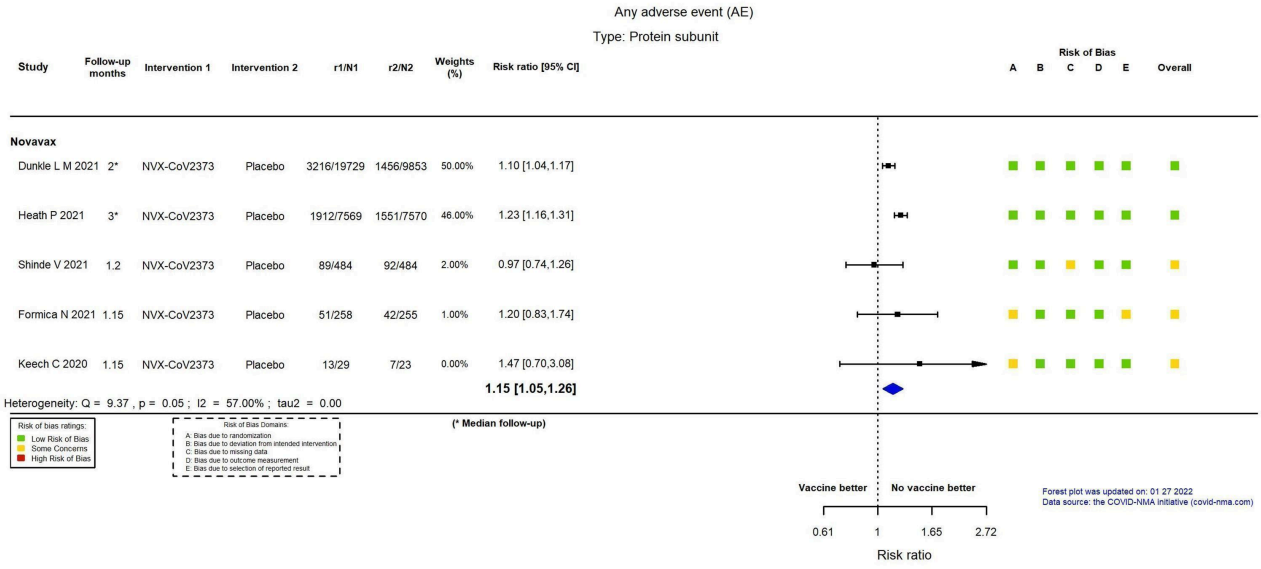
Figure 36. Analysis 4.1.5: protein subunit vaccine. Outcome: systemic reactogenicity events.



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).

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



Important outcomes

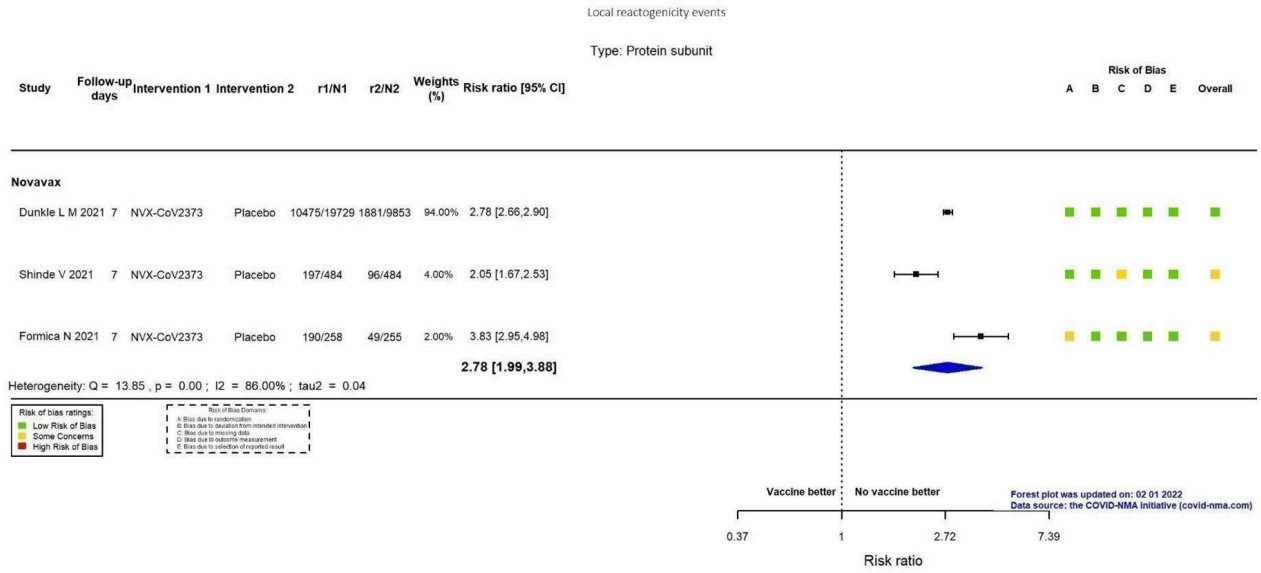
Immunogenetic outcomes

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



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).

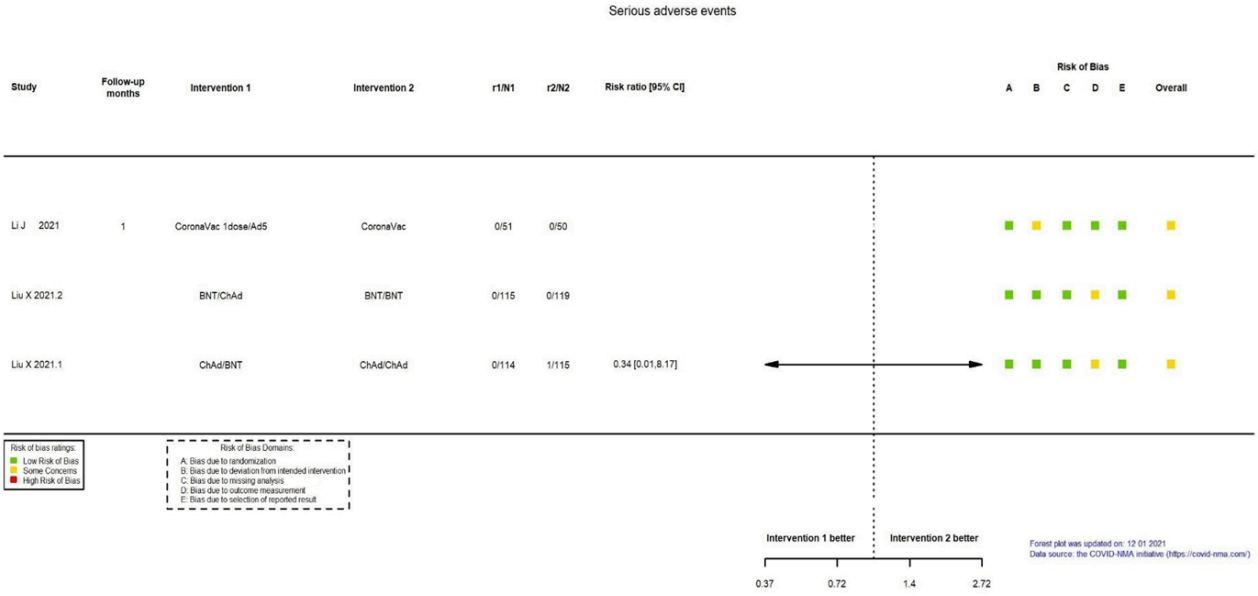
The outcomes 'SARS-CoV-2 infection after complete vaccination', 'symptomatic COVID-19 after complete vaccination', 'severe or critical COVID-19', 'all-cause mortality', 'systemic reactogenicity events' and 'vaccine-enhanced disease' were not reported for these comparisons.

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).

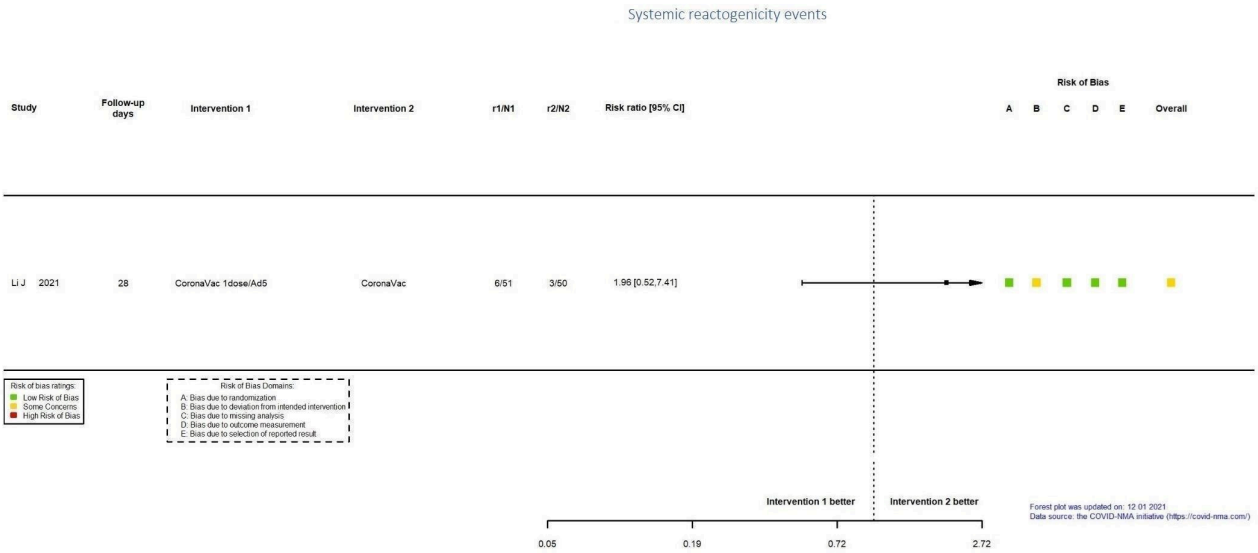
Figure 39. Analysis 5.1.1: heterologous vaccination scheme versus homologous vaccination scheme. Outcome: serious adverse events (SAEs). Liu X 2021.1 and Liu X 2021.2 are different comparisons for the same report (Liu 2021).



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).

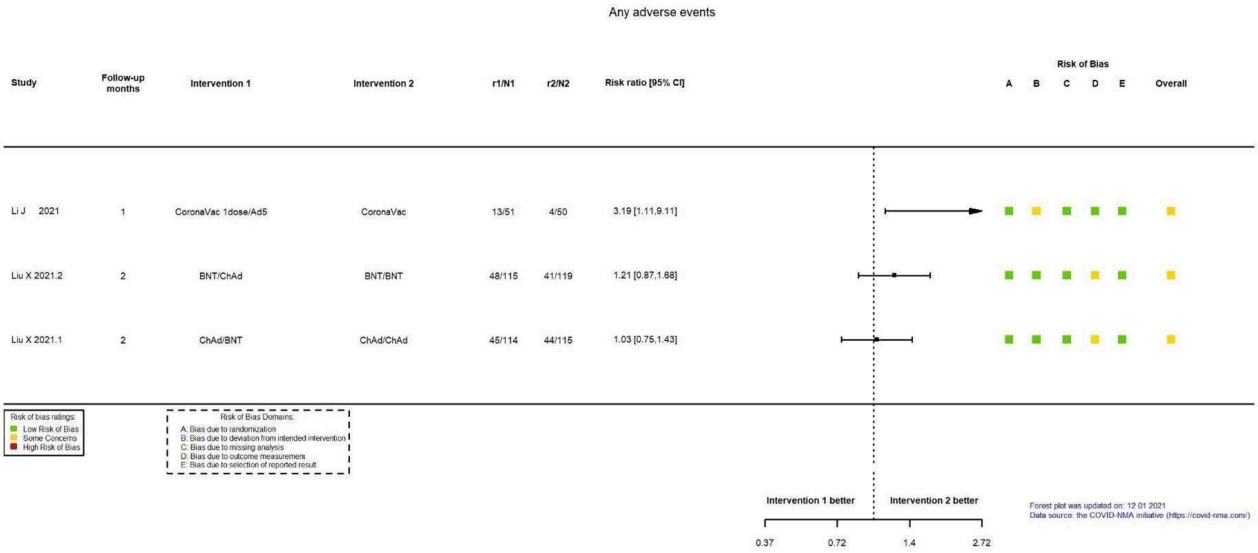
Figure 40. Analysis 5.1.2: heterologous vaccination scheme versus homologous vaccination scheme. Outcome: systemic reactogenicity events.



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.

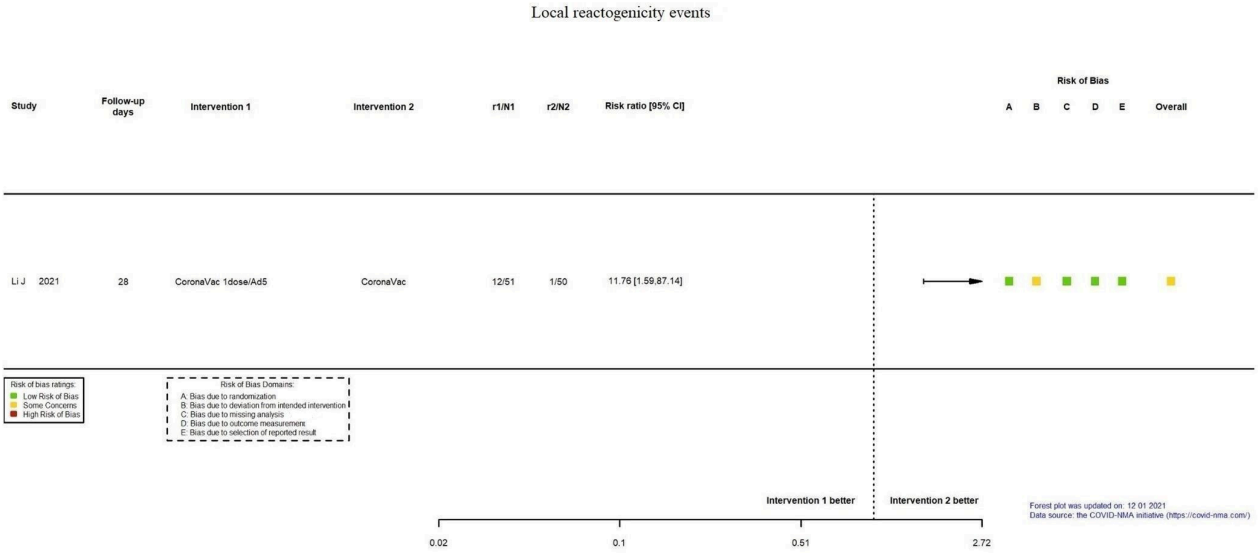
The heterologous schedule ChAdOx1/BNT162b2 elicited a larger immune cellular response compared to the homologous schedule ChAdOx1/ChAdOx1 (GMR of number of spot-forming cells (SFCs) per million peripheral blood mononuclear cell (PBMC)) 3.9 (95% CI 2.9 to 5.3)).

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).

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)

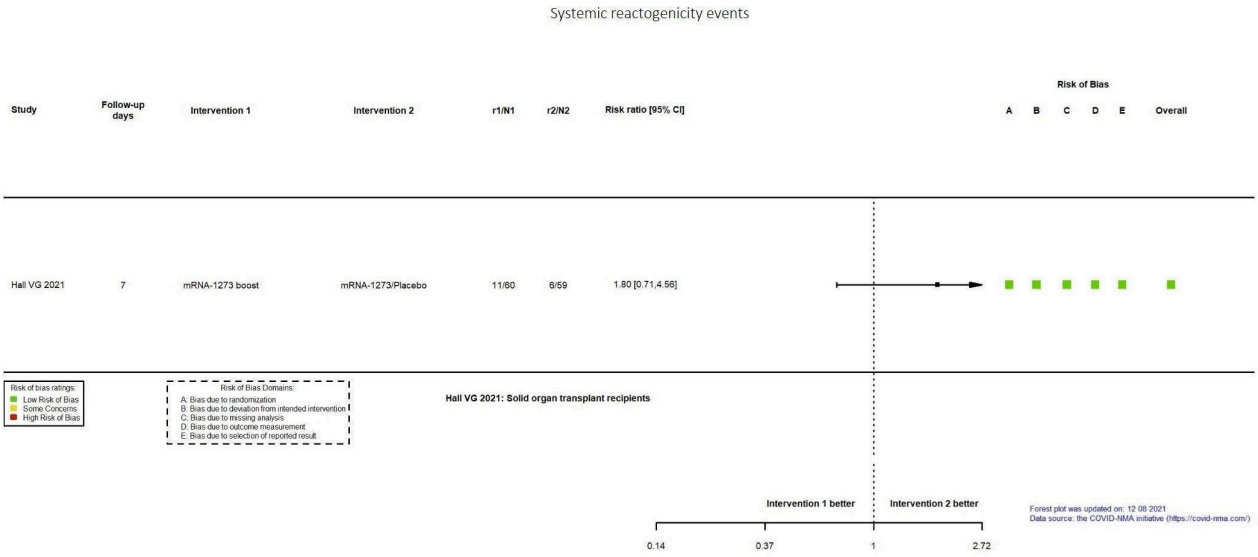
Hall 2021 compared a booster dose of mRNA-1273 to placebo after complete vaccination of mRNA-1273 in kidney transplant recipients. They reported three outcomes of interest.

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).

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



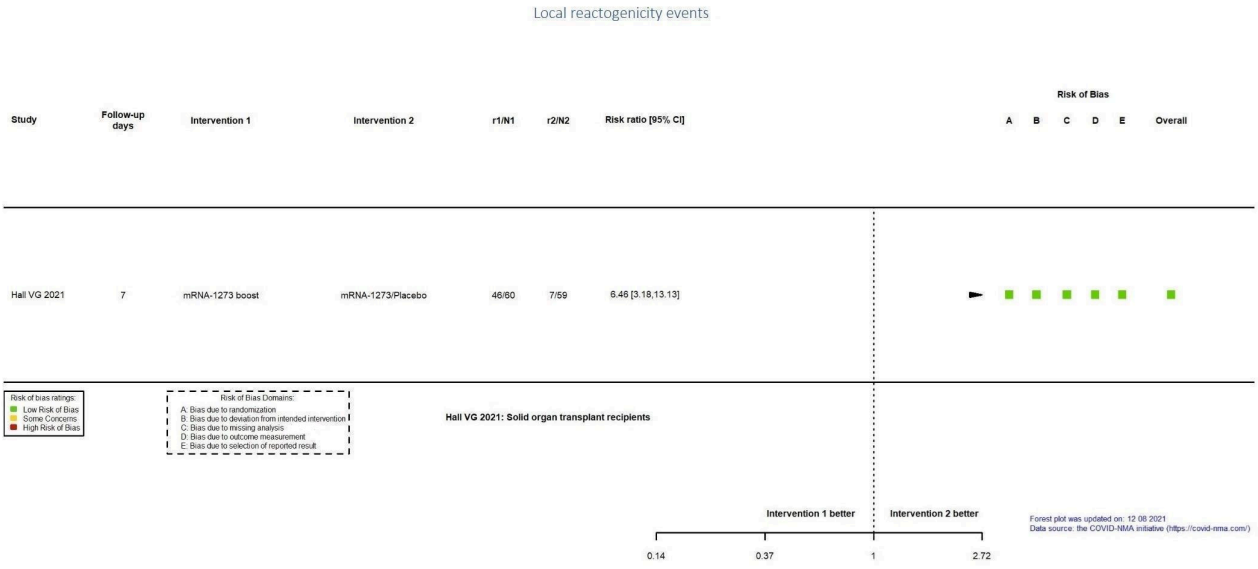
Immunogenicity outcomes

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.



FINLAY-FR-1 booster versus no booster dose

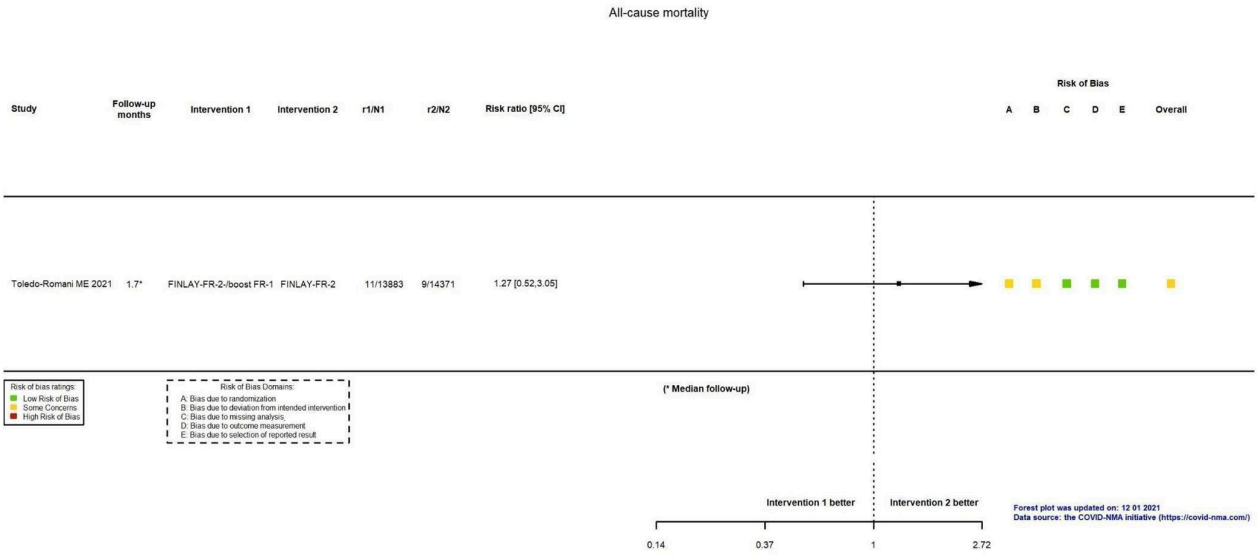
All-cause mortality

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.

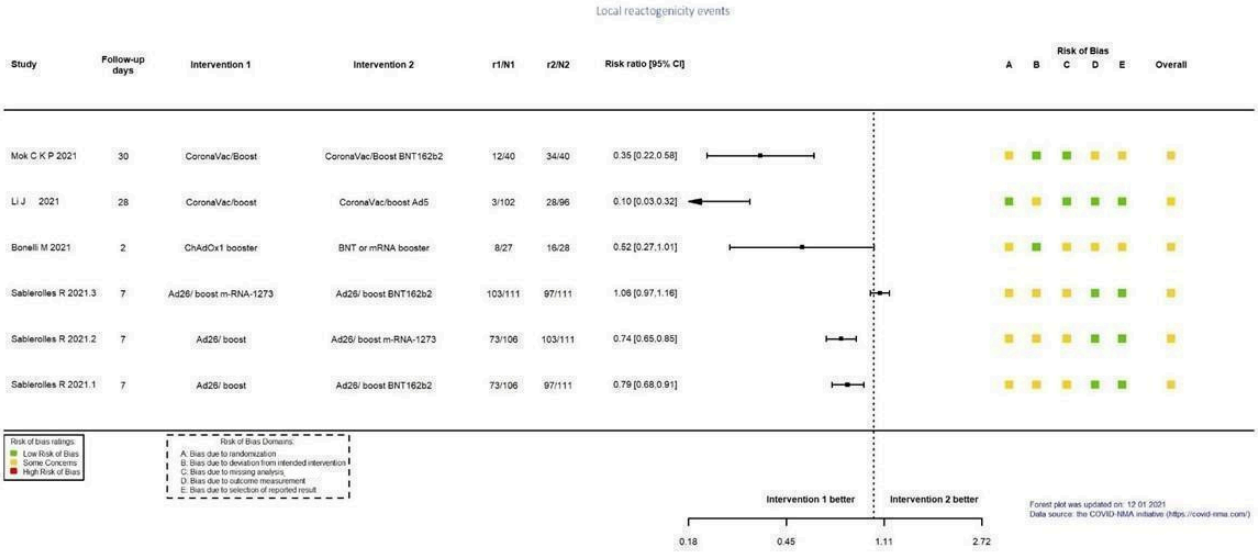
Immunogenicity outcomes

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).

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.

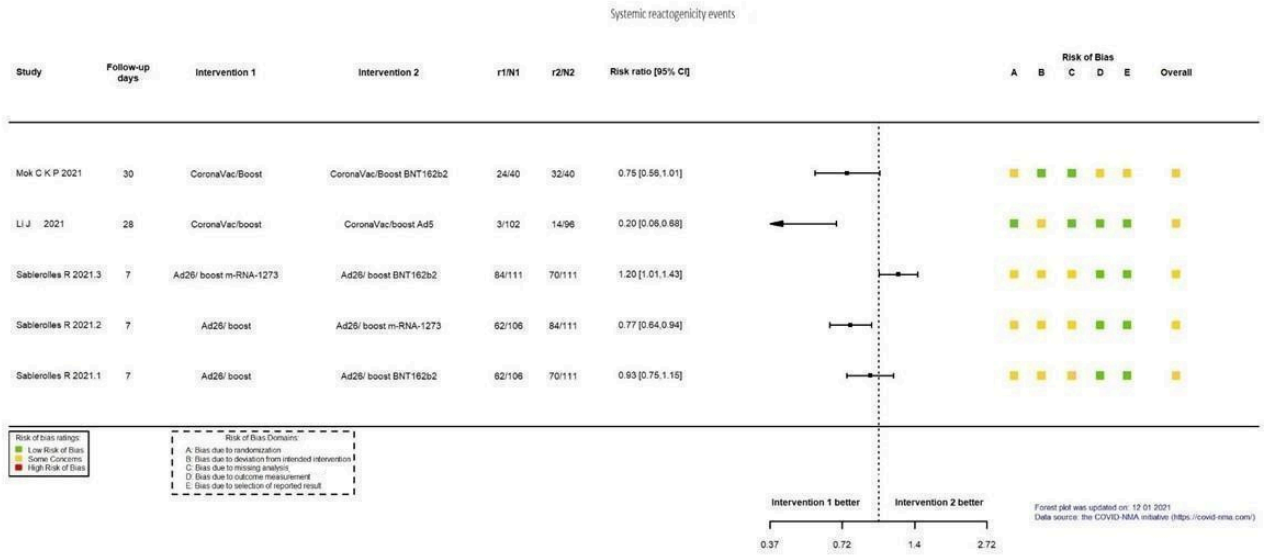
Ad26.COV2.S with homologous booster versus heterologous mRNA-1273 booster

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).

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).

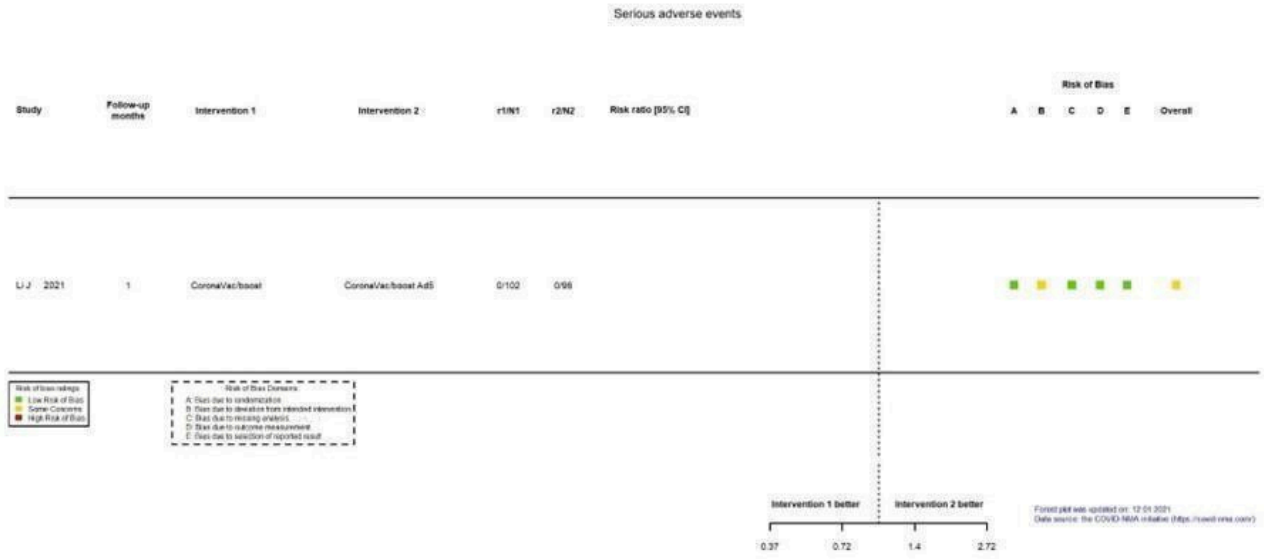
CoronaVac with homologous booster versus heterologous Ad5 booster

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).

Figure 48. Analysis 6.2.1: homologous booster versus heterologous booster. Outcome: serious adverse events.



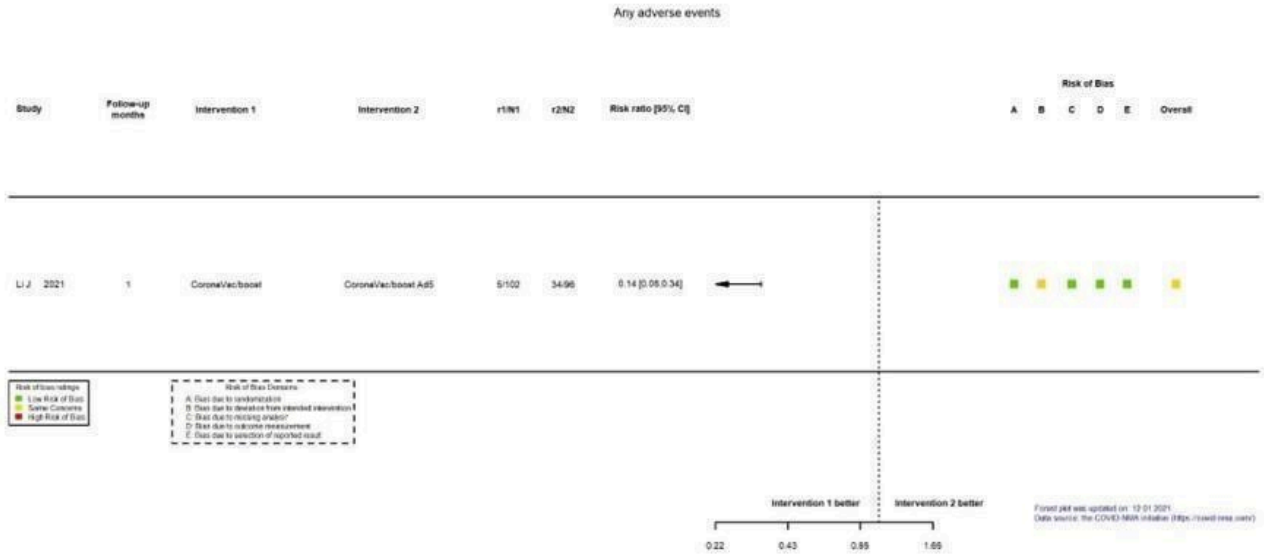
Systemic reactogenicity events

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

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).

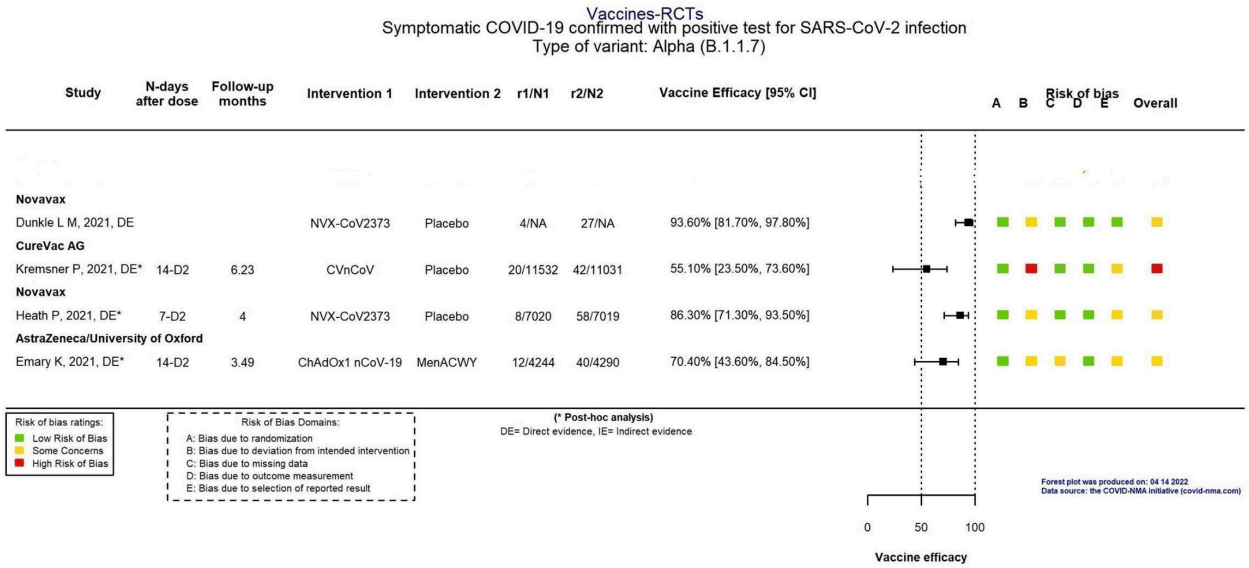
We considered the direct evidence when study reports provided evidence on a sequenced sample. When sequencing was not performed, we extrapolated the exposure to variants from the prevalence in the study setting.

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).

Figure 50. Analysis 7.1.1: variant-Alpha. Outcome: confirmed symptomatic COVID-19 after complete vaccination.

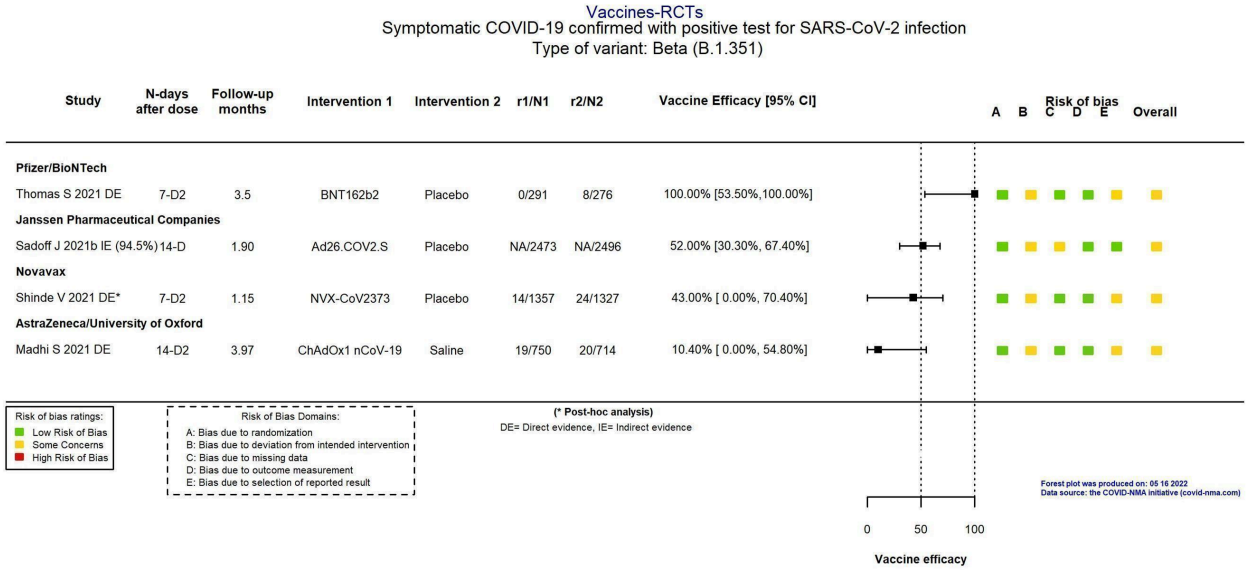


Beta variant (B.1.351)

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).

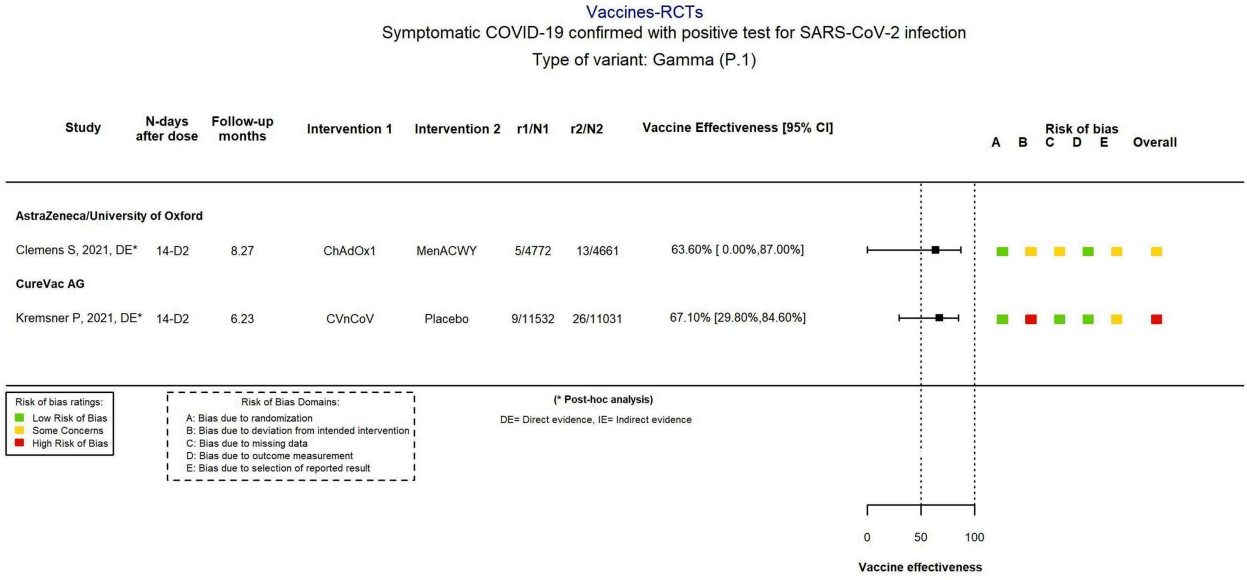
Figure 51. Analysis 7.2.1: variant-Beta. Outcome: confirmed symptomatic COVID-19 after complete vaccination.



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).

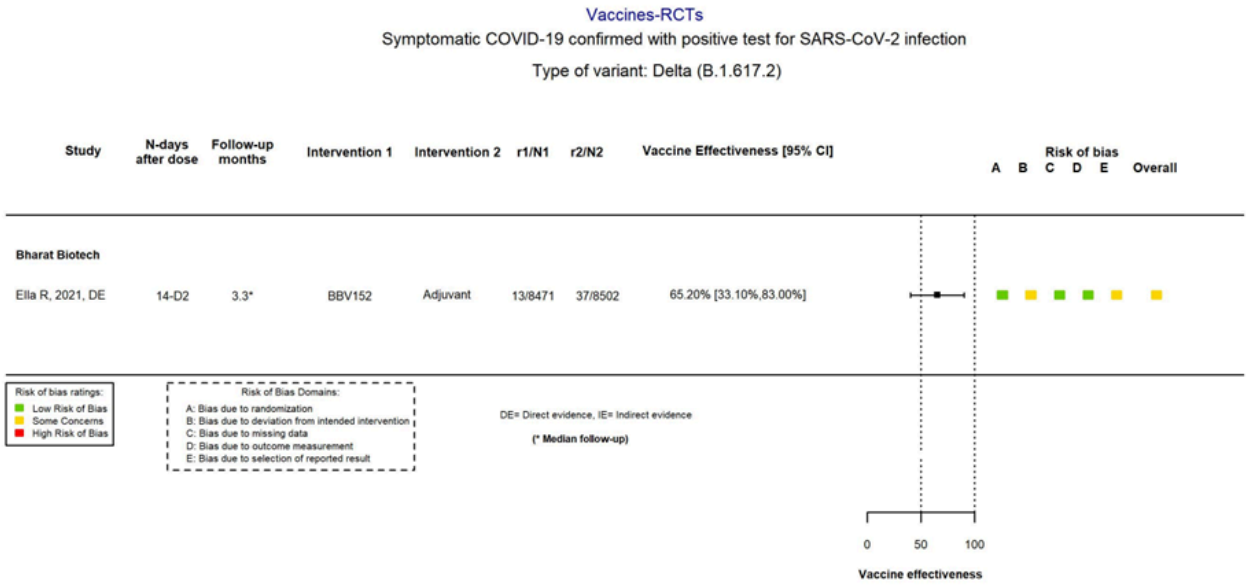
Figure 52. Analysis 7.3.1: variant-Gamma. Outcome: confirmed symptomatic COVID-19 after complete vaccination.



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.

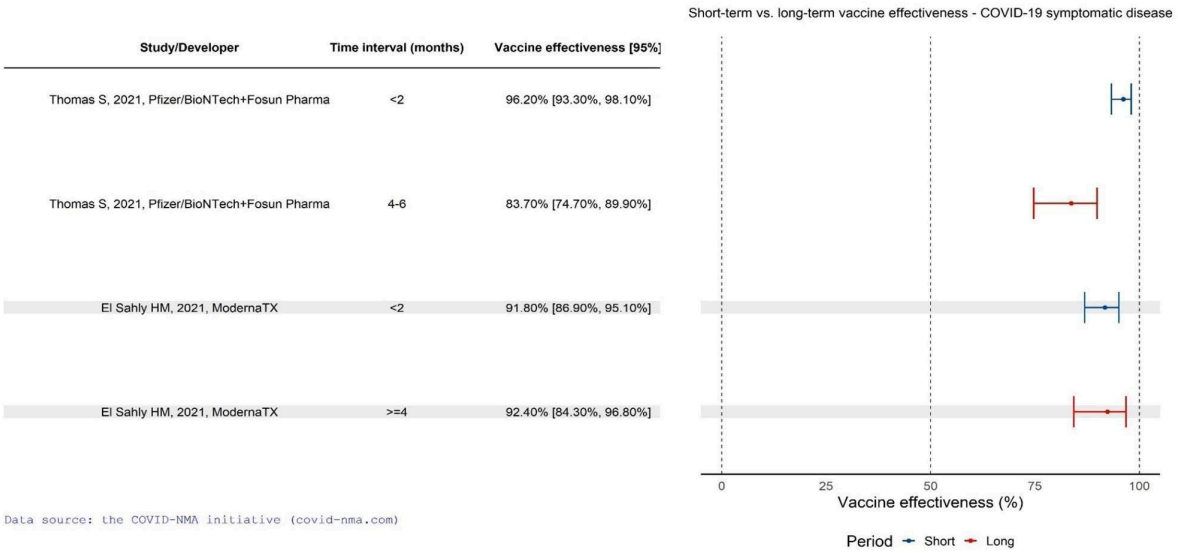


Assessment of vaccine efficacy over time

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;

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.

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

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.

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- Editorial Assistant (conducted editorial policy checks and supported editorial team): Leticia Rodrigues, Cochrane Central Editorial Service.
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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
Methods
Participants

Al Kaabi 2021 *(Continued)*

Interventions
Outcomes
Notes

Asano 2022

Study characteristics
Methods
Participants
Interventions
Outcomes
Notes

Bonelli 2021

Study characteristics
Methods
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Interventions
Outcomes
Notes

Bueno 2021

Study characteristics
Methods
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Clemens 2021

Study characteristics
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Dunkle 2021

Study characteristics
Methods
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Interventions
Outcomes
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Ella 2021a

Study characteristics
Methods
Participants
Interventions
Outcomes
Notes

Ella 2021b

Study characteristics
Methods
Participants
Interventions

Ella 2021b *(Continued)*

Outcomes
Notes

El Sahly 2021

Study characteristics
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Outcomes
Notes

Emary 2021

Study characteristics
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Interventions
Outcomes
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Fadlyana 2021

Study characteristics
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Interventions
Outcomes
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Falsey 2021

Study characteristics
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Formica 2021

Study characteristics
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Frenck 2021

Study characteristics
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Interventions
Outcomes
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Guo 2021

Study characteristics
Methods
Participants
Interventions

Guo 2021 *(Continued)*

Outcomes
Notes

Hall 2021

Study characteristics
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Interventions
Outcomes
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Han 2021

Study characteristics
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Heath 2021

Study characteristics
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Keech 2020

Study characteristics
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Kremsner 2021

Study characteristics
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Kulkarni 2021

Study characteristics
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Li 2021a

Study characteristics
Methods
Participants
Interventions

Li 2021a *(Continued)*

Outcomes
Notes

Liu 2021

Study characteristics
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Logunov 2021

Study characteristics
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Madhi 2021a

Study characteristics
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Madhi 2021b

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Mok 2021

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Palacios 2020

Study characteristics
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Sablerolles 2021

Study characteristics
Methods
Participants
Interventions

Sablerolles 2021 *(Continued)*

Outcomes
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Sadoff 2021a

Study characteristics
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Sadoff 2021b

Study characteristics
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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

Study characteristics
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Outcomes
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Voysey 2021a

Study characteristics
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Interventions

Voysey 2021a *(Continued)*

Outcomes
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Walsh 2020

Study characteristics
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Wu 2021a

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Xia 2020

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Xia 2021

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Zhang 2021

Study characteristics
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Outcomes
Notes

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

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)	0.94 (0.48 to 1.86) 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	—	—	—	0.94 (0.48 to 1.86) 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	—	—	—	—	—	—	—

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

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)	—	—

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)

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)

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)

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.

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		

(Continued)

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

(Continued)

		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

(Continued)

	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

(Continued)

	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

(Continued)

		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

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

(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.

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.

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

(Continued)

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

(Continued)

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

(Continued)

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

(Continued)

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

(Continued)

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
ChiCTR2100049530	2 August 2021	Not recruiting	Parallel	ChAdTS-S	360	Phase 2
TCTR20210907003	7 September 2021	Not recruiting	Sequential assignment	ChAdOx1 nCoV-19	60	Phase 1/ Phase 2
TCTR20211004005	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
EUCTR2020-005226-28-IT	23 November 2020	Ongoing	Parallel	ChAdOx1 nCoV-19	40,000	Phase 3
ChiCTR2100044249	12 March 2021	Ongoing	Adaptive	Ad5-nCoV	40,000	Phase 3
EUCTR2020-002584-63-DE	12 August 2020	Ongoing	Parallel	Ad26.COV2.S	225	Phase 2
EUCTR2020-005801-14-PL	30 December 2020	Ongoing	Parallel	Ad26.COV2.S	570	Phase 3
EUCTR2021-002693-10-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

(Continued)

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

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

(Continued)

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/2021/04/032942	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

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
PACTR202108616960606	6 August 2021	Not recruiting	Factorial	CpG 1018/alum adjuvant + scb-2019	600	Phase 3
ACTRN12620001308921	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	20 November 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

(Continued)

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

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

(Continued)

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

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

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

(Continued)

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

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**

[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

(Continued)

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)

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

(Continued)

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

(Continued)

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

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

(Continued)

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

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**

[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

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**

[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

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."

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

(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

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

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.

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

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

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

(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

(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:**

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

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).

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.

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

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

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).

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

(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**

[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).

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.

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**

(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**

(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:**

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

(Continued)

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

(Continued)

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

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	*	✓	✓	✓	✓	✓	✓

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	*	*	✓

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	✓	✓	✓	✓	✓	✓	✓

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	✓

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	✓	✓	✓	✓	✓	✓

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

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	✓	✓	✓	✓	*	✓	✓

(Continued)	NCT04324606; NCT04400838; NCT04444674)

[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	*	*	*

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	*	*	*	✓	✓	✓	✓

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	✓	✓	✓

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	*	✓	✓	✓	✓	✓	✓

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	✓

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

				Critical outcomes						
Study ID	**Study follow-up (months)**	**Gam-COV-ID-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	*	✓	✓	✓	*	*	✓

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

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	*	*	*	*	✓	✓	✓

[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	*	✓	✓

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	*	*	*	*	✓	✓	✓

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	*	✓	✓

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	*	*	*	*	✓	✓	*

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	*	✓	✓

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	*	*	*	*	✓	*	✓

[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

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	*	✓	✓	*	✓	✓	✓

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	✓

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	*

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

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		
				✓		✓		✓		

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		

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		
				✓		✓		*		

Boosters

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**		
				*		*		✓		

[a]Trial in immunocompromized participants.

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		
				*		*		*		

Booster versus booster

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**		
				*		*		✓		

[a]Trial in immunocompromized participants.

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**		
				✓	✓			✓		

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		
				*		*		✓		

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		
				*		*		✓		

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**		
				*		*		✓		

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**		
				*		*		✓		

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

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						

CI: confidence interval; GMR: geometric mean ratio; GMT: geometric mean titre.

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)					

CI: confidence interval; GMR: geometric mean ratio; GMT: geometric mean titre.

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

(Continued)

	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)					

(Continued)

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)					

CI: confidence interval; GMR: geometric mean ratio; GMT: geometric mean titre.

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)					

CI: confidence interval; GMR: geometric mean ratio; GMT: geometric mean titre.

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)					

CI: confidence interval; GMR: geometric mean ratio; GMT: geometric mean titre.

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)					

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

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

(Continued)

		(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

(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

(Continued)

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

(Continued)

	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

(Continued)

		(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

(Continued)

	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

(Continued)

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

NR: not reported; RNA: ribonucleic acid.

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

(Continued)

	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

(Continued)

	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

(Continued)

				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

(Continued)

	(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

(Continued)

		(28)						
	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
Protein subunit	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

(Continued)

	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

(Continued)

	(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

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

(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

(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

(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

(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

(Continued)

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%)

(Continued)

All-cause mortality	1	30,346	Risk Ratio (M-H, Random, 95% CI)	0.94 (0.48 to 1.86)	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

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

CI: confidence interval; N/A: not applicable.

Appendix 16. Specific antibody geometric mean titre

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)					

CI: confidence interval; ELISA: enzyme-linked immunosorbent assay; GMR: geometric mean rate; GMT: geometric mean titre; IgG: immunoglobulin G; RBD: receptor-binding domain.

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)					

(Continued)

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

(Continued)

		(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)					

CI: confidence interval; GMR: geometric mean rate; GMT: geometric mean titre.

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)					

CI: confidence interval; ELISA: enzyme-linked immunosorbent assay; GMR: geometric mean rate; GMT: geometric mean titre; IgG: immunoglobulin G; RBD: receptor-binding domain.

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)					

CI: confidence interval; GMR: geometric mean rate; GMT: geometric mean titre.

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)					

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

(Continued)

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.

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

(Continued)

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		

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

(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

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

(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

(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

Date	Event	Description
12 December 2022	Amended	'Acknowledgements' updated.

HISTORY

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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

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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

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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

DECLARATIONS OF INTEREST

Carolina Graña: none known.

Lina Ghosn: none known.

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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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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.