COVID-19 VACCINES

RECOMMENDATION A

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

a. BNT162b2 (given as 0.3ml (30ug) intramuscular injections, in 2 doses, 21 days apart)

b. mRNA-1273 (given as 0.5ml (100ug) intramuscular injections, in 2 doses, 28 days apart)

c. ChAdOx1 (given as 0.5 ml (5×10^6 vp) intramuscular injections, in 2 doses, at least 12 weeks apart)

d. Gam-COVID-Vac (given as 0.5ml rAd-26S 0.5ml intramuscular injection, then rAd-5S 0.5ml intramuscular injection 21 days after)

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).

RECOMMENDATION B

We recommend the use of these vaccines in older adults (>64-year-old) to prevent symptomatic SARS-CoV-2 Infection. *(Low quality of evidence; Strong recommendation)*

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.

RECOMMENDATION C

We recommend the use of these vaccines in pregnant and lactating women after consultation with their healthcare provider. *(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.

RECOMMENDATION D

We recommend the use of these vaccines in adults who have stable medical comorbidities and are at risk for severe infection to prevent SARS-CoV-2 infection. *(Moderate quality of evidence; Strong recommendation)*

RECOMMENDATION E

We recommend against the use of these vaccines in children to prevent SARS-CoV-2 infection: *(Low to very low quality of evidence; Conditional recommendation)*

- BNT162b2: <16 years old
- mRNA-1273, ChAdOx1, Gam-COVID-Vac: <18 years old

Consensus Issues

The quality of evidence was presented as a range since only the available ChAdOx1 trial data included 12 to 18 years old, while the other trials have none. Likewise, the strength of recommendation was changed from strong to conditional since the evidence assessed were still from interim reports and it was noted that in the latter part of the trials there were protocol amendments to include the younger population, hence, once available, the full report may already provide data on vaccine efficacy among children.

RECOMMENDATION F

We recommend the use of these vaccines in immunocompromised patients (i.e., diagnosed with HIV, hepatitis B and C), after clearance from their physician, to prevent SARS-CoV-2 infections. *(Low quality of evidence; Conditional recommendation)*

RECOMMENDATION G

We recommend against the use of these vaccines in persons with known allergies to polysorbate and/or PEG. *(Moderate to high quality of evidence; Strong recommendation)*

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.

EVIDENCE SUMMARY

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

Marie Carmela Lapitan, MD, John Jefferson Besa, MD, Maria Teresa S. Tolosa, MD, FPDS, DipCE

Key Findings

As of February 24, 2021, interim trial data on the safety and efficacy of four COVID-19 vaccines have been made publicly available. The BNT162b2, the mRNA-1273, the ChAdOx1 and the Gam-COVID-Vac vaccines demonstrated satisfactory vaccine efficacy against symptomatic COVID-19 infection among adults in the short term with moderate certainty. Data on the efficacy against severe COVID-19 infection, asymptomatic COVID-19 infection and death from COVID-19 infection are still inconclusive. Vaccination with these vaccines was associated with higher adverse reactions compared to control, although serious adverse event rates were comparable with the control. These adverse events, from reactions to the vaccines, were mild to moderate and of short duration. Long term efficacy and safety data are still lacking. Despite these limitations, the benefit of protection against symptomatic COVID-19 infection given by vaccination outweighs the transient local and systemic adverse reactions to the vaccine.

Introduction

In March 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 quarantines 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 control the spread of the disease and the pandemic, numerous COVID-19 vaccines are in development. These vaccines are based on different platforms including mRNA and DNA technologies, viral-vectored, protein subunit, inactivated and live-attenuated vaccines. Most COVID-19 candidate vaccines express the spike protein or parts of it to induce an immunogenic response.

This review is a systematic appraisal of the publicly available Phase 3 clinical trial results of candidate COVID-19 vaccines as of February 24, 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”, “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 recent emergency use authorization by regulatory agencies, the US-Food and Drug Authority (US-FDA), the European Medicines Agency (EMA), the United Kingdom Medicines and Health Products Regulatory Agency (MHRA) websites were also searched for relevant authorization documents and trial reports for each vaccine. The WHO site was also searched for supporting documents for SAGE meetings on vaccines. The date of last search for this review was February 24, 2021.

Selection and quality assessment of systematic reviews and included studies

The two investigators reviewed the identified trials for eligibility. 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 asymptomatic COVID-19 disease
- Incidence of hospitalization or mechanical ventilation among patients with 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 1st dose was also determined

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 systematic review, the following study characteristics were extracted: population details such as inclusion and exclusion criteria, interventions (vaccine), comparators, outcomes, data sources, study proponents, study sites and study sponsor. Study design peculiarities and status

of the study implementation were also noted. Data on the vaccine used such as its type, active substance, and mechanism of action, as well as its storage and cold chain parameters, including the shipping and transport considerations, storage and shelf life, were extracted.

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. Pooling of data across trials using the same vaccine type was planned. However, this was not done in this review because of the paucity of available trial results. As only interim analysis results were available, with varying outcome assessment timepoints, no pooling was done for this review.

Subgroup analysis considered were: sex, age (<65 years old vs >/=65 years, vs >=75yo), pediatric vs adults, ethnicity with a focus among Asians, baseline seropositivity status/ evidence of previous infection, risk for acquiring COVID 19 (e.g. frontline essential workers) and confirmed stable HIV disease.

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.

Results

Search Results

Search of the COVID-19 Living OVerview of Evidence (L·OVE) platform performed on February 24, 2021 yielded 48 records. After screening for eligibility based on titles and abstracts, 8 papers were phase 2/3 trial results on the efficacy and safety of four different COVID-19 vaccines. [3-10] Two papers presented the interim results of trials on mRNA vaccines, BNT162b2 (3) and mRNA-1273. [4] Five reports were on the pooled interim results of 4 trials that used a non-replicating viral vector vaccine, ChAdOx1. [5-9] One report was on the interim results of a trial that used a combination viral vector vaccine, Gam-COVID-Vac. [10]

A search of the regulatory authority websites provided additional reports providing data on these trials. The USFDA [11] EMA [12] [13] UKMHRA [14] and the WHO SAGE [15] [16] authorization documents provided additional information for BNT162b2 vaccine. The USFDA [17-19], the EMA [20] [(21] and the WHO SAGE [22] [23] authorization documents provided additional information for the mRNA-1273 vaccine. The UK-MHRA [24], the EMA [25] and the WHO [26] [27] authorization assessment report provided additional information for the ChAdOx1 vaccine.

Included Studies: 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. The vaccines studied were the BNT162b2, the mRNA-1273, the ChAdOx1 and the Gam-COVID-Vac.

The trial on BNT162b2 randomized 43,651 adults with 21,823 receiving the vaccine. Interim results after a median follow up of 2 months are available. The trial investigating mRNA-1273 randomized 30,351 participants, with 15,181 receiving the vaccine, with a median follow up of 2 months. The published reports on the ChAdOx1 vaccine were the pooled interim results of four phase 2/3 trials. These trials were considered as one study for the purpose of this rapid review. The pooled data included 23,745 participants with 12,021 receiving the vaccine. The efficacy data included 8,596 receiving the vaccine. Most of the outcome data included in the review are from the initial report after a median follow up of 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 design. The trial that investigated Gam-COVID-Vac included 21,977 participants with 16,501 receiving the vaccine.

All available reports presented the results of the interim analysis of ongoing trials. Hence, results for some of the planned efficacy and safety outcomes 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.

Results: Efficacy

Available trial data for all four vaccines demonstrated sufficient efficacy rates in the prevention of symptomatic COVID-19 infection, based on a threshold of at least 50% set by the WHO, within a median follow up two months after vaccination of the BNT162b2 and mRNA-1273, 3 months after vaccination of the ChAdOx1, and 48 days after vaccination of the Gam-COVID-Vac. No long-term efficacy data were available for all four vaccines.

BNT162b2

BNT162b2 demonstrated a vaccine efficacy (VE) of 95% (95%CI 90.3, 97.6) for the prevention of symptomatic COVID-19 infection starting at 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 66.8, 99.9). A precise estimate on the protective effect of BNT162b2 on the occurrence of severe COVID-19 infection is lacking (VE = 75.0%, 95%CI -152.6, 99.5). BNT162b2 also showed an efficacy of 52.5% (95%CI 29.5, 68.4) after the first dose, 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 2 months post Dose 2, the BNT162b2 cumulative curve is stable which would suggest continued protection. Asymptomatic COVID-19 infection prevention was not assessed. No data on the impact of the vaccine on hospitalization, ICU admission or deaths associated with COVID-19 infection were reported.

mRNA-1273

mRNA-1273 showed a vaccine efficacy of 93.6% (95%CI 88.5, 96.4) 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, 95.2%). No case of severe COVID-19 infection occurred in the vaccine group while 30 occurred with the placebo group during the reported follow up period, demonstrating high efficacy of mRNA-1273 in preventing severe COVID-19 infection, but with a wide confidence interval. mRNA-1273 showed an efficacy of 69.5% (95%CI 43.5, 92.7) after a single dose. Cumulative incidence curves revealed low rates until Day 14 after Dose 1 and subsequent divergence with more cases of infections occurring in the placebo group than the mRNA-1273 group. Asymptomatic COVID-19 infection prevention was not assessed. No data on the impact of the vaccine on hospitalization, ICU admission or deaths associated with COVID-19 infection were reported.

ChAdOx1

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

In the subgroup of study participants who received a low (2.5 x10^6 vp) first dose and a standard (5x10^6 vp) second dose, vaccine efficacy was at 80.7% (95%CI 62.1, 90.2). 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 highest with a dosing interval of at least 12 weeks (VE 81.3%, 95%CI 60.3, 91.2), when 2 standard doses were given.

Gam-COVID-Vac

Gam-COVID-Vac demonstrated an overall vaccine efficacy of 91.1%. (95%CI 83.6, 95.1) for the prevention of symptomatic COVID-19 infection beginning 7 days after the administration of the 2nd dose, with a median follow up of 48 days. It showed a single dose vaccine efficacy of 73.1%. (63.7, 80.1) beginning at 21 days after. Severe COVID-19 infection 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.

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

Results: Safety

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

BNT162b2

Most local and systemic adverse reactions to the vaccine were mild to moderate in severity, transient and of short duration. The most common local adverse reaction was pain at the injection site (78-85% vs.12-14% in 16-55yo and 66-71% vs. 8-9% in >55yo.). Most were mild or moderate in severity with no case of a life-threatening reaction. Onset was between day 1 and day 3 of the vaccination, with a mean duration between 1-2 days. Headache (25-52%) and fatigue (34-59%) were the most common systemic reactions. Most were mild and moderate in severity. Median onset was at day 2 to 3, with a median duration of 1 day.

More participants in the vaccine groups reported at least one adverse event 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.

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 hemorrhagic stroke, one case of myocardial infarction and two cases of unknown cause of death.

mRNA-1273

More local and systemic adverse reactions were reported in the mRNA-1273 group than in the placebo group. The most commonly reported local adverse reaction was pain (83% vs. 20%), while fatigue and headache were the most commonly reported systemic reaction after mRNA-1273 vaccination. More adverse events were reported in the vaccine group, largely attributed to the local and systemic reactions after vaccination. Rates of severe AEs were similar in both treatment groups (1.4 vs. 1.3%). More frequently reported severe AEs reported in the vaccine group compared to the placebo were headache, myalgia, arthralgia, injection site erythema, and injection site pain.

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

ChAdOx1

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

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

Gam-COVID-Vac

General adverse event data were not available for Gam-COVID-Vac, pending verification by the independent assessors in the trial. Serious adverse event rates were similar between the two treatment groups. Four deaths were reported in the trial publication. Three deaths were in the vaccine group, one from a fractured thoracic vertebra and two from COVID-19 infection. The first patient developed symptoms 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.

Detailed safety data are presented in Appendix 4.

Authorizations

BNT162b2

BNT162b2 (Cominarty) 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 Cominarty mRNA vaccine for emergency use [18].

mRNA-1273

mRNA-1273 (Moderna) received emergency use authorization from USFDA on December 18, 2020. The WHO approved the listing of mRNA-1273 on January 21, 2021.

ChAdOx1

ChAdOx1 (Astra Zeneca, University of Oxford) 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.

Gam-COVID-Vac

Gam-COVID-Vac is registered for use in the Russian Federation and in 35 other countries. [28]

Research Gaps

The current available evidence on vaccine efficacy and safety is limited, both in terms of design and based on the fact that all trials 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. 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. Impact of the vaccine on transmission to unvaccinated persons, viral shedding
4. Long-term efficacy / durability of protection
5. Onset of protection, particularly in the multidose vaccines (although there is some suggestion that there is partial protection after the first dose)
6. Long-term safety data

7. Interaction with other vaccines
8. Risk of vaccine-associated enhanced disease

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Appendix 1: Characteristics of Included Studies

Trial Identifier	**Polack 2020 (C4591001)**	**Zaks 2020 (mRNA-1273-P301)**	**Voysey 2020 / Voysey 2021 (COV001, 002, 003, 005)**	**Logunov 2021 (RESIST)**
Vaccine	**BNT162b2**	**mRNA-1273**	**ChAdOx1 nCoV19 / AZD1222**	**Gam-COVID-Vac**
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	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	43, 651 (V:21,823 C:21,828)	30,351 (V:15,181 C:15,170)	Efficacy: 11,636 (V:5,807 C:5,829) Safety: 23,745 (V:12,021 C:11,724) VOYSEY2020 Efficacy: 17,178 (V:8597 C: 8581) VOYSEY2021 P4, T1	21,977 (V: 16,501 C: 5, 476) (3:1)
Inclusions		adults at risk of SARS-CoV-2 infection who have no known history of SARS-CoV-2 infection	Healthy adults, priority given to health professionals and adults with high potential for exposure to SARS-CoV-2	>= 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

Trial Identifier	**Polack 2020 (C4591001)**	**Zaks 2020 (mRNA-1273-P301)**	**Voysey 2020 / Voysey 2021 (COV001, 002, 003, 005)**	**Logunov 2021 (RESIST)**
Vaccine	**BNT162b2**	**mRNA-1273**	**ChAdOx1 nCoV19 / AZD1222**	**Gam-COVID-Vac**
• 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)	18 years and older >64 yo : 24.8% BADEN T1 >=65 and < 75 : 20.2% >= 75 and <85 : 4.3% >=85 : 0.3% BADEN TS2	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
• 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	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
• Immunocompro-mised	Yes, included those with stable disease, included those with HIV (0.3%), HCV, HBV; balanced between groups; <u>BUT were not included in the efficacy analysis</u>	HIV positive 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	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	No	No
• With concomitant comorbidities	Yes, stable disease (46%) With Charlson comorbidity (20.5%) EMA T3	Yes, stable disease (16%)	Yes, (36.1%) UKMHRA T7	Yes: 3687/14994 (24.7) vs 1235/4892(25.2%) LOGUNOV T1
• With previous COVID infection	No	No	No mention	No

● With known previous exposure to COVID	No	No mention	No mention	No

Trial Identifier	**Polack 2020 (C4591001)**	**Zaks 2020 (mRNA-1273-P301)**	**Voysey 2020 / Voysey 2021 (COV001, 002, 003, 005)**	**Logunov 2021 (RESIST)**
Vaccine	**BNT162b2**	**mRNA-1273**	**ChAdOx1 nCoV19 / AZD1222**	**Gam-COVID-Vac**
● Seropositive at baseline	Yes (6%)	Yes (2.2%) BADEN TS2	Yes (373/20675, 1.8%) COV002+3 VOYSEY TS2	No
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	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	mRNA	mRNA	Viral vector (adenovirus)	Combined viral vector (adenovirus)
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	Recombinant, replication-deficient chimpanzee adenoviral vector containing the SARS-CoV-2 structural surface glycoprotein antigen gene with a tissue plasminogen activator leader sequence	Recombinant Adenovirus serotype 26 and rAd serotype 5 which carry the gene for SARS-CoV-2 full length glycoprotein S in the amount of (1.0 $\pm$ 0.5) x 10^{11} particles per dose
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	-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	**Polack 2020 (C4591001)**	**Zaks 2020 (mRNA-1273-P301)**	**Voysey 2020 / Voysey 2021 (COV001, 002, 003, 005)**	**Logunov 2021 (RESIST)**
Vaccine	**BNT162b2**	**mRNA-1273**	**ChAdOx1 nCoV19 / AZD1222**	**Gam-COVID-Vac**
• 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	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 shelf life after dilution/ opening	at 2-30”C, must be used immediately, discard after 6 hours	6 hours at 2’ to 25’C	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	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	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	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	L-histidine, L-histidine hydrochloride monohydrate, magnesium chloride hexahydrate, polysorbate 80 (E433), ethanol, sucrose, sodium chloride, disodium edatate, water for injection EMA P18	Component I and II Tris (hydroxymethyl) aminomethane, sodium chloride, sucrose, magnesium chloride hexahydrate, ethylenediaminetetraacetic acid (EDTA) disodium salt dihydrate, polysorbate-80, ethanol 95%, and water for injection.
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	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	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

			study results, with interval between doses up to 12 weeks	Administered intramuscularly separately with a 21-day interval
Number randomized	21,823 (at final analysis)	15,181	8, 597 (efficacy) 12,021 (safety)	16,501
Trial Identifier	**Polack 2020 (C4591001)**	**Zaks 2020 (mRNA-1273-P301)**	**Voysey 2020 / Voysey 2021 (COV001, 002, 003, 005)**	**Logunov 2021 (RESIST)**
Vaccine	**BNT162b2**	**mRNA-1273**	**ChAdOx1 nCoV19 / AZD1222**	**Gam-COVID-Vac**
COMPARATOR				
Type, dosing and administration	0.3ml saline intramuscular injection, 21 days apart	0.5 ml of 0.9% sodium chloride (saline) intramuscular injection, on a 2-dose injection schedule on Day 1 and Day 29	0.5 ml Meningococcal group ACWY conjugate vaccine (MenACWY) 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	21,828 (at final analysis)	15,170	8,581 (efficacy) 11,724 (safety)	5,476
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	

Trial Identifier	**Polack 2020 (C4591001)**	**Zaks 2020 (mRNA-1273-P301)**	**Voysey 2020 / Voysey 2021 (COV001, 002, 003, 005)**	**Logunov 2021 (RESIST)**
Vaccine	**BNT162b2**	**mRNA-1273**	**ChAdOx1 nCoV19 / AZD1222**	**Gam-COVID-Vac**
OUTCOMES				
Primary efficacy endpoints	COVID-19 incidence per 1000 person-years of follow up in participants without evidence of past SARS-CoV-2 infection before and during vaccination regimen – cases confirmed >= 7 days after Dose 2 COVID-19 incidence per 1000 person-years of follow up in participants with and without evidence of past SARS-CoV-2 infection before and during vaccination regimen – cases confirmed >= 7 days after Dose 2 COVID-19 infection : at least 1 of the following symptoms and SARs-CoV-2 NAAT positive test during, or within 4 days before or after, the symptomatic period : fever, new or increased cough, new or increased shortness of breath, chills, new or increased muscle pain, new loss of taste or smell, sore throat, diarrhea, vomiting	Prevention of protocol-defined COVID-19 occurring at least 14 days after the second dose in participants with negative SARS-CoV-2 status at baseline Vaccine efficacy : percent reduction (mRNA-1273 vs placebo) in the hazard of the primary endpoint (VE = 1-HR) COVID-19 infection : at least TWO of systemic symptoms of fever, chills, myalgia, headache, sore throat OR at least ONE of respiratory signs/symptoms of cough, shortness of breath or difficulty breathing or clinical or radiological evidence of pneumonia. AND have at least one NP swab, nasal swab, or saliva sample positive for SARS-CoV-2 by RT-PCR	Virologically confirmed, symptomatic COVID-19 in participants that were COVID-19 naïve at the time of randomization who received at least 2 doses of vaccine or placebo, occurring more than 14 days after the booster dose Vaccine efficacy : 1-adjusted risk (vaccine vs control) Symptomatic COVID-19 : NAAT-positive swab combined with at least one qualifying symptom of fever, cough, shortness of breath or anosmia or ageusia)	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
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	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	**Polack 2020 (C4591001)**	**Zaks 2020 (mRNA-1273-P301)**	**Voysey 2020 / Voysey 2021 (COV001, 002, 003, 005)**	**Logunov 2021 (RESIST)**
Vaccine	**BNT162b2**	**mRNA-1273**	**ChAdOx1 nCoV19 / AZD1222**	**Gam-COVID-Vac**
Secondary endpoints	COVID-19 confirmed at least 14 days after Dose 2: COVID-19 incidence per 1000 person-years of follow up in participants either (1) without or (2) with and without evidence of past SARS-CoV-2 infection before and during vaccination regimen – cases confirmed either (1) >= 7 days after Dose 2 or (2) >=14 days after Dose 2 Severe COVID-19 : incidence per 1000 person-years of follow up in participants either (1) without or (2) with and without evidence of past SARS-CoV-2 infection before and during vaccination regimen – cases confirmed either (1) >= 7 days after Dose 2 or (2) >=14 days after Dose 2 *Severe COVID 19 : at least 1 of the following : clinical signs at rest indicative of severe systemic illness, respiratory failure, evidence of shock, significant acute renal, hepatic, or neurological dysfunction; admission to an ICU; death	Vaccine efficacy in the prevention of : - severe COVID-19 - COVID-19 based on a less restrictive definition (*) occurring 14 days after the second dose - Death due to COVID-19 - COVID-19 occurring at least 14 days after the first dose of vaccine (including cases that occurred after the 2nd dose) - COVID-19 occurring at least 14 days after the second dose, regardless of prior SARS-CoV-2 infection (*) : positive NP swab, nasal swab, or saliva sample (or respiratory sample, if hospitalized) for SARS-CoV-2 by RT-PCR AND one of the following : fever, chills, cough, shortness of breath, fatigue, muscle aches, headache, new loss of taste or smell, sore throat, nasal congestion or rhinorrhea, nausea or vomiting, or diarrhea Vaccine-enhanced disease	Vaccine efficacy on : - hospital admissions associated with COVID-19 - intensive care unit admissions associated with COVID-19 - severe COVID-19, virologically confirmed - Asymptomatic SARS-CoV2 infection - death associated with COVID-19 - all-cause LRTI ..at time frames from 21 days after single dose, or 7 days after a 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	Severity of the clinical course of COVID-19 - 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 agains SARS-CoV-2 glycoprotein S - Proportion of participants with antibioidies against SARS-CoV-2 N protein; - Changes in SARS-CoV-2 neutralising antibody titres (increase) - Changes in antigen-specific cellular immunity level (increase in cell-mediated immune response to antigen) * serious adverse events – diagnosed based on the event requiring hospital admission
Subgroups considered in the analysis				
● Age	Yes :	Yes :	Yes	Yes
● Sex	Yes	Yes	Yes	Yes
● Ethnic groups	Yes	Yes	Yes (country)	No
● Baseline seropositivity status / evidence of previous infection	Yes	Yes	Yes	NA
● Medical comorbidities	Yes	Yes	Yes	No
● Immunocompromised / HIV disease	Yes	No	Specified special analysis for HIV patients (COV005)	No

Trial Identifier	**Polack 2020 (C4591001)**	**Zaks 2020 (mRNA-1273-P301)**	**Voysey 2020 / Voysey 2021 (COV001, 002, 003, 005)**	**Logunov 2021 (RESIST)**
Vaccine	**BNT162b2**	**mRNA-1273**	**ChAdOx1 nCoV19 / AZD1222**	**Gam-COVID-Vac**
● Risk for acquiring COVID infection	No	Yes	Not mentioned	No
● Risk for progression to severe COVID	No	Yes	Not mentioned	No
● Dosing regimen	No	No	Yes, including control type	No
Follow up				
● Planned	24 months	759 days	1 year	180 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)		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	Efficacy : ● Preliminary : November 4, 2020 ● Final : November 14, 2020 Safety : November 14 2020 * with additional mortality data	Efficacy : ● Preliminary : November 7, 2020 ● Final : November 25, 2020 Safety : November 11, 2020 and November 25 With additional data on deaths as of December 3.	November 4, 2020	November 24, 2020
METHODS / OTHER TRIAL PARAMETERS				
Blinding				Participants, investigators and study staff masked
Study Sites	USA, Argentina, brazil, Turkey, South Africa, Germany		UK, Brazil, South Africa	Russia
Study Sponsor	BioNTech, Inc, Pfizer	ModernaTX,Inc	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 paper and regulatory submission)	Interim analysis (published paper and regulatory submission)	Interim analysis (included pooled data only from COV002 and COV003 trials), published papers and regulatory submissions	Interim analysis (published paper)

Trial Identifier	**Polack 2020 (C4591001)**	**Zaks 2020 (mRNA-1273-P301)**	**Voysey 2020 / Voysey 2021 (COV001, 002, 003, 005)**	**Logunov 2021 (RESIST)**
Vaccine	**BNT162b2**	**mRNA-1273**	**ChAdOx1 nCoV19 / AZD1222**	**Gam-COVID-Vac**
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 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)	 Unbalanced (169 vs 155) Unbalanced (6+2 vs 9+8) (V vs C , SD + LD) Balanced (1867+320 vs 1842 + 312) Balanced	

Appendix 2: Methodological Quality Assessment of Included Studies

	Polack 2020 (C4591001)		**Zaks 2020 (mRNA-1273-P301)**		**Voysey 2020 (COV002, 003, 005)**		**Logunov 2021 (RESIST)**	
	BNT162b2		**mRNA-1273**		**ChAdOx1 nCoV19 / AZD1222**		**Gam-COVID-Vac**	
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	U	Interactive web response system; statistician generated the sequence	L
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	Interactive web response system;	L
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	Pariticipants, investigators and all study staff were 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	Interim analysis;	L / H
Selective reporting	Interim analysis	U	Interim analysis	U	Interim analysis	U	Interim analysis Adverse event not reported; pending verification	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 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	12/15170 (<0.1%) EMA T17 FAS BADEN TS16 FAS	187/15181 (1.2%) EMA T17 FAS BADEN TS16 FAS	93.6 (88.6, 96.5) EMA T17 FAS BADEN TS16 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	173/15170 (1.1%) 59.0 FDA SL27	87.9 (81.0, 82.7) FDA SL27
- 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			
- >=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	7/13857 (<0.1%) 2.5 FDA SL27	127/13792 (0.9%) FDA SL27	94.5 (88.4, 97.8) FDA SL27
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, 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			

Trial Identifier	**Polack 2020 (C4591001)**			**Zaks 2020 (mRNA-1273-P301)**		
Vaccine	**BNT162b2**			**mRNA-1273**		
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	30/13883 (0.2%) FDA T18 PPS	100% (NE, 100%) FDA T18 PPS
- 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						
Hospitalization due to COVID, complete dosing, seronegative only						
- after 7 days						
- after 14 days						
- 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						
- after 21 days						
ICU admission due to COVID, complete dosing, seronegative ONLY						
- after 7 days						
- after 14 days						
- after 21 days						

Trial Identifier	**Polack 2020 (C4591001)**			**Zaks 2020 (mRNA-1273-P301)**		
Vaccine	**BNT162b2**			**mRNA-1273**		
Death due to COVID, complete dosing, seronegative ONLY						
- after 7 days						
- after 14 days				0/13143 (0%)	1/14073 (<0.1%)	
- 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			
>=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	
SPECIAL POPULATIONS : COVID 19 infection, complete dosing, seronegative only						
>= 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 EMA T18 PPS	3/676 (0.4%) FDA T10 PPS 7/688 (0.1%) EMA T18 PPS	
< 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	

Trial Identifier	**Polack 2020 (C4591001)**			**Zaks 2020 (mRNA-1273-P301)**		
Vaccine	**BNT162b2**			**mRNA-1273**		
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	
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	

Appendix 3b: 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**
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			
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						
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**		
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						
- 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%) 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%			
- 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 doae 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						
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 3c: 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

Appendix 4: Detailed Safety Outcomes

	BNT162b2 [1]		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		
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		
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 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)	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	Some concerns (interim analysis) (incomplete ffup)	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) (incomplete ffup) (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) (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 : 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 : 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
11 : 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									
	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	Some concerns (interim analysis) (incomplete ffup)	Not assessed	Not serious	Not serious	Some concerns	5770/21621 (26.7%)	2638/21631 (12.2%)	2.19 (2.10-2.28)	+++ Moderate
5. Severe adverse event	Some concerns (interim analysis) (incomplete ffup)	Not assessed	Not serious	Not serious	Some concerns	240/21621 (1.1%)	139/21631 (0.6%)	1.73 (1.40-2.13)	+++ Moderate
6: Serious adverse event	Some concerns (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	Some concerns (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	Some concerns (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	Some concerns (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: 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, after 1st dose before Dose 2	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 (interim analysis) (incomplete ffup)	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) (incomplete ffup)	Not assessed	Not assessed	Serious (wide CI)	Not assessed	0/13143 (0%)	1/14073 (<0.1%)	100% (NE, 100)	++ Low
SUBGROUPS									
8 : 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 : COVID-19 infection, older adults (>=75yo)	Some concerns (interim analysis) (incomplete ffup	Not assessed	Not serious	Serious (wide CI)	Not assessed	0/623 (0%)	3/676 (0.4%)	100% (NE, 100%)	++ Low
10 : 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 : COVID-19 infection, Asian	Some concerns (interim analysis) (not reported)	Not assessed	Not serious	Not reported	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	3631/15185 (23.9%)	3277/15166 (19.4%)	1.17 (1.12, 1.22)	+++ 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	7 /15185 (<0.1)	5/15166 (<0.1)	1.40 (0.44, 4.40)	++ Low
8 : Withdrawals due to adverse event	Some concerns (interim analysis) (incomplete ffup)	Not assessed	Not serious	Not serious	Some concerns	50/15185 (0.3%)	80/15166 (0.5%)	0.62 (0.44, 0.89)	+++ Moderate
9 : Death	Some concerns (interim analysis) (incomplete 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: 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 : 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
11: 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
12 : COVID-19 infection, >= 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

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	13/14064 (0.1%)	47/4601 (1.0%)	91.1% (83.6, 95.1)	+++ Moderate
2 : Moderate & Severe COVID-19 infection *(after 21d)*	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	0/14964 (0%)	20/4902 (0.4%)	100% (94.4, 100.0)	+++ 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) (incomplete ffup)	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) (not reported)	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