ORIGINAL ARTICLE

Are Vaccines Effective and Safe for the Prevention of COVID-19 Infections? A Living Systematic Review

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ABSTRACT

Introduction. In the attempt to control the spread of the disease and the pandemic, numerous COVID-19 vaccines are in development. A review of the evidence on their efficacy and safety are critical.

Methods. A search for trials was done using the COVID-19 Living OVerview of Evidence (L·OVE) platform. We also searched for relevant authorization documents and trial reports for COVID-19 vaccines of the US-Food and Drug Authority (US-FDA), the European Medicines Agency (EMA), the United Kingdom Medicines and Health Products Regulatory Agency (MHRA), and the WHO website. We included studies that fulfilled the following inclusion criteria: population – humans; intervention – COVID-19 vaccines; comparison – control or placebo; outcomes – efficacy and adverse events; methods – phase 3 randomized trials. Two reviewers independently screened the reports, assessed the methodological quality, and extracted the data on the trial characteristics and results on vaccine efficacy and safety. The date of last search was March 11, 2021.

Results. Interim results of trials investigating five vaccines were identified and included in the review. All five vaccines demonstrated satisfactory vaccine efficacy (VE) against symptomatic COVID-19 infection among adults in the short term with moderate certainty of evidence: BNT162b2, VE 95% (95% CI 90.3, 97.6); mRNA-1273, VE 93.6% (95% CI 88.6, 96.5); ChAdOx1, VE 66.7% (95% CI 57.4, 74.0), Gam-COVID-Vac, VE 91.1% (95% CI 83.6, 95.1); and Ad26.CoV2.S, VE 67.2% (95% CI 59.3, 73.7). Data on the efficacy against severe COVID-19 infection and asymptomatic COVID-19 infection are still inconclusive, except for Ad26.CoV2.S, which demonstrated good efficacy in preventing moderate and/or severe COVID-19 infection and acceptable protection against asymptomatic COVID-19 infection 28 days after vaccination (moderate certainty of evidence). Efficacy data on preventing death from COVID-19 infection are still inconclusive. Very limited phase 3 trial data is available to inform vaccine efficacy against the different variants of SARS-CoV-2. Vaccination with these five vaccines was associated with higher adverse reactions compared to control. These adverse events, due to reactions to the vaccines, were mild to moderate and of short duration. Available evidence on vaccine efficacy and safety is limited, mainly due to the short follow up and the small sample size of specific populations.

Conclusion. BNT162b2, mRNA-1273, ChAdOx1, Gam-COVID-Vac and Ad26.CoV.S vaccines demonstrated satisfactory vaccine efficacy against symptomatic COVID-19 infection among adults in the short term with moderate certainty of evidence. Data on the efficacy against severe COVID-19 infection, asymptomatic COVID-19 infection, and death from COVID-19 infection are still inconclusive. Long-term efficacy and safety data, and data on the efficacy against variant strains of SARS-CoV-2 are still lacking.

Key Words: COVID-19, SARS-CoV-2, vaccines, phase 3, randomized controlled trials, systematic review

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INTRODUCTION

In March 2020, the World Health Organization declared the SARS-CoV-2 as a global pandemic. While non-pharmacologic preventive measures such as physical distancing, universal wearing of masks, contact tracing, and strict isolation and quarantine protocols reduce viral transmission, an effective and safe vaccine against SARS-CoV-2 is an invaluable asset in curbing the spread and reducing morbidity and mortality. Hence, in the attempt to control the spread of the disease and the pandemic, numerous COVID-19 vaccines are in development. These vaccines are based on different platforms including mRNA and DNA technologies, viral-vectored, protein subunit, inactivated and live-attenuated vaccines. Most COVID-19 candidate vaccines express the spike protein or parts of it to induce an immunogenic response.

As resources are constrained especially after a year into the pandemic, up-to-date information regarding the effectiveness of public health measures is of paramount importance. A living systematic review aims to provide the necessary efficacy and safety data on humans of COVID-19 vaccines from randomized controlled trials to the stakeholders and policymakers for informed decision making for the proper allocation of resources for vaccine acquisition and utilization.

METHODS

Literature search

A search for trials was done using the COVID-19 Living OVerview of Evidence (L·OVE) platform (www.app.iloveevidence.com/covid19), selecting "vaccination", "primary studies" and using "RCT" and "reporting data" as additional filters. Press releases, systematic reviews, additional information from systematic reviews were excluded.

With the recent emergency use authorization by regulatory agencies, the US-Food and Drug Authority (US-FDA), the European Medicines Agency (EMA), the United Kingdom Medicines and Health Products Regulatory Agency (MHRA) websites were also searched for relevant authorization documents and trial reports for each vaccine. The WHO site was also searched for supporting documents for SAGE meetings on vaccines. Searches were performed every week and the review was updated as trial data was made available. The date of last search for this review was March 11, 2021.

Selection and quality assessment of systematic reviews and included studies

Two reviewers assessed the identified trials for eligibility. Phase 3 randomized placebo-controlled trials with the following characteristics were included: 1) Population: humans, without age or sex limitations; 2) Intervention: vaccines targeted for the prevention of COVID-19 infection; 3) Comparator: placebo or active control; 4) Outcomes: vaccine efficacy for reducing COVID-19 disease of any severity, severe COVID-19 disease, hospitalization or mechanical ventilation among patients with COVID-19 disease, and deaths due to COVID-19. Efficacy assessment time points were noted, as declared by the primary authors. For multi-dose vaccines, vaccine efficacy after the 1st dose was also determined. Efficacy against variant strains of concern was also determined. Vaccine safety outcomes considered included: rates for reactogenicity/adverse reactions, adverse events, serious adverse events, related serious adverse events and vaccine-associated enhanced disease.

Two reviewers independently assessed the methodological quality of these trials based on the Cochrane Risk of Bias tool version 1.0.[1] Any disagreements were resolved by consensus. The methodological assessment for the trials investigating the ChAdOx1 vaccine was done as a composite, given the similarity in the design and implementation of the trials.

Data extraction and analysis

The following study characteristics were extracted: population details such as inclusion and exclusion criteria, interventions (vaccine), comparators, outcomes, data sources, study proponents, study sites and study sponsor. Study design peculiarities and status of study implementation were also noted. In particular, median follow up and the date of database lock were noted. An electronic data extraction form created for this review was used. No attempt was made to contact the trial authors for additional information.

Data was analyzed per vaccine type. When results were available for both per protocol and intention to treat (ITT) analysis, we used the value of the ITT analysis. We planned to pool data across trials using the same vaccine type. However, this was not done in this review because only interim analysis results were available, with varying outcome assessment timepoints.

Subgroup analysis considered were: sex, age (<65 years vs ≥65 years, vs ≥75 years), pediatric vs adults, ethnicity with a focus among Asians, baseline seropositivity status/evidence of previous infection, risk for acquiring COVID 19 (e.g., frontline essential workers), presence of medical comorbidities, confirmed stable HIV disease, and infection with strains of variants of concern. For this review, no subgroup analysis for pediatric cases was done due to the absence of data.

Rating the quality of evidence

The Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach was used to assess the certainty of the evidence related to the outcomes as listed above.[2] The interpretation of the evidence was based on the five GRADE considerations: risk of bias or study limitations, imprecision, inconsistency, indirectness and publication bias. The evidence was downgraded by one level

for serious (or by two for very serious) study limitations (risk of bias), indirectness of the evidence, serious inconsistency, imprecision of effect estimates or potential publication bias.

This review is part of the Philippine COVID Living Clinical Practice Guidelines project funded by the Philippine Council for Health Research and Development. Updated versions of this review as they are presented to the expert panel for consideration in the guidelines are posted in the project website.

RESULTS

Search Results

After searching the COVID-19 Living OVerview of Evidence (L·OVE) platform and screening titles and abstracts for eligibility, we identified eight papers with phase 2/3 trial results on the efficacy and safety of four different COVID-19 vaccines.[3-10] Two reports presented interim results of the trials, which used mRNA vaccines, BNT162b2[3] and mRNA-1273.[4] Five reports were on four trials that used a non-replicating viral vector vaccine, ChAdOx1.[5-9]

A search of the regulatory authority websites yielded additional data on these trials and interim trial data on a fifth vaccine, also a viral vector type, Ad26S.COV.2. [11,12] The USFDA[13] EMA[14,15] UK-MHRA[16] and the WHO SAGE[17,18] authorization documents provided additional information for BNT162b2 vaccine. The USFDA,[19-21] EMA, [22,23] and the WHO SAGE [24,25] authorization documents provided additional information for the mRNA-1273 vaccine. The UK-MHRA,[26] the EMA,[27] and WHO SAGE [28,29] authorization assessment reports provided additional information for the ChAdOx1 vaccine. The USFDA briefing document and the EMA authorization summary of product characteristics document provided information on the Ad26.CoV2.S trial results.[11,12] Details of the study design of the Ad26.CoV2.S trial were taken from the protocol available from the manufacturer/sponsor's website.[30]

Characteristics of Included Studies

All trials identified were phase 2/3 randomized controlled trials comparing a COVID-19 vaccine to placebo or an active control. The vaccines studied were BNT162b2, mRNA-1273, ChAdOx1, Gam-COVID-Vac and Ad26.CoV2.S.

The trial on BNT162b2 randomized 43,651 adults with 21,823 receiving the vaccine. Interim results after a median follow up of 2 months are available. The trial investigating mRNA-1273 randomized 30,351 participants, with 15,181 receiving the vaccine, with a median follow up of 2 months. The published reports on the ChAdOx1 vaccine were the pooled interim results of four phase 2/3 trials. These trials were considered as one study for the purpose of this rapid review. The pooled data included 23,745 participants with 12,021 receiving the vaccine. The efficacy data included 8,596 receiving the vaccine. Most of the outcome data included in the review are from the initial report after a median follow up of two months. A more recent interim report after three months of follow up provided updated results for vaccine efficacy on symptomatic, severe and asymptomatic COVID infection, and on the vaccine efficacy at different dosing intervals.[7] The characteristics of these individual trials were detailed out when there were significant differences noted. Methodological assessment for these trials was made as a composite, given the general similarity in trial design. The trial that investigated Gam-COVID-Vac included 21,977 participants with 16,501 receiving the vaccine. The Ad26.CoV2.S trial randomized 43,783 participants with 21,895 receiving the vaccine.

All available reports presented the results of the interim analysis of ongoing trials. Hence, results for some of the planned efficacy and safety outcomes were still not available.

Details of the characteristics of the included studies are in Appendix Table 1.

Methodological Quality of Included Studies

The methodological quality of included studies were generally satisfactory. However, there were some uncertainties regarding the specific randomization methodology in the trials using BNT162b2 and ChAdOx1, and in the allocation concealment in the trial using ChAdOx1.

All available reports presented the results of the interim analysis of ongoing trials, resulting in a high risk of bias in terms of completeness of the follow up. Because of the short follow up, high risk of bias may also present in the reporting of some of the outcomes, such as hospitalization, severe COVID infection and deaths due to COVID due to the relative rarity of these events. Hence, results for some of the planned efficacy and safety outcomes are still not available.

Details of the methodological quality assessments are in Appendix Table 2.

RESULTS

Efficacy

Available trial data for all five vaccines demonstrate sufficient efficacy rates in the prevention of symptomatic COVID-19 infection, based on a threshold of at least 50% set by the WHO, within a median follow up of three months after vaccination of the ChAdOx1, two months after vaccination of the BNT162b2, mRNA-1273, and Ad26.CoV2.S, and 48 days after vaccination of the Gam-COVID-Vac. No long-term efficacy data are available for all five vaccines.

BNT162b2

BNT162b2 demonstrated a vaccine efficacy (VE) of 95% (95% CI 90.3, 97.6) for the prevention of symptomatic COVID-19 infection starting at seven days after the 2nd dose, at a median follow up of 2 months. Similar high efficacy was shown for subgroups based on age, sex, race, ethnicity, body mass index or the presence of underlying condition associated with high risk of COVID-19 complications. The

vaccine showed high protective efficacy in the older adults at least 65 years (VE 95%, 95%CI 66.7, 99.9). A precise estimate on the protective effect of BNT162b2 on the occurrence of severe COVID-19 infection is lacking (VE=75.0%, 95% CI -152.6, 99.5). BNT162b2 also showed an efficacy of 52.4% (95% CI 29.5, 68.4) after the first dose but before the second dose. Symptomatic COVID-19 disease seems to occur similarly for both the BNT162b2 and placebo groups until approximately 14 days after the 1st dose, then cumulative curves diverge with more cases accumulating in the placebo group rather than in the BNT162b2 group. During the follow-up time of approximately 2 months post-2nd dose, the BNT162b2 cumulative curve was stable suggesting continued protection. Asymptomatic COVID-19 infection prevention was not assessed. No data on the impact of the vaccine on hospitalization, ICU admission or deaths associated with COVID-19 infection were reported.

mRNA-1273

mRNA-1273 showed a vaccine efficacy of 93.6% (95%CI 88.6, 96.5) starting at 14 days after the 2nd dose, at a median follow up of two months. Similar efficacy was demonstrated for subgroups based on age, sex, race, ethnicity, risk factor and baseline SARS-CoV-2 serology status. mRNA-1273 demonstrated good vaccine efficacy for older adults at least 65 years old (VE 86.4%, 95% CI 61.4, 95.5). No case of severe COVID-19 infection occurred in the vaccine group while 30 occurred with the placebo group during the reported follow-up period, demonstrating high efficacy of mRNA-1273 in preventing severe COVID-19 infection, but with a wide confidence interval. mRNA-1273 showed an efficacy of 69.5% (95% CI 43.5, 92.7) after a single dose. Cumulative incidence curves revealed low rates until day 14 after the 1st dose and subsequent divergence with more cases of infections occurring in the placebo group than the mRNA-1273 group. Asymptomatic COVID-19 infection prevention was not assessed. No data on the impact of the vaccine on hospitalization, ICU admission or deaths associated with COVID-19 infection were reported.

ChAdOx1

ChAdOx1 had an overall vaccine efficacy of 66.7% (95% CI 57.4, 74.0) in preventing symptomatic COVID-19 infection 14 days after the second dose, with a median follow up of 3 months. Subgroup analysis for vaccine efficacy for the older individuals, Asians and those at high risk of infection was not available. For the prevention of severe COVID-19 infection after 14 days of the 1st dose, with a median follow up of 2 months, ChAdOx1 had a vaccine efficacy of 97.6% (95% CI 46.0, 97.1). Only one event of severe COVID 19 infection was recorded, occurring in the control group, after 14 days following the second dose, precluding any conclusive assessment on this outcome. ChAdOx1 demonstrated a vaccine efficacy of 73% (95% CI 48.8, 85.8) 21 days after the first dose and before the second dose. Based on the UK trial (COV002), ChAdOx1 did not provide protection against asymptomatic COVID-19 infection, having a vaccine efficacy of 22.2% (95% CI -9.1, 45.0) after a three-month follow up. All 9 hospitalizations occurring 14 days after the 2nd dose occurred in the control group.

In its follow-up report with a median follow up of 3 months, the overall vaccine efficacy was at 80.7% (95% CI 62.1, 90.2) in the subgroup of study participants who received a low (2.5×10^6 vp) first dose and a standard (5×10^6 vp) second dose. For those who received two standard doses, vaccine efficacy was 63.1% (95% CI 51.8, 71.7). Subgroup analysis of vaccine efficacy based on dosing interval was also available. Vaccine efficacy was noted to be highest with a dosing interval of at least 12 weeks (VE 81.3%, 95% CI 60.3, 91.2), when two standard doses were given.

A secondary subgroup analysis of the COV002 ChAdOx1 trial data of COVID-19 cases from October 1, 2020 to January 14, 2021 investigated its efficacy on symptomatic and asymptomatic COVID-19 infection with the B.1.1.7 variant when such variant was peaking in November 2020 in the UK.[9] It showed clinical efficacy of ChAdOx1 vaccine against symptomatic COVID disease with the B.1.1.7 variant (VE = 74.6%, 95% CI 41.6, 88.9) (Appendix 3c). It should be noted this estimate was based on only 48% of the total cases (120 sequenced of the 250 cases). The study also demonstrated significantly lower viral load among those with a PCR-positive swab in the vaccine group compared to those in the control group, suggesting possible lower likelihood of viral transmission.

Gam-COVID-Vac

Gam-COVID-Vac demonstrated an overall vaccine efficacy of 91.1%. (95% CI 83.6, 95.1) for the prevention of symptomatic COVID-19 infection beginning 7 days after the administration of the 2nd dose, with a median follow up of 48 days. It showed a first-dose vaccine efficacy of 73.1% (63.7, 80.1) at 21 days. Severe COVID-19 disease was only seen in the control group starting at 21 days after administration of the first dose (VE = 100%, 95%CI 94.4-100.0). Subgroup analysis on the vaccine efficacy for the >60 year old population showed high protection (VE = 91.8%, 95% CI 67.1, 98.3). Data on hospitalization, ICU admission, associated death rates or asymptomatic COVID-19 infection were not reported.

Ad26.CoV2.S

Ad26.CoV2.S demonstrated vaccine efficacies of 67.2% (95% CI 59.3, 73.7) for the prevention of symptomatic COVID-19 disease, 66.9% (95% CI 59.0, 73.5) for the prevention of moderate to severe disease, and 76.3% (95% CI 57.9, 87.5) for preventing severe disease, beginning at 14 days after vaccination, at a median follow up of two months. Notably, very few events of mild COVID-19 infection were reported in the study. Subgroup analysis showed that Ad26.CoV2.S provided adequate protection against moderate-to-

severe COVID-19 infection to older adults aged ≥60 years and to those with at least one comorbidity. Cumulative incidence of moderate to severe/critical COVID-19 diverge following day 14 with more cases accumulating in the placebo group rather than the vaccine group. Vaccine efficacy against specific SARS-CoV-2 variants was planned in the study. However, as sequencing of all cases was still incomplete at the time of the report, the investigators deemed that the vaccine efficacy against specific SARS-CoV-2 variants was not evaluable. Nonetheless, their findings were included in this review.

Starting at 14 days after vaccination, Ad26.CoV2.S vaccination showed high protection against hospitalization with moderate certainty (VE = 93.1%, 95% CI 72.7, 99.2). The two hospitalizations in the vaccine group were in participants who were ≥60 years of age with comorbidities. Low certainty evidence showed that it does not seem to provide protection against asymptomatic COVID-19 infection (VE = 20%, 95% CI -7.0, 40.4). As of Feb 5, 2021, no COVID-related deaths were reported in the vaccination group compared with seven in the placebo group.

The summary of findings on efficacy are in Table 1. Details are in Appendix Tables 3 to 7.

Safety

Available trial data for BNT162b2, mRNA-1273, ChAdOx1 and Ad26.CoV2.S vaccines demonstrated acceptable safety profiles. General adverse event rates were not available for the Gam-COVID-Vac. Serious adverse event rates and related serious adverse event rates associated with the four vaccine groups were not significantly different from those with the control groups. No long-term safety data are available for all five vaccines.

BNT162b2

Most local and systemic adverse reactions to the vaccine were mild to moderate in severity, transient and of short duration. The most common local adverse reaction was pain at the injection site (78-85% in the vaccine group vs.12-14% in the placebo group among 16-55 year old participants and 66-71% in the vaccine group vs. 8-9% in the placebo group in >55 year old participants). Most were mild or moderate in severity with no reported life-threatening reaction. Onset was between the first and third day of the vaccination, with a mean duration between one to two days. Headache (25-52%) and fatigue (34-59%) were the most common systemic reactions. Most were mild and moderate in severity. Median

Table 1. Summary of efficacy of vaccines vs placebo

Outcome	BNT162b2 vs placebo	Certainty of Evidence	mRNA-1273 vs placebo	Certainty of Evidence	ChAdOx1 vs control	Certainty of Evidence	Gam-COVID-Vac vs placebo	Certainty of Evidence	Ad26.CoV2.S vs placebo	Certainty of Evidence
1. ***Symptomatic COVID-19 infection***	95.0 (90.3, 97.6)	+++ Moderate	93.6 (88.5, 96.4)	+++ Moderate	66.7% (57.4, 74.0)	+++ Moderate	67.2% (59.3, 73.7)	++ Moderate	67.2% (59.3, 73.7) **used values for FDA harmonized cases*	++ Moderate
2. ***Severe COVID-19 infection***	75.0 (-152.6, 99.5)	++ Low	100% (NE, 100%)	++ Low	100%	++ Low	NA	NA	76.3% (57.9, 87.5) **including non-centrally confirmed*	+++ Moderate
3. ***Moderate & Severe COVID-19 infection***	NA	NA	NA	NA	NA	NA	100% (94.4, 100.0) **21 d after dose 1*	++ Low	66.9% (59.0, 73.5) **centrally confirmed*	+++ Moderate
4. ***COVID-19 infection, after 1st dose***	52.4 (29.5, 68.4) **before 2nd dose*	++ Low	69.5 (43.5, 92.7) **before 2nd dose*	+++ Moderate	73.0% (48.8, 85.8) *at >21 days	+++ Moderate	73.1 (63.7, 80.1) **at >21 days*	+++ Moderate	NA	NA
5. ***Death due to COVID-19***	NA	NA	100% (NE, 100)	++ Low	NA	NA	NA	NA	100%	++ Low
6. ***Asymptomatic COVID-19 infection***	NA	NA	NA	NA	22.2% (-9.1, 45.0)	++ Low	NA	NA	20.0% (-7.0, 40.4) *from day 1 to 29	++ Low
7. ***Hospitalization***	NA	NA	NA	NA	100%	++ Low	NA	NA	91.3% (72.7, 99.2) *including non-centrally confirmed	+++ Moderate

onset was on the second to the third day post vaccination, with a median duration of one day.

More participants in the vaccine groups reported at least one adverse event (AE) compared to the control group. The AEs reported were largely attributable to local adverse reactions. More severe AEs occurred more often in the vaccine group (1.2% vs. 0.6%, RR 1.73 95%CI 1.4, 2.13). Lymphadenopathy, nausea and hypersensitivity were reported more often in the vaccine group. Similar frequency of serious adverse events was observed between the treatment groups.

Four cases of Bell's palsy (facial paralysis) were observed after BNT182b2 vaccination, and were assessed by the study physicians to be related to the study intervention. However, the US-FDA opined that there is no clear basis for such an association as the observed frequency of the reported Bell's palsy in the vaccine group was consistent with the expected rate in the general population.[13]

Two deaths were reported in the BNT162b2 group with the reported causes of death as atherosclerotic disease and cardiac arrest. Both cases were not considered related to the vaccine and pre-existing diseases were deemed as the more likely cause of the death, rather than the vaccine. Four deaths were reported in the placebo group; one case of a hemorrhagic stroke, one case of myocardial infarction and two cases of unknown cause of death.

mRNA-1273

More local and systemic adverse reactions were reported in the mRNA-1273 group than in the placebo group. The most commonly reported local adverse reaction was pain (84% vs. 20%), while fatigue and headache were the most commonly reported systemic reaction after mRNA-1273 vaccination. More adverse events were reported in the vaccine group, largely attributed to the local and systemic reactions after vaccination. Rates of severe AEs were similar in both treatment groups (1.4 vs. 1.3%). More frequently reported severe AEs reported in the vaccine group compared to the placebo were headache, myalgia, arthralgia, injection site erythema, and injection site pain.

At the end of the first interim analysis phase (November 14, 2020), each treatment group had four deaths. As of December 3, 2020, six deaths were reported in the vaccine group. The causes of deaths were: cardiopulmonary arrest in a >75-year-old patient with preexisting cardiac disease; myocardial infarction in a >75-year-old patient with preexisting cardiac disease; multi-organ failure from obstructive nephrolithiasis with complications; suicide; and two cases were found dead at home of uncertain cause of death. All deaths were deemed unrelated to the vaccine.

ChAdOx1

The most frequently reported adverse reactions associated with ChAdOx1 vaccination were injection site tenderness (64% vs 39%), injection site pain (54% vs 37%), fatigue (61% vs 38%), malaise (44% vs 20%), fever and chills, arthralgia and nausea. Majority of the adverse reactions were mild to moderate in severity and resolved within 7 days. More adverse events were reported in the vaccine group (38% vs 8%; RR 1.36, 95% CI 1.29, 1.43). The incidence of severe adverse events was low (<2%) and similar between the two treatment groups. The most frequent adverse events were those commonly observed following vaccination. The incidence of serious adverse events was also low in the study, balanced between the treatment groups (0.7% in vaccine group vs 0.8% in control).

As of the study data publication, one death was reported in the vaccine arm and two in the control arm. The cause was not specified in the paper. In the UKMHRA public assessment report, two deaths were reported in the participants who received the vaccine; one HIV positive patient died from *Pneumocystic jirovecii* pneumonia and one died from metastatic ovarian cancer. These deaths were assessed as not related to the vaccine. Four deaths were reported in the placebo group: one from COVID-19 pneumonia, one from craniocerebral injury, one from homicide and one from traumatic injury.

Gam-COVID-Vac

General adverse event data were not available for Gam-COVID-Vac, pending verification by the independent assessors in the trial. Serious adverse event rates were similar between the two treatment groups. Four deaths were reported in the trial publication. Three deaths were in the vaccine group, one from a fractured thoracic vertebra and two from COVID-19 infection. The first patient developed symptoms four days after vaccination with the first dose and had severe cardiopulmonary disease. The second patient developed symptoms five days after vaccination with the first dose and had uncontrolled endocrinological and cardiopulmonary comorbidities. One death occurred in the control group due to a hemorrhagic stroke.

Ad26.CoV2.S

Most frequently reported local adverse reaction was pain at the injection site followed by erythema and swelling. Most were mild and lasting a median of 2–3 days. Most frequently reported systemic adverse reactions were headache, fatigue, myalgia and nausea. Median time of onset was within 2 days of vaccination with a median duration of 1–2 days. Overall rates of unsolicited adverse events including severe ARs, serious adverse events, and related serious adverse events were similar between the treatment groups. The US FDA noted slight numerical imbalances between treatments groups, with higher numbers reported in the vaccine group, for the following adverse events: embolic and thrombotic events, convulsions, tinnitus, angioedema, wheezing, arthritis, and peripheral neuropathy. Those found to be possibly related to the vaccine were from vaccine reactogenicity.

Seven serious adverse events were reported in the vaccine group, of which three were assessed by the USFDA

as likely related to the vaccine: two cases of hypersensitivity reaction / systemic reactogenicity to the vaccine and one case of brachial neuritis / radiculitis brachia.

Five deaths were reported in the vaccine group. Two were due to respiratory infections not due to COVID: one was in a 61-year-old participant and another in a 42-year-old with HIV. The third death was in a 66-year-old who died of unknown causes after waking up with shortness of breath. The causes of death in the other two cases were not mentioned but were assessed as not related to the vaccine. Of the twenty deaths in the placebo group (as of February 5), eight were COVID-related. The other causes of deaths in the placebo group were not available.

The summary of findings tables on safety are in Appendix Tables 8 to 12.

DISCUSSION

Currently available data demonstrate short-term efficacy and safety of five vaccines, BNT162b2, mRNA-1273, ChAdOx1, Gam-COVID-Vac and Ad26.CoV.S against symptomatic COVID-19 infection. The short-term protection provided by the vaccine in terms of reducing the risk of developing symptomatic COVID-19 infection outweighs the transient reactogenic and systemic effects of the vaccines among the participants included in the trial. As a result, emergency use authorizations have been granted to these vaccines. BNT162b2 (Comirnaty) received emergency use authorization (EUA) from the UKMHRA, USFDA, and the EMA. On December 31, 2020, the WHO listed the Comirnaty mRNA vaccine for emergency use. The Philippine FDA issued its first COVID vaccine EUA to BNT 162b2 on January 11, 2021. mRNA-1273 (Moderna) received emergency use authorization from USFDA, and the WHO. ChAdOx1 (Astra Zeneca, University of Oxford) received emergency use authorization from the UKMHRA, the EMA and the WHO. The Philippine FDA has issued an EUA for ChAdOx1 on January 28, 2021. Gam-COVID-Vac (Sputnik V) is registered for use in more than 50 countries, including the Philippines which issued its EUA on March 19, 2021. Ad26.CoV.S received its authorization from the USFDA and the EMA. Thus, vaccination using any of these vaccines may be recommended among adults in the light of the current pandemic.

However, a careful risk/benefit assessment and discussion should be made when considering vaccination in the populations which were not included or were included but in very small numbers in the clinical trials. These include children, pregnant and lactating women, immunocompromised and the frail and elderly. Since there is only short-term follow up of these trials, a pharmacovigilance program and a regular review of the evidence is required and implemented should vaccination using these vaccines be rolled out.

The current available evidence on vaccine efficacy and safety is limited, mainly due to the limitations in the design of the clinical trials and due to the available data from the short follow up on only a median of 2 months for all the studies. The efficacy of COVID-19 vaccines on reducing the impact of the disease is lacking, particularly on the severe COVID infections and deaths due to COVID infection as the available estimates have wide intervals. Information regarding the impact of vaccination on hospitalization was also limited, as it was a prespecified outcome only in the trial using ChAdOx1, and was not reported in the other trials. Efficacy against asymptomatic infection is still uncertain. Therefore, vaccine effect on transmission, especially by asymptomatic cases, remains unknown.

The efficacy and safety of these vaccines on certain populations are unknown, having been excluded from the trials. These include pregnant and breastfeeding women, immunocompromised patients, children and previously diagnosed COVID patients. Among the immunocompromised patients, only those with stable disease were included and only comprised less than 1% of the study population. Persons with HIV, while included in the trials, were not included in the interim efficacy analyses reports included in this review. The very small numbers of seropositive participants at baseline (2-6% of the study population) and the frail elderly included in the trial preclude firm conclusions on the effect of vaccines in these populations. Persons with other medical conditions were included in the trials but only if their comorbidities were controlled. Hence, caution needs to be employed in the vaccination of patients with significant and uncontrolled medical diseases.

Other uncertainties include the impact of the vaccine on transmission to unvaccinated persons, viral shedding, long-term efficacy/durability of protection, onset of protection, particularly in the multidose vaccines (although there is some suggestion that there is partial protection after the first dose), long-term safety results, interaction with other vaccines and the risk of vaccine-associated enhanced disease. These unknowns do not provide information on the need for booster doses or regular vaccinations in the future. The completion of the current trials may provide some of the information although additional trials and population-based pharmacovigilance activities may need to be implemented to close all the knowledge gaps.

The efficacy of these vaccines on the emerging variant strains of concern is very limited. Very limited early reports on ChAdoX1 and Ad26.CoV.S efficacies on some of these variants are worrisome. Continued surveillance and a review of the real world evidence on the vaccine efficacies should be done as the vaccination program rolls out globally. Emphasis should be made on the continued implementation of non-pharmacological measures on infection control such as wearing masks, practicing physical distancing and regular handwashing even with vaccination.

This systematic review presents the landmark registration trial data of five COVID-19 vaccines. The impact of vaccines in the control of pandemic does not rely solely

on its efficacy and safety. Their timely acquisition and procurement, proper storage and distribution, ethical allocation, and efficient program implementation are other important consideration for an effective vaccination program to combat the pandemic.

CONCLUSION

The BNT162b2, mRNA-1273, ChAdOx1, Gam-COVID-Vac and Ad26.CoV.S vaccines demonstrated satisfactory vaccine efficacy against symptomatic COVID-19 infection among adults in the short term, based on moderate certainty of evidence. Data on the efficacy against severe COVID-19 infection, asymptomatic COVID-19 infection and death from COVID-19 infection are still inconclusive. Vaccination with these vaccines was associated with higher adverse reactions compared to control. These adverse events, from reactions to the vaccines, were mild to moderate and of short duration. Long term efficacy and safety data are still lacking.

Statement of Authorship

All authors participated in the data collection and analysis and approved the final version submitted.

Author Disclosure

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APPENDICES

Appendix Table 1. Characteristics of included studies

Trial Identifier	Polack 2020 (C4591001)	Zaks 2020 (mRNA-1273-P301)	Voysey 2020 (COV002, 003, 005)
Vaccine	BNT162b2	mRNA-1273	ChAdOx1 nCoV19 / AZD1222
Population			
Total Randomized	43,651 (V:21,823 C:21,828)	30,351 (V:15,181 C:15,170)	Efficacy: 11,636 (V:5,807 C:5,829) Safety: 23,745 (V:12,021 C:11,724)
Inclusions	Age 16 years or older	Adults at risk of SARS-CoV-2 infection who have no known history of SARS-CoV-2 infection	Healthy adults, priority given to health professionals and adults with high potential for exposure to SARS-CoV-2
Exclusions	Pregnant and breastfeeding women Age <12 years Previous clinical or microbiological diagnosis of COVID-19 Current COVID-19 infection History of severe allergic reaction to vaccine	Pregnant and breastfeeding women Known history of SARS-CoV-2 infection Received immunosuppressants	Pregnancy and lactation Current diagnosis of cancer Continuous use of anticoagulants Uncontrolled medical disease History of allergic reaction Confirmed or suspected immunosuppressive or immunodeficient state (except for specific HIV group)
Intervention (Vaccine)			
Type	mRNA	mRNA	Viral vector
Active substance	Single-stranded, 5'-capped mRNA that is translated into a codon-optimized sequence encoding the spike antigen of SARS-CoV-2.	LNP dispersion of an mRNA encoding the prefusion stabilized S protein of SARS-CoV-2 formulated in LNPs composed of 4 lipids that encodes for the full-length spike (S) protein of SARS-CoV-2, modified to introduce 2 proline residues to stabilize the S protein (S2P) in a prefusion conformation	Recombinant, replication-deficient chimpanzee adenoviral vector containing the SARS-CoV-2 structural surface glycoprotein antigen gene with a tissue plasminogen activator leader sequence
Dosing and administration	0.3 ml (30 ug BNT162b2) intramuscular injection, 21 days apart (predefined window: 19–42 days after dose 1) interval in trial (19 to 45 days)	0.5 ml (100 ug mRNA-1273) intramuscular injection, on a 2-dose injection schedule on day 1 and day 29	0.5 ml (3.5-6.5x 10^{10} viral particles), intramuscular injection, 2 doses 4 weeks apart (COV002 and COV003: originally designed as single dose, protocol amendment in July 2020 for a booster made based on the immunogenicity study results, with interval between doses up to 12 weeks
Number randomized	21,823	15,181	5,807 (COV002 and COV003)
Comparator			
Type, dosing and administration	0.3ml saline intramuscular injection, 21 days apart	0.5 ml of 0.9% sodium chloride (saline) intramuscular injection, on a 2-dose injection schedule on day 1 and day 29	0.5 ml Meningococcal group ACWY conjugate vaccine (MenACWY) OR 0.5 ml Normal saline, intramuscular injection, 2 doses, 4 weeks apart
Number randomized	21,828 (at final analysis)	15,170	5,829 (COV002 and COV003)

Logunov 2021 (RESIST)	Janssen 2021 (ENSEMBLE-COV3001)
Gam-COVID-Vac	Ad26.CoV2.S
21,977 (V: 16,501 C: 5, 476) (3:1)	44, 325 (V: 21,895 C: 21,888)
≥18 y.o. (18-111), negative HIV, hep B & C and syphilis; seronegative, negative RT-PCR for SARS-CoV-2, no history of COVID-19 infection, no contact with anyone with COVID-19 infection in the preceding 14 days, no history of vaccine-induced reactions	Stage 1: ≥18 y.o., <60 y Stage 2: including >60 y May have underlying illness (but not associated with increased risk of progression to severe COVID) as long as signs and symptoms are stable and well-controlled; included stable and well controlled HIV infection
Any vaccination in the 30 days before enrolment Steroid or immunoglobulins in the 30 days before enrolment Immunosuppression in the 3 months before Pregnant and breast feeding Acute coronary syndrome or stroke in the year before Blood donation 2 months before Immunodeficiency in the 5-6 months before Anorexia or protein deficiency History of alcohol or drug addiction Previous COVID infection	Clinically significant acute illness Known or suspected allergy or history of anaphylaxis or other serious adverse reactions to vaccines or their excipients Received a vaccine within 28 days before or after planned administration of study vaccine Previously received COVID-19 vaccine Received investigational drug for prophylaxis of COVID-19 within 30 days Received IgG or monoclonal antibodies within 3 months, convalescent plasma within 4 months, investigational vaccines within 6 months Abnormal function of the immune system Received treatment with Ig within 3 months With comorbidities that might be associated with an increased risk of progression to severe COVID10 (moderate to severe asthma, chronic lung disease, COPD, pulmonary fibrosis, serious heart conditions, moderate to severe high blood pressure, obesity, chronic liver disease, sickle cell disease, end stage renal disease, organ transplantation, cancer, HIV and other immunodeficiencies, surgery requiring hospitalization within 12 weeks before vaccination)
Combined viral vector (adenovirus)	Viral vector (adenovirus)
rAd type 26 and rAd type 5 which carry the gene for SARS-CoV-2 full length glycoprotein S	Replication-incompetent recombinant adenovirus type 26 (Ad26)-vectored vaccine encoding a stabilized variant of the SARS-CoV-2 spike (S) protein
2 vector components: rAd26-S and rAd5-S full dose of 10^{11} viral particles per dose of each recombinant adenovirus 0.5 ml/dose Administered intramuscularly separately with a 21-day interval	5 x 10^{10} viral particles administered as a single intramuscular dose (0.5 ml)
16,501	22,174
Vaccine buffer composition without the recombinant adenoviruses 0.5ml / 0.5 ml IM on days 1 and 21	0.9% sodium chloride solution, 0.5 ml
5,476	22,151

Appendix Table 1. Characteristics of included studies *(continued)*

Trial Identifier	Polack 2020 (C4591001)	Zaks 2020 (mRNA-1273-P301)	Voysey 2020 (COV002, 003, 005)
Outcomes			
Primary efficacy endpoints	COVID-19 incidence per 1000 person-years of follow up in participants without evidence of past SARS-CoV-2 infection before and during vaccination regimen – cases confirmed ≥ 7 days after dose 2 COVID-19 incidence per 1000 person-years of follow up in participants with and without evidence of past SARS-CoV-2 infection before and during vaccination regimen – cases confirmed ≥ 7 days after dose 2 COVID-19 infection: at least 1 of the following symptoms and SARs-CoV-2 NAAT positive test during, or within 4 days before or after, the symptomatic period: fever, new or increased cough, new or increased shortness of breath, chills, new or increased muscle pain, new loss of taste or smell, sore throat, diarrhea, vomiting	Prevention of protocol-defined COVID-19 occurring at least 14 days after the second dose in participants with negative SARS-CoV-2 status at baseline Vaccine efficacy: percent reduction (mRNA-1273 vs placebo) in the hazard of the primary endpoint (VE = 1-HR) COVID-19 infection: at least TWO of systemic symptoms of fever, chills, myalgia, headache, sore throat OR at least ONE of respiratory signs/ symptoms of cough, shortness of breath or difficulty breathing or clinical or radiological evidence of pneumonia. AND have at least one NP swab, nasal swab, or saliva sample positive for SARS-CoV-2 by RT-PCR	Virologically confirmed, symptomatic COVID-19 in participants that were COVID-19 naïve at the time of randomization who received at least 2 doses of vaccine or placebo, occurring more than 14 days after the booster dose Vaccine efficacy: 1-adjusted risk (vaccine vs control) Symptomatic COVID-19: NAAT-positive swab combined with at least one qualifying symptom of fever, cough, shortness of breath or anosmia or ageusia)
Primary safety endpoints	Reactogenicity Adverse events Serious adverse events (up to 6 months after dose 2) Withdrawal due to adverse events Deaths	Reactogenicity: solicited systemic and local adverse reactions occurring during the 7 days following each dose Unsolicited adverse events for 28 days following each injection Adverse events leading to discontinuation of dosing or study participation from day 1 to day 759 Medically attended adverse events Severe adverse events from day 1 to day 759	Reactogenicity Unsolicited AEs from start of each dose to day 28 Serious adverse events from first vaccination to 364 days Adverse events of special interest
Secondary endpoints	COVID-19 confirmed at least 14 days after dose 2: COVID-19 incidence per 1000 person-years of follow up in participants either (1) without or (2) with and without evidence of past SARS-CoV-2 infection before and during vaccination regimen – cases confirmed either (1) ≥ 7 days after dose 2 or (2) ≥14 days after dose 2 Severe COVID-19: incidence per 1000 person-years of follow up in participants either (1) without or (2) with and without evidence of past SARS-CoV-2 infection before and during vaccination regimen – cases confirmed either (1) ≥ 7 days after dose 2 or (2) ≥ 14 days after dose 2 *Severe COVID-19: at least 1 of the following: clinical signs at rest indicative of severe systemic illness, respiratory failure, evidence of shock, significant acute renal, hepatic, or neurological dysfunction; admission to an ICU; death	Vaccine efficacy in the prevention of: - severe COVID-19 - COVID-19 based on a less restrictive definition (*) occurring 14 days after the second dose - Death due to COVID-19 - COVID-19 occurring at least 14 days after the first dose of vaccine (including cases that occurred after the 2nd dose) - COVID-19 occurring at least 14 days after the second dose, regardless of prior SARS-CoV-2 infection (*): positive NP swab, nasal swab, or saliva sample (or respiratory sample, if hospitalized) for SARS-CoV-2 by RT-PCR AND one of the following: fever, chills, cough, shortness of breath, fatigue, muscle aches, headache, new loss of taste or smell, sore throat, nasal congestion or rhinorrhea, nausea or vomiting, or diarrhea Vaccine-enhanced disease	Vaccine efficacy on: - hospital admissions associated with COVID-19 - intensive care unit admissions associated with COVID-19 - severe COVID-19, virologically confirmed - asymptomatic SARS-CoV2 infection - death associated with COVID-19 - all-cause LRTI at time frames from 21 days after single dose, or 7 days after a 2nd dose, or >14 days after 2nd dose Incidence of asymptomatic SARS-CoV-2 infection occurring ≥ 22 days post first dose (COV002) Seroconversion against non-Spike SARS-CoV-2 antigens *Severe COVID: ≥ grade 6 in the WHO clinical progression scale *Asymptomatic COVID: PCR-confirmed COVID with no symptom record

Logunov 2021 (RESIST)	Janssen 2021 (ENSEMBLE-COV3001)
Proportion of participants with COVID-19 confirmed by PCR from day 21 after receiving the first dose (i.e., at time of 2nd dose) within 6 months Percentage of trials subjects with coronavirus disease 2019 developed with in 6 months after the first dose Mild: T<38.5°C, cough, weakness, sore throat; no symptoms of moderate and severe course Moderate: T>38.5°C, RR >22/min, shortness of breath during physical exertion, pneumonia (confirmed by lung CT), O_2 sat <95%, CRP >10 ml/L Severe: RR >30/min, O_2 sat ≤ 93%, O_2 partial pressure / H_1O_2 ≤ 300mmHg, progression of changes in the lungs by x-ray. CT, ultrasonography, decreased level of consciousness, agitation; unstable hemodynamics (SBP< 90 mmHg or DBP <60 mmHg, diuresis <20 ml/hr)	Efficacy to prevent centrally confirmed, moderate to severe/critical COVID-19 occurring (1) at least 14 days after vaccination and (2) at least 28 days after vaccination Moderate COVID-19: RT-PCR positive or molecular test result from any respiratory tract sample and Any 1: RR ≥ 20/min, abnormal SpO_2 but still >93% on room air, clinical or radiological evidence of pneumonia, radiologic evidence of deep vein thrombosis, shortness of breath or difficulty breathing OR any 2 of the following: fever, HR ≥90, shaking chills or rigors, sore throat, cough, malaise, headache, muscle pain, GI symptoms, new or changing olfactory or taste disorders, red or bruised feet or toes. Severe/critical COVID-19: RT-PCR or molecular test result and any of the ff: clinical signs of severe systemic illness, respiratory failure, evidence of shock, significant severe acute renal, hepatic or neurologic dysfunction, admission to ICU, death.
Incidence and severity of adverse events	- Solicited local and systemic adverse reactions for 7 days following vaccination - Unsolicited AE for 28 days following vaccination - Medically attended AEs - SAEs from day 1 to 104 weeks Vaccine-enhanced disease
- Efficacy of the Gam-COVID-Vac combined vector vaccine against the SARS-CoV-2 induced coronavirus compared to placebo, based on the severity of the clinical course of COVID-19 - Changes in antibody levels against SARS-CoV-2 glycoprotein S - Proportion of participants with antibodies against SARS-CoV-2 N protein - Changes in SARS-CoV-2 neutralizing antibody titers (increase) - Changes in antigen-specific cellular immunity level (increase in cell-mediated immune response to antigen) * serious adverse events – diagnosed on the basis	Vaccine efficacy on: - Severe/critical COVID-19 - COVID-19 requiring medical intervention - COVID-19 related death - Any symptomatic COVID-19 - Asymptomatic COVID-19 10 as inferred through seroconversion - COVID-19 per the FDA harmonized COVID-19 case definition

Appendix Table 1. Characteristics of included studies *(continued)*

Trial Identifier	Polack 2020 (C4591001)	Zaks 2020 (mRNA-1273-P301)	Voysey 2020 (COV002, 003, 005)
Follow up			
Planned	24 months	759 days	1 year
At data cutoff of interim report (first interim analysis)	Average of 2 months after 2nd dose 92% followed up for at least 1 month after 2nd dose 50% followed up at least 2 months after 2nd dose Longest follow up 12-13 weeks after 2nd dose (n= 382 BNT162b2, n=398 placebo)		Mean duration of follow up was 105 days post-dose 1 and 62 days post-dose 2
Date of data cut-off for latest available trial data	Efficacy Preliminary: November 4, 2020 Final: November 14, 2020 Safety: November 14, 2020 *with additional mortality data	Efficacy Preliminary: November 7, 2020 Final: November 25, 2020 Safety: November 11, 2020 and November 25 *with additional data on deaths as of December 3	November 4, 2020
Methods / Other Trial Parameters			
Study sites	USA, Argentina, Brazil, Turkey, South Africa, Germany		UK, Brazil, South Africa
Study sponsor	BioNTech, Inc, Pfizer	ModernaTX,Inc	University of Oxford, AstraZeneca

Appendix Table 2. Methodological quality assessment of included studies

Trial identifier	Polack 2020 (C4591001)		Zaks 2020 (mRNA-1273-P301)		Voysey 2020 (COV002, 003, 005)	
Vaccine	BNT162b2		mRNA-1273		ChAdOx1 nCoV19/AZD1222	
Randomization	Through the use of IRT system	U	Through the use of IRT system, using pre-generated randomization schedule	L	No mention on method in the protocol	U
Allocation	Through the use of IRT system	L	Through the use of a centralized IRT system	L	No mention on method in the protocol Unclear	U
Blinding	Blinding included the investigator, investigator staff and the participants (observer-binded)	L	Observer-blinded	L	COV002 and 3 are single blinded COV005 is double blinded Outcome assessors blinded, endpoint review committee blinded	L
Follow up	Interim analysis; low dropout rates, missing data explained, some imbalance across groups but overall counts balanced	L/H	Interim analysis; low dropout rates, missing data explained, some imbalances across groups but overall counts balanced	L/ H	Interim analysis; low dropout rates, missing data explained, some imbalances across groups Variable dosing intervals but assessed per ITT	L/ H
Selective reporting	Interim analysis	U	Interim analysis	U	Interim analysis	U
Others	Protocol amendments included addition of pediatric population during the conduct of the study				Initially designed to assess a single-dose vaccine but protocol amended for a booster dose after a review of the antibody response data from a Ph2 study	

L, Low risk of bias; U, Unclear/unreported; L/H, Low risk per design, but with serious concerns/high risk for bias for the currently available outcome data since data is available only for a subset of the study population and only for a short follow-up period

	Logunov 2021 (RESIST)	Janssen 2021 (ENSEMBLE-COV3001)
	180 days	24 months
	Median time from first dose to database lock was 48 days (IQR 39-58)	Median follow up of 8 weeks after vaccination (58 days) range 1-124 days
	November 24, 2020	January 22, 2021 *with additional data at February 5, 2021
	Russia	US, Brazil, South Africa, Latin America
	Gamaleya Research Institute of Epidemiology and Microbiology, Health Ministry of the Russian Federation	Janssen Vaccines & Prevention B.V>

	Logunov 2021 (RESIST)		Janssen 2021 (ENSEMBLE-COV3001)	
	Gam-COVID-Vac		Ad26.CoV2.S	
	Interactive web response system; statistician generated the sequence	L	Computer-generated randomization schedule prepared before the study	L
	Interactive web response system	L	Interactive web response system will assign a unique intervention code	L
	Participants, investigators and all study staff were blinded	L	Participant, care provider, outcomes assessor	L
	Interim analysis;	L / H	Interim analysis; Non-random selection of study population for the solicited AEs (depended on ability of center to report)	L/H
	Interim analysis Adverse event not reported; pending verification	U	Interim analysis	U

Appendix Table 3. Summary of findings table on efficacy of BNT162b2 vs placebo

Efficacy Outcome (at >7 days after dose 2)	Quality Assessment					Summary of Findings			Certainty of Evidence
	Risk of Bias	Inconsistency	Indirectness	Imprecision	Overall Assessment	Vaccine n/N (%)	Control n/N (%)	Vaccine Efficacy % (95% CI)	
1. Symptomatic COVID-19 infection	Some concerns (interim analysis) (incomplete ff-up)	Not assessed	Not serious	Not serious	Some concerns	8/17411 (<0.1)	162/17511 (0.9)	95.0 (90.3, 97.6)	++ Moderate
2. Severe COVID-19 infection	Some concerns (interim analysis) (incomplete ff-up)	Not assessed	Not serious	Serious (wide CI)	Serious	1/21314 (<0.1)	4/21259 (<0.1)	75.0 (-152.6, 99.5)	++ Low
3. COVID-19 infection, after 1st dose, before 2nd dose	Some concerns (interim analysis) (incomplete ff-up)	Not assessed	Not serious	Serious (crosses threshold)	Some concerns	39/21314 (0.2)	82/21258 (0.4)	52.4 (29.5, 68.4)	++ Low
Subgroups									
1. Symptomatic COVID-19 infection, older adults (≥65 yo)	Some concerns (interim analysis) (incomplete ff-up)	Not assessed	Not serious	Not serious	Some concerns	1/3848 (<0.1)	19/3880 (0.5%)	94.7 (66.7, 99.9)	+++ Moderate
2. Symptomatic COVID-19 infection, older adults (≥75 yo)	Some concerns (interim analysis) (incomplete ff-up)	Not assessed	Not serious	Serious (wide CI)	Serious	0/774 (0)	5/785 (0.6)	100 (-13.1, 100.0)	++ Low
3. Symptomatic COVID-19 infection, at risk	Some concerns (interim analysis) (incomplete ff-up)	Not assessed	Not serious	Not serious	Serious	4/ 8030 (<0.1)	86/8029 (1.1)	95.3 (87.7, 98.8)	+++ Moderate
4. Symptomatic COVID-19 infection, Asian	Some concerns (interim analysis) (incomplete ff-up)	Not assessed	Not serious	Serious (wide CI)	Serious	1/176 (0.1)	4/796 (0.5)	74.6 (-156.6, 99.5)	++ Low

Appendix Table 4. Summary of findings table on efficacy of mRNA-1273 vs placebo

Efficacy Outcome (at >14 days after dose 2)	Quality Assessment					Summary of Findings			Certainty of Evidence
	Risk of Bias	Inconsistency	Indirectness	Imprecision	Overall Assessment	Vaccine n/N (%)	Control n/N (%)	Vaccine Efficacy % (95% CI)	
1. Symptomatic COVID-19 infection	Some concerns (interim analysis) (incomplete ff-up)	Not assessed	Not serious	Not serious	Some concerns	12/14550 (<0.1)	185/14413 (1.3)	93.6 (88.5, 96.4)	+++ Moderate
2. Severe COVID-19 infection	Some concerns (interim analysis) (incomplete ff-up)	Not assessed	Not serious	Serious (wide CI)	Serious	0/13934 (0)	30/13883 (0.2)	100 (NE, 100)	++ Low
3. COVID-19 infection, after 1st dose, before 2nd dose	Some concerns (interim analysis) (incomplete ff-up)	Not assessed	Not serious	Not serious	Some concerns	14/15180 (0.1)	46/15170 (0.3)	69.5 (43.5, 92.7)	+++ Moderate
4. Death due to COVID-19	Some concerns (interim analysis) (incomplete ff-up)	Not assessed	Not assessed	Serious (wide CI)	Not assessed	0/13143 (0)	1/14073 (<0.1)	100 (NE, 100)	++ Low
Subgroups									
1. Symptomatic COVID-19 infection, older adults (≥65yo)	Some concerns (interim analysis) (incomplete ff-up)	Not assessed	Not serious	Not serious	Some concerns	4/3583 (0.1)	29/3552 (0.8)	86.4 (61.4, 95.2)	+++ Moderate
2. Symptomatic COVID-19 infection, older adults (≥75yo)	Some concerns (interim analysis) (incomplete ff-up)	Not assessed	Not serious	Serious (wide CI)	Not assessed	0/623 (0)	3/676 (0.4)	100 (NE, 100)	++ Low
3. Symptomatic COVID-19 infection, at risk	Some concerns (interim analysis) (incomplete ff-up)	Not assessed	Not serious	Not serious	Some concerns	4/3206 (0.1)	43/3167 (1.4)	90.9 (74.7, 96.7)	+++ Moderate

Appendix Table 5. Summary of findings table on efficacy of ChAdOx1 vs control (MenACWY / saline)

Efficacy Outcome (at >14 days after dose 2)	Quality Assessment					Summary of Findings			Certainty of Evidence
	Risk of Bias	Inconsis-tency	Indirect-ness	Impreci-sion	Overall Assess-ment	Vaccine n/N (%)	Control n/N (%)	Vaccine Efficacy % (95% CI)	
1. Symptomatic COVID-19 infection	Some concerns (interim analysis) (incomplete ff-up)	Not assessed	Not serious	Not serious	Some concerns	84/8597 (1.0)	248/8581 (2.9)	66.7 (57.4, 74.0)	+++ Moderate
2. Severe COVID-19 infection	Some concerns (interim analysis) (incomplete ff-up)	Not assessed	Not serious	Serious (wide CI)	Serious	0/12021 (0)	1/11724 (<0.1)	100	++ Low
3. COVID-19 infection, after 1st dose (at >21 days)	Some concerns (interim analysis) (incomplete ff-up)	Not assessed	Not serious	Not serious	Some concerns	12/7998 (0.15)	44/7982 (0.55)	73.0 (48.8, 85.8)	+++ Moderate
4. Asymptomatic COVID-19 infection	Some concerns (interim analysis) (incomplete ff-up)	Not assessed	Not assessed	Serious (wide CI)	Serious	57/4071 (1.4)	73/4139 (1.8)	22.2 (-9.1, 45.0)	++ Low
5. Hospitalization	Some concerns (interim analysis) (incomplete ff-up)	Not assessed	Not serious	Serious (wide CI)	Serious	0/11794 (0)	9/11776 (<0.1)	100	++ Low
Subgroups									
1. Symptomatic COVID-19 infection, LD/SD	Some concerns (interim analysis) (incomplete ff-up)	Not assessed	Not serious	Not serious	Some concerns	10/1396 (0.2)	51/1402 (3.6)	80.7 (62.1, 90.2)	+++ Moderate
2. Symptomatic COVID-19 infection, SD/SD, ≥ 12weeks interval	Some concerns (interim analysis) (incomplete ff-up)	Not assessed	Not serious	Not serious	Some concerns	8/1293 (0.6)	45/1356 (3.3)	81.3 (60.3, 91.2)	+++ Moderate
3. Symptomatic COVID-19 infection, B.1.1.7 variant	Serious (interim analysis) (missing data) (incomplete ff-up)	Not assessed	Not serious	Not serious	Serious	7/4236	27/4270	74.6 (41.6, 88.9)	++ Low
4. Symptomatic COVID-19 infection, LD/SD	Some concerns (interim analysis) (incomplete ff-up)	Not assessed	Not serious	Not serious	Some concerns	10/1396 (0.2)	51/1402 (3.6)	80.7 (62.1, 90.2)	+++ Moderate
5. Symptomatic COVID-19 infection, SD/SD, ≥ 12weeks interval	Some concerns (interim analysis) (incomplete ff-up)	Not assessed	Not serious	Not serious	Some concerns	8/1293 (0.6)	45/1356 (3.3)	81.3 (60.3, 91.2)	+++ Moderate
6. Symptomatic COVID-19 infection, B.1.1.7 variant	Serious (interim analysis) (missing data) (incomplete ff-up)	Not assessed	Not serious	Not serious	Serious	7/4236	27/4270	74.6 (41.6, 88.9)	++ Low

Appendix Table 6. Summary of findings table on efficacy of Gam-COVID-Vac vs placebo (vaccine buffer)

Efficacy Outcome (at >7 days after dose 2)	Quality Assessment					Summary of Findings			Certainty of Evidence
	Risk of Bias	Inconsis-tency	Indirect-ness	Impreci-sion	Overall Assess-ment	Vaccine n/N (%)	Control n/N (%)	Vaccine Efficacy % (95% CI)	
1. Symptomatic COVID-19 infection	Some concerns (interim analysis) (incomplete ff-up)	Not assessed	Not serious	Not serious	Some concerns	13/14094 (0.1)	47/4601 (1.0)	91.1 (83.8, 95.1)	+++ Moderate
2. Moderate & Severe COVID-19 infection (21 d after dose 1)	Some concerns (interim analysis) (incomplete ff-up)	Not assessed	Not serious	Serious (wide CI)	Serious	0/14964 (0)	20/4902 (0.4)	100 (94.4, 100.0)	++ Low
3. COVID-19 infection, after 1st dose (at >21 days)	Some concerns (interim analysis) (incomplete ff-up)	Not assessed	Not serious	Not serious	Some concerns	79/16427 (0.5)	96/5435 (1.8)	73.1 (63.7, 80.1)	+++ Moderate

Appendix Table 7. Summary of findings table on efficacy of Ad26.CoV.S vs placebo

Efficacy Outcome >14 days after	Quality Assessment					Summary of Findings			Certainty of Evidence
	Risk of Bias	Inconsis-tency	Indirect-ness	Impreci-sion	Overall Assess-ment	Vaccine n/N (%)	Control n/N (%)	Vaccine Efficacy % (95% CI)	
1. Symptomatic COVID-19 infection (used values for FDA harmonized cases)	Some concerns (interim analysis) (incomplete ff-up)	Not assessed	Not serious	Not serious	Some concerns	114/19514 (0.6)	345/19544 (1.8)	67.2 (59.3, 73.7)	++ Moderate
2a. Moderate & Severe COVID-19 infection (centrally confirmed)	Some concerns (interim analysis) (incomplete ff-up)	Not assessed	Not serious	Not serious	Some concerns	116/19514 (0.6)	348/19544 (1.8)	66.9 (59.0, 73.5)	+++ Moderate
2b. Severe COVID-19 infection (including non-centrally confirmed)	Some concerns (interim analysis) (incomplete ff-up)	Not assessed	Not serious	Not serious	Some concerns	19/19514 (<0.1)	80/19544 (0.4)	76.3 (57.9, 87.5)	+++ Moderate
3. Asymptomatic COVID-19 infection (from Day 1 to 29)	Some concerns (interim analysis) (incomplete ff-up)	Not assessed	Not serious	Serious	Serious	87/19739 (0.4)	109/19809 (0.6)	20.0 (-7.0, 40.4)	++ Low
4. Hospitalization (including non-centrally confirmed)	Some concerns (interim analysis) (incomplete ff-up)	Not assessed	Not serious	Not serious	Some concerns	2/19514 (<0.1)	29/19544 (0.1)	91.3 (72.7, 99.2)	+++ Moderate
5. Death due to COVID-19	Some concerns (interim analysis) (incomplete ff-up)	Not assessed	Not serious	Serious	Serious	0/19514 (0)	7/19544 (<0.1)	100	++ Low
Subgroups									
1. Moderate-severe COVID-19 infection, older adults (≥ 60yo)	Some concerns (interim analysis) (incomplete ff-up)	Not assessed	Not serious	Not serious	Some concerns	16/3970 (0.4)	68/3992 (1.7)	76.5 (59.1, 87.3)	+++ Moderate
2. Moderate-severe COVID-19 infection, at risk	Some concerns (interim analysis) (incomplete ff-up)	Not assessed	Not serious	Not serious	Some concerns	70/7777 (0.1)	194/7798 (2.5)	64.2 (52.7, 73.1)	+++ Moderate
3. Symptomatic COVID-19 infection, Asian	Some concerns (interim analysis) (incomplete ff-up)	Not assessed	Not serious	Serious	Serious	6/714 (0.8)	12/649 (1.8)	54.4 (-31.1, 86.0)	++ Low
4. Moderate-severe COVID-19 infection, B.1.351 variant	Serious (interim analysis) (missing data) (incomplete ff-up)	Not assessed	Not serious	Not serious	Serious	43/2473 (1.7)	90/2496 (3.6)	52.0 (30.3, 67.4)	++ Low
5. Severe COVID-19 infection, B.1.351 variant	Serious (interim analysis) (missing data) (incomplete ff-up)	Not assessed	Not serious	Not serious	Serious	8/2473 (0.3)	30/2496 (1.2)	73.1 (40.0, 89.4)	++ Low
6. Moderate-severe COVID-19 infection, P1 lineage	Serious (interim analysis) (missing data) (incomplete ff-up)	Not assessed	Not serious	Not serious	Serious	39/3370 (1.2)	114/3355 (3.4)	66.2 (51.0, 77.1)	++ Low
7. Severe COVID-19 infection, P2 lineage	Serious (interim analysis) (missing data) (incomplete ff-up)	Not assessed	Not serious	Serious (wide CI, breaches threshold)	Serious	2/3370 (<0.1)	11/3355 (0.3)	81.9 (17.0, 98.1)	+ Very Low

Appendix Table 8. Summary of findings table on safety of BNT162b2 vs placebo

Safety Outcome	Quality Assessment					Summary of Findings			Certainty of Evidence
	Risk of Bias	Inconsis-tency	Indirect-ness	Impreci-sion	Overall Assess-ment	Vaccine n/N (%)	Control n/N (%)	Relative Risk (95% CI)	
1. Symptomatic COVID-19 infection (used values for FDA harmonized cases)	Some concerns (interim analysis) (incomplete ff-up)	Not assessed	Not serious	Not serious	Some concerns	5770/2162 (26.7)	2638/21631 (12.2)	2.19 (2.10, 2.28)	++ Moderate
2a. Moderate & Severe COVID-19 infection (centrally confirmed)	Some concerns (interim analysis) (incomplete ff-up)	Not assessed	Not serious	Not serious	Some concerns	240/21621 (1.1)	139/21631 (0.6)	1.73 (1.40, 2.13)	+++ Moderate
2b. Severe COVID-19 infection (including non-centrally confirmed)	Some concerns (interim analysis) (incomplete ff-up)	Not assessed	Not serious	Serious (wide CI)	Serious	126/21621 (0.6)	111/21631 (0.5)	1.14 (0.88, 1.46)	++ Low
3. Asymptomatic COVID-19 infection (from Day 1 to 29)	Some concerns (interim analysis) (incomplete ff-up)	Not assessed	Not serious	Serious (wide CI)	Serious	4/21621 (<0.1)	0/21631 (0)	9.00 (0.48, 67.15)	++ Low
4. Hospitalization (including non-centrally confirmed)	Some concerns (interim analysis) (incomplete ff-up)	Not assessed	Not serious	Serious (wide CI)	Serious	37/21621 (0.2)	30/21631 (0.1)	1.23 (0.76, 2.00)	++ Low
5. Death due to COVID-19	Some concerns (interim analysis) (incomplete ff-up)	Not assessed	Not serious	Serious (wide CI)	Serious	2/21621 (<0.1)	4/21631 (<0.1)	0.5 (0.09, 2.73)	++ Low

Appendix Table 9. Summary of findings table on safety of mRNA-1273 vs placebo

Safety Outcome	Quality Assessment					Summary of Findings			Certainty of Evidence
	Risk of Bias	Inconsis-tency	Indirect-ness	Impreci-sion	Overall Assess-ment	Vaccine n/N (%)	Control n/N (%)	Relative Risk (95% CI)	
1. Adverse reaction	Not serious	Not assessed	Not serious	Not serious	Not serious	14338/15176 (94.5)	9027/15162 (59.5)	1.59 (1.57, 1.61)	++++ High
2. Local adverse reaction	Not serious	Not assessed	Not serious	Not serious	Not serious	13962/15176 (92.0)	4381/15162 (28.0)	3.18 (3.10, 3.27)	++++ High
3. Systemic adverse reaction	Not serious	Not assessed	Not serious	Not serious	Not serious	12553/15176 (82.7)	8032/15162 (53.0)	1.56 (1.54, 1.59)	++++ High
4. Adverse event	Some concerns (interim analysis) (incomplete ff-up)	Not assessed	Not serious	Not serious	Some concerns	3631/15185 (23.9)	3277/15166 (19.4)	1.17 (1.12, 1.22)	+++ Moderate
5. Severe adverse event	Some concerns (interim analysis) (incomplete ff-up)	Not assessed	Not serious	Serious (wide CI)	Serious	234/15185 (1.5)	202/15166 (1.3)	1.16 (0.96, 1.39)	++ Low
6. Serious adverse event	Some concerns (interim analysis) (incomplete ff-up)	Not assessed	Not serious	Serious (wide CI)	Serious	93/15185 (0.5)	89/15166 (0.6)	1.04 (0.78, 1.39)	++ Low
7. Related serious adverse event	Some concerns (interim analysis) (incomplete ff-up)	Not assessed	Not serious	Serious (wide CI)	Serious	7 /15185 (<0.1)	5/15166 (<0.1)	1.40 (0.44, 4.40)	++ Low
8. Withdrawals due to adverse event	Some concerns (interim analysis) (incomplete ff-up)	Not assessed	Not serious	Not serious	Some concerns	50/15185 (0.3)	80/15166 (0.5)	0.62 (0.44, 0.89)	+++ Moderate
9. Death	Some concerns (interim analysis) (incomplete ff-up)	Not assessed	Not serious	Serious (wide CI)	Serious	6/15185 (<0.1)	7/15165 (<0.1)	0.86 (0.29, 2.55)	++ Low

Appendix Table 10. Summary of findings table on safety of ChAdOx1 vs control (MenACWY / saline)

Safety Outcome	Quality Assessment					Summary of Findings			Certainty of Evidence
	Risk of Bias	Inconsistency	Indirectness	Imprecision	Overall Assessment	Vaccine n/N (%)	Control n/N (%)	Relative Risk (95% CI)	
1. Adverse reaction	Not serious	Not assessed	Not serious	Not serious	Not serious	2277/2648 (86.0)	1791/2497 (71.7)	1.20 (1.16, 1.23)	++++ High
2. Local adverse reaction	Not serious	Not assessed	Not serious	Not serious	Not serious	1979/2648 (74.7)	1258/2497 (50.4)	1.48 (1.42, 1.55)	++++ High
3. Systemic adverse reaction	Not serious	Not assessed	Not serious	Not serious	Not serious	1932/2648 (73.0)	1488/2497 (59.6)	1.22 (1.18, 1.27)	++++ High
4. Adverse event	Some concerns (interim analysis) (incomplete ff-up)	Not assessed	Not serious	Not serious	Some concerns	2207/5807 (38)	1632/5829 (28)	1.36 (1.29, 1.43)	+++ Moderate
5. Serious adverse event	Some concerns (interim analysis) (incomplete ff-up)	Not assessed	Not serious	Serious (wide CI)	Serious	79/12021 (0.7)	89/11724 (0.8)	0.87 (0.64, 1.17)	++ Low
6. Related serious adverse event	Some concerns (interim analysis) (incomplete ff-up)	Not assessed	Not assessed	Serious (wide CI)	Serious	3/12021 (<0.1)	2/11724 (<0.1)	1.46 (0.24, 8.75)	++ Low
7. Death	Some concerns (interim analysis) (incomplete ff-up)	Not assessed	Not serious	Serious (wide CI)	Serious	2/12021 (<0.1)	4/11724 (<0.1)	0.49 (0.09, 2.66)	++ Low

Appendix Table 11. Summary of findings table on safety of Gam-COVID-Vac vs placebo

Safety Outcome	Quality Assessment					Summary of Findings			Certainty of Evidence
	Risk of Bias	Inconsistency	Indirectness	Imprecision	Overall Assessment	Vaccine n/N (%)	Control n/N (%)	Relative Risk (95% CI)	
1. Serious adverse event	Some concerns (interim analysis) (incomplete ff-up)	Not assessed	Not serious	Serious (wide CI)	Serious	45/16427 (0.3)	23/5435 (0.4)	0.65 (0.39, 1.07)	++ Low
2. Death	Some concerns (interim analysis) (incomplete ff-up)	Not assessed	Not serious	Serious (wide CI)	Serious	3/16427 (<0.1)	1/5435 (<0.1)	0.99 (0.10, 9.54)	++ Low

Appendix Table 12. Summary of findings table on safety of Ad26.CoV.S vs placebo

Safety Outcome	Quality Assessment					Summary of Findings			Certainty of Evidence
	Risk of Bias	Inconsistency	Indirectness	Imprecision	Overall Assessment	Vaccine n/N (%)	Control n/N (%)	Relative Risk (95% CI)	
1. Local adverse reaction	Not serious	Not assessed	Not serious	Not serious	Not serious	1685/3356 (50.2)	657/3380 (19.4)	2.58 (2.39, 2.79)	++++ High
2. Systemic adverse reaction	Not serious	Not assessed	Not serious	Not serious	Not serious	1850/3356 (55.1)	1185/3380 (35.1)	1.57 (1.49, 1.66)	++++ High
3. Adverse event	Some concerns (interim analysis) (incomplete ff-up)	Not assessed	Not serious	Serious (wide CI)	Serious	440/3356 (13.1)	407/3380 (12.0)	1.09 (0.96, 1.24)	+++ Moderate
4. Serious adverse event	Some concerns (interim analysis) (incomplete ff-up)	Not assessed	Not serious	Not serious	Some concerns	83/21895 (0.4)	96/21888 (0.4)	0.86 (0.64, 1.16)	+++ Moderate
5. Related serious adverse event	Some concerns (interim analysis) (incomplete ff-up)	Not assessed	Not serious	Serious	Serious	7/21895 (<0.1)	2/21888 (<0.1)	3.5 (0.73, 16.84)	++ Low
6. Withdrawals due to adverse event	Some concerns (interim analysis) (incomplete ff-up)	Not assessed	Not serious	Serious	Serious	0/21895 (0)	0/21888 (0)	NE	NA
7. Death	Some concerns (interim analysis) (incomplete ff-up)	Not assessed	Not serious	Not serious	Some concerns	5/21895 (<0.1)	20/21888 (<0.1)	0.25 (0.09, 0.67)	+++ Moderate