Are vaccines effective and safe in the prevention of COVID-19 infections? : A Systematic Review

Version May 28, 2021

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What's new in this version (compared to the April 10 version)

1. Latest search of the literature: May 13 for trial data and regulatory site reports and April 17 for real world evidence.
2. Additional trial data on the results on children (12-15 y/o) for BNT162b2 from the USFDA report.
3. Additional trial data from the publication of the Ad26.COV2.S study with the addition of severe adverse event data in the Summary of Findings/GRADE tables and details in the thromboembolic events, which occurred during the trial.
4. Additional efficacy and safety data for CoronaVac from latest preprints and additional regulatory reports with corresponding update of the Summary of Findings / GRADE tables
5. Updated and expanded real world evidence on the efficacy and safety of BNT162b2, mRNA-1273, ChAdOx1, Ad26.COV2.S and CoronaVac, with additional detailed tables of information in the Appendix.
6. Expanded report on the vaccine-induced thrombotic thrombocytopenic cases associated with ChAdOx1 and Ad26.COV2.S

RECOMMENDATIONS

We recommend the use of the following vaccines to prevent symptomatic SARS-CoV-2 infection in **adults**: *(Moderate quality of evidence; Strong recommendation)*

a. **BNT162b2 (Pfizer/BioNTech)** (given as 0.3ml (30ug) intramuscular injections, in 2 doses, 21 days apart)
b. **mRNA-1273 (Moderna)** (given as 0.5ml (100ug) intramuscular injections, in 2 doses, 28 days apart)
c. **ChAdOx1 (AstraZeneca)** (given as 0.5 ml (5×10^6 vp) intramuscular injections, in 2 doses, **at least 12 weeks** apart)
d. **Gam-COVID-Vac (Gamaleya)** (given as rAd-26 0.5ml intramuscular injection, then rAd-5S 0.5 ml intramuscular injection 21 days after)
e. **Ad26.COV2.S (Janssen/Johnson&Johnson) (**given as 0.5ml single dose intramuscular injection)

We recommend the use of **CoronaVac (Sinovac)** (given as 0.5ml (600SU) intramuscular injection, in 2 doses, at 28 days apart) to prevent symptomatic SARS-CoV-2 infection among **adults:** *(Low quality of evidence; Strong recommendation)*

Consensus Issues

It was noted that ChAdOx1 was originally designed for a 21-day dosing interval, but because of some problems in logistics during the trial, different dosing intervals were implemented and the vaccine efficacy per dosing interval was recorded. The above recommendation, i.e., at least 12 weeks, reflects the dosing interval with the highest observed vaccine efficacy of 81.3% (95% CI 60.3, 91.2).

Regarding Coronavac, a strong recommendation was made despite the low quality of evidence because the panel considered its availability and the high vaccine efficacy in preventing severe COVID-19. Although a 14-day dosing interval was used in the trial, the recommendation of a 28-day dosing interval was based on the submission of the manufacturer to the Hongkong Food and Health Bureau. A longer interval showed higher vaccine efficacy rates based on the immunogenicity data (seroconversion on 14-days versus 28-days) and the result of the subgroup analysis (<21 days versus >21 days). It was likewise explained that in general, increasing the interval between the doses of vaccines provides better immunogenicity by giving ample time for the population of lymphocytes in the lymph nodes to be replenished, thus resulting to a more robust immune response.

We recommend the use of BNT162b2 (Pfizer/BioNTech), mRNA-1273 (Moderna), ChAdOx1 (Astrazeneca), Gam-COVID-Vac (Gamaleya) and Ad26.COV2.S (Janssen/ Johnson&Johnson) vaccines to prevent symptomatic SARS-CoV-2 infection in **older adults (>64 year old)**. *(Low quality of evidence; Strong recommendation)*

There is insufficient evidence to recommend the use of CoronaVac to prevent symptomatic SARS-CoV-2 Infection in **older adults (>60-year-old)** *(Very low quality of evidence)*

Consensus Issues

The strength of recommendation was changed from conditional to strong because although the quality of evidence is low, the benefits of vaccinating the elderly who are at risk of severe disease outweigh the harm as reported in the evidence presented, which showed lower adverse event rates in the said population compared to the younger group.

The panel did not make a recommendation for or against the use of CoronaVac in the elderly due to the very low quality of evidence wherein the interim analysis showed imprecision because of the very wide confidence interval for symptomatic COVID-19 and there is no disaggregation of data into mild, moderate or severe COVID-19 in older adults ≥60 y/o. There is also no data on harm.

We recommend the use of BNT162b2 (Pfizer/BioNTech), mRNA-1273 (Moderna), ChAdOx1 (Astrazeneca), Gam-COVID-Vac (Gamaleya) and Ad26.COV2.S (Janssen/ Johnson&Johnson) vaccines in **pregnant and lactating women** after consultation with a physician. *(Very low quality of evidence; Conditional recommendation)*

Consensus Issues

The quality of evidence was changed from low to very low given that there was no evidence on either efficacy or safety in pregnant and lactating women because they were excluded from the trials. Regarding the risk of COVID-19 infection in the fetus, there is no evidence to date of vertical transmission, but there is increased incidence of premature birth and other complications arising from the pregnancy itself. There is also lack of evidence on transmitting COVID-19 infection through breastmilk. The risk of horizontal transmission in the household versus from the mother is the same provided that infection prevention and control (IPC) measures are observed. It was emphasized that the discussion with a physician should involve informing the women of the benefits and risks of the vaccination, specific to its timing of administration during the pregnancy. Physicians should be educated on these risks and benefits for the delivery of proper advice.

There was a discussion on the registry involving Pfizer and Moderna vaccines, where pregnant women who get vaccinated can volunteer to join and report their outcomes. This real-world analysis showed that there was no difference in the incidence of early trimester complications. Moreover, it was mentioned that the WHO report already included eight (8) pregnancies after the J&J vaccination, which noted the following results: one (1) spontaneous abortion, one (1) elective abortion, and the rest have no reported congenital anomalies.

We recommend the use of BNT162b2 (Pfizer/BioNTech), mRNA-1273 (Moderna), ChAdOx1 (Astrazeneca), Gam-COVID-Vac (Gamaleya) and Ad26.COV2.S (Janssen/ Johnson&Johnson) vaccines to prevent SARS-CoV-2 infection in **adults who have stable medical comorbidities and are at risk for severe infection**. *(Moderate quality of evidence; Strong recommendation)*

We suggest the use of CoronaVac to prevent SARS-CoV-2 infection in **adults who have stable medical comorbidities and are at risk for severe infection**. *(Very low quality of evidence; Conditional recommendation)*

Consensus Issues

A conditional recommendation was made for Coronavac because the panel considered the absence of any estimate of vaccine efficacy specific for this subgroup. Although the Brazilian trial included healthcare workers with stable medical comorbidities, the proportion of this subgroup as well as the vaccine efficacy for this specific population are unknown. As such, the panel considered the estimates of vaccine efficacy for the entire trial population as indirect evidence to support its use on those with comorbidities.

We recommend the use of BNT162b2 (Pfizer/BioNTech), mRNA-1273 (Moderna), ChAdOx1 (Astrazeneca), Gam-COVID-Vac (Gamaleya) and Ad26.COV2.S (Janssen/ Johnson&Johnson) vaccines to prevent SARS-CoV-2 infections in **immunocompromised patients** (i.e., diagnosed with HIV, hepatitis B and C, those with cancer undergoing chemotherapy, transplant patients receiving immune-suppression) after medical clearance from a physician. *(Low quality of evidence; Strong recommendation)*

Consensus Issues

Despite the low quality of evidence, a strong recommendation was made because the benefits of vaccination outweigh any potential harm. While there are no specific subgroup results for the immunocompromised patients and the expected vaccine efficacy would be lower, the vaccine will still give them protection against COVID-19. The panel also emphasized that a medical clearance from any physician should be sufficient to facilitate the vaccination.

We recommend the use of BNT162b2 (Pfizer/BNT162b2) to prevent symptomatic SARS-CoV-2 infection in **children at least 12 years old**. *(Moderate quality of evidence; Strong recommendation)*

There is no evidence on the use of mRNA-1273 (Moderna), ChAdOx1 (AstraZeneca), Gam-COVID-Vac (Gamaleya) and Ad26.COV2.S (Janssen/Johnson&Johnson), and CoronaVac (Sinovac) in children (<18 years old) to prevent SARS-CoV-2 infection.

Consensus Issues

The updated recommendation regarding the use of the vaccines in children was based mainly on the preliminary results in the BNT162b2 clinical trial data from its adolescent population, demonstrating clear benefit over harm.

ChAdOx1 also included children in the trial protocol, however, the results are still pending. Based on existing protocols, children are excluded in the clinical trials of mRNA-1273, GamCOVID-Vac, Ad26.COV2.S and CoronaVac. There is no statement of planned recruitment for the younger population.

We recommend against the use of these vaccines in individuals who have known allergies to the contents/excipients of the vaccine, such as polysorbate (ChAdOx1, Gam-COVID-Vac and Ad26.COV2.S) and polyethylene glycol or PEG200 DMG (BNT162b2 and mRNA-1273)**.** *(Moderate to high quality of evidence; Strong recommendation)*

Consensus Issues

It was clarified that the recommendation was specific for polysorbate and PEG because these two (2) excipients are notorious for hypersensitivity reactions based on different regulatory authorities. CoronoVac does not contain any of these, but the Philippine Society of Allergy, Asthma and Immunology (PSAAI) has been receiving reports on allergic reactions to CoronaVac and this is currently being investigated.

Other Consensus Issues

The panel agreed to place in a separate document (i.e., guidance or standard operating procedure) the recommendations on (1) advising the recipients regarding adverse reaction and adverse events as well as the (2) implementation of a pharmacovigilance program and regular evidence review upon vaccine use.

There was a concern raised on the policy of other countries that they will only consider a person "vaccinated" if s/he is immunized with a vaccine that has Emergency Use Authorization (EUA) in their country. This will affect the outbound Overseas Filipino Workers and may drive brand preference.

It was emphasized that while we are certain that COVID-19 vaccines reduce severe disease, hospitalization and death, there are still unanswered questions on the duration of protection. Wearing of masks is still necessary, since there is information on protection but not yet on the prevention of transmission.

Key Findings

As of May 13, 2021 preliminary Phase 3 trial data on the safety and efficacy of six COVID-19 vaccines have been made publicly available. The BNT162b2 (Pfizer/BioNTech), the mRNA-1273 (Moderna), the ChAdOx1 (AstraZeneca), the Gam-COVID-Vac (Gamaleya), and the Ad26.Cov2.S (Janssen/Johnson&Johnson) vaccines demonstrated satisfactory vaccine efficacy against symptomatic COVID-19 infection among adults in the short term with moderate certainty. Limited available information provides low certainty evidence that the CoronaVac (Sinovac) vaccine also provides satisfactory protection against symptomatic COVID-19 infection among adults. Updated trial report showed that BNT162b2 (Pfizer/BioNTech) is highly efficacious and safe against symptomatic COVID-19 infection for children aged 12 to 15 years old. Data on the efficacy against severe COVID-19 infection and asymptomatic COVID-19 infection are still inconclusive, except for Ad26.CoV2.S, which demonstrated, with moderate certainty, good efficacy in preventing moderate and/or severe COVID-19 infection and acceptable protection against asymptomatic COVID-19 infection 28 days after vaccination. Efficacy data on preventing death from COVID-19 infection are still inconclusive due to the low number of events recorded in these preliminary reports. Very limited clinical trial data are available to inform vaccine efficacy against the different variants of SARS-CoV-2.

Administration of these vaccines was associated with higher proportions of adverse reactions compared with the control, although serious adverse event rates were comparable. These adverse events, mostly from reactions to the vaccines, were mild to moderate and of short duration. Long term efficacy and safety data are still lacking.

Real world evidence supports clinical trial findings on the efficacy of BNT162b2, mRNA-1273, ChAdOx1, Gam-COVID-Vac and CoronaVac. As of April 17, no RWE data on effectiveness is available for Ad26.Cov2.S A rare phenomenon, the vaccine-induced immune thrombotic

thrombocytopenia has been found to have a possible link with the use of ChAdOx1 and Ad26.COV2.S. However, regulatory authorities have maintained a positive benefit-risk ratio for the continued use of these vaccines. No safety signals have been identified with the mRNA vaccines. Cases of anaphylaxis have been reported with the mRNA vaccines and with ChAdOx1 but they remain in very low numbers. Deaths after vaccination are also rare and often assessed as not related. Many case reports on various adverse events following COVID-19 vaccination have increasingly appeared in the literature.

Introduction

On March 11, 2020, the World Health Organization declared the SARS-CoV-2 as a global pandemic. While preventive measures such as physical distancing, universal wearing of masks, contact tracing, and strict isolation and quarantine control viral transmission, an effective and safe vaccine against SARS-CoV-2 will prove to be an invaluable asset in curbing the spread and reducing the associated morbidities and mortalities. Hence, in the attempt to contain 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, and inactivated and live-attenuated vaccines. Most COVID-19 candidate vaccines express the spike protein or parts of it to induce an immunogenic response.

This review investigates the available publicly available phase 3 clinical trial results of candidate COVID-19 vaccines as of May 13, 2021, and the real-world evidence of their safety and efficacy as of April 17, 2021.

Review 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,” “SARS-CoV-2 vaccines,” “primary studies” and using “RCT” and “reporting data” as additional filters. Press releases, systematic reviews, and additional information from systematic reviews were excluded.

With the emergency use authorization issued by regulatory agencies, the US-Food and Drug Authority (US-FDA), the European Medicines Agency (EMA), the United Kingdom Medicines and Healthcare 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 Strategic Advisory Group of Experts on Immunization (SAGE) meetings on vaccines. The date of the last search of these sites for this review was on May 13, 2021.

In the light of the emergency use authorization issued by the Philippine Food and Drug Authority for CoronaVac (Sinovac) without any publicly available trial data at that time, an extraordinary search of regulatory sites from other countries that have issued similar authorizations was made. Of these, the Food and Health Bureau site of the Government of the Hong Kong Special Administrative Region and the Indonesian National Drug Information of the Indonesian Food and Drug Authority website (Pusat Informasi Obat Nasional – Badan Pengawas Obat dan Makanan) were searched on April 2, 2021 and April 10, 2021, respectively.

Similarly, an extraordinary search for phase 3 clinical trial data was made for BBV152 (Covaxin) with the issuance of an emergency use authorization by the Philippine Food and Drug Authority. The regulatory site for Mexico was searched for trial data on May 18, 2021.

Selection and quality assessment of systematic reviews and included studies

The two investigators reviewed the identified trials for eligibility. Phase 2/3 or Phase 3 randomized placebo-controlled trials with populations, interventions, comparators and outcomes specified below were included in the review.

Population: humans, without age or sex limitations

Intervention: vaccines targeted for the prevention of COVID-19 infection

Comparator: placebo or active control

Outcomes:

Vaccine Efficacy: Reduction in the hazard ratio for the following outcomes, without and with vaccination:

- Incidence of COVID-19 disease of any severity
- Incidence of severe COVID-19 disease
- Incidence of hospitalization or mechanical ventilation among patients with COVID-19 disease
- Incidence of ICU admission
- Incidence of asymptomatic COVID-19 disease
- Deaths due to COVID-19

Efficacy assessment time points included were: within 7 days after full dose, after 7 days /14 days /28 days /1year / and 2 years of the full dose

For multi-dose vaccines, vaccine efficacy after the 1st dose was also determined

Vaccine efficacy for the different strains of SARS-CoV-2 infection was also sought. A separate living systematic review on the efficacy of the vaccines for the variants and mutations of concern, which includes both clinical outcomes and immunogenicity data, is also being undertaken.

Vaccine Safety:

- reactogenicity / adverse reactions
- adverse events
- serious adverse events
- related serious adverse events
- adverse events of special interest (per vaccine type)
- vaccine-associated enhanced disease – a condition that would occur when a vaccinated person subsequently infected with the virus develops a more severe disease than they would if they were not vaccinated

Methods: Phase 3 randomized clinical trials

Two reviewers independently assessed the methodological quality of these trials based on the Cochrane Risk of Bias tool version 1. [1]

Data extraction and analysis

For this review, the following study characteristics were extracted: population details such as inclusion and exclusion criteria, interventions (vaccine), comparators, outcomes (and their

respective definitions), data sources, study proponents, study sites and study sponsor. Study design peculiarities and status of the study implementation were also noted. Data on the vaccine used such as its type, active substance and excipients, as well as its storage and cold chain parameters, including the shipping and transport considerations, storage and shelf life, were collected.

Data was analyzed per vaccine type. When results were available for both per protocol and intention to treat (ITT) analysis, both were extracted but the value of the ITT analysis was used in the summary of findings in this review. When several efficacy rates were provided for different definitions, the value for the more generally applicable condition was used in the summary of findings in this review. (e.g. for centrally-confirmed versus non-centrally confirmed cases, the non-centrally confirmed cases counts were used in the Gam-COVID-Vac and Ad26.COV2.S trials wherein swabs were sent to a central laboratory for confirmatory testing). When efficacy rates at different time points were available, the value for the planned primary outcome was used in the summary of findings table. However, for Ad26.COV2.S, two evidence summary tables for efficacy were generated, one each for the two outcome assessment timepoints. Pooling of data across trials using the same vaccine type was planned. As only interim analysis results were available, with varying outcome assessment time points and definitions, no pooling was done for this review.

Subgroup analysis considered included the following: age (<65 years old vs ≥ 65 years, vs ≥75yo), pediatric vs adults, ethnicity with a focus among Asians, baseline seropositivity status or evidence of previous infection, risk of acquiring or exposure to COVID19 such as health care workers and frontliners, presence of comorbidities, and confirmed stable HIV disease. Efficacy against specific strains of COVID-19 infection was also determined.

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.

Search for Real World Evidence

Emergency use authorizations for the different COVID-19 vaccines allowed for the roll out of the vaccination programs in several countries around the world beginning December 2020. Since then, real world evidence on the effectiveness and safety of these vaccines has been accumulating, providing some form of validation of the clinical trial results.

A separate search was performed on the COVID-19 Living OVerview of Evidence (L·OVE) platform, using “vaccination”, “SARS-CoV-2 vaccines”, “primary studies” “non-RCT:” and “reporting data” as filters for the real-world evidence studies. This search was performed on April 17, 2021. Observational studies on populations at risk for COVID-19 infection reporting the outcomes of vaccinations in terms of incidences of COVID-19 infection and adverse event rates using any of the six vaccines compared with a non-vaccinated cohort were included in this review. All eligible studies and reports were summarized per vaccine used. Study characteristics presented included: study design, study site, population included, vaccination period, and outcomes reported.

A search of key regulatory sites was performed to review the safety reports on the vaccines. These sites include the US-CDC, the UKMHRA, the EMA(PRAC), and the PFDA. The latest search was done on April 12, 2021.

Results

Search Results (Clinical Trials)

Search of the COVID-19 Living OVerview of Evidence (L·OVE) platform performed on May 13, 2021 yielded 86 records. After screening for eligibility based on titles and abstracts and eliminating duplicates (of the full publication of preprints) eleven publications and three regulatory reports were identified to be providing phase 2/3 trial results on the efficacy and safety of six different COVID-19 vaccines. Two papers presented the preliminary results of trials that used mRNA vaccines, BNT162b2 [3] and mRNA-1273. [4] Three reports were on the pooled interim results of four trials that used a non-replicating viral vector vaccine, ChAdOx1. [5] [6] [7] One was an exploratory analysis of a subgroup of the previously reported multi-country trial of the same vaccine, [8] while another was a trial involving the same vaccine in a smaller population. [9] One report was on the preliminary results of a trial that used a combination viral vector vaccine, Gam-COVID-Vac. [10] One publication was on the preliminary results of a trial that used a vector vaccine, Ad26.COV2.S. [11] Two were preprints presenting the results of the Phase 2/3 trial of the inactivated virus, CoronaVac, which provided access to trial data not available in the previous versions of this review. [12] [13] Three records were of the USFDA regulatory review reports of the BNT162b2, [14] the mRNA-1273 [15] and the Ad26.COV2.S. [16]

A search of the regulatory authority websites on May 13, 2021 yielded reports providing additional data on these vaccines. While several reports from each regulatory site were available for each vaccine, only those that provided data used in this report are cited. The USFDA [14] [17] [18], EMA [19] [20], UKMHRA [21] [22] and the WHO SAGE [23] [24] authorization assessment documents provided additional information for BNT162b2 vaccine. The USFDA [15] [25] the EMA [26] [27] and the WHO SAGE [28] [29] authorization assessment documents provided additional information for the mRNA-1273 vaccine. The UK-MHRA [30], the EMA [31] [32] and the WHO [33] [34] authorization assessment reports provided additional information for the ChAdOx1 vaccine. The USFDA [16] [35], the EMA [36] [37] and the WHO [38] [39] authorization documents provided information on the Ad26.CoV2.S trial results. Details of the study designs of the Ad26.COV2.S trial were taken from the protocol available from the manufacturer/sponsor's website. [40]

The search of the FHB-HKSAR website yielded two reports containing phase 3 clinical trial data for CoronaVac, the advisory panel report [41] and the product insert. [42] The available efficacy data were from one trial site only (Brazil). The Indonesian National Drug Information's fact sheet on the EUA for CoronaVac provided additional safety and efficacy data from the Indonesian and Turkish trial sites. [43] Details of the trial design were taken from the published protocol for its Brazilian study site. [44] The study design of the trial done in Chile was from trial registration at the Clinicaltrails.gov website. [45]

The search of the Mexican Comision Federal Para la Proteccion Contra Riesgos Sanitarios (Federal Commission for the Protection against Sanitary Risks) website only yielded an announcement of the emergency use authorization of Covaxin on April 6, 2021. No accompanying report containing trial data was available.

In the light of the publication of the results of the trial upon which the updated USFDA Factsheet containing data on the use of BNT162b2 on children aged 12-15 years old, the details were included despite the publication outside the date of the last search of this review. (46)

Included Studies (Clinical Trials): Characteristics and Quality Assessment

All trials identified were Phase 2/3 randomized controlled trials comparing a COVID-19 vaccine and placebo or an active control. One of the trials compared two dosing intervals. The vaccines studied were the BNT162b2 (Pfizer/BioNTech), the mRNA-1273 (Moderna), the ChAdOx1 (AstraZeneca), the Gam-COVID-Vac (Gamaleya), the Ad26.COV2.S (Janssen/ Johnson & Johnson) and the CoronaVac (Sinovac).

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. An updated report from the US FDA provided data on the expansion of the trial population with the addition of 2,260 randomized adolescents (aged 12 to 15 years old). The report provided the two-month follow up results of 1,308 of them, 660 having received the vaccine. [18]

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 2 months. A more recent interim report after 3 months 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. The methodological assessment for these trials was made as a composite, given the general similarity in the trial designs.

The trial on Gam-COVID-Vac included 21,977 participants with 16,501 receiving the vaccine (at 3:1 randomization). Results presented were after a mean follow up of 48 days.

The Ad26.COV2.S trial randomized 43,783 participants with 21,895 receiving the vaccine, with reported outcomes after a median of 2 months.

The CoronaVac Brazilian trial enrolled 12,396 healthcare workers with 6,202 receiving at least one dose of the vaccine. The reported outcomes were after a median follow up of 73 days. Its Chilean trial planned to recruit 2300 adults but the interim report included only 434 participants and only included safety and immunogenicity data. The Indonesian trial site included only 620 participants. The Turkish site only reported outcomes from 1,322 participants from a planned 13,000 trial population. Hence only the Brazilian trial data were included in this review. The methodological assessment was only for the Brazilian trial, based on the published clinical trial protocol.

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

Details of the characteristics of the included studies are in Appendix 1. Details of the methodological quality assessments are in Appendix 2.

Clinical Trial Results: Efficacy

Sufficient vaccine efficacy rates in the prevention of symptomatic COVID-19 infection were based on a threshold of at least a point estimate of 50% and at least a 30% lower border of the 95%CI as set by the WHO. [47] Available trial data for all six vaccines demonstrated sufficient efficacy rates at 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, 48 days after vaccination with Gam-COVID-Vac, and 73 days after CoronaVac vaccination (Brazilian trial). Vaccine efficacies for the prevention of the different severities of COVID-19 infection and for the different subgroups were variable across the different vaccines. Long-term efficacy data was not available for all six vaccines.

BNT162b2 (Pfizer/BioNTech)

BNT162b2 demonstrated a vaccine efficacy (VE) of 95% (95%CI 90.3, 97.6) for the prevention of symptomatic COVID-19 infection starting at 7 days after dose 2, 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). Similarly, a high protective efficacy for adolescents (aged 12-15year old) was shown (VE 100%, 95%CI 75.3, 100.0). 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 Dose 1, 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 two months post Dose 2, the BNT162b2 cumulative curve remained stable suggesting continued protection. Prevention of asymptomatic COVID-19 infection was not assessed. No data were reported on the impact of the vaccine on hospitalization, ICU admission or deaths associated with COVID-19 infection.

mRNA-1273 (Moderna)

mRNA-1273 showed a vaccine efficacy of 93.6% (95%CI 88.6, 96.5) starting at 14 days after dose 2, 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 cases occurred in the placebo group during the reported follow up period, showing high efficacy of mRNA-1273 in preventing severe COVID-19 infection, with all events occurring in the placebo group. mRNA-1273 showed an efficacy of 69.5% (95%CI 43.5, 92.7) after a single dose. Cumulative incidence curves revealed low rates after Dose 1 until Day 14 and subsequent divergence with more cases of infections occurring in the placebo group than the mRNA-1273 group. Prevention of asymptomatic COVID-19 infection was not assessed. No participant who received the vaccine was hospitalized (vs 2 in the placebo group), admitted to ICU (vs 1 in the placebo group) or died due to COVID-19 (vs 1 in the placebo group), giving a vaccine efficacy of 100% for these outcomes.

ChAdOx1 (AstraZeneca)

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 dose1, 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 nine hospitalizations occurring 14 days after the 2nd dose occurred in the control group.

In its follow up report with 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 x10^6 vp) first dose and a standard (5x10^6 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. [48] It showed good clinical efficacy of ChAdOx1 vaccine against symptomatic COVID disease with the B.1.1.7 variant (VE = 74.6%, 85%CI 41.6, 88.9) (Appendix 3d). It should be noted that 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 (Gamaleya)

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 second 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 (Janssen/Johnson&Johnson)

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 among older adults aged ≥60 years old and among 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 and preliminary data were presented in the USFDA report. However, as sequencing of all cases was still incomplete at the time of the report, the investigators deemed 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.

CoronaVac (Sinovac)

Based on the results from its Brazilian trial site result contained in the FHB-HKA report, CoronaVac demonstrated a vaccine efficacy of 50.65% (95%CI 35.94, 61.98) for the prevention of symptomatic COVID-19 infection after at least 2 weeks upon completion of two doses of vaccination with a 14-day interval in a study involving more than 12,000 health care professionals. Vaccine efficacy for moderate and severe cases was 100% (95% CI 56.37, 100) and for severe cases was 100% (95%CI 16.93, 100). One death was reported in the placebo group. Due to the very low number of elderly (≥ 60years old) participants in the trial (n=416), the available vaccine efficacy for this subgroup was at very low certainty (VE = 51.11% (95%CI -166.93, 91.04). The data cutoff cited in this report was December 16, 2020.

The vaccine efficacy reported for the Brazilian site by the Indonesian FDA, with a cut off date of January 9 2021, was 78% (58 cases in the vaccine group and 160 cases in the placebo group).

The Indonesian fact sheet reported the vaccine efficacies from the Indonesian trial site (VE= 65.3%, based on seven COVID cases in the vaccine group and 18 cases in the placebo group), and from the Turkish site (VE – 91.25%, based on three COVID cases from the vaccine group and 26 cases from the placebo group). No severe cases were reported in the Indonesian fact sheet for these two trials sites. It is not clear if recruitment has been completed or if the entire trial population has achieved the minimum follow up period in these trial sites.

The efficacy data included in the GRADE tables for this review included only the Brazilian trial data, based on the figures reported by the FHB-HKA.

Detailed efficacy data for all six vaccines are presented in Appendix 3.

Clinical Trial Results: Safety

Available trial data for the 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 these five vaccine groups were not significantly different from those with the control groups. Only reactogenicity and adverse event rates were available from the Brazilian trial of CoronaVac and no information on serious adverse events were reported. While the other CoronaVac trial sites reported some safety data, the number of participants considered was

significantly less than the planned trial population and thus were not included in this review. No long-term safety data are available for all six vaccines.

BNT162b2 (Pfizer/BioNTech)

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 case of a life-threatening reaction was recorded. 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 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 USFDA 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. [14]

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 (Moderna)

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.

As of November 25, 2020, there were 7 SAE's in the mRNA-1273 group (vs. 3 in the placebo), of which 3 were assessed by the investigator and the FDA as related to the vaccine. One was a case of intractable nausea and vomiting and two were cases of facial swelling in two females with prior dermal filler cosmetic injection.

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.

As of December 2, 2020, 6 pregnancies in the vaccine group have been reported in the regulatory reports. No outcomes of these pregnancies were recorded.

ChAdOx1 (AstraZeneca)

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 among the participants who received the vaccine; one HIV positive patient died from *Pneumocystiis 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.

As vaccination with ChAdOx1 in the general population was implemented, reports on thromboembolic events occurring post-immunization emerged in various European countries. A condition now termed as vaccine-induced immune thrombotic thrombocytopenia has since been recognized as a rare serious adverse event related to ChAdOx1. A more detailed description is made in the real-world evidence safety section of this review.

Gam-COVID-Vac (Gamaleya)

Detailed adverse event data were not available for Gam-COVID-Vac, pending verification by the independent assessors in the trial. The most common adverse events reported in the trial were flu-like illness, injection site reactions, headache and asthenia and were mostly mild (grade 1) in severity. Ninety-one severe (grade 3) adverse events were reported in the vaccine group while 31 events were reported in the placebo group.

The frequency of serious adverse events was low and the rates were similar between the two treatment groups (0.3% vs 0.4%). 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 4 days after vaccination with the first dose and had severe cardiopulmonary disease. The second patient developed symptoms 5 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. No association was found between vaccine administration and the serious adverse events and deaths in the trial.

Ad26.COV2.S (Janssen/Johnson&Johnson)

Most frequently reported local adverse reaction was pain at the injection site (48.6%) followed by erythema and swelling. Most were mild and lasting a median of 2-3 days. Most frequently reported systemic adverse reactions were headache (38.9%), fatigue, myalgia and nausea. Median time of onset was within 2 days of vaccination with a median duration of 1-2 days. Reports of solicited reactions were less common among participants ≥ 60 years old. 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 (5/21,895, <0.1%). 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 Feb 5 (20/21,888, <0.1%), eight were COVID-related. The other causes of deaths in the placebo group were not available.

The trial publication provided details of 14 thromboembolic events encountered at the time of the interim analysis. Ten of these were in participants who received Ad26.COV2.S. Nearly all cases were males, except for one. Six were cases of deep vein thrombosis, four cases of pulmonary embolism and one case of transverse sinus thrombosis with cerebral hemorrhage. Only one case of DVT in a male was classified as related to the vaccine. The singular case of transverse sinus thrombosis was classified as unrelated to the vaccination although he was also found to be thrombocytopenic and with anti-PF4 antibodies. These characteristics are common to the vaccine-induced thrombotic thrombocytopenia observed with the use of ChAdOx and Ad26.COV2.S in the vaccination programs in Europe.

The WHO background document on the SAGE recommendation of Ad26.COV2.S noted 8 pregnancies reported from the protocol VAC31518COV3001. There was one case of spontaneous abortion and another case of elective abortion. None of the pregnancies reported any congenital malformations. The WHO-SAGE assessed that the data was not suggestive on a pregnancy-related safety concern. [38]

CoronaVac (Sinovac)

Safety data for CoronaVac were available from three trial sites (Brazil, Indonesia and Turkey) as reported in the regulatory documents from HK and Indonesia However, these were limited to reactogenicity and adverse events. Safety data was available only from a portion of the included patients from the Indonesian trial. Data from the Chile site were presented in a preprint. However, due to the large discrepancy between the planned trial population as per protocol registration (n=2300) and the reported population in the preprint (n=434), the reviewers deemed that

recruitment is not yet complete. Only the Brazilian trial site data were included in the summary of findings table in this review at this time.

The very common adverse events reported for CoronaVac were pain at the injection site, headache and fatigue. Common adverse events were swelling at the injection site, pruritus, erythema, induration, myalgia, nausea, vomiting, diarrhea, arthralgia, cough, chills, loss of appetite, rhinorrhea, sore throat, nasal congestion and abdominal pain. The adverse event rates were driven mainly by reactogenicity to the vaccine. Severe (grade 3) adverse events were rare (<0.1%). Details of the nature of these adverse events were not detailed. Serious adverse event rates were similar between groups. There were two deaths in the trial, one due to cardiopulmonary arrest (placebo group), and due to medication overdose (vaccine group). The investigators assessed these deaths as unrelated to the vaccination.

Adverse event rates from the Indonesian trial were similar between the vaccine and placebo groups. Overall adverse event rate for CoronaVac was 71.6% (290/405) and 71.1% (96/135) for the placebo group. Solicited local adverse reaction rates were 50.9% (206/405) and 43.7% (59/135) for CoronaVac and placebo, respectively. Solicited systemic adverse reaction rates were 41.9%% (170/405) and 25.2% (34/135) for CoronaVac and placebo, respectively.

Detailed safety data are presented in Appendix 4a-c.

The evidence profiles and summary of findings tables on the efficacy and safety of the six vaccines are presented in Appendix 5.

Search Results (Real World Evidence)

The search of the COVID-19 Living Overview of Evidence (L·OVE) platform for real world evidence on COVID-19 vaccines performed on April 17, 2021 yielded 971 records. Based on titles and abstracts and after screening for eligibility, and eliminating duplicates, 27 records presented real world data on vaccine effectiveness were included in the review. Thirteen provided data on BNT162b2, [49-61] five on BNT162b2 and ChAdOx1, [62-66] five on BNT162b2 and mRNA-1273, [67-71] and two on Coronavac. [72] [73]. One provided data on Gam-COVID-Vac. [74] One study presented trends of infection rates among a the vaccinated subpopulation *vis-a-vis* the COVID-19 vaccination roll out without specifying the vaccine used. [75] No study reported real world effectiveness data for Ad16.COV2.S.

In terms of real-world safety reports, 22 reports were identified. Six studies reported safety events related to at least two vaccines. [76-80] Nine reported data on BNT162b2. [81-87] Four reported data on mRNA-1273. [88-91] Five presented data on ChAdOx1 safety events. [92-96]. One study provided safety data on Coronavac.[97]

A search of the regulatory websites for safety reports was performed from March 1 to April 12, 2021. The CDC site yielded four reports providing real world safety data. [83] [98-100] Four reports from the EMA were retrieved, three of which were specifically on the thromboembolic events associated with ChAdOx1. [101-104] The UK MHRA released two reports used in this version of the review. [105] [106] The Philippine FDA released five reports, the latest of which was used in this version of the review. [107] Among the Latin American regulatory sites, a report from the Instituto de Salud Publica de Chile (Public Health Institute of Chile) with safety data was used in this review. [108]

Real World Evidence Results: Effectiveness

In general, available reports on the real-world evidence of the BNT162b2, mRNA-1273, ChAdOx1, Gam-COVID-Vac and Coronavac demonstrated good vaccine efficacies in preventing symptomatic COVID-19 infection, corroborating the results of the clinical trials. Available data on the impact of COVID vaccines on hospitalization and deaths were also positive.

Details of the studies on effectiveness and their methodological assessment are presented in Appendix 6.

BNT162b2 (Pfizer/BioNTech)

Twenty-three studies provided real world evidence on the effectiveness of BNT162b2. Three were test negative case control studies. [62] [64] [67] Three were matched cohort studies on the general population.[53] [68] [69] Nine were prospective cohort studies and the rest were retrospective cohort studies.

In general, all studies demonstrated vaccine effectiveness rates that support the clinical trial results. Reported vaccine effectiveness rates for the prevention of symptomatic COVID-19 disease among the general population were 51% [52], 85% [49] and 94%. [53] Both studies involving the high-risk population (i.e healthcare workers), showed similar effectiveness rates of 85%. [49] [69] In the older population, the adjusted odds ratio for any COVID infection 28 to 34 days after the first dose (or 7 days after the 2nd dose) among the 70 year old or older was 0.36 (95% CI 0.31-0.49), and 0.21 (95%CI 0.14-0.32) among the 80 years and older. [62] Adequate protection against hospitalization was also demonstrated with reported effectiveness rates ranging from 43% to 71% among those older than 80 year old [56] [64] and 60% and 87% [53] [69] in the general population. Vaccine effectiveness against severe COVID-19 infection was reported at 92% in the match cohort study in Israel. [53] Vaccine effectiveness against mechanical ventilation among the older population was estimated at 67% in a cohort study comparing the proportions in the unvaccinated hospitalized patients younger than 50 years old and in the vaccinated patients who were older than 70 years old. [60] Vaccine effectiveness against death was reported by one study in the US at 100%. [69]

Publications on cohort studies among healthcare workers in Spain demonstrated satisfactory protective effects of BNT162b2 against COVID infection, hospitalization and death. [51] [54]

Five studies reported real world effectiveness outcomes in populations where both mRNA vaccines were used. Details are presented in the mRNA-1273 section below.

mRNA-1273 (Moderna)

Five studies, all done in the USA, provided real world effectiveness data for mRNA-1273. These studies were on populations where BNT162b2 or mRNA-1273 was used, and did not report effectiveness outcomes separately for each of the vaccine.

A test negative case control study among the population of California showed the real world VE against COVID infection after 15 days after the second dose of an mRNA vaccine to be at 85.7% (95%CI 67.2, 93.9). [67] Another prospective cohort study among healthcare workers and frontliners reported a higher vaccine effectiveness against COVID infection after at least 14 days after the second dose of an mRNA vaccine at 90% (95%CI 68-97). [71] A propensity matched cohort study performed using data from an electronic health record database in the US reported outcomes of vaccination with BNT162b2 and mRNA-1273.[69] The study did not report the outcomes of each vaccine separately. It demonstrated effectiveness rates against any PCR-

confirmed COVID infection of 75% (95%CI 67.4 to 81.1) from Day 15 onwards after the first dose, 88.7% (95%CI 68.4 to 97.1) 7 days after the second dose, and 92.5% (95%CI 70.2 to 99.1%) from 7 to 14 days after the second dose. The vaccine effectiveness against hospitalization hospital admission (60%, 95%CI 14 to 79) and ICU admission (18%, 95%CI –140 to 72) could be derived from this study based on the reported relative risks assessed at least 14 days after dose 1. Two deaths were reported in the study, both in the unvaccinated group. Another matched cohort study among health care facility residents showed 1.1 to 3.8 fewer hospitalization and/or deaths per 100 infected persons per day after vaccination with an mRNA vaccine.[68]

ChAdOx1 (AstraZeneca)

Five studies, all done in the UK, provided real world evidence on the effectiveness of ChAdOx1. A prospective cohort study among residents of long term care facilities in England demonstrated decreasing risk of infection after a single dose of ChAdOx1. [65] The lowest risk was observed at 35-48 days after vaccination with a reported aHR of 0.32 (95%CI 0.15, 0.86). A retrospective cohort study among the general population in Northwest London showed a vaccine efficacy of 74% (HR 0.26, 95%CI 0.19-0.35) for ChAdOx1 against COVID-PCR positive infection. [63] This study also noted a decline in hospital admission and death rates among the vaccinated population (including those who received BNT162b2).

Protection against hospitalization by ChAdOx1 was further evident in three studies. The EAVE II was a prospective population-based cohort study in Scotland. [66] It showed a vaccine effectiveness rate of 94% (95%CI 73 to 99) after 28 to 35 days after the first dose of ChAdOx1 against COVID-19 related hospitalization. One test negative case control study among adults 80 years and older reported vaccine effectiveness rate of 80.4% (95% CI 36.4, 94.5) against hospitalization assessed at least 14 days after the first dose. [64] Another, done among those 70 years or older showed an adjusted odds ratio of 0.40 (95%CI 0.27 to 0.29) against any COVID-19 infection 28 to 34 days after the first dose. This study also demonstrated a vaccine effectiveness rate of 37%, based on a hazards ratio of 0.63 (95%CI 0.41 – 0.97) 14 days and later after dose 1 against hospitalization among those 80 years and older. [62]

Gam-COVID-Vac (Gamaleya)

One retrospective study among healthcare workers in Buenos Aires used Gam-COVID-Vac in 80% of its population. [74] It reported a 35% decline in infection rates among the vaccinated population compared to 10% increase in infection rates among the general population during the same observation period.

Ad26.COV2.S (Janssen/Johnson&Johnson)

No real world evidence on the effectiveness of Ad26.COV2.S was available at the time of this review.

CoronaVac (Sinovac)

Two studies provided real world evidence on the effectiveness of CoronaVac on health care workers in Latin America. One study showed an adjusted OR of 0.50 (95%CI 0.29, 0.89) at 14 days after the first dose. [73] The study from Brazil showed a similar vaccine effectiveness rate of 50.7% (95%CI 33.3, 62.5) beginning at 2 weeks after the 2nd dose and a rate of 73.8% (95%CI 57, 84.8) at 5 weeks after. This also reported lower hospitalization numbers among those who were vaccinated. The singular death in the study was in the unvaccinated group. [72]

Real World Evidence Results: Safety

Early safety reports by the major regulatory agencies support a positive benefit-harm ratio for the use the COVID-19 vaccines. Very low anaphylactic rates were reported. Deaths after vaccination were rare and serious adverse event counts were generally low. Nearly all were judged not to be directly related to the vaccination. However, beginning late March, concerns about thromboembolic events associated with the ChAdOx1 vaccine and later the Ad26.COV2.S vaccine resulted in several regulatory review and pauses in the use of these vaccines. Reports of these cases, as well as other adverse events associated with the different vaccines have been increasing in the published literature.

Details on the post vaccination program implementation vaccine safety reports from regulatory agencies are presented in Appendix 7.

BNT162b2 (Pfizer/BioNTech)

The US CDC released a COVID-19 safety monitoring report covering December 14 to January 13, 2021 covering the first month after the vaccination roll out using BNT162b2 and mRNA-1273. [98] During this period, 13,794,904 vaccine doses were administered (no breakdown based on vaccine types was provided in the report) and 6,994 adverse event reports were received and processed by the Vaccine Adverse Events Reporting System (VAERS) for both vaccines. Majority (90.8%) was classified as non-serious and 9.2% as serious. A total of 113 deaths were reported, 65% of which were among long-term care facility residents. No causal relationship between COVID-19 vaccination and death was established.

Based on the VAERS report, 341 (6.3%) serious adverse events were reported after the first dose and 21 (21.2%) after the second dose. The most frequently reported symptoms were headache (21.8% after dose 1, 18.1% after dose 2), fatigue (16.8%, 7.3%) and dizziness (16.7%, 8.3%). The V-safe system reported significant reactogenicity with higher rates noted after the second dose. The most common complaints were injection site pain, fatigue, headache and myalgia.

Forty-six reports of anaphylaxis have been confirmed after receipt of BNT162b2. [98] The estimated anaphylaxis rate for BNT162b2 is 4.7 cases per million doses administered. [80]

The EMA released a safety update on BNT162b2 (Comirnaty) on January 28, 2021. [101] It cited an estimated frequency of anaphylaxis of approximately 11 cases per million doses of the vaccine administered in the US. In its review of reports about deaths in the frail elderly individuals after vaccination in Norway, the EMA's safety committee did not find any safety concern.

In the April 9, 2021 issue of the UKMHRA Coronavirus vaccine- weekly summary of Yellow Card report (as of March 28, 2021), the UK government received 43,491 Yellow Card (i.e., adverse event) reports with 124,371 suspected reactions after an estimated 10.9 million first doses of BNT162b2 and around 3.7 million second doses of mostly BNT162b2. [106] Majority of the reports were related to injection site reactions and generalized symptoms shortly after vaccination. A total of 259 reports of spontaneous adverse reactions associated with anaphylaxis or anaphylactoid reactions were received. The number of reported Bell's palsy, while not detailed in the report, did not suggest an increased risk following vaccination. The MHRA reported 302 deaths shortly after vaccination with BNT162b2, mostly among the elderly with underlying illness. A link between vaccination and death was not established.

Data from the VigiBase®, a database maintained by WHO containing vaccine safety reports, covering the period from Dec 15, 2020 to January 24, 2021 revealed 337 deaths after BNT162b2 administration. [76] This number represented 0.4% of all adverse event reports after BNT162b2.

The report from the Institute of Public Health of Chile showed low adverse event and anaphylaxis rates after 292, 534 doses of BNT162b2. [108] Only 11 cases of anaphylactic reaction were reported after BNT162B2 vaccination.

A questionnaire survey among 877 healthcare workers in the Czech Republic who received BNT162b2 vaccines reported 93.1% reported at least one side effect after vaccination. The most common side effect was injection site pain (89.8%), followed by fatigue (62.2%), headache (45.6%), muscle pain (37.1%), and chills (33.9%). Only 1.3% of the study group reported severe side effects that required medical intervention. [86] A similar profile of adverse events were reported among healthcare workers from South Korea who received BNT162b2 vaccines.[84]

In a study among cancer patients in the UK, BNT162b2 was found to be well tolerated with 54.3% reporting no toxicity events after the first dose and an even higher proportion (71%) reporting no events after the second dose. [85] These rates were noted to be significantly higher than the healthy controls.

A study on the cutaneous reactions after mRNA vaccination (17% related to BNT162b2, 83% with mRNA-1273) reported delayed large local reaction being the most common, followed by local injection site reactions, urticarial eruptions and morbiliform eruptions.[78] Additional less common reactions included pernio/chilblains, cosmetic filler reactions, zoster, herpes simplex flares, and pityriasis rosea-like reactions. It was also observed that most patients with first-dose reactions did not have a second dose reaction.

A case report was published in February 2021 documenting the occurrence of Guillan-Barre syndrome after BNT162b2 vaccination. [87] This was a case of an 82-year-old female who initially reported generalized malaise and body aches during the first week after receiving her first dose of BNT162b2. Symptoms progressed and she noticed increased difficulty in walking. She was assessed to have a motor strength of 4/5 bilaterally, decreased sensations to pinprick in bilateral lower extremities up to the knees and areflexia in both upper and lower extremities. MRI of the lumbar spine demonstrated enhancement of cauda equina nerve roots consistent with the diagnosis of Guillain-Barre syndrome. She improved with intravenous immunoglobulins and was eventually discharged to a rehabilitation facility.

The issue of neurologic events following BNT162b2 vaccination was further illustrated in a prospective observational cohort study from Mexico. [82] The report noted that 65.1% of the adverse events following immunization (AEFI) were neurologic, with 76% occurring in women. Majority was non-serious, with headache, transient sensory symptoms and weakness being the most common. Of the serious AEFIs 52% were neurologic, of which 7 were seizures (0.99/100,000 doses), four were functional syndrome (0.56/100,000 doses) and three were Guillain-Barre syndrome (0.43/1000 doses) and two were acute transverse myelitis.

A phenomenon of “COVID toes-like syndrome” was reported in a women who presented with sudden toe pain 4 days after the first injection of BNT162b2. [81] This was followed at 10 days post vaccination with non-tender violaceous toes of the left foot. Laboratory exams ruled out cholesterol embolization, infective endocarditis and systemic sclerosis. The authors theorized a microvasculitis from vascular damage.

mRNA-1273 (Moderna)

(See report of the US CDC above on the combined reporting of safety with BNT162b2).

Based on the VAERS report, 258 (18.8%) serious adverse events were noted after the first dose. No information was yet available for the outcomes after the second dose. The most frequently reported adverse events were headache (25.3%), chills (19.0%), nausea (16.7%), fatigue (16.6%) and dizziness (16.6%). There was significant reactogenicity after mRNA-1273 vaccination, with injection site pain being the most common symptom.

Sixteen reports of anaphylaxis have been confirmed after receipt of the mRNA-1273 vaccine. [99] The estimated anaphylaxis rate for mRNA-1273 is 2.5 cases per million doses administered. [80]

Data from the VigiBase®, revealed 78 deaths after mRNA-1273 administration, representing 1.23% of all adverse event reports after mRNA-1273. [76]

Cutaneous reactions after mRNA-1273 vaccination have been described in the above BNT162b2 section. [78]

ChAdOx1 (AstraZeneca)

The UKMHRA April 9 2021 report on the status of their Yellow Card adverse event reporting after COVID-19 vaccination. [106] After the administration of 19.5 million doses of the ChAdOx1 vaccine, 116,162 reports including a total of 440,871 suspected reactions were received. The report included 455 cases of spontaneous adverse reactions associated with anaphylaxis or anaphylactoid reactions. The number of deaths after vaccination was 472. The report also included 79 cases of blood clotting cases (see below for details).

The Philippine FDA released a report on suspected adverse reaction to COVID 19 vaccines covering March 1 to April 11, 2021. [107] For the 511,199 doses of ChAdOx1 administered, 17,727 adverse event reports were received, of which 203 were classified as serious. No details on the nature of the serious adverse events were available in the report. The local severe allergic reaction rate was noted to be 0.0006%. The most common adverse events were general symptoms and reactions in the administration site.

Data from the VigiBase®, revealed 9 deaths after ChAdOx1 administration, representing 0.07% of all adverse event reports after ChAdOx1. [76]

Beginning March, several European countries suspended the use of ChAdOx1 because of increasing reports of thromboembolic events among the recipients of this vaccine. A detailed discussion on this issue is presented below.

Gam-COVID-Vac (Gamaleya)

No phase IV or real-world safety report has been identified for Gam-COVID-Vac.

Ad26.COV2.S (Janssen/Johnson&Johnson)

The available real world evidence on the safety of Ad26.CoV2.S is limited to the reported thromboembolic events which prompted USFDA and CDC to recommend a pause in its use and conduct an investigation. A detailed discussion on this issue is presented below.

CoronaVac (Sinovac)

The Philippine FDA disclosed 7,140 cases of adverse events after 515,359 first doses and 140,043 second doses of CoronaVac administered as of its April 11, 2021 report. One hundred sixty-one were considered serious with no details provided. The local severe allergic reaction rate

was noted to be 0.009%. No vaccine related deaths were reported. The most common symptoms were related to reactions at the administration site, followed by neurologic symptoms such as dizziness, headache, and syncope. [107] The Instituto de Salud Publico de Chile reported 49 anaphylactic reactions after 3,378,552 doses of CoronaVac administered. [108]

Thromboembolic events linked to ChAdOx1 and Ad26.CoV.2

On March 11, 2021, Norway was the first country to suspend the use of ChAdOx1 after the death of a person who developed blood clots post vaccination. Several other European countries halted ChAdOx1 use in the following weeks.

Three publications detailed the clinical presentation, course and management of ChAdOx1 vaccine-associated thromboembolic cases seen in Norway and Germany. [95] [92] [96] The Nordic report presented five cases occurring in a population of more than 130,000 vaccinated persons. The German study discussed 11 cases seen when more than 82 million doses have been administered in the European Union. Thirteen of these cases were women and all were less than 55 years of age. All presented with symptoms beginning 5 to 16 days after the first dose of vaccination. Clinical presentations include cerebral venous thrombosis, splanchnic vein thrombosis, pulmonary embolism, hepatic and portal vein thrombosis and other various thromboembolic sites. One presented with disseminated coagulopathy. All presented with thrombocytopenia, elevated D-dimer levels, elevated levels of IgG antibodies to PF4-polyanion complexes, normal INR and normal activated thromboplastin time. The authors reported good response to platelet transfusion and early intravenous immune globulin. Nine of these 16 patients died. This new phenomenon was termed as vaccine-induced immune thrombotic thrombocytopenia by the authors.

In the light of the suspension of vaccination with the ChAdOx1 in several European countries due to reports of thromboembolic cases after vaccination, the EMA's safety committee performed a preliminary review of the issue in mid-March. [102] The report of this review stated that the vaccine is not associated with an increase in the overall risk of thromboembolic events in those who received it. However, it also stated that the vaccine may be associated with very rare cases of blood clots associated with thrombocytopenia. The review included seven cases of disseminated intravascular coagulation and 18 cases of cerebral venous sinus thrombosis (CVST). A causal link was not proven but a further analysis is recommended. An update of the product information was also recommended.

At this time, the UKMHRA Yellow Card Adverse Reporting included five reports of cerebral vein sinus thrombosis occurring together with thrombocytopenia under detailed review. A causal association of this event with the vaccine has not been established. Review of the reports did not suggest that vaccines played a role in the deaths. [105]

In the EMA-PRAC report released on April 7, it concluded a possible link of cases of blood clots with low blood platelets with the ChAdOx1 vaccine, after a review of 62 cases of cerebral venous sinus thrombosis and 24 cases of splanchnic vein thrombosis in the EU drug safety database as of March 22, 2021. Eighteen of these cases were fatal. [103] [104]

In its April 8 Yellow Card Report, the UKMHRA reported 79 cases of thromboembolic events (44 cases of cerebral venous sinus thrombosis, 25 cases of thrombosis of other major veins), of which 19 died. All cases occurred after a first dose. [106]

Despite the possible link of the vaccination to these thromboembolic events, both regulatory agencies confirmed that the overall benefit-harm ratio for the ChAdOx1 vaccine remains positive.

On April 13, 2021, the USFDA and CDC halted the use of Ad26.CoV2.S in its vaccine rollout pending an investigation of 6 cases of clotting events, of which 1 was fatal. [100] After a review and with no additional reported cases, the USFDA and CDC lifted its recommended pause on April 23 after a determining that the risk of VITT is very low. [109]

Authorizations (as of May 13, 2021)

BNT162b2 (Pfizer/BioNTech)

BNT162b2 (Comirnaty) received emergency use authorization from the UK MHRA on December 1, 2020, from the USFDA on December 11, 2020 and from the EMA on December 21, 2020. On December 31, 2020, the WHO listed the Comirnaty mRNA vaccine for emergency use. [110] The Philippine FDA issued the emergency use authorization for BNT162b2 last January 14, 2021. [111]

mRNA-1273 (Moderna)

mRNA-1273 (Moderna) received emergency use authorization from USFDA on December 18, 2020. The WHO approved the listing of mRNA-1273 for emergency use on January 21, 2021. On May 5, 2021, the Philippine FDA issued the emergency use authorization for mRNA-1273 (Moderna). [112]

ChAdOx1 (AstraZeneca)

ChAdOx1 (Vaxzervia) received emergency use authorization from the UKMHRA on December 30, 2020 and from the EMA on January 29, 2021. The WHO has included it in its emergency use listing on February 8, 2021. The Philippine FDA issued the emergency use authorization for ChAdOx1 on January 28, 2021. [113]

Gam-COVID-Vac (Gamaleya)

Gam-COVID-Vac (Sputnik V) is registered for use in the Russian Federation and in 50 other countries.(114) On March 19, 2021, the Philippine FDA issued the emergency use authorization for Gam-COVID-Vac. [115]

Ad26.COV2.S (Janssen/Johnson&Johnson)

Ad26.CoV2.S received emergency use authorization from the USFDA on February 26, 2021 EMA recommended a conditional marketing authorization for this vaccine on March 11, 2021. [116] The WHO added this vaccine to its emergency use list last March 12, 2021. [117] The Philippine FDA issued the emergency use authorization for As26.COV2.S on April 19, 2021. [118]

CoronaVac (Sinovac)

CoronaVac was given a conditional marketing authorization by the FHB-HKSAR on February 9. 2021. [41] Of note is that the authorization was for a dosing interval schedule of 28 days instead of the 14 day interval used in the trial. In its assessment report, the Advisor Panel accepted this recommendation by the sponsor based on the immunogenicity data and a better vaccine efficacy in the subgroup analysis of a dosing interval greater than 21 days compared to less than 21 days. The Philippine FDA issued the emergency use authorization for CoronaVac (Sinovac) on February 22, 2021 with a similar recommendation regarding the dosing interval. [119] In addition, it recommended against the use of CoronaVac for healthcare workers with exposure to COVID-19 patients.

Research Gaps

The current available evidence on vaccine efficacy and safety is limited, in terms of the design of the trials and based on the fact all are still ongoing. Uncertainties include the following:

1. Efficacy of COVID-19 vaccines on reducing the impact of the disease
    a. On severe COVID infections (available estimates on vaccine efficacies have wide confidence intervals)
    b. On hospitalization and ICU admission
    c. On death
    d. Against asymptomatic infection
2. Efficacy and safety of COVID-19 vaccines on certain populations:
    a. pregnant and breastfeeding women
    b. immunocompromised patients
    c. children
    d. previously diagnosed COVID patients
    e. seropositive patients at baseline (available estimates have wide confidence intervals)
    f. frail elderly
3. Efficacy of COVID-19 vaccines against different viral strains
4. Efficacy and safety of combination of different COVID-19 vaccines
5. Impact of the vaccine on transmission to unvaccinated persons, viral shedding
6. Long-term efficacy / duration of protection
7. For multidose vaccines:
    a. Onset of protection (although there is some suggestion that there is partial protection after the first dose)
    b. Impact of different dosing intervals
    c. Optimum dosing interval
    d. Duration of protection by the first dose
8. Long-term safety data
9. Interaction with other vaccines and safe interval between vaccinations for different diseases
10. Risk of vaccine-associated enhanced disease

References

[1] Higgins J, Green S. Cochrane handbook for systematic reviews. Higgins J, Green S, editors. The Cochrane Collaboration; 2011.

[2] Guyatt GH. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. BMJ. 2008;336:924–6.

[3] Polack F, Thomas S, Kitchin N, Absalon J, Gurtman A, Lockhart S. Efficacy of the BNT162b2 mRNA Covid-19 Vaccine. N Engl J Med. 2020;383(27):2603–15.

[4] Baden L, El Sahly H, Essink B, Kotloff K, Frey S, Novak R. Efficacy and Safety of the mRNA-1273 SARS-CoV-2 Vaccine. N Engl J Med. 2020;

[5] Voysey M, Clemens S, Madhi S, Weckx L, Folegatti P, Aley P. Safety and efficacy of the ChAdOx1 nCoV-19 vaccine (AZD1222) against SARS-CoV-2: an interim analysis of four randomised controlled trials in Brazil, South Africa, and the UK. Lancet. 2021;397(10269):99–111.

[6] Ramasamy M, Minassian A, Ewer K, Flaxman A, Folegatti P, Owens D. Safety and immunogenicity of ChAdOx1 nCoV-19 vaccine administered in a prime-boost regimen in young and old adults (COV002): a single-blind, randomised, controlled, phase 2/3 trial. Lancet. 2020;396(10267):1979–93.

[7] Voysey M, Clemens S, Madhi S, Weckx L. Single-dose administration and the influence of the timing of the booster dose on immunogenicity and efficacy of ChAdOx1 nCoV-19 (AZD1222) vaccine: a pooled analysis of four randomised trials. Lancet [Internet]. 2021; Available from: https://doi.org/10.1016/S0140-6736(21)00432-3

[8] Emary KR, Golubchick T, Aley PK, Ariani C, Angus B, Sagida B, et al. Efficacy of ChAdOx1 nCoV-19 (AZD1222) vaccine against SARS-CoV-2 variant of concern 202012/01 (B.1.1.7): an exploratory analysis of a randomised controlled trial. Lancet [Internet]. 2021;397:1351–62. Available from: https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(21)00628-0/fulltext

[9] Madhi S, Baillie V, Cutland C, Voysey A, Koen L, Fairlie K. Efficacy of the ChAdOx1 nCoV-19 Covid-19 Vaccine against the B.1.351 Variant [Internet]. New England Journal of Medicine. 2021. Available from: https://www.nejm.org/doi/pdf/10.1056/NEJMoa2102214?articleTools=true

[10] Logunov D, Dolzhikova I, Shcheblakov D, Tukhavtulin A, Zubkhova O. Safety and efficacy of an rAd26 and rAd5 vector-based heterologous prime-boost COVID-19 vaccine: an interim analysis of a randomised controlled phase 3 trial in Russia. Lancet [Internet]. 2021; Available from: https://doi.org/10.1016/%0DS0140-6736(21)00234-8

[11] Sadoff J, Gray G, Vandebosch A, Cardenas V, Shukarev G, Grinsztejn B. Safety and Efficacy of Single-Dose Ad26.COV2.S Vaccine against Covid-19 [Internet]. N Engl J Med. 2021 [cited 2021 Apr 23]. Available from: https://www.nejm.org/doi/pdf/10.1056/NEJMoa2101544?articleTools=true

[12] Palacios R, Batista A, Albuquerque CS, Patiño E, Santos J, Conde M. Efficacy and Safety of a COVID-19 Inactivated Vaccine in Healthcare Professionals in Brazil: The PROFISCOV Study [Internet]. SSRN. 2021 [cited 2021 Apr 12]. Available from: https://papers.ssrn.com/sol3/papers.cfm?abstract_id=3822780

[13] Bueno S, Abarca K, Gonzales P, Galvez N, Soto G, Duarte L. Interim report : Safety and immunogenicity of an inactivated vaccine against SARS-CoV-2 in healthy chilean adults in a Phase 3 clinical trial [Internet]. MedRxiv. 2021. Available from: April 1, 2021

[14] Vaccines and Related Biological Products Advisory Committee Meeting December 10, 2020 Meeting FDA Briefing Document Pfizer BioNTech COVID 19 Vaccine. In [cited 2020 Dec 31]. Available from: https://www.fda.gov/media/144245/download

[15] Vaccines and Related Biological Products Advisory Committee Meeting December

17, 2020 Meeting Presentation - FDA Review of Efficacy and Safety of Moderna COVID-19 Vaccine Emergency Use Authorization Request [Internet]. [cited 2020 Dec 21]. Available from: https://www.fda.gov/media/144585/download

[16] Vaccines and Related Biological Products Advisory Committee Meeting February 26, 2021. FDA Briefing Document Janssen Ad26.COV2.S Vaccine for the Prevention of COVID-19 [Internet]. 2021. [cited 2021 Mar 5]. Available from: https://www.fda.gov/media/146217/download

[17] Vaccines and Related Biological Products Advisory Committee Meeting December 10, 2020 Meeting Sponsor Briefing Document Pfizer BioNTech COVID 19 Vaccine [Internet]. [cited 2021 Apr 23]. Available from: https://www.fda.gov/media/144246/download

[18] US FDA. FACT SHEET FOR HEALTHCARE PROVIDERS ADMINISTERING VACCINE (VACCINATION PROVIDERS) EMERGENCY USE AUTHORIZATION (EUA) OF THE PFIZER-BIONTECH COVID-19 VACCINE TO PREVENT CORONAVIRUS DISEASE 2019 (COVID-19) [Internet]. [cited 2021 May 11]. Available from: https://www.fda.gov/media/144413/download

[19] European Medicines Agency (EMA). Comirnaty - Assessment Report. 21 December 2020 [Internet]. [cited 2020 Dec 21]. Available from: www.ema.europa.eu/en/medicines/human/EPAR/comirnaty#assessment-history-section

[20] European Medicines Agency (EMA) . Comirnaty - Product Information [Internet]. [cited 2020 Dec 21]. Available from: https://www.ema.europa.eu/en/documents/product-information/comirnaty-epar-product-information_en.pdf

[21] UK Medicines and Healthcare Products Regulatory Agency (MHRA). Summary of the Public Assessment Report for the Pfizer/BioNTech COVID-19 vaccine [Internet]. [cited 2020 Dec 30]. Available from: https://www.gov.uk/government/publications/regulatory-approval-of-pfizer-biontech-vaccine-for-covid-19/summary-public-assessment-report-for-pfizerbiontech-covid-19-vaccine

[22] UK Medicines and Healthcare Products Regulatory Authority (MHRA). Conditions of Authorisation for Pfizer/BioNTech COVID-19 vaccine [Internet]. [cited 2020 Dec 30]. Available from: https://www.gov.uk/government/publications/regulatory-approval-of-pfizer-biontech-vaccine-for-covid-19/conditions-of-authorisation-for-pfizerbiontech-covid-19-vaccine

[23] World Health Organization (WHO). Background document on the mRNA vaccine BNT162b2 (Pfizer-BioNTech) against COVID-19. 14 January 2021 [Internet]. [cited 2021 Apr 23]. Available from: https://www.who.int/publications/i?healthtopics=b6bd35a3-cf4f-4851-8e80-85cb0068335b

[24] World Health Organization. (2020). mRNA vaccines against COVID-19: Pfizer-BioNTech COVID-19 vaccine BNT162b2: prepared by the Strategic Advisory Group of Experts (SAGE) on immunization working group on COVID-19 vaccines, 22 December 2020 [Internet]. [cited 2021 Jan 4]. Available from: https://apps.who.int/iris/handle/10665/338096

[25] Vaccines and Related Biological Products Advisory Committtee. US Food and Drugs Administration (USFDA). mRNA-1273 Sponsor Briefing Document Vaccines and Related Biological Products Advisory Committee Meeting December 17, 2020. In [cited 2020 Dec 21]. Available from: https://www.fda.gov/media/144452/download

[26] European Medicines Agency (EMA). Public Assessment Report. COVID-19 Vaccine Moderna. [Internet]. [cited 2021 Feb 9]. Available from: https://www.ema.europa.eu/en/documents/assessment-report/covid-19-vaccine-

moderna-epar-public-assessment-report_en.pdf
[27] European Medicines Agency (EMA). Moderna Product Information. [Internet]. [cited 2021 Feb 9]. Available from: https://www.ema.europa.eu/en/documents/product-information/covid-19-vaccine-moderna-epar-product-information_en.pdf
[28] World Health Organization (WHO) WHO-2019-nCoV-vaccines-SAGE-recommendation-mRNA-1273-background-2021. [Internet]. [cited 2021 Jan 19]. Available from: https://apps.who.int/iris/handle/10665/339218
[29] World Health Organization (WHO). Interim recommendations for use of the Moderna mRNA-1273 vaccine against COVID-19. Interim guidance 15 January 2021 [Internet]. [cited 2021 Jan 25]. Available from: https://www.who.int/publications/i/item/interim-recommendations-for-use-of-the-moderna-mrna-1273-vaccine-against-covid-19
[30] UK Medicine and Healthcare Products Regulatory Agency (MHRA). Public Assessment Report Authorisation for Temporary Supply COVID-19 Vaccine AstraZeneca, solution for injection in multidose container COVID-19 Vaccine (ChAdOx1-S [recombinant]) [Internet]. [cited 2021 Jan 6]. Available from: https://www.gov.uk/government/publications/regulatory-approval-of-covid-19-vaccine-astrazeneca/summary-of-the-public-assessment-report-for-astrazeneca-covid-19-vaccine
[31] European Medicines Agency Committee for Medicinal Products for Human Use (EMA-CHMP). Assessment Report. COVID-19 Vaccine AstraZeneca. January 29 2021 [Internet]. 2021 [cited 2021 Apr 23]. Available from: https://www.ema.europa.eu/en/documents/assessment-report/vaxzevria-previously-covid-19-vaccine-astrazeneca-epar-public-assessment-report_en.pdf
[32] European Medicines Agency (EMA). Summary of Product Characteristics. COVID-19 Vaccine (ChAdOx1-S [recombinant]). 2021.
[33] World Health Organization. Background document on the AZD1222 vaccine against COVID-19 developed by Oxford University and AstraZeneca. 2021;1222(March). Available from: https://apps.who.int/iris/bitstream/handle/10665/339882/WHO-2019-nCoV-vaccines-SAGE-recommendation-AZD1222-background-2021.2-eng.pdf?sequence=1&isAllowed=y
[34] World Health Organization (WHO). Interim recommendations for use of the ChAdOx1-S [recombinant] vaccine against COVID-19 (AstraZeneca COVID-19 vaccine AZD1222, SII Covishield, SK Bioscience). Updated 21 Apr 2021.
[35] Janssen Biotech, Inc. COVID-19 Vaccine Ad26.COV2.S. Sponsor Briefing Document Addendum [Internet]. [cited 2021 Mar 5]. Available from: https://www.fda.gov/media/146218/download
[36] European Medicines Agency (EMA). COVID-19 vaccine Janssen EPAR product information. [Internet]. [cited 2021 Mar 11]. Available from: https://www.ema.europa.eu/en/documents/product-information/covid-19-vaccine-janssen-epar-product-information_en.pdf
[37] European Medicines Agency (EMA). Summary of Product Characteristics. COVID-19 vaccine (Ad26.COV2.S [recombinant]). [Internet]. [cited 2021 Mar 24]. Available from: https://www.ema.europa.eu/en/documents/product-information/covid-19-vaccine-janssen-epar-product-information_en.pdf
[38] World Health Organization. Background document on the Janssen Ad26.COV2.S (COVID-19) vaccine [Internet]. [cited 2021 Apr 6]. Available from: https://www.who.int/publications/i?healthtopics=b6bd35a3-cf4f-4851-8e80-85cb0068335b
[39] World Health Organization (WHO). Interim recommendations for the use of the Janssen Ad26.COV2.S (COVID-19) vaccine. 17 March 2021 [Internet]. [cited 2021 Apr 23]. Available from: https://www.who.int/publications/i?healthtopics=b6bd35a3-

cf4f-4851-8e80-85cb0068335b
[40] Janssen Vaccines & Prevention B.V. A Randomized, Double-blind, Placebo-controlled Phase 3 Study to Assess the Efficacy and Safety of Ad26.COV2.S for the Prevention of SARS-CoV-2-mediated COVID-19 in Adults Aged 18 Years and Older. ENSEMBLE. Protocol VAC31 [Internet]. 2020 [cited 2021 Feb 28]. Available from: https://www.jnj.com/coronavirus/ensemble-1-study-protocol,
[41] Food and Health Bureau. The Government of Hong Kong Special Autonomous. Report on Evaluation of Safety, Efficacy and Quality of CoronaVac COVID-19 Vaccine (Vero Cell) Inactivated [Internet]. 2021. [cited 2021 Apr 2]. Available from: https://www.fhb.gov.hk/download/our_work/health/201200/e_evaluation_report_CoronaVac.pdf
[42] Food and Health Bureau. The Government of Hong Kong Special Autonomous. COVID-19 Vaccine (Vero Cell) Inactivated Product Information (Detailed). 2021.
[43] Badan Pengawas Obat dan Makanan (Indonesia Food and Drug Administration). Fact sheet for health care providers emergency use authorization (EUA) of Coronavac [Internet]. [cited 2021 Apr 10]. Available from: http://pionas.pom.go.id/obat-baru/coronavac-suspensi-injeksi-3-mcg05-ml
[44] Palacios R, Patino EG, Piorelli R de O, Conde TRP, Bautista AP. Double-blind, randomized, placebo-controlled phase III clinical trial to evaluate the efficacy and safety of treating healthcare professionals with the adsorbed COVID-19 (inactivated) vaccine manufactures by Sinovac - PROFISCOV: A structured summary of a . Trials. 2020;853–5.
[45] Abarca K, Kaergis A, Bueno S, Gonzales P. Efficacy, safety, and immunogenicity of two vaccination schedules of an inactivated vaccine against COVID-19 in Adults (CoronaVac3CL) [Internet]. Clinicaltrials.Gov. [cited 2021 Apr 5]. Available from: https://clinicaltrials.gov/ct2/show/record/NCT04651790
[46] Frenck R, Klein N, Kitchin N, Gurtman A, Absalon J, Lockhart S, et al. Safety, Immunogenicity, and Efficacy of the BNT162b2 Covid-19 Vaccine in Adolescents [Internet]. N Engl J Med. 2021 [cited 2021 May 28]. Available from: https://www.nejm.org/doi/10.1056/NEJMoa2107456
[47] World Health Organization. Evaluation of COVID-19 vaccine effectiveness. Interim Guidance 17 March 2021. 2021.
[48] Emary K, Golubchik T, Aley P, Ariani C, Angus B. Efficacy of ChAdOx1 nCoV-19 (AZD1222) vaccine against SARS-CoV-2 VOC 202012/01 (B.1.1.7) [Internet]. SSRN Electronic Journal. [cited 2021 Mar 8]. Available from: https://papers.ssrn.com/sol3/papers.cfm?abstract_id=3779160
[49] Amit S, Regev-Rochay G, Afek A, Kreiss Y, Leshem E. Early rate reductions of SARS-CoV-2 infection and COVID-19 in BNT162b2 vaccine recipients [Internet]. Lancet. 2021 [cited 2021 Mar 9]. Available from: https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(21)00448-7/fulltext
[50] Britton A, KM JS, Edens C, SA N, SM B, Shang N, et al. Effectiveness of the Pfizer-BioNTech COVID-19 Vaccine Among Residents of Two Skilled Nursing Facilities Experiencing COVID-19 Outbreaks - Connecticut, December 2020-February 2021. MMWR Morb Mortal Wkly Rep [Internet]. 2021;70(11):396–401. Available from: http://www.epistemonikos.org/documents/4ea6bdb3868dac76a2b6ac17f346c4f0545b9e81
[51] Cabezas C, Coma E, Mora-Fernandez N, Li X, Martinez-Marcos M, Fina-Aviles F, et al. Effects of BNT162b2 mRNA Vaccination on COVID-19 Disease, Hospitalisation and Mortality in Nursing Homes and Healthcare Workers: A Prospective Cohort Study Including 28,594 Nursing Home Residents, 26,238 Nursing Home Staff, and 61,951 Healthcare Workers i. SSRN [Internet]. 2021; Available from:

https://papers.ssrn.com/sol3/papers.cfm?abstract_id=3815682

[52] Chodick G, Tene L, Patalon T, Gazit S, Ben-Tov A, Cohen D, et al. The effectiveness of the first dose of BNT162 b 2 vaccine in reducing SARS-CoV-2 infection 13-24 days after immunization: real-world evidence. medRxiv [Internet]. 2021; Available from: http://www.epistemonikos.org/documents/1ff25b4cb7b9b006523f8e022be2ea21eecc0c79

[53] Dagan N, Barda N, Kepten E, Miron O, Perchick S, Katz M, et al. BNT162b2 mRNA Covid-19 vaccine in a nationwide mass vaccination setting. N Engl J Med [Internet]. 2021; Available from: https://doi.org/10.1056/NEJMoa2101765

[54] Guijarro C, Galan IM, Perez-Fernandez E, Martinez-Ponce DC, Goyanes MJ, Castilla V, et al. Dramatic drop of new SARS-CoV-2 infections among health care workers after the first dose of the BNT162b2 mRNA Covid-19 Vaccine. medRxiv [Internet]. 2021; Available from: http://www.epistemonikos.org/documents/bd8ac8fc1f5bc489ab082fdbfe6150e2e7d6f7bc

[55] Haas EJ, Angulo FJ, McLaughlin JM, Anis E, Singer SR, Khan F, et al. Nationwide Vaccination Campaign with BNT162b2 in Israel Demonstrates High Vaccine Effectiveness and Marked Declines in Incidence of SARS-CoV-2 Infections and COVID-19 Cases, Hospitalizations, and Deaths. SSRN [Internet]. 2021; Available from: http://www.epistemonikos.org/documents/0ccf39331a250aaef0bc7b095d16cf3c976ec55a

[56] Hall V, Foulkes S, Saei A, Andrews N, Oguti B, Charlett A, et al. Effectiveness of BNT162b2 mRNA vaccine against infection and COVID-19 vaccine coverage in healthcare workers in England, multicentre prospective cohort study (the SIREN study). SSRN. 2021.

[57] Jones N, Rivett L, Seaman S, RJ S, Warne B, Workman C, et al. Single-dose BNT162b2 vaccine protects against asymptomatic SARS-CoV-2 infection. Elife [Internet]. 2021;10. Available from: http://www.epistemonikos.org/documents/2f5773b3ef002738bd289b3fe8401696591231d5

[58] Monge S, Olmedo C, Alejos B, Lapena M, Sierra MJ, Limia A. Direct and indirect effectiveness of mRNA vaccination against SARS-CoV-2 infection in long-term care facilities in Spain. medRxiv [Internet]. 2021; Available from: https://www.medrxiv.org/content/10.1101/2021.04.08.21255055v1

[59] Moustsen-Helms IR, Emborg H-D, Nielsen J, Nielsen KF, Krause TG, Molbak K, et al. Vaccine effectiveness after 1st and 2nd dose of the BNT162b2 mRNA Covid-19 Vaccine in long-term care facility residents and healthcare workers - a Danish cohort study. medRxiv [Internet]. 2021; Available from: http://www.epistemonikos.org/documents/53c4ee49af74968e43cc779456d74f51c3436dff

[60] Rinott E, Youngster I, Lewis Y. Reduction in COVID-19 Patients Requiring Mechanical Ventilation Following Implementation of a National COVID-19 Vaccination Program - Israel, December 2020-February 2021. MMWR Morb Mortal Wkly Rep. 2021. p. 326–8.

[61] Zacay G, Shasha D, Bareket R, Kadim I, Sikron FH, Tsamir J, et al. BNT162b2 Vaccine Effectiveness in Preventing Asymptomatic Infection with SARS-CoV-2 Virus: A Nationwide Historical Cohort Study. SSRN [Internet]. 2021; Available from: http://www.epistemonikos.org/documents/47ca04d87dfe9db54fee471b364c6a07f0d129a0

[62] Bernal JL, Andrews N, Gower C, Stowe J, Robertson C, Tessier E, et al. Early

effectiveness of COVID-19 vaccination with BNT162b2 mRNA vaccine and ChAdOx1 adenovirus vector vaccine on symptomatic disease, hospitalisations and mortality in older adults in England [Internet]. MedRxiv. 2021 [cited 2021 Mar 9]. Available from: https://www.medrxiv.org/content/10.1101/2021.03.01.21252652v1

[63] Glampson B, Brittain J, Kaura A, Mulla A, Mercuri L, Brett S, et al. North West London Covid-19 Vaccination Programme: Real-world evidence for Vaccine uptake and effectiveness. medRxiv [Internet]. 2021; Available from: https://www.medrxiv.org/content/10.1101/2021.04.08.21254580v1.full.pdf

[64] Hyams C, Marlow R, Maseko Z, King J, Ward L, Fox K. Assessing the effectiveness of BNT162b2 and ChAdOx1nCoV-19 COVID-19 vaccination in prevention of hospitalisations in elderly and frail adults: a single centre test negative case-control study. SSRN. 2021.

[65] Shrotri M, Krutikov M, Palmer T, Giddings R, Azmi B, Subbarao S, et al. Vaccine effectiveness of the first dose of ChAdOx1 nCoV-19 and BNT162b2 against SARS-CoV-2 infection in residents of Long-Term Care Facilities (VIVALDI study). medRxiv [Internet]. 2021; Available from: http://www.epistemonikos.org/documents/5132158a4d58353fd7b74cb64be8f2e6b67efaf7

[66] Vasileiou E, Simpson CR, Robertson C, Shi T, Kerr S, Utkarsh A, et al. Effectiveness of first dose of COVID-19 vaccines against hospital admissions in Scotland: national prospective cohort study of 5.4 million people [Internet]. SSRN Electronic Journal. 2021 [cited 2021 Mar 9]. Available from: https://papers.ssrn.com/sol3/papers.cfm?abstract_id=3789264

[67] Andrejko K, Pry JM, Myers JF, Jewell NP, Openshaw J, Watt J, et al. Early evidence of COVID-19 vaccine effectiveness within the general population of California. medRxiv [Internet]. 2021; Available from: http://www.epistemonikos.org/documents/8040757f20fb5b63a6cd46ac066cb780ae6f8541

[68] Mor V, Gutman R, Yang X, EM W, KW M, RA F, et al. Short-term impact of nursing home SARS-CoV-2 vaccinations on new infections, hospitalizations, and deaths. J Am Geriatr Soc [Internet]. 2021; Available from: http://www.epistemonikos.org/documents/0d6978157e70cc56490b8161f0baa4d070da14fa

[69] Pawlowski C, Lenehan P, Puranik A, Agarwal V, Venkataksrihnan A, Niesen M, et al. FDA-authorized COVID-19 vaccines are effective per real-world evidence synthesized across a multi-state health system [Internet]. MedRxiv. 2021 [cited 2021 Mar 5]. Available from: https://doi.org/10.1101/2021.02.15.21251623

[70] Roghani A. The Influence of Covid-19 Vaccine on Daily Cases, Hospitalization, and Death Rate in Tennessee: A Case Study in the United States. medRxiv [Internet]. 2021; Available from: http://www.epistemonikos.org/documents/1eed60fe61d77b4fd5f24cc34a5f3b91d2352773

[71] Thompson M, Burgess J, Naleway A, Tyner H, Yoon S, Meece J, et al. Interim Estimates of Vaccine Effectiveness of BNT162b2 and mRNA-1273 COVID-19 Vaccines in Preventing SARS-CoV-2 Infection Among Health Care Personnel, First Responders, and Other Essential and Frontline Workers - Eight U.S. Locations, December 2020-March. MMWR Morb Mortal Wkly Rep [Internet]. 2021;70(13):495–500. Available from: http://www.epistemonikos.org/documents/303b1dd4437be9fe0660353ae503f615be077c77

[72] de Faria E, Guedes AR, Oliveira MS, Moreira MVG, Maia FL, Barboza AS, et al.

Performance of vaccination with CoronaVac in a cohort of healthcare workers (HCW) - preliminary report. medRxiv [Internet]. 2021; Available from: http://www.epistemonikos.org/documents/62d22737346dfe78bba89d35c0789a470838c139

[73] Hitchings M, Ranzani OT, Torres MSS, Oliveira SB de, Almiron M, Said R, et al. Effectiveness of CoronaVac in the setting of high SARS-CoV-2 P.1 variant transmission in Brazil: A test-negative case-control study. medRxiv [Internet]. 2021; Available from: http://www.epistemonikos.org/documents/554770e434a57651e335c3b16e4d26e62795ed0a

[74] Luzuriaga JP, Marsico F, Garcia E, González V, Kreplak N, Pifano M, et al. Impact of vaccines against COVID-19 on the incidence of new SARS-COV2 infections in health care workers of the Province of Buenos Aires. 2021; Available from: https://preprints.scielo.org/index.php/scielo/preprint/view/2068/3406

[75] Rivkees S, Roberson S, Blackmore C. Outcomes of COVID-19 Vaccination Efforts in Florida from December 14, 2020 to March 15, 2021 on Older Individuals. medRxiv [Internet]. 2021; Available from: http://www.epistemonikos.org/documents/24ced7ae24bdd6585ffa245e35617596eb55618a

[76] Dutta S, Kaur RJ, Charan J, Bhardwaj P, Sharma P, Ambwani S, et al. Serious adverse events reported from the COVID-19 vaccines: A descriptive study based on WHO database. medRxiv [Internet]. 2021; Available from: https://www.medrxiv.org/content/10.1101/2021.03.23.21253433v1.full.pdf

[77] Mathioudakis A, Ghrew M, Ustianowski A, Ahmad S, Borrow R, LP P, et al. Self-Reported Real-World Safety and Reactogenicity of COVID-19 Vaccines: A Vaccine Recipient Survey. Life (Basel, Switzerland) [Internet]. 2021;11(3). Available from: https://www.mdpi.com/2075-1729/11/3/249

[78] McMahon D, Amerson E, Rosenbach M, Lipoff J, Moustafa D, Tyagi A, et al. Cutaneous Reactions Reported after Moderna and Pfizer COVID-19 Vaccination: A Registry-Based Study of 414 Cases. J Am Acad Dermatol [Internet]. 2021; Available from: http://www.epistemonikos.org/documents/640a98a9e5c75d5faf21bba63eb92d115d353023

[79] Mortazavi S. Coronavirus Disease (COVID-19) Vaccination Associated Axillary Adenopathy: Imaging Findings and Follow-Up Recommendations in 23 Women. AJR Am J Roentgenol [Internet]. 2021; Available from: http://www.epistemonikos.org/documents/47429f8c5d15be0f99b3845912d38d662c15035a

[80] Shimabukuro T, Cole M, JR S. Reports of Anaphylaxis After Receipt of mRNA COVID-19 Vaccines in the US-December 14, 2020-January 18, 2021. JAMA [Internet]. 2021; Available from: http://www.epistemonikos.org/documents/9e146cd9b0b0e17214584b3f68682e41454a6034

[81] Davido B, Mascitti H, Fortier-Beaulieu M, Jaffal K, P de T. “Blue toes” following vaccination with the BNT162b2 mRNA COVID-19 vaccine. J Travel Med [Internet]. 2021; Available from: http://www.epistemonikos.org/documents/1066cc91c713cb890ee0b0a2e403b915a1141fbf

[82] García-Grimshaw M, Ceballos-Liceaga SE, Hernández-Vanegas LE, Núñez I, Hernández-Valdivia N, Carrillo-García DA, et al. Systemic and Neurologic Adverse Events Among 704,003 First-Dose Recipients of the Pfizer-Biontech (BNT162b2)

mRNA COVID-19 Vaccine in Mexico. SSRN [Internet]. 2021; Available from: http://www.epistemonikos.org/documents/9623d8f06c619da3b9b56f54d7a4adecebbe09e0

[83] Gee J, Marquez P, Su J, Calvert G, Liu R, Myers T, et al. First Month of COVID-19 Vaccine Safety Monitoring — United States, December 14, 2020–January 13, 2021 [Internet]. Vol. 70, Morbidity Mortality Weekly Report. 2021 [cited 2021 Mar 22]. p. 283–8. Available from: https://www.cdc.gov/mmwr/volumes/70/wr/pdfs/mm7008e3-H.pdf

[84] Kim S, Wi Y, Yun S, Ryu J, Shin J, Lee E, et al. Adverse Events in Healthcare Workers after the First Dose of ChAdOx1 nCoV-19 or BNT162b2 mRNA COVID-19 Vaccination: a Single Center Experience. J Korean Med Sci [Internet]. 2021;36(14):e107. Available from: http://www.epistemonikos.org/documents/48c6eb652f4eefc5627c4e815737f997ea13c49b

[85] Monin-Aldama L, Laing A, Munoz-Ruiz M, McKenzie D, I del M del B, Alaguthurai T, et al. Interim results of the safety and immune-efficacy of 1 versus 2 doses of COVID-19 vaccine BNT162b2 for cancer patients in the context of the UK vaccine priority guidelines. medRxiv [Internet]. 2021; Available from: http://www.epistemonikos.org/documents/310daffd483993141c2e7d5307c8d8daff474069

[86] Riad A, Klugarova J, Koscik M, Klugar M, Riad A, Pokorna A, et al. Prevalence of covid-19 vaccine side effects among healthcare workers in the Czech Republic. J Clin Med [Internet]. 2021;10(7). Available from: http://www.epistemonikos.org/documents/2e6ace3dc0630f1bd3244d375cb81ac390de91f5

[87] Waheed S, Bayas A, Hindi F, Rizvi Z, PS E. Neurological Complications of COVID-19: Guillain-Barre Syndrome Following Pfizer COVID-19 Vaccine. Cureus [Internet]. 2021;13(2):e13426. Available from: http://www.epistemonikos.org/documents/8de11dd4bd7fbf0a9cb2bb8ed619bf773c1774f1

[88] CDC. Local Reactions, Systemic Reactions, Adverse Events, and Serious Adverse Events: Moderna COVID-19 Vaccine. CDC Website [Internet]. 2021; Available from: http://www.epistemonikos.org/documents/7c8223e8474331b949d0763a091fde114a9ca943

[89] COVID-19 Response Team FDA. Allergic Reactions Including Anaphylaxis After Receipt of the First Dose of Moderna COVID-19 Vaccine - United States, December 21, 2020-January 10, 2021. MMWR Morb Mortal Wkly Rep [Internet]. 2021;70(4):125–9. Available from: http://www.epistemonikos.org/documents/a06b60b5e02770c92d14b0f86fe85e708af3e13f

[90] Julian J, Mathern D, Fernando D. Idiopathic Thrombocytopenic Purpura and the Moderna Covid-19 Vaccine – A Case Report. Ann Emerg Med [Internet]. 2021; Available from: https://www.annemergmed.com/article/S0196-0644(21)00122-0/pdf

[91] Kadali R, Janagama R, Peruru S, Gajula V, Madathala R, Chennaiahgari N, et al. Adverse effects of COVID-19 mRNA-1273 vaccine: A randomized, cross-sectional study on healthcare workers with detailed self-reported symptoms. J Med Virol [Internet]. 2021; Available from: https://onlinelibrary.wiley.com/doi/epdf/10.1002/jmv.26996?src=getftr

[92] Greinacher A, Thiele T, Warkentin T, Weisser K, Kryle P, Eichinger S. Thrombotic Thrombocytopenia after ChAdOx1 nCov-19 Vaccination. N Engl J Med. 2021.

[93] Kaur U, Ojha B, Pathak BK, Singh A, Giri KR, Singh A, et al. A prospective

observational safety study on ChAdOx1 nCoV- 19 corona virus vaccine (recombinant) use in healthcare workers- first results from India. medRxiv [Internet]. 2021; Available from: https://www.medrxiv.org/content/10.1101/2021.04.03.21254823v1.full.pdf

[94] Mehta P, Mangion S, Benger M, Stanton B, Czuprynska J, Arya R, et al. Cerebral venous sinus thrombosis and thrombocytopenia after COVID-19 vaccination - a report of two UK cases. Brain Behav Immun [Internet]. 2021; Available from: https://www.sciencedirect.com/science/article/pii/S088915912100163X?pes=vor

[95] Schultz NH, Sorvoll IH, Michelsen AE, Munthe LA, Lund-Johansen F, Aanodt A-H. Thrombosis and Thrombocytopenia after ChAdOx1 nCoV-19 Vaccination [Internet]. N Engl J Med. 2021 [cited 2021 Apr 9]. Available from: https://www.nejm.org/doi/full/10.1056/NEJMoa2104882

[96] Wolf M, Bazner H, Luz B, Niehaus L, Bhogal P, Henkes H. Thrombocytopenia and intracranial venous sinus thrombosis after “covid-19 vaccine astrazeneca” exposure. J Clin Med [Internet]. 2021;10(8). Available from: https://www.mdpi.com/2077-0383/10/8/1599

[97] Riad A, Sağıroğlu D, Üstün B, Attia S, Klugar M. Prevalence and Risk Factors of CoronaVac Side Effects: An Independent Cross-Sectional Study Among Healthcare Workers in Turkey [Internet]. SSRN. 2021 [cited 2021 Apr 24]. Available from: https://papers.ssrn.com/sol3/papers.cfm?abstract_id=3820571

[98] CDC COVID-19 Response Team. Allergic Reactions Including Anaphylaxis After Receipt of the First Dose of Pfizer-BioNTech COVID-19 Vaccine - United States, December 14-23, 2021 [Internet]. MMWR Morb Mortal Wkly Rep. 2021 [cited 2021 Apr 11]. Available from: https://www.cdc.gov/mmwr/volumes/70/wr/pdfs/mm7002e1-H.pdf

[99] CDC COVID-19 Response Team. Allergic Reactions Including Anaphylaxis After Receiving First Dose of Moderna COVID-19 Vaccine - United States December 21, 2020 - January 10, 2021. MMWR Morb Mortal Wkly Rep. 2021.

[100] CDC. Cases of cerebral venous sinus thrombosis with thrombocytopenia after receipt of the Johnson & Johnson COVID-19 Vaccine.

[101] European Medicines Agency (EMA). COVID-19 vaccine safety update. Comirnaty BioNTech Manufacturing GmbH. 28 Jan 2021. [Internet]. [cited 2021 Mar 24]. Available from: https://www.ema.europa.eu/en/documents/covid-19-vaccine-safety-update/covid-19-vaccine-safety-update-comirnaty-january-2021_en.pdf

[102] European Medicines Agency. COVID-19 Vaccine AstraZeneca : benefits still outweigh the risks despite possible link to rare blood clots with low blood platelets. [Internet]. [cited 2021 Mar 24]. Available from: https://www.ema.europa.eu/en/news/covid-19-vaccine-astrazeneca-benefits-still-outweigh-risks-despite-possible-link-rare-blood-clots

[103] European Medicines Association. AstraZeneca’s COVID-19 vaccine: EMA findspossible link to very rare cases of unusualblood clots with low blood platelets.

[104] EMA Pharmacovigilance Risk Assessment Committee. Signal assessment report on embolic and thrombotic events (SMQ) with COVID-19 Vaccine (ChAdOx1-S [recombinant]) – COVID-19 Vaccine AstraZeneca (Other viral vaccines) [Internet]. [cited 2021 Apr 11]. Available from: https://www.ema.europa.eu/en/documents/prac-recommendation/signal-assessment-report-embolic-thrombotic-events-smq-covid-19-vaccine-chadox1-s-recombinant-covid_en.pdf

[105] UK MHRA. Coronavirus vaccine - weekly summary of Yellow Card reporting. Updated 18 Mar 2021 [Internet]. [cited 2021 Mar 24]. Available from: https://www.gov.uk/government/publications/coronavirus-covid-19-vaccine-adverse-reactions/coronavirus-vaccine-summary-of-yellow-card-reporting

[106] UK MHRA. Coronavirus vaccine - weekly summary of YellowCard reporting. Updated

8 April 2021.
[107] Food and Drug Administration Philippines. Reports of Adverse Reaction to COVID-19 Vaccines (01 to 11 April 2021) [Internet]. [cited 2021 Mar 25]. Available from: https://www.fda.gov.ph/wp-content/uploads/2021/04/Reports-of-Suspected-Adverse-Reaction-to-COVID-19-Vaccines-as-of-11-April-2021-ver-3.pdf
[108] Instituto de Salud Publica de Chile. Reacciones anafilacticas asociadas a la administracion de las vaculas SARS-CoV-2 - Evaluacion de reportes de esavi y recomendaciones para las vacunas Pfizer-BioNTech y Coronavac [Internet]. Nota Informativa De Farmacovigilancia. 2021 [cited 2021 Apr 12]. Available from: https://www.ispch.cl/wp-content/uploads/2021/03/INF-FARMACOVIGILANCIA.pdf
[109] CDC. FDA and CDC Lift Recommended Pause on Johnson & Johnson (Janssen) COVID-19 Vaccine Use Following Thorough Safety Review [Internet]. [cited 2021 Apr 23]. Available from: https://www.fda.gov/news-events/press-announcements/fda-and-cdc-lift-recommended-pause-johnson-johnson-janssen-covid-19-vaccine-use-following-thorough
[110] WHO issues its first emergency use validation for a covid-19 vaccine. WHO news release Dec 31 [Internet]. [cited 2021 Jan 4]. Available from: https://www.who.int/news/item/31-12-2020-who-issues-its-first-emergency-use-validation-for-a-covid-19-vaccine-and-emphasizes-need-for-equitable-global-access
[111] Food and Drug Administration Philippines. FDA Philippines Grants Emergency Use Authorization to Pfizer-BioNTech COVID19 Vaccine [Internet]. [cited 2021 Feb 25]. Available from: https://www.fda.gov.ph/wp-content/uploads/2021/02/EUA-Pfizer-Website.pdf,
[112] Food and Drug Administration Philippines. Emergency Use Authorization (EUA) for COVID-19 mRNA Vaccine (Nucleoside Modified) (COVID-19 Vaccine Moderna) [Internet]. 2021 [cited 2021 May 13]. Available from: https://www.fda.gov.ph/wp-content/uploads/2021/05/EUA-Moderna-Website.pdf
[113] Food and Drug Administration Philippines. Emergency Use Authorization (EUA) for COVID-19 Vaccine (ChAdOx1- S[recombinant]) (COVID-19 Vaccine AstraZeneca).
[114] Sputnik V General Information [Internet]. [cited 2021 Feb 24]. Available from: https://sputnikvaccine.com/about-vaccine/
[115] Food and Drug Administration Philippines. Emergency Use Authorization (EUA) for Gamaleya National Center of Epidemiology and Microbiology Sputnik V Gam-COVID-Vac COVID-19 Vaccine [Internet]. [cited 2021 Mar 24]. Available from: https://www.fda.gov.ph/wp-content/uploads/2021/03/EUA-Gamaleya-Website.pdf
[116] European Medicines Agency (EMA). EMA recommends COVID-19 Vaccine Janssen for authorisation in the EU. [Internet]. [cited 2021 Mar 11]. Available from: https://www.ema.europa.eu/en/news/ema-recommends-covid-19-vaccine-janssen-authorisation-eu
[117] WHO adds Janssen vaccine to list of safe and effective emergency tools against COVID-19. 2021.
[118] Food and Drug Administration Philippines. Emergency Use Authorization (EUA) for COVID-19 Vaccine (Ad26.COV2-S [recombinant]), Grand River Aseptic Manufacturing, Michigan, USA Site [Internet]. 2021. [cited 2021 Apr 23]. Available from: https://www.fda.gov.ph/wp-content/uploads/2021/04/EUA-Janssen-Website.pdf
[119] Food and Drug Administration Philippines. Emergency Use Authorization (EUA) for SARS-CoV-2 Vaccine (Vero Cell) Inactivated [Coronavac] Sinovac Life Sciences Co., Ltd [Internet]. [cited 2021 Mar 24]. Available from: https://www.fda.gov.ph/wp-content/uploads/2021/03/EUA-SINOVAC-WEBSITE-3-1.pdf

Appendix 1 : Characteristics of Included Studies

Appendix 1a : Characteristics of Included Studies : Polack 2020 (BNT162b2) and Zaks 2020 (mRNA-1273)

Trial Identifier	**Polack 2020 (C4591001)**	**Zaks 2020 (mRNA-1273-P301)**
Vaccine	**BNT162b2**	**mRNA-1273**
Data Sources	• Trial publication of interim analysis • US FDA authorization briefing document reviews • EMA assessment report, product information and summary of product characteristics • MHRA public assessment report, conditions of authorization • WHO –SAGE review document • Clinical trial registry	Trial publication of interim analysis FDA authorization briefing document reviews EMA assessment report, product information and summary of product characteristics WHO-SAGE review document Clinical trial protocol Clinical trial registry
POPULATION		
Total Randomized	43, 651 (V:21,823 C:21,828)	30,351 (V:15,181 C:15,170)
Inclusions		adults at high risk of SARS-CoV-2 infection who have no known history of SARS-CoV-2 infection *high (location or circumstance put them at appreciable risk of exposure) - – EMA Healthcare workers : 25% - EMA T9
• Age	16 years and older (but protocol amendment included 12-15 year old, but limited results available at time of review) interim report included 16-85 yo >64yo – 21.9% >55 yo ~42.6% UKMHRA T5 > 75 (4.4%) EMA P76 (TABLE) 12-15 yo = 2260 (V :1131 vs C :1129) FDA FS P19	18 years and older (protocol required at least 25% must at least 65yo or a risk for severe COVID) >64 yo : 24.8% BADEN T1 25.3% EMA T9 >=65 and < 75 : 20.2% >= 75 and <85 : 4.3% >=85 : 0.3% BADEN TS2
• Race/ Ethnicity	All (83% white, 77% from the US) Asian : 4.4% UKMHRA T5 EMA P76 (TABLE)	All (63% white) Asian (1382/30,351, 4.6%) BADEN T1, EMA T9
• Immunocompromised	Yes, included those with stable disease, included those with HIV (0.3%), HCV, HBV; balanced between groups; BUT were not included in the efficacy analysis	HIVpositive participants with CD4 count ≥350 cells/mm3 and an undetectable HIV viral load within the past year [low level variations from 50-500 viral copies which do not lead to changes in antiretroviral therapy [ART] are permitted]).

		176 (0.6%) randomized EMA P118
● Pregnant and breastfeeding	No	No
Trial Identifier	**Polack 2020 (C4591001)**	**Zaks 2020 (mRNA-1273-P301)**
Vaccine	**BNT162b2**	**mRNA-1273**
● With concomitant comorbidities	Yes, stable disease (46%) With Charlson comorbidity (20.5%) EMA T3	Yes, stable disease (16%) With one high risk condition present (18.5%) – EMA T9
Trial Identifier	Polack 2020 (C4591001)	Zaks 2020 (mRNA-1273-P301)
Vaccine	BNT162b2	mRNA-1273
● With previous COVID infection	No	No
● With known previous exposure to COVID	No	No mention
● Seropositive at baseline	Yes (6%)	Yes (2.2%) BADEN TS2
Exclusions	Pregnant and breastfeeding women Age <12years 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 or immunodeficient state Acutely ill or febrile 72 hours prior to or at screening Prior administration of COVID vaccine or participation in another interventional study to prevent or treat COVID Received systemtic OgG or blood products
INTERVENTION (VACCINE)		
Type	mRNA	mRNA
Active substance	single-stranded, 5'-capped mRNA that is translated into a codon-optimised 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
Storage and Cold chain considerations		
● Shipping and transport	passive thermal shipping containers for air and road shipments at temperature conditions of -90 to -60'C, in a thermal container from manufacturer to dosing site	Stored between -25' to -15'C
● Storage and shelf life prior to dilution/ opening	Storage from manufacturer : ● in a thermal container at -90 to -60"C for 6 months ● in a freezer at -80 to -60'C for 6 months Storage after initial thawing, prior to dilution: ● at 2-8"C for 5 days (120 hours) ● at 30'C for not more than 2 hours refreezing not allowed	May be stored between 2' to 8'C for up to 30 days prior to first use. Unopened vials may be stored between 8' to 25' C for up to 12 hours

Trial Identifier	**Polack 2020 (C4591001)**	**Zaks 2020 (mRNA-1273-P301)**
Vaccine	**BNT162b2**	**mRNA-1273**
• Storage and shelflife after dilution/ opening	at 2-30”C, must be used immediately, discard after 6 hours	6 hours at 2’ to 25’C
Final product		
Form and use	2ml multidose (5 doses) glass vial that must be thawed prior to dilution; diluted after thawing with 1.8ml saline and used immediately	Multidose (10 doses) vial containing a frozen suspension that must be thawed prior to administration
Excipients	ALC-0315, ALC-0159 (polyethylene glycol), DSPC, cholesterol, potassium chloride, potassium dihydrogen, phosphate, sodium chloride, disodium phosphate dehydrate, sucrose, water for injection EMA SPC P21	Lipid MS-102, cholesterol, 1,2-distearoyl-sn-glycero-3-phosphocholine (DSPC), PEG200 DMG), tromethamol, acetic acid, sodium acetate trihydrate, sucrose, water for injection EMA PI P17
Trial-specific considerations		
Dosing and administration	0.3 ml (30ug BNT162b2) intramuscular injection, 21 days apart (predefined window : 19 – 42 days after Dose 1) interval in trial (19 to 45 days)	0.5 ml (100ug mRNA-1273) intramuscular injection, on a 2-dose injection schedule on Day 1 and Day 29
Number randomized	21,823 (at final analysis)	15,181
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
Number randomized	21,828 (at final analysis)	15,170
ACTUAL VACCINATION INTERVAL	na	na
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

Trial Identifier	**Polack 2020 (C4591001)**	**Zaks 2020 (mRNA-1273-P301)**
Vaccine	**BNT162b2**	**mRNA-1273**
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 during 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
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
Subgroups considered in the analysis		
● Age	Yes :	Yes :
● Sex	Yes	Yes
● Ethnic groups	Yes	Yes
● Baseline seropositivity status / evidence of previous infection	Yes	Yes
● Medical comorbidities	Yes	Yes
● Immunocompromised / HIV disease	Yes	No
● Risk for acquiring COVID infection	No	Yes
● Risk for progression to severe COVID	No	Yes
● Dosing regimen	No	No

Trial Identifier	**Polack 2020 (C4591001)**	**Zaks 2020 (mRNA-1273-P301)**
Vaccine	**BNT162b2**	**mRNA-1273**
Follow up		
● Planned	24 months	759 days
● 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 Dose 2 Longest follow up 12-13 weeks after dose 2 (n= 382 BNT162b2, n=398 placebo)	
Date of Data Cut-off date for latest available trial data	Efficacy : ● Preliminary : November 4, 2020 ● Final : November 14, 2020 Safety : November 14 2020 ● with additional mortality data Cut off for preliminary report for adolescents : Mar 13 2021	Efficacy : ● Preliminary : November 7, 2020 ● Final : November 25, 2020 (Nov 21 for EMA?) Safety : November 11, 2020 and November 25 With additional data on deaths as of December 3.
METHODS / OTHER TRIAL PARAMETERS		
Blinding		
Study Sites	USA, Argentina, brazil, Turkey, South Africa, Germany	
Study Sponsor	BioNTech, Inc, Pfizer	ModernaTX,Inc
Type of report available as of this rapid review	Interim analysis (published paper and regulatory submission)	Interim analysis (published paper and regulatory submission)
Others		
Trial subject disposition - not vaccinated Withdrawn from vaccination - discontinued from vaccination - withdrawal by subject - discontinuation due to AE - Lost to ffup Withdrawn from study - withdrawal by subject - Lost to ffup - Adverse event Efficacy Populations - Excluded from Dose 1 pop - Excluded from Dose 2 pop - Excluded from 7 days pop - Did not receive Dose 2 - Protocol deviation	(V vs P) Balanced Balanced Unbalanced (45 vs 9) Unbalanced (20 vs 12) Balanced Unbalanced (84 vs 157) Balanced Balanced (8 vs 5) Balanced (55 vs 45) Balanced (1257 vs 1292) Unbalanced (1790 vs 1584) Balanced (1550 vs 1561) Unbalanced (311 vs 61)	 Unbalanced (28 vs 40) Unbalanced (120 vs 168)] Unbalanced (67 vs 120) Unbalanced (2 vs 9) Unbalanced (3 vs 0) Unbalanced (12 vs 24)

Appendix 1b : Characteristics of Included Studies : Voysey 2020/2021 (ChAdOx1), Logunov 2021 (Gam-COVID-Vac),

Trial Identifier	**Voysey 2020 / Voysey 2021 (COV001, 002, 003, 005)**	**Logunov 2021 (RESIST)**
Vaccine	**ChAdOx1 nCoV19 / AZD1222**	**Gam-COVID-Vac**
Data Sources	Trial publication of interim analysis including supplementary information Clinical trial registry UKMHRA assessment report EMA assessment report, product information and summary of product characteristics WHO-SAGE review document Trial publication update, including supplementary information	Trial publication of interim analysis including supplementary appendix Clinical trial registry
POPULATION		
Total Randomized	Efficacy : 11,636 (V:5,807 C:5,829) Safety : 23,745 (V:12,021 C:11,724) VOYSEY2020 Efficacy : 17,178 (V:8597 C: 8581) VOYSEY2021 P4, T1	21,977 (V: 16,501 C: 5, 476) (3:1)
Inclusions	Healthy adults, priority given to health professionals and adults with high potential for exposure to SARS-CoV-2 (CoV002, CoV003)	>= 18 yo (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
• Age	COV002 : 18 to 55, later included 5 yo. and above COV003 : >=18 COV005 : 18-65 years Overall : >64 yo ~9.7% >= 70 ~3.8% >70yo : COV002 : 412 + 424 = 836/8207 COV003 : 72 + 65 = 137/ 6753 COV001 and 005 = none Overall : 973 / 17178 (5.7%) VOYSEY2021 S1	18 years old or older (18-111) >60 : 1611 + 533 = 10.8% vs 10.9% no children LOGUNOV T1 mean : 45.3 y

Trial Identifier	**Voysey 2020 / Voysey 2021 (COV001, 002, 003, 005)**	**Logunov 2021 (RESIST)**
Vaccine	**ChAdOx1 nCoV19 / AZD1222**	**Gam-COVID-Vac**
● Race/ Ethnicity	All (75.5% white) Asian 724/20665 (3.5%) COV002+3 VOYSEY TS4 calculated Asian 605/17178 (3.5%) (no Asians in COV005) VOYSEY2021 S1 calculated	White (98.5% vs 98.5%) Asians 217 + 69 (1.5% vs 1.4%) LOGUNOV T1
● Immunocompromised	Included HIV patients (but are in the open-label subgroup and all will receive the vaccine)	Immunosuppressor intake within 3 months before enrollment excluded; excluded TB and chronic systemic infections, excluded history of splenectomy, neutropenia, agranulocytosis, active HIV, syphilis and hep B or C
● Pregnant and breastfeeding	No	No
● With concomitant comorbidities	Yes, (36.1%) UKMHRA T7	Yes : 3687/14994 (24.7) v.1235/4892(25.2%) LOGUNOV T1
● With previous COVID infection	No mention	No
● With known previous exposure to COVID	No mention	No
● Seropositive at baseline	Yes (373/20675, 1.8%) COV002+3 VOYSEY TS2	No
Exclusions	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)	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 56 months before Anorexia or protein deficiency History of alcohol or drug addiction Previous COVID infection
INTERVENTION (VACCINE)		
Type	Viral vector (adenovirus)	Combined viral vector (adenovirus)
Active substance	Recombinant, replication-deficient chimpanzee adenoviral vector containing the SARS-CoV-2 structural surface glycoprotein antigen gene with a tissue plasminogen activator leader sequence	rAd type 26 and rAd type 5 which carry the gene for SARS-CoV-2 full length glycoprotein S
Storage and Cold chain considerations		
● Shipping and transport	-80'C (for those manufactured by Advent) 2-8'C (for those manufactured by Cobra Biologics) Distribution during deployment should be controlled at 2-8'C	Not available

Trial Identifier	**Voysey 2020 / Voysey 2021 (COV001, 002, 003, 005)**	**Logunov 2021 (RESIST)**
Vaccine	**ChAdOx1 nCoV19 / AZD1222**	**Gam-COVID-Vac**
• Storage and shelf life prior to dilution/ opening	In general, the finished product is stored at 2-8'C with a shelf life of 6 months for the unopened vials	Not available
• Storage and shelflife after dilution/ opening	6 hours at 2-25'c Once opened, the vial should be stored between 2-25'C and used as soon as possible, After 6 hours, unused vaccine left in the vial should be discarded.	Not available
Final product		
Form and use	Available in 2 sizes : 10-dose (5 ml of vaccine) 6 ml vial or an 8-dose (4ml of vaccine) 5ml vial 1 dose (0.5ml) contains ChAdOx1-S recombinant 5 x 10^{10} viral particles	Not available
Excipients	L-histidine, L-histidine hydrochloride monohydrate, magnesium chloride hexahydrate, polysorbate 80 (E433), ethanol, sucrose, sodium chloride, disodium edatate, water for injection EMA P18	Tirs (hydroxymethyl) aminomethane, sodium chloride, sucros, magnesium chloride hexahydrate, EDTA disodium salt hydrate, polysorbate-80, ethanol 95%, and water for injection LOGUNOV 2021 APPENDIX1
Trial-specific considerations		
Dosing and administration	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)	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
Number randomized	8, 597 (efficacy) 12,021 (safety)	16,501
COMPARATOR		
Type, dosing and administration	0.5 ml Meningococcal group ACWY conjugate vaccine (MenACWY) at dose 1, and 0.5 Normal saline at dose 2, 4 weeks apart OR 0.5 ml Normal saline, intramuscular injection, 2 doses, 4 weeks apart	Vaccine buffer composition without the recombinant adenoviruses 0.5ml / 0.5ml IM on days 1 and 21
Number randomized	8,581 (efficacy) 11,724 (safety)	5,476

Trial Identifier	**Voysey 2020 / Voysey 2021 (COV001, 002, 003, 005)**	**Logunov 2021 (RESIST)**
Vaccine	**ChAdOx1 nCoV19 / AZD1222**	**Gam-COVID-Vac**
ACTUAL VACCINATION INTERVAL	< 6 weeks : V : 1702 / 5807 (29.3%) C : 1698 / 5829 (29.1%) 6-8weeks : V : 957 / 5807 (16.5%) C : 907/ 5829 (15.6%) 9-11weeks : V : 1504 / 5807 (25.9%) C : 1576 / 5829 (27.0%) >=12 weeks : V : 1644 / 5807 (28.3%) C : 1648/ 5829 (28.3%) VOYSEY TS5 calculated UKMHRA T5	
OUTCOMES		
Primary efficacy endpoints	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)	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), O2sat <95%, CRP >10ml/l Severe : RR >30/min, O2sat <= 93%, O2partial pressure / H1O2 <= 300mmHg, progression of changes in the lungs by xray. CT, ultrasonography, decreased level of consciousness, agitation; unstable hemodynamics (SBP< 90mmHg or DBP <60mmHg, diuresis <20ml/hr)
Primary safety endpoints	- Reactogenicity - Unsolicited AEs from start of each dose to Day28 - Serious adverse events from first vaccination to 364 days - Adverse events of special interest	Incidence and severity of adverse events

Trial Identifier	**Voysey 2020 / Voysey 2021 (COV001, 002, 003, 005)**	**Logunov 2021 (RESIST)**
Vaccine	**ChAdOx1 nCoV19 / AZD1222**	**Gam-COVID-Vac**
Secondary endpoints	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 second dose, or >14 days after second 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	- 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 neutralising 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 of the event requiring hospital admission
Subgroups considered in the analysis		
● Age	Yes	Yes
● Sex	Yes	Yes
● Ethnic groups	Yes (country)	No
● Baseline seropositivity status / evidence of previous infection	Yes	NA
● Medical comorbidities	Yes	No
● Immunocompromised / HIV disease	Specified special analysis for HIV patients (COV005)	No
● Risk for acquiring COVID infection	Not mentioned	No
● Risk for progression to severe COVID	Not mentioned	No
● Dosing regimen	Yes, including control type	No

Trial Identifier	**Voysey 2020 / Voysey 2021 (COV001, 002, 003, 005)**	**Logunov 2021 (RESIST)**
Vaccine	**ChAdOx1 nCoV19 / AZD1222**	**Gam-COVID-Vac**
Follow up		
● Planned	1 year	180 days
● At data cutoff of interim report (first interim analysis)	Mean duration of follow up was 105 days post dose 1 and 62 days post dose 2	Median time from first dose to database lock was 48days (IQR 39-58)
Date of Data Cut-off date for latest available trial data	November 4, 2020	November 24, 2020
METHODS / OTHER TRIAL PARAMETERS		
Blinding		Participants, investigators and study staff masked
Study Sites	UK, Brazil, South Africa	Russia
Study Sponsor	University of Oxford, AstraZeneca	Gamaleya Research Institute of Epidemiology and Microbiology, Health Ministry of the Russian Federation
Type of report available as of this rapid review	Interim analysis, published papers and regulatory submissions	Interim analysis (published paper)
Others	Planned pooled analysis of 4 trials For inclusion into the pooling, trial has to have a minimum of 5 primary endpoint defined cases that occurred >=15 days after 2nd dose randomized between SDSD and control	
Trial subject disposition - not vaccinated Withdrawn from vaccination - discontinued from vaccination - withdrawal by subject - discontinuation due to AE - Lost to ffup Withdrawn from study - withdrawal by subject - Lost to ffup - Adverse event	 Unbalanced (169 vs 155) Unbalanced (6+2 vs 9+8) (V vs C , SD + LD) Balanced (1867+320 vs 1842 + 312) Balanced	

Appendix 1c : Characteristics of Included Studies : CoronaVac 2021 (CoronaVac) and Janssen 2021 (Ad26.CoV2.S)

Trial Identifier	**Janssen 2021 (ENSEMBLE - COV3001)**	**CoronaVac 2021 (PROFISCOV)**
Vaccine	**Ad26.CoV2.S**	**CoronaVac (Vero Cell)**
Data Sources	FDA briefing document FDA EMA assessment report EMA Clinical trial protocol ENSEMBLE Clinical trial publication Sadoff	FHB-HKSAR assessment report FHB-HKSAR Product Insert (detailed) CoronaVac HK PI Clinical trial protocol PROFISCOV (ENG) Indonesian Food and Drug Authority Fact sheet BPOM FS Bueno et al Preprint Bueno Palacios et al Preprint Palacios
POPULATION		
Total Randomized	44, 325 (V : 21,895 C: 21,888) FDA T4 T5 – full analysis set 43,783 randomized 43783 received intervention (V : 21,895, C : 21,888) Sadoff T1	Brazil • Randomized : 12,408 Palacios p13 • Received at least 1 dose : 12,396 Palacios p13 • Target : 13,060 (Brazil) (PROTOCOL P9) Turkey : 7371 PI 2964 BPOM FS p 6 Indonesia : 1620 BPOM FS p5 Chile :
Inclusions	Stage 1 : >=18 yo, <60y Stage 2 : including >60 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 (CD4 count>300, viral load <50 copies, on stable ART x 6 months, no or stable comorbidities x 6 mo)	Adults over 18 years of age or older; Healthcare professionals who work in direct contact care of people with possible or confirmed COVID-19 cases PROFISCOV (ENG) P8 Palacios p11
• Age	18 years old and above mean – 50.7y(18-100) EMA P7 median = 52 >=60 yo = 33.5% (Sadoff T1) >= 65 yo = 19.6% >= 75 yo = 3.5% FDA T7 (FAS)	Older person recruited later >=60 years = 316 (5.1%) FHB-HKSAR P PI Palacios AT1 p26 -- 632(5.1%) total, 316(5.1%) vaccine group >60 (60-84y) = 600 BPOM p8
Trial Identifier	Janssen 2021 (ENSEMBLE - COV3001)	Coronavac 2021 (PROFISCOV-Brazil)
Vaccine	Ad26.CoV2.S	CoronaVac (Vero Cell)
• Race/ Ethnicity	58.7% white 3.3% Asians FDA T7 (FAS) Saddof T1	Asians 2.5% Palacios AT1 p26
• Immunocompromised	Included 1218 HIV patients (stable) FDA T8 (FAS)	
• Pregnant and breastfeeding	No	No
• With concomitant comorbidities	40.8% with at lease 1 comorbidity FDA T8 / FDA T7 (FAS) Sadoff T1	55.9% Palacios AT1 p27

Trial Identifier	**Janssen 2021 (ENSEMBLE - COV3001)**	**CoronaVac 2021 (PROFISCOV)**
Vaccine	**Ad26.CoV2.S**	**CoronaVac (Vero Cell)**
• With previous COVID infection	No	Initially no, but later allowed
• With known previous exposure to COVID	No mention	Brazil : healthcare workers Palacios p7 Chile : healthcare workers in contact with COVID patients Bueno p7
• Seropositive at baseline	Yes 9.6% overall FDA T7 (FAS), Sadoff T1 9.8% in vaccine group EMA P5, Sadoff T1	Initially no, but later allowed (later dropped restriction of prior infection)
Exclusions	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 COVID19 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 COVID19 (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 immunedefidiencies, surgery requiring hospitalization within 12 weeks before vaccination)	Pregnancy, breastfeeding; Uncontrolled neurological, cardiac, pulmonary, hepatic or renal disease, according to anamnesis or physical examination. impaired immune system including: neoplasms (except basal cell carcinoma), congenital or acquired immunodeficiencies and uncontrolled autoimmune diseases Alcohol or drug abuse in the last 12 months History of severe allergic reaction or anaphylaxis to the vaccine or components of the study vaccine; History of asplenia; Previous participation in a COVID-19 vaccine evaluation study or previous exposure to a COVID-19 vaccine; Use of immunosuppressive therapies six months prior to inclusion in the study or scheduled to be used within two years of inclusion. Have received an immunosuppressive dose of corticosteroids in the last three months Have received blood products (transfusions or immunoglobulins) in the last three months before inclusion Have received vaccination with live attenuated virus in the last 28 days or inactivated vaccine in the last 14 days prior to inclusion in the study, or have immunization scheduled for the first 28 days after inclusion in the study; History of bleeding disorders (for example, deficiency of clotting factors, coagulopathy, platelet dysfunction), or previous history of bleeding or significant bruising after IM injection or venipuncture; PROFISCOV (ENG) P8

Trial Identifier	**Janssen 2021 (ENSEMBLE - COV3001)**	**CoronaVac 2021 (PROFISCOV)**
Vaccine	**Ad26.CoV2.S**	**CoronaVac (Vero Cell)**
INTERVENTION (VACCINE)		
Type	Viral vector (adenovirus)	Inactivated virus
Active substance	Replication-incompetent recombinant adenovirus type 26 (Ad26)-vectored vaccine encoding a stabilized variant of the SARS-CoV-2 spike (S) protein FDA P12	Adsorbed (Inactivated) coronavirus SARS-CoV-2 (strain CZ02) and grown in an African green monkey kidney cell (Vero Cell), PROFISCOV (ENG) P17
Storage and Cold chain considerations		
● Shipping and transport		
● Storage and shelf life prior to dilution/ opening	2 years when stored at -25'C to – 15'C EMA P10 shelf life of 3 months as a refrigerated suspension at 2'C to 8"C FDA P12	2-8'C FHB HK-SAR P6 12 months shelf life FHB HK-SAR P6
● Storage and shelflife after dilution/ opening	unpunctured vials may be stored 9-25"C for up to 12 hours Punctured vials should be held between 2 to 8"C for up to 6 hours; or at room temperature (max 25"C) for up to 2 hours FDA P12 Product can be stored between 2'C-8'C for a max of 6 hours or remain at room temp (Max 25'C) up to 3 hours after first puncture of the vial EMA _10	
Form and use	Multidose vaccine (5 doses)	Prefilled syringe containing 0.5ml (600 SU) solution
Excipients	Citric acid monohydrate, trisodium citrate dehydrate, ethanol, 2-hydroxypropyl-B-cyclodextrin (HBCD), polysorbate 80, sodium chloride, sodium hydroxide and hydrochloric acid FDA P12	aluminum hydroxide, disodium hydrogen phosphate dodecahydrate, sodium dihydrogen phosphate monohydrate and sodium chloride. PROFISCOV (ENG) P26
Trial-specific considerations		
Dosing and administration	5 x 10^{10}vp administered as a single intramuscular dose (0.5ml) FDA P12	0.5ml solution (600SU of inactivated SARS-CoV-2 virus) administered 2 weeks apart intramuscular PROFISCOV (ENG) P27
Number randomized	22,174 21,895 (efficacy population) Sadoff T1	Brazil : 6,202 PI p1 / 2165 Palacios P13 Indonesia : 1620 BPOM p Turkey : 2964 BPOM p (planned population : 13000) Chile : 434 Bueno p11 (planned population : 2300)
COMPARATOR		
Type, dosing and administration	0.9% sodium chloride solution, 0.5ml	Aluminum hydroxide diluent, 0.5ml
Number randomized	22,151	Brazil : 6,194 PI p1 6201 Palacios p13

Trial Identifier	**Janssen 2021 (ENSEMBLE - COV3001)**	**CoronaVac 2021 (PROFISCOV)**
Vaccine	**Ad26.CoV2.S**	**CoronaVac (Vero Cell)**
OUTCOMES		
Primary efficacy endpoints	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 SpO2 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 of symptomatic cases of virologically confirmed COVID-19 two weeks after the second vaccination PROFISCOV (ENG) P9 COVID-19 infection definition as stated by the FDA guide : At least one symptom for 2 days or more with a SARS-CoV-2 NAAT : fever of chills, cough, shortness of breath, fatigue, muscle or body pain, headache, loss of smell or new taste, sore thorat, nasal congestion or runny nose, nausea or vomiting, diarrhea PROFISCOV (ENG) P52 Severe COVID – any lab-confirmed COVID-infection with one or more : clinical signes at reast indicating severe systemic disease (RR>= 30, HR >= 125/min, O2sat <=93% or PaO2 <300mmHg, respiratory failure (need for high flow supplemental O2, non-invasive ventilation, mechanical ventilation, or extracorporeal oxygenation), evidence of shock, major acute renal, hepatic or neurological dysfunction, admission to ICU, death PROFISCOV (ENG) P53
Primary safety endpoints	- Solicited local and systemic adverse reactions during 7 days following vaccination - Unsolicited AE during 28 days following vaccination - Medically attended AEs - SAEs from Day 1 to 104 weeks - Vaccine-enhanced disease	frequency of solicited and unsolicited local and systemic adverse reactions during the period of one week after vaccination stratified by age group (adults 18-59 years and elders 60 years of age or more). Adverse reactions are defined as adverse events that have a reasonable causal relationship to vaccination PROFISCOV (ENG) P9
Secondary endpoints	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	- incidence of cases of COVID-19 confirmed virologically, two weeks after the first vaccination. – - Incidence of symptomatic and asymptomatic SARS-CoV-2 infections detected serologically and / or virologically, two weeks after the second vaccination.. - Incidence of severe cases of COVID-19 confirmed virologically two weeks after second dose. - Frequency of adverse reactions to the vaccine, local and systemic, solicited and unsolicited, after each of the two doses, within the period of four weeks after vaccination stratified by age groups - Frequency of severe COVID-19 cases in participants who received at least one dose - frequency of Adverse Events of Special Interest - Immunogenicity Serological confirmation of SARS-CoV-2 infections will be by a four-fold increase in the level of IgG titers in validated serological assays PROFISCOV (ENG) P9-10

Trial Identifier	**Janssen 2021 (ENSEMBLE - COV3001)**	**CoronaVac 2021 (PROFISCOV)**
Vaccine	**Ad26.CoV2.S**	**CoronaVac (Vero Cell)**
Subgroups considered in the analysis		
● Age	Yes	Yes (18-59 vs >=60)
● Sex	Yes	Yes
● Ethnic groups	Yes	
● Baseline seropositivity status / evidence of previous infection	Yes	Yes
● Medical comorbidities	Yes	Yes
● Immunocompromised / HIV disease	No	
● Risk for acquiring COVID infection	Yes, based on comorbidities (those with risk of severe disease excluded)	
● Risk for progression to severe COVID	Excluded in stage 1 of recruitment	
● Dosing regimen	Not applicable	Yes (1st dose, dosing interval)
Follow up		
● Planned	24 months	1 year PROTOCOL ENG P29
● At data cutoff of interim report (first interim analysis)	Median follow up of 8 weeks after vaccination (58days) range 1-124 days – EMA P7	December 16, 2020 (Brazil) Palacios p13
Date of Data Cut-off date for latest available trial data	January 22, 2021 With additional data at Feb 5,2021	December 16,2020 (Brazil) FHB HK-SAR P8 / Palacios p13 January 9, 2021 (Brazil) BPOM FS p10 December 23,2020 (Turkey) BPOM FS p10 January 8, 2021 (Indonesia) BPOM FS p10
METHODS / OTHER TRIAL PARAMETERS		
Blinding	Participants, caregivers, investigators and outcome assessors	"followed blindly" patients, clinical care team PROTOCOL P29 "non blind study nurse" Bueno p8 "All participants, investigators, and laboratory staff were masked to arm allocation" Bueno p7 Cases confirmed by Clinical Endoint Adjudication Committee PI p2 / Palacios p12
Study Sites	US, Brazil, South Africa, Chile, Argentina, Colombia, Peru	Brazil, Turkey, Indonesia, Chile
Study Sponsor	Janssen Vaccines & Prevention B.V>	Sinovac
Type of report available as of this rapid review	Interim analysis, based on FDA (regulatory) report	Interim analysis preprints, Regulatory agency report summary, Clinical trial protocol and trial registration
Others	Phased recruitment, young patients in the early phase, older patients included in the latter phase	Some information across different reports do not match

Appendix 2a : Methodological Quality Assessment of Included Studies (Polack, Zaks, Voysey)

	Polack 2020 (C4591001)		Zaks 2020 (mRNA-1273-P301)		Voysey 2020 / 2021 (COV002, 003, 005)	
	BNT162b2		**mRNA-1273**		**ChAdOx1 nCoV19 / AZD1222**	
Randomization	Through the use of IRT system	U	Through the use of IRT system, using pregenerated randomization schedule	L	No mention on method in the protocol or paper	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

Appendix 2b : Methodological Quality Assessment of Included Studies (Logunov, Janssen, Coronavac)

	Logunov 2021 (RESIST)		**Janssen 2021 (COV3001)**		**Coronavac 2021 * (PROFISCOV)**	
	Gam-COVID-Vac		**Ad26.CoV2.S**		**CoronaVac**	
Randomization	Interactive web response system; statistician generated the sequence	L	Computer-generated randomization schedule prepared before the study	L	Electronic central randomization system Randomization by independent statistician	L
Allocation	Interactive web response system;	L	Interactive web response system will assign a unique intervention code	L	Electronic central randomization system	L
Blinding	Participants, investigators and all study staff were blinded	L	Participant, care provider, outcomes assessor	L	Patient, clinical care team, Cases confirmed by central adjudication committee	L
Follow up	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; Only one site with reported complete recruitment ~800+ with incomplete follow up at time of data cutoff ~1400 did not receive dose 2	U/H
Selective reporting	Interim analysis Adverse event not reported; pending verification	U	Interim analysis; some serology data not yet available	U	Interim analysis Full trial report not available Some data conflicting across several reports Missing data (for adverse events) Target trial population not matched to reported population	U/H
Others						

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

** Methodological quality assessment for the CoronaVac, particularly in the Follow up and Selective Reporting domains, is guarded in the light of the very limited information presented in the publicly available documents and conflicting data across reports.*

Appendix 3a : Detailed Efficacy Outcomes, BNT162b2 and mRNA-1273

Trial Identifier	Polack 2020 (C4591001)			Zaks 2020 (mRNA-1273-P301)		
Vaccine	BNT162b2			mRNA-1273		
	Vaccine cases / no.at risk (%) incidence rate per 1000 person years	**Control** cases / no.at risk (%) incidence rate per 1000 person years	**Vaccine Efficacy**	**Vaccine** cases / no.at risk (%) incidence rate per 1000 person years	**Control** cases / no.at risk (%) incidence rate per 1000 person years	**Vaccine Efficacy**
COVID-19 Infection (as defined by trialist), complete dosing, seronegative ONLY						
- after 7 days	8/17411 (<0.1%) 2.214 POLACK T2 UKMHRA T6 EMA T5 FDA T9	162/17511 (0.9%) 2.222 POLACK T2 UKMHRA T6 EMA T5 FDA T9	95.0 (90.3,97.6) POLACK T2 UKMHRA T6 EMA T5 FDA T9			
- after 14 days	8/16612 (<0.1%) 1.887 FDA T14 8/18175 (<0.1%) EMA T13	139/16663 (0.8%) 1.893 FDA T14 139/18261 (0.8%) EMA T13	94.2 (88.7, 97.2) FDA T14 94.2 (88.7, 97.2) EMA T13	12/14550 (<0.1%) 3.6 EMA T13 mITT BADEN TS17mITT 11/14134 (<0.1%) BADEN F4 PPS 11/13934 (<0.1%) FDA T17 PPS	185/14413 (1.3%) 54.7 EMA T13 mITT BADEN TS17mITT 185/14073 BADEN F4 PPS 185/13883 (1.3%) FDA T17 PPS	93.6 (88.5,96.4) EMA T13 mITT BADEN TS17mITT 94.1 (89.3, 96.8) BADEN F4 PPS 94.1 (89.3, 96.8) FDA T17 PPS
- after 21 days						
COVID-19 Infection (as defined by trialist), complete dosing, seronegative AND seropositive						
- after 7 days	9/18559 (<0.1%) 2.332 POLACK T2 EMA T5 FDA T10	169/18708 (0.9%) 2.345 POLACK T2 EMA T5 FDA T10	94.6 (89.9, 97.3) POLACK T2 EMA T5 FDA T10			
- after 14 days	8/17645 (<0.1%) 1.984 FDA T15 8/19965 (<0.1%) EMA T13	144/17746 (0.8%) 1.995 FDA T15 144/20171 (0.8%) EMA T13	94.4 (89.1,97.3) FDA T14 94.4 (89.1, 97.3) EMA T13	12/15181 (<0.1%) BADEN TS16 FAS 12/15169 (<0.1%) EMA T17 FAS	187/15170 (1.2%) BADEN TS16 FAS 187/14983 (1.2%) EMA T17 FAS	93.6 (88.6, 96.5) BADEN TS16 FAS 93.6 (88.6, 96.5) EMA T17 FAS
- after 21 days						

Trial Identifier	**Polack 2020 (C4591001)**			**Zaks 2020 (mRNA-1273-P301)**		
Vaccine	**BNT162b2**			**mRNA-1273**		
COVID-19 Infection (as defined by trialist) occurring after 1st dose, seronegative ONLY						
- all	50/21314 (0.2%) POLACK F3 EMA T7 FDA T11	275/21258 (1.3%) POLACK F3 EMA T7 FDA T11	82.0 (75.6,86.9) POLACK T2 EMA T7 FDA T11	21/15180 (0.1%) 7.1 FDA SL27 11/14073 BADEN TS16	173/15170 (1.1%) 59.0 FDA SL27 225/14073 BADEN TS16	87.9 (81.0, 82.7) FDA SL27 95.2 (91.2, 97.4) BADEN TS16
- anytime after dose 1 before dose 2	39/21314 (0.2%) POLACK F3 EMA T7 FDA T11	82/21258 (0.4%) POLACK F3 EMA T7 FDA T11	52.4 (29.5,68.4) POLACK F3 EMA T7 FDA T11	14/15180 (0.1%) 11.3 (1237.6) FDA SL27	46/15170 (0.3%) 37.0 (1242.1) FDA SL27	69.5 (43.5, 92.7) FDA SL27
- >=10 days after dose 1 before dose 2	6/21669 (<0.1%) EMA T7	45/21686 (0.2%) EMA T7	86.7 (68.6,95.4) EMA T7			
- >21 days after dose 1 before dose 2						
- dose 2 to 7 days after dose 2	2/21669 (<0.1%) POLACK F3 EMA T7 FDA T11	21/21686 (0.1%) POLACK F3 EMA T7 FDA T11	90.5 (61.0, 98.9) POLACK F3 EMA T7 FDA T11			
Anytime after dose 2				7/13857 (<0.1%) 2.5 FDA SL27	127/13792 (0.9%) FDA SL27	94.5 (88.4, 97.8) FDA SL27
- >=7 days after dose 2	9/21669 (<0.1%) POLACK F3 EMA T7 FDA T11	172/21686 (0.1%) POLACK F3 EMA T7 FDA T11	94.8 (89.8, 97.6) POLACK F3 EMA T7 FDA T11			
COVID-19 Infection (as defined by trialist), after 1st dose, seronegative AND seropositive						
- after 7 days						
- after 14 days						
- after 21 days						

Trial Identifier	**Polack 2020 (C4591001)**			**Zaks 2020 (mRNA-1273-P301)**		
Vaccine	**BNT162b2**			**mRNA-1273**		
Severe COVID-19 Infection, complete dosing, seronegative ONLY						
- after 7 days	1/17411 (<0.1%) 2.215 UKMHRA P32 EMA T12 FDA T16 1/21314 (<0.1%) POLACK TS5 mITT	3/17511 (<0.1%) 2.232 UKMHRA P32 EMA T12 FDA T16 4/21259 (<0.1%) POLACK TS5 mITT	66.4 (-124.8, 96.3) UKMHRA P32 EMA T12 FDA T16 75.0 (-152.6, 99.5) POLACK TS5 mITT			
Severe COVID-19 Infection, complete dosing, seronegative ONLY						
- after 14 days	1/16612 (<0.1%) 1.888 FDA T19	3/16663 (<0.1%) 1.901 FDA T19	66.4 (-124.7. 96.3) FDA T19	0/13934 (0%) FDA T18 PPS 0/14134 (0%) EMA T15 PP	30/13883 (0.2%) FDA T18 PPS 30/14043 (0.2%) EMA T15 PP	100% FDA T18 PPS 100% (NE, 100%) EMA T15 PP 100% (86.9, 100) WHO P5
- after 21 days						
Severe COVID-19 Infection, complete dosing, seronegative AND seropositive						
- after 7 days after dose 2	1/18566 (<0.1%) 2.333 FDA T17	3/18733 (<0.1%) 2.358 FDA T17	66.3 (-125.5, 96.3) FDA T17			
- after 14 days	1/17652 (<0.1%) 1.985 FDA T20	3/17792 (<0.1%) 2.007 FDA T20	66.3 (-125.6,96.3) FDA T20			
- after 21 days						
Asymptomatic COVID-19 infection, complete dosing, seronegative only						
- after 7 days						
- after 14 days						
- after 21 days						
Asymptomatic COVID-19 infection, complete dosing, seropositive AND seronegative						
- after 7 days						
- after 14 days after 2nd dose						
- after 21 days after 2nd dose						

Trial Identifier	**Polack 2020 (C4591001)**			**Zaks 2020 (mRNA-1273-P301)**		
Vaccine	**BNT162b2**			**mRNA-1273**		
Hospitalization due to COVID, complete dosing, seronegative only						
- after 7 days						
- after 14 days				0/14134 (0%) EMA P145 0/13934 (0%)	9*/14043 (0.2%) EMA P145 Severe* 9/13883 (<0.1%)	100%
- after 21 days						
Hospitalization due to COVID, complete dosing, seropositive AND seronegative						
- after 7 days						
- after 14 days after 2nd dose						
- after 21 days after 2nd dose						
ICU admission due to COVID, complete dosing, seronegative AND seropositive						
- after 7 days						
- after 14 days				0/14134 (0%) EMA P145 0/13934 (0%)	2*/14043 (<0.1%) EMA P145 Severe* 2/13883) (0.2%)	100%
- after 21 days						
ICU admission due to COVID, complete dosing, seronegative ONLY						
- after 7 days						
- after 14 days						
- after 21 days						
Death due to COVID, complete dosing, seronegative ONLY						
- after 7 days						
- after 14 days				0/13143 (0%) EMA P99	1/14073 (<0.1%) EMA P99	100%
- after 21 days						
Death due to COVID, complete dosing, seronegative AND seropositive						
- after 7 days						
- after 14 days						
- after 21 days						
SPECIAL POPULATIONS : COVID 19 infection, complete dosing, seronegative only						
>=65 years old, after 7 days of 2nd dose	1/3848 (<0.1%) 0.508 POLACK T3 EMA T8 FDA T12	19/3880 (0.5%) 0.511 POLACK T3 EMA T8 FDA T12	94.7 (66.7,99.9) POLACK T3 EMA T8 FDA T12			

Trial Identifier	**Polack 2020 (C4591001)**			**Zaks 2020 (mRNA-1273-P301)**		
Vaccine	**BNT162b2**			**mRNA-1273**		
SPECIAL POPULATIONS : COVID 19 infection, complete dosing, seronegative only						
>=65 years old, after 14 days of 2nd dose				4/3583 (0.1%) BADEN F4 EMA T18 PPS FDA T17 PPS	29/3552 (0.8%) BADEN F4 EMA T18 PPS FDA T17 PPS	86.4% (61.4, 95.5) BADEN F4 WHO P4 FDA T17 PPS
>= 75 years old, after 7 days of 2nd dose	0/774 (0%) 0.102 POLACK T3 EMA T10 FDA P57	5/785 (0.6%) 0.106 POLACK T3 EMA T10 FDA P57	100% (-13.1, 100.0) POLACK T3 EMA T10 FDA P57	0/623 (0%) FDA T10 PPS 0/630 (0%) EMA T18 PPS	3/676 (0.4%) FDA T10 PPS 7/688 (0.1%) EMA T18 PPS	100% 100%
< 18 years old	0/66 EMA P97	0/68 EMA P97	Unevaluable			
At high risk for COVID at 7 days after 2nd dose	4 / 8030 (<0.1%) 1.025 POLACK TS4 FDA T13	86/8029 (1.1%) 1.025 POLACK TS4 FDA T13	95.3 (87.7, 98.8) POLACK TS4 FDA T13			
At high risk for COVID, at 14 days after 2nd dose				4/3206 (0.1%) BADEN F4 EMA T18 PPS 1/3116 (<0.1%) FDA T13 PPS	43/3167 (1.4%) BADEN F4 EMA T18 PPS 24/3075 (0.8%) FDA T13 PPS	90.9% (74.7, 96.7) BADEN F4 EMA T18 PPS
Seropositive at baseline	1/526 (0.2%) EMA T9 (seronegative and positive)	1/567 (0.2%) EMA T8 (seronegative and positive)	-7.1 (-8309.9, 98.9) EMA T8 (seronegative and positive)	0/341 FDA T12 0/343 (0.3%) BADEN TS17 mITT	1/334 (0.3%) FDA T12 1/337 (0.3%) BADEN TS17 mITT	100%
Asian	1/764 (0.1%) 0.092 EMA T10	4/769 (0.5%) 0.093 EMA T10	74.6 (-156.6, 99.5) EMA T10	0/616 FDA T10 0/620 EMA T18 PPS	3/684 (0.4%) FDA T10 5/689 (0.7%) EMA T18 PPS	 100%

Appendix 3b : Additional efficacy and safety outcomes for BNT162b2 (for children aged 12-15 years)

	BNT162b2 No with event/Total No. Surveillance time (No. at risk)	**Control** No with event/Total No. Surveillance time (No. at risk)	**Vaccine Efficacy**
Covid-19 occurrence at least 7 days after dose 2 FRENCK 2021 T3			
Without evidence of previous infection	0/1005 0.154 (1001)	16/978 0.147 (972)	100 (75.3, 100)
With or without evidence of previous infection	0/1119 0.170 (1109)	18/1110 0.163 (1094)	100 (78.1, 100)
First COVID-19 occurrence after dose 1 FRENCK 2021 TS3			
After dose 1	3/1131 0.257 (1120)	35/1129 0.250 (1119)	91.6 (73.5, 98.4)
After dose 1 to before dose 2	3/1131 0.065 (1120)	12/1129 0.065 (1119)	75.1(7.6, 95.5)
After dose 1 to <11 days after dose1	3/1131 0.034 (1120)	4/1129 0.034 (1119)	25.1 (-342.6, 89.0)
>=11 days after dose 1 to before dose 2	0/1131 0.032 (1117)	8/1129 0.031 (1115)	100 (41.6, 100)
First COVID-19 occurrence after dose 2 to 7 days after dose 2 FRENCK 2021 TS3			
After dose 2	0/1131 0.021 (1114)	5/1129 0.021 (1105)	100 (-8.1, 100)
>=7 days after dose 2	0/1131 0.170 (1113)	18/1129 0.164 (1106)	100 (78.0, 100)
>= 7 days after dose 2 to <2 months after dose 2	0/1131 0.137 (1113)	16/1129 0.134 (1100)	100 (74.8, 100)
>= 2 months after dose 2 to <4 months after dose 2	0/1131 0.031 (654)	2/1129 0.029 (624)	100 (-399.9, 100)

Appendix 3c : Detailed Efficacy Outcomes, ChAdOx1 and Gam-COVID-Vac

Trial Identifier	Voysey 2020 (COV002, 003, 005)			Logunov 2021		
Vaccine	ChAdOx1 nCoV19 / AZD1222			Gam-COVID-Vac		
	Vaccine cases / no.at risk (%) incidence rate per 1000 person years	**Control** cases / no.at risk (%) incidence rate per 1000 person years	**Vaccine Efficacy**	**Vaccine** cases / no.at risk (%) incidence rate per 1000 person years	**Control** cases / no.at risk (%) incidence rate per 1000 person years	**Vaccine Efficacy**
Symptomatic COVID-19 Infection (as defined by trialist), complete dosing, seronegative ONLY						
- at day of dose 2						
- after 7 days				13/14094 (0.1%) LOGUNOV T2	47/4601 (1.0%) LOGUNOV T2	91.1% (83.8, 95.1) LOGUNOV T2
- after 14 days	30/5807 (0.52%) COVID NMA VOYSEY T2 84/8597 (1.0%) VOYSEY2021 T1	101/5829 (1.73%) COVID NMA VOYSEY T2 248/8581 (2.9%) VOYSEY2021 T1)	70.4 (54.8,80.6) COVID NMA VOYSEY T2 UKMHRA T8 66.7% (57.4, 74.0) VOYSEY2021 T1			
- after 21 days	51/6307 (0.8%) 39.7 VOYSEY T4	141/6297 (2.2%) 110.5 VOYSEY T4	64.1 (50.5, 73.9) VOYSEY T4			
Symptomatic COVID-19 Infection (as defined by trialist), complete dosing, seronegative AND seropositive						
- after 7 days						
- after 14 days	30/5807 (0.5%) 44.2	101/5829 (1.5%) 149.2	70.4 (54.8, 80.6)			
- after 21 days						
Symptomatic COVID-19 Infection (as defined by trialist) occurring after 1st dose, seronegative ONLY						
- all				79/16427 (0.5%) LOGUNOV T2	96/5435 (1.8%) LOGUNOV T2	73.1 (63.7, 80.1) LOGUNOV T2
- anytime after dose 1 before dose 2						
- >=10 days after dose 1 before dose 2						
- >+14 days after dose 1				30/14999 (0.2%) LOGUNOV T2	79/4950 (1.6%) LOGUNOV T2	87.6% (81.1, 91.8) LOGUNOV T2
=>21 days after dose 1 before dose 2	12/7998 (0.15%) UKMHRA T10	44/7982 (0.55%) UKMHRA T10	73.0% (48.8-85.8) UKMHRA T10	16/14964 (0.1%) LOGUNOV T2	62/4902 (1.3%) LOGUNOV T2	91.6% (85.6, 95.2) LOGUNOV T2
- dose 2 to 7 days after dose 2						
- >=7 days after dose 2						

Trial Identifier	**Voysey 2020 (COV002, 003, 005)**			**Logunov 2021**		
Vaccine	**ChAdOx1 nCoV19 / AZD1222**			**Gam-COVID-Vac**		
Symptomatic COVID-19 Infection (as defined by trialist), after 1st dose, seronegative AND seropositive						
- after 7 days						
- after 14 days						
- after 21 days						
Severe COVID-19 Infection, after dose 1, seronegative ONLY (Moderate to severe combined for Gam-COVID-Vac)						
- after 7 days						
- after 14 days	2/12021 (<0.1%) VOYSEY T5	16/11724 (0.1%) VOYSEY T5	97.6% (46-97.1) calculated			
- after 21 days				0/14964 (0%) *(Mod&Sev, after dose 1)* LOGUNOV T2 LOGUNOV S8	20/4902 (0.4%) *(Mod&Sev, after dose 1)* LOGUNOV T2 LOGUNOV S8	100% (94.4 – 100.0) LOGUNOV T2 LOGUNOV S8
Severe COVID-19 Infection, complete dosing, seronegative ONLY						
- after 7 days						
- after 14 days	0/ 12021 (0%) VOYSEY T5	1 / 11724 (<0.1%) VOYSEY T5	100%			
- after 21 days						
Severe COVID-19 Infection, complete dosing, seronegative AND seropositive						
- after 7 days after dose 2						
- after 14 days	0/12021 (0%)	1/11724 (<0.1%)	100%			
- after 21 days						
Asymptomatic COVID infection, complete dosing, seronegative ONLY						
- after 7 days						
- after 14 days	57/4071 (1.4%) VOYSEY2021 T1	73/4139 (1.8%) VOYSEY2021 T1	22.2% (-9.1, 45.0) VOYSEY2021 T1			
- after 21 days						
Hospitalization due to COVID, complete dosing, seronegative only						
- after 7 days						
- after 14 days	0/12021 (0%) VOYSEY T5 0/11794 (0%) VOYSEY2021 TS3	5/11724 (<0.1%) VOYSEY T5 9/11776 (<0.1%) VOYSEY2021 TS3	100% calculated 100% calculated			
- after 21 days						

Trial Identifier	**Voysey 2020 (COV002, 003, 005)**			**Logunov 2021**		
Vaccine	**ChAdOx1 nCoV19 / AZD1222**			**Gam-COVID-Vac**		
Hospitalization due to COVID, complete dosing, seropositive AND seronegative						
- after 7 days						
- after 14 days after 2nd dose						
- after 21 days after 2nd dose						
ICU admission due to COVID, complete dosing, seronegative ONLY						
- after 7 days						
- after 14 days						
- after 21 days						
ICU admission due to COVID, complete dosing, seronegative AND seropositive						
- after 7 days						
- after 14 days						
- after 21 days						
Death due to COVID, complete dosing, seronegative ONLY						
- after 7 days						
- after 14 days						
- after 21 days						
Death due to COVID, complete dosing, seronegative AND seropositive						
- after 7 days						
- after 14 days						
- after 21 days						
SPECIAL POPULATIONS : COVID 19 infection, complete dosing, seronegative only						
> 60 years old, at day of dose 2, 21 days after dose 1				2/1611 (0.1%) LOGUNOV T2	8/533 (1.5%) LOGUNOV T2	91.8% (67.1-98.3) LOGUNOV T2
>=65 years old, after 7 days of 2nd dose						
>=65 years old, after 14 days of 2nd dose						
>= 75 years old, after 7 days of 2nd dose						
< 18 years old	(12-15yo) 0/1001 (0%) FDA FS T9	16/972 (1.6%) FDA FS T9	100% (75.3, 100.0) FDA FS T9			
At high risk for COVID at 7 days after 2nd dose						
At high risk for COVID, at 14 days after 2nd dose	na	na	73.4% (48.5, 86.3) UKMHRA P33			

Appendix 3d : Additional efficacy outcomes for ChAdOx1

	ChAdOx1	Control	Vaccine Efficacy
By Dosing Regimen, >14 days after dose 2			
Low Dose / Standard Dose	10/1396 (0.2%) VOYSEY2021 T1	51/1402 (3.6%) VOYSEY2021 T1	80.7% (62.1, 90.2) VOYSEY2021 T1
Standard Dose / Standard Dose	74/7201 (1.0%) VOYSEY2021 T1	197/7179 (2.7%) VOYSEY2021 T1	63.1% (51.8, 71.7) VOYSEY2021 T1
By dosing interval, >14 days after dose 2			
<6 weeks interval (SD/SD only)	35/3890 (0.9%) VOYSEY2021 T1	76/3856 (2.0%) VOYSEY2021 T1	55.1% (33.0, 69.9) VOYSEY2021 T1
6-8 weeks (SD/SD only)	20/1112 (1.8%) VOYSEY2021 T1	44/1009 (4.4%) VOYSEY2021 T1	59.9% (32.0, 76.4) VOYSEY2021 T1
9-11 weeks (SD/SD only)	11/906 (1.2%) VOYSEY2021 T1	32/958 (3.3%) VOYSEY2021 T1	63.7% (28.0, 81.7) VOYSEY2021 T1
>=12 weeks (SD/SD only)	8/1293 (0.6%) VOYSEY2021 T1	45/1356 (3.3%) VOYSEY2021 T1	81.3% (60.3, 91.2) VOYSEY2021 T1
Asymptomatic COVID-19, more than 14 days after 2nd dose (SD/SD)	41/2692 (1.5%) VOYSEY2021 T1	42/2751 (1.5%) VOYSEY2021 T1	2.0% (-50.7, 36.2) VOYSEY2021 T1
Asymptomatic COVID-19, more than 14 days after 2nd dose (LD/SD)	16/1379 (1.2%) VOYSEY2021 T1	31/1385 (2.2%) VOYSEY2021 T1	49.3% (7.4, 72.2) VOYSEY2021 T1
Symptomatic COVID-19 with B.1.1.7 variant, LD/SD and SD/SD (N- 34, 14% (34/250) of sequenced sample for COV002)	7/4236 (0.2%) EMARY2021 T1	27/4270 (0.6%) EMARY2021 T1	74.6% (41.6%, 88.9%) EMARY2021 T1
Asymptomatic COVID-19 with B.1.1.7 variant LD/SD and SD/SD (N-14, 7% (14/208) of sequenced sample for COV002)	6/4236 (0.14%) EMARY2021 T1	8/4270 (0.18%) EMARY2021 T1	26.5% (-112.05, 74.5%) EMARY2021 T1

Appendix 3e : Detailed Efficacy Outcomes for Ad26.CoV2.S, CoronaVac

Trial Identifier	**Janssen 2021 (ENSEMBLE- COV3001)**			**Coronavac (PROFISCOV)**		
Vaccine	**Ad26.CoV.S**			**CoronaVac**		
	Vaccine cases / no.at risk (%) incidence rate per 1000 person years	**Control** cases / no.at risk (%) incidence rate per 1000 person years	**Vaccine Efficacy**	**Vaccine** cases / no.at risk (%) incidence rate per 1000 person years	**Control** cases / no.at risk (%) incidence rate per 1000 person years	**Vaccine Efficacy**
Symptomatic COVID-19 Infection (as defined by trialist), complete dosing, seronegative ONLY						
- at day of dose 2						
- after 14 days	117/19514 (0.6%) FDA T15 Sadoff T2	351/19544 (1.8%) FDA T15 Sadoff T2	66.9% (59.1, 73.4) FDA T15 Sadoff T2	85/4953 (1.7%) 754.6 FHB HK-SAR P8 Palacios p25	168/4870 (3.4%) 736.5 FHB HK-SAR P6 Palacios p25	50.65% (35.94, 61.98) FHB HK-SAR P6 50.7% (35.9, 62.0) Palacios p25
FDA harmonized COVID-19 cases	114/19514 (0.6%) FDA T15 Sadoff T2	345/19544 (1.8%) FDA T15 Sadoff T2	67.2 (59.3, 73.7) FDA T15 Sadoff T2	7/? BPOM FS p 10	18/? BPOM FS p 10	65% (INDO) BPOM FS p 10
- after 28 days	66/19306 (0.3%) FDA T15	195/19178 (1.0%) FDA T15	66.5% (55.5,75.1) FDA T15			
FDA harmonized COVID-19 cases	65/19306 (0.3%) FDA T15	193/19178 (1.0%) FDA T15	66.7% (55.6, 75.2) FDA T15			
- after 21 days						
COVID-19 Infection (as defined by trialist), complete dosing, seronegative AND seropositive						
- after 7 days						
- after 14 days						
- after 21 days						
COVID-19 Infection (as defined by trialist) occurring after 1st dose, seronegative ONLY						
- all						
- anytime after dose 1 before dose 2						
- >=10 days after dose 1 before dose 2						
- >+14 days after dose 1				94/5717 (1.6%) Palacios p25	219/5714 (3.8%) Palacios p25	57.9% (46.4, 66.9) Palacios p25
=>21 days after dose 1 before dose 2						
- Between 14 to 28 days				1/5709 (<0.1%) Palacios T3.5 p 55	17/5697 (0.3%) Palacios T3.5 p 55	94.0% (55.1, 99.2) Palacios T3.5 p55
- dose 2 to 7 days after dose 2						
- >=7 days after dose 2						

Trial Identifier	**Janssen 2021 (ENSEMBLE- COV3001)**			**Coronavac (PROFISCOV)**		
Vaccine	**Ad26.CoV.S**			**CoronaVac**		
COVID-19 Infection (as defined by trialist), after 1st dose, seronegative AND seropositive						
- after 14 days						
- after 28 days						
Severe COVID-19 Infection, after dose 1, seronegative ONLY						
- after 14 days						
- after 28 days						
Moderate to severe COVID-19 Infection, complete dosing, seronegative ONLY						
- after 14 days centrally confirmed only	116/19514 (0.6%) FDA T10 Sadoff T2	348/19544 (1.8%) FDA T10 Sadoff T2	66.9% (59.0, 73.4) FDA T10 Sadoff T2 66.3% (non-centrally confirmed) FDA P25	5/4953 (0.1%) 755.6 PI T3	30/4870 (0.6%) 737.9 PI T3	100% (56.37, 100) PI T3 FHB HK-SAR P6
- after 28 days	66/19306 (0.4%) FDA T10 Sadoff T2	193/19178 (1.0%) FDA T10 Sadoff T2	66.1% (55.0, 74.8) FDA T10 Sadoff T2 65.5% (non-centrally confirmed) FDA P25			
Severe COVID-19 Infection, complete dosing, seronegative ONLY						
- after 14 days including non-centrally confirmed	14/19514 (<0.1%) FDA T16 Sadoff T2 19/19514 (<0.1%) FDA T16 14/19630 (<0.1%) EMA T3	60/19544 (0.3%) FDA T15 Sadoff T2 80/19544 (0.4%) FDA T16 60/19691 (<0.3%) EMA T3	76.7% (54.6, 89.1) FDA T15 Sadoff T2 76.3% (57.9, 87.5) FDA T16 76.7% (54.6, 89.1) EMA T3	Score >= 4 0/4953 (0%) 755.6 PI T3 Severe 0/4953 (0%) Palacios p28	Score >= 4 10/4870 (0.2%) 753.2 PI T3 Severe 6/4870 (0.1%) Palacios p28	Score >= 4 100% (56.37, 100) PI T3 FHB HK-SAR P6 Severe 100% (16.9, 100) Palacios p28
- after 28 days including non-centrally confirmed	5/19306 (<0.1%) FDA T16 8/19306 (<0.1%) FDA T16 5/19630 (<0.1%) EMA T3	34/19178 (0.2%) FDA T16 48/19178 (0.3%) FDA T16 34/19691 (0.2%) EMA T3	85.4% (54.2, 96.9) FDA T16 83.5 % (54.2, 96.9) FDA T16 85.4% (54.2, 96.9) EMA T3			

Trial Identifier	**Janssen 2021 (ENSEMBLE- COV3001)**			**Coronavac (PROFISCOV)**		
Vaccine	**Ad26.CoV.S**			**CoronaVac**		
Severe COVID-19 Infection, complete dosing, seronegative AND seropositive						
- after 7 days						
- after 14 days						
- after 21 days						
Asymptomatic COVID infection, complete dosing, seronegative ONLY (+PCR and/or serology without previous symptoms)						
- after 7 days						
- from Day 1-29	87/19739 (0.4%) (1556.2) FDA T20	109/19809 (0.6%) (1559.3) FDA T20	20.0% (-7.0, 40.4) FDA T20			
- after Day 29	10/19301 (<0.1%) (3098.0) FDA T20	38/19162 (0.2%) (3061.5) FDA T20	74.0% (46.8,88.4) FDA T20			
Hospitalization due to COVID, complete dosing, seronegative only						
- after 7 days						
- at least 14 days after centrally confirmed	2/19514* (<0.1%) (3202.8) FDA T18	11/19544* (<0.1%) (3125.9) FDA T18	81.8 (16.7, 98.0) FDA T18			
including not centrally confirmed	2/19514* (<0.1%) (3125.8) FDA T18 * Used PPS denominator	29/19544* (0.1%) (3125.1) FDA T18 * Used PPS denominator	93.1 (72.7, 99.2) FDA T18			
- at least 28 days after centrally confirmed	0/19306* (0%) (3106.3) FDA T18	6/19178* (<0.1%) (3084.4) FDA T18	100 (15.7, 100) FDA T18			
including non-centrally confirmed	0/19306* (0%) (3106.3) FDA T18 * Used PPS denominator Sadoff FS5	16/19178* (<0.1%) (3083.9) FDA T18 * Used PPS denominator Sadoff FS5	100 (74.3,100) FDA T18 Sadoff FS5			
Hospitalization due to COVID, complete dosing, seropositive AND seronegative						
- after 7 days						
- after 14 days after 2nd dose (dose 1 for JnJ)						
- after 21 days after 2nd dose						

Trial Identifier	**Janssen 2021 (ENSEMBLE- COV3001)**			**Coronavac (PROFISCOV)**		
Vaccine	**Ad26.CoV.S**			**CoronaVac**		
ICU admission due to COVID, complete dosing, seronegative ONLY						
- after 7 days						
- after 14 days						
- after 21 days						
ICU admission due to COVID, complete dosing, seronegative AND seropositive						
- after 7 days						
- after 14 days						
- after 21 days						
Death due to COVID, complete dosing, seronegative ONLY						
- overall (including non-centrally confirmed cases)	0/19514 (0%) FDA P34 (used PPS as denominator)	7/19544 (<0.1%) FDA T19 (used PPS as denominator)	100% calculated FDA P34			
- after 14 days						
- after 21 days						
Death due to COVID, complete dosing, seronegative AND seropositive						
- after 7 days						
- after 14 days						
- after 21 days						
SPECIAL POPULATIONS : Moderate to Severe COVID 19 infection, complete dosing, seronegative only						
>=60 years old, after 14 days	16/3970 (0.4%) FDA T12	68/3992 (1.7%) FDA T12	76.5 (59.1, 87.3) FDA T12	2/212 (0.9%) Palacios p29	4/207 (1.9%) Palacios p29	51.11% (-166.93, 91.04) FHB HK-SAR P9 Palacios p29
>=65 years old, after 28 days	12/3928 (0.3%) FDA T2	38/3925 (1.0%) FDA T12	68.6 (38.6, 85.1) FDA T12			
>= 75 years old, after 14 days	0/19630 (0%) EMA T2 1/751 (0.1%) FDA T12	8/19691 (<0.1%) EMA T2 9/690 (1.3%) FDA T12	100 (45.90, 100) EMA T2 89.7(26.0, 99.8) FDA T12			
>= 75 years old, after 28 days	0/19630 (0%) EMA T2 0/740 (0%) FDA T12	3/19691 (0%) EMA T2 4/673 (0.6%) FDA T12	NE NE			
< 18 years old						

Trial Identifier	**Janssen 2021 (COV3001)**			**Coronavac (PROFISCOV)**		
Vaccine	**Ad26.CoV.S**			**CoronaVac**		
At high risk for COVID at >= 14 days after (with one comorbidity)	70/7777 (0.9%) FDA T13 Sadoff FS7	194/7798 (2.5%) FDA T13 Sadoff FS7	64.2 (52.7, 73.1) FDA T13 Sadoff FS7	44/2731 (1.6%) Palacios p29	86/2730 (3.2%) Palacios p29	48.9% (26.6, 64.5) Palacios p29
At high risk for COVID, at >=28 days after (with one comorbidity)	44/7684 (0.6%) FDA T13 Sadoff FS7	105/7626 (1.4%) FDA T13 Sadoff FS7	58.6 (40.6, 71.6) FDA T13 Sadoff FS7			
Asians, 14 days	6/714 (0.8%) FDA T12 Sadoff FS7	12/649 (1.8%) FDA T12 Sadoff FS7	54.4 (-31.1, 86.0) FDA T12 Sadoff FS7	1/125 (0.8%) Palacios p30	3/125 (2.4%) Palacios p30	66.0% (-226.8, 96.5) Palacios p30
Asians, 28 days	2/689 (0.2%) FDA T12 Sadoff FS7	7/626 (1.1%) FDA T12 Sadoff FS7	74.0 (-36.5, 97.4) FDA T12 Sadoff FS7			

Appendix 3f : Additional efficacy outcomes for Ad26.COV2.S (FDA T22)

Subgroup		Ad26.COV2.S	Control	Vaccine Efficacy
73% sequenced 94% Wuhan variant (**D614G**) no P1 no B1.1.7	Moderate to severe COVID-19			
	- At least 14 days after	51/9119 (0.6%)	196/9086 (2.2%)	74.4% (65.0,81.6)
	- At least 28 days after	32/8958 (0.4%)	112/8835 (1.3%)	72.0% (58.2, 81.7)
	Severe COVID-19			
	- At least 14 days after	4/9119 (<0.1%)	18/9086 (0.2%)	78.0% (33.1, 94.6)
	- At least 28 days after	1/8958 (<0.1%)	7/8835 (<0.1%)	85.9% (-9.4, 99.7)
66.9% sequenced 94.5% South African variant (**B.1.351)** no P1 no B1.1.7	Moderate to severe COVID-19			
	- At least 14 days after	43/2473 (1.7%)	90/2496 (3.6%)	52.0% (30.3, 67.4)
	- At least 28 days after	23/2449 (0.9%)	64/2463 (2.6%)	64% (41.2, 78.7)
	Severe COVID-19			
	- At least 14 days after	8/2473 (0.3%)	30/2496 (1.2%)	73.1% (40.0, 89.4)
	- At least 28 days after	4/2449 (0.2%)	22/2463 (0.9%)	81.7% (46.2, 95.4)
69.3% sequenced 69.4% **P.2 lineage** 30.6% D614G no P1 no B1.1.7	Moderate to severe COVID-19			
	- At least 14 days after	39/3370 (1.2%)	114/3355 (3.4%)	66.2% (51.0, 77.1)
	- At least 28 days after	24/3354 (0.7%)	74/3312 (2.2%)	68.1% (48.8, 80.7)
	Severe COVID-19			
	- At least 14 days after	2/3370 (<0.1%)	11/3355 (0.3%)	81.9% (17.0, 98.1)
	- At least 28 days after	1/3354 (<0.1%)	8/3312 (0.2%)	87.6% (7.8, 99.7)

Appendix 4a : Detailed Safety Outcomes (BNT162b2, mRNA-1273, ChAdOx1, Gam-COVID-Vac)

	BNT162b2		mRNA-1273		ChAdOx1		Gam-COVID-Vac	
	Vaccine	**Control**	**Vaccine**	**Control**	**Vaccine**	**Control**	**Vaccine**	**Control**
Solicited adverse reaction	*(rates reported per dose and by age group)*	*(rates reported per dose and by age group)*	14338/15176 (94.5%) FDA T19	9027/15162 (59.5%) FDA T19	2277/2648 (86.0%) UKMHRA T14	1791/2497 (71.7%) UKMHRA T14	na	na
Local adverse reactions	*(rates reported per dose and by age group)*	*(rates reported per dose and by age group)*	13962/15176 (92%) FDA T19	4381/15162 (28.0%) FDA T19	1979/2648 (74.7%) UKMHRA T14	1258/2497 (50.4%) UKMHRA T14	na	na
Systemic adverse reactions	*(rates reported per dose and by age group)*	*(rates reported per dose and by age group)*	12553/15176 (82.7%) FDA T19	8032/15162 (53.0%) FDA T19	1932/2648 (73.0%) UKMHRA T14	1488/2497 (59.6%) UKMHRA T14	na	na
Adverse events (any)	5770/21621 (26.7%) POLACK TS3 UKMHRA T12 EMA T17 FDA T8	2638/21631 (12.2%) POLACK TS3 UKMHRA T12 EMA T17 FDA T8	3631/15185 (23.9%) FDA T25	3277/15166 (19.4%) FDA T25	4539/12021 (37.8%) UKMHRA T17	3266/11724 (27.9%) UKMHRA T17	na	na
Severe adverse events (any)	240/21621 (1.1%) POLACK TS3 UKMHRA T12 EMA T17 FDA T8	139/21631 (0.6%) POLACK TS3 UKMHRA T12 EMA T17 FDA T8	234/15185 (1.5%) FDA T25	202/15166 (1.3%) FDA T25	na	na	91 events (gr 3) LOGUNOV P8	31 events (gr3) LOGUNOV P8
Serious adverse events (any)	126/21621 (0.6%) POLACK TS3 UKMHRA T12 EMA T17 FDA T8	111/21631 (0.5%) POLACK TS3 UKMHRA T12 EMA T17 FDA T8	93/15185 (0.6%) FDA T25	89/15166 (0.6%) FDA T25	79/12021 (0.7%) VOYSEY TS6	89/11724 (0.8%) VOYSEY TS6	45/16427 (0.3%) LOGUNOV P8 LOGUNOV S4	23/5435 (0.4%) LOGUNOV P8 LOGUNOV S4
Related serious adverse event	4/21621 (<0.1%) POLACK TS3 UKMHRA T12 EMA T17 FDA T6	0/21631 (0%) POLACK TS3 UKMHRA T12 EMA T17 FDA T6	7 /15185 (<0.1%) FDA T27	5/15166 (<0.1%) FDA T27	3/12021 (0.1%) UKMHRA P46	2/11724 (<0.1%) UKMHRA P46	na	na
Withdrawals due to adverse event	37/21621 (0.2%) POLACK TS3 UKMHRA T12 EMA T17 FDA T8	30/21631 (0.1%) POLACK TS3 UKMHRA T12 EMA T17 FDA T8	50/15185 (0.3%)	80/15166 (0.5%)	na	na	na	na
Death	2/21621 <0.1%) POLACK TS3 UKMHRA T12 EMA T17 FDA T8	4/21631 (<0.1%) POLACK TS3 UKMHRA T12 EMA T17 FDA T8	4/15184 (<0.1%) FDA T19 Dec 3 cutoff 6/15185 (<0.1%) EMA P116 FDA P42	4/15165 (<0.1%) FDA T19 7/15165 (<0.1%) EMA P116 FDA P42	2/12021 (<0.1%) UKMHRA P46	4/11724 (<0.1%) UKMHRA P46	3/16427 (<0.1%) LOGUNOV P8	1/5435 (<0.1%) LOGUNOV P8

Appendix 4b : Detailed Safety Outcomes (Ad26.CoV2.S, CoronaVac)

	Ad26.CoV.2		CoronaVac	
	Vaccine	**Control**	**Vaccine**	**Control**
Solicited adverse reaction	na	na	4536/6202 (73.1%) PI T2 Palacios T3-1 p36	3714/6194 (60.0%) PI T2 Palacios T3-1 p36
Local adverse reactions	1685/3356 (50.2%) FDA T23	657/3380 (19.4%) FDA T23	3815/6202 (61.51%) PI T2 Palacios T3-2 p37	2143 / 6194 (34.6%) PI T2 Palacios T3-2 p37
Systemic adverse reactions	1850/3356 (55.1%) FDA T23	1185/3380 (35.1%) FDA T23	2999/6202 (48.4%) PI T2 Palacios T3-2 p37	2947/6194 (47.6%) PI T2 Palacios T3-2 p37
Adverse events (any)	440/3356* (13.1%) FDA T23 * up to 28 days after vaccination	407/3380* (12.0%) FDA T23 * up to 28 days after vaccination	na	na
Severe adverse events (any)	19/3356 (0.6%) Sadoff TS7	18/3380 (0.5%) Sadoff TS7	98/6202 (1.6%) Palacios T3-1 p36	128/6194 (2.1) Palacios T3-1 p36
Serious adverse events (any)	83/21895 (0.4%) FDA T23	96/21888 (0.4%) FDA T23	33/6202 (0.5%) Palacios p14	31/6194 (0.5%) Palacios p14
Related serious adverse event	7/21895 (<0.1%) FDA T23	2/21888 (<0.1%) FDA T23	na	na
Withdrawals due to adverse event	0/21895 (0) FDA T23	0/21888 (0) FDA T23	na	na
Death	3/21895 (<0.1%) FDA T21 As of Feb 5 5/21895 (<0.1%) FDA P36	16/21888 (<0.1%) FDA T21 As of Feb 5 20/21888 (<0.1%) FDA P36	1/6202 (<0.1%) Palacios p14	1/6194 (<0.1%) Palacios p14

Appendix 4c : Additional Safety Outcomes for BNT162b2 (for children aged 12-15 years old)

Source : FRENCK TS2	**BNT162b2 n/N (%)**	**Control n/N (%)**
Any event	68/1131 (6.0)	67/1129 (5.9)
Any related adverse event	33/1131 (2.9)	21/1129 (1.9)
Any severe adverse event	7/1131 (0.6)	2/1129 (0.2)
Any life threatening adverse event	1/1131 (0.1)	1/1129 (0.1)
Any serious adverse event	4/1131 (0.4)	1/1129 (0.1)
Any related serious adverse event	0	0
Any severe serious adverse event	2/1131 (0.2)	0
Any serious life-threatening adverse event	0	1/1129 (0.1)
Any adverse event leading to discontinuation	2/1131 (0.2)	0
Any related adverse event leading to discontinuation	1/1131 (0.1)	0
Any severe adverse event leading to discontinuation	1/1131 (0.1)	0
Any life-threating adverse event leading to discontinuation	1/1131 (0.1)	0
Death	0	0

Appendix 5 : Evidence profile and summary of findings table

COMPARISON : BNT162b2 vs placebo									
Efficacy Outcome (at >7days after dose2)	**Quality Assessment**					**Summary of Findings**			
	Risk of Bias	**Inconsistency**	**Indirectness**	**Imprecision**	**Overall Assessment**	**Vaccine**	**Control**	**Vaccine Efficacy**	**Certainty**
1: Symptomatic COVID-19 infection	Some concerns (interim analysis) (incomplete ffup)	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 ffup)	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 ffup)	Not assessed	Not serious	Serious (crosses threshold)	Some concerns	39/21314 (0.2%)	82/21258 (0.4%)	52.4 (29.5, 68.4)	++ Low
4. Asymptomatic COVID-19 infection	Not assessed (not an outcome)	Not assessed	Not assessed	Not assessed	Not assessed	na	na	na	na
5 : Hospitalization	Not assessed (not an outcome)	Not assessed	Not assessed	Not assessed	Not assessed	na	na	na	na
6 : ICU Admission	Not assessed (not an outcome)	Not assessed	Not assessed	Not assessed	Not assessed	na	na	na	na
7 : Death due to COVID-19	Some concerns (interim analysis) (no event)	Not assessed	Not assessed	Not assessed (no event)	Not assessed	na	na	na	na
SUBGROUPS									
8 : Symptomatic COVID-19 infection, older adults (>=65yo)	Some concerns (interim analysis) (incomplete ffup)	Not assessed	Not serious	Not serious	Some concerns	1/3848 (<0.1%)	19/3880 (0.5%)	94.7 (66.7, 99.9)	+++ Moderate
9 : Symptomatic COVID-19 infection, older adults (>=75yo)	Some concerns (interim analysis) (incomplete ffup)	Not assessed	Not serious	Serious (wide CI)	Serious	0/774 (0%)	5/785 (0.6%)	100% (-13.1, 100.0)	++ Low
10. Symptomatic COVID-19 infection, adolescents (12-15 yo)	Some concerns (interim analysis) (incomplete ffup)	Not assessed	Not serious	Not serious	Some concerns	0/1001 (0%)	16/972 (1.6%)	100% (75.3,100.0)	+++ Moderate
11 : Symptomatic COVID-19 infection, at risk	Some concerns (interim analysis) (incomplete ffup)	Not assessed	Not serious	Not serious	Serious	4/ 8030 (<0.1%)	86/8029 (1.1%)	95.3 (87.7, 98.8)	+++ Moderate
12 :Symptomatic COVID-19 infection, Asian	Some concerns (interim analysis) (incomplete ffup)	Not assessed	Not serious	Serious (wide CI)	Serious	1/764 (0.1%)	4/769 (0.5%)	74.6 (-156.6, 99.5)	++ Low
COMPARISON : BNT162b2 vs placebo									
Efficacy	**Quality Assessment**					**Summary of Findings**			**Certainty**

Outcome (at >7days after dose2)	**Risk of Bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Overall Assessment**	**Vaccine**	**Control**	**Vaccine Efficacy**	
13. Symptomatic COVID-19 infection, B.1.1.7 variant	Not assessed (not an outcome)	Not assessed	Not assessed	Not assessed	Not assessed	na	na	na	Na
14. Symptomatic COVID-19 infection, B.1.351 variant	Not assessed (not an outcome)	Not assessed	Not assessed	Not assessed	Not assessed	na	na	na	na
15. Symptomatic COVID-19 infection, P1/P2 lineage	Not assessed (not an outcome)	Not assessed	Not assessed	Not assessed	Not assessed	na	na	na	na

COMPARISON : BNT162b2 vs placebo									
	Quality Assessment					Summary of Findings			
Safety Outcome	Risk of Bias	Inconsistency	Indirectness	Imprecision	Overall Assessment	Vaccine	Control	Relative Risk	Certainty
1 : Adverse reaction	Not serious	Not assessed	Not assessed	Not assessed	Not assessed (no overall)	na	na	na	na
2. Local adverse reaction	Not serious	Not assessed	Not assessed	Not assessed	Not assessed (no overall)	na	na	na	na
3. Systemic adverse reaction	Not serious	Not assessed	Not assessed	Not assessed	Not assessed (no overall)	na	na	na	na
4 : Adverse event	Serious (interim analysis) (incomplete ffup)	Not assessed	Not serious	Not serious	Serious	5770/21621 (26.7%)	2638/21631 (12.2%)	2.19 (2.10-2.28)	+++ Moderate
5. Severe adverse event	Serious (interim analysis) (incomplete ffup)	Not assessed	Not serious	Not serious	Serious	240/21621 (1.1%)	139/21631 (0.6%)	1.73 (1.40-2.13)	+++ Moderate
6: Serious adverse event	Serious (interim analysis) (incomplete ffup)	Not assessed	Not serious	Serious (wide CI)	Serious	126/21621 (0.6%)	111/21631 (0.5%)	1.14 (0.88-1.46)	++ Low
7: Related serious adverse event	Serious (interim analysis)	Not assessed	Not serious	Serious (wide CI)	Serious	4/21621 (<0.1%)	0/21631 (0%)	9.00 (0.48-167.15)	++ Low
8 : Withdrawals due to adverse event	Serious (interim analysis) (incomplete ffup)	Not assessed	Not serious	Serious (wide CI)	Serious	37/21621 (0.2%)	30/21631 (0.1%)	1.23 (0.76-2.00)	++ Low
9 : Death	Serious (interim analysis) (incomplete ffup)	Not assessed	Not serious	Serious (wide CI)	Serious	2/21621 (<0.1%)	4/21631 (<0.1%)	0.5 (0.09-2.73)	++ Low

COMPARISON : mRNA-1273 vs placebo									
Efficacy Outcome (at >14days after dose2)	**Quality Assessment**					**Summary of Findings**			
	Risk of Bias	**Inconsistency**	**Indirectness**	**Imprecision**	**Overall Assessment**	**Vaccine**	**Control**	**Vaccine Efficacy**	**Certainty**
1: Symptomatic COVID-19 infection	Some concerns (interim analysis) (incomplete ffup)	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 ffup)	Not assessed	Not serious	Serious (wide CI)	Serious	0/13934 (0%)	30/13883 (0.2%)	100% (NE, 100%)	++ Low
3 : COVID-19 infection, postD1, preD2	Some concerns (interim analysis) (incomplete ffup)	Not assessed	Not serious	Not serious	Some concerns	14/15180 (0.1%)	46/15170 (0.3%)	69.5 (43.5, 92.7)	+++ Moderate
4. Asymptomatic COVID-19 infection	Some concerns (Not reported)	Not assessed	Not assessed	Not assessed	Not assessed	na	na	na	na
5 : Hospitalization	Some concerns (interim analysis) (incomplete ffup)	Not assessed	Not assessed	Serious (wide CI)	Serious	0/13934 (0%)	9/13883 (<0.1%)	100% (NE, 100%)	++ Low
6 : ICU Admission	Some concerns (interim analysis) (incomplete ffup)	Not assessed	Not assessed	Serious (wide CI)	Serious	0/13934 (0%)	2/13883 (<0.1%)	100% (NE, 100%)	++ Low
7 : Death due to COVID-19	Some concerns (interim analysis) (incomplete ffup)	Not assessed	Not assessed	Serious (wide CI)	Not assessed	0/13143 (0%)	1/14073 (<0.1%)	100% (NE, 100)	++ Low
SUBGROUPS									
8 : Symptomatic COVID-19 infection, older adults (>=65yo)	Some concerns (interim analysis) (incomplete ffup)	Not assessed	Not serious	Not serious	Some concerns	4/3583 (0.1%)	29/3552 (0.8%)	86.4 (61.4,95.2)	+++ Moderate
9 : Symptomatic COVID-19 infection, older adults (>=75yo)	Some concerns (interim analysis) (incomplete ffup)	Not assessed	Not serious	Very serious (wide CI)	Very serious	0/630 (0%)	7/688 (0.4%)	100% (NE, 100%)	++ Very Low
10 : Symptomatic COVID-19 infection, at risk	Some concerns (interim analysis) (incomplete ffup)	Not assessed	Not serious	Not serious	Some concerns	4/3206 (0.1%)	43/3167 (1.4%)	90.9 (74.7,96.7)	+++ Moderate
11 : Symptomatic COVID-19 infection, Asian	Some concerns (interim analysis) (incomplete ffup)	Not assessed	Not serious	Very serious (wide CI)	Very serious	0/620 (0%)	5/689 (0.7%)	100% (NE, 100%)	++ Very Low
12. Symptomatic COVID-19 infection, B.1.1.7 variant	Not assessed (not an outcome)	Not assessed	Not assessed	Not assessed	Not assessed	na	na	na	na
13. Symptomatic COVID-19 infection, B.1.351 variant	Not assessed (not an outcome)	Not assessed	Not assessed	Not assessed	Not assessed	na	na	na	na
14. Symptomatic COVID-19 infection, P1/P2 lineage	Not assessed (not an outcome)	Not assessed	Not assessed	Not assessed	Not assessed	na	na	na	na

COMPARISON : mRNA-1273 vs placebo									
	Quality Assessment					Summary of Findings			
Safety Outcome	Risk of Bias	Inconsistency	Indirectness	Imprecision	Overall Assessment	Vaccine	Control	Relative Risk	Certainty
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%)	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 ffup)	Not assessed	Not serious	Not serious	Some concerns	3632/15185 (23.9%)	3277/15166 (21.6%)	1.11 (1.06, 1.15)	+++ Moderate
5. Severe adverse event	Some concerns (interim analysis) (incomplete ffup)	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 ffup)	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 ffup)	Not assessed	Not serious	Serious (wide CI)	Serious	6/15185 (<0.1)	4/15166 (<0.1)	1.50 (0.42, 5.31)	++ Low
8 : Withdrawals due to adverse event	Some concerns (interim analysis) (incomplete ffup)	Not assessed	Not serious	Not serious	Some concerns	50/15185 (0.3%)	80/15166 (0.5%)	0.62 (0.42, 0.89)	+++ Moderate
9 : Death	Some concerns (interim analysis) (incomplete ffup)	Not assessed	Not serious	Serious (wide CI)	Serious	6/15185 (<0.1)	7/15165 (<0.1)	0.86 (0.29, 2.55)	++ Low

COMPARISON : ChAdOx1 vs control (MenACWY / saline)									
Efficacy Outcome (>14 days after dose 2)	**Quality Assessment**					**Summary of Findings**			
	Risk of Bias	**Inconsistency**	**Indirectness**	**Imprecision**	**Overall Assessment**	**Vaccine**	**Control**	**Vaccine Efficacy**	**Certainty**
1: Symptomatic COVID-19 infection	Some concerns (interim analysis) (incomplete ffup)	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 ffup)	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 ffup)	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 ffup)	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 ffup)	Not assessed	Not serious	Serious (wide CI)	Serious	0/11794 (0%)	9/11776 (<0.1%)	100%	++ Low
6 : ICU Admission	Some concerns (interim analysis) (incomplete ffup)	Not assessed	Not assessed	Not assessed	Not assessed	na	na	na	na
7 : Death due to COVID-19	Some concerns (interim analysis) (incomplete ffup) (no event)	Not assessed	Not assessed	Not assessed (no event)	Not assessed	na	na	na	na
SUBGROUPS									
8 : Symptomatic COVID-19 infection, older adults (>=65yo)	Some concerns (interim analysis) (not reported)	Not assessed	Not assessed	Not assessed	Not assessed	na	na	na	na
9 : Symptomatic COVID-19 infection, older adults (>=75yo)	Some concerns (interim analysis) (not reported)	Not assessed	Not serious	Not assessed	Not assessed	na	na	na	na
10 : Symptomatic COVID-19 infection, at risk	Some concerns (interim analysis) (not reported)	Not assessed	Not serious	Not assessed	Not assessed	na	na	na	na
11 : Symptomatic COVID-19 infection, Asian	Some concerns (interim analysis) (not reported)	Not assessed	Not serious	Not assessed	Not assessed	na	na	na	na
11: Symptomatic COVID-19 infection, LD/SD	Some concerns (interim analysis) (incomplete ffup)	Not assessed	Not serious	Not serious	Some concerns	10/1396 (0.2%)	51/1402 (3.6%)	80.7% (62.1, 90.2)	+++ Moderate

COMPARISON : ChAdOx1 vs control (MenACWY / saline)									
Efficacy Outcome (>14 days after dose 2)	**Quality Assessment**					**Summary of Findings**			
	Risk of Bias	**Inconsistency**	**Indirectness**	**Imprecision**	**Overall Assessment**	**Vaccine**	**Control**	**Vaccine Efficacy**	**Certainty**
12 : Symptomatic COVID-19 infection, SD/SD, >= 12weeks interval	Some concerns (interim analysis) (incomplete ffup)	Not assessed	Not serious	Not serious	Some concerns	8/1293 (0.6%)	45/1356 (3.3%)	81.3% (60.3, 91.2)	+++ Moderate
13. Symptomatic COVID-19 infection, B.1.1.7 variant	Serious (interim analysis) (missing data) (incomplete ffup)	Not assessed	Not serious	Not serious	Serious	7/4236	27/4270	74.6% (41.6, 88.9)	++ Low
14. Symptomatic COVID-19 infection, B.1.351 variant	Not assessed (not an outcome)	Not assessed	Not assessed	Not assessed	Not assessed	na	na	na	na
15. Symptomatic COVID-19 infection, P1/P2 lineage	Not assessed (not an outcome)	Not assessed	Not assessed	Not assessed	Not assessed	na	na	na	na

COMPARISON : ChAdOx1 vs control (MenACWY / saline)									
	Quality Assessment					Summary of Findings			
Safety Outcome	Risk of Bias	Inconsistency	Indirectness	Imprecision	Overall Assessment	Vaccine	Control	Relative Risk	Certainty
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 ffup)	Not assessed	Not serious	Not serious	Some concerns	2207/5807 (38%)	1632/5829 (28%)	1.36 (1.29, 1.43)	+++ Moderate
5. Severe adverse event	Some concerns (interim analysis) (incomplete ffup)	Not assessed	Not assessed	Not assessed	Not assessed (not reported)	na	na	na	na
6: Serious adverse event	Some concerns (interim analysis) (incomplete ffup)	Not assessed	Not serious	Serious (wide CI)	Serious	79/12021 (0.7%)	89/11724 (0.8%)	0.87 (0.64, 1.17)	++ Low
7: Related serious adverse event	Some concerns (interim analysis) (incomplete ffup)	Not assessed	Not assessed	Serious (wide CI)	Serious	3/12021 (<0.1%)	2/11724 (<0.1%)	1.46 (0.24, 8.75)	++ Low
8 : Withdrawals due to adverse event	Some concerns (interim analysis) (incomplete ffup)	Not assessed	Not assessed	Not assessed	Not assessed (not reported)	na	na	na	na
9 : Death	Some concerns (interim analysis) (incomplete ffup)	Not assessed	Not serious	Serious (wide CI)	Serious	2/12021 (<0.1%)	4/11724 (<0.1%)	0.49 (0.09-2.66)	++ Low

COMPARISON : Gam-COVID-Vac vs placebo (Vaccine buffer)									
Efficacy Outcome (>7 days after dose 2)	**Quality Assessment**					**Summary of Findings**			
	Risk of Bias	**Inconsistency**	**Indirectness**	**Imprecision**	**Overall Assessment**	**Vaccine**	**Control**	**Vaccine Efficacy**	**Certainty**
1: Symptomatic COVID-19 infection	Some concerns (interim analysis) (incomplete ffup)	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 *(after 21d after dose 1*	Some concerns (interim analysis) (incomplete ffup)	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 ffup)	Not assessed	Not serious	Not serious	Some concerns	79/16427 (0.5%)	96/5435 (1.8%)	73.1 (63.7, 80.1)	+++ Moderate
4. Asymptomatic COVID-19 infection	Some concerns (interim analysis) (not reported)	Not assessed	Not assessed	Not assessed	Not assessed	na	na	na	na
5 : Hospitalization	Some concerns (interim analysis) (not reported)	Not assessed	Not serious	Not assessed	Not assessed	na	na	na	na
6 : ICU Admission	Some concerns (interim analysis) (not reported)	Not assessed	Not assessed	Not assessed	Not assessed	na	na	na	na
7 : Death due to COVID-19	Some concerns (interim analysis) (no event)	Not assessed	Not assessed	Not assessed (no event)	Not assessed	na	na	na	na
SUBGROUPS									
8 : COVID-19 infection, older adults (>=65yo)	Some concerns (interim analysis) (not reported)	Not assessed	Not assessed	Not assessed	Not assessed	na	na	na	na
9 : COVID-19 infection, older adults (>=75yo)	Some concerns (interim analysis) (not reported)	Not assessed	Not serious	Not assessed	Not assessed	na	na	na	na
10 : COVID-19 infection, at risk*	Some concerns (interim analysis) (not reported)	Not assessed	Not serious	Not assessed	Not assessed	na	na	na	na
11 : COVID-19 infection, Asian	Some concerns (interim analysis) (not reported)	Not assessed	Not serious	Not assessed	Not assessed	na	na	na	na

COMPARISON : Gam-COVD-Vac vs placebo (vaccine buffer)									
	Quality Assessment					Summary of Findings			
Safety Outcome	Risk of Bias	Inconsistency	Indirectness	Imprecision	Overall Assessment	Vaccine	Control	Relative Risk	Certainty
1 : Adverse reaction	Some concerns (interim analysis) (not reported)	Not assessed	Not assessed	Not assessed	Not assessed (not reported)	na	na	na	na
2 : Local adverse reaction	Some concerns (interim analysis) (not reported)	Not assessed	Not assessed	Not assessed	Not assessed (not reported)	na	na	na	na
3. Systemic adverse reaction	Some concerns (interim analysis) (not reported)	Not assessed	Not assessed	Not assessed	Not assessed (not reported)	na	na	na	na
4 : Adverse event	Some concerns (interim analysis) (not reported)	Not assessed	Not assessed	Not assessed	Not assessed (not reported)	na	na	na	na
5. Severe adverse event	Some concerns (interim analysis) (not fully reported)	Not assessed	Not assessed	Not assessed	Not assessed (not reported)	na	na	na	na
6: Serious adverse event	Some concerns (interim analysis) (incomplete ffup)	Not assessed	Not serious	Serious (wide CI)	Serious	45/16427 (0.3%)	23/5435 (0.4%)	0.65 (0.39, 1.07)	++ Low
7: Related serious adverse event	Some concerns (interim analysis) (not reported)	Not assessed	Not assessed	Not assessed	Not assessed (not reported)	na	na	na	na
8 : Withdrawals due to adverse event	Some concerns (interim analysis) (not reported)	Not assessed	Not assessed	Not assessed	Not assessed (not reported)	na	na	na	na
9 : Death	Some concerns (interim analysis) (incomplete ffup)	Not assessed	Not serious	Serious (wide CI)	Serious	3/16427 (<0.1%)	1/5435 (<0.1%)	0.99 (0.10-9.54)	++ Low

COMPARISON : Ad26.CoV2.S vs placebo									
Efficacy Outcome >14 days after	**Quality Assessment**					**Summary of Findings**			
	Risk of Bias	**Inconsistency**	**Indirectness**	**Imprecision**	**Overall Assessment**	**Vaccine**	**Control**	**Vaccine Efficacy**	**Certainty**
1: Symptomatic COVID-19 infection *(used values for FDA harmonized cases)*	Some concerns (interim analysis) (incomplete ffup)	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 ffup)	Not assessed	Not serious	Not serious	Some concerns	116/19514 (0.6%)	348/19544 (1.8%)	66.9% (59.0, 73.4)	+++ Moderate
2b : Severe COVID-19 infection *(including non-centrally confirmed)*	Some concerns (interim analysis) (incomplete ffup)	Not assessed	Not serious	Not serious	Some concerns	19/19514 (<0.1%)	80/19544 (0.4%)	76.3% (57.9, 87.5)	+++ Moderate
3 : COVID-19 infection, after 1st dose	Some concerns (interim analysis) (not assessed)	Not assessed	Not assessed	Not assessed	Not assessed	na	na	na	na
4. Asymptomatic COVID-19 infection *(from Day 1 to 29) (+PCR and/or serology)*	Some concerns (interim analysis) (incomplete ffup)	Not assessed	Not serious	Serious	Serious	87/19739 (0.4%)	109/19809 (0.6%)	20.0% (-7.0, 40.4)	++ Low
5 : Hospitalization *(including non-centrally confirmed)*	Some concerns (interim analysis) (incomplete ffup)	Not assessed	Not serious	Not serious	Some concerns	2/19514 (<0.1%)	29/19544 (0.1%)	93.1% (72.7, 99.2)	+++ Moderate
6 : ICU Admission	Some concerns (interim analysis) (not assessed)	Not assessed	Not assessed	Not assessed	Not assessed	na	na	na	na
7 : Death due to COVID-19	Some concerns (interim analysis) (incomplete ffup)	Not assessed	Not serious	Serious	Serious	0/19514 (0.%)	7/19544 (<0.1%)	100% (NE)	++ Low
SUBGROUPS									
8 : Moderate-Severe COVID-19 infection, older adults(>=60yo)	Some concerns (interim analysis) (incomplete ffup)	Not assessed	Not serious	Not serious	Some concerns	16/3970 (0.4%)	68/3992 (1.7%)	76.5 (59.1, 87.3)	+++ Moderate
9 : Moderate-Severe COVID-19 infection, older adults(>=75yo)	Some concerns (interim analysis) (incomplete ffup)	Not assessed	Not serious	Serious	Serious	1/751 (0.1%)	9/690 (1.3%)	89.7% (26.0,99.8)	++ Low
10 : Moderate-Severe COVID-19 infection, at risk	Some concerns (interim analysis) (incomplete ffup)	Not assessed	Not serious	Not serious	Some concerns	70/7777 (0.1%)	194/7798 (2.5%)	64.2 (52.7, 73.1)	+++ Moderate
11 : Symptomatic COVID-19 infection, Asian	Some concerns (interim analysis) (incomplete ffup)	Not assessed	Not serious	Serious	Serious	6/714 (0.8%)	12/649 (1.8%)	54.4 (-31.1, 86.0)	++ Low

COMPARISON : Ad26.CoV2.S vs placebo									
Efficacy Outcome >14 days after	**Quality Assessment**					**Summary of Findings**			
	Risk of Bias	**Inconsistency**	**Indirectness**	**Imprecision**	**Overall Assessment**	**Vaccine**	**Control**	**Vaccine Efficacy**	**Certainty**
12: Symptomatic COVID-19 infection, B.1.1.7 variant	Not assessed (interim analysis) (not an outcome)	Not assessed	Not serious	Not serious	Not assessed	na	na	na	na
13: Moderate-Severe COVID-19 infection, B.1.351 variant	Serious (interim analysis) (missing data) (incomplete ffup)	Not assessed	Not serious	Not serious	Serious	43/2473 (1.7%)	90/2496 (3.6%)	52.0% (30.3, 67.4)	++ Low
14: Severe COVID-19 infection, B.1.351 variant	Serious (interim analysis) (missing data) (incomplete ffup)	Not assessed	Not serious	Not serious	Serious	8/2473 (0.3%)	30/2496 (1.2%)	73.1% (40.0, 89.4)	++ Low
15: Moderate-Severe COVID-19 infection, P1 lineage	Serious (interim analysis) (missing data) (incomplete ffup)	Not assessed	Not serious	Not serious	Serious	39/3370 (1.2%)	114/3355 (3.4%)	66.2% (51.0, 77.1)	++ Low
16. Severe COVID-19 infection, P2 lineage	Serious (interim analysis) (missing data) (incomplete ffup)	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

COMPARISON : Ad26.CoV2.S vs placebo									
Efficacy Outcome >28 days after	**Quality Assessment**					**Summary of Findings**			
	Risk of Bias	**Inconsistency**	**Indirectness**	**Imprecision**	**Overall Assessment**	**Vaccine**	**Control**	**Vaccine Efficacy**	**Certainty**
1: Symptomatic COVID-19 infection *(used values for FDA harmonized cases)*	Some concerns (interim analysis) (incomplete ffup)	Not assessed	Not serious	Not serious	Some concerns	65/19306 (0.3%)	193/19178 (1.0%)	66.7% (55.6, 75.2)	+++ Moderate
2a : Moderate & Severe COVID-19 infection *(centrally confirmed)*	Some concerns (interim analysis) (incomplete ffup)	Not assessed	Not serious	Not serious	Some concerns	66/19306 (0.3%)	193/19178 (1.0%)	66.1% (55.0, 74.8)	+++ Moderate
2b : Severe COVID-19 infection *(including non-centrally confirmed)*	Some concerns (interim analysis) (incomplete ffup)	Not assessed	Not serious	Not serious	Some concerns	8/19306 (<0.1%)	48/19178 (0.3%)	83.5 % (54.2, 96.9)	+++ Moderate
3 : COVID-19 infection, after 1st dose	Some concerns (interim analysis) (not assessed)	Not assessed	Not assessed	Not assessed	Not assessed	na	na	na	na
4. Asymptomatic COVID-19 infection *(after Day 29)*	Some concerns (interim analysis) (incomplete ffup)	Not assessed	Not serious	Not serious	Some concerns	10/19301 (<0.1%)	38/19162 (0.2%)	74.0% (46.8,88.4)	+++ Moderate
5 : Hospitalization *(including non-centrally confirmed)*	Some concerns (interim analysis) (incomplete ffup)	Not assessed	Not serious	Not serious	Some concerns	0/19306 (0%)	16/19178 (<0.1%)	100 (74.3,100)	+++ Moderate
6 : ICU Admission	Some concerns (interim analysis) (not assessed)	Not assessed	Not assessed	Not assessed	Not assessed	na	na	na	na
7 : Death due to COVID-19 *(including non-centrally confirmed, overall)*	Some concerns (interim analysis) (incomplete ffup)	Not assessed	Not serious	Serious (wide CI)	Serious	0/19514 (0%)	7/19544 (<0.1%)	100%	++ Low
SUBGROUPS									
8 : Moderate-Severe COVID-19 infection, older adults (>=65yo)	Some concerns (interim analysis) (incomplete ffup)	Not assessed	Not serious	Not serious	Some concerns	12/3928 (0.3%)	38/3925 (1.0%)	68.6% (38.6, 85.1)	+++ Moderate
9 : Moderate-Severe COVID-19 infection, older adults (>=75yo)	Some concerns (interim analysis) (incomplete ffup)	Not assessed	Not serious	Serious	Serious	0/740 (0%)	4/673 (0.6%)	NE	++ Low

Efficacy Outcome >28 days after	Quality Assessment					Summary of Findings			
	Risk of Bias	Inconsistency	Indirectness	Imprecision	Overall Assessment	Vaccine	Control	Vaccine Efficacy	Certainty
10 : Moderate-Severe COVID-19 infection, at risk *(with one comorbidity)*	Some concerns (interim analysis) (incomplete ffup)	Not assessed	Not serious	Not serious	Some concerns	44/7684 (0.6%)	105/7626 (1.4%)	58.6% (40.6, 71.6)	+++ Moderate
11 : Symptomatic COVID-19 infection, Asian	Some concerns (interim analysis) (incomplete ffup)	Not assessed	Not serious	Serious (wide CI)	Serious	2/689 (0.2%)	7/626 (1.1%)	74.0 % (-36.5, 97.4)	++ Low
12: Symptomatic COVID-19 infection, B.1.1.7 variant	Not assessed (interim analysis) (not an outcome)	Not assessed	Not serious	Not serious	Not assessed	na	na	na	na
13: Moderate-Severe COVID-19 infection, B.1.351 variant	Serious (interim analysis) (missing data) (incomplete ffup)	Not assessed	Not serious	Not serious	Serious	23/2449 (0.9%)	64/2463 (2.6%)	64% (41.2, 78.7)	++ Low
14: Severe COVID-19 infection, B.1.351 variant	Serious (interim analysis) (missing data) (incomplete ffup)	Not assessed	Not serious	Not serious	Serious	4/2449 (0.2%)	22/2463 (0.9%)	81.7% (46.2, 95.4)	++ Low
15: Moderate-Severe COVID-19 infection, P2 lineage	Serious (interim analysis) (missing data) (incomplete ffup)	Not assessed	Not serious	Not serious	Serious	24/3354 (0.7%)	74/3312 (2.2%)	68.1% (48.8, 80.7)	++ Low
16. Severe COVID-19 infection, P2 lineage	Serious (interim analysis) (missing data) (incomplete ffup)	Not assessed	Not serious	Serious (wide CI, breaches threshold)	Serious	1/3354 (<0.1%)	8/3312 (0.2%)	87.6% (7.8, 99.7)	+ Very Low

COMPARISON : Ad26.CoV2.S vs placebo									
	Quality Assessment					Summary of Findings			
Safety Outcome	Risk of Bias	Inconsistency	Indirectness	Imprecision	Overall Assessment	Vaccine	Control	Relative Risk	Certainty
1 : Adverse reaction	Some concerns (interim analysis) (not assessed)	Not assessed	Not assessed	Not assessed	Not assessed	na	na	na	na
2 : 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
3. 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
4 : Adverse event	Some concerns (interim analysis) (incomplete ffup)	Not assessed	Not serious	Serious (wide CI)	Serious	440/3356 (13.1%)	407/3380 (12.0%)	1.09 (0.96, 1.24)	+++ Moderate
5. Severe adverse event	Some concerns (interim analysis) (incomplete ffup)	Not assessed	Not assessed	Serious (wide CI)	Serious	19/3356 (0.6%)	18/3380 (0.5%)	1.06 (0.56, 2.02)	+++ Moderate
6: Serious adverse event	Some concerns (interim analysis) (incomplete ffup)	Not assessed	Not serious	Not serious	Some concerns	83/21895 (0.4%)	96/21888 (0.4%)	0.86 (0.64, 1.16)	+++ Moderate
7: Related serious adverse event	Some concerns (interim analysis) (incomplete ffup)	Not assessed	Not serious	Serious	Serious	7/21895 (<0.1%)	2/21888 (<0.1%)	3.5 (0.73, 16.84)	++ Low
8 : Withdrawals due to adverse event	Some concerns (interim analysis) (incomplete ffup)	Not assessed	Not serious	Serious	Serious	0/21895 (0)	0/21888 (0)	Unevaluable	na
9 : Death	Some concerns (interim analysis) (incomplete ffup)	Not assessed	Not serious	Not serious	Some concerns	5/21895 (<0.1%)	20/21888 (<0.1%)	0.25 (0.09,0.67)	+++ Moderate

COMPARISON : CoronaVac vs placebo									
Efficacy Outcome (at >14days after dose2)	**Quality Assessment**					**Summary of Findings**			
	Risk of Bias	**Inconsistency**	**Indirectness**	**Imprecision**	**Overall Assessment**	**Vaccine**	**Control**	**Vaccine Efficacy**	**Certainty**
1: Symptomatic COVID-19 infection	Serious (incomplete ffup) (missing data)	Not assessed	Not serious	Not serious	Serious (2 steps)	85/4953 (1.7%)	168/4870 (3.4%)	50.65% (35.94-61.98)	++ Low
2 : Severe COVID-19 infection	Serious (incomplete ffup) (unclear missing data)	Not assessed	Not serious	Serious (breaches threshold)	Serious	0/4953 (0%)	10/4870 (0.2%)	100% (16.93, 100)	+ Very Low
3 : COVID-19 infection, after 1st dose before Dose 2	Serious (incomplete ffup) (unclear missing data)	Not assessed	Not assessed	Serious Not serious	Serious (2 steps)	94/5717 (1.6%)	219/5714 (3.8%)	57.9% (46.4, 66.9)	na
4. Asymptomatic COVID-19 infection	Serious (not reported)	Not assessed	Not assessed	Not assessed	Not assessed	na	na	na	na
5 : Hospitalization	Serious (not reported)	Not assessed	Not assessed	Not assessed	Not assessed	na	na	na	na
6 : ICU Admission	Serious (not reported)	Not assessed	Not assessed	Not assessed	Not assessed	na	na	na	na
7 : Death due to COVID-19	Serious (not reported)	Not assessed	Not assessed	Not assessed	Not assessed	na	na	na	na
SUBGROUPS									
8 : Symptomatic COVID-19 infection, older adults (>=60yo)	Serious (incomplete ffup) (Missing data)	Not assessed	Not serious	Serious (wide CI)	Very serious	2/212 (0.9%)	4/207 (1.9%)	51.11% (-166.93, 91.04)	+ Very Low
9 : Symptomatic COVID-19 infection, older adults (>=75yo)	Serious (not reported)	Not assessed	Not assessed	Not assessed	Not assessed	na	na	na	na
10 : Symptomatic COVID-19 infection, at risk	Serious (incomplete ffup) (Missing data)	Not assessed	Not serious	Serious (wide CI)	Very serious	44/2731 (1.6%)	86/2730 (3.2%)	48.9% (26.6, 64.5)	+ Very Low
11 : Symptomatic COVID-19 infection, Asian	Serious (incomplete ffup) (Missing data)	Not assessed	Not serious	Serious (wide CI)	Very serious	1/125 (0.8%)	3/125 (2.4%)	66.0% (-226.8, 96.5)	+ Very Low

COMPARISON : CoronaVac vs placebo									
	Quality Assessment					Summary of Findings			
Safety Outcome	Risk of Bias	Inconsistency	Indirectness	Imprecision	Overall Assessment	Vaccine	Control	Relative Risk	Certainty
1 : Adverse reaction	Serious (incomplete ffup) (unclear missing data)	Not assessed	Not serious	Not serious	Serious	4536/6202 (73.14%)	3714/6194 (59.96%)	1.22 (1.19, 1.25)	++ Low
2. Local adverse reaction	Serious (incomplete ffup) (unclear missing data)	Not assessed	Not serious	Not serious	Serious	3815/6202 (61.51%)	2104 / 6194 (34.6%)	1.81 (1.74, 1.88)	++ Low
3. Systemic adverse reaction	Serious (incomplete ffup) (unclear missing data)	Not assessed	Not serious	Not serious	Serious	2999/6202 (48.36%)	2947/6194 (47.58%)	1.02 (0.98, 1.05)	++ Low
4 : Adverse event	Serious (interim analysis) (not reported)	Not assessed	Not assessed	Not assessed	Not assessed	na	na	na	na
5. Severe adverse event	Serious (interim analysis) (not reported)	Not assessed	Not assessed	Not assessed	Serious	98/6202 (1.6%)	128/6194 (2.1)	0.76 (0.59,0.99)	++ Low
6: Serious adverse event	Serious (incomplete ffup) (unclear missing data)	Not assessed	Not serious	Not serious	Serious	33/6202 (0.5%)	31/6194 (0.5%)	1.06 (0.65, 1.73)	++ Low
7: Related serious adverse event	Serious (not reported)	Not assessed	Not assessed	Not assessed	Not assessed	na	na	na	na
8 : Withdrawals due to adverse event	Serious (not reported)	Not assessed	Not assessed	Not assessed	Not assessed	na	na	na	na
9 : Death	Serious (incomplete ffup) (unclear missing data)	Not assessed	Not serious	Serious (wide CI)	Very Serious	1/6202 (<0.1%)	1/6194 (<0.1%)	1.00 (0.06, 15.96)	+ Very Low

Appendix 6 : Real World Evidence Studies on Efficacy

6a. Characteristics and reported outcomes of studies on real world evidence of COVID vaccine efficacy

STUDY	VACCINES	DESIGN	POPULATION	OUTCOMES	RESULTS
Amit	BNT162b2	Retrospective cohort	Health care workers, Israel	PCR positive rate, symptomatic COVID rates	Rate reduction for PCR positive outcome 1-14 days after 1st dose : 30% (95%CI 2, 50) 15-21 days after 1st dose : 65% (95%CI 43, 79) 22-28 days after 1st dose : 86% (95%CI (70, 94) Rate reduction for symptomatic COVID infection 1-14 days after 1st dose : 47% (95%CI 17, 66) 15-21 days after 1st dose : 76% (95%CI 51, 88) 22-28 days after 1st dose : 94% (95%CI 76, 99)
Andrejko	BNT162b2 mRNA-1273	Test negative case control	General population, California USA	VE for PCR positive infection	Vaccine efficacies 1-7 days after 1st dose : 19.7% (95%CI -125.9, 72) 8-14 days after 1st dose: 66.3%(95%CI -68.7, 93.3) >15 days after 1st dose : 58.9% (95%CI -9.7, 84.5) 1-7 days after 2nd dose 73.8% (95%CI 14.7, 91.9) 8-14 days after 2nd dose : 78.4% (95%CI 23.2, 94.3) >15 days after 2nd dose : 85.7% (95%CI 67.2,93.9)
Bernal	BNT162b2 ChAdOx1	Test negative case control	General population, (>=70 years) England UK	OR for symptomatic COVID infection after 1st dose HR for hospitalization and death	Adjusted OR (95%CI) for any COVID infection BNT162b2, 80 years and older Day 14-20 after 1st dose : 1.06 (0.92-1.33) Day 28-24 after 1st dose : 0.41 (0.32-0.54) Day 7-13 after 2nd dose : 0.21 (0.14-0.32) BNT162b2, 70 years and older Day 14-20 after 1st dose : 0.63 (0.56-0.71) Day 28-24 after 1st dose : 0.39 (0.31-0.49) ChAdOx1, 70 years and older Day 14-20 after 1st dose : 0.78 (0.68-0.89) Day 28-24 after 1st dose : 0.40 (0.27-0.59) Adjusted HR (95%CI) for Hospitalization for over 80yo. BNT162b2 D1-13 after 1st dose : 0.98 (0.86-1.11) D14 and later after 1st dose : 0.57 (0.48-0.67) ChAdOx1 D1-13 after 1st dose : 0.98 (0.78-1.24) D14 and later after 1st dose : 0.63 (0.41-0.97)

STUDY	VACCINES	DESIGN	POPULATION	OUTCOMES	RESULTS
Bernal (cont'd)					Adjusted HR for death, over 80 years old BNT162b2 D1-13 after 1st dose : 0.74 (0.62-0.90) D14 and later after 1st dose : 0.49 (0.38-0.63)
Britton	BNT162b2	Retrospective cohort	Skilled nursing facility residents Connecticut, USA	VE for COVID infection	After 1st dose : VE = 63% (95%CI 33, 79), 7 days after 2nd dose : VE 66% (95%CI 29, 83) 14 days after 2nd dose : VE = 60% (95%CI 33,77)
Cabezas	BNT162b2	Prospective cohort	Health care workers, nursing home residents, nursing care home staff, Catalonia, Spain	COVID infection rates Hospitalization Deaths	adjusted HR for COVID Infection NH Residents / NH Staff / HCWs Total followup: 0.38 (0.35, 0.42) / 0.43 (0.39, 0.49) / 0.41 (0.38, 0.45) after 1st dose: 0.53 (0.49, 0.58) / 0.60 (0.53, 0.67) / 0.57 (0.53, 0.63) 12 days after 1st dose: 0.77 (0.69, 0.86) / 0.8 (0.68, 0.93) / 0.85 (0.77, 0.95) after 2nd dose: 0.08 (0.07, 0.09) / 0.12 (0.10, 0.15) / 0.05 (0.04, 0.07) adjusted HR hospital admission / deaths Total followup: 0.22 (0.18, 0.27) / 0.15 (0.12, 0.18) after 1st dose: 0.45 (0.36, 0.56) / 0.50 (0.40, 0,63) 12 days after 1st dose: 0.30 (0.18, 0.51) / 0.47 (0.25, 0.89) after 2nd dose: 0.03 (0.02, 0.05) / 0.02 (0.01, 0.03)
Chodick	BNT162b2	Retrospective cohort	General population, Israel	VE for COVID infection	Symptomatic COVID 19 disease : Over all :51.4% (95%CI 7.1, 78.0) >=60 year old : 44.5% Jewish ultraorthodox : 53.5%
Dagan	BNT162b2	Matched cohort	General population, Israel	VE for symptomatic COVID infection, severe COVID, hospitalization, death, asymptomatic disease	VE (95%CI) after 7 days after 2nd dose Symptomatic COVID 19 disease : 94% (87, 100) Severe COVID 19 disease : 92% (75, 100) Hospitalization : 87% (55, 100) Asymptomatic disease : 92% (88, 95) Symptomatic disease, >=70 year old : 98% (90,100) Symptomatic disease, >= 1 comorbidity : 95% (88, 100) No deaths reported

STUDY	VACCINES	DESIGN	POPULATION	OUTCOMES	RESULTS
De Faria	Coronavac	Retrospective cohort	Health care workers, Sao Paolo, Brazil	VE for symptomatic COVID infection, hospitalization, death	Estimated effectiveness was 50.7% (95% CI: 33.3-62.5%); 51.8% (95%CI: 30.0-66.0%); 68.4% (95%CI: 51.0-80.8%); and 73.8% (95%CI: 57.0-84.8%) at 2, 3, 4, and 5 weeks after the 2nd dose of CoronaVac; 9 hospitalizations: 6 not vaccinated, 1 vaccinated with 1 dose 1 died, unvaccinated
Glampson	BNT162b2 ChAdOx1	Retrospective cohort	General population, Northwest London, UK	PCR test, hospitalization due to COVID, deaths	VE 74% (HR 0.26, 95%CI 0.19-0.35) for ChAdOx1 and 78% (HR 0.22,95%CI 0.18-0.27) for BNT162b2 also noted decline in hospital admission and death rates
Guijarro	BNT162b2	Retrospective cohort	Health care workers Alarcon, Spain	Infection rates	incidence reduction by 63% at 2-4 weeks pD1; 99% reduction at 5-7wks after first dose or 1 week after the second dose; reductions significantly different from the declines in the community
Haas	BNT162b2	Retrospective cohort	General population Israel	VE for COVID infection, asymptomatic infection, symptomatic infection, hospitalization, severe and critical infection, death	>= 7 days after 2nd dose / >=14 days after 2nd dose COVID infection: 94.1 (93.4-94.7) / 96.2 (95.9, 96.5) asymptomatic infection: 90.4 (89.1,91.5) / 94.1 (93.5, 94.6) symptomatic: 96.3 (95.9, 96.7) / 97.6 (97.4, 97.9) hospitalization: 96.0 (95.2, 96.6) / 97.5 (97.1, 97.9) severe and critical: 96.2 (95.5, 96.8) / 97.9 (97.5, 98.3) deaths: 93.3 (91.5, 94.8) / 96.6 (95.1, 97.6)
Hall	BNT162b2	Prospective cohort	Health care workers, support staff and administrative staff at hospital sites USA	aHR for PCR-confirmed COVID infection (regardless of symptoms)	Adjusted HR (95%CI) At least 21 days after 1st dose : 0.30 (0.15 – 0.45) At least 7 days after 2nd dose : 0.15 (0.40-0.26)

STUDY	VACCINES	DESIGN	POPULATION	OUTCOMES	RESULTS
Hitchings	CoronaVac	Test negative matched case control	Health care workers, Manaus, Brazil	VE for symptomatic infection and all infection	0-13 days after 1st vaccine dose symptomatic infection aOR = 1.69 (1.09- 2.64) all infection aOR= 1.85 (1.26- 2.71) ≥14 days after 1st vaccine dose symptomatic infection aOR = 0.50 (0.29- 0.89) all infection aOR = 0.65 (0.40-1.07)
Hyams	BNT162b2 ChAdOx1	Test negative case control	>80 year old hospitalized with COVID or other acute respiratory disease Bristol, UK	aOR / VE for COVID-related hospital admission	BNT162b2 aOR (95%CI) : 0.286 (0.138-0.569) VE (95%CI) : 71.4% (43.1 – 86.2) ChAdOx1 aOR (95%CI) : 0.196 (0.055 – 0.636) VE (95%CI) : 80.4% (36.4-94.5)
Jones	BNT162b2	Prospective cohort	Health care workers Cambridge, UK	Asymptomatic infection, symptomatic infection	compared unvaccinated and those <12 days and >= 12 days after vaccinatino. RTPCR postivie asymptomatic 26/3252 (0.8%) vs 13/3535 (0.4%, vs 4/1989 (0.2%); also note reduction in both symptomatic and asymptomtic RTPCR positive (56/3370 (1.7%) unvaccinated vs 8/2018 (0.4%) vaccinated
Luzuriaga	GamCOVIDVac (81%) BBIBP-CorV (10.3%) Covishield (8.7%)	Retrospective cohort	Health care workers Buenos Aires, Argentina	Infection rate	decline in infection rate by 35% among HCPs after vaccination program compared to a 10% increase in the general population
Monge	BNT162b2 (99.8%) mRNA-1273 (0.2%)	Retrospective cohort	Long term care facility residents (>=65yo) Spain	VE for infection	VE for partially vaccinated = 57% (95%CI 56.1%, 58.3%), VE VE for fully vaccinated 81.8% (81, 82.7%) Overall VE : 57.2% (95%CI 56.1, 58.3) 0-14 days after D1 : 28.5% (95%CI 26.4, 30.7) 15-21 days after D1 : 51% (95%CI 9.7, 52.3) 22-28 days after D1 : 61.9% (95%CI 60.8, 63) >= 29 days after D1 : 81.2% (95%CI 80.2, 82)
Mor	BNT162b2 mRNA-1273	Matched cohort	Health facility residents USA	Infection rate, hospitalization, death	Early vaccinated cohort had 1.6 (95%CI 0.2-3.2) and 2.5 (1.2,4) fewer incident infections per 100 at risk residents in the first and second week after vaccination; 1.1 to 3.8 fewer hospitalization and/or deaths per 100 infected residents per day

STUDY	VACCINES	DESIGN	POPULATION	OUTCOMES	RESULTS
Mousten-Helms	BNT162b2	Retrospective cohort	Longterm care facility residents and health care workers Denmark	VE for PCR(+) test	VE (95%CI) *note : expressed as a decimal, hence 0.21 = 21%* LTCF Residents 0-14 after D1: -0.40 (-0.62, 0.02) >14 days after D1 until D2 : 0.21 (-.11, 0.44) 0-7 days after D2 : 0.52 (0.27, 0.69) >7 days after D2 : 0.64 (0.14, 0.84) HCWs 0-14 after D1 : -1.04 (-1.18, -0.91) >14 days after D1 until D2: 0.17 (0.04, 0.28) 0-7 days after D2 : 0.46 (0.28, 0.59)
Pawlowski	BNT162b2 mRNA-1273	Matched cohort	General population in a health system USA	VE for PCR confirmed COVID infection RR for hospitalization, ICU admission, death	VE (95%CI) for PCR-confirmed COVID infection Day 15 onwards after 1st dose : 75.0% (67.4, 81.1) Day 36 onwards (2 doses) : 88.7% (68.4, 97.1) Days 36-42 : 92.5% (70.2, 99.1) Relative Risk (95%CI) 14-day hospital admission : 0.4 (0.21, 0.86) 14-day ICU admission : 0.82 (0.28, 3.6) 14-day mortality : 0 (0, 51)
Rinott	BNT162b2	Retrospective cohort	Admitted patients Israel	Proportion of ventilated patients	Reduction in ratio of ventilated patients aged >=70 to <50 years : 67%
Rivkees	Not Mentioned	Prospective cohort	General population, Florida USA	Infection rates, hospitalization, deaths	After vaccination, decline in new cases, hospitalization and death in those 65 yo and older relative to Mid January were 82, 80 and 92% lower number of cases, hospit, and death for younger than 65 were 80, 60 and 87 % lower
Roghani	BNT162b2 mRNA-1273	Prospective cohort	General population Tennessee USA	14-day mortality	decline in cases in the young from 0,2% to 0.05%, decline in hospitalization in the older group from 0.010 to 0.003%, death rate in over 71 years declined from 0.015% to 0.003% at end of study period
Shrotri	BNT162b2 ChAdOx1	Prospective cohort	Longterm care facility residents England UK	Hazards ratio for infection after single dose vaccination	Adjusted Hazards Ratio, days after first dose ChAdOx1 14-20 days : aHR = 0.95 (95%CI 0.5, 1.84); 28-34 days : aHR = 0.33 (95%CI 0.16,0.68); 35-48 days : aHR = 0.32 (95%CI 0.15, 0.66)

STUDY	VACCINES	DESIGN	POPULATION	OUTCOMES	RESULTS
Shrotri (cont'd)					BNT162b2 14-20 days : aHR = 0.94 (95%CI 0.5, 1.79) 28-34 days : aHR = 0.47 (95%CI 0.20, 1.06) 35-48 days : aHR = 0.35 (95%CI 0.17, 0.71)
Thompson	BNT162b2 mRNA-1273	Prospective cohort	Health care workers USA	VE for PCR (+) per 1000 person days	VE for partially immunized (>= 14 days after 1st dose : 80% (95%CI 59-90) VE fully immunized >= 14 days after second dose = 90% (95%CI 68-97)
Vasileiou	BNT162b2 ChAdOx1	Prospective cohort	General population Scotland UK	VE against hospitalization	VE against hospitalizations 28 days after first dose : BNT162b2 = 85% (95%CI 76,91) ChAdOx1 = 94% (95%CI 73,99)
Zacay	BNT162b2	Retrospective cohort	Health care workers, longterm care facility employees and residents, Israel	VE for infection	Vaccine efficacies : At 1-13 days after first dose: 48% (95%CI 36-57) At >=14 days after first dose: 61% (95%CI 49-71) At 1-6days after second dose: 82% (95%CI 71-89) At >=7days after second dose : 89% (95%CI 82-94)

6b. Methodological assessment of studies on real world evidence of COVID vaccine efficacy

Study	Design	Age				Gender				Exposure Risk				Comorbidities			
		A	B	C	RoB	A	B	C	RoB	A	B	C	RoB	A	B	C	RoB
Amit	RC	no	na	na	high	no	na	na	high	yes	nm	yes	low	no	na	na	high
Andrejko	TNCC	yes	yes	yes	low	yes	nm	yes	low	no	na	na	high	no	na	na	high
Bernal	TNCC	yes	nm	yes	low	yes	nm	yes	low	yes	nm	yes	low	no	na	na	high
Britton	RC	no	na	na	high	no	na	na	high	no	na	na	high	no	na	na	high
Cabezas	PC	yes	no	yes	low	yes	yes	yes	low	yes	nm	nm	uncl	yes	yes	yes	low
Chodick	RC	yes	yes	na	low	yes	yes	na	low	yes	yes	na	low	yes	yes	na	low
Dagan	MC	yes	yes	na	low	yes	yes	na	low	yes	yes	na	low	yes	yes	na	low
de Faria	RC	no	na	na	high	no	na	na	high	no	na	na	high	no	na	na	high
Glampson	RC	yes	nm	yes	low	yes	nm	yes	low	no	na	na	high	no	na	na	high
Guijarro	RC	no	na	na	high	no	na	na	high	no	na	na	high	no	na	na	high
Haas	RC	yes	nm	yes	low	yes	nm	yes	low	no	na	na	high	no	na	na	hight
Hall	PC	yes	no	yes	low	yes	no	yes	low	yes	yes	yes	low	yes	yes	yes	low
Hitchings	TNCC	yes	yes	yes	low	yes	yes	yes	low	yes	yes	yes	low	no	na	na	high
Hyams	TNCC	yes	yes	na	low	yes	nm	yes	low	yes	nm	yes	low	no	na	na	high
Jones	PC	no	na	na	high	no	na	na	high	no	na	na	high	no	na	na	high
Luzriaga	RC	no	na	na	high	no	na	na	high	no	na	na	high	no	na	na	high
Monge	RC	no	na	na	high	no	na	na	high	no	na	na	high	no	na	na	high
Moor	MC	no	na	na	high	yes	yes	none	low	no	na	na	high	no	na	na	high
Mousten Helm	RC	yes	nm	yes	low	yes	nm	yes	low	yes	yes	na	low	yes	nm	yes	low
Palowski	MC	yes	nm	yes	low	yes	nm	yes	low	no	na	na	high	yes	nm	yes	low
Rinott	RC	yes	no	no	high	no	na	na	high	no	na	na	high	no	na	na	high
Rivkees	PC	yes	yes	na	low	no	nm	na	high	no	nm	na	high	no	nm	na	high
Roghani	PC	no	na	na	high	no	na	na	high	no	na	na	high	no	na	na	high
Shrotri	PC	yes	nm	yes	low	yes	nm	yes	low	no	na	na	high	no	na	na	high
Thompson	PC	yes	yes	na	low	yes	no	no	high	no	na	na	high	no	na	na	high
Vasilieou	PC	yes	nm	yes	low	yes	nm	yes	low	yes	nm	yes	low	yes	nm	yes	low
Zacay	RC	no	na	na	high	no	na	na	high	no	na	na	high	no	na	na	high

A – assessed ; B – balanced; C – controlled; RoB – risk of bias
nm – not mentioned ; na – not applicable; uncl - unclear
RC – retrospective cohort; PC – prospective cohort; TNCC – test negative case control; MC – matched cohort

Appendix 7: Real World Evidence Reports on Safety

7a. BNT162b2 (Pfizer/BioNTech)

REGULATORY AGENCY REPORT	Date of Report (Coverage)	No. of Doses administered	Reported No. of Adverse Events	Reports of Anaphylaxis	Reports of Deaths	Other specified AEs Reported
US CDC https://www.cdc.gov/mmwr/volumes/70/wr/pdfs/mm7002e1-H.pdf	Jan 6, 2021 (Dec 14 – 23)	1,893,360	4939 (0.2%)	21 (rate of 11.1 per million)		86 non anaphylazis allergic reactions 61 non allergic adverse events
US CDC https://www.cdc.gov/mmwr/volumes/70/wr/pdfs/mm7008e3-H.pdf	Feb 19, 2021 (Dec 14 – Jan 13)	13, 794, 904 (both Pfizer and Moderna)	After D1 : 5087 nonserious SAE 341 serious SAE After D2 : 152 nonserious 21 SAE	4.5 cases per million doses 46 cases after Pfizer	113 (78 in long term care facilities)	Headache (22.4% of reported) Fatigue (16.5%) Dizziness (16.5%)
VAERS V-Safe Survey (CDC) https://www.cdc.gov/mmwr/volumes/70/wr/pdfs/mm7008e3-H.pdf	Feb 19, 2021	814,648				Pain at injection site (D1:72%, D2:79%) Fatigue (D1:21%, D2: 53%) Headache(D1:17.5%, D2: 43.4%}
EMA https://www.ema.europa.eu/en/documents/covid-19-vaccine-safety-update/covid-19-vaccine-safety-update-comirnaty-january-2021_en.pdf	Jan 28, 2021			11 cases per million (citing the US report)		
UKMHRA https://www.gov.uk/government/publications/coronavirus-covid-19-vaccine-adverse-reactions/coronavirus-vaccine-summary-of-yellow-card-reporting	April 9. 2021 (up to March 28, 2021)	10.9 million first doses and 3.7 million second doses (mostly Pfizer)	43,491 yellow card reports, 124,371 suspected reactions	259 spontaneous adverse reactions associated with anaphylaxis or anaphylactoid reactions	302 deaths after vaccination	

Instituto de Salud Publica de Chile https://www.ispch.cl/wp-content/uploads/2021/03/INF-FARMACOVIGILANCIA.pdf	March 12 2021 (Dec 24 to Mar 2)	292,534 doses		6 (+5) anaphylactic reactions reported		

7b. mRNA-1273 (Moderna)

REGULATORY AGENCY REPORT	Date of Report (Coverage)	No. of Doses administered	Reported No. of Adverse Events	Reports of Anaphylaxis	Reports of Deaths	Other specified AEs Reported
US CDC https://www.cdc.gov/mmwr/volumes/70/wr/pdfs/mm7004e1-H.pdf	Jan 22 (Dec 21 – Jan 10)	4,041,396	1266 (0.03%)	10 (2.5 cases per million)		47 non allergic adverse events 47 non anaphylaxis allergic reactions
US CDC https://www.cdc.gov/mmwr/volumes/70/wr/pdfs/mm7008e3-H.pdf	Feb 19, 2021 (Dec 14 – Jan 13)	13, 794, 904 (both Pfizer and Moderna)	1115 nonserious AE 258 SAEs after dose 1	4.5 cases per million doses 16 cases after Moderna		Headache = 347 (25.3% of reported) Fatigue – 228 (16.6%) Dizziness – 228 (16.6%)
VAERS V-Safe Survey (CDC) https://www.cdc.gov/mmwr/volumes/70/wr/pdfs/mm7008e3-H.pdf	Feb 19, 2021	787, 417				Pain at injection site (D1:78.1%) Fatigue (D1:25.1%) Headache(D1:19.9%}

7c. ChAdOx1 (AstraZeneca)

REGULATORY AGENCY REPORT	Date of Report (Coverage)	No. of Doses administered	Reported No. of Adverse Events	Reports of Anaphylaxis	Reports of Deaths	Other specified AEs Reported
UKMHRA https://www.gov.uk/government/publications/coronavirus-covid-19-vaccine-adverse-reactions/coronavirus-vaccine-summary-of-yellow-card-reporting	March 28, 2021	19.5 million first doses	116,162 yellow card reports, 440,871 suspected reactions	455 spontaneous adverse reactions associated with	472 deaths after vaccincation	79 blood clotting cases : - 44/79 – CSVT - 35/79 thrombosis of other major veins - 19/79 died - all occurred after first dose
EMA https://www.ema.europa.eu/en/news/astrazenecas-covid-19-vaccine-ema-finds-possible-link-very-rare-cases-unusual-blood-clots-low-blood	April 7 2021 (as of 22 March, from EudraVigilance)	Around 25 million (from EEA and UK)		18 deaths (of reported thrombotic events)		62 cases of CVT 24 cases of splanchnic vein thrombosis
PFDA https://www.fda.gov.ph/wp-content/uploads/2021/04/Reports-of-Suspected-Adverse-Reaction-to-COVID-19-Vaccines-as-of-11-April-2021-ver-3.pdf	March 7-Apr 11, 2021	511,199 vaccinated individuals	17,727 reports 17,524 non serious events 203 serious (other than death)	0.0006%		General symptoms and reactions to admin site = 23,458 Neuro symptms (dizziness, etc0 -8,627 Musculoskeletal (back pain, joint pains) – 5,372 GI symptoms = 2,347 Skin symptoms (cold sweat, rash) – 1,491

7d. Gam-COVID-Vac (Gamaleya)

REGULATORY AGENCY REPORT	Date of Report (Coverage)	No. of Doses administered	Reported No. of Adverse Events	Reports of Anaphylaxis	Reports of Deaths	Other specified AEs Reported
No reports available						

7e. Ad26.COV2.S (Janssen/Johnson&Johnson)

REGULATORY AGENCY REPORT	Date of Report (Coverage)	No. of Doses administered	Reported No. of Adverse Events	Reports of Anaphylaxis	Reports of Deaths	Other specified AEs Reported
US CDS https://emergency.cdc.gov/han/2021/han00442.asp	April 12, 2021 (start of US rollout)	6.25 M	6 cases	-	1 (due to VITT)	Vaccine-induced thrombotic thrombocytopenia (VITT)

7f. CoronaVac (Sinovac)

REGULATORY AGENCY REPORT	Date of Report (Coverage)	No. of Doses administered	Reported No. of Adverse Events	Reports of Anaphylaxis	Reports of Deaths	Other specified AEs Reported
PFDA https://www.fda.gov.ph/wp-content/uploads/2021/04/Reports-of-Suspected-Adverse-Reaction-to-COVID-19-Vaccines-as-of-11-April-2021-ver-3.pdf	March 1-April 11, 2021	515,359 vaccinated individuals with first dose 140,043 with the second dose	7,140 reports 6,979 non serious 161 serious (other than death)	0.0009%		General symptoms and reactions to admin site = 2,982 Skin symptoms (cold sweat, rashes) – 1,394 Neuro symptms (dizziness, etc0 -2,396 GI symptoms = 806 Musculoskeletal (back pain, joint pains) – 523 Vascular symptoms - 470 Infections - 259
Instituto de Salud Publica de Chile https://www.ispch.cl/wp-content/uploads/2021/03/INF-FARMACOVIGILANCIA.pdf	March 12 2021 (Dec 24 to Mar 2)	3,378,552 doses		21 (+28) anaphylactic reactions reported		