PHILIPPINE COVID-19 LIVING CLINICAL PRACTICE GUIDELINES

As of January 2022

VACCINES and PROPHYLACTIC INTERVENTIONS for COVID-19

EVIDENCE and RECOMMENDATIONS

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Disclaimer

As a living guideline, the recommendations will be updated, and new recommendations will be added as the evidence evolves. The living recommendations are based on the best evidence available in scientific literature at the time of its formulation. However, this living CPG is not a comprehensive guide to all practice questions and management options on COVID-19. This is not meant to restrict the practitioner in using sound clinical judgement and sharing the decision with the patient, and from considering other management options according to the patient's particular needs and preferences. This CPG can serve to inform policy, but it is not meant to serve as a basis for approving or denying financial coverage or insurance claims merely because of nonconformance with recommendations. Neither are the recommendations supposed to be considered as legal rules for dictating certain modes of action to the exclusion of others.

Contact Us

Send us an email at covidcpg.ph@gmail.com for any questions or clarifications on the outputs and process of this Living CPG. You may also suggest a clinical question for the consideration of the Living Clinical Practice Guidelines COVID-19 Taskforce.

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Quick Guide on How to Interpret the Evidence

Evidence on Therapy

Table 1. Ways of expressing effectiveness

Outcome	Summary of result within each group	Comparison of results between two groups
Dichotomous (e.g. lived or died, BP controlled or not)	Proportion (e.g. deaths per 100 patients)	Relative risk reduction, absolute risk reduction, relative risk (see Table 2)
	Rate = e.g. deaths per 100 patients	Hazard ratio = rate in treatment/rate in control group
Continuous (e.g. blood pressure in mmHg, quality of life on a scale of 0 to 1)	Mean (e.g. mean blood pressure)	Mean difference = mean in control – mean in treatment group

When researchers express the effect of treatment using the relative risk reduction, absolute risk reduction, or relative risk, they often give us a range of possibilities rather than a single estimate. This range of possibilities is called a '95% Confidence Interval (95% CI)' to mean 'we are 95% sure that the true effect of a drug lies in this range'. Go through Table 2, to discover how helpful 95% CIs are.

Table 2. Interpreting 95% Confidence Intervals (CIs)

Measure of effectiveness and interpretation of estimates	Interpretation of 95% Confidence Intervals (CIs)			
	Superior (treatment surely better than control)	Inferior (treatment surely worse than control)	Inconclusive (we need more studies)	Equivalent (the treatments are equal)[a]
Relative Risk (RR) = R_t/ R_c	Both ends of 95% CI <1.0	Both ends of 95% CI > 1.0	95% CI wide; straddles 1.0	95% CI narrow; straddles 1.0
<1.0 Treatment beneficial =1.0 Treatment no effect >1.0 Treatment harmful	Example: RR = 0.7 [95% CI: 0.6, 0.8]	Example: RR = 2.4 [95% CI: 1.8, 3.2]	Example: RR = 1 [95% CI: 0.2, 5.3]	Example: RR = 1 [95% CI: 0.9, 1.1]
Absolute Risk Reduction (ARR) = R_c - R_t (usually in percent)	Both ends of 95% CI >0%	Both ends of 95% CI <0%	95% CI straddles 0%; either end is far from 0%	95% CI straddles 0%; either end is close to 0%
>0% Treatment beneficial =0% Treatment no effect <0% Treatment harmful	Example: ARR = 2% [95% CI: 1%, 3%]	Example: ARR = -3% [95% CI: -7%, -1%]	Example: ARR = 1% [95% CI: -20%, 32%]	Example: ARR =0.2% [95% CI: -0.1%, 0.5%]

[a] In both inconclusive and equivalent results, the 95% CI interval straddles the point of no effect (ARR = 0% or RR = 1.0). One end reflects the worst possible harm, while the other end reflects the best possible benefit. The only difference is that, in equivalence, either end is close to "no effect" (i.e. any benefit is ignorable and any harm is ignorable too). Consider the ends of the 95% CI to make sure you agree that the benefits and harms are ignorable.

R_c is the rate of the outcomes in the Control group
R_t is the rate of the outcome in the Treatment group

Note: The interpretations in this table only hold if the dichotomous events are expressed as adverse rather than desirable events, e.g. death rather than survival, treatment failure rather that cure, or disease rather than disease-free. When dichotomous outcomes are expressed as desirable events, the interpretation of benefit and harm is reversed.

The balloons below (Figure 1) label the most important parts of the forest plot. Go through these labels and familiarize yourself with the anatomy of the graph. Once you feel sufficiently familiar with the anatomy, go through the notes below on what the forest plot can signify.

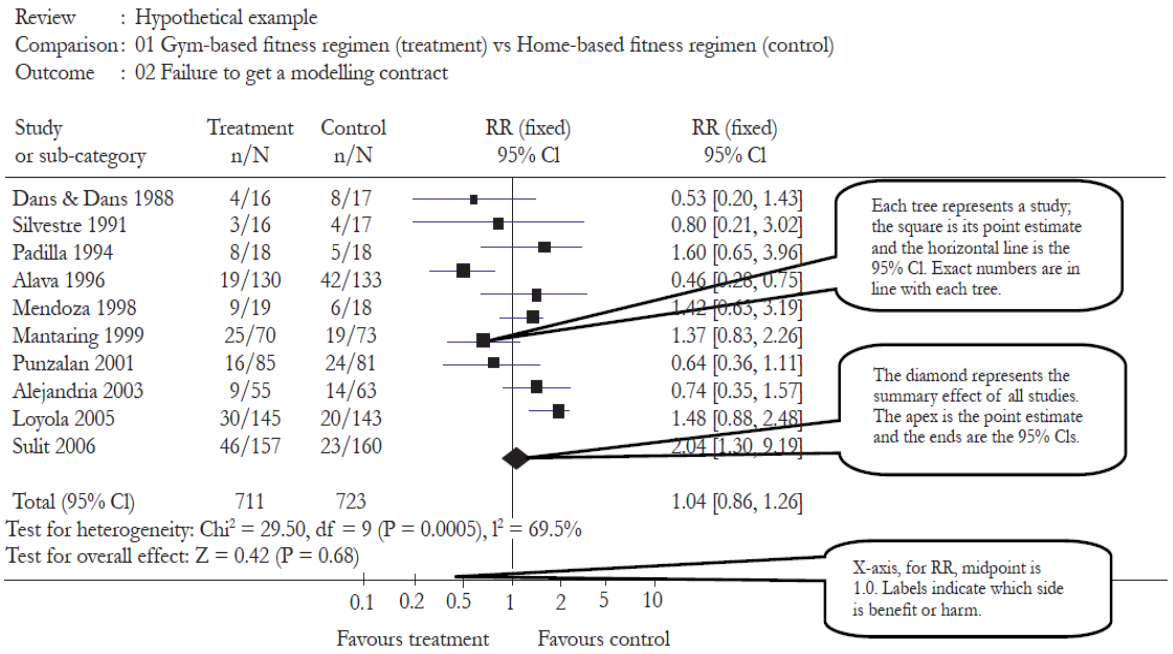


Figure 1. How to interpret forest plots

REFERENCE

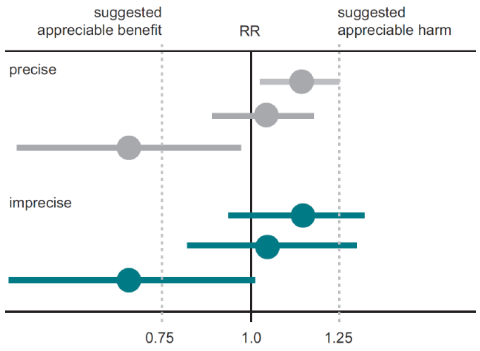
Dans, AL, et al. (2017). Painless Evidence-Based Medicine, 2nd Ed. UK: John Wiley & Sons Ltd.

GRADE Approach in Assessing the Quality of Evidence

(GRADE: Grading of Recommendations Assessment, Development and Evaluation)

These quality ratings apply to the body of evidence assessed for the research question, not to individual studies. Evidence based on randomized controlled trials is initially given a high-quality rating and evidence from observational studies is given a low-quality rating. The level is then adjusted according to the following criteria.

Table 3. Standard criteria for grading of evidence

Domain	Grade	Characteristic
Study Design	0	All randomized controlled trials
	-1	All observational studies
Study Design Limitations	0	Most of the pooled effect provided by studies, with low risk of bias ("A")
	-1	Most of the pooled effect provided by studies with moderate ("B") or high ("C") risk of bias. Studies with high risk of bias weighs <40%
	-2	Most of the pooled effect provided by studies with moderate ("B") or high ("C") risk of bias. Studies with high risk of bias weighs ≥40%
	Note: *Low risk of bias (no limitations or minor limitations) – "A"* *Moderate risk of bias (serious limitations or potentially very serious limitations including unclear concealment of allocation or serious limitations, excluding limitations on randomization or concealment of allocation) – "B"* *High risk of bias (limitations for randomization, concealment of allocation, including small blocked randomization (<10) or other very serious, crucial methodological limitations) – "C"*	
Imprecision	0	The confidence interval is precise according to the figure below. The total cumulative study population is not very small (i.e. sample size is more than 300 participants) and the total number of events is more than 30. 
	-1	One of the above-mentioned conditions is not fulfilled.
	-2	The two above-mentioned are not fulfilled.
	Note: *If the total number of events is less than 30 and the total cumulative sample size is appropriately large (e.g. above 3000 patients, consider not downgrading the evidence).* *If there are no events in both intervention and control groups, the quality of evidence in the specific outcome should be regarded as very low.*	
Inconsistency	0	No severe heterogeneity (I^2< 60% or X^2<0.05)
	-1	Severe, non-explained, heterogeneity (I^2 ≥60% or X^2<0.05)

Domain	Grade	Characteristic
		If heterogeneity could be caused by publication bias or imprecision due to small studies, downgrade only for publication bias or imprecision (i.e. the same weakness should not be downgraded twice)
Indirectness	0	No indirectness
	-1	Presence of indirect comparison, population, intervention, comparator, or outcome
Publication Bias	0	No evident asymmetry in the funnel plot or less than five studies to be plotted.
	-1	Evident asymmetry in funnel plot with at least five studies

Table 4. Quality of evidence in GRADE

Quality Level	Definition
High	We are very confident that the true effect lies close to that of the estimate of the effect.
Moderate	We are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low	Our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of effect.
Very Low	We have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

REFERENCE

Schünemann H, Brozek J, Oxman A, editors. GRADE handbook for grading quality of evidence and strength of recommendations. The GRADE Working Group. Available at: https://gdt.gradepro.org/app/handbook/handbook.html.

Evidence Base

List of Questions

This section presents the evidence base for the recommendations for the vaccines and prophylactic interventions for COVID-19. The following key questions were addressed:

Q1. Among persons at risk, what is the clinical efficacy, effectiveness and safety of BBIBP-CorV (Sinopharm) in the prevention of SARS-CoV-2 infection?

Q2. Is CoronaVac (Sinovac) effective and safe in the prevention of COVID-19-infections?

Q3. Is vaccination with BBV152 (Covaxin/Bharat) effective and safe in the prevention of COVID-19 infections?

Q4. Is NVX-Cov2373 (Novavax) effective and safe in the prevention of COVID-19 infection?

Q5. Are vaccines effective and safe in the prevention of COVID-19 infections?

Q6. Is rAd26 (Sputnik Light) effective and safe in the prevention of COVID-19 infections?: A Rapid Review

Q7. Among adults who received the standard full doses of any COVID-19 vaccine, what is the clinical and immunologic efficacy and effectiveness and safety of a booster?

Q8. Among adults, what is the clinical and immunologic efficacy and effectiveness and safety of heterologous COVID-19 vaccination compared to standard homologous COVID-19 vaccination in preventing COVID-19 infection?

Q9. Are COVID-19 vaccines efficacious in preventing COVID-19 infections caused by the B.1.617.2 (Delta) Variant?

Q10. Among children <18 years old, what is the efficacy/effectiveness and safety of COVID-19 vaccines compared to placebo in preventing COVID-19?

Q11. Is COVID-19 vaccination effective and safe among pregnant and lactating individuals and their infants in the prevention of COVID-19 infections?

Q12. Is BCG vaccination effective and safe in the prevention of COVID-19 infections?

Q13. Among close contacts of COVID-19 patients, should casirivimab + imdevimab cocktail be used as post-exposure prophylaxis?

Q14. Should melatonin be used in the prevention of COVID-19 infection?

Q15. Should Vitamin D supplementation be used in the prevention of COVID-19 infection?

Q16. Should zinc supplementation be used in the prevention of COVID-19 infection?

Q1. Among persons at risk, what is the clinical efficacy, effectiveness and safety of BBIBP-CorV (Sinopharm) in the prevention of SARS-CoV-2 infection?

As of 02 December 2021

RECOMMENDATIONS

We recommend the use of BBIBP-CorV (Sinopharm), given as 200U (WIV04) or 4ug (HBO2) in 0.5 ml in 2 doses, 21 days apart, to prevent symptomatic and asymptomatic COVID-19 infection among healthy adults (18 to 59 years old). *(Moderate certainty of evidence; Strong recommendation)*

We suggest the use of BBIBP-CorV to prevent severe COVID-19 infection among healthy adults (18 to 59 years old). *(Low certainty of evidence; Weak recommendation)*

We suggest the use of BBIBP-CorV to prevent symptomatic COVID-19 infection in the following:

a. **Adults with comorbidities** (*Very low certainty of evidence; Weak recommendation)*
b. **Older persons (60 years and older)** (*Very low certainty of evidence; Weak recommendation)*

There is insufficient evidence to recommend for or against the use of BBIBP-CorV to prevent COVID-19 infection among the following:

a. **Children (3-17 years old)** (*Very low certainty of evidence)*
b. **Immunocompromised population** (*Very low certainty of evidence)*
c. **Pregnant and lactating women** (*Very low certainty of evidence)*

In areas where the SARS-CoV-2 variants of concern are prevalent, there is insufficient evidence to recommend for or against the use of BBIBP-CorV to prevent COVID. (*Very low certainty of evidence)*

Consensus Issues

The decision of the Panel to defer any recommendation for the use of BBIBP-CorV on children and the immunocompromised was based on the limited evidence of efficacy. As no correlate of protection has been established for COVID-19 vaccines, the Panel did not feel that immunogenic response was sufficient to make a recommendation, especially from studies with a small number of participants. The same issue was considered in withholding a recommendation with the use of BBIBP-CorV against the SARS-COV-2 variants of concern.

KEY FINDINGS

The evidence base for the clinical efficacy, effectiveness, and safety of BBIBP-CorV (Sinopharm), as of October 29, 2021 included one network meta-analysis, four randomized controlled trials, 14 observational studies and two regulatory authority reports. Trial results showed that BBIBP-CorV, particularly the HB02 formulation, provided sufficient protection against symptomatic and asymptomatic COVID-19 infection, within a follow up period of 77days. Limited information was available regarding effectiveness against severe infection and on protection for the older

population. Immunologic studies show that the vaccine is immunogenic even among children. Limited information from observational studies on the effectiveness of the vaccine for the immunocompromised suggested some protection and immunogenicity. Available safety data shows acceptable safety profile with no adverse event of interest reported.

INTRODUCTION

Despite the global roll out of COVID-19 vaccines beginning last quarter of 2020, the development of novel vaccines against SARS-CoV-2 continue. Among the many vaccine platforms, inactivated vaccines are the most extensively studied. It is considered safe and are widely used for the prevention other respiratory infections. It is also easily stored and shipped, making it suitable for wide use in low-resourced countries such as the Philippines.

BBIBP-CorV, an inactivated viral vaccine based on the HBO2 strain, was developed through a collaboration between the Chinese Center for Disease Control and Prevention and the Beijing Institute of Biological Products (BIBP)/China National Biotec Group Company Limited (CNBG). Two formulations of the vaccine has since been developed using two different strains, the HB02 and the WIV04. The latter strain was developed by the Wuhan Insitute of Biological Products, also in collaboration with CNBG. Both are offered as a two-dose regimen, 21 to 28 days apart.

BBIBP-CorV (Sinopharm) was first granted Emergency Use Authorization by the Philippine Food and Drug Administration (PFDA) on August 19, 2021.[1] As of October 24, 2021, 750,978 doses have been administered in the country.[2]

This review describes the current available evidence supporting the efficacy, effectiveness and safety of BBIBP-CorV in the prevention of COVID-19.

REVIEW METHODS

General Search Results

As of October 29, 2021, 19 studies and 2 regulatory reports were identified as providing information on the performance of BBIBP-CorV as a vaccine against SARS-CoV-2. One network meta-analysis presented the neutralizing antibody response of BBIBP-CorV in relation to the other vaccines.[3] Four studies were randomized controlled trials, one providing both clinical and immunologic efficacy and safety,[4] and the rest providing immunologic and safety outcomes.[5-7] Two studies provided data on the performance of BBIBP-CorV against variants of concern.[8-9] Five observational studies were on the immunocompromised population. One study reported on the immunogenic outcomes of a booster dose.[10]

The risk of bias assessment of all included studies are in Table 2.

RESULTS

Clinical Efficacy

The pivotal Phase 3 trial establishing the efficacy and safety of BBIBP-CorV involved over 41,000 health adults, with over 26,000 receiving the vaccine (WIV04=13,459; HBO2=13,465). Results after a median follow up of 77 days (112 days as per WHO-SAGE report) showed sufficient protection against COVID-19 infection. Vaccine

effectiveness (VE) against symptomatic COVID-19 infection was reported as 72.8 (95% CI 58.1-82.4) for WIV04 and 78.1 (95% CI 64.8-86.3) for HB02. On the other hand, VE against any infection (i.e. including asymptomatic infection) were 64.0 (95 %CI 48.8-74.7) for WIV04 and 73.5 (95% CI 60.6-82.2) for HB02. Severe infection was noted only in 2 cases, both in the control group precluding any estimation of VE for this outcome.[4]

Table 3 details the characteristics of the pivotal trial for BBIBP-CorV. Detailed outcomes are in Table 9 and 10.

Immunogenicity

A network meta-analysis on neutralizing antibody responses across the different COVID-19 vaccines included 11 studies, of which one used BBiBP-CorV. BBIBP-CorV was considered to produce very large effect on the level of neutralizing antibodies (SMD >1.3), similar with the ChAdOx1 (AstraZeneca), BNT162b2 (Pfizer), and Gam-COVID-Vac (Sputnik V).[3]

The reference trial in the above NMA was the Phase 1/2 trial of BBIBP-CorV (HB02) on healthy adults that investigated on the immunogenicity of varying doses and dosing intervals. In this study, neutralizing antibody titers were significantly increased in those who received the vaccine compared with the control. Titers were noted to higher in the young (18 to 59 years old) compared to the older population. Titers were higher after the two-dose 4ug regimen, compared with the single dose 8ug.[6]

Another Phase 1/2 RCT using BBIBP-CorV involved children aged 3 to 17 years, showing significant increase in neutralizing antibody titers after 2 doses of the vaccine with no further increase after the third dose, and with the 4ug and 8ug doses having higher titers than the 2ug dose. All treatment groups reached 100% seropositivity.[7]

One randomized controlled trial involving healthcare workers compared the immunogenic responses of two doses of BBIBP-CorV at 14-, 21-, and 28-day intervals. The three groups showed 100% seroconversion. Those in the 21- and 28-day interval elicited significantly higher neutralizing antibody levels compared to those in the 14-day interval group.[5]

In a longitudinal study among healthcare workers, 100% seroconversion for anti-spike specific antibodies was observed after the second dose of BBIBP-CorV. Three months later, titers significantly dropped but still significantly higher than pre-vaccination. This study also showed that previously infected individuals generated significantly higher titers after BBIBP-CorV vaccination at all timepoints compared to the infection-naïve.[11]

A prospective study involving mostly elderly vaccine recipients suggested decreased immune response from BBIBP-CorV in the older population. (see below)[12]

Immunogenicity of BBIBP-CorV among immunocompromised population is discussed in the section below.

Real World Evidence: Effectiveness

General Population

Two studies on the real-world clinical effectiveness were identified, limited to reporting breakthrough infections after BBIBP-CorV vaccination. One was a prospective cohort on 82 healthcare workers which reported four cases of infection after the first dose, two immediately after the second dose, and two getting the infection more than 14 days after second dose. It was unclear how long the follow up was in this study.[11]

A case series involving an extended family of 54 members showed only partial protection provided by BBIBP vaccination. Nearly all vaccinated members developed breakthrough infection. Hospitalization was necessary in 43% (10/23) of those who received only one dose whereas it was needed in only 5% (1/20) in those who received two doses. The only death in the study was from among the unvaccinated members.[13]

Clinical Efficacy and Effectiveness On Special Populations of Interest (Older persons, Children, Immunocompromised, Pregnant Women)

Older population

Older persons (>=60 years of age) were recruited late in the Phase 3 trial and thus composed only a small proportion of the study population included (WIV04=213, HB02=201) in the interim report with shorter follow-up duration. No events were recorded in both the vaccine and placebo groups during the observation period of the trial report, precluding any estimation of vaccine efficacy in this group.[4,14] In the Phase 1 trial, neutralizing antibody titers were noted to be significantly less in the older population compared to the young.[6]

The lower immunogenic response to BBIBP-CorV among the older persons was also shown in a prospective cohort study 450 BBIBP-CorV vaccinees, mostly elderly individuals who requested for antibody measurements after a median follow up of 23 days after the second dose. This study demonstrated that increasing age correlated with a lack of antibody production with the estimated probability of the lack of antibody response at 25% for those aged 60 years and 50% for those aged 80 years old. When compared to a randomly selected sample from 50 BNT162b2 vaccinees, antibody titers with BBIBP-CorV were significantly lower in this study.[12]

Children

Since children were excluded in the regulatory trial, no clinical efficacy data was found for children. Only immunogenicity data was available.

A Phase 1/2 placebo-controlled RCT involving children from 3 to 17 years compared immunogenic responses to three different doses (2, 4, and 8ug) given as three doses (day 0, 28, and 56). All groups reached 100% seroconversion. However, significantly higher titers were seen in those who received 4ug and 8ug dose compared to 2ug after the first and second doses. The titers were similar after the third dose.[7]

Pregnant women

Pregnant women were excluded in the clinical trial of BBIBP-CorV. However, the WHO SAGE report noted that in the Phase 3 trials submitted for the review, five pregnancies were reported in the vaccine group (HB02). At the time of the SAGE review, pregnancy and birth outcomes were still being monitored.[14]

Immunocompromised

Five studies involving the immunocompromised were found. Three involved patients with multiple sclerosis,[15-17] one on patients on dialysis[18] and one on cancer patients.[19]

Two studies among multiple sclerosis patients focused on safety outcomes of BBIBP-CorV vaccination. One study reported that 16.2% had at least one neurologic side effect during the at-risk period (most common were motor symptoms and vertigo). Six (1.2%) vaccinees experienced relapse during the at risk period.[15] Another study followed 583 patients with multiple sclerosis after 1 dose of BBIBP. No serious adverse event was reported. At least one transient symptom was experienced by 60% of vaccines including constitutional symptoms (51%) and headache (9%). Five (0.9%) reported relapse after vaccination.[16]

One small series of multiple sclerosis patients on disease modifying therapies showed seroconversion rates of 42-100%.[17]

One study on dialysis patients receiving 2 doses of BBIBP-CorV (HB02 strain) reported an overall case fatality rate in vaccinated individuals as 4.3% (8/187), compared to 8.7% (28/324) in the unvaccinated. Serologic studies performed in a subgroup of 270 patients who were seronegative at baseline showed that 41% had suboptimal levels 14 to 21 days after the second dose.[18]

Cancer patients with solid and hematological tumors (n=364) were given two doses of BBIBP-CorV. Overall seropositivity rates were high (80.7% for neutralizing antibodies, 77% for anti-IgG). Seroconversion was found to be higher in patients with breast cancer (93.3%) and upper GI cancers (94.7%). Lowest rates were found in patients with hematologic malignancies (61.9%). The rate of seroconversion was higher in patients less than 60 years old. Local side effect rate was 15% and these were mostly mild. Severe local side effect was experienced by 2.2%. The most common systemic side effect was fever (31.6%). One patient (2.7%) experienced breakthrough infection after the first dose and three (8.3%) after the second dose.[19]

Safety

Regulatory Clinical Trial Evidence

Four randomized trials provided safety data, one of which involved children. All were consistent in demonstrating adverse event rates after BBIBP-CorV as comparable with the control.[4-7] Overall adverse event rates (including adverse reactions) ranged from 3.2% to 45%. Unsolicited adverse event rates within 28 days ranged from 3.7% to 29%. The most common local adverse reaction was pain at the injection site. The Phase 2 trial in children found a dose dependent increase in local pain at injection site compared with placebo.[7] Fever and headache were the most common systemic adverse reaction. All adverse reactions were mild to moderate. No serious adverse events were reported in 3 trials and was only 0.4-0.5% in the Phase 3 trial, which were similar to the control group. Two serious adverse events were assessed to be possibly related to the HB02 vaccine. One was a demyelinating disease developing in a 50 year old man after the first dose and one was a case of severe emesis in a 35-year old woman after the second dose.[4] One case of allergic purpura in a child assessed as severe and vaccine related was noted after the second BBIBP-CorV dose.[7]

Detailed safety outcomes from the Phase 3 trial are in Table 9.

Real World Evidence of Safety

Three studies were found reporting on real world evidence on safety of BBIBP-CorV. The rates found in these studies were consistent with those in the clinical trials. Two were surveys done using online platforms. Both showed adverse reaction rates similar to those found in the clinical trials. The first compared adults vaccinated with BBIBP-CorV (n=513) and BNT162b2 (n=491).[20] The second study analyzed 1080 survey responses from those who received at least one dose of BBIBP-CorV. Most of the respondents were female. Injection site pain was the most common adverse event. Twenty four percent of the respondents did not have any adverse events after vaccination.[21]

One prospective study among 406 healthcare workers was specifically performed to determine the incidence of thrombotic events and to determine any change in the presence of autoantibodies pre- and post-vaccination. After an eight-week follow up, no thrombotic event occurred. No significant difference was noted in the presence of all 10 autoantibodies between pre- and post- vaccination samples. Seven cases presented with anti-PF4 heparin antibodies but none of them exhibited any sign of thrombotic disorder.[10]

In the October 24, 2021 report of the Philippine Food and Drug Administration, 86 adverse events were associated with BBIBP-CorV (Sinopharm), after 750,978 doses administered locally. Five of these were classified as serious, with no further description of the cases given. The top reported events were pyrexia (25.6%), cough (15.1%), dizziness (13.95%), and headache (13.95%).[2]

Reports on Adverse Events of Interest

The WHO SAGE report cited two cases of Bell's palsy in the trial, one in the placebo group and one in the BBIBP-CorV group. One thrombotic event was reported among the 29,240 trial participants in the vaccine group. This was in a 50 year old man who had prior history of blood clots before vaccination and suffered abdominal pains 7 days after the first dose of BIBP, confirmed to be due to a thrombus.[14]

Effectiveness Against Variants

Two studies investigated the effectiveness of BBIBP-CorV against the variants of concern based on immunogenic response. The first study used 12 random serum samples from trial patients extracted 28 days after the second dose of BBIBP-CorV. It found a 1.6-fold reduction in GMTs against the Beta variant compared to the Wuhan strain.[8] The second study involving 282 infection-naïve vaccinees showed significantly lower titers to Alpha (1.3-fold reduction), Beta (10-fold) and Delta (1.38-fold) compared to WT at 2 weeks after the second dose of BBIBP-CorV.[9]

Tables 9 and 10 present the summary of findings and certainty of the evidence for BBIBP-CorV.

Duration of Protection

One prospective study on 82 healthcare workers demonstrated that anti-spike specific antibody titers significantly dropped three months after the second dose, but still to a

level higher than after the first dose. The decline was greater in those without prior infection.[11]

Booster Vaccination

One study investigated the effect of a booster dose of BBIBP-CorV six months after the primary vaccination in 50 volunteer healthcare workers. It showed increased neutralizing antibody titers peaking at two weeks post-boost with a 10.6 fold rise. All antibodies (anti-spike, RBD, N) were detectable post-boost. B cells for spike and RBD were likewise increased post-boost. T-cell response was enhanced by the boost by 2.3-fold. In those who remained seronegative after the primary vaccination, seroconversion for neutralizing antibodies, B-cell and T-cell responses were noted post boost but to a lesser extent compared to those who responded to the primary vaccination.[22]

AUTHORIZATIONS

The Philippine FDA has issued three EUAs for BBIBP-CorV (Sinopharm) from 3 manufacturers on August 19, 2021 (WIV04–WIBP), on September 10, 2021 (HB02 – BIBP), and on October 14, 2021 (Hayat-Vax, strain unspecified).[23]

The WHO has included BBIBP-CorV (Sinopharm) in its emergency use listing based on the SAGE recommendations (only for HB02) for its administration to 18 years and above (2 doses at interval of 3 weeks but with flexibility to extend to 4-week intervals) on May 7, 2021. In its updated guidance on October 28, 2021, the WHO-SAGE indicated that additional dose of the vaccine may be needed as part of an extended primary series for populations where the immune response following the standard primary series is deemed likely to be insufficient, such as the older persons and immunocompromised individuals.[24]

RESEARCH GAPS

The following are identified research gaps regarding BBIBP-CorV vaccination for COVID-19 infection prevention: The efficacy/effectiveness of BBIBP-CorV in special populations such as the older and very old patients, children, immunocompromised (eg. HIV) populations; the duration of protection / long term efficacy or effectiveness; its long-term safety; its clinical efficacy and effectiveness against infection with variants of concern; studies on heterologous primary vaccination; and its use in booster vaccinations.

ONGOING TRIALS

The search performed on October 31, 2021 of the Clinicaltrials.gov registry showed eight trials on BBIBP-CorV (Sinopharm). Table 11 details these trials.

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Appendix 1: Evidence to Decision

Table 1. Summary of Judgements Prior to Panel Discussion (N=7)

FACTORS	JUDGEMENT						RESEARCH EVIDENCE/ADDITIONAL CONSIDERATIONS
Problem	No	Yes (7)					
Benefits	Large	Moderate (6)	Small	Uncertain (1)			• In a Phase 3 trial involving 41,000 healthy adults: Vaccine effectiveness (VE) against symptomatic COVID-19 infection was reported as 72.8 (95% CI 58.1-82.4) for WIV04 and 78.1 (95% CI 64.8-86.3) for HB02.
Harm	Large	Small (5)	Uncertain (2)				• Four randomized trials were consistent in demonstrating adverse event rates after BBIBP-CorV as comparable with the control. • Overall adverse event rates (including adverse reactions) ranged from 3.2% to 45%. The most common local adverse reaction was pain at the injection site. • Isolated case reports from WHO SAGE include: 2 cases of Bell's palsy and 1 thrombotic event.
Certainty of evidence	High	Moderate (4)	Low (3)	Very Low			• Very low to high
Balance of effects	Favors vaccine (5)	Does not favor vaccine	Uncertain (2)				
Values	Important uncertainty or variability	Possibly important uncertainty or variability (3)	Possibly no important uncertainty or variability (3)	No important uncertainty or variability (1)			
Resources required	Uncertain	Large cost	Moderate cost (6)	Negligible cost or savings	Moderate savings (1)	Large savings	• Sale price of Sinopharm varies from $19-$36 (PHP 950-PHP 1820). • The required storage temperature for Sinopharm is 2-8 degrees Celsius, not allowed to be frozen. It must be protected from light.
Certainty of evidence of resources required	No included studies (7)	Very low	Low	Moderate	High		
Cost effectiveness	No included studies (7)	Favors the comparison	Does not favor either the intervention or the comparison	Favors the intervention			
Equity	Uncertain (2)	Reduced	Probably no impact	Increased (5)			• PHL FDA EUA indication is for clinically healthy people (aged 18 years old and above) susceptible to the virus. • Addresses wide disparity in vaccine coverage: 85.1% fully-vaccinated senior citizens in NCR; only 28.3% in BARMM
Acceptability	Uncertain (1)	No	Yes (6)				• BBIBP-CorV (Sinopharm) was granted Emergency Use Authorization by the Philippine Food and Drug Administration (PFDA) on August 19, 2021.
Feasibility	Uncertain (1)	No	Yes (6)				

Appendix 2. Risk of Bias Assessment of Included Studies

Study ID	Design	Randomization	Allocation Concealment	Blinding Particip	Blinding Carer/ Assessor	Followup	Selective Reporting	Others	Age	Comorbidities	Exposure	Confounding	OVERALL
Abu-Halaweh (Jordan)	Prospective cohort	HIGH	HIGH	HIGH	HIGH	HIGH	UNCLEAR	NA	HIGH	HIGH	HIGH	HIGH	SERIOUS
Al Kaabi (UAE, Egypt)	RCT Ph3	LOW	LOW	LOW	LOW	HIGH	LOW	NA	NA	NA	NA	NA	SOME CONCERNS
Ariamanesh (Iran)	Single cohort	HIGH	HIGH	HIGH	HIGH	HIGH	UNCLEAR	NA	HIGH	HIGH	HIGH	HIGH	SERIOUS
Badano (Argentina)	Single cohort	HIGH	HIGH	HIGH	HIGH	HIGH	UNCLEAR	NA	HIGH	HIGH	HIGH	HIGH	SERIOUS
Drulovic (Serbia)	Single cohort	HIGH	HIGH	HIGH	HIGH	HIGH	UNCLEAR	HIGH	HIGH	HIGH	HIGH	HIGH	VERY SERIOUS
Etemadifar (Iran)	Prospective cohort	HIGH	HIGH	HIGH	HIGH	HIGH	UNCLEAR	HIGH	HIGH	HIGH	HIGH	HIGH	SERIOUS
Feng (China)	RCT Ph4	LOW	UNCLEAR	UNCLEAR	UNCLEAR	HIGH	LOW	NA	NA	NA	NA	NA	SERIOUS
Ferecii (Hungary)	prospective cohort	HIGH	HIGH	HIGH	HIGH	HIGH	UNCLEAR	NA	HIGH	HIGH	HIGH	HIGH	SERIOUS
Holt (UAE)	Prospective cohort	HIGH	HIGH	HIGH	HIGH	HIGH	UNCLEAR	NA	NA	NA	NA	NA	SERIOUS
Huang (China)	Single cohort	HIGH	HIGH	HIGH	UNCLEAR	UNCLEAR	UNCLEAR	HIGH	HIGH	HIGH	HIGH	HIGH	SERIOUS
Jahromi (Bahrain)	Single cohort	HIGH	HIGH	HIGH	HIGH	HIGH	UNCLEAR	HIGH	HIGH	HIGH	HIGH	HIGH	VERY SERIOUS
Jeewandara (Sri Lanka)	Single cohort	HIGH	HIGH	HIGH	UNCLEAR	LOW	UNCLEAR	NA	HIGH	HIGH	HIGH	HIGH	SERIOUS
Liu (China)	Single cohort	HIGH	HIGH	HIGH	HIGH	HIGH	UNCLEAR	NA	HIGH	HIGH	HIGH	HIGH	SERIOUS
Liu Y (China)	Single cohort	HIGH	HIGH	HIGH	HIGH	LOW	UNCLEAR	NA	HIGH	HIGH	HIGH	HIGH	SERIOUS
Saeed (UAE)	Single cohort	HIGH	HIGH	HIGH	HIGH	HIGH	UNCLEAR	NA	HIGH	HIGH	HIGH	HIGH	SERIOUS
Sahraian (Iran)	Single cohort	HIGH	HIGH	HIGH	HIGH	HIGH	UNCLEAR	NA	HIGH	HIGH	HIGH	HIGH	SERIOUS
Xia1 (China)	RCT Ph 1/2 (Adult)	LOW	LOW	LOW	LOW	LOW	UNCLEAR	NA	NA	NA	NA	NA	NOT SERIOUS
Xia2 (China)	RCT Ph 1/2 (Children)	LOW	LOW	LOW	LOW	LOW	UNCLEAR	NA	NA	NA	NA	NA	NOT SERIOUS

Appendix 3. Characteristics of the Randomized Controlled Trial (Ph3) on the Efficacy and Safety of BBIBP-CorV

Trial Identifier	**ChiCTR2100041705, ChiCTR2100041706**
Vaccine	**BBIBP-CorV (Sinopharm)**
Data Sources	**AlKaabi (main paper, protocol and supplement), WHO SAGE Background Report**
POPULATION	
Total Randomized	40,411
Inclusions:	18 years and above, judged as healthy
● Age	18 years and above, but older (>60 years) recruited late in the study
● Gender	Both: 84.4% men
● Race/Ethnicity	Multicountry: 23.3% UAE
● Immunocompromised	Excluded
● Pregnant and breastfeeding	Excluded
● With concomitant comorbidities	Excluded
● With previous COVID infection	Excluded
● With known previous exposure to COVID	Not mentioned
● Seropositive at baseline	6.4%
Exclusions	Acute cases of SARS-CoV-2 infection, with medical history of SARS or MERS, fever, positive urinary pregnancy, with previous severe allergic reactions or known allergy to inactivated SARS-CoV-2 vaccine, with medical history or family history of convulsion, epilepsy, encephalopathy or mental illness, congenital malformation or developmental disorder, genetic defects, severe malnutrition, known or suspected acute respiratory disease, severe cardiovascular disease, severe liver disease, severe kidney disease, uncontrollable hypertension, diabetic complications, malignant tumors, acute diseases, diagnosed with congenital or acquired immune deficiency, HIV infection, lymphoma, or other autoimmune diseases, history of coagulation dysfunction, receiving anti-TB therapy, receiving immune enhancement or inhibitory therapy within 3 months, vaccinated live attenuated vaccine within 1 month before, received blood products within 3 months, received other investigational drugs
INTERVENTION (VACCINE)	
Type	Inactivated virus
Active substance	Inactivated SARS-CoV-2 (WIV04 or HB02 strain) in aluminum hydroxide adjuvant
STORAGE AND COLD CHAIN CONSIDERATIONS	
● Shipping and transport	2-8’C
● Storage and shelf life prior to dilution/ opening	2-8’C
FINAL PRODUCT	
Form and use	WIBP: 200U/dose BIBP: 4ug/dose
Excipients	aluminum hydroxide adjuvant
TRIAL-SPECIFIC CONSIDERATIONS	
Dosing and administration	WIV04 (WIBP), 200WU/dose in 0.5ml, 2 doses 21d interval (+7) HB02 (BIBP), 4ug vp/dose in 0.5ml, 2 doses 21d interval (+7)
Number randomized	WIV04 (WIBP) = 13470 (13066 received D2) HB02 (BIBP) = 13470 (13086 received D2)
COMPARATOR	
Type, dosing and administration	Aluminum adjuvant, 0.5ml, 2 doses 21d interval (+7)
Number randomized	13,471 (13,071 received D2)
OUTCOMES	
Primary efficacy endpoints	Vaccine efficacy against COVID-19 (symptomatic infection) 14 days following 2 doses, confirmed cases confirmed by EAC blinded review
Primary safety endpoints	- Incidence of any adverse reactions/events within 30 mins after each dose - Incidence of solicited adverse reactions within 7 days - Unsolicited adverse reaction with d8-21 after first dose and d8-28 after 2nd dose

	- Incidence of serious adverse events from D1 to 12 months
Secondary endpoints Exploratory endpoints Immunogenicity	- Vaccine efficacy against severe cases and deaths - Anti-SARS-CoV-2 neutralizing antibody protective level against COVID-19 - Occurrence of ADE/VED after immunization - 4-fold increase rate, GMT and GMI of anti-SORS-COV-2 neutralizing antibody in after full course of immunization: 14d, 28d, 3 mos, 6 mos, 9 mos, 12 mos
Post Hoc	- Asymptomatic infection - Infection after first dose, before second dose
SUBGROUPS CONSIDERED IN THE ANALYSIS	
● Age	> 60 years old (only 213 in WIV04 and 201 in HBO2, and 198 in alum), but cases during the study so no efficacy was calculated
● Sex	No
● Ethnic groups	No
● Baseline seropositivity status / evidence of previous infection	Noted outcomes but too small to do subgroup analysis, only 1 case in the alum group
● Medical comorbidities	No
● Immunocompromised / HIV disease	excluded
● Risk for acquiring COVID infection	no
● Risk for progression to severe COVID	no
● Dosing regimen	21 day interval (+7 days)
FOLLOW UP	
● Planned	1.5 years
● At data cutoff of interim report (first interim analysis)	Median duration 77 days (1-121) * WHO report : 122 days
Date of Data Cut-off date for latest available trial data	December 20, 2020
METHODS / OTHER TRIAL PARAMETERS	
Blinding	No mention
Study Sites	China
Study Sponsor	China National Biotec Group Company Ltd, Wuhan Institute of Biological Products, Beijing Institute of Biological Products
Type of report available as of this rapid review	Full publication with supplement
Others	Balanced withdrawal/ late exclusions across groups including reasons for exclusion

Appendix 4. Characteristics and Results of Clinical Trials on BBIBP-CorV

Study ID	Design	Population	Intervention / Comparison	Outcome (Followup/Assessment) Result
Al Kaabi	RCT (Interim analysis)	>18yo without any history of COVID-19 WIV04 = 13,459 HBO2 = 13, 465 Alum = 13, 458	2 doses of either WIV04 and HB02 (21 days apart) Control: Aluminum hydroxide	VE of WIV04 / HB02 Symptomatic: (median ffup: 77days) 72.8 (58.1-82.4) / 78.1 (64.8-86.3) Severe: (median ffup: 77days) 100% / 100% (2 cases in placebo) Asymptomatic: (median ffup: 77days) 64.0 (48.8-74.7) / 73.5 (60.6-82.2) GMT d14 after 2nd dose WIV04: 94.5 (89.7 – 99.5) HB02: 156 (149.6 – 162.7) Placebo: 2.7 (2.6 – 2.8) Seroconversion d14 after 2nd dose WIV04: 99.3% HB02: 100% WIV04 / HB02 / placebo Total AR rate: 44.2 / 41.7 / 46.5% Pain at injection site: 24.3 / 19.4 / 27.9% Headache: 12.9 / 13.1 / 12.6 No increase in solicited AE during 8-28 days after injection Unsolicited AE increased: 11.1-16.1 / 10.7 - 15.5 / 10.6-15.4 Total AE: 48.3 / 46.1 / 50.5 SAE: 0.5% / 0.4% / 0.6% *Related SAE, both in placebo: demyelinating myelitis after D1 and severe emesis after D2
Xia 1	RCT	Healthy adults Ph1: 18 to 80 y/o Ph2: 18 to 59 y/o	BBIBO-CorV (HBO2) Phase 1: 2 dose (28d) 2, 4, 8ug Phase 2: 8 ug (1d) 4 ug (14, 21, 28d) Control: placebo (alum with saline)	Phase 1: At least 1 AR: 29%, all mild to moderate No serious AE with 28 days Most common systemic AR: fever, no difference across groups NaB, significantly higher than placebo but titers higher in the young (18-59yo) compared to the older Phase 2: At least 1 AR: 23% Higher rate with 8ug, decreasing rate in increasing dosing interval Most common systemic AR: fever, no difference across groups NAB higher with 2 doses, highest with 4ug
Xia 2	RCT	3 to 17 y/o. Ph 1 = 216 Ph 2 = 810 (Vac = 540, pla = 1 80)	BBIBP-CorV doses: 2, 4, 8 ug 3 dose schedules (0, 28, 56) Control: placebo (alum with saline)	• Dose dependent increase in overall injection site ARs in vaccine groups compared with control • Most common systemic reaction was fever (12.7%) and cough (8.7%); not different from placebo • Only 1 vaccine related AE = grade 3 allergic purpura after D2 in 6-12 yo cohort • Significantly higher titers with 4 and 8ug compared to 2ug after D1 and D2 but all the same at D3
Feng et al.	RCT	18-59yo in the occupational high-risk population N = 809 14 day: 270 (256 ffup) 21d: 270 (247 ffup) 28d: 269 (241 ffup)	BBIBP 4ug at 14, 21, or 28-day intervals (Strain not specified)	Seroconversion of neutralizing antibodies (28days pD2) PP 14d: 100% 21d: 100% 28d: 100% ITT 14d: 94.8% 21d: 91.5% 28d: 89.6% GMT (28 days pD2) PP 14d: 98.4 21d: 134.4 28d: 145.5 ITT 14d: 93.5 21d: 122 28d: 129.8 *The same trend of having lower seroconversion rate in the 14day group compared to the other groups was seen even if different cutoff values were used. Overall AE rate 14d: 4.1% 21d: 4.8% 28d: 3.7% Solicited AR: 3.2% Unsolicited AE: 0.99% No significant difference across 3 dosing groups No reported serious AE

Appendix 5. Characteristics of Studies on the Real-World Evidence of BBIBP-CorV (EFFECTIVENESS, General Population and immunocompromised)

Study ID	Design	Population	Intervention	Comparison	Follow up	Outcomes Reported
Jahromi et al.	Case series	54 members of an extended family	BBIBP 26 partially vacc 20 fully vacc	Unvaccinated (n=8)		(Total) Infection / Hospital / Death Unvaccinated: 8 / 3/ 1 Partial: 23 /10 /0 Fully: 20 / 1 /0
Holt	Comparative cohort	Patients on dialysis with negative baseline titers (n=187)	2 doses of BBIBP (HBO2) 21-day interval (+7 days)	Unvaccinated (n=234)	14-21 days after 2nd dose	Case fatality rate Among unvaccinated: 8.7% (28/324) Among vaccinated: 4.3% (8/187)

Appendix 6. Characteristics of Studies on the Real World Evidence of BBIBP-CorV (SAFETY, General Population and Immunocompromised)

Study ID	Design	Population	Intervention	Comparison	Follow up	Outcomes Reported
Saeed	Cross-sectional survey (Self-administered via social media sites)	1080 responses, general population	One or 2 doses of BBIBP (Strain not specified)	none		• 24.4% did not have any side effects • After 1st dose: site pain (42.2%), fatigue (12.2%), headache (9.6%) • After 2nd dose: site pain (32.6%), fatigue (16.3%), lethargy (13.7%) • SE after both doses were more prevalent in <49yo group. • More females suffered from SE than males.
Etemadifar	Prospective cohort	Subjects with multiple sclerosis (Vaccinated: 517) (Unvacc: 174)	2 doses of BBIBP (Strain not specified)	Unvaccinated	At-risk period: Vaccinated cohort - 2 weeks after 1st dose and 2 weeks after 2nd dose Unvaccinated cohort – 1-year period before the study	• 16.2% (n = 84) of vaccinated had at least one neurologic side effect during the at-risk period (most common were motor symptoms and vertigo) • Six vaccinees experienced MS relapse during the at-risk period. • No significant difference between relapse rates of vaccinated and unvaccinated subjects in the year prior. • No SAE reported.
Sahraian et al.	Cross-sectional study using a questionnaire via social networks	583 subjects with multiple sclerosis	1 dose of BBIBP (Strain not specified)			• No serious AE • At least one transient complaint by 60% of vaccinees • Most common are constitutional symptoms (51%), headache (9%) • Only 5 (0.9%) reported MS relapse after vaccination
Ariamanesh et al.	Single cohort using questionnaire survey	Adult patients with cancer (N = 364)	2 doses of BBIBP (Strain not specified)		2 months after 2nd dose	• Local SE • Mild: 5.4% • Severe: 2.2% • Most common systemic SE: fever (31.6%)

Appendix 7. Characteristics and Results of Studies on the Immunogenicity of BBIBP-CorV (Observational studies)

Study ID	Population (n)	Vaccine Regimen	Extraction time	Result
Liu	Healthcare workers N = 50	2 doses of BBIBP with a 28-day interval and a third booster shot six months after prime vaccination (Strain not specified)	d180 before boost d187, d194, d208 after boost	• Six months after primary vaccination, 36/50 tested negative for NAB • Serologic response induced within 1 week of booster dose. Peak concentration of NAbs reached at 2 weeks (10.6-fold rise) • All antibodies (anti spike, RBD, N) were detectable post boost. • Increased B cells post boost (for spike and RBD B cells) • CD8 and CD4 T cell response enhanced by booster 2.7- and 5.9-fold respectively. • In those who remained seronegative after the primary vaccination, seroconversion for NAb, B-cell and T-cell response was noted post boost but to a lesser extent compared to those who responded to the primary vaccination. NAb levels peaked at 2 weeks after the boost.
Badano	Healthcare workers with or without exposure to SARS-COV-2 N = 82	2 doses of BBIBP (Strain not specified)	21 to 30 days after 1st dose and 2nd dose 3 months after 2nd dose	• 100% seroconversion for anti-S IgG after D2 (40% after D1) • Significant increase in titers after D2 • Significant drop in titers after 3 months • 4 infections after D1, 2 immediately after D2, 2 more than 14 days after D2
Jeewandara	282 participants (seronegative at baseline)		2 weeks after 2nd dose	• 95% seroconversion overall • Lower seroconversion rates with individuals >60yo vs 20-39 yo (93.3% vs 98.9%); higher in males, no diff in those with comorbidities
Holt	Patients on dialysis with negative baseline titers N = 270	2 doses of BBIBP (HBO2) 21-day interval (+7 days)	14-21 days after 2nd dose	• Positive anti-spike antibodies: 56.5% (41% had suboptimal antibody levels) • Overall GM anti-spike: 13.3 (11-15.8) • Overall GM NAb: 13 (10.9-15.6)
Ariamanesh	Adult patients with cancer (N = 364)	2 doses of BBIBP (Strain not specified)	2 months after 2nd dose	• NAb seropositive: 80.7% • antiS IgG seropositive: 77.1% • 1 patient tested (+) after D1, 3 tested (+) after D2 • Rate of seroconversion was higher in patients <60yo. • Rate of seroconversion higher in patients with breast cancer (93.3%) and upper GI cancers (94.7%). Lowest rates were found in patients with hematologic malignancies (61.9%). • Antibody response higher in those receiving radiotherapy alone or endocrine therapy (97%) compared to those in chemotherapy (83.5%).

Appendix 8. Characteristics and Results of Studies on the Immunogenicity of BBV152 against Variants of Concern

Study ID	Population (n)	Test used (Timing of Extraction)	Variants Tested	Reference strain	Result
Huang	12 trial participants	Geometric mean titre (GMT)	Beta (501Y.V2)	WT or D614G strain	• All samples showed preserved neutralization against the Beta variant • Compared with titers against WT or D614G strain, GMT from BBIBP decreased from 110.9 to 71.5, or a 1.6-fold reduction • Reduction is significantly less than those reported from convalescent plasma or antisera from mRNA vaccine recipients.
Jeewandara	282 participants (seronegative at baseline)	Anti-RBD antibodies	Alpha Beta Delta	anti-RBD antibodies to WT, Alpha, Beta and Delta IFN-gamma at 2 weeks after second dose (N=66)	• 95% seroconversion overall • Lower seroconversion rates with individuals >60yo vs 20-39 y/o (93.3% vs 98.9%); higher in males, no diff in those with comorbidities • At 6 weeks (2 weeks post D2), there were significantly less titers to Alpha (1.3-fold red), Beta (10-fold) and Delta (1.38-fold) compared to WT. • Noted increased T and B cell response at 2wks post D2 but less than those observed with some other vaccines.

Appendix 9. Summary of Findings Table on the Efficacy of BBIBP-CorV

Efficacy Outcome (at > 14 days after dose 2)	Studies	Quality Assessment					Summary of Findings			Certainty
		Risk of Bias	Inconsistency	Indirectness	Imprecision	Overall Assessment	Vaccine n/N (%)	Control n/N (%)	Vaccine Efficacy (CI)	
1: Symptomatic COVID-19 infection, seronegative at baseline	RCT	Some concerns (Short ff-up)	Not assessed	Not serious	Not serious	Some concerns	26/12743 [a] 21/12726 [b]	95/12737	72.8[a] (58.1-82.4) 78.1[b] (64.8-86.3)	+++ Moderate
2 : Severe COVID-19 infection, seronegative at baseline	1 RCT	Serious (Short ff-up)	Not assessed	Not serious	Serious (Low case numbers	Serious	0/12743 [a] 0/12726 [b]	2/12737	100% (NE)	++ Low
3. Asymptomatic COVID-19 infection, seronegative at baseline	1 RCT	Serious (Short ff-up)	Not assessed	Not serious	Not serious	Serious	16/12727 [a] 10/12713 [b]	21/12722		+++ Moderate
4. Any COVID-19 infection, seronegative at base line	1 RCT	Serious (Short ff-up)	Not assessed	Not serious	Not serious	Serious	42/12727 [a] 31/12713 [b]	116/12722	64.0 [a] (48.8-74.7) 73.5 [b] (60.6-82.2)	+++ Moderate
5. Symptomatic COVID-19 infection after first dose, before the second dose	1 RCT	Serious (Short ff-up)	Not assessed	Not serious	Not serious	Serious	43/12727 [a] 27/12713 [b]	43/12722	50.3% [a] (33.5-62.7) 65.5% [b] (52.0-75.1%)	+++ Moderate
6. Symptomatic COVID-19 infection, older adults (>=60yo), seronegative at baseline	1 RCT OBS	Serious Short ff-up	Not assessed	Serious (immuno)	Serious (Low case numbers	Very Serious	No reported events in the Ph3 trial; Immunologic studies showed significantly lower titers in the older population; 1 observational immunologic study showed 25-50% probability of seronegativity in the older population			++ Very Low
7. Symptomatic COVID-19 infection, with pre-existing medical condition	2 OBS	Serious Short ff-up	Not assessed	Serious (population data)	Not serious	Serious	Estimates of VE in studies from general population, assuming inclusion of persons with comorbidities, show similar rates with clinical trials on healthy persons			++ Low
8. Symptomatic COVID-91 infection, children (<18yo)	1 RCT	Serious Short ff-up	Not assessed	Serious (Immuno)	Not assessed	Very Serious	Significant immunogenic response observed, with significant increases in humoral and cellular responses			++ Low
9. Any COVID-19 infection, B.1.1.7/Alpha variant	1 OBS	Serious (observational)	Not assessed	Serious (Immuno)	Not assessed	Very Serious	1.3-fold reduction in titers			+ Very Low
10. Any COVID-19 infection, B.1.151/Beta variant	2 OBS	Serious (observational)	Serious	Serious (Immuno)	Not assessed	Very Serious	1.6 to 10-fold reduction in titers			+ Very Low
10. Any COVID-19 infection, B.167.2/Delta lineage	1 OBS	Serious (observational)	Not assessed	Serious (Immuno)	Not assessed	Very Serious	1.4-fold reduction in titers			+ Very Low

Appendix 10. Summary of Findings Table on the Safety of BBIBP-CorV

Safety Outcome	Studies	Quality Assessment					Summary of Findings			Certainty
		Risk of Bias	Inconsistency	Indirectness	Imprecision	Overall Assessment	Vaccine [1]	Control [1]	Relative Risk (95%CI)	
1: Solicited adverse reaction	4 RCT[1]	Not serious	Not serious	Not serious	Not serious	Not serious	5595/13464(41.6%) [a] 5270/13471(39.1%) [b]	5935/13453(44.1%)		++++ High
2: Local adverse reaction	4 RCT[1]	Not serious	Not serious	Not serious	Not serious	Not serious	3450/13464 (25.6%) [a] 2786/13471 (20.7%) [b]	3906/13453 (29.9%)		++++ High
3: Systemic adverse reaction	4 RCT[1]	Not serious	Not serious	Not serious	Not serious	Not serious	3695/13464 (27.4%) [a] 3810/13471 (28.3%) [b]	3743/13453 (27.8%)		++++ High
4. Unsolicited adverse event (28d)	4 RCT[1]	Not serious	Not serious	Not serious	Not serious	Not serious	2162/13464 (16.1%) [a] 2094/13464 (15.5%) [b]	2075/13453 (15.4%)		++++ High
5: Serious adverse event	4 RCT[1]	Serious (short ffup)	Not serious	Not serious	Not serious	Not serious	64/13646 (0.5%) [a] 59/13471 (0.4%) [b]	78/13453 (0.6%)	0.83 [a] 0.67 [b]	+++ Moderate

Appendix 11. Ongoing Trials Registered at the Clinicaltrials.gov Registry on BBIBP-CorV

NCT Number	Title	Status	Interventions	Outcome Measures	Sponsor/ Collaborators	Study Type	Completion Date
NCT04946565	The Impact of Sinopharm COVID-19 Vaccination on Male Fertility	Recruiting	Diagnostic Test: Semen analysis	• Sperm density count/ml • Total sperm count per ejaculate • Percentage of motile sperm • Percentage of abnormal sperm forms • Morning serum testosterone	Cairo University	Observational	30-Aug-22
NCT04988048	Collaborative Study to Evaluate Heterologous Vaccination Against Covid-19 in Argentina	Recruiting	Biological: COVID-19 vaccines	• Antibody against Spike protein measurement by ELISA test • Incidence of adverse events by measurement of the number of reactions after vaccination • Neutralising Antibody against Spike protein and cellular immune response	Ministry of Public Health, Argentina Russian Direct Investment Fund	Interventional	15-Feb-22
NCT04984408	Efficacy, Immunogenicity and Safety of BBIBP-CorV Vaccine Against Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) Infection.	Not yet recruiting	Biological: BBIBP-CorV - Inactivated SARS-CoV-2 vaccine (Vero cell)|Biological: influenza season quadrivalent Influenza Vaccine (Flu Quadrivalent)	• Protection conferred by BBIBP-CorV vaccine against any COVID-19 disease • Incidence of solicited adverse events, unsolicited adverse events and serious adverse events and adverse events of special interest (AESIs) • Protection conferred by BBIBP-CorV vaccine against symptomatic COVID-19 disease • Protection conferred by BBIBP-CorV vaccine against asymptomatic SARS-CoV-2 infection (any SARS-CoV-2 variant) • Protection conferred by BBIBP-CorV vaccine against severe COVID-19 disease and COVID-19 associated death. • Geometric Mean Titers (GMT) and Geometric Mean Fold Rise (GMFR) of anti-SARS-CoV-2 neutralizing antibody in subset of participants • Incidence of solicited adverse events, unsolicited adverse events and serious adverse events and adverse events of special interest (AESIs) in HIV-infected adults • Geometric Mean Titers (GMT) and Geometric Mean Fold Rise (GMFR) of anti-SARS-CoV-2 neutralizing antibody in subset of participants in HIV-infected adults • SARS-CoV-2 sequence variants among HIV-infected and HIV-uninfected, BBIBP-CorV vaccine and placebo recipients • Geometric Mean Titers (GMT) and Geometric Mean Fold Rise (GMFR) of anti-SARS-CoV-2 neutralizing antibody in the Arm 3 as compared to Arm 1 and 2 (subset participants). • Incidence of adverse event (AE) after each vaccination, serious adverse event (SAE), adverse events of special interests (AESIs) according to Brighton Collaboration list for COVID-19	International Vaccine Institute	Interventional	30-Sep-24

				vaccine studies among participants receiving the study vaccines. • Humoral and cellular immune responses of HIV-infected participants as compared to HIV-uninfected vaccine and control arms (subset participants of Arms 1 and 2) • Geometric Mean Titers (GMT) and Geometric Mean Fold Rise (GMFR) of anti-SARS-CoV-2 neutralizing antibody following booster dose of BBIBP-CorV vaccine • Incidence of solicited adverse events, unsolicited adverse events and serious adverse events and adverse events of special interest (AESIs) among HIV uninfected adults.			
NCT04885764	Profiling Antibody Status and Vaccine Effectiveness in Post Vaccination With SARS CoV2 in Ain Shams University	Recruiting	Biological: Astrazeneca/Oxford Vaccine Biological: Sinopharm vaccine	Short-term effectiveness	Ain Shams University	Interventional	1-Dec-21
NCT04993560	Safety and Efficacy of COVID-19 Prime-boost Vaccine in Bahrain	Completed	Biological: BBIBP-CorV Biological: BNT162b2	Change from Baseline Immunogenicity at 8 weeks Reactogenicity	Royal College of Surgeons in Ireland - Medical University of Bahrain The National Taskforce for Combatting COVID-19- Kingdom of Bahrain Bahrain Defence Force Royal Medical Services Ministry of Health, Bahrain Bahrain International Exhibition & Convention Centre	Observational	19-Oct-21
NCT04729374	COVID-19 Vaccine Induced Adaptive Immune Responses	Recruiting		Concentration of anti-SARS-CoV-2 neutralizing antibody in serum|Concentration of serum anti-SARS-CoV-2 binding antibody|Rate of anti-SARS-CoV-2 T cell response|The rate of SARS-CoV-2 infection|Rate of anti-SARS-CoV-2 B cell response	The Affiliated Nanjing Drum Tower Hospital of Nanjing University Medical School	Observational	31-Dec-23

NCT04834869	COVID-19 Vaccines Safety Tracking (CoVaST)	Recruiting	Biological: BNT162b2 Biological: mRNA-1273 Biological: AZD1222 Biological: CoronaVac Biological: Sinopharm Biological: Gam-COVID-Vac Biological: JNJ-78436735 Biological: CVnCoV Biological: NVX-CoV2373 Biological: BBV152	Local Side Effects Systemic Side Effects Unrecognized Side Effects	Masaryk University	Observational	31-Jan-22
NCT04998240	Mix and Match Heterologous Prime-Boost Study Using Approved COVID-19 Vaccines in Mozambique	Not yet recruiting	Biological: BBIBP-CorV - Inactivated SARS-CoV-2 vaccine (Vero cell) Biological: AZD1222 (replication-deficient Ad type 5 vector expressing full-length spike protein)	Geometric Mean Titers (GMTs) of anti-SARS-CoV-2 neutralizing antibodies Incidence of SAEs and AESI observed at any time point during the entire study period Incidence of solicited reactions within 7 days (local reactions) and 14 days (systemic reactions) Incidence of unsolicited adverse events that are within 28 days after each vaccination Incidence of changes in laboratory safety measures from baseline to day 28 after each vaccination Geometric Mean Titers (GMTs) and Geometric Mean Fold Rise (GMFR)	International Vaccine Institute The Coalition for Epidemic Preparedness Innovations (CEPI) Instituto Nacional de SaÃºde (INS), Mozambique University of Antananarivo International Centre for Diarrhoeal Disease Research, Bangladesh Harvard University Heidelberg University	Interventional	30-Oct-22

Q2. Is CoronaVac (Sinovac) effective and safe in the prevention of COVID-19-infections?

As of 28 October 2021

RECOMMENDATIONS

1. **We recommend the use of the CoronaVac (Sinovac), given as (given as 0.5 mL (600SU) to prevent symptomatic SARS-CoV-2 infection in**:
   - Healthy Adults *(Low certainty of evidence; Strong recommendation)*
   - Pregnant women in their first trimester after consultation with a physician *(Very Low certainty of evidence; Strong recommendation)*
   - Pregnant women in their 2nd and 3rd trimester and lactating women *(Very Low certainty of evidence; Strong recommendation)*
   - Adults who have medical comorbidities *(including chronic respiratory disease and infection, cardiovascular disease, chronic kidney disease, cerebrovascular disease, diabetes mellitus, obesity, neurologic disorder, chronic liver disease and others like sickle cell disease, thalassemia, or Down's syndrome, as per DOH guidelines dated April 5, 2021 on the A3 Priority Group) (Low certainty of evidence; Strong recommendation)*
   - Immunocompromised patients after medical clearance from a physician *(the immunocompromised include those diagnosed with HIV, hepatitis B and C, those with cancer undergoing chemotherapy, transplant patients receiving immunosuppression) (Low certainty of evidence; Strong recommendation)*

2. **We suggest the use of CoronaVac (Sinovac) to prevent SARS-CoV-2 infection in older adults (>60 years old)**. *(Low certainty of evidence; Weak recommendation)*

3. **We suggest against the use of CoronaVac (Sinovac) to prevent SARS-CoV-2 infection in children (3 to 17 years old)** *(Very Low certainty of evidence; Weak recommendation)*

4. **In areas where Delta is the predominant variant of concern, we recommend the use of CoronaVac (Sinovac)** *(Very Low certainty of evidence; Strong recommendation)*

5. **Under the current context of low vaccine coverage and inadequate vaccine supply, we recommend against booster vaccination using CoronaVac (Sinovac) in the healthy, adult population (18 years old and above)** *(Low certainty of evidence; Strong recommendation)*

6. **For immunocompromised patients who received primary CoronaVac (Sinovac) vaccination, we recommend for heterologous booster vaccination** *(Very Low certainty of evidence; Strong recommendation)*

Consensus Issues

In the light of new evidence since the last version of the guidelines, the panel revised the wordings and updated the strengths of the recommendations accordingly.

The panel members were divided and could not reach consensus regarding homologous booster vaccination for CoronaVac. Despite three rounds of voting and additional evidence search followed by a Delphi and a fourth round of voting, no consensus was reached. The arguments for and against homologous boosting of these 4 vaccines in the immunocompromised are as follows:

FOR:

1. The immunocompromised are vulnerable and at risk of severe COVID-19 infection and should be given the necessary protection from effective vaccination.
2. Primary vaccination has been found to result in poor immunogenic response in this population. Without a third/additional dose, these patients remain relatively unprotected and would likely have breakthrough infections.
3. Majority of the local population, and this likely includes the immunocompromised, received either ChAdOx1 or CoronaVac as their primary vaccination. Hence, despite the lack of a strong evidence of efficacy/effectiveness, giving them a booster using the same vaccine is better than not giving one.

AGAINST:

1. Homologous boosting using these vaccines for this population may turn out to be a waste of precious resources, given the lack of evidence that demonstrates clinical or even immunologic effectiveness and safety.
2. Ongoing trials and continued evidence generation may soon provide the necessary answer to the question and it may be prudent to wait for their results.
3. Heterologous boosting may be a better option, considering the current evidence of a satisfactory benefit/harm ratio.

The panel gave a strong recommendation for heterologous booster vaccination despite the low certainty of the evidence because of its significantly better immunogenic response compared to homologous boosting combined with the acceptable safety profile. More importantly, with the inconsistent supply of vaccines, and the need for the provide an effective vaccination regimen to the immunocompromised, the heterologous booster vaccination may be the only available option at this time.

WHAT'S NEW IN THIS VERSION AND KEY FINDINGS

The updated search on September 7, 2021 provided additional real-world evidence on the clinical effectiveness of CoronaVac in the general, as well as the immunocompromised population, in whom immune response to the vaccine is diminished. One trial showed that CoronaVac was immunogenic and safe among children aged 3 to 17 years old. Studies among the immunocompromised population showed reduced immunologic responses after CoronaVac vaccination. Additional evidence showed sufficient protection against COVID-19 infection by the Delta variant despite decreased immunologic response elicited by CoronaVac against the variant of concern. However, available evidence suggests escape from immunity against the Gamma variant after CoronaVac vaccination. It is also uncertain whether a booster results in additional protection against infection in terms of clinical outcomes. Studies suggest declining immunologic marker levels over time with concomitant decreased vaccine effectiveness in the older population. The effect of booster vaccination in providing additional protection is limited.

REVIEW METHODS

This review searched the following resources for its evidence base (date of the last search):

1. PubMed (September 7, 2021)
2. COVID NMA (September 1, 2021)
3. Iloveevidence.com (September 7, 2021)
4. Metaevidence.org (September 1,2021)
5. WHO Situational reports (September 3, 2021)
6. IVAC-JHI Vaccine effectiveness summary reports (September 2, 2021)

RESULTS

Clinical Efficacy

Three (3) randomized controlled trials on the clinical efficacy of CoronaVac against COVID-19 infection were identified. These were Phase 3 trials conducted in Brazil, Turkey and Indonesia.[1-3] The data from Indonesia was taken from the regulatory report. The reported vaccine efficacy values for symptomatic COVID-19 infection ranged from 50.70% (95% CI 35.90-62.00) from the Brazilian trial involving healthcare workers, to 65.3% from Indonesia and to 83.5% (95% CI 65.4-92.1) in the general population from the trial in Turkey. The VE for >60 years old was 51.1% (95% CI -166.9 to 91.0).

Three (3) additional randomized trials on the efficacy of CoronaVac presented only immunogenicity outcomes. Two (2) studies were on adults from China and from Chile [4,5] and one (1) on children from China.[6] Generally, CoronaVac immunization resulted in a significant increase in the immunogenicity markers measured at 28 days after the second dose.

Appendix 2 presents the detailed characteristics of the clinical trials on CoronaVac.

Appendix 3 presents the vaccine efficacy rates (3a) and immunogenicity outcomes (3b) from the trials on CoronaVac.

Real World Evidence: Effectiveness

Epidemiologic Studies

The search yielded two (2) epidemiologic studies from Brazil demonstrating the effectiveness of vaccination, where CoronaVac was used in a significant proportion of the population, together with other vaccines.

The first study investigated the seven-day moving average of COVID-19 cases in Brazil from March 2020 to May 2021. It compared the proportion of cases, severe cases, and deaths in each age group before the vaccine roll out for the particular age group versus two weeks after the roll out onwards. CoronaVac comprised 40.8% of all administered doses during the study period (ChAdOx1 = 46.4%, BNT162b2 = 9.9%, Ad26.CoV2.S = 2.9%). The study found moderate reduction in the number of COVID-19 cases (-0.21, 95%CI -0.01 to -0.39), and a pronounced reduction in severe cases (-0.55, 95% CI -0.34 to -0.76) and deaths associated with vaccination.[7]

The second study also from Brazil was an analysis of mortality trends among the 70-year-old and older population from January 2021, at the beginning of the national vaccination roll out (Coronavac = 65.4% of all doses given, ChAdOx1 = 29.8%) at

week 1 to 4 and at week 15 to 19. The study showed that the proportionate COVID-19 mortality among the aged 80 years and older fell rapidly from week 6 onwards (from 26.1% to 11.5%), while those aged 70 to 79 years old started to drop at week 15 (from 24.1% to 18.2%), whereas proportionate mortality due to non-COVID causes remained relatively stable throughout the study period (~30% for the 80 years and older, ~20% for the 70 to 79 years old). The decline in the mortality rate coincided with the increasing vaccination coverage in the said population groups.[8]

Observational Clinical Studies

Six (6) studies were identified providing real world evidence on the effectiveness of CoronaVac. These studies implemented a 28-day dosing interval of CoronaVac, in contrast to the 14-day interval used in most of the clinical trials.

Two (2) were population-based studies in Latin America validating the vaccine efficacy (against symptomatic COVID-19) rates ranging from 50-84% reported in clinical trials.[9,10] The prospective, national cohort study in Chile included 10,187,720 participants, aged 16 years or older who received at least one dose of the CoronaVac vaccine between February 2 and May 1, 2021, or did not receive any COVID-19 vaccination. Among the fully vaccinated (>14 days from the administration of the second dose), the adjusted vaccine effectiveness was 65.9% (95% CI 65.2-66.6) for the prevention of COVID-19 and 87.5% (95% CI 86.7-88.2) for the prevention of hospitalization, 90.3% (95% CI, 89.1-91.3) for the prevention of ICU admission, and 86.3% (95% CI 84.5-87.9) for the prevention of COVID-19 related death.[10] The retrospective cohort done in Brazil enrolled 25,752,013 individuals who received at least one dose of CoronaVac from January to April 2021. The adjusted vaccine effectiveness rates among the fully vaccinated were as follows: 52.7% (95% CI 52.1-53.4) against any infection, 72.8% (95% CI 71.8-73.7) against hospitalization, 73.8% (95% CI 72.2-75.2) against ICU admission and 73.7% (95% CI 72.3-75) against COVID-19 death.[10]

A population registry-based study on the elderly (75 years and older) from Brazil compared the deaths by COVID-19 among the unvaccinated and those who died 21 days or later after the first dose of CoronaVac. It showed significantly lower death rates among those who received the first dose and among those who received two doses compared to those who were not vaccinated (0.45% and 0.08% vs. 9.21%). The study reported attributable protection ratios of 95.1% (95% CI 94.7-95.5) after the first dose of CoronaVac and 99.1% (95% CI 98.9-99.3) after two doses. Increasing protection was also observed with increasing age: 70 to 79 years old: 86.3 (95% CI 84.7-87.7), 80 to 89 years old: 97.6 (95% CI 97.2-97.9) and 90 and older: 99.3 (95% CI 99.1-99.5).[11]

Three (3) studies were on healthcare workers from Brazil.[12,13] The first study showed an adjusted vaccine effectiveness (aVE) rate of 50.7% (95% CI 33.3-62.5) beginning at two weeks after the second dose, increasing to a rate of 73.8% (95% CI 57-84.8) 5 weeks later.[12] The second study was a test negative case control conducted during the Gamma variant surge, which showed that two doses of CoronaVac was not associated with a reduction in the odds of symptomatic COVID-19 infection (aVE = 37.1%, 95% CI -53.3 to 74.2).[13]

Finally, a cross-sectional study done among 4,260 healthcare workers in Brazil who received at least one dose of CoronaVac showed that 193 (38.7%) cases tested positive on RT-PCR within the first 9 weeks from vaccination. This rate was found to be significantly higher compared to those who received ChAdOx1 (positive rate = 30.3%).[14]

Appendix 4a outlines the characteristics and risk of bias of studies providing clinical effectiveness of CoronaVac.

Immunogenicity Studies

The search identified 10 immunogenicity studies on CoronaVac involving different populations. In general, they showed satisfactory seroconversion after two doses of CoronaVac. The following observations regarding factors influencing immunogenicity were consistent across the different studies: (a) greater immunologic response (both seropositivity and titers) to CoronaVac is seen among those with previous history of COVID-19 infection compared to the infection naïve [15-18] and (b) immunologic response decreases with age.[15-21] The two studies that investigated the relationship between the presence of comorbidities and immune response showed conflicting results.[17,22]

Appendix 4b presents the characteristics and detailed results of immunogenicity studies on CoronaVac.

Safety

Safety outcomes in the clinical trials consistently showed significantly higher reactogenicity rates with CoronaVac compared to placebo. Local adverse reaction rates associated with CoronaVac across the trials ranged from 12% to 61%. Pain at the injection site was consistently cited as the most common local adverse event, with reported rates from 11% to 61%. Systemic reaction rates ranged from 10% to 58%. Headache, fatigue, and malaise were the most commonly reported systemic adverse reactions. Serious adverse event rates associated with CoronaVac across the trials were low (<5%) and not significantly different from placebo. Most serious adverse events (SAE) were assessed to be unrelated to the vaccination. Only one (1) trial reported vaccine-related SAEs, which included systemic allergic reaction, seizure, and encephalitis.[2] One (1) trial reported one death in the vaccine group, caused by medication overdose, which was assessed to be unrelated to the vaccine.[1]

Appendix 5 presents the characteristics and detailed results of the studies providing safety information on CoronaVac.

Safety Reports from Regulatory Agencies

The Pan American Health Organization's report on July 12, 2021, provided the adverse events from immunization (AEFI) and serious adverse event rates for CoronaVac used in the region as of June 30, 2021. After 57,486,521 doses administered, 36,340 events were reported, of which 3,353 were classified as serious. The total AEFI events per 100,000 doses was 63.2 (range = 5.1-603.5) and the serious events per 100,000 doses was 5.8 (range = 0.0-10.3).[23] In the report on July 29, 2021, it quoted the Chilean authority report covering the period December 24, 2020 to May 14, 2021, with 2,619,095 doses of CoronaVac administered. The AEFI rate per 100,000 doses administered was 36.8 with a total of 5,103 events recorded. There

were 121 reported cases of anaphylaxis, 36 cases of seizures, 28 cases of Bell's palsy, 16 thromboembolic events, and 4 cases of Guillain-Barre syndome. In the same report, the reported rate of AEFI for CoronaVac in Portugal was 915.25 per 100,000 doses administered.[24]

The Hong Kong Health Department has administered 2,253,000 doses of CoronaVac as of July 31, 2021 with a reported frequency of adverse events at 2,242. Seventeen deaths following CoronaVac vaccination were also reported but upon review, the death cases were not causally linked with vaccination.[25]

The Philippine FDA, as of September 5, 2021, reported that 20,427,037 doses of CoronaVac were administered with 24,559 reports of adverse reactions. The most reported events were increased blood pressure followed by headache and injection site pain.[26]

Specific Adverse Event: Cutaneous and Allergic Reactions

A multicenter, online questionnaire-based, cross-sectional study that enrolled 221 HCWs in Turkey enumerated the cutaneous and allergic reactions following a first dose of CoronaVac vaccine.[27] Urticaria was the most frequently reported cutaneous reaction. The study also reported one case of anaphylaxis, and three cases each of angioedema and type IV allergic cutaneous rash (including erythema multiforme). Reactivation of herpes zoster and herpes simplex were also observed in two patients each. Another published case series reported on six healthcare workers who developed cutaneous reactions following CoronaVac vaccination.[28] There were two cases of urticaria with angioedema and two cases without angioedema. The other two developed erythema multiforme and pityriasis rosea. Other case reports described one case of systemic drug-related intertriginous and flexural exanthema (SDRIFE)-like eruption [29], another case of erythema multiforme [30], and generalized pustular psoriasis following CoronaVac vaccination.[31]

Specific Adverse Event: Nephrotic Syndrome

There were two reports of nephrotic syndrome following vaccination with one dose of CoronaVac. [32,33] The first case was of a 65-year-old man from Turkey who developed pedal edema, ascites, and acute weight gain one week after receiving the vaccine.[32] Similarly, a 67-year-old woman from Turkey presented with hypertension and pedal edema 2 weeks post-vaccination.[33] A diagnosis of minimal change disease was made on both cases, based on kidney biopsy. The second case received a second dose of the vaccine and subsequently developed headache and recurrence of generalized edema. The second biopsy revealed interstitial nephritis. The authors hypothesized that the patient may have become sensitized to the components after the first dose of the vaccine.

Specific Adverse Event: Optic Neuritis and Subacute Thyroiditis

A patient who developed bilateral optic neuritis and acute thyroiditis following CoronaVac vaccination was also described in a case report.[34] The case presented with rapidly progressive low visual acuity and pain on movement of the left eye and headache. Fundus examination revealed bilateral disc swelling, more pronounced in the left eye. A diagnosis of concurrent subacute thyroiditis was made based on elevated levels of thyroid stimulating hormone with normal thyroxine (T4), increased

anti-thyroglobulin, and anti-thyroid peroxidase. The report was the first case of acute thyroiditis and optic neuritis after COVID-19 vaccination.

Specific Adverse Event: Bell's Palsy

Bell's palsy following CoronaVac vaccination has been reported in post-vaccination adverse event surveillance.[35] A case series and a nested case-control study done in Hong Kong reported that the age standardized incidence of clinically confirmed Bell's palsy was 66.9 cases per 100,000 person-years (95% CI 37.2-96.6). The age-standardized incidence difference compared with the background incidence in the same period in 2020 was 41.5 (95% CI, 11.7-71.4), equivalent to additional 4.8 cases per 100,000 people within 42 days of receiving CoronaVac. In the nested case control analysis, the adjusted OR was 2.384 (95% CI 1.415-4.022) for risk of Bell's palsy following CoronaVac vaccination.

Children

Clinical Efficacy and Effectiveness

The search failed to identify a study reporting on the clinical efficacy or effectiveness of CoronaVac on children.

Immunogenicity

One (1) randomized, double-blind, placebo-controlled Phase 2/3 study reported on the immunogenicity of CoronaVac in children from 3 to 17 years.[6] The intervention group was blocked into two: (1) high dose (3.0ug) and (2) low dose (1.5ug).

The Phase 1 intervention group had 100% seroconversion rates for both doses. None of the participants in the placebo group became seropositive. In Phase 2, seroconversion rates were as follows: 1.5ug: 96.8% (95% CI 93.1-98.8), 3.0ug: 100% (95% CI 98.0-100.0), placebo: 0% (95% CI 0.0-3.9) (p value: <0.0001). CoronaVac was found to be highly immunogenic with GMTs generally higher than those found in adults. The observed GMT of the 3.0ug group was significantly higher than that of the 1.5ug across all age subgroups.

Safety

Incidences of adverse reactions were generally similar across the treatment groups with no dose-related concerns on safety. Overall adverse event rates within 28 days of vaccination were similar between the treatment groups (29% for 3.0ug vs. 24% for placebo). Only pain at the injection site was noted to occur more frequently in the vaccine group (16% for 3.0ug dose vs. 2% for placebo). No case of hypersensitivity was observed in both vaccine groups (1 case was noted in the control group).

Pregnant Women

The search did not yield any study providing information on the safety and efficacy or effectiveness of CoronaVac in pregnant women. The Brazilian regulatory trial reported one pregnancy in the vaccine group, which resulted in an abortion. The placebo group had two abortions in the three pregnancies reported.[1]

Immunocompromised Population

Available evidence on the use of CoronaVac among the immunocompromised is limited to immunogenicity and safety. The search identified three (3) studies; two

involving patients with immune-mediated disease and one on cancer patients under systemic treatment. No study with vaccine effectiveness has been identified.

A Phase 4 prospective controlled trial evaluated the immunogenicity and safety of CoronaVac in a cohort that enrolled 910 adults with autoimmune rheumatic diseases (ARD) and 182 age- and sex-frequency matched healthy adults.[36] Primary outcome was the reduction of greater than 15% in anti-SARS-CoV-2 IgG seroconversion and neutralizing antibody (Nab) positivity six weeks after the second dose. Lower anti-SARS-CoV-2 IgG seroconversion (70.4% vs. 95.5%, p<0.001) and Nab positivity (56.3% vs. 79.3%, p <0.001) were noted at Day 69 among adults with autoimmune rheumatic diseases (ARD) compared to the controls. Short-term immunogenicity was still acceptable, albeit reduced. Adverse effects reported were mild.

A cross-sectional study was conducted in Turkey among hospital workers and elderly people, which identified a subgroup with immune-mediated disease (IMD), mostly rheumatic disease.[18] It showed that they were less likely to have detectable antibodies than controls (92.7% vs. 99.7%, p < 0.001). Multivariate logistic regression analysis showed that having IMD [OR 17.31, (95% CI 3.57–85.95), p< 0.001] and being 60 years or more [OR 4.32, (95% CI 1.20–15.50), p = 0.025] were found to be independently associated with having negative antibody result.

A multicenter, prospective, observational study evaluated the immunogenicity and safety of CoronaVac vaccine in 47 patients with cancer receiving active systemic therapy.[20] More than half of the entire patient group developed immunogenicity (antibody level > 1 IU/mL) 30/47 (63.8%) four weeks after the second dose of the vaccine. Seropositivity rate was 59.5% (25/42) in those receiving at least one cytotoxic drug and 100% (5/5) for those receiving monoclonal antibodies and immunotherapy. Age was predictive of immunogenicity (OR 0.830, p = 0.043).

Appendix 6 details the characteristics and risk of bias of studies discussed in this section.

Effectiveness Against Variants

Six (6) studies provided information on the effectiveness of CoronaVac against the variants of concern. Four (4) studies provided clinical outcomes while two (2) were immunologic studies. Two of the four clinical studies dealt with the Delta variant and two were on the Gamma variant. Both immunologic studies were on the Delta variant.

Two (2) observational studies were conducted during the Delta outbreak and genomic sequencing of the infected cases was assumed.[37,38] In these two studies, other vaccines were used aside from CoronaVac. No separate vaccine effectiveness was presented for each vaccine. Both studies showed adjusted vaccine effectiveness estimates similar to the vaccine efficacy estimates in the clinical trials, such as sufficient protection against COVID-19 infection, including severe disease.

The first study was a retrospective cohort study from China among persons identified as cases or close contacts of infected patients who tested positive during the Delta outbreak.[37] Two vaccines in use in the studied population were CoronaVac (51% among partially vaccinated and 58% among fully vaccinated) and ChAdox1. The

adjusted vaccine effectiveness for pneumonia in the fully vaccinated was 69.5% (95% CI 42.8–96.3). No case of severe infection was found in the vaccinated cohort.

The second study was a test negative case control study also from China among COVID-19 patients aged 150 to 59 years old and close contacts.[38] Genomic sequencing of a sample of the study population showed majority of the infections were caused by the Delta variant. In this study, the adjusted vaccine effectiveness against any infection was 59% (95% CI 15.0–81.6) for the fully vaccinated. The aVE for moderate infection was 70.2% (95% CI 29.6–89.3). Again, no case of severe infection was reported among the vaccinated cohort.

Two test negative case control studies from Brazil investigated the effect of CoronaVac during the period when the Gamma variant was the prevalent strain.[13,39] Both studies showed decreased adjusted vaccine effectiveness against any infection, hospitalization, and death due to COVID-19 disease, compared to the estimates in the clinical trials. Of particular note are the low adjusted vaccine effectiveness estimates among the elderly population aged 80 years and older in the study from Sao Paolo breaching the cutoffs for sufficient protection set by the WHO.[39] The aVE for hospitalization in this age group was at 38.9% (95% CI 21.4 -52.5) and the aVE for death with COVID was at 44% (95% CI 20.3-60.6).
The two immunogenic studies involved the investigation of CoronaVac effectiveness against the Delta variant.[40,41] The first study, from China, included sera from 20 persons who had received their second CoronaVac dose 7 to 14 days prior. In this study, 19 out of the 20 sera had substantial serum neutralizing activity against D614G spiked pseudotyped viruses. Compared with activity against D614G, 65% (13/20) of sera from the CoronaVac recipients were decreased below the threshold of serum neutralizing ability for the Delta variant. The average neutralization potency of CoronaVac recipients were also decreased 2.5-fold (GMT 36) as compared to the D614G (GMT 89).[40]

Another immunologic study conducted in Thailand investigated the effect of SARS-CoV-2 variants of concerns to vaccine and infection-induced antibodies.[41] In this study, sera from 60 vaccinated (2 doses of CoronaVac) healthcare workers were used. Neutralizing antibodies against the wild type, Alpha, Beta, and Delta variants were measured. The study found out that relatively low neutralizing antibody titers were elicited by CoronaVac compared to natural infection. Results also showed that quantifiable antibody titers against Delta were present in only 69.17% of vaccinated sera as compared to 99.17% against the wild type. Furthermore, only 48.33% of vaccinated participants had neutralizing antibody titers of at least 20 (which is the cutoff for neutralizing antibody positivity) against the Delta variant, as compared to 98.33% against the wild type. It was noted in the study that natural infection consistently produced a greater percentage of antibody positivity as compared to CoronaVac recipients across all the tested variants. The authors state that despite a robust S1-RBD-binding IgG and 100% seropositivity sera from CoronaVac and previously infected recipients, they had significantly reduced neutralizing capacities against all the three variants of concern tested.

Appendix 7 presents the characteristics and results of the studies on CoronaVac clinical effectiveness (7a) and immune response (7b) against the variants of concern.

Duration of Protection

To answer the question of duration of protection offered by CoronaVac, the review searched for studies that presented vaccine effectiveness or immunogenicity data over time. Five studies were identified; three provided immunogenic information while two reported clinical effectiveness data.

A study from Turkey among 272 health workers who received 2 doses of CoronaVac and were assessed for anti-RBD, anti-spike, and anti-nucleocapsid IgG antibody concentrations (by CLIA reaction) at one, three, and six months post vaccination. This study found that the antibody concentrations were statistically decreased at the third month but with median concentrations still above the reactive level. However, it found that for the group of healthcare workers with a prior history of infection, the decrease in antibody concentrations was not found to be statistically significant. In terms of seropositivity rates for the anti-RBD antibodies, the study found that the decline from first to the third month was not statistically significant (98.2% vs. 97.8%). The decline in the anti-spike / anti-nucleocapsid IgG antibodies seropositivity rates from the first to the third month was 93% to 87.5%, which was statistically significant. Similarly, the decline in the median antibody levels from the 1st to the 3rd month) was significant for both anti-S-RBD IgG (29.14 to 10.46 AU/ml) and anti-spike/anti-N IgG (198 to 6.16 AU/ml).[42]

Another study reported on 158 individuals who received 2 doses of an inactivated COVID-19 vaccine (3ug dose in an Al(OH)3) adjuvant) 14 or 28 days apart and were assessed for antibody titers and positivity until 180 days after the second dose. The antibody levels peaked at day 28 after the second dose and subsequently declined. Neutralizing, anti-S and anti-N antibody seropositivity rates were generally halved by the sixth month post vaccination from 92-100% to 35-52%.[43]

A similar study in Thailand evaluated the change in immune response over a 12-week period after CoronaVac given at a 21-to-28-day interval. It showed the median SARS-CoV-2 sVNT significantly declined from 77% (95% CI 58.5-87.9) inhibition to 38.7% (95% CI 22.1-55.7).[44]

The interim report of the regulatory trial from Brazil provided the vaccine efficacies from 14 to 98 days from the first dose of CoronaVac, showing marginal change over time. The VE within 28 days of the first dose (14 days after second dose) increased from 42%, peaked at 60% on the 56th day, and gradually, but minimally, declined to 52% at 98 days post-first dose.[1]

A retrospective review of linked population-based health registries in Brazil was done among infection naive individuals who received their first COVID-19 vaccine dose (CoronaVac or ChAdOx1) between January 18, 2021 and July 24 2021.[10] The study followed these individuals to assess infection, hospitalization, admission to ICU, and death with laboratory-confirmed diagnosis SARS-CoV-2 infection until three months post-vaccination. The study found that CoronaVac vaccination was associated with decreased and maintenance of a low hospitalization incidence up to 84 days in all vaccinated individuals up to 79 years of age. However, for those 80 years and older, incidence levels were lowest 28 days after the second dose, and gradually increased afterward, but to a level that was still lower that those observed at the reference level (within 13 days after the first dose).

Appendix 8 presents the characteristics and detailed results of studies on duration of protection after CoronaVac immunization.

Booster Doses

Homologous Booster

Four (4) studies provided information on the effectiveness of CoronaVac as a booster, although outcomes were limited to immunologic response. Both studies were randomized controlled trials performed in China among healthy adults, which showed increased neutralizing antibody titers and greater positivity rates after a third dose compared to levels after the second dose.[4,45] This immunogenic response was demonstrated whether the third dose was given early (1 month after the second dose) or late (6 months after). In the older group (>/= 60 years old), the seropositivity rate was not significantly increased after the third dose compared to the second dose (100% vs. 97.7%).[4] Safety data from these trials showed generally low adverse event rates associated with the booster dose. The CoronaVac booster dose showed similar local and systemic adverse reaction rates compared with that of the second dose. Serious adverse event rates were low and similar to that of the placebo. No vaccine-related serious adverse events were reported.

A case series of 76 individuals who received a third dose of CoronaVac at an unspecified time after the second dose showed seroconversion of 100% neutralizing antibody with GMTs of 57.9 and 36.8 for S and N antibodies. Increased T cell response of the IFN-γ secretion against S and N antigens was also observed. Furthermore, a significant difference in the IFN-γ levels one month after the second and third doses was reported.[46]

Finally, a subgroup of the Phase 2/3 registration trial for CoronaVac received a booster dose six months after the second. It demonstrated a 60% higher neutralization activity after the third dose inoculation when compared with the second dose. The reported GMT values were 1,176 after the third dose compared with 660 after the second dose. It also showed lesser reductions in activity against the variants of concern (Beta, Gamma, and Delta) with the third compared with the second dose.[47]

Heterologous Booster

A cross-sectional study among healthy adults 18 to 59 years old primed with two doses of CoronaVac compared the effect of a homologous CoronaVac booster and a heterologous booster using a recombinant adenovirus type-5-vectored vaccine (Convidencia).[48] The booster doses were given 3 to 6 months after the second dose. Results showed increased immunogenicity after either booster dose, with significantly higher neutralizing antibody titers with heterologous booster at 14 days (33.6 vs. 197.4) and 28 days (35.3 vs. 150.3) compared with homologous vaccination. Seropositivity rates were 100% for both regimens at 14 days post-boost, and 99% for CoronaVac and 100% for Convidencia at 28 days. Heterologous prime-boost immunization had significantly more local (29.2% vs. 2.9%) and systemic (14.6% vs. 2.9%) reactions. No study was identified using CoronaVac as a heterologous booster to another vaccine regimen.

The characteristics and the results of these booster studies are detailed in tables that may be found in Appendix 9-11.

ONGOING TRIALS

As of September 7, 2021, 35 trials are registered in *clinicaltrials.gov* involving CoronaVac as an intervention. Four trials included children and adolescents. Nine are observational studies, while 13 are Phase 4 trials. Eight trials are recruiting.

Appendix 12 shows the details of these registered trials.

AUTHORIZATIONS

The WHO issued its recommendations on the use of CoronaVac on May 24, 2021 after the SAGE meeting on April 29, 2021.[49] The Philippine FDA issued an emergency use authorization for CoronaVac on February 22, 2021.[50]

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Appendix 1. Evidence to Decision

Summary of Initial Judgements Prior to Panel Discussion (N = 10)

FACTORS	JUDGEMENT						RESEARCH EVIDENCE/ADDITIONAL CONSIDERATIONS
Problem	No	Yes (10)					
Benefits	Large (6)	Moderate (3)	Small	Uncertain (1)			• Epidemiological and observational studies showed increased rates of CoronoVac vaccination coincided with a decline in COVID-19 cases, reduction in severe cases, and in mortality rates. • Immunogenicity studies showed satisfactory seroconversion after 2 doses of Coronavac.
Harm	Large	Small (10)	Uncertain				• Randomized controlled trials reported adverse reactions, ranging from local (e.g., pain at injection site) (12-61%) to systemic (headache, fatigue) (10-58%), with <5% showing serious adverse events and no reported deaths.
Certainty of evidence	High	Moderate (4)	Low (6)	Very low			• Very low to moderate
Balance of effects	Favors vaccine (10)	Does not favor vaccine	Uncertain				
Values	Important uncertainty or variability	Possibly important uncertainty or variability (6)	Possibly no important uncertainty or variability (2)	No important uncertainty or variability (2)			
Resources required	Uncertain (2)	Large cost (3)	Moderate cost (3)	Negligible cost or savings (1)	Moderate savings	Large savings (1)	• It is affordable but the total budget allocation is not proportionate to the target vaccinees.
Certainty of evidence of resources required	No included studies (8)	Very low	Low (1)	Moderate (1)	High		
Cost effectiveness	No included studies (9)	Favors the comparison	Does not favor either the intervention or the comparison	Favors the intervention (1)			
Equity	Uncertain (2)	Reduced	Probably no impact (2)	Increased (6)			• PHL FDA EUA indication is for clinically healthy people (aged 18 years old and above) susceptible to the virus. • This product is not recommended for use among healthcare workers with exposure to COVID-19 patients. • Addresses wide disparity in vaccine coverage: 85.1% fully-vaccinated senior citizens in NCR; only 28.3% in BARMM..
Acceptability	Uncertain (2)	No	Yes (8)				• CoronoVac was given EUA by the Philippine FDA on February 22, 2021
Feasibility	Uncertain (2)	No	Yes (8)				

Appendix 2. Characteristics of Randomized Clinical Trials on CoronaVac efficacy and safety

Study ID (Country)	Population	Intervention (n)	Comparator (n)	Outcomes	Methods (Risk of Bias)
Wu (China)	60 years and older Exclusion High risk history History of SARS or SARS-CoV-2 T > 37°C	CoronaVac 1.5ug / 3.0ug / 6.0 ug Administered IM on 0 and 28 days	Placebo (aluminum hydroxide only) Ph I = 36	• Vaccine-related adverse events within 28 days after each dose • Seroconversion rate of neutralizing antibodies at 28 days after D2 • Geometric mean titer of neutralizing antibodies to SARS-COV-2 • Increase of seroconversion rate • Increase in GMT • Severe adverse events	• Ph 1 = 72 • Randomization codes generated by the randomization statistician using SAS software • Randomization code assigned to each participant in sequence in the order of enrollment • Participants, investigators, laboratory staff masked • (Low risk)
Tanriover/ Akova (Turkey)	18-59 years old No history of COVID-19 Negative PCR and antibody test for SARS-CoV-2 K1; healthcare workers K2: general population Exclusion: Immunosuppressive therapy; bleeding disorders; asplenia ; receipt of any blood products or immunoglobulins within 3 months Planned follow up = 1 year	Coronavac 3ug (600SU) given at 0 and 14 days (N = 6,646) - safety	Placebo (N = 3,568) - safety	• Incidence of symptomatic COVID-19 confirmed by RT-PCR at least 14 days after D2 • Incidence of hospitalization or mortality • COVID-19 confirmed by RT PCR • Adverse events: solicited, unsolicited, systemic, local, • Neutralizing antibody and IgG at 14 and 28 days after each dose: • Seroconversion rate • Seropositivity rate • Geometric mean titer • Adverse reactions from day of vaccination to 28 days after D2 • Adverse reaction within 7 days • Serious adverse event to 1 year after second dose	• Randomized by interactive web response system • Participants and practitioners masked to group allocation • Incomplete follow-up (interim report with median follow-up of 90 days of ff-up after first dose) • Sampling for antibody assays at least 14 days after D2 • (Low risk)

Bueno (Chile)	Health care workers 18 years and older
	(N = 434)
	Excluded: history of confirmed COVID-19, pregnancy, allergy to vaccine components, immunocompromised
		CoronaVac 3.0ug, 2 doses, 14 days apart
		
		(N = 270)
		(N = 39 for immunogenicity study)
			Placebo
			
			(N = 164)
				• Antibody and cell-mediated immunity results
				  - Seroconversion (anti RBD IgG, anti-N Nab, IFN-G
				• Safety
				  - Solicited AE
				  - Unsolicited AE within 7 days
				• Any AE within 28 days of each dose
				• Serious AE
				• Events of special interest
				• Falls
					• Randomization using sealed enveloped system integrated into the eCRF
					• Participants, investigators and lab staff masked to allocation
					• Interim analysis
					• (Low risk, incomplete ff-up)
					• Immunogenicity, specimen taken at 14, 28 and 42 days after each dose, by ELISA

Palacios (Brazil) Preprint	Healthy health professionals caring for COVID patients (N = 12,396); Only 5% were 60 years and older; 55.9% with comorbidities (N = 9,823) Excluded pregnant, previous COVID-19 vaccines, acute symptoms of COVID	CoronaVac 3.0ug, 14 days apart (N = 6,195) - safety (N = 4,953) - efficacy	Placebo (N = 6,201) - safety (N = 4,870)	• Symptomatic RT-PCR confirmed infection 14 days after 2nd dose: 50.7 (36-62) • Moderate infection: 83.7 (58-93.7) • Severe infection: 100 (56.4-100) • Adverse events up to 28 days after immunization: Local, systemic, serious AEs; Deaths • Neutralization assays GMT and seroconversion for variants	• Randomization by IWRS • Coding received only by pharmacist not involved in trial • Participants and study staff and lab techs unaware of product allocation • Interim report • Underpowered for safety • (Low risk)

Han (China)	Healthy children from age 3 to 17 years old Total enrolled: Ph I = 72, Ph 2 = 480 Exclusion: • Travel or residence history in communities with case reports, or contact history with someone infected with SARS-CoV-2) • History of severe acute respiratory syndrome or SARS-CoV-2 infection (as reported by participants) • Axillary temperature of more than 37·0° • History of allergy to any vaccine component Balanced age, gender distribution, ethnicity between groups	CoronaVac inactivated vaccine 1.5 or 3.0ug in 0.5ml aluminum hydroxide adjuvant, 2 doses, 28 days apart Ph1: 36, Ph2 1.5ug: 192, 3.0ug: 192	Placebo (aluminum hydroxide only) Ph 1: 36 Ph2: 96	• Safety ○ Any vaccine related AE within 28 days after administration ▪ Solicited AEs – first 7 days ▪ Spontaneous reporting of AEs – until 28 days ○ Serious adverse events (until 12 months) ○ Abnormal changes in lab measurement at day 3 • Immunogenic ○ Seroconversion rate of neutralizing antibodies at day 28 after second dose • Seropositive rates (4-fold rise from baseline) • GMT of neutralizing antibodies to live SARS-CoV-2 (positive cut off was 1/8) • Geometric mean increase • Planned follow up until 12 months after dose 2	• Ph1 – age de-escalation and dose escalation study (n= 72) • Ph2 – main safety/efficacy trial • Randomization codes generated by the randomization statistician using SAS software • Randomization code assigned to each participant in sequence in the order of enrollment • Participants, investigators, laboratory staff masked • Interim analysis, planned follow up to 12 months after dose 2 • All planned outcomes reported • (Low Risk)

Appendix 3: Vaccine efficacy results of Clinical Trials on CoronaVac

A. Vaccine efficacy (Clinical outcomes)

VACCINE EFFICACY / EFFECTIVENESS PARAMETERS VE (95% CI)	STUDIES		
	TANRIOVER (Turkey)	PALACIOS* (Brazil)	Indonesia Regulatory
	18-59 years old 3.0ug, 0, 14d	18-59 years old; >= 60 years old	18-59 years old;
SYMPTOMATIC COVID-19 Infection (as defined by trialist), complete dosing, seronegative ONLY, after 14 days	83.5% (65.4-92.1)	50.5%	65.3%
SYMPTOMATIC COVID-19 Infection (as defined by trialist), complete dosing, seronegative AND seropositive, after 14 days		50.7% (35.7-62.2); >+ 60: 51.1% (-166.9-91.0)	
SYMPTOMATIC COVID-19 Infection (as defined by trialist) occurring after 1st dose, seronegative ONLY			
- >=10 days after dose 1 before dose 2	46.4% (0.4-71.2)		
SYMPTOMATIC COVID-19 Infection (as defined by trialist), after 1st dose, seronegative AND seropositive, after 14 days		57.9% (46.3-66.9)	
Severe COVID-19 Infection, complete dosing, seronegative AND seropositive, after 14 days		100% (56.4-100.0)	
Asymptomatic COVID-19 infection, complete dosing, seropositive AND seronegative, after 14 days			
ANY COVID-19 Infection (as defined by trialist), complete dosing, seronegative AND seropositive, after 14 days			
Hospitalization due to COVID, complete dosing, seronegative only, after 14 days	100% (20.4-100.)		
Hospitalization due to COVID, complete dosing, seropositive AND seronegative after 14 days			
ICU admission due to COVID, complete dosing, seronegative AND seropositive, after 14 days			
Death due to COVID, complete dosing, seronegative ONLY, after 14 days			
SPECIAL POPULATIONS: COVID 19 infection, complete dosing, seronegative only			
>=65 years old, after 14 days of 2nd dose			
< 18 years old			
At high risk for COVID, at 14 days after 2nd dose		48.9% (26.6-64.5)	
Seropositive at baseline		49.5%	
Asian		66.0% (-226.8-96.5)	
Healthcare workers		50.7% (35.7-62.2)	
Children			

B. Vaccine efficacy (Immunologic outcomes)

Immunologic Outcomes	STUDIES		
	Wu (China)	Bueno (Chile)	Han (Chan)
	60 years and older	18 years and older	3-17 years old
Neutralizing antibody seroconversion	Phase 1 Day 28 after 1st dose - 3ug: 54.2% (95% CI 32.8-74.5) - 6ug: 62.5% (95% CI 40.6-81.2) Not significant (p = 0.058) Day 28 after 2nd dose - 3ug: 100% (95% CI 85.8-100.0) - 6ug: 95,7% (95% CI 78.1-99.9) Not significant (p = 0.489) Phase 2 Day 28 after 2nd dose - 1.5ug: 90.7% (95% CI 83.1-95.7) - 3ug: 98% (95% CI 92.8-99.8) - 6ug: 99% (95% CI 94.5-100.0) No significant difference in between groups	Anti-S1-RBD IgG 18 to 59 years old After 14 days: 47.8% After 28 days: 95.6% After 42 days: 95.6% >/= 60 years Anti-S1-RBD IgG After 14 days: 18.1% After 28 days: 100.0% After 42 days: 87.5% Anti N protein 18 to 59 years old After 14 days: 8.7% After 28 days: 17.4% After 42 days: 13.0% >/= 60 years Anti-S1-RBD IgG After 14 days: 0% After 28 days: 20.0% After 42 days: 37.5%	Phase 1 Day 28 1.5ug: 100% (95% CI 87.2-100.0) 3.0ug: 100% (95% CI 86.8-100.0) Placebo: 0% (95% CI 0.0-20.6) Phase 2 1.5ug: 96.8% (95% CI 93.1-98.8) 3.0 ug: 100% (95% CI 98.0-100.0) Placebo: 0% (95% CI 0.0-3.9)
Geometric mean titer (GMT) of neutralizing antibody	Phase 1 Day 28 after 1st dose - 3ug 6.9 (95% CI 4.6-10.2) - 6ug 9.1 (95% CI 6.4-13.0) Not significant (p = 0.278) Day 28 after 2nd dose - 3ug 54.9 (95% CI 38.6-78.2) - 6ug 64.4 (95% CI 41.5-99.7) Not significant (p = 0.560) Phase 2 Day 28 after 2nd dose - 1.5ug: 23.4 (95% CI 19.4-28.3) - 3ug: 42.2 (95% CI 35.2-50.6) - 6ug: 49.9 (95% CI 42.2-58.9) 1.5ug vs 3ug p<0.0001 1.5ug vs 6ug p<0.0001	Anti-S1-RBD IgG 18 to 59 years old After 14 days: 23.1 After 28 days: 1755 After 42 days: 1878 >/= 60 years After 14 days: 45.1 After 28 days: 1860.2 After 42 days: 1878 Anti N protein 18-59 years old After 14 days: 5.3 After 28 days: 8.0 After 42 days: 9.2 >/= 60 years After 14 days: 5.5 After 28 days: 9.6 After 42 days: 32.6	Phase 1 Day 28 1.5ug: 55 (95% CI 38.9-77.9) 3.0 ug: 117.4 (95% CI 87.8-157) p = 0.0012 Phase 2 Day 28 1.5ug: 86.4 (95% CI 73.9-101.0) 3.0ug: 142.2 (95% CI 124.7-162.1) P<0.0001
Cell-mediated immunity		No significant difference was observed between 18 to 59 and >/= 60 years old groups	

Appendix 4. Real World Effectiveness Studies

A. Characteristics and Results of Studies on the Clinical Effectiveness of CoronaVac

Study ID	Design Risk of Bias	Population	Intervention/ Exposure	Control	Follow up	Outcomes Reported
Alencar (Brazil)	Retrospective cohort Linked databases Poorly defined unexposed group Limited control of confounders (HIGH RISK)	Elderly population (age >/=75 y/o) (N = 132,777)	At least 1 dose of CoronaVac	Unvaccinated population Number of unvaccinated people was calculated as the difference between estimated population and the number of vaccinated individuals	Unclear	Protection ratio against death After 1st dose Deaths: 778/174,006 (0.45%) Protection ratio: 20.59 (19.07-22.22) Attributable protection ratio: 95.1 (94.7-95.5) After 2 doses Deaths: 108/132,777 (0.08%) Protection ratio: 113.17 (93.5-136.99) Attributable protection ratio: 99.1 (98.9-99.3) Unvaccinated Deaths: 3769/40,941 (9.21%) Increasing protection with increasing age 70-79 y/o: 86.3 (84.7-87.7) 80-89: 97.6 (97.2-97.9) 90 and older: 99.3 (99.1 – 99.5)
Cerquiera-Silva (Brazil)	Retrospective Cohort Adjusted for age, sex, region of residence, socioeconomic status, month of 1st dose	General population (N = 75,919, 840) CoronaVac = 25,752,013 Excluded: vaccinated besides ChAdOx1 or CoronaVac; inconsistent records; confirmed COVID-19 before vaccine administration; missing data for covariates	CoronaVac, 2 doses, median interval = 27 days (IQR 21-28)	Unvaccinated population		VE for infection, hospitalization, ICU admission, death Fully Vaccinated: VE vs Infection: 52.7% (95%CI 52.1-53.4) VS vs Hospitalization: 72.8% (95%CI 71.8-73.7) VE vs ICU admission: 73.8% (95%CI 72.2-75.2) VE vs Death: 73.7%, (95%CI 72.3 to 75.) Partially vaccinated - 18.6% (95% CI, 17.6-19.6) against infection - 28.1% (95% CI, 26.3-29.9) against hospitalization - 28.5% (95% CI, 25.4-31.4) against ICU admission - 29.4% (95% CI 26.7-31.9) against COVID-19 related death Effectiveness declined with increasing age 90y and older: VE against death: 33.6% Effectiveness declined over time (by 84 days) in those 90y/o and older

Study ID	Design Risk of Bias	Population	Intervention/ Exposure	Control	Follow up	Outcomes Reported
De Faria (Brazil)	Retrospective cohort Compared actual and predicted infection rates (based on population)	Healthcare workers N1 = 22,402 N2 = 21,652	Coronavac 2 doses, 2-4 weeks apart	Predicted infection rate based on general population infection rates	2-5 weeks post vaccination	VE for lab-confirmed symptomatic COVID infection 2wks post D2: 50.7% (95%CI 33.3-62.5) 3wks post D2: 51.8% (95%CI 30.0-66.0) 4wks post D2: 68.4% (95%CI 51.03-80.8) 5wks post D2: 73.8% (95%CI 57.0-84.8)
Jara (Chile)	Prospective cohort Controlled for age, sex, region of residence, income, nationality, underlying conditions Follow-up relatively short, may not account for late outcomes but similar to the duration of follow up in efficacy trials	Aged 16 years or older who received at least one dose of the CoronaVac vaccine during the mass national vaccine campaign or no receipt of COVID-19 vaccination; affiliated to the national public health insurance Excluded probable / confirmed COVID on or before study period; received BNT162b2 N = 10,187,720 Unvaccinated: 5,471,728 (53.7%)	At least 1 dose of CoronaVac Partially vaccinated: 70million person days 524,418 (5.3%) Fully vaccinated: 92 million days 4,173,574 (41.0%)	Unvaccinated		COVID-19 cases: 218,784 Hospitalizations: 22, 866 ICU admissions: 7873 Deaths: 4042 Fully vaccinated: VEs (Note: VEs similar in 60yo and older) Infection: 65.9 (65.2-66.6) Hospitalization: 87.5 (86.7-88.2) ICU admission: 90.3 (89.1-91.4) Death: 86.3 (84.5-87.8) Partially vaccinated Infection: 15.5 (14.2-16.8) Hospitalization: 37.4 (34.9-39.9) ICU admission: 44.7 (40.8-48.3) Death: 45.7 (40.9-50.2)
Hitchings (Brazil)	Test negative case control	Healthcare workers	CoronaVac	Negative RT PCR	Not mentioned	2 doses, 14 days later aVE for any infection: 37.1%, 95% CI, -53.3 to 74.2)
Toniasso (Brazil)	Cross-sectional study	Healthcare workers suspected of having COVID-19 infection	CoronaVac at least 1 dose N = 399	NA	Not mentioned	38.7% positive diagnosis (breakthrough)

B. Characteristics and Results of Observational Studies on the Immunologic Response of CoronaVaC

Study ID (Country)	Population	N	Timing of Extraction (After D2)	Outcomes Reported (Test used) Result
Bayram (Turkey) March 4 and 10, 2021 Preprint	Healthcare workers, 18 years and older, received 2 doses at 28-day interval	1012	21 days	Anti-spike IgG (CLIA) Seropositivity (cut of = 50AU/ml) 1008/1012 (99.6%) overall By hx of COVID-19: 703/706 (99.66%) - no hx of COVID-19 259/259 (100%) - with hx of COVID-19 the rest had unknown status By age group: 18-34: 100% 35-59: 99.2% ≥60: 95.7% Titers (median, range) 1022.40 (10.10-66923.70)
Bichara (Brazil) March to April 2021	Patients who voluntarily sought care (no reason indicated)	358 (205 - Anti-S 153 - Anti-RBD)	30 days	Anti-S1 and S2 (CMIA/CLIA) Seropositivity 159/205 (77.6%) overall By age group: 21-40 years old: 91% 41-60 years old: 83% 61-80 years old: 73% >80 years old: 62% Anti-RBD (surrogate virus neutralization test) Seropositivity 111/153 (72.6%) overall By age group: 21-40 years old: 93% 41-60 years old: 76% 61-80 years old: 72% >80 years old: 47%
Bochnia Bueno (Brazil) Preprint	Healthcare workers	133	20 days (D40 since 2nd dose was given at D20)	Anti-N (Architect-I System) 69/133 (51.87%) Anti-S1 (CMIA/CLIA and EIA) 129/133 (97%) [1 of 4 who did not seroconvert had seroconverted by D60]

Appendix 5. Characteristics of Studies Reporting Safety Outcomes of CoronaVac and their Results

Study ID (Country)	Population (design)	CoronaVac dosing regimen	Results
Wu (China)	60 years and older (RCT-Ph1/2)	1,5, 3.0, 6.0ug 2 doses 28-day interval	Adverse reaction rates (28days): Vaccine (3.0ug) vs Placebo Any: 20% s 21% Local reaction: 12% s 4% Most common: pain (11% vs 4%) Systemic reaction: 10% vs 16% Most common: fever (4% vs 1%), fatigue (3% vs 1%) Serious adverse events: 1% vs 0% (Pancreatitis) All unrelated to vaccine
Bueno (Chile)	Adults 18 years and older (RCT- Ph3)	3.0 ug 2 doses 14-day interval	Adverse reaction rates: Vaccine vs Placebo Pain at injection site: 55.6% vs 40.0% Most were mild and resolved in 2 days Headache most frequent systemic AE: 48.8% vs 48.5% Followed by fatigue (27.5% vs 26.8%) and myalgia (23.8% vs 22.6%) No serious adverse event or event of special interest occurred in the trial 3 COVID-19 cases (breakthrough)
Tanriover (Turkey)	18 to 59 years old (RCT-Ph3)	3.0ug 2 doses 14-day interval	Adverse event rates: Vaccine vs Placebo Total: 18.9% vs 16.9% (p=0.011) Solicited: 17.3% vs 15.1% (p=0.0039) Systemic AE: 17.7% vs 16.0% (p=0.0263) Most common: fatigue (8.2% vs 7.0%, p = 0.02), headache (5.9% vs 5.9%) Local AE: 2.7% vs 1.5% (p=<0.001) Most common: Pain (2.4% vs 1.1%) Serious AE: 6 vs 5 events
Palacios (Brazil)	Healthcare workers (RCT-Ph3)	3.0 ug 2 doses 14-day interval	Adverse event rates: Vaccine vs Placebo Adverse reaction = 77.1% vs 66.4% Local AER = 61.5% vs 34.6% Mainly pain at injection site = 60.3% vs 32.5% Systemic reaction = 48.4% vs 47.6% Most common: Headache and fatigue Unsolicited AE = 36.8 % vs 35.8% SAE = 33 vs 31 patients 2 deaths not related to vaccination - CP arrest (placebo) - Medication overdose (CoronaVac)
Han (China)	Children aged 3 to 17years old (RCT-Ph1/2)	1.5ug or 3.0ug 2 doses 28 days apart	Adverse event rates: 1.5ug vs 3.0ug vs placebo Any adverse reaction 0-7d: 23% vs **27%** vs 19% (p=0.28) Pain at injection site: 16% vs **16%** vs 2%, (p<0.001) Fever: 4% vs 5% vs 4% Hypersensitivity 0 vs 0 vs 1% (p=0.93) Any unsolicited AE (28d): 26% vs **29%** vs 24% (p=0.55)
Indonesia	18-59 years old	3.0 ug	Adverse event rates: Vaccine vs placebo

RCT	N = 1620 Safety analysis – 540 (RCT- Ph3)	14-28 days interval	Overall: 71.6% vs 71.1% Solicited Local: 51.3% vs 44.4% Solicited Systemic: 58.5% vs 54.8% Unsolicited Local: 2.4% vs 0.7% Unsolicited Systemic: 43.7% vs 43.7% Local pain: 32.3% vs 21.5% / 30.5% vs 30.1%
Karachin (Turkey)	With solid organ tumors receiving active systemic therapy >18 years old with no previous COVID-19 (Case series)		Local reactions (1st & 2nd dose, respectively): pain at injection site (94.2%; 6.3%); swelling (2.1%; 0%); itchiness (2.1%; 0%); erythema (0%; 4.2%) Systemic reactions: fever (2.1%; 2.1%); myalgia (2.1%; 0%); fatigue (4.2%; 10.5%); headache (2.1%; 0%) No serious side effects or deaths
Riad (Jordan)	Healthcare workers who received at least one dose within 30 days prior to the survey (Cross-sectional study)		Local SE: injection site pain (41.5%), site swelling (2.6%), and redness (1.4%) Systemic: fatigue (23.6%) was the most common followed by headache, muscle pain, joint pain, and nausea. Fever and lymphadenopathy were not commonly reported

Appendix 6. Characteristics and Results of Studies on CoronaVac among Immunocompromised Patients

Study	Design	Population	Outcomes	Results
Medeiros-Ribeiro	Phase 4, prospective non-randomized controlled trial Controlled for sex and age	910 adults with autoimmune rheumatic diseases and 182 age- and sex- frequency matched health adults	Primary Reduction of >/= 15% in anti-SARS-CoV-2 IgG seroconversion (SC) and neutralizing antibody (Nab) positivity 6 weeks after the second dose Secondary outcomes IgG SC and Nab positivity at Day 28 IgG titers and neutralizing activity at Day 28 and Day 69 Vaccine safety	Lower anti-SARS COV2 IgG SC (70.4 vs 95.5% p<0.001) and Nab positivity (56.3 vs 79.3%, p <0.001) at Day 69 among adults with autoimmune rheumatic diseases (ARD) compared to the controls IgG titers (12.1 versus 29.7, *P* < 0.001) and median neutralization activity (58.7 versus 64.5%, *P* = 0.013) were also lower at Day 69 in patients with ARD. At Day 28, patients with ARD presented with lower IgG frequency (18.7 versus 34.6%, *P* < 0.001) and Nab positivity (20.6 versus 36.3%, *P* < 0.001) than that of the CG. There were no moderate/severe adverse event
Karacin (Turkey)	Multicenter, prospective, observational study (unmatched) Controlled for confounders	47 cancer patients receiving systemic therapy who received 2 doses CoronaVac, 28 days apart Titers taken 4 weeks after the last dose of the vaccine	Immunogenicity antibody level more than 1 IU/mL	Immunogenicity rate 63.8% (30/47) in the entire patient group 59.5% (25/42) among those receiving at least one cytotoxic drug 100% (5/5) among those receiving monoclonal antibody or immunotherapy alone Age was independent risk factor (OR 0.830, p -0.043)

Appendix 7: Characteristics and Results of Studies on Effectiveness of CoronaVac on Variants of Concern

A. Characteristics and Results of Studies on the Clinical Effectiveness of CoronaVac against Variants of Concern

Study ID	Design (Risk of Bias)	Population	Variants Tested	Outcomes Reported Results
Kang (China)	Retrospective Cohort Adjusted for age, sex, occupation, street, contact frequency *(Serious Risk / Low Certainty)*	Person identified as cases or close contacts of infected patients who tested positive (N = 10,813) during Delta outbreak Unvaccinated = 5,888 Immed D1 Partially vaccinated = Immed D2 = Fully vaccinated = 1,407 Vaccines in use included ChAdOx1 D1 = 2,526 (51.29% CoronaVac) D2 = 1,046 (58.29% CoronaVac)	Delta	<u>aVE for pneumonia</u> Unvaccinated: n = 85 Partially Vaccinated: n =12 aVE = 8.4% (95% CI -47.6 to 64.4) Fully Vaccinated: n = 5 aVE = 69.5% (95% CI 42.8-96.3) <u>aVE for severe illness</u> Unvaccinated: n = 19 No event in vaccinated (NOTE: aVEs are for the combined effects of ChAdOx1 and CoronaVac. No separate analysis for each of the vaccine)
Li (China)	Test negative case control Adjusted for age and gender (cases were older) Exposure risk considered balanced between groups *(Serious Risk/ Low Certainty)*	18 to 59 year olds among COVID-19 patients and close contacts SARS-CoV-2 positive cases (N = 74) Test-negative controls (N = 292) Fully vaccinated – at least 14 days after D2 Partially vaccinated – at least 14 days from D1 and <14 days after D2 Unvaccinated – included those at <14days after D1 Two vaccines used: CoronaVac (61.3%) and CNBG	Delta (population-based and genomic sequencing of partial sample of study population)	<u>aVE for any infection</u> Partially Vaccinated: 13.8% (95% CI -60.2 to 54.8 Fully Vaccinated: 59.0% (95% CI 16-81.6) <u>aVE for mild infection</u> Fully Vaccinated: -29.4% (95% CI -369.4 to 67.9) <u>aVE for moderate infection</u> Partially Vaccinated: 11.2% (95% CI -72.5 to 55.5) Fully Vaccinated: 70.2% (95% CI 29.6-89.3) <u>aVE for Severe infection</u> No case among vaccinated, 2 cases in unvaccinated Noted higher VEs in the younger population (NOT : aVEs are for the combine effects of ChAdOx1 and CoronaVac. No separate analysis for each of the vaccine)
Hitchings (Manaus, Brazil)	Test negative, matched case control Matched by sample collection date, age, neighborhood residence Logistic regression covariates: sex, occupation category, race, number of health interactions, COVID infection since start of pandemic	Health care workers >/= 18 years old residing in Manaus, received CoronaVac Cases = positive SARS-CoV-2 RT-PCR test and absence of a positive test in the preceding 90-day period N1 = 590 symptoma N2 = 218 asymptomatic Controls = test negative	Gamma (population-based)	aOR symptomatic infection at least 14 days after D2: 0.62 (0.26-1.46) (37.1%, -53.3 to 74.2) aVE asymptomatic infection 100%

Ranzani (Sao Paolo, Brazil)	Matched test negative case control Matching by date of testing, age, sex, race, residence, previous COVID-19 status 1 case to 5 controls	>/= 70 years old Cases – test positive within 10 days of symptoms, no positive result in the preceding 90 days Controls – test negative, no positive result within the preceding 90 days and subsequent 14 days Coronavac 2-to-4-week interval	Gamma (population based)	Confirmed symptomatic infection 14 days after D2 aVE = 46.8% (38.7 to 53.8%), declining with increasing age. For >80y/o: 32.7% (17 to 45.5%) Hospitalization aVE = 55.5% (46.5 to 62.9), declining with age >/= 80: 38.9% (21.4% to 52.5) death with COVID aVE = 61.2% (48.9 to 70.5%), declining with age >/=80: 44% (20.3 to 60.6)

B. Characteristics and Results of Immunogenicity Studies on the Immune Response to CoronaVac against Variants of Concern

Study ID	Population	Timing of Extraction	Reference Strain	Variant/s Tested	Outcome (Test Used) Result
Hu (China)	Sera from 20 vaccinated patients	7 to 14 days post D2	D614G	Delta	Neutralizing antibody response (Pseudovirus-based neutralization assay): Neutralizing activity (positivity) 65% (13/20) below the threshold Decline in neutralization potency compared to control: 2.5- fold – reduction
Vacharathit (Thailand)	Health workers who received 2 doses of Coronavac (N = 60)	Not mentioned	WT Sera from unvaccinated and naturally infected COVID-19 patients (Mar –May 2020 and Apr-May 2021)	Delta	Live virus neutralization: GMT for Nab (Table 1) WT: 640 (95% CI 320-1280) Alpha: 40 (95% CI 17.5-40) Beta: 20 (95% CI 10-40) Delta: 10 (95% CI 10-40) % NaB positivity WT: 98.33% Alpha: 75% Beta: 70% Delta: 48.33% GMT IgG (s-1-RBD binding IgG WT: 774.48 (95% CI 607.22-987.82) Alpha: 44.64 (95% CI 35-56.94) Beta: 35.03 (95% CI 27.46-44.68) Delta: 24.48 (95% CI 19.2-31.23) Fold-reduction: 3.0

Appendix 8. Characteristics and Results of Studies on Duration of Protection after CoronaVac Immunization

Study ID	Population	N	Vaccine Regimen	Outcomes / Results
Jantarabenjakul (Thailand) Preprint	Healthcare workers 18 years old and above with no history of COVID-19: SV grp (21 to 28 days interval) (N = 94) AZ grp (8 to 10 weeks interval) (N = 91) COVID-19 group (hospitalized March to April 2020) (N = 111) - Mild (N = 58) - COVID-19 pneumonia (N = 53)	 94 91 111 58 53	SV grp: 4 & 12 weeks [IQR 23 (22-24) days] AZ grp: 4 weeks [IQR 19 (16-21) days] COVID-19 group: 4±2 weeks after diagnoses [IQR 35 (30-38) days]	Neutralizing Ab (blocking ELISA) (% inhibition) (cut-off ≥68%inhibition) • SV (4 weeks after): 77.0 (58.5-87.9) (no significant difference in age; p=0.18); 57/94 (60.6%) [≥68%inhibition] - 20-30 y/o: 83.2% (58.5-87.9) - 31-50 y/o: 77.3% (59.1-87.5) - 51-60 y/o: 73.4% (49.3-83.2) • SV (12 weeks after): 38.7 (22.1-55.7) (significant decrease from 4 weeks; p<0.001); 11/90 (12.2%) - 20-30 y/o: 40% (31.7-66) - 31-50 y/o: 43.7% (21.2-57.4) - 51-60 y/o: 32.4% (15.3-43.3) • AZ: 90.4 (75.2-96.2) %inhibition; 78/91 (85.7%) - 20-30 y/o: 88.2% (76.6-95.8) - 31-50 y/o: 95.8% (75.6-97.9) - 51-60 y/o: 90.2% (72.5-95.3) • Mild COVID-19: 80.8 (61.5-92.1) • COVID-19 pneumonia: 94.5 (88.1-95.8) The SV group had a level of SARS-CoV-2 neutralizing antibodies comparable to the mild COVID-19 group. In contrast, the AZ group had a higher level of neutralizing antibodies comparable to the COVID-19 pneumonia group SARS-CoV-2 total Ab (ECLIA) [1 U/ml = 0.972 BAU/ml] (cut-off ≥132 U/ ml) • SV: 188.6 (115.6-312.2) U/ml (no significant difference in age; p=0.28); 194 (118.9-321.2) BAU/ml [67/94 (71.3%)] - 20-30 y/o: 275.8 U/ml; 283.7 (104-596.9) BAU/ml - 31-50 y/o: 193 (118.9-290.4) BAU/ml - 51-60 y/o: 185.6 U/ml; 190.9 (133.6-294.5) BAU/ml • AZ: 794.2 (497.9-1383.0) U/ml; 817.1 (512.2-1422.8) BAU/ml [91/91(100%)] - 20-30 y/o: 599.8 (472.9-889.6) BAU/ml - 31-50 y/o: 960.5 (531.1-2005.1) BAU/ml - 51-60 y/o: 865.4 (512.2-1704.7) BAU/ml • Mild COVID-19: 66.9 (19.7-170.2) U/ml • COVID-19 pneumonia: 794.2 (497.9-1383) U/ ml • The anti-SARS-CoV-2 total antibodies of the AZ group were significantly higher than the COVID-19 pneumonia group (P<0.001) There was a significant decrease in neutralizing antibody levels from 4 weeks to 12 weeks for Sinovac, which was seen in the 3 age groups
Kara	Healthcare workers	272	1 month & 3 months	Anti-S-RBD-IgG (CLIA) (AU/ml) [significant decrease, p<0.001]

(Turkey) Preprint	45 (16.5%) had previous COVID-19 5 (1.8%) infected after the 2nd dose (mild)			1 month vs 3 months • Median: 29.14 vs. 10.46 • Mean: 44.60 vs. 27.80 Seroconversion rates [significant decease, p=0.004] 1 vs 3 months 1 month vs 3 months: 98.2% vs 97.8% Total anti-spike/anti-nucleocapsid-IgG antibody (CLIA) [significant decrease, p<0.001], 1 month vs. 3 months • Median: 19.80 vs. 6.16 • Mean: 36.95 vs. 30.55 Seroconversion rates [not significant decrease, p=1.000] 1 month vs 3 months: 93% vs. 87.3% Antibody concentrations were statistically significantly decreased at the third month among those with no previous infection, but with the median concentrations never falling below the reactive level.
Liao (China)	Adult volunteers aged 18–59 years	158	2 doses (3ug in an Al(OH)3) adjuvant 14 or 28 days apart	Neutralizing antibody peaked at day 28 after the second dose and subsequently exhibited a gradual declining tendency Antibody positivity rates: 0/14 dosing at 6 months : Anti-S IgG declined to 52.1% Anti-N IgG declined to 50.7% 0/28 dosing at 6 months Anti-S IgG: declined to 52.4% Anti-N IgG: declined to 45.3%
Palacios (Brazil) Preprint	Healthy health professionals caring for COVID patients (N=12396); only 5% were 60yrs and older 55.9% with comorbidities (n = 9823) Excluded pregnant, previous COVID-19 vaccines, acute symptoms of COVID	CoronaVac (n=6195) - safety (n= 4953) - efficacy Placebo (n=6201) - safety (n=4870)- efficacy	CoronaVac 3.0ug, 14 days apart	VE 28 days after 1st dose: 42.5% (32.9-50.7) 56 days after 1st dose: 60.4% (56.5-63.9) 98 days after 1st dose: 52.5% (55.1-99.2)
Cerquiera-Silva (Brazil)	General population (N – 75,919, 840) enrolled 25,752,013	General population (N – 75,919, 840)	CoronaVac, 2 doses, median interval = 27 days (IQR 21-28)	79 years and younger: decreased in (and maintenance of low) hospitalization incidence up to 84 days 80-89 and >/= 90 years: decreased incidence 28 days (lowest)

	Excluded ; vaccinated besides ChAdOx1 or CoronaVac; inconsistent records; confirmed COVID-19 before vaccine administration; missing data for covariates	enrolled 25,752,013		Incidence increased afterward but were lower than those observed during the reference period or for partially vaccinated individuals.

Appendix Table 9. Characteristics of Studies on the Effect of CoronaVac booster dose

STUDY ID (Country)	STUDY DESIGN	STUDY POPULATION	INTERVENTION / EXPOSURE	CONTROL	FOLLOW UP	OUTCOMES
Wu (China) Preprint	RCT Randomized – code by a statistician, assignment in sequence, Participant, investigator, lab staff masked to group allocation Balanced drop out with reason (in original trial), Balanced drop out from original study to current trial but not clear reason for drop out	Healthy adults >/=60 years old, participants in the Phase 2 trial N = 303	3rd dose at 8 months or more after V2 1.5ug N = 85 3ug N = 90 6ug N = 81	Placebo = 47	28 days	• GMT of NAb to live SARS-CoV-2 on D180 after V2 and 7, 14, 28 days after V3 • Seropositivity rate (cut off at 1/8) • Safety: local and systemic adverse event rates(days 0-7), spontaneous recording of adverse event rate till day 28 • Serious adverse events till 6 months after V2
Pan (China) Preprint	RCT Randomized Sealed envelopes Triple blinded	Adults 18 to 59 years old N = 504	3ug and 6ug, 14 or 28 day interval, V3 at 28 days after V2	Placebo, 14 or 28 day interval, Placebo V3 at 6mos after V2	Planned 1 year for safety Actual follow up 6 months	• GMT of NAbs to live SARS CoV 2 • Seropositivity / seroconversion • At 6 months after V2, 14 days after V3 and 6 months after V3 • Reactogenicity • Serious adverse event
Liao (China)	Case series	Adult volunteers aged 18 to 59 years who received third dose (N = 76)	3ug, 14 or 28 day interval, V3 at an unspecified time	NA (self-control at D2)		• Both the 0/14 and 0/28 schedules showed seroconversion of 100% neutralizing antibody with GMTs of 57.9 and 36.8
Wang (China)	Subgroup analysis of Phase I/II	16 to 69 years old	3rd dose 6 months after 2nd (schedule: months 0, 1, and 7) N = 38 volunteers	22 COVID-19 convalescents 6 health participants	4 weeks after the final vaccination 1.3 months after infection (convalescents)	• After the 3rd dose, there was robust recall humoral response to efficiently neutralize circulating variants • NAb titer surged by ~8-fold (from 7 to 53) at week 1, peaked by ~25-fold increase (up to 177) at week 2 after the 3rd-booster and slowly decreased over time • 3rd dose had minimal reduction in neutralization titers against VOCs when compared to 2 doses
Li M (China)	RCT IWRS Observer blinded	Heathy 18 to 59 years old primed with 2 doses of CoronaVac	Ad5 at 3-6 months after V2 (N = 50)	3rd dose of CoronaVac 3-6 months after V2 (N = 51)	14 and 28 days after 28 days (AE)	Neutralizing antibodies (cytopathic effect (CPE)-based microneutralization assay) <u>14 days GMT</u> 3 doses (Ad5): 197.4 (167.7, 232.4) 3 doses (SV): 33.6 (28.3, 39.8) p<0.001 <u>28 days GMT</u> 3 doses (Ad5): 150.3 (128.6, 175.7) 3 doses (SV): 35.3 (29.4, 42.4) p<0.001 Seropositivity (titer ≥1:4) <u>14 days</u> 3 doses (Ad5): 100.0 (1.0, 1.0)

						3 doses (SV): 100.0 (1.0, 1.0) p<0.001 28 days 3 doses (Ad5): 100.0 (1.0, 1.0) 3 doses (SV): 99.0 (0.9, 1.0) p<0.001 SAFETY (28 days) Local: 3 doses (Ad5): 28 (29.2%) 3 doses (SV): 3 (2.9%) Systemic: 3 doses (AD5): 14 (14.6%) 3 doses (SV): 3 (2.9%)

Appendix 10. Details of Immunologic Results of Studies on CoronaVac booster dose

GEOMETRIC MEAN TITERS									
Study	**Vaccine (Dose)**	**Units**	**3rd dose**				**No 3rd dose / 2nd dose only**		
			N	**Interval from D2**	**Testing Interval from D3**	**GMT (95% CI)**	**N**	**Testing Interval from D2**	**GMT (95% CI)**
NEUTRALIZING ANTIBODY TITERS (GMT)									
Wu	CoronaVac (3μg)	Mean antibody titer	86	8m	28d	342.8 (266.4-441.1)	43	28d	2.0 (2.0-2.1)
Pan	CoronaVac (3μg, D0, 28, 56)	Mean antibody titer	53	28d	28d	49.7 (39.9-61.9)	59	28d	39.6 (30.1-52.2)
% POSITIVITY									
Study	**Vaccine (Dose)**	**Units**	**3rd dose**				**No 3rd dose / 2nd dose only**		
			N	**Interval from D2**	**Testing Interval from D3**	**% (%95 CI)**	**N**	**Testing Interval from D2**	**% (%95 CI)**
% NEUTRALIZING ANTIBODY POSITIVITY									
Wu	CoronaVac (3μg)	Number of seropositives	86	8m	28d	100% (95.80-100.00)	43	28d	0 (0%) (0.00-8.22)
Pan	CoronaVac (3μg, D0, 28, 56)	Seropositivity rate	53	28d	28d	98.1% (89.9-100.0)	59	28d	94.9% (85.9-98.9)
Pan	CoronaVac (3μg, D0, 28, 208)	Seropositivity rate	49	180d	28d	100% (92.7-100.0)	56	28d	100% (93.8-100.0)

Appendix 11. Details of Safety Results of Studies on CoronaVac booster dose

Safety Outcome Parameter	Study	Follow up	3rd Dose	2nd Dose
			n/N (%)	n/N (%)
Local adverse reaction (within 28 days)	Wu	28d	3/90 (3.33%)	1/47 (2.13%)
	Pan (S1)	28d	3/55 (5.45%)	0/26 (0%)
	Pan (S2)	28d	8/55 (14.55%)	2/30 (6.67%)
	Pan (S3)	28d	2/54 (3.7%)	0/26 (0%)
	Pan (S4)	28d	8/52 (15.38%)	1/28 (3.57%)
Systemic adverse reaction (within 28 days)	Wu	28d	2/90 (2.22%)	2/47 (4.26%)
Any adverse event (within 28 days)	Wu	28d	5/90 (5.56%)	2/47 (4.26%)
	Pan (S1)	28d	5/55 (9.09%)	0/30 (0%)
	Pan (S2)	28d	10/55 (18.18%)	3/30 (10%)
	Pan (S3)	28d	3/54 (5.56%)	0/30 (0%)
	Pan (S4)	28d	8/52 (15.38%)	2/28 (7.14%)
Any adverse event (within one year)	na	na	na	na
Severe adverse event	na	na	na	na
Serious adverse event	Wu	28d	5/101 (4.95%)	2/49 (4.08%)
	Pan	6m	1/60 (1.67%)	0/30 (0%)
	Pan	6m	0/60 (0%)	0/30 (0%)
Related serious adverse event	na	na	na	na
Deaths	na	na	na	na

Appendix 12. Characteristics of Ongoing Trials

NCT Number	Title	Status	Age	Phases	Study Type	Study Designs	Completion Date	URL
NCT04801667	Evaluate the Impact, Safety, Tolerability and Immunogenicity of the Coronavac Vaccine in Kidney Transplant Recipients	Active, not recruiting	18 Years to 100 Years Â (Adult, Older Adult)	Phase 4	Interventional	Allocation: N/A|Intervention Model: Single Group Assignment|Masking: None (Open Label)|Primary Purpose: Health Services Research	1-Mar-23	https://ClinicalTrials.gov/show/NCT04801667
NCT04754698	COVID-19 CoronaVac in Patients With Autoimmune Rheumatic Diseases and HIV/AIDS	Active, not recruiting	18 Years and older Â (Adult, Older Adult)	Phase 4	Interventional	Allocation: Non-Randomized|Intervention Model: Parallel Assignment|Masking: None (Open Label)|Primary Purpose: Prevention	31-May-22	https://ClinicalTrials.gov/show/NCT04754698
NCT04854408	Evaluation of the Effect of Coronavac Vaccine (Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2 Vaccine) on Healthcare Workers' Menstrual Patterns	Completed	18 Years to 45 Years Â (Adult)		Observational	Observational Model: Other|Time Perspective: Prospective	9-May-21	https://ClinicalTrials.gov/show/NCT04854408
NCT04789356	Effectiveness of the Adsorbed Vaccine COVID-19 (Coronavac) Among Education and Public Safety Workers With Risk Factors for Severity	Active, not recruiting	18 Years to 49 Years Â (Adult)	Phase 4	Interventional	Allocation: Non-Randomized|Intervention Model: Parallel Assignment|Masking: None (Open Label)|Primary Purpose: Treatment	Mar-22	https://ClinicalTrials.gov/show/NCT04789356
NCT04942405	Efficacy, Immunogenicity, and Safety of the Inactivated COVID-19 Vaccine (TURKOVAC) Versus the CoronaVac Vaccine	Recruiting	18 Years to 55 Years Â (Adult)	Phase 3	Interventional	Allocation: Randomized|Intervention Model: Parallel Assignment|Masking: Triple (Participant, Care Provider, Investigator)|Primary Purpose: Prevention	31-Mar-23	https://ClinicalTrials.gov/show/NCT04942405
NCT04974164	Effectiveness of COVID-19 Vaccine for Prevention of COVID-19 in the Dominican Republic	Not yet recruiting	18 Years and older Â (Adult, Older Adult)		Observational	Observational Model: Case-Control|Time Perspective: Prospective	11-Apr-22	https://ClinicalTrials.gov/show/NCT04974164
NCT04756830	A Study to Assess the Safety and Immunogenicity of the Coronavac Vaccine Against COVID-19	Active, not recruiting	18 Years and older Â (Adult, Older Adult)	Phase 4	Interventional	Allocation: N/A|Intervention Model: Single Group Assignment|Masking: None (Open Label)|Primary Purpose: Prevention	Jun-23	https://ClinicalTrials.gov/show/NCT04756830
NCT04765215	Investigation of the Effectiveness of CoronaVac Vaccine in Cancer Patients With Active Chemotherapy and Comparison With Healthy People.	Active, not recruiting	18 Years to 90 Years Â (Adult, Older Adult)		Observational	Observational Model: Case-Control|Time Perspective: Prospective	31-Mar-22	https://ClinicalTrials.gov/show/NCT04765215

NCT Number	Title	Status	Age	Phases	Study Type	Study Designs	Completion Date	URL
NCT04884685	Safety of an Inactivated SARS-CoV-2 Vaccine (CoronaVac) in Children and Adolescents	Active, not recruiting	3 Years to 17 Years Â (Child)	Phase 2	Interventional	Allocation: Randomized|Intervention Model: Parallel Assignment|Masking: Double (Participant, Investigator)|Primary Purpose: Prevention	3-Jan-22	https://ClinicalTrials.gov/show/NCT04884685
NCT04894227	Lot-to-lot Consistency of an Inactivated SARS-CoV-2 Vaccine for Prevention of COVID-19 in Healthy Adults	Active, not recruiting	26 Years to 45 Years Â (Adult)	Phase 4	Interventional	Allocation: Randomized|Intervention Model: Parallel Assignment|Masking: Double (Participant, Investigator)|Primary Purpose: Prevention	30-Nov-21	https://ClinicalTrials.gov/show/NCT04894227
NCT04979949	Booster Vaccination Against SARS-CoV-2	Recruiting	18 Years to 60 Years Â (Adult)	Phase 2	Interventional	Allocation: Randomized|Intervention Model: Parallel Assignment|Masking: Triple (Participant, Care Provider, Investigator)|Primary Purpose: Prevention	12-Jul-22	https://ClinicalTrials.gov/show/NCT04979949
NCT04651790	Efficacy, Safety, and Immunogenicity of Two Vaccination Schedules of an Inactivated Vaccine Against COVID-19 in Adults	Recruiting	18 Years and older Â (Adult, Older Adult)	Phase 3	Interventional	Allocation: Randomized|Intervention Model: Parallel Assignment|Masking: None (Open Label)|Primary Purpose: Prevention	Mar-22	https://ClinicalTrials.gov/show/NCT04651790
NCT04800133	Covid-19 Vaccination in Adolescents	Recruiting	11 Years to 100 Years Â (Child, Adult, Older Adult)	Phase 2	Interventional	Allocation: Non-Randomized|Intervention Model: Parallel Assignment|Masking: None (Open Label)|Primary Purpose: Prevention	31-Mar-25	https://ClinicalTrials.gov/show/NCT04800133
NCT04898946	Serological Response to mRNA and Inactivated COVID-19 Vaccine in Health Care Workers in Hong Kong	Recruiting	18 Years and older Â (Adult, Older Adult)		Observational	Observational Model: Cohort|Time Perspective: Prospective	8-Mar-22	https://ClinicalTrials.gov/show/NCT04898946
NCT04611243	Lung Function, Exercise Capacity, and Serology Responses in Patients With COVID-19	Recruiting	18 Years and older Â (Adult, Older Adult)		Observational	Observational Model: Cohort|Time Perspective: Prospective	17-Feb-25	https://ClinicalTrials.gov/show/NCT04611243
NCT04953325	Immunogenicity and Safety of an Inactivated COVID-19 Vaccine	Recruiting	18 Years and older Â (Adult, Older Adult)	Phase 4	Interventional	Allocation: Randomized|Intervention Model: Parallel Assignment|Masking: None (Open Label)|Primary Purpose: Prevention	31-Jan-22	https://ClinicalTrials.gov/show/NCT04953325

NCT Number	Title	Status	Age	Phases	Study Type	Study Designs	Completion Date	URL
NCT04888793	Immune Response to Anti COVID-19 Vaccine in Immunocompromised Patients: a Cohort Study	Recruiting	18 Years and older Â (Adult, Older Adult)		Observational	Observational Model: Cohort|Time Perspective: Prospective	20-Dec-21	https://ClinicalTrials.gov/show/NCT04888793
NCT04992208	Safety of an Inactivated SARS-CoV-2 Vaccine for Prevention of COVID-19 in Children and Adolescents	Not yet recruiting	3 Years to 17 Years Â (Child)	Phase 4	Interventional	Allocation: N/A|Intervention Model: Single Group Assignment|Masking: None (Open Label)|Primary Purpose: Prevention	25-Dec-22	https://ClinicalTrials.gov/show/NCT04992208
NCT04911790	Safety of an Inactivated SARS-CoV-2 Vaccine for Prevention of COVID-19 in Adults	Recruiting	18 Years and older Â (Adult, Older Adult)	Phase 4	Interventional	Allocation: N/A|Intervention Model: Single Group Assignment|Masking: None (Open Label)|Primary Purpose: Prevention	31-Dec-22	https://ClinicalTrials.gov/show/NCT04911790
NCT04962308	Clinical Trial of Inactivated SARS-CoV-2 Vaccine for Prevention of COVID-19 in Healthy Adults	Recruiting	18 Years to 59 Years Â (Adult)	Phase 4	Interventional	Allocation: Randomized|Intervention Model: Parallel Assignment|Masking: None (Open Label)|Primary Purpose: Prevention	19-Dec-21	https://ClinicalTrials.gov/show/NCT04962308
NCT04751721	Oxidative Stress Parameters, Trace Element and Quality of Life in Women Before and After Covid-19 Vaccines	Not yet recruiting	35 Years to 65 Years Â (Adult, Older Adult)	Not Applicable	Interventional	Allocation: N/A|Intervention Model: Single Group Assignment|Masking: None (Open Label)|Primary Purpose: Screening	Apr-21	https://ClinicalTrials.gov/show/NCT04751721
NCT04992260	Efficacy, Immunogenicity and Safety of COVID-19 Vaccine , Inactivated in Children and Adolescents	Not yet recruiting	6 Months to 17 Years Â (Child)	Phase 3	Interventional	Allocation: Randomized|Intervention Model: Parallel Assignment|Masking: Double (Participant, Investigator)|Primary Purpose: Prevention	1-Apr-23	https://ClinicalTrials.gov/show/NCT04992260
NCT04747821	An Effectiveness Study of the Sinovac's Adsorbed COVID-19 (Inactivated) Vaccine	Active, not recruiting	18 Years and older Â (Adult, Older Adult)	Phase 4	Interventional	Allocation: Randomized|Intervention Model: Parallel Assignment|Masking: None (Open Label)|Primary Purpose: Prevention	Feb-22	https://ClinicalTrials.gov/show/NCT04747821
NCT04456595	Clinical Trial of Efficacy and Safety of Sinovac's Adsorbed COVID-19 (Inactivated) Vaccine in Healthcare Professionals	Active, not recruiting	18 Years and older Â (Adult, Older Adult)	Phase 3	Interventional	Allocation: Randomized|Intervention Model: Parallel Assignment|Masking: Quadruple (Participant, Care Provider, Investigator, Outcomes Assessor)|Primary Purpose: Prevention	Feb-22	https://ClinicalTrials.gov/show/NCT04456595
NCT04751695	Oxidative Stress Parameters, Trace Element and Quality of Life in Men Before and After Covid-19 Vaccines	Not yet recruiting	35 Years to 65 Years Â (Adult, Older Adult)	Not Applicable	Interventional	Allocation: N/A|Intervention Model: Single Group Assignment|Masking: None (Open Label)|Primary Purpose: Screening	Apr-21	https://ClinicalTrials.gov/show/NCT04751695

NCT Number	Title	Status	Age	Phases	Study Type	Study Designs	Completion Date	URL
NCT05026879	Adverse Events Report of Inactivated COVID-19 Vaccine	Completed	18 Years and older Â (Adult, Older Adult)		Observational	Observational Model: Cohort|Time Perspective: Cross-Sectional	14-Mar-21	https://ClinicalTrials.gov/show/NCT05026879
NCT04582344	Clinical Trial For SARS-CoV-2 Vaccine (COVID-19)	Active, not recruiting	18 Years to 59 Years Â (Adult)	Phase 3	Interventional	Allocation: Randomized|Intervention Model: Parallel Assignment|Masking: Triple (Participant, Care Provider, Investigator)|Primary Purpose: Prevention	15-Apr-22	https://ClinicalTrials.gov/show/NCT04582344
NCT04952727	Study on Sequential Immunization of Inactivated COVID-19 Vaccine and Recombinant COVID-19 Vaccine (Ad5 Vector)	Not yet recruiting	60 Years and older Â (Adult, Older Adult)	Phase 4	Interventional	Allocation: Randomized|Intervention Model: Parallel Assignment|Masking: Triple (Participant, Investigator, Outcomes Assessor)|Primary Purpose: Prevention	2-Mar-22	https://ClinicalTrials.gov/show/NCT04952727
NCT04892459	Study on Sequential Immunization of Inactivated SARS-CoV-2 Vaccine and Recombinant SARS-CoV-2 Vaccine (Ad5 Vector)	Active, not recruiting	18 Years to 59 Years Â (Adult)	Phase 4	Interventional	Allocation: Randomized|Intervention Model: Parallel Assignment|Masking: Triple (Participant, Investigator, Outcomes Assessor)|Primary Purpose: Prevention	25-Dec-21	https://ClinicalTrials.gov/show/NCT04892459
NCT04992182	Reactogenicity, Safety, and Immunogenicity of Covid-19 Vaccine Booster	Active, not recruiting	18 Years and older Â (Adult, Older Adult)	Phase 2	Interventional	Allocation: Randomized|Intervention Model: Parallel Assignment|Masking: Double (Participant, Investigator)|Primary Purpose: Treatment	30-Jun-22	https://ClinicalTrials.gov/show/NCT04992182
NCT04845048	Active Pharmacovigilance Study of Adsorbed COVID-19 (Inactivated) Vaccine	Not yet recruiting	18 Years and older Â (Adult, Older Adult)		Observational	Observational Model: Cohort|Time Perspective: Prospective	Nov-21	https://ClinicalTrials.gov/show/NCT04845048
NCT04775069	Antibody Response to COVID-19 Vaccines in Liver Disease Patients	Recruiting	18 Years and older Â (Adult, Older Adult)	Phase 4	Interventional	Allocation: Non-Randomized|Intervention Model: Parallel Assignment|Masking: None (Open Label)|Primary Purpose: Prevention	31-Mar-22	https://ClinicalTrials.gov/show/NCT04775069
NCT05033834	Covid-19 Infection in After Vaccination	Not yet recruiting	18 Years to 80 Years Â (Adult, Older Adult)		Observational	Observational Model: Cohort|Time Perspective: Prospective	31-Dec-22	https://ClinicalTrials.gov/show/NCT05033834
NCT04834869	COVID-19 Vaccines Safety Tracking (CoVaST)	Recruiting	18 Years and older Â (Adult, Older Adult)		Observational	Observational Model: Other|Time Perspective: Prospective	31-Jan-22	https://ClinicalTrials.gov/show/NCT04834869
NCT05029245	IntraDermal Versus Intramuscular ComirnatyÂ® Efficacy Study	Not yet recruiting	18 Years and older Â (Adult, Older Adult)	Phase 3	Interventional	Allocation: Randomized|Intervention Model: Parallel Assignment|Masking: Single (Participant)|Primary Purpose: Prevention	31-Oct-22	https://ClinicalTrials.gov/show/NCT05029245

Q3. Is vaccination with BBV152 (Covaxin/Bharat) effective and safe in the prevention of COVID-19 infections?

As of 21 October 2021

RECOMMENDATIONS

1. **We recommend the use of BBV152 (Covaxin/Bharat), 0.5 mL/dose, in a two-dose regimen, 28 days apart for the prevention of symptomatic COVID-19 infection in healthy adults**. *(Moderate quality of evidence; Strong recommendation)*

2. **We suggest the use of BBV152 (Covaxin/Bharat), 0.5 mL/dose, in a two-dose regimen, 28 days apart for the prevention of symptomatic COVID-19 infection**:
   a. Adults who have stable medical co-morbidities and are at high risk for severe infection *(Low quality of evidence; Weak recommendation)*
   b. Healthy, older adults (>60 years old) *(Low quality of evidence; Weak recommendation)*
   c. Pregnant and lactating women, after discussing with a physician *(No direct evidence; Weak recommendation)*
   d. Immunocompromised patients, after discussing with a physician *(No direct evidence; Weak recommendation)*

3. **We suggest against the use of BBV152 (Covaxin/Bharat) for the prevention of COVID-19 in children and adolescents**. *(No evidence; Weak recommendation)*

4. **We recommend against the use of BBV152 (Covaxin/Bharat) in individuals who have known allergies to its contents/excipients**. *(Best practice statement)*

(*Note: The recommendation regarding the use of BBV152 in the context of the Delta variant is included in the Delta variant review)*

KEY FINDINGS

The search performed on September 20, 2021 included one (1) randomized controlled clinical trial (RCT) (n=25,798) and seven (7) observational studies, which provided evidence on the efficacy, effectiveness, and safety of BBV152 (Covaxin/Bharat) in the prevention of SARS-CoV-2 infection, including those due to the variants of concern.

INTRODUCTION

In the effort against the COVID-19 pandemic, equal worldwide distribution of safe and effective vaccines is key. As India has had the second highest number of COVID-19 infections, Bharat Biotech and the Indian Council of Medical Research developed the BBV152 vaccine (Covaxin®), which was approved for emergency use in the country on January 3, 2021.[1] BBV152 was produced from the virus strain (NIV-2020-770) with the Asp614Gly mutation isolated and sequenced from a patient infected with COVID-19. This whole virion βpropiolactone-inactivated SARS-CoV-2 vaccine with a toll-like receptor 7/8 agonist molecule absorbed to alum (Algel-IMDG) leads to a Th1 response. It is a liquid suspension given intramuscularly at 0.5 mL/dose, in a two-dose

regimen, 28 days apart.[2] BBV152 has no reconstitution requirement, needing only refrigerator storage at 2 to 8˚C with a shelf life of approximately 2 years.[1]

In order to aid future decisions for vaccine procurement, this review was done on the clinical efficacy, effectiveness, and safety of BBV152 (Covaxin/Bharat).

REVIEW METHODS

General Search Results

As of September 20, 2021, eight (8) studies were included in this review. Only one (1) was a randomized controlled trial (RCT), which investigated the efficacy of BBV152 compared to placebo, while four (4) were observational studies. Two (2) were case series of adverse events, and one (1) was a review that cited safety reports. Two (2) reported on effectiveness on variants. Several reports were also identified in the search that mentioned the use of BBV152 but were excluded in this review because BBV152 was used in a very small minority of the study population and no separate results were presented for the subgroup.

RESULTS

Clinical Efficacy

A double-blind, randomized, controlled Phase 3 trial is currently being conducted in 25 Indian hospitals to evaluate the overall vaccine efficacy (VE) after two doses of BBV152 compared with placebo in preventing COVID-19 infection among participants who were seronegative at baseline. After a median follow up of 146 days, VE for the prevention of symptomatic COVID-19 infection was 77.8% (95% CI 65.2-86.4) at 2 weeks post 2nd dose. Vaccine efficacy was 93.4% (95% CI 57.1-99.8) against severe disease and 63.6% (95% CI 29-82.4) for asymptomatic infection. VE for symptomatic COVID-19 infection among those at least 60 years of age was 67.8% (95% CI 8-90).[3]

The characteristics of this included trial are presented in Appendix 2 while the risk of bias assessment is presented in Appendix 3.

Summary of findings and GRADE profile on BBV152 efficacy is presented in Appendix 6.

Real World Evidence: Effectiveness

General Population

While reports on vaccine breakthrough infection of COVID-19 exists, all involved multiple vaccines and BBV152 was used in a minority of the study population. As no separate reporting of the outcomes of interest were given per vaccine type, clear information on BBV152 effectiveness could not be extracted in the studies identified in the search.

Health Care Workers

The cross-sectional Coronavirus Vaccine-induced Antibody Titre (COVAT) study assessed the outcomes of 93 health care workers (HCWs) who received two doses of BBV152. In this study, at Days 21-36 after the second dose, the breakthrough infection rate was recorded at 2.2%. All of which were mild cases and all recovered.[4]

Clinical Efficacy and Effectiveness on Special Populations of Interest (older persons, children, immunocompromised, and pregnant women)
No study was identified on the real-world evidence on BBV152 on older persons, the immunocompromised, children or pregnant women.

Safety
Regulatory Clinical Trial Evidence
In the Phase 3 trial, after a median follow up of 146 days after the first dose for 93% of the study population, five (5) deaths in the BBV152 recipients and ten (10) in those who received the placebo were reported. All causes were assessed to be unrelated to the vaccination. Deaths in the BBV152 group were due to cerebellar hemorrhage, hemorrhagic stroke, ovarian cancer with metastases, sudden cardiac death, and COVID-19 infection. Meanwhile, the causes of death in the placebo group included alcohol overdose, myocardial infarction, cardiac arrest with underlying hypertension, COVID 19, and two (2) from yet undetermined causes.[3]

Only local injection pain had an incidence greater than 1% among the local solicited adverse events. The most frequent solicited systemic adverse event was headache, which occurred in less than 1% in both groups. Apart from a lower incidence of adverse events after the second dose compared to the first, and being slightly higher in the BBV152 group compared to the placebo, there were no significant differences observed in solicited, unsolicited, and serious adverse events rates in the two treatment groups. No anaphylactic events were noted. Long-term safety outcomes are still underway.[3]

Summary of findings and GRADE profile on BBV152 safety is presented in Appendix 7.

Real World Evidence: Safety
In the cross-sectional COVAT study that included healthcare workers who received two (2) doses of BBV152, 11.1% (10/90) were reported to have mild to moderate side effects. No serious solicited or unsolicited side effects were noted. When compared with ChAdOx1 recipients in the same study, BBV152 recipients reported less adverse events.[4]

The characteristics and detailed results of this trial are presented in Appendix 4.

Reports on Adverse Events of Interest
Immune thrombocytopenic purpura (ITP) in a SARS-CoV-2 seropositive participant at baseline was reported as a possible related serious adverse event in one (1) patient in the BBV152 group in the regulatory trial. The event occurred 39 days after the second dose and resolved in four (4) days.[3]

In the National AEFI Committee report to the Union Health Ministry of India, of more than 2,300 adverse events, as cited in the review by Rajpurohit et. al, no potential thromboembolic events following BBV152 administration was included.[5]

Other Reported Adverse Events
One (1) case report documented a 60-year-old diabetic and hypertensive who developed herpes zoster four (4) days after receiving BBV152.[6] Another case report documented a 34-year-old woman developing new-onset subacute thyroiditis after receiving the first dose of BBV152.[7]

Effectiveness Against Variants of Concern
Alpha
One (1) study showed a 1.4-fold reduction in the titers with the Alpha-variant compared to the B.1 strain in the sera of BBV152 vaccinees, although the confidence intervals were overlapping [8] Another study showed no significant difference in the neutralizing antibody titers with the Alpha strain compared with the hCOV19/India/20-20770 and the hCoV-19/India/202Q11 from the BBV152 sera.[9]

Beta
Two (2) studies showed a 3-fold reduction in antibody neutralization after Beta-variant infection, compared with the reference strain, among BBV152 vaccine recipients.[8,10]

Delta
The same two (2) studies above also reported reduced immune response after Delta-variant infection among BBV152 vaccine recipients, but at a slightly lesser degree compared to the Beta-variant. The declines were 2.7-fold [10] and 2.9-fold.[8]

In addition, the regulatory trial reported a vaccine efficacy of 65.2% (95% CI 33.1–83.0) among the 50 Delta-variant positive confirmed cases. It also showed significantly lower viral loads among the breakthrough symptomatic infection cases in the vaccine versus placebo groups.[3]

Gamma
No study was identified that investigated on the effect of BBV152 vaccine against the Gamma-variant.

Appendix 5 presents the characteristics and the details of the studies on the performance of the BBV152 vaccine against variants of concern.

Heterologous Vaccination
One (1) study reported on the outcomes of BBV152 in a heterologous vaccination regimen. In Uttar Pradesh, India, a group of individuals were inadvertently given ChAdOx1 (Covishield) followed by BBV152 after an interval of six (6) weeks.[8] Immunologic responses showed that IgG and neutralizing antibody titers of the heterologous group were significantly higher when compared to those who received the homologous ChAdOx1-ChAdOx1 and homologous BBV152-BBV152 regimen.[8] Heterologous vaccination was also noted to produce higher antibody titers against the variants of concern (Alpha, Beta, and Delta) compared to homologous BBV152 vaccination, with heterologous titers at 3-fold higher levels.[8]

In the same study, no serious adverse events were reported following immunization with the heterologous regimen. The most common local adverse event in all groups was pain at injection site, while the most common systemic adverse events were fever

and malaise. Overall, the adverse event frequency in the heterologous group was similar to that in the homologous groups.

AUTHORIZATIONS

The Philippine FDA granted emergency use authorization for BBV152 (Covaxin/Bharat) on June 21, 2021.[11]

As of September 27, 2021, the application for WHO emergency use listing is still under process.

ONGOING TRIALS

The search performed on September 7, 2021 of the Clinicaltrials.gov registry showed four (4) ongoing trials.

Appendix 8 presents the details of the ongoing trials of BBV152.

RESEARCH GAPS

Research gaps regarding BBV152 vaccination for COVID-19 infection prevention include its efficacy, effectiveness, and safety in special populations such as the older and very old patients, children, and immunocompromised populations. Other gaps identified are the duration of protection, long term efficacy or effectiveness, and long-term safety of the vaccine. Lastly, the clinical efficacy or effectiveness and safety of heterologous vaccination as well as its clinical efficacy or effectiveness against infection with variants of concern are also identified research gaps

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EXCLUDED STUDIES

The following studies were not included in the evidence summary with the reasons as stated:

Study Title	Reason for Exclusion
Sapkal et. al. "Neutralization of VUI B.1.1.28 P2 variant with sera of COVID-19 recovered cases and recipients of Covaxin an inactivated COVID-19 vaccine"	Discussed effect on variant under investigation only
Sapkal, et. al. "Neutralization of B.1.1.28 P2 variant with sera of natural SARS-CoV-2 infection and recipients of BBV152 vaccine"	Discussed effect on variant under investigation only
Ghosh et al "Genomic profiles of vaccine breakthrough SARS-CoV-2 strains from Odisha, India" - MedRxiv	Covaxin only given to a minority of the population, no usable outcome.
R Pandurangaiah et al. "Post vaccination COVID-19 infection among health care workers in secondary medical care centre" - International Journal of Clinical Obstetrics and Gynaecology	Covaxin only give to a minority of the population, no subgroup analysis
Sharma et. Al. "Breakthrough infection with SARS-CoV-2 and its predictors among healthcare workers in a medical college and hospital complex in Delhi, India"	Covaxin only given to a minority of the population, no subgroup analysis
Tyagi et. al. "Breakthrough COVID19 infections after vaccinations in healthcare and other workers in a chronic care medical facility in New Delhi, India" - Diabetes and Metabolic Syndrome: Clinical Research and Reviews 2021	Covaxin only given to a minority of the population, no subgroup analysis
Farinholt et. al. "Transmission event of SARS-COV-2 Delta variant reveals multiple vaccine breakthrough infections" - MedRxiv July 12, 2021"	Covaxin only given to a minority of the population, no subgroup analysis
Cherian et. al. "Safety of the ChAdOx1 nCoV-19 and the BBV152 vaccines in 724 patients with rheumatic diseases: a post-vaccination cross-sectional survey"	Covaxin only given to a minority of the population, no subgroup analysis
Dash et. al. "Breakthrough SARS-CoV-2 infections in an eastern state of India: A preliminary report" - Research Square 2021	Covaxin only given to a minority of the population, no subgroup analysis
Guha et. al. "The incidence and in-hospital mortality of COVID-19 patients post-vaccination in eastern India" – MedRxiv July 22, 2021	Covaxin only given to a minority of the population, no event of interest reported with Covaxin
Shenoy et. al. "Immunogenicity of the ChAdOx1 nCoV-19 and the BBV152 Vaccines in Patients with Autoimmune Rheumatic Diseases"	Covaxin only given to a minority of the population, no event of interest reported with Covaxin
Singh Awadhesh Kumar Singh et. al. "Antibody Response after First-dose of ChAdOx1 nCov-19 and BBV-152 Health Care Workers in India: Preliminiary Results of Cross-Sectional Coronavirus Vaccine-induced Antibody Titre (COVAT) study" - MedRxiv. April 13, 2021	Covaxin only given to a minority of the population, no subgroup analysis for outcomes of interest

Appendix 1. Evidence to Decision

Table 1. Summary of Initial Judgements Prior to Panel Discussion (N = 9)

FACTORS	JUDGEMENT						RESEARCH EVIDENCE/ADDITIONAL CONSIDERATIONS
Problem	No	Yes (9)					
Benefits	Large (5)	Moderate (4)	Small	Uncertain			• VE 93.4% (95% CI 57.1-99.8) against severe disease and 63.6% (95% CI 29-82.4) for asymptomatic infection. • VE for symptomatic COVID-19 infection among those at least 60 years of age was 67.8% (95% CI 8-90).
Harm	Large	Small (8)	Uncertain (1)				• Only local injection pain had an incidence greater than 1% among the local solicited adverse events. • Long-term safety outcomes are still underway.
Certainty of evidence	High (1)	Moderate (3)	Low (5)	Very Low			• Very low to moderate
Balance of effects	Favors vaccine (9)	Does not favor vaccine	Uncertain				
Values	Important uncertainty or variability	Possibly important uncertainty or variability (4)	Possibly no important uncertainty or variability (3)	No important uncertainty or variability (2)			
Resources required	Uncertain	Large cost	Moderate cost (7)	Negligible cost or savings (1)	Moderate savings	Large savings (1)	• A single dose of Covaxin would cost around $14 (approximately PHP 710). Two doses are needed per individual. No reconstitution requirement, needing only refrigerator storage at 2 to 8˚C and has a shelf life of approximately 2 years.
Certainty of evidence of resources required	No included studies (7)	Very low (1)	Low (1)	Moderate	High		
Cost effectiveness	No included studies (8)	Favors the comparison	Does not favor either the intervention or the comparison	Favors the intervention (1)			
Equity	Uncertain (6)	Reduced	Probably no impact (2)	Increased (1)			
Acceptability	Uncertain (6)	No	Yes (3)				
Feasibility	Uncertain (1)	No	Yes (8)				

Appendix 2. Characteristics of the Randomized Controlled Trial (Ph3) on the Efficacy and Safety of Covaxin

Trial Identifier	**NCT04641481**
Vaccine	**BBV152 (Covaxin)**
Data Sources	Ella et. Al., "Efficacy, safety, and lot to lot immunogenicity of an inactivated SARS-CoV-2 vaccine (BBV152): A, double-blind, randomised, controlled phase 3 trial. MedRxiv 2021. https://doi.org/10.1101/2021.06.30.21259439
POPULATION	
Total Randomized	25,798 (16,973 per protocol, excluding seropositives)
Inclusions	
• Age	18 to 99 years old
• Race/ Ethnicity	Indian
• Immunocompromised	Excluded
• Pregnant and breastfeeding	Excluded
• With concomitant comorbidities	Participants with good general health as determined by the discretion of the investigator, or participants with stable medical conditions. A stable medical condition is defined as a disease not requiring significant change in therapy or hospitalization or worsening disease during the 3 months before enrolment.
• With previous COVID infection	Excluded
• With known previous exposure to COVID	Excluded
• Seropositive at baseline	(30%) Excluded in per protocol analysis but included at safety dataset
Exclusions	• History of any other COVID-19 investigational or licensed vaccination • Known history of SARS-CoV-2 infection, as declared by the subject • For women, positive urine pregnancy test before the first dose of vaccination or any time during the study period • Temperature >38.0°C (100.4°F) or symptoms of an acute self-limited illness such as an upper respiratory infection or gastroenteritis within three days prior to each dose of vaccine • Resident of COVID-19 infection in the same household • Known case of HIV, hepatitis B, or hepatitis C infection • Receipt of any licensed/experimental vaccine within four weeks before enrolment in this study • Receipt of immunoglobulin or other blood products within the three months before vaccination in this study • Immunosuppression as a result of an underlying illness or treatment with immunosuppressive or cytotoxic drugs, or use of anticancer chemotherapy or radiation therapy within the preceding 36 months • Immunoglobulins, anti-cytokine antibodies, and blood products within 6 months prior to study vaccination, during, and 21 days following the last dose of vaccination • Pregnancy, lactation, or willingness/intention to become pregnant during the first 6 months after enrolment • Severe and/or uncontrolled cardiovascular disease, respiratory disease, gastrointestinal disease, liver disease, renal disease, an endocrine disorder, and neurological illness (mild/moderate well-controlled comorbidities are allowed)
INTERVENTION (VACCINE)	
Type	Whole-virion ß-propiolactone-inactivated SARS-CoV-2 vaccine
Active substance	BBV152 (6µg virus antigen-Algel - Imidazoquinoline)
STORAGE AND COLD CHAIN CONSIDERATIONS	
• Shipping and transport	Supplied and stored in single use glass vials, with no on site dose preparation necessary
• Storage and shelf life prior to dilution/ opening	2 to 8°C, approximately 2 years
• Storage and shelf-life after dilution/opening	28 days
FINAL PRODUCT	
Form and use	Liquid suspension
Excipients	N/A
TRIAL-SPECIFIC CONSIDERATIONS	
Dosing and administration	0.5 mL/vial on days 0 and 28
Number randomized	12,879
COMPARATOR	
Type, dosing and administration	Phosphate buffered saline with Alum (without antigen), 0.5 mL
Number randomized	12,874
ACTUAL VACCINATION INTERVAL	28 days

OUTCOMES	Based on per protocol population including randomly assigned participants who were seronegative at baseline and received two doses of either vaccine or placebo, and remained on study at least 14 days after their second dose with no previous virologically-confirmed SARS-CoV-2 infection [Time Frame: Day 42 to Month 12]
Primary efficacy endpoints	RT-PCR positive symptomatic cases of COVID-19 with onset at least 14 days after 2nd dose: **77.8% vaccine efficacy (95% CI 65.2–86.4)**
Primary safety endpoints	None
Secondary endpoints	• RT-PCR positive Severe Symptomatic COVID-19 cases: vaccine efficacy of **93.4% (95% CI: 57.1–99.8)** • RT-PCR positive symptomatic COVID-19 cases 18-59 years of age: **79.4% (66.0–88.2)** • RT-PCR positive symptomatic COVID-19 cases 60 years of age or older: efficacy of **67.8% (8.0–90.0)** • RT-PCR positive COVID-19 asymptomatic and symptomatic cases occurring from two weeks after the second vaccination • Immunogenicity: Lot-to-Lot consistency of three consecutive GMP Lots [Time Frame: Day 0 to Day 42] Assessed based Wild-type SARS-CoV-2 Specific Neutralizing Antibody (nAb) • Geometric Mean Titer (GMT) of SARS-CoV-2 Specific Neutralizing Antibody (nAb) [Time Frame: Day 0 to Month 12] Specific Neutralizing Antibody (nAb Reactogenicity and Safety [Time Frame: Day 42 to Month 12] Solicited, Unsolicited, Serious Adverse Events
SUBGROUPS CONSIDERED IN THE ANALYSIS	
Age	18-59 years, 60 or older (10.7%)
Sex	Female, Male
Ethnic groups	N/A
Baseline seropositivity status / evidence of previous infection	Positive for anti-SARS-CoV-2 IgG, 30% seropositive at baseline excluded from per protocol analysis but contributed to safety dataset
Medical comorbidities	Stable cardiovascular disease, stable respiratory disease, controlled diabetes, stable liver disease, severe obesity (BMI>35), other stable comorbidities, multiple risk categories
Immunocompromised /HIV disease	Excluded
Risk for acquiring COVID infection	Participants considered to be at-risk of acquiring COVID-19 were prioritized, so a total of 2,750 participants were above 60 years of age and 7,065 reported at least one pre-existing medical condition across ages
Risk for progression to severe COVID	N/A
Dosing regimen	N/A
FOLLOW-UP	
Planned	Day 42 to Month 12
At data cutoff of interim report (first interim analysis)	Day 56 (1 month after second dose) Median of 146 days after first dose (92.3%)
Date of Data Cut-off date for latest available trial data	May 17, 2021 ß
METHODS / OTHER TRIAL PARAMETERS	
Blinding	Participants, investigators, study coordinators, study-related personnel, sponsor, and study nurses responsible for vaccine preparation and administration
Study Sites	25 centers in India
Study Sponsor	Bharat Biotech International Limited
Type of report available as of this rapid review	Preprint
Others	
Trial subject disposition - Not vaccinated Withdrawn from vaccination - Discontinued from vaccination - Withdrawal by subject - Discontinuation due to AE - Lost to ff-up Withdrawn from study - Withdrawal by subject - Lost to ff-up - 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	Trial subject disposition - Not vaccinated: 45 Withdrawn from vaccination - Discontinued from vaccination: 1334 - Withdrawal by subject: 486 - Discontinuation due to AE: 23 - Lost to ff-up: 361 Withdrawn from study: 408 - Withdrawal by subject: 151 - Lost to ff-up: 232 - Adverse event: 3 Efficacy Populations - Excluded from Dose 1 pop: 45 - Excluded from Dose 2 pop: 1334 - Excluded from 7 days pop: - Did not receive Dose 2: 1334 Protocol deviation

Appendix 3. Risk of Bias Assessment of Included Studies

STUDY ID	STUDY DESIGN	RANDOMIZATION	ALLOCATION CONCEALMENT	BLINDING OF PARTICIPANTS	BLINDING OF INVESTIGATORS	BLINDING OF ASSESSORS	MISSING OUTCOMES/ FOLLOW UP	SELECTIVE REPORTING	OVERALL CONTROL FOR CONFOUNDERS
Ella et al July 2021	RCT	Low	Low	Low	Low	Low	Low	High	Unclear
Singh et al 2021	Prospective cohort	N/A	N/A	N/A	N/A	N/A	Low	Low	High

Appendix 4. Characteristics of Studies on the Real-World Evidence of BBV152

Study ID	Design	Population	Intervention	Comparison	Follow up	Outcomes Reported
Singh et al 2021 N = 515	Prospective Cohort Study	>18 years old, health care workers who received first dose of vaccine, including COVID-19 recovered (>6 weeks before first dose)	Covishield	Covaxin	Day 21 after first dose, Day 21-28 of second dose, Day 83-97 (3 months), and Day 173-187 (6 months) after second dose	• SARS-CoV-2 spike antibody positivity rates after first dose of vaccine • Comparison of SARS-CoV-2 spike antibody between Covishield and Covaxin • Post vaccination (second dose) adverse events) • Post vaccination SARS-CoV-2 infection

Appendix 5. Characteristics and Results of Studies on the Effectiveness of BBV152 against Variants of Concern

Study ID	Population (n)	Variants Tested	Reference Strain	Immunologic Parameter (Test Used)	Extraction time	Result
Sapkal JTM	38	Alpha	hCoV-19/India/2020770 and hCoV-19/India/2020Q111	Neutralizing antibody titers (PRNT50)	Not mentioned	Titers not statistically significant across strains
Kant	*Heterologous group:* 18 participants: 11 male, 7 female; median age of 62 years, *Homologous groups:* 40 individuals each; CS (22 males, median age of 65.5 years), CV (23 females, median age of 56 years)	Alpha, Beta and Delta strains	B.1	Geometric mean titre (GMT)	9 weeks after second vaccine dose	GMTs for CV group against: - B1: 156.6 (95% CI 105.2-233.1) - Alpha: 112.4 (95% CI:76.56-164.9), ***1.39-fold reduction*** - Beta: 52.09 (95% CI 34.9-77.73) ***3.00-fold reduction*** - Delta: 54.37 (95% CI 27.26-108.4) ***2.88-fold reduction*** GMTs for heterologous group against: - B1: 539.54 (95% CI 263.9-1103) - Alpha: 396.1(95% CI 199.1-788) ***1.36-fold reduction*** - Beta: 151 (95% CI 80.2-284.3) ***3.57-fold reduction*** - Delta: 241.2 (95% CI 74.99-775.9) ***2.24-fold reduction*** ***Heterologous titers higher than homologous (3-fold higher)***
Yadav	20 COVID-19 recovered cases	Beta and Delta variants	B.1 (D614G)	Geometric mean titre (GMT)	28 days after 2 doses of Covaxin	GMTs for vaccinees sera against: - Beta: 61.57 (95% CI 36.3 4-104.3) - Delta: 68.97 (95% CI 24.72-192.4) - B1: 187.5 (95% CI 129.3 –271.9) GMT ratio of B.1 to: - Beta: 3.3 (95% CI 2.4-4.5) - Delta: 4.6 (95% CI: 2.2-9.5) ***Fold reduction (computed)*** ***Beta: 3.04-fold*** ***Delta: 2.72-fold*** Significant reduction in neutralization titre for Beta and Delta variants in comparison to B.1 (P value <0.0001)

Appendix 6. Summary of Findings Table of Efficacy of BBV152

Efficacy Outcome (at >14 days after dose2)		Quality Assessment					Summary of Findings			Certainty
		Risk of Bias	Inconsistency	Indirectness	Imprecision	Overall Assessment	Vaccine n/N (%)	Control n/N (%)	Vaccine Efficacy (CI)	
1: Symptomatic COVID-19 infection, seronegative at baseline	1 RCT	Serious Short ff-up	Not assessed	Not serious	Not serious	Serious	24/8471 (0.28)	106/8502 (1.25)	77.8 (65.2-86.4)	+++ Moderate
2: Severe COVID-19 infection, seronegative at baseline	1 RCT	Serious Short ff-up	Not assessed	Not serious	Not serious	Serious	1/8471 (0.01)	15/8505 (0.18)	93.4 (57.1-99.8)	+++ Moderate
3. Asymptomatic COVID-19 infection, seronegative at baseline	1 RCT	Serious Short ff-up	Not assessed	Not serious	Serious	Very Serious	13/3248 (0.40)	33/3041 (1.09)	63.6 (29-82.4)	++ Low
4. Any COVID-19 infection, seronegative at base line	1 RCT	Serious Short ff-up	Not assessed	Not serious	Not serious	Serious	19/3248 (0.58%	56/3041 (1.84)	68.8 (46.7-82.5)	+++ Moderate
5: Symptomatic COVID-19 infection, older adults (>=60yo), seronegative at baseline	1 RCT	Serious Short ff-up	Not assessed	Not serious	Serious	Very Serious	5/893 (0.56)	16/965 (1.66)	67.8 (8-90)	++ Low
6. Symptomatic COVID-19 infection, with pre-existing medical condition (at risk for severe infection)	1 RCT	Serious Short ff-up	Not assessed	Not serious	Not serious	Serious	12/2328 (0.52)	37/2518 (1.47)	66.2 (33.8-84)	+++ Moderate
7. Symptomatic COVID-91 infection, children (<18yo)	0	Not assessed	Not assessed	Not assessed	Not assessed	Not assessed	n/a	n/a	n/a	n/a
8. Any COVID-19 infection, B.1.1.7/Alpha variant	1 RCT	Serious Missing data Short ff-up	Not assessed	Not serious	Serious (very low event counts)	Very Serious	1/8471 (0.01)	3/8502 (0.04)	—	++ Low
9. Any COVID-19 infection, B.1.151/Beta variant	2 OBS	Very serious Uncontrolled confounders	Not serious	Serious immunologic	Not assessed	Very Serious	(titers)	(titers)	reduced	+ very Low
10. Any COVID-19 infection, B.167.2/Delta lineage	1 OBS	Serious Missing data Short ff-up	Not assessed	Not serious	Not serious	Not serious	13/8471 (0.15)	37/8502 (0.44)	65.2 (33.1-83)	+ Low

Appendix 7. Summary of Findings Table on the Safety of BBV152

COMPARISON : BBV152 vs placebo									
Safety Outcome	Quality Assessment					Summary of Findings			Certainty
	Risk of Bias	Inconsistency	Indirectness	Imprecision	Overall Assessment	Vaccine	Control	Relative Risk (95%CI)	
1: Solicited adverse reaction	Not serious	Not serious	Not serious	Serious	Serious	1223/12879 (9.5%)	1136/12874 (8.8%)	1.08 (0.996 to - 1.162)	+++ Moderate
2: Local adverse reaction	Not serious	Not serious	Not serious	Serious	Serious	709/12879 (5.5%)	659/12874 (5.12%)	1.08 (0.97 to - 1.19)	+++ Moderate
3: Any systemic adverse events	Not concern	Not serious	Not serious	Not serious	Not Serious	562/12879 (4.4%)	452/12874 (3.5%)	1.24 (1.1-1.40)	++++ High
4: Serious adverse event	Serious (short ff-up)	Not serious	Not serious	Not serious	Serious	39/12879 (0.30%)	60/12874 (0.47%)	0.64 (0.43-0.97)	+++ Moderate
5: Related serious adverse event (All medically attended adverse events (MAAEs)	Serious (short ff-up)	Not serious	Not serious	Serious	Serious	301/12879 (2.3%)	319/12874 (2.5%)	0.94 (0.81-1.1)	++ Low
6: Withdrawals due to adverse event	Not assessed	Not assessed	Not assessed	Not assessed	Not assessed	Not assessed	Not assessed	Not assessed	Not assessed
7: Death	Not serious (short ff-up)	Not serious	Not serious	Serious	Serious	5/12879 (0.04%)	10/12874 (0.08%)	0.5 (0.17-1.46)	+++ Moderate

Appendix 8. Ongoing Trials Registered at the Clinicaltrials.gov Registry on BBV152

NCT Number	Title	Status	Outcome Measures	Age	Phases	Study Designs	Completion Date	Locations	URL
NCT04471519	Whole-Virion Inactivated SARS-CoV-2 Vaccine (BBV152) for COVID-19 in Healthy Volunteers	Active, not recruiting	Phase 1: Occurrence of adverse events and Serious Adverse events|Phase 2: Evaluation of Neutralizing Antibody Titers|Phase 1: Evaluation of Neutralizing Antibody Titers|Phase 2: Occurrence of adverse events and Serious Adverse events	12 Years to 65 Years Â (Child, Adult, Older Adult)	Phase 1|Phase 2	Allocation: Randomized|Intervention Model: Parallel Assignment|Masking: Quadruple (Participant, Care Provider, Investigator, Outcomes Assessor)|Primary Purpose: Prevention	30-Jun-21	King George Hospital, Visakhapatnam, Andhra Pradesh, India|All India Institute of Medical Sciences, Patna, Bihar, India|Pt BD SHARMA,PGIMS/UHS, Rohtak, Haryana, India|Jeevan Rekha Hospital, Belgaum, Karnataka, India|Gillukar Multispeciality Hospital, Nagpur, Maharastra, India|All India Institute of Medical Sciences, Delhi, New Delhi, India|Institute of Medical Sciences and SUM Hospital, Bhubaneswar, Orissa, India|SRM Hospital & Research center, Chennai, Tamilnadu, India|Nizam's Institute of Medical Sciences, Hyderabad, Telangana, India|Rana Hospital and Trauma Center, Gorakhpur, Uttar Pradesh, India|Prakhar Hospital, Kanpur, Uttar Pradesh, India|Redkar Hospital and Research Centre, Goa, India	https://ClinicalTrials.gov/show/NCT04471519
NCT04641481	An Efficacy and Safety Clinical Trial of an Investigational COVID-19 Vaccine (BBV152) in Adult Volunteers	Active, not recruiting	First occurrence of Virologically confirmed (RT-PCR positive) symptomatic cases of COVID-19.|First occurence of Virologically confirmed (RT-PCR positive) symptomatic cases of COVID-19 based on the case definition for the secondary efficacy symptomatic endpoint.|Virologically confirmed (RT-PCR positive) severe cases of COVID-19|Virologically confirmed COVID-19 cases of any severity occurring among participants 18 through 59 years of age and â‰¥60 years of age.|Virologically confirmed COVID-19 asymptomatic and symptomatic cases occurring from two weeks after the second vaccination.|Reactogenicity and Safety|The occurrence of enhanced respiratory disease episodes.|Immunogenicity: Lot-to-Lot consistency of three consecutive GMP Lots|Geometric Mean Titer (GMT) of SARS-CoV-2 Specific Neutralizing Antibody (nAb)	18 Years to 99 Years Â (Adult, Older Adult)	Phase 3	Allocation: Randomized|Intervention Model: Parallel Assignment|Masking: Quadruple (Participant, Care Provider, Investigator, Outcomes Assessor)|Primary Purpose: Prevention	Dec-22	Pt BD SHARMA,PGIMS/UHS, Rohtak, Haryana, India	https://ClinicalTrials.gov/show/NCT04641481
NCT04918797	COVAXIN in a Pediatric Cohort	Recruiting	Reactogenicity|Immunogenecity|Immunogenicity	2 Years to 18 Years Â (Child, Adult)	Phase 2|Phase 3	Allocation: N/A|Intervention Model: Single Group Assignment|Masking: None (Open Label)|Primary Purpose: Prevention	25-Jan-22	Victoria Government Hospital, Visakhapatnam, Andhra Pradesh, India|All India Institute of Medical Sciences, Patna, Bihar, India|Cheluvambha Hospital, Mysore, Karnataka, India|Meditrina Institute of Medical Sciences, Nagpur, Maharashtra, India|Jawahar Lal Nehru Medical college, Ajmer, Rajasthan, India|Pranam Hospitals Hyderabad, Hyderabad, Telangana, India|Prakhar Hospital, Kanpur, Uttar Pradesh, India	https://ClinicalTrials.gov/show/NCT04918797
NCT04834869	COVID-19 Vaccines Safety Tracking (CoVaST)	Recruiting	Local Side Effects|Systemic Side Effects|Unrecognized Side Effects	18 Years and older Â (Adult, Older Adult)		Observational Model: Other|Time Perspective: Prospective	31-Jan-22	American College of Physicians, Philadelphia, Pennsylvania, United States|McMaster University, Hamilton, Ontario, Canada|University of Split, Split, Croatia|Masaryk University, Brno, Czechia|University of Tartu, Tartu, Estonia|Jimma University, Jimma, Ethiopia|Justus-Liebig University Giessen, Giessen, Germany|University of Ghana, Accra, Ghana|Sinaloa's Pediatric Hospital, CuliacÃ¡n, Mexico|Medical University of Silesia, Katowice, Poland|Nursing School of Coimbra, Coimbra, Portugal|Irkutsk Scientific Center of Siberian Branch of Russian Academy of Sciences, Irkutsk, Russian Federation|University of Belgrade, Belgrade, Serbia|University of Ljubljana, Ljubljana, Slovenia	https://ClinicalTrials.gov/show/NCT04834869

Q4. Is NVX-Cov2373 (Novavax) effective and safe in the prevention of COVID-19 infection?

As of 27 December 2021

RECOMMENDATIONS

We suggest the use of NVX-CoV2373 (Novavax), given as 5ug (with 50ug Matrix M1 adjuvant) two doses, intramuscular, 21 days apart, for the prevention of symptomatic and severe SARS-CoV-2 infection in healthy adults. *(Low certainty of evidence; Weak recommendation)*

We suggest the use of NVX-CoV2373 (Novavax), given as 5ug (with 50ug Matrix M1 adjuvant) two doses, intramuscular, 21 days apart, for the prevention of symptomatic SARS-CoV-2 infection in older adults (>65 years old). *(Low certainty of evidence; Weak recommendation)*

We suggest the use of NVX-CoV2373 (Novavax), given as 5ug (with 50ug Matrix M1 adjuvant) two doses, intramuscular, 21 days apart, for the prevention of symptomatic SARS-CoV-2 infection in adults with comorbidities. *(Moderate certainty of evidence; Weak recommendation)*

We suggest against the use of NVX-CoV2373 (Novavax), for the prevention of symptomatic SARS-CoV-2 infection in the immunocompromised population (specifically HIV positive individuals). *(Very low certainty of evidence; Weak recommendation)*

We suggest against the use of NVX-CoV2373 for the prevention of symptomatic SARS-CoV-2 infection among pregnant and lactating women. *(No direct evidence; Weak recommendation)*

In areas where the Alpha variant is predominant, we suggest the use of the NVX-CoV2373 (Novavax) given as 5ug (with 50ug Matrix-M1 adjuvant), two doses, intramuscular, 21 days apart, to prevent symptomatic SARS-CoV-2 infection. *(Low certainty of evidence; Weak recommendation)*

In areas where the Beta variant is predominant, we suggest against the use of the NVX-CoV2373 (Novavax) to prevent symptomatic SARS-CoV-2 infection. *(Low certainty of evidence; Weak recommendation)*

There is insufficient evidence to recommend for or against the use of NVX-2373 for the prevention of symptomatic SARS-CoV-2 infection among children.

We recommend against the use of the NVX-CoV2373 (Novavax) in individuals who have known allergies to its contents/excipients, such as Matrix-M1. *(Best practice statement)*

Consensus Issues
The Panel highly considered equity issues in the recommendations for the use of NVX-2373 in the prevention of SARS-CoV-2 infection. However, in the case of populations who were at high risk of severe infection and are immunocompromised such as the HIV positive individuals and in the pregnant and lactating women, the Panel took into consideration the lower efficacy estimates and the wide confidence interval with the lower border breaching the 30% threshold combined with the signal of additional harm with the higher adverse reaction risk so that a recommendation against the use of the vaccine was given.

KEY FINDINGS

The evidence base on the efficacy and safety of NVX-Cov2373, as of November 12, 2021, includes five RCTs and one comparative cohort study. Results show that the vaccine provides excellent protection against symptomatic COVID-19 among healthy adults, among older persons above 65 years of age, among high-risk groups and those with comorbidities. The vaccine is highly immunogenic. Effectiveness is preserved against the Alpha variant, but one study showed potential loss of effect against the Beta variant. The vaccine is reactogenic.

INTRODUCTION

The NVX-Cov2373 vaccine (manufactured by US company Novavax) is a recombinant nanoparticle vaccine containing the spike glycoprotein of the prototype strain plus Matrix-M adjuvant. The vaccine is given intramuscularly in 2 doses, 21 days apart. It is stable and can be stored at temperatures 2-8°C.[1] It received its first authorization for emergency use from Indonesia last November 1, 2021.[2]

This review describes the current available evidence supporting the efficacy, effectiveness and safety of NVX-Cov2373 (Novavax) in the prevention of COVID-19.

REVIEW METHODS

Search Strategy

The search followed the strategy used for all the vaccine reviews in this series. Briefly, this covered PubMed, living COVID-19 evidence registries including the Living Overview Evidence platform, the COVID-NMA and the Metaevidence.org, the reference list of the WHO Situational reports, the WHO COVID-19 literature on coronavirus disease database and the VIEW-Hub Resource Library.

Assessment of Risk of Bias and Certainty of Evidence

The assessment of the risk of bias and certainty of evidence for this review followed that of the vaccine reviews in this series. Briefly, the risk of bias of randomized controlled trials was assessed using the Cochrane Risk of Bias tool version 1, which includes the following domains: random sequence generation; allocation concealment; blinding of participants and personnel; blinding of outcome assessment; incomplete outcome data; and selective reporting.

The risk of bias of observational comparative studies will be assessed using the same domains as the Cochrane Risk of Bias v.1 tool. Sequence generation and allocation concealment will be assessed by default as ‘high risk of bias’ given the non-

randomized nature of these studies. In addition to the Cochrane RoB tool item, assessment of the control of the following confounders were done: age, presence of comorbidities and the risk of exposure, and if applicable, the prevailing variant of concern (for sampling performed at different time periods for the treatment groups). For each study, a pragmatic approach will used to assess the risk of confounding bias.

The following were considered in sequence:

- Was the prognostic confounder considered (yes/no)? If ‘no’, the study is at ‘high’ risk of bias for this confounder. If ‘yes’ go to question 2.
- Was the confounder balanced between the intervention(s) and control group(s) (yes/no)? If ‘yes’, the study is a ‘low’ risk of bias. If ‘no’, go to question 3.
- Was the confounder controlled for in the analysis, for example by statistical adjustment such as univariate or multivariate analysis or propensity score matching? If ‘yes’ the study was at ‘low’ risk of bias. If ‘no’ the study was ‘high’ risk of bias.

If majority or all the confounders were controlled for, the study was assessed as low risk for confounding but overall, the study were classified as being high risk or having serious risk of bias.

Non-comparative observational studies (e.g. case series, single cohort) were assessed to be of high/serious risk of bias.

General Search Results

As of November 12, 2021, six study reports were identified on the effect of NVX-CoV2373 on SARS-CoV-2 infection. Two were Phase 3 randomized controlled trials (RCT), three were Phase 1-2 RCTs and one was a comparative cohort study. Two studies provided clinical efficacy data, two reported on immunogenicity, four provided safety data, and two reported on the effect of the vaccine on the Alpha and Beta variants.

All the RCTs were assessed as low risk of bias.

Table 2 presents the risk of bias assessment of the included studies.

RESULTS

Clinical Efficacy

Two Phase 3 RCTs reported sufficient protection provided by NVX-CoV2373 against symptomatic COVID-19 after a follow up of 2-3 months. Both studies were consistent in their reported vaccine effectiveness rates overall and in the different subgroups and settings.[1,3]

NVX-CoV2373 provides excellent protection against symptomatic COVID-19 with vaccine effectiveness of 89.7% (95% CI 80.2-84.6) and 90.4% (95% CI 82.9-94.6), measured at least 7 days after the second dose. All cases in the vaccine treatment groups for both studies were mild. Hence, VEs for moderate and severe were 100%, with wide confidence intervals for the VE for severe due to small event counts. Two deaths related to COVID-19 were reported in one trial, one in the vaccine group and one in the placebo group.[1] The death in the vaccine group occurred before the second dose. VEs for subgroups also showed good protection offered by NVX-CoV2373: VE for older persons aged 65 years and older was reported at 88.9% (95%

CI 12.8-98.6), for high risk groups at 91.0% (95% CI 83.6-95.0) and for those with comorbidities at 90.9% (95%CI 70.2-97.2).

VE after the first dose was available from one study at 83.4% (95% CI 73.6-89.5).[1]

On the other hand, one Phase II RCT done which included 18- to 84-year old patients showed a lower overall VE at 49.4% (95% CI 6.1-72.8). Notable for this study was that it included stable HIV positive patients, and it was conducted during the Beta variant predominance in South Africa. Among the HIV negative patients, VE was observed to be 60.1% (95% CI 19.9-80.1).[4]

The detailed study characteristics of these Phase 3 trials are in Table 3. The Phase 2 study details are in Table 4.

Immunogenicity
Immunogenicity of NVX-CoV2373 was reported by the Phase 1 and 2 studies. Both were consistent in their findings that the vaccine is highly immunogenic, with significant geometric mean fold rises (GMFR) from baseline for anti-spike IgG and neutralizing antibodies compared to placebo. Seroconversion rates were uniformly high. Values were higher in the vaccine recipients when compared to the convalescent subpopulation. Lower GMFRs and seroconversion rates were observed in the older subpopulations. Minimal differences were seen between the low (5µg) and high (25µg) doses. ELISA anti-spike IgG geometric mean ELISA units (GMEUs) and neutralizing antibody geometric mean fold rises (GMFRs) were greater in the adjuvanted vaccine than those without the adjuvant. Strong T-cell response also demonstrated in the adjuvanted, with similar response levels reached regardless of dose.[5,6]

Real World Evidence: Effectiveness
No real-world evidence on NVX-CoV2373 was found.

Clinical Efficacy and Effectiveness On Special Populations of Interest (Older persons, Children, Immunocompromised, Pregnant Women)
Older population
One Phase 3 trial reported sufficient protection given by NVX-CoV2373 for the older population, with VEs at 88.9% (95% CI 12-98).[1] The Phase 1-2 trials showed significantly lower immunogenic response among the older compared to the younger population.[5-6] However, high seroconversion rates after the 2-dose vaccine regimen (97% for anti-spike binding IgG and 100% for neutralizing antibodies) were still achieved, and the titers seen from the sera of vaccinated older persons were higher than titers from convalescent plasma.[5]

Immunocompromised: HIV Positive patients
One Phase 2 study, which included HIV positive patients, showed only an infection rate of 1.56% among vaccinated cases after a 35-day follow-up, against a 27.7% rate among the unvaccinated. Based on these rates, the calculated (unadjusted) VE for HIV positive patients is 94.4%.[4]

Children, pregnant and lactating women
No study was identified providing information on the effect of NVX-CoV2373 on children, pregnant and lactating women and the immunocompromised.

Safety

Regulatory Clinical Trial Evidence

The regulatory trials (Phase 1-3) of NVX-CoV2373 all provided safety information. Results were consistent in these regulatory trials.[1,3,5,6]

Solicited adverse events (local and systemic) were seen more frequently in the vaccine group compared to placebo. Most were mild to moderate and transient. Rates were higher in the young vaccine recipients compared to the older subgroup and in the second dose compared to the first. The most common local adverse event was injection site pain. The most common systemic adverse events reported were headache, myalgia, and fatigue.

Unsolicited adverse events were slightly higher in the vaccine group but not statistically significantly different. Serious adverse events, medically-attended adverse events, and discontinuation and death rates were low and similar between groups. Serious adverse events noted in the vaccine group were mostly assessed as non-vaccine related. One related serious adverse event (myocarditis) was reported in one vaccine recipient in one trial, which occurred 3 days after the second dose.[1]

Real World Evidence of Safety

As NVX-CoV2373 has not been authorized for use in any country, no real-world evidence is available.

Reports on Adverse Events of Interest

Apart from those stated in the clinical trials, no report on adverse events of interest was found.

Effectiveness Against Variants

Alpha

The two Phase 3 trials demonstrated adequate clinical efficacy of NVX-CoV2373 against symptomatic COVID-19 infection caused by the Alpha variant, with VE rates of 86.3% (95% CI 71.3-93.5)[1] and 93.6% (95% CI 81.7-97.8).[3]

Beta

One Phase 2 trial showed reduced and possible ineffectiveness of NVX-CoV2373 against the Beta variant, with a VE of 51% (95% CI -0.6 to 76.2).[4] One immunogenicity study based on sera from 23 vaccine recipients taken 14 days after the 2nd dose showed a 6.8- to 14.5-fold reduction in antibody titers with the Beta strain compared to D614G.[7]

Gamma, Delta

No report has been identified that studied the effect of NVX-CoV2373 on the Gamma and Delta variants.

Booster Vaccination

No study was identified using NVX-CoV2373 in a booster vaccination regimen.

Details of the study characteristics and results included in this review are presented in Table 4.

AUTHORIZATIONS

Indonesia is the first country to grant emergency use authorization for NVX-CoV2373 (Novavax) on November 1, 2021. The application for WHO EUL listing is under process as of November 13, 2021.

RESEARCH GAPS

The following are identified research gaps regarding NVX-Cov2373 vaccination for COVID-19 infection prevention: The efficacy/effectiveness of BBIBP-CorV in special populations such as the older and very old patients, children, immunocompromised (eg. HIV) populations; the duration of protection / long term efficacy or effectiveness; its long-term safety; its clinical efficacy and effectiveness against infection with variants of concern such as the Delta variant; studies on heterologous primary vaccination; and its use in booster vaccinations.

ONGOING TRIALS

The search performed on November 12, 2021 of the Clinicaltrials.gov registry showed six active trials on NVX-Cov2373. Two of the trials have released interim reports. One trial is on children. Table 7 details these trials.

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Appendix 1. Evidence to Decision

Table 1. Summary of initial judgements prior to the panel discussion (N=10)

FACTORS	JUDGEMENT						RESEARCH EVIDENCE/ADDITIONAL CONSIDERATIONS
Problem	No	Yes (10)					
Benefits	Large (8)	Moderate (2)	Small	Uncertain			• NVX-CoV2373 provides excellent protection against symptomatic COVID-19 with vaccine effectiveness of 89.7% (95%CI 80.2 to 84.6) and 90.4% (95%CI 82.9 to 94.6), measured at least 7 days after the second dose.
Harm	Large	Moderate	Small (6)	Trivial (2)	Varies (1)	Uncertain (1)	• Most adverse events were mild to moderate and transient, with higher rates among: (1) young vaccine recipients, and (2) after second dose. • Most common local adverse event: injection site pain. • Most common systemic adverse events: headache, myalgia and fatigue. • One related serious adverse event: myocarditis.
Certainty of evidence	High (2)	Moderate (4)	Low (4)	Very low			• Low to high
Balance of effects	Favors vaccine (7)	Probably favors vaccine (3)	Does not favor diagnostic/treatment or no diagnostic/treatment	Probably favors no diagnostic/treatment	Favors no diagnostic/treatment	Don't know	
Values	Important uncertainty or variability (1)	Possibly important uncertainty or variability (4)	Possibly NO important uncertainty or variability (4)	No important uncertainty or variability (1)			
Resources required	Uncertain	Large cost	Moderate Cost (6)	Negligible cost (3)	Moderate savings	Large savings (1)	• Novavax is priced at P366. Two doses are needed per individual. • Can be stored, transported and handled at standard refrigerator temperatures (2-8°C).
Certainty of evidence of resources required	No included studies (10)	Very low	Low	Moderate	High		
Equity	Uncertain	Probably reduced (2)	Probably no impact (1)	Probably increased (4)	Increased (1)	Varies (2)	• Addresses wide disparity in vaccine coverage: 85.1% fully-vaccinated senior citizens in NCR; only 28.3% in BARMM.
Acceptability	Uncertain	No	Probably no	Probably yes (4)	Yes (6)	Varies	• The Philippine FDA granted emergency use authorization for NVX-CoV2373 (Novavax) last November 18, 2021
Feasibility	Uncertain	No	Probably no	Probably yes (4)	Yes (6)	Varies	

Appendix 2. Risk of Bias Assessment of Included Studies

Study ID	Design	Randomization	Allocation Concealment	Blinding Particip	Blinding Carer/ Assessor	Followup	Selective Reporting	Others	Age	Comorbidities	Exposure	Confounding	OVERALL
Heath	RCT	LOW	LOW	UNCLEAR	LOW	HIGH [a]	LOW	NA	NA	NA	NA	NA	LOW
Dunkle	RCT	LOW	LOW	LOW	LOW	HIGH [a]	LOW	NA	NA	NA	NA	NA	LOW
Formica	RCT	LOW	LOW	LOW	LOW	LOW	LOW	NA	NA	NA	NA	NA	LOW
Keech	RCT	LOW	LOW	LOW	LOW	LOW	LOW	NA	NA	NA	NA	NA	LOW
Shinde	RCT	LOW	LOW	LOW	LOW	HIGH [b]	UNCLEAR	NA	NA	NA	NA	NA	LOW
Shen	Comparative cohort, immuno	HIGH	HIGH	UNCLEAR	UNCLEAR	LOW	UNCLEAR	NA	HIGH	HIGH	HIGH	HIGH	HIGH

[a] interim report
[b] interim report, safety data not reported for all

Appendix 3. Characteristics of the Randomized Controlled Trial (Ph3) on the Efficacy and Safety of NVX-Cor2373

Trial Identifier	**PREVENT-19**	
Vaccine	**NVX-CoV2373**	
Data Sources	**Heath 2021 NEJM, supplem**	**Dunkle MedRxiv**
POPULATION		
Total Randomized	15,187	29,949
Inclusion Criteria		
• Age	18-84 years, healthy	At least 18 years
• Gender	Yes	Yes
• Race/ Ethnicity	Yes	Yes
• Immunocompromised	Excluded, but included stable HIV infection	Well controlled HIV infection
• Pregnant and breastfeeding	excluded	excluded
• With concomitant comorbidities	With stable chronic medical conditions	With stable chronic medical condition
• With previous COVID infection	excluded	excluded
• With known previous exposure to COVID	Not mentioned	excluded
• Seropositive at baseline	included	included
Exclusions	History of lab confirmed COVID-19 infection Participation in other COVID-19 studies Administration of immunoglobulins and other blood products within 3 months Immunosuppressive or immunodeficient state Pregnancy, lactation, willingness/intention Diagnosis/treatment for cancer Bleeding disorder, anticoagulant Received any live vaccine within 4 weeks or any vaccine Significant chronic cardiovascular, enod, medical problem, neurologic Any autoimmune or immunodeficiency disease/condition	Known previous lab-confirmed COVID infection or known immunosuppression
INTERVENTION (VACCINE)		
Type	Protein subunit	
Active substance	Spike protein nanoparticle	
Trial-specific considerations		
Dosing and administration	2 x 5ug SARS-CoV-2 rS with 50ug Matrix M1 adjuvant intramuscularly, 21 days apart (subgroup received influenza vaccine with the first dose, given as open label)	2 x 5ug SARS-CoV-2 rS with 50ug Matrix M1 adjuvant intramuscularly, 21 days apart
Number randomized	7569	19714 (17,312 per protocol)
COMPARATOR		
Type, dosing and administration	Saline, 0.5ml, intramuscular, 21 days apart	Saline, 0.5ml, intramuscular, 21 days apart
Number randomized	7020	9868 (8140 per protocol)
OUTCOMES		
Primary efficacy endpoints	Efficacy against occurrence of virologically confirmed symptomatic mild, moderate, or severe COVID-19 from 7 days after the second dose, as defined by the FDA	Preventing the first episode of PRT-PCR confirmed symptomatic mild, moderate, severe COVID-19 (as per FDA criteria) with onset of >=7 days after the second dose
Primary safety endpoints	Solicited local and systemic adverse	-

	events for 7 days after each dose Unsolicited adverse events through 28 days after 2nd dose Serious adverse events, adverse events of special interest, medically attended adverse events from first dose through 1 year after the 2nd dose (safety data excludes the 400 participants who were enrolled in the influenza vaccine substudy) ** SEE SUPPL TS3	
Secondary endpoints Exploratory endpoints Immunogenicity	- VE against symptomatic COVID by SARS-CoV-2 strain (variants)	- Protection against RT-PCR confirmed COVID 19 due to non-VOC/VOI strains - Infection by subgroups - Safety, reactogenicity
Subgroups considered in the analysis		
● Age	Median age = 56 years, 27.9% were 65 years or older	Median age : 47 years 11.8% were 65 years or older
● Sex	48% females	48.2% females
● Ethnic groups	2.9% Asians	
● Baseline seropositivity status / evidence of previous infection	4.2%	6.3% (NVX), 6.9% (pla)
● Medical comorbidities	44.6% had one or more comorbidity	47.3% with one or more comorbidity
● Immunocompromised / HIV disease	Not mentioned	
● Risk for acquiring COVID infection	Not mentioned	
● Risk for progression to severe COVID	44.6%	
FOLLOW-UP		
Planned	1 year	
At data cutoff of interim report (first interim analysis)	Around 3 months (98 days)	
Date of Data Cut-off date for latest available trial data	Not mentioned	
METHODS / OTHER TRIAL PARAMETERS		
Risk of bias	Centralized IVRS Cases determined in a blinded fashion Observer-blind	
Study Sites	33 sites in the UK	
Study Sponsor	Novavax	
Type of report available as of this rapid review	Published interim report	
Others		
Risk of bias	Centralized IVRS Cases determined in a blinded fashion Observer-blind	

Appendix 4. Characteristics and Results of Clinical Trials on NVX-Cov2373

Study ID	Design	Population	Intervention / Comparison	Outcome (Followup/Assessment) Result
Shinde	RCT (Ph2) Double-blinded Interim report at 35 days Follow-up (planned 1 year)	18 to 84 years, with a subgroup of 18 to 64 years with HIV infection (stable) N=4387 randomized Vac: 2199 Pla: 2188 30% seropositive at baseline 41 sera samples used for genomic sequencing	5ug NVX-CoV2373 with 50ug Matrix-M1 adjuvant, 2 doses, 21 days apart Placebo (saline)	Symptomatic COVID infection starting D8 after 2nd dose Vac: 15, mild to moderate Pla: 29, one severe VE = 49.4% (6.1 to 72.8) Subgroup: HIV negative: 60.1% (19.9 to 80.1) Seropositive at baseline: 52.2% (24.8 to 81.7) Effectiveness against Beta (41 samples) VE = 51.0% (-0.6 to 76.2) for HIV negative VE = 43% (-9.8 to 70.4) for HIV positive and negative Reactogenicity (7 days) - more severe local adverse events among seronegative participants in the vaccine group (4% vs 1%) - most common systemic adverse reaction: headache, muscle pain, fatigue - more common in vaccine group were medically attended AEs and serious A2 13. vs.6 / 2.vs 1
Shen	Comparative cohort (vs mRNA-1273 and convalescent plasma) Immunogenicity study	Randomly selected sera from convalescent persons and vaccine recipients mRNA-1273: 26 NVX-CoV2373: 23	Reference strain: D614G	GMT ID50 titer vs Beta 14.5 times lower for NVX GMT ID50 titer vs B.1.429 8.6x lower GMT ID80 vs Beta 6.8x lower
Keech	RCT Ph1-2	18 to 59 years old, healthy N = 133	NVX-CoV2373, 5ug and 25 ug, with or without Matrix M1 adjuvant, 2 doses, 21 days apart Placebo (83 received the vaccine with adjuvant, 25 without adjuvant, 23 placebo)	Antispike titers at days 0,7,21,28 and 35 - Geometric mean fold rises (GMFR) of vaccine recipients with adjuvant exceeded those without at day 21, further increase at day 35 - Responses in the 2-dose 5 and 25-ug adjuvanted regimen were similar NAB titers – response similar to above Reactogenicity at 7 days - absent or mild in the majority, similar across groups - 2 participants in the vaccine groups have severe AEs (headache, fatigue and malaise) Adverse events through day 35 - no serious AE or AE of special interest

Formica	RCT Ph 2 Observer blinded	18 to 84 y/o stable medical condition n= 1288 randomized placebo = 255 5ug 2 doses = 257 5ug one dose = 257 25ug 2 doses = 258 25ug 1 dose = 256	NVX-CoV2373, 5ug and 25 ug, with or without Matrix M1 adjuvant, 2 doses, 21 days apart Placebo	Antispike IgG titers and seropositivity at 0, 21, 35 GMFRs similar in both doses Seroconversion rates similar 98 vs 100 Responses significantly lower in the older age group Neutralizing Ab Similar pattern of response as in IgG Reactogenicity within 7 days - local AEs more in high dose for tenderness and pain - local AEs higher in younger - no grade 4 events - systemic more frequent in vaccine group Unsolicited AEs Similar rates: pla (17%), low dose (17%), high dose (18%) 7 discontinuations, 2 in placebo, 5 in vaccine 8 SAEs in vaccine group, all unrelated Authors conclusion: Matrix-M1 adjuvanted rSARS-CoV-2 nanoparticle vaccine was highly immunogenic and well tolerated in younger and older participants.
Heath	RCT Ph 3 Randomized, observer-blinded, placebo-controlled	18 to 84 yrs.old 27.9% aged 65 and older 44.6% with comorbidities conducted in the UK N = 15,187	NVX-CoV2372 5ug x 2 doses, 21 days apart VS Placebo	Virologically confirmed symptomatic COVID-19 at least 7 days after 2nd dose VE against symptomatic COVID-19 89.7% (95% CI 80.2, 94.6) all 5 severe cases occurred in the placebo group VE in participants 65 years old and over: 88.9% (95% CI 12.8, 98.6) VE against Alpha: 86.3% (95% CI, 71.3 to 93.5) VE against non-Alpha: 96.4% (95% CI, 73.8 to 99.4) Solicited and unsolicited local and systemic AE more frequently reported in vaccine group
Dunkle	RCT Ph3 Randomized, observer-blinded, placebo-controlled	United States and Mexico N = 29,949 12.6% 65 years or older		VE against RT-PCR confirmed symptomatic COVID-19 in naïve participants at least 7 days from 2nd dose All moderate to severe cases occurred in placebo group VE against VOC/VOI 92.6% (95% CI 83.6, 96.7) – mainly alpha variant VE against symptomatic COVID-19 90.4% (95% CI 82.9, 94.6) VE against moderate- to- severe COVID-19 100% (87, 100) VE against severe COVID-19 100% (34.6, 100) post hoc analysis

Appendix 5. Summary of Findings Table of Efficacy of NVX-CoV2373

Efficacy Outcome (at >7 days after dose 2)	N Study design	Quality Assessment					Summary of Findings			Certainty
		Risk of Bias	Inconsistency	Indirectness	Imprecision	Overall Assessment	Vaccine n/N (%)	Control n/N (%)	Vaccine Efficacy (CI)	
1: Symptomatic COVID-19 infection, seronegative at baseline	3 RCT	Serious (short ffup)	Serious (1 study with low VE)	Not serious	Not serious	Serious	10/7020 (0.1%)[a] 14/17312 (0.08%)[b] 15/1357 (1.1%)[c]	96/7019 (1.4%)[a] 63/8140 (0.78%)[b] 29/1327 (2.2)[c]	89.7% (80.2, 94.6)[a] 90.4% (82.9, 94.6)[b] 49.4% (6.1, 72.8)[c]	++ Low
2: Severe COVID-19 infection	2 RCT	Serious (short ffup)	Not serious	Not serious	Serious	Serious	0/7207 (0%)[a] 0/17312(0%)[b]	5/7019 (.07%)[a] 4/8140(4.2%)[b]	90.9% (-0.64, 100)[a] 100% (34.6, 100%)[b]	++ Low
3: Asymptomatic COVID-19 infection, seronegative at baseline	0	Not available	na	na	na	na	na	na	na	na
4: Any COVID-19 infection, seronegative at base line	0	Not available	na	na	na	na	na	na	na	na
5: Symptomatic COVID-19 infection after first dose, before the second dose	1 RCT	Serious (short ffup)	Not assessed	Not serious	Not serious	Serious	na	na	83.4% (73.6, 89.5)[a]	na
6: Symptomatic COVID-19 infection, older adults (>=65yo), seronegative at baseline	1 RCT	Serious (short ffup)	Not assessed	Not serious	Serious	Serious	1/1953 (0.05%)[a]	9/1957 (0.5%)[a]	88.9 (20.2, 99.7)[a]	++ Low
7: Symptomatic COVID-19 infection, with pre-existing medical condition	2 RCT	Serious (short ffup)	Not serious	Not serious	Not serious	Serious	3/3117 (0.09%)[a] 7/8109 (0.08%)[b]	33/3143 (1.0%)[a] 34/3910 (0.9%)[b]	90.9 (70.4, 97.2)[a] 90.8 (79.2, 95.9)[b]	+++ Moderate
8: Symptomatic COVID-19 infection, children (<18yo)	0	Not available	na	na	na	na	na	na	na	na
9: Symptomatic COVID-19 infection, HIV positive adults	1 RCT	Serious (short ffup)	Not assessed	Not serious	Very serious (wide CI)	Very Serious	4/76 (5.27%)[c]	2/72 (2.78%)[c]	-89.0% (-903.0, 64.21)[c]	+ Very Low
10: Any COVID-19 infection, B.1.1.7/Alpha variant	2 RCT	Serious (short ffup)	Not assessed	Not serious	Not serious	Serious	8/7020 (0.1%)[a] 4/17312 (0.02%)[b]	58/7020 (0.8%)[a] 27/8140 (0.33%)	86.3 (71.3, 93.5)[a] 93.6% (81.7, 97.8)[b]	+++ Moderate
11. Any COVID-19 infection, B.1.151/Beta variant	1 RCT	Serious (short ffup)	Not assessed	Not serious	Serious	Serious			43% (-9.8, 70.4)[a]	++ Low
12. Any COVID-19 infection, B.167.2/Delta variant	0	Not available	na	na	na	na	na	na	na	na

Appendix 6. Summary of Findings Table on the Safety of NVX-CoV2373

Safety Outcome	N Study design	Quality Assessment					Summary of Findings			Certainty
		Risk of Bias	Inconsistency	Indirectness	Imprecision	Overall Assessment	Vaccine	Control	Relative Risk (95%CI)	
1: Solicited adverse reaction	0	Not available	na	na	na	na	na	na	na	na
2: Local adverse reaction	2 RCT	Not serious	Not assessed	Not serious	Not serious	Not serious	57.6% (D1)[a] 76.6% (D2)[a] 58.0% (D1)[b] 78.0% (D2)[b]	17.9% (D1)[a] 16.4% (D2)[a] 21.1% (D1)[b] 21.7% (D2)[b]	3.2 (2.8, 3.7)[a] 4.7 (4.0,5.4)[a] 2.7 (2.4, 3.1)[b] 3.6 (3.2, 4.1)[b]	++++ High
3: Systemic adverse reaction	2 RCT	Not serious	Not serious	Not serious	Not serious	Not serious	45.7% (D1)[a] 64.0% (D2)[a] 47.7% (D1)[b] 69.5% (D2)[b]	36.3% (D1)[a] 30.0% (D2)[a] 40.0% (D1)[b] 35.9% (D2)[b]	1.3 (1,1, 1.4)[a] 2.1 (1.6, 2.9)[a] 1.2 (1.1, 1.3)[b] 1.9 (1.8, 2.1)[b]	++++ High
4. Unsolicited adverse event (28d)	3 RCT	Not serious	Not serious	Not serious	Not serious	Not serious	25.3%[a] 21.8[b] 17%[c]	20.5%[a] 18.2%[b] 17%[c]	1.2 (1.0, 1.5)[a] 1.4 (0.9,1.4)[b] 1.0	++++ High
5. Severe adverse event	1 RCT	Serious (short ffup)	Not serious	Not serious	Serious	Not serious	76/7569 (1.0%)[a]	64/7570 (0.8%)[a]	1.2 (0.85, 1.65)	++ Low
6: Serious adverse event	2 RCT	Serious (short ffup)	Not serious	Not serious	Serious	Not serious	0.6%[a] 1.2%[b]	0.6%[a] 1.3%[b]	1.0 (0.65,1.5)[a] 0.9 (0.7, 1.1)[b]	++ Low
7: Medically attended adverse events (MAAEs)	1 RCT	Serious (short ffup)	Not serious	Not serious	Not serious	Not serious	285/7569 (3.8%)[a]	295/7570 (3.9%)[a]	0.97 (0.8,1.1)[a]	+++ Moderate
7: Withdrawals due to adverse event	1 RCT	Serious (short ffup)	Not assessed	Not serious	Serious	Serious	17/7569 (0.2%)[a] 0.3%	16/7570 (0.2%) 0.1%	1.1 (0.5, 2.1)[a] 3.0 (0.3, 28.8)	++ Low
8: Death	1 RCT	Serious	Not assessed	Not serious	Serious	Serious	2/7569 (0.02%)[a]	1/7570 (0.01%)	2.0 (0.18, 22.1)[b]	++ Low

[a] Heath
[b] Dunkle
[c] Formica

Appendix 7. Ongoing Trials Registered at the Clinicaltrials.gov Registry on NVX-CoV2373 (as of Nov 12 2021)

NCT Number	Title	Status	Interventions	Sponsor /Collaborators	Age	Phases	Study Type	Study Designs	Start Date	Completion Date
NCT05112848	A Study to Evaluate Safety and Immunogenicity of a COVID-19 Vaccine in People Living with HIV at Risk for SARS-CoV-2 (COVID-19)	Not yet recruiting	Biological: NVX-CoV2373	Novavax	18 Years to 65 Years (Adult, Older Adult)	Phase 2	Interventional	Allocation: Randomized|Intervention Model: Parallel Assignment|Masking: Quadruple (Participant, Care Provider, Investigator, Outcomes Assessor) |Primary Purpose: Prevention	Nov-21	Jul-22
NCT04533399	A Study Looking at the Effectiveness and Safety of a COVID-19 Vaccine in South African Adults	Recruiting	Biological: SARS-CoV-2 rS/Matrix-M1 Adjuvant|Other: Placebo	Novavax| Bill and Melinda Gates Foundation	18 Years to 84 Years (Adult, Older Adult)	Phase 2	Interventional	Allocation: Randomized|Intervention Model: Sequential Assignment|Masking: Quadruple (Participant, Care Provider, Investigator, Outcomes Assessor) |Primary Purpose: Prevention	17-Aug-20	Nov-21
NCT04583995	A Study Looking at the Effectiveness, Immune Response, and Safety of a COVID-19 Vaccine in Adults in the United Kingdom	Active, not recruiting	Biological: SARS-CoV-2 rS/Matrix M1-Adjuvant|Other: Placebo|Biological: Licensed seasonal influenza vaccine	Novavax	18 Years to 84 Years (Adult, Older Adult)	Phase 3	Interventional	Allocation: Randomized|Intervention Model: Parallel Assignment|Masking: Quadruple (Participant, Care Provider, Investigator, Outcomes Assessor) |Primary Purpose: Prevention	28-Nov-20	14-Jan-22
NCT04611802	A Study to Evaluate the Efficacy, Immune Response, and Safety of a COVID-19 Vaccine in Adults 18 Years With a Pediatric Expansion in Adolescents (12 to < 18 Years) at Risk for SARS-CoV-2	Active, not recruiting	Biological: SARS-CoV-2 rS/Matrix-M1 Adjuvant (Initial Vaccination Period) |Other: Placebo (Initial Vaccination Period) |Biological: SARS-CoV-2 rS/Matrix-M1 Adjuvant (Crossover Vaccination period)|Other: Placebo (Crossover Vaccination period)	Novavax| Department of Health and Human Services	12 Years and older (Child, Adult, Older Adult)	Phase 3	Interventional	Allocation: Randomized|Intervention Model: Crossover Assignment|Masking: Quadruple (Participant, Care Provider, Investigator, Outcomes Assessor) |Primary Purpose: Prevention	27-Dec-20	30-Jun-23

NCT04368988	Evaluation of the Safety and Immunogenicity of a SARS-CoV-2 rS Nanoparticle Vaccine With/Without Matrix-M Adjuvant	Active, not recruiting	Biological: SARS-CoV-2 rS - Phase 1|Biological: SARS-CoV-2 rS/Matrix-M Adjuvant - Phase 1|Other: Normal saline solution (NSS), Placebo - Phase 1|Other: Normal saline solution (NSS), Placebo - Phase 2|Biological: SARS-CoV-2 rS/Matrix-M Adjuvant, Day 0 - Phase 1|Other: Normal saline solution (NSS), Placebo, Day 21 - Phase 1|Biological: SARS-CoV-2 rS/Matrix-M Adjuvant - Phase 2	Novavax| Coalition for Epidemic Preparedness Innovations	18 Years to 84 Years (Adult, Older Adult)	Phase 1|Phase 2	Interventional	Allocation: Randomized|Intervention Model: Parallel Assignment|Masking: Quadruple (Participant, Care Provider, Investigator, Outcomes Assessor) |Primary Purpose: Prevention	25-May-20	21-May-22
NCT04834869	COVID-19 Vaccines Safety Tracking (CoVaST)	Recruiting	Biological: BNT162b2|Biological: mRNA-1273|Biological: AZD1222|Biological:CoronaVac|Biological:Sinopharm|Biological Gam-COVID-Vac|Biological: JNJ-78436735|Biological:CVnCoV|Biological: NVX-CoV2373|Biological: BBV152	Masaryk University	18 Years and older (Adult, Older Adult)		Observational	Observational Model: Other|Time Perspective: Prospective	1-Apr-21	31-Jan-22

Q5. Are vaccines effective and safe in the prevention of COVID-19 infections?

As of 29 April 2021

RECOMMENDATIONS

We recommend the use of the following vaccines to prevent symptomatic SARS-CoV-2 infection in adults: *(Moderate certainty 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 certainty 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).

With regard to Coronavac, a strong recommendation was made despite the low certainty of evidence because the panel considered its availability and the very high vaccine efficacy in preventing severe COVID-19. Although a 14-day dosing interval was utilized in the trial, it was noted that the recommendation on a 28-day dosing interval was based on the submission of the manufacturer to the Hongkong Food and Health Bureau. It was assumed that a longer duration may have better vaccine efficacy 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 will provide better immunogenicity because it will give ample time for the population of lymphocytes in the lymph nodes to be replenished, thus resulting in 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 certainty 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 certainty of evidence)*

Consensus Issues
The strength of recommendation was changed from weak to strong because, although the certainty 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 agreed not to recommend CoronaVac due to the very low certainty of evidence wherein the interim analysis showed imprecision because of the very wide confidence interval for symptomatic COVID-19. Moreover, there was no disaggregation of data into mild, moderate or severe COVID-19 in older adults ≥60 y/o. There was also no data on harm.

RECOMMENDATIONS

We recommend the use of these vaccines in pregnant and lactating women after consultation with a physician. *(Very low certainty of evidence; Weak recommendation)*

Consensus Issues
The certainty 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 these women of the benefits and risks of vaccination, specific to the timing of its 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, while the rest had no reported congenital anomalies

RECOMMENDATIONS

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 those who are at risk for severe infection. *(Moderate certainty of evidence; Strong recommendation)*

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

Consensus Issues
A weak recommendation was made for Coronavac because the panel took into account 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.

RECOMMENDATIONS

We recommend the use of these 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 certainty of evidence; Strong recommendation)*

Consensus Issues
Despite the low certainty of evidence, a strong recommendation was made because the benefits of vaccination outweigh any potential harm. It was noted that there are no specific subgroup results for the immunocompromised patients and the expected vaccine efficacy would be lower, but then 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.

RECOMMENDATIONS

We recommend against the use of these vaccines in children to prevent SARS-CoV-2 infection: *(Weak recommendation)*

- BNT162b2: <16 years old
- ChAdOx1: <18 years old

There is no evidence on the use of mRNA-1273, GamCOVID-Vac, Ad26.COV2.S and CoronaVac in children to prevent SARS-CoV-2 infection.

Consensus Issues
A weak recommendation was made for BNT162b2 and ChAdOx1 because these are the only vaccines that included children in the trial protocol, the results of which

are still pending. It was clarified that the recommendation against its use was not because of safety issues.

Based on the 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.

RECOMMENDATIONS

We recommend against the use of particular vaccines in individuals who have known allergies to the contents/excipients of that 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 certainty 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.

KEY FINDINGS

As of April 23, 2021, interim 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. 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. Very limited Phase 3 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. A rare phenomenon, the vaccine-induced 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-ratio for its continued use. 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.

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 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 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 investigated the available publicly available phase 3 clinical trial results of candidate COVID-19 vaccines and the real world evidence of their safety and efficacy as of April 23, 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 April 23, 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.

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 (eg. 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 time points. 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 Certainty 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. This search was performed on April 23, 2021. Observational studies on populations at risk for COVID-19 infection reporting the outcomes of vaccinations in terms of incidences of COVID-19 infection 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 of the vaccines. These sites included 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 April 23, 2021 yielded 73 records. After screening for eligibility based on titles and abstracts and eliminating duplicates (of the full publication of preprints), ten publications 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 interim results of trials that used mRNA vaccines, BNT162b2 [3] and mRNA-1273 [4]. Five reports were on the pooled interim results of four 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]. One publication was on the interim 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 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 April 23, 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], EMA [18-19], UKMHRA [20-21] and the WHO SAGE [22-23] authorization assessment documents provided additional information for BNT162b2 vaccine. The USFDA [15] [24], the EMA [25-26] and the WHO SAGE [27-28] authorization assessment documents provided additional information for the mRNA-1273 vaccine. The UK-MHRA [29], the EMA [30-31] and the WHO [32-33] authorization assessment reports provided additional information for the ChAdOx1 vaccine. The USFDA [16] [34], the EMA [35-36] and the WHO [37-38] 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 [39].

The search of the FHB-HKSAR website yielded 2 reports containing phase 3 clinical trial data for CoronaVac, the advisory panel report [40] and the product insert [41]. The available efficacy data were from one trial site only (Brazil). The Indonesian National Drug Information's fact sheet on the EAU for CoronaVac provided additional safety and efficacy data from the Indonesian and Turkish trial sites [42]. Details of the trial design were taken from the published protocol for its Brazilian study site [43]. The study design of the trial done in Chile was from trial registration at the Clinicaltrails.gov website [44].

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 were 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 were 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 that investigated 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 1620 participants while the Turkish site had 1322. It was not clear if the available efficacy and safety data from these trials were the total trial population and the follow up was not clear. 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 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.

Clinical Trial Results: Efficacy

Available trial data for all six vaccines demonstrated sufficient efficacy rates in the prevention of symptomatic COVID-19 infection, based on a threshold of at least a point estimate of 50% and at least a 30% lower border of the 95%CI set by the WHO [45], within a median follow up of three months after vaccination of the ChAdOx1; two months after vaccination of the BNT162b2, mRNA-1273, and Ad26.COV2.S; 48 days after vaccination with Gam-COVID-Vac; and 73 days for CoronaVac (Brazilian trial). Vaccine efficacies against the different severities of COVID-19 infection and for the different subgroups were variable across the different vaccines. No long-term efficacy data are 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%). A precise estimate on the protective effect of BNT162b2 on the occurrence of severe COVID-19 infection was 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 seemed to occur similarly for both the BNT162b2 and placebo groups until approximately 14 days after Dose 1, then cumulative curves diverged 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 was stable, suggesting continued protection. Asymptomatic COVID-19 infection prevention was not assessed. No data on the impact of the vaccine on hospitalization, ICU admission or deaths associated with COVID-19 infection were reported.

mRNA-1273 (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 cases of severe COVID-19 infection occurred in the vaccine group while 30 occurred in 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 after Dose 1 until Day 14 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 (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 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 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 this variant was peaking in November 2020 in the UK [46]. 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 3c). 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 2nd dose, with a median follow up of 48 days. It showed a first-dose vaccine efficacy of 73.1% (95% CI 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 and 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 diverged 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 its Brazilian trial site result, 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 after completion of two doses of vaccination with a 14-day interval. 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 (≥60 years 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.

While data from the trial in Turkey were also available in the product information document from the FHB-HKSAR, they were only from <20% of the trial population after only 29 COVID-19 cases were recorded. Hence, the data were not included in this review.

The vaccine efficacy reported for the Brazilian site by the Indonesian FDA, from a cut-off date of January 8, 2021, was 63.5% based on 7 COVID cases in the vaccine group and 18 cases in the placebo group. The report also stated that no severe, critical cases or deaths due to COVID-19 had occurred in the Brazilian trial site.

The Indonesian fact sheet also reported the vaccine efficacies from the Indonesian trial site (VE 65.3%, based on 7 COVID cases in the vaccine group and 18 cases in the placebo group), and from the Turkish site (VE 91.25%, based on 3 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 was not clear if recruitment had been completed or if the entire trial population had achieved the minimum follow up period in these trial sites.

Hence, the efficacy data included in the GRADE tables for this review included only the Brazilian trial data.

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 in 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 recorded. Onset was between the first and third day of 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 or 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.

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

ChAdOx1 (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 *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 (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)

The most frequently reported local adverse reaction was pain at the injection site (48.6%) followed by erythema and swelling. Most were mild and lasted 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 [37].

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 Indonesia 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 was 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 specified, but serious adverse event rates were similar between groups. There were two deaths in the trial, one due to cardiopulmonary arrest

(placebo group), and the other 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 [47-59], five on BNT162b2 and ChAdOx1 [60-64], five on BNT162b2 and mRNA-1273 [65-69], and two on Coronavac [70-71]. One provided data on Gam-COVID-Vac [72]. 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 [73]. 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 [74-78]. Nine reported data on BNT162b2 [79-85]. Four reported data on mRNA-1273 [86-89]. Five presented data on ChAdOx1 safety events [90-94]. One study provided safety data on Coronavac [95].

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 [81] [96-98]. Four reports from the EMA were retrieved, three of which were specifically on the thromboembolic events associated with ChAdOx1 [99-102]. The UK MHRA released two reports used in this version of the review [103-104]. The Philippine FDA released five reports, the latest of which was used in this version of the review [105]. 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 [106].

Real World Evidence Results: Efficacy/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 efficacy and their methodological assessment are presented in Appendix 6.

BNT162b2 (Pfizer/BioNTech)
Twenty-three studies provided real world evidence on the efficacy of BNT162b2. Three were test negative case control studies [60] [62] [65]. Three were matched cohort studies on the general population [51] [66-67]. Nine were prospective cohort studies and the rest were retrospective cohort studies.

In general, all studies demonstrated VEs that support the clinical trial results. Reported VEs for the prevention of symptomatic COVID-19 disease among the general population were 51% [50], 85% [47] and 94% [51]. Both studies involving the high-risk population (i.e., healthcare workers), showed similar VEs of 85% [47] [67]. 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 those 70 years old and older was 0.36 (95% CI 0.31-0.49), and 0.21 (95% CI 0.14-0.32) among those 80 years and older [60]. Adequate protection against hospitalization was also demonstrated with reported VEs ranging from 43% to 71% among those older than 80 years [54] [62], and 60% and 87% [51] [67] in the general population. Vaccine efficacy against severe COVID-19 infection was reported at 92% in the match cohort study in Israel [51]. Vaccine efficacy 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 [58]. Vaccine efficacy against death was reported by one study in the US at 100% [67].

Publications on cohort studies among healthcare workers in Spain demonstrated satisfactory protective effects of BNT162b2 against COVID infection, hospitalization and death [49] [52].
Five studies reported real world efficacy 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 efficacy data for mRNA-1273. These studies were on populations where BNT162b2 or mRNA-1273 was used, and did not report efficacy outcomes separately for each of the vaccines.

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%) [65]. Another prospective cohort study among healthcare workers and frontliners reported a higher vaccine efficacy against COVID infection after at least 14 days following the second dose of an mRNA vaccine at 90% (95% CI 68-97%) [69]. 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 [67]. The study did not report the outcomes of each vaccine separately. It demonstrated VE against any PCR-confirmed COVID infection of 75% (95% CI 67.4-81.1%) from Day 15 onwards after the first dose, 88.7% (95% CI 68.4-97.1%) 7 days after the second dose, and 92.5% (95% CI 70.2-99.1%) from 7 to 14 days after the second dose. The VEs against hospitalization, specifying hospital admission (VE 60%, 95% CI 14-79%) and ICU admission (VE 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 [66].

ChAdOx1 (AstraZeneca)

Five studies, all done in the UK, provided real world evidence on the efficacy 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 [63]. 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 [61]. 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 [64]. It showed a vaccine efficacy of 94% (95% CI 73-99%) after 28 to 35 days following the first dose of ChAdOx1 against COVID-19 related hospitalization. One test negative case control study among adults 80 years and older reported vaccine efficacy of 80.4% (95% CI 36.4-94.5%) against hospitalization assessed at least 14 days after the first dose. [62]. Another, done among those 70 years and older showed an adjusted odds ratio of 0.40 (95% CI 0.27-0.29) against any COVID-19 infection 28 to 34 days after the first dose. This study also demonstrated a vaccine efficacy 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 [60].

Gam-COVID-Vac (Gamaleya)

One retrospective study among healthcare workers in Buenos Aires used Gam-COVID-Vac in 80% of its population [72]. 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 efficacy 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 [71]. The study from Brazil showed a similar VE of 50.7% (95% CI 33.3-62.5%) beginning at 2 weeks after the 2nd dose and a VE of 73.8% (95% CI 57-84.8) at 5 weeks after. It also reported lower hospitalization numbers among those who were vaccinated. The singular death in the study was in the unvaccinated group [70].

Real World Evidence Results: Safety

Early safety reports by the major regulatory agencies support a positive benefit-harm ratio for the use of 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, encompassing the first month after the vaccination roll out using BNT162b2 and mRNA-1273 [96]. 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 had been confirmed after receipt of BNT162b2 [96]. The estimated anaphylaxis rate for BNT162b2 was 4.7 cases per million doses administered [78].
The EMA released a safety update on BNT162b2 (Comirnaty) on January 28, 2021 [99]. 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 [104]. 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 [74]. 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 [106]. 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 [84]. A similar profile of adverse events were reported among healthcare workers from South Korea who received BNT162b2 vaccines [82].
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 [83]. 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 [76]. 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 Guillian-Barre syndrome after BNT162b2 vaccination [85]. 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 Guillian 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 [80]. The report noted that 65.1% of the adverse events following immunization (AEFI) were neurologic, with 76% occurring in women. Majority were non-serious, with headache, transient sensory symptoms and weakness being the most common. Of the serious AEFIs 52% were neurologic, of which seven were seizures (0.99/100,000 doses), four were functional syndrome (0.56/100,000 doses), three were Guillian 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 [79]. 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 [97]. The estimated anaphylaxis rate for mRNA-1273 is 2.5 cases per million doses administered [78].

Data from the VigiBase®, revealed 78 deaths after mRNA-1273 administration, representing 1.23% of all adverse event reports after mRNA-1273 [74].

Cutaneous reactions after mRNA-1273 vaccination have been described in the above BNT162b2 section [76].

ChAdOx1 (AstraZeneca)

The UKMHRA April 9, 2021 report on the status of their Yellow Card adverse event reporting after COVID-19 vaccination [104]: 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 [105]. 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 [74].

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 [105]. The Instituto de Salud Publico de Chile reported 49 anaphylactic reactions after 3,378,552 doses of Coronavac administered [106].

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 [93] [90] [94]. 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 had 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 reports of thromboembolic cases after vaccination, the EMA's safety committee performed a preliminary review of the issue in mid March [100]. 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 was 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. [103]

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 [101-102].

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 the first dose [104].

Despite the possible link of the vaccination to these thromboembolic events, both regulatory agencies confirmed 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 [98]. After a review and with no additional reported cases, the USFDA and CDC lifted its recommended pause on April 23 after determining that the risk of VITT was very low [107].

AUTHORIZATIONS (AS OF APRIL 23, 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 [108]. The Philippine FDA issued the emergency use authorization for BNT162b2 last January 14, 2021 [109].

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.

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 [110].

Gam-COVID-Vac (Gamaleya)

Gam-COVID-Vac (Sputnik V) is registered for use in the Russian Federation and in 50 other countries [111]. On March 19, 2021, the Philippine FDA issued the emergency use authorization for Gam-COVID-Vac [112].

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 [113]. The WHO added this vaccine to its emergency use list last March 12, 2021 [114]. The Philippine FDA issued the emergency use authorization for As26.COV2.S on April 19, 2021 [115].

CoronaVac (Sinovac)
CoronaVac was given a conditional marketing authorization by the FHB-HKSAR on February 9, 2021 [40]. 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 [116]. 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 that 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

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Q6. Is rAd26 (Sputnik Light) effective and safe in the prevention of COVID-19 infections?

As of 04 November 2021

RECOMMENDATIONS

We suggest the use of the rAd26 (Sputnik Light), given as 10^{11}vp per 0.5ml, single dose, intramuscularly to prevent symptomatic SARS-CoV-2 infection in:

a. Healthy adults *(Low certainty, Weak recommendation)*
b. Older adults (60 years and older) *(Low certainty, Weak recommendation)*
c. Adults with comorbidities *(Low certainty, Weak recommendation)*

We suggest against the use of rAd26 (Sputnik Light) to prevent symptomatic SARS-CoV-2 infection in:

a. Children (3-17 years) *(No evidence, Weak recommendation)*
b. Pregnant and lactating women *(No evidence, Weak recommendation)*
c. Immunocompromised *(No evidence, Weak recommendation)*

In areas where Alpha, Beta or Delta is the predominant variant of concern, we suggest the use of rAd26 (Sputnik Light) to prevent COVID-19 infection. *(Very Low certainty, Weak recommendation)*

Consensus Issues
The Panel was unanimous in all their recommendations. No issues were raised during the meeting.

KEY FINDINGS

Five observational studies provided low to very low certainty evidence on the effectiveness and safety of rAd26 (Sputnik Light) against COVID-19 infection. Immunogenicity studies showed that rAd26 induced significant humoral and cellular response against SARS-COV-2 and its variants. Observational studies found rAd26 to provide sufficient protection against COVID-19 infection, hospitalization and death, particularly for the older person and those with comorbidities. Associated adverse events were mostly due to reactogenicity and were mild and transient. No evidence was found on the effect of rAd26 on children, pregnant women and the immunocompromised.

INTRODUCTION

A COVID-19 vaccine that is easy to manufacture and administer is needed to address the global supply shortage and hasten wide vaccine coverage. The development of the rAd26 (Sputnik Light), an Ad26-vectored vaccine similar to the first dose of the Gam-COVID-Vac heterologous prime-boost vaccination (rAd26-S + rAd5) was a response to this need. One dose of rAd26 contains 10^{11}vp per 0.5ml and is given intramuscularly. The vaccine is produced as a 5-dose 3 ml vial or a 0.5ml ampule, stored at -18 to -22'C with a shelf life of 10 months.[1]

REVIEW METHODS

The search followed the strategy used for all the vaccine reviews in this series. Briefly, this covered Pubmed, living COVID-19 evidence registries including the Living

Overview Evidence platform, the COVID-NMA and the Metaevidence.org, the reference list of the WHO Situational reports, the WHO COVID-19 literature on coronavirus disease database and the VIEW-Hub Resource Library.

RESULTS

Search Results

The search performed on October 31, 2021 yielded five studies on the effect of rAd26 (Sputnik Light) for the prevention of COVID-19 disease. All were nonrandomized studies. One is a Phase1/2 open label comparative immunologic study(1), one is a matched cohort population-based study(2), one is a retrospective cohort (3) and two were single cohort self-controlled immunologic studies.(4)(5)

Clinical Efficacy

No randomized controlled trial has been identified providing clinical efficacy data for rAd26 (Sputnik Light).

Real World Evidence: Effectiveness

Two studies provided clinical effectiveness information on rAd26, one of which was in the background of Delta variant predominance.

A matched cohort study demonstrated the protective effect of rAd26 among the older population (aged 60 to 79 years old) in Buenos Aires, Argentina. Matching was based on age and the presence of comorbidities. After an observation period of 21 to 40 days post-vaccination, the vaccine effectiveness of rAd26 for laboratory-confirmed infection was 78.6% (95% CI 74.8-81.7), for hospitalization was 87.6% (95% CI 80.3-92.2), and for mortality was 84.8% (95% CI 75.0-90.7). A subgroup analysis among those with comorbidities showed VE rates for laboratory–confirmed infection was 78.6% (95% CI 73.2-82.8), for hospitalization was 87.1% (95% CI 76.9-92.7), and for death was 87.5 (95% CI 75.9-93.5).[2]

The study providing rAd26 effectiveness against variants is presented below.

Immunogenicity

One open label, prospective non-randomized Phase 1/2 study was identified that provided immunogenicity evidence supporting the use of rAd26 vaccination.[1] The study population included 110 participants with a mean age of 35.4 years, mostly infection naïve (87% seronegative at baseline), without concomitant disease and with “general” (or low) risk of infection. The outcomes of the study included self-reported adverse events (see safety section below), and immunologic parameters at baseline, day 1, day 10 and day 28 post vaccination including CD3, CD4, CD8, CD16, CD19, CD4/8 cells, total IgM, IgG, IgA, IgE titers, compared with convalescent plasma.

Vaccination increased RBD-specific IgGs as early as day 10 (GMR 69.39), reaching maximal levels on day 28 (GMT 2395) and day 42 (GMT 2285). Seropositivity was 99.07% by day 28 post vaccination. The study noted a difference in the rate of rise in titers between those who were seronegative at baseline (i.e. infection naïve) and those who were seropositive. The seronegative subpopulation’s titer started to increase at day 10 and was maximal at day 28. On the other hand, the seropositives demonstrated a significant increase in titers at day 10 and a non-significant decrease at day 28 and day 42 compared with day 10. Compared with the convalescent plasma titers, post-

vaccination titers were lower in the seronegative group but higher in the seropositives at all time points. Neutralizing antibody seropositivity rates were 62.7% at day 28 post vaccination and 83.2% at day 42. Titers were 16.25 by day 28 and 24.45 by day 42. Cellular response was studied in 25 seronegative-baseline samples. Results showed that antigen-specific IFN-γ secretion were found in 96% of seronegatives at day 10 after immunization.

Table 2 details the Phase 1/2 study providing immunologic effectiveness and safety data for rAd26.

Similar findings were reported in a single cohort study involving 84 Moscow residents vaccinated with rAd26 and their blood was collected prior to and on days 7 and 21 after vaccination. Immunologic (humoral and cellular) response was robust and immediate on the 7th day in previously infected participants whereas titers peaked at 21 days in the infection naïve. A reduced response to the Delta variant was also shown in this study.[3]

Another single cohort study from Pakistan involving 100 patients showed that there was seroconversion of 85% of participants 21 days after rAd26 administration. High titers (>250AU/ml) were seen in 34.9% of the participants.[4]

Safety

Only one study (the above-mentioned Phase 1/2 open label study) provided the safety data for rAd26 (Sputnik Light). It reported an overall adverse event rate of 67.2% within 28 days after injection, mostly from local and systemic reactogenicity. All reported events were mild to moderate (Grade 1-2). Local adverse events were less common, with pain at injection site being the most common at 5.5%. Systemic adverse event rate was 65.5% with flu-like symptoms being the most common (49.1%). No serious adverse event was reported.[1]

Special Populations

The search failed to identify any study on the effect of rAd26 on children, pregnant women and the immunocompromised.

Effectiveness Against Variants

The effect of rAd26 on the Alpha and Beta variants was reported by one study. It was shown to have minimal decline in effectiveness (in terms of immunogenicity at day 28) against the Alpha (1.11-fold decline) and Beta (1.99-fold decline) variants when compared against the B.1.1.1 strain.[1] No clinical outcomes were available.

A retrospective study done in Russia at the peak of the Delta surge showed high efficacy of rAd26 against the variant in the first three months after vaccination. VE against COVID infection was established at 69.85% (95% CI 64.08-74.70).[5] In the Russian study mentioned earlier, a 2-fold reduction in neutralizing antibody response was demonstrated against the Delta variant by serum from rAd26 vaccine recipients.[3]

No study was identified on the effect of rAd26 on the Gamma variant.

Table 3 details all the observational studies included in the review. Table 4 presents the risk of bias assessment. Table 5 and 6 presents the summary of findings table.

Booster Vaccination
No study was identified using rAd26 as part of a booster vaccination regimen.

AUTHORIZATIONS

On August 20, 2021, the Philippine FDA granted emergency use authorization to rAd26 (Sputnik Light) for the prevention of COVID-19 infection for persons 18 years and older.[6] As of November 1, 2021, rAd26 (Sputnik Light) received authorization for use in 17 other countries, apart from the Philippines.[7]

ONGOING TRIALS

As of November 1, 2021, two studies on Sputnik Light are registered in Clinicaltrials.gov. Table 7 presents the details of these studies.

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Appendix 1. Evidence to Decision

Table 1. Summary of Initial Judgements Prior to Panel Discussion (N = 8)

FACTORS	JUDGEMENT						RESEARCH EVIDENCE/ADDITIONAL CONSIDERATIONS
Problem	No	Yes (8)					
Benefits	Large (2)	Moderate (5)	Small	Uncertain (1)			• Significant increase in antibody titers from day 28 to day 42, with seropositivity day 28 values reaching 99.7% (RBD-binding antibodies) day 42 values reaching 83.2% (neutralizing antibodies). Minimal decline in immunogenicity at day 28 for Alpha (1.11-fold) and Beta (1.99-fold).
Harm	Large (2)	Small (5)	Uncertain (1)				• Overall adverse event rate of 67.2%, mostly mild to moderate in severity, with local (e.g., pain at injection site) and systemic reactogenicity (e.g., flu-like symptoms). • No serious adverse events reported.
Certainty of evidence	High	Moderate	Low (1)	Very Low (7)			• Very low
Balance of effects	Favors vaccine (7)	Does not favor vaccine (1)	Uncertain				
Values	Important uncertainty or variability	Possibly important uncertainty or variability (4)	Possibly no important uncertainty or variability (3)	No important uncertainty or variability (1)			
Resources required	Uncertain	Large cost	Moderate cost (6)	Negligible cost or savings	Moderate savings (1)	Large savings (1)	• Storage of Sputnik Light is at -18°C to -22°C, requiring the use of freezers. • Sputnik Light (India Rs 700), approximately PHP 470.12.
Certainty of evidence of resources required	No included studies (8)	Very low	Low	Moderate	High		
Cost effectiveness	No included studies (8)	Favors the comparison	Does not favor either the intervention or the comparison	Favors the intervention			
Equity	Uncertain (8)	Reduced	Probably no impact	Increased			• Addresses wide disparity in vaccine coverage: 85.1% fully-vaccinated senior citizens in NCR; only 28.3% in BARMM
Acceptability	Uncertain (1)	No	Yes (7)				• Sputnik Light was given EUA by the Philippine FDA on August 20, 2021.
Feasibility	Uncertain	No	Yes (8)				

Appendix 2. Characteristics and results of the Phase 1/2 study on rAd26 (Sputnik Light)

Parameter	Description
Data Source	Preprint article: Tukhvatulin 2021 (SSRN) Clinical trial protocol registration: NCT04713488
Population	- N=110 (30 included in IFN-γ and 30 in T cell proliferation analysis) - Females 50% - Mean (SD) age: 35.4 (14.84) - Age >= 60 = 16% - All white ethnicity - Risk of infection: 93% general, 7% medium - Concomitant disease: 92.5% none - Dropouts: 2 withdrew consent, 1 missed day 42 assessment Exclusions: - history of COVID-19 or prior contact with patients with COVID-19 within 14 days of participation - receipt of any other vaccines within 30 days - therapy with steroids, immunoglobulins, other blood-derived products within 30 days - intake of immunosuppressive drugs for more than 3 months - allergy to immunobiological preparations including any vaccine component
Intervention	rAd26 at 10^{11}vp per 0.5ml, single dose, intramuscular (storage: -18 to -22'C, shelf life 10 months, 5-dose 3ml vial or 0.5ml amp)
Control	none
Outcomes	Blood chemistries/Lab results at 0 and 28 days Immune parameters (at 0,1 day, 10 days, 28 days post vaccination): - absolute and relative numbers of CD3, CD4, CD8, CD16, CD19, CD4/8 cells, total IgM, IgG, IgA, IgE - Change from baseline of IgG at 10 days, 28 days, 42 days, 90 days, and 180 days) - Neutralizing antibody response (day 1, day 28, day 42, microneutralization assay) - Cell-mediated immune response at day 1, day 10: CD4+ and CD8+ T cells, quantity of interferon-gamma producing cells (day 10) Self-reported adverse events (at day 10, day 28 and day 42 post vaccination)
Methods	Open label, prospective Comparative study for immunologic response versus plasma taken from convalescent donors Immune tests used: - ELISA for IgG and IgG - Microneutralization assay for neutralizing antibody - Flow cytometry by IFN-gamma release of PBMCs using ELIS and ELISpot methods Timing of blood extractions: 0, 28 and 42 days Safety and reactogenicity up to day 28
Risk of Bias Assessment	Observational study Unclear sampling, with missing data, no control of confounders Overall certainty: LOW
Results: Safety	reported up to 28 days post vaccination: - any AE: 74 (67.2%), all Grade 1and 2 - pain in injection site: 6 (5.5%) - redness: 1 (0.9%) - systemic AE: 72 (65.5%) - flu-like symptoms: 54 (49.1%) - fatigue: 6 (5.5%) - headache: 5 (4.5%) - no serious adverse events reported
Results: Immunologic	RBD specific IgG (mean titers): - seronegative: start of increase at day 10 and maximal at day 28 - seropositive: significant increase at day 10 and non-significant decrease at day 28 and day 42 compared with day 10 titers In comparison with convalescent plasma, post-vaccination titers were lower in the seronegatives but higher in the seropositives at all timepoints RBD specific IgG (seropositivity): 99.07% by day 28 for all (seronegative and seropositive) Neutralizing antibody seroconversion: day 28=62.7%, day 42=83.2% Versus Alpha and Beta (N=96), vs B.1.1.1 strain - versus Alpha: 1.11-fold reduction in Nab titers - versus Beta: 1.99-fold reduction Cellular immune response: - IFN-g positivity 96% at day 10 with median 554.3 spots per 1 million - Antigen-specific IFN-γ secretion 96% positive rAd26 neutralizing GMT: increased from 18.2 to 782.9 at day 28

Appendix 3. Characteristics and Results of Real World Evidence on rAd26 (Sputnik Light)

Study ID	Design	Population	Intervention / Comparator	Outcomes/Results
Gonzales (Argentina)	Matched cohort Matched by age, gender, comorbidities	Older adults (60 to 79 years old)	rAd26 vaccinated: 60-69: 12195 70-79: 28192 Unvaccinated: 60-69: 12345 (matched) 70-79: 26633	• VE (95% CI) • After 40 days of monitoring • VE for lab-confirmed infection - Overall: 78.6 (74.8-81.7) - 60-69y/o: 82.9 (77.9-86.8) - 70-79y/o: 74.7 (69.0-79.4) - With comorbidity: 78.6 (73.2-82.8) • VE for hospitalization - Overall: 87.6 (80.3-92.2) - 60-69y/o: 86.3 (65.2-94.6) - 70-79y/o: 88.3 (80.0-93.1) - With comorbidity: 87.1 (76.9-92.7) • VE for death: - Overall: 84.8 (75.0-90.7) - 60-69y/o: 87.3 (58.0-96.2) - 70-79y/o: 85.1 (75.5 – 95.5) - With comorbidity: 87.5 (75.9-93.5)
Dolzhikova (Russia)	Retrospective cohort (linked databases) / Case-control Study performed at the time of Delta variant predominance No adjustments mentioned, VEs presented by age bands	General population, at least 18 years old	rAd26 vaccinated Unvaccinated, with no prior infection	• VE (95% CI) • Overall: 69.85 (64.08-74.70) - Vaccinated: 126: 28322 (Dis/No Dis) - Unvaccinated: 82196: 5569885 (Dis/No Dis) • 18-59 y/o: 75.28 (69.24-80.13) • 60+ y/o: 51.98 (35.61-64.19)
Saeed (Pakistan)	Single cohort	100 adults	rAd26 vaccination	• 21 days post vaccination • Anti-spike IgG seroconversion (>1.5 AU/ml): 85% - >250AU/ml: 34.9% - >100AU/ml: 12.7% - >25 AU/ml: 9.5% - >1.5 – 2.5: 27%
Komissarov (Russia)	Single cohort	84 Moscow residents	Pre-vaccination antibody and T-cell response levels	Pre vaccination / day 7 / day 21 Anti-RBD IgG (seropositive rate) 52.4% / 57.1%, 100% * described 3 types of response: (1) no increase on day 7 but elevated at day 21 (2) immediate rise on day 7 with further increase at day 21 (3) minimal change throughout Virus neutralizing activity vs B.1.1.1 and B.1.617.2 strains 2-fold reduction in VNA vs delta compared with B.1.1.1 strain IFN-gamma ELISpot (T-cell response specific to S-protein) 36.1% / 86.6% / 96.4%

Appendix 4. Risk of Bias Assessment of Included Studie

Study ID	Design	Randomization	Allocation Concealment	Blinding Particip	Blinding Carer/ Assessor	Follow-up	Selective Reporting	Others	Age	Comorbidities	Exposure	Confounding	OVERALL
Tukhvatulin (Russia)	Prospective single cohort	HIGH	HIGH	HIGH	HIGH	HIGH	UNCLEAR	NA	HIGH	HIGH	HIGH	HIGH	SERIOUS
Gonzales (Argentina)	Matched cohort	HIGH	HIGH	HIGH	HIGH	HIGH	UNCLEAR	NA	LOW	LOW	UNCLEAR	LOW	SERIOUS
Dolzhikova (Russia)	Retro cohort	HIGH	HIGH	HIGH	HIGH	HIGH	UNCLEAR	NA	LOW	HIGH	HIGH	HIGH	SERIOUS
Saeed (Pakistan)	Single cohort	HIGH	HIGH	HIGH	HIGH	LOW	UNCLEAR	NA	HIGH	HIGH	HIGH	HIGH	SERIOUS
Komissarov (Russia)	Single cohort	HIGH	HIGH	HIGH	HIGH	LOW	UNCLEAR	NA	HIGH	HIGH	HIGH	HIGH	SERIOUS

Appendix 5. Summary of Findings Table on the Efficacy of rAd26 (Sputnik Light)

Efficacy Outcome		Quality Assessment					Summary of Findings			Certainty
		Risk of Bias	Inconsistency	Indirectness	Imprecision	Overall Assessment	Vaccine n/N (%)	Control n/N (%)	Vaccine Efficacy (CI)	
1: Symptomatic COVID-19 infection	1 OBS	Serious (observational)	Not assessed	Not assessed	Not assessed	Serious	na	na	69.8% (64.1-74.7)	++ Low
2: Severe COVID-19 infection	1 OBS	Serious (observational)	Not assessed	Not serious	Not serious	Serious	na	na	87.6% (80.3-92.2)	++ Low
3. Asymptomatic COVID-19 infection	na	Not assessed	Not assessed	Not assessed	Not assessed	Not assessed	na	na	na	na
4. Any COVID-19 infection	1 OBS	Serious (observational)	Not assessed	Not serious	Not serious	Serious	na	na	78.6 % (74.8-81.9)	++ Low
5. Symptomatic COVID-19 infection after first dose, before the second dose	na	Not assessed	Not assessed	Not assessed	Not assessed	Not assessed	na	na	na	na
6. Death from COVID-19 infection	1 OBS	Serious (observational)	Not assessed	Not serious	Not serious	Serious	na	na	84.8% (75.0-90.7)	na
7. Symptomatic COVID-19 infection, older adults (>=60yo)	2 OBS	Serious (observational)	Not serious	Not serious	Not serious	Serious	na	na	78.6 % (74.8-81.9) 52% *(Delta)* (35.6-64.2)	++ Low
8. Symptomatic COVID-19 infection, with pre-existing medical condition	1 OBS	Serious (observational)	Not assessed	Not serious	Not serious	Serious	na	na	78.6% (73.2-82.8)	++ Low
9. Symptomatic COVID-91 infection, children (<18yo)	na	Not assessed	Not assessed	Not assessed	Not assessed	Not assessed	na	na	na	na
10. Any COVID-19 infection, B.1.1.7/Alpha variant	1 OBS	Serious (observational)	Not assessed	Serious (Immuno)	Not assessed	Very Serious	1.11-fold reduction in neutralizing antibody titers			+ Very Low
11. Any COVID-19 infection, B.1.151/Beta variant	1 OBS	Serious (observational)	Not assessed	Serious (Immuno)	Not assessed	Very serious	1.99-fold reduction in neutralizing antibody titers			++ Very Low
12. Any COVID-19 infection, B.167.2/Delta lineage	1 OBS	Serious (observational)	Not assessed	Not serious	Not assessed	Serious	126: 28322 (Dis/No Dis)	82196: 5569885 (Dis/No Dis)	69.85 (64.08-74.70)	++ Low

Appendix 6. Summary of Findings Table on the Safety of rAd26 (Sputnik Light)

Safety Outcome		Quality Assessment					Summary of Findings			Certainty
		Risk of Bias	Inconsistency	Indirectness	Imprecision	Overall Assessment	Vaccine	Control	Relative Risk (95%CI)	
1: Solicited adverse reaction	1 OBS	Serious (observational)	Not reported	Not reported	Not reported	Serious	67.2%	na	na	++ Low
2: Local adverse reaction	1 OBS	Serious (observational)	Not serious	Not serious	Not serious	Serious	5.5%	na	na	++ Low
3: Systemic adverse reaction	1 OBS	Serious (observational)	Not serious	Not serious	Not serious	Serious	65.5%	Na	Na	++ Low
4. Unsolicited adverse event (28d)	na	Not reported	Not serious	Not serious	Not serious	Not reported	na	na	na	na
5: Serious adverse event	1 OBS	Serious (short ffup)	Not serious	Not serious	Serious (no event)	Very serious	0%			+ Very Low
6: Related serious adverse event (All medically attended adverse events (MAAEs)	na	Not reported	Not reported	Not reported	Not reported	Not reported	na	na	na	na
7: Withdrawals due to adverse event	na	Not reported	Not reported	Not reported	Not reported	Not reported	na	na	na	na
8: Death	na	Not reported	Not reported	Not reported	Not reported	Not reported	na	na	na	na

Appendix 7. Trials on Sputnik Light registered in Clinicaltrials.gov as of November 1, 2021

NCT Number	Title	Status	Outcome Measures	Sponsor/Collaborators	Phases	Completion Date
NCT04741061	Study to Evaluate Efficacy, Immunogenicity and Safety of the Sputnik-Light	Recruiting	Incidence and severity of adverse events in study subjects | Percentage of study subjects with COVID-19 cases developed after vaccination | Humoral immunogenicity (Quantitative IgG antibodies to SARS-CoV-2 S Protein) | Humoral immunogenicity (IgG SARS-CoV-2 N-antibodies)	Gamaleya Research Institute of Epidemiology and Microbiology, Health Ministry of the Russian Federation | Russian Direct Investment Fund | CRO: iPharma | Government of the city of Moscow	Phase 3	31-Jan-22
NCT04713488	An Open Study on the Safety, Tolerability, and Immunogenicity of "Sputnik Light" Vaccine	Active, not recruiting	Changing of antibody levels against the SARS-CoV-2 glycoprotein S | Number of Participants With Adverse Events | Changing of virus neutralizing antibody titer | Changing of antigen-specific cellular immunity level	Gamaleya Research Institute of Epidemiology and Microbiology, Health Ministry of the Russian Federation | Russian Direct Investment Fund	Phase 1 Phase 2	31-Jul-21

Q7. Among adults who received the standard full doses of any COVID-19 vaccine, what is the clinical and immunologic efficacy and effectiveness and safety of a booster?

As of 27 December 2021

RECOMMENDATIONS

We suggest the following homologous booster vaccination regimen for the general adult population:

a. **BNT162b2** *(Low certainty of evidence; Weak recommendation)*
b. **mRNA-1273** *(Low certainty of evidence; Weak recommendation)*
c. **ChAdOx1** *(Very low certainty of evidence; Weak recommendation)*
d. **Ad26.Cov2.S** *(Very low certainty of evidence; Weak recommendation)*
e. **CoronaVac** *(Very low certainty of evidence; Weak recommendation)*
f. **BBIBP-CorV** *(Very low certainty of evidence; Weak recommendation)*

There is insufficient evidence to recommend the following homologous booster vaccination in the general population:

a. **Gam-COVID-Vac**
b. **BBV152**

We suggest the following heterologous booster vaccination regimen for the general adult population:

a. **BNT162b2 primary, mRNA-1273 booster** *(Very low certainty of evidence; Weak recommendation)*
b. **BNT162b2 primary, Ad26.CoV2.S booster** *(Very low certainty of evidence; Weak recommendation)*
c. **mRNA-1273 primary, BNT162b2 booster** *(Very low certainty of evidence; Weak recommendation)*
d. **mRNA-1273 primary, Ad26.CoV2.S booster** *(Very low certainty of evidence; Weak recommendation)*
e. **ChAdOx1 primary, BNT162b2 booster** *(Very low certainty of evidence; Weak recommendation)*
f. **Ad26.COV2.S primary, BNT162b2 booster** *(Very low certainty of evidence; Weak recommendation)*
g. **Ad26.COV2.S primary, mRNA-1273 booster** *(Very low certainty of evidence; Weak recommendation)*
h. **CoronaVac primary, BNT162b2 booster** *(Very low certainty of evidence; Weak recommendation)*
i. **CoronaVac primary, ChAdOx1 booster** *(Very low certainty of evidence; Weak recommendation)*
j. **BBIBP-CorV primary, BNT162b2 booster** *(Very low certainty of evidence; Weak recommendation)*

There is insufficient evidence to recommend the use of the heterologous booster vaccination regimens other than the combinations included above in the general adult population.

We suggest the following homologous booster vaccination for the immunocompromised population:

a. **BNT162b2** *(Very low certainty of evidence; Weak recommendation)*
b. **mRNA-1273** *(Low certainty of evidence; Weak recommendation)*

There is insufficient evidence to recommend the following homologous booster vaccination for the immunocompromised population:

a. **ChAdOx1**
b. **Ad26.CoV2.S**
c. **CoronaVac**
d. **Gam-COVID-Vac**
e. **BBV152**
f. **BBIBP-CorV**

We suggest the following heterologous booster vaccination regimen for the immunocompromised population:

a. **an mRNA vaccine primary, another mRNA vaccine *booster*** *(Very low certainty of evidence; Weak recommendation)*
b. **an mRNA vaccine primary, ChAdOx1 booster** *(Low certainty of evidence; Weak recommendation)*
c. **BNT162b2 primary, mRNA-1273 booster** *Very low certainty of evidence; Weak recommendation)*
d. **BNT162b2 primary, Ad26.CoV2.S booster** *Very low certainty of evidence; Weak recommendation)*
e. **mRNA-1273 primary, Ad26.CoV2.S booster** *Very low certainty of evidence; Weak recommendation)*

There is insufficient evidence to recommend the use of the heterologous booster vaccination regimen other than the combinations included above in the immunocompromised population.

Consensus Issues

The main considerations in the recommendations of the Panel were the positive benefit/harm ratio of the administration of a booster compared with no boosters and increasing vaccine equity, providing flexibility, and optimizing available vaccines by recommending the use of vaccine booster regimen despite low certainty of evidence and for those with comparatively lower efficacy (compared to other combinations).

KEY FINDINGS AND WHAT'S NEW IN THIS UPDATE

51 studies are now included in the review, including: 8 randomized trials; 16 studies involving immunocompromised population; and 20 studies on heterologous booster vaccination. Clinical outcomes of booster vaccination remain to be available only for BNT162b2 homologous vaccination from three observational studies and from on study which included BBIBP-CorV. A new study provides vaccine effectiveness estimates for BNT162b2 homologous vaccination. Immunogenicity studies among the general population comparing pre- and post-boost humoral response consistently show significant increases titers and seropositivity rates regardless of the booster regimen. Available data on cellular response after boosters among the general population is limited and suggests increased response. Immunogenic response after boosters among the immunocompromised showed inconsistency. Low certainty evidence suggests booster vaccination to be safe, with heterologous booster

vaccination associated with higher adverse reaction rates compared with homologous booster vaccination.

INTRODUCTION

The need for additional dose of a COVID-19 vaccine after completion of the standard approved dosing regimen has been raised in the light of poor response of immunocompromised patients, the findings of declining antibody titers over time, and the emergence of SARS-CoV-2 variants of concern that reduces vaccine effectiveness. However, in the background of vaccine supply shortage, the administration of booster doses must be based on sound evidence of its efficacy, effectiveness and safety.

EVIDENCE ACQUISITION AND ANALYSIS

The evidence base was searched for studies investigating the efficacy, effectiveness and safety of the administration of an additional COVID-19 vaccine dose to the primary vaccination regimen in the prevention of COVID-19 infection. (See Appendix B for the detailed search strategy) For this review, a booster is defined as any additional COVID-19 vaccine administered after primary vaccination, regardless of the dose and timing (i.e. interval of administration of the additional dose and the last dose of the primary vaccination).

Randomized controlled trials (RCTs) were primarily sought for efficacy outcomes. Studies providing clinical outcomes such as vaccine efficacy or effectiveness, infection rates, protection rates were preferred. In the absence of such, observational studies and studies providing immunogenicity results were also considered. Immunologic response was presented as fold-increase in antibody titers or T-cell counts after the booster dose compared to the primary vaccination. The fold-changes (rise, increase, decline or decrease) in these titers were calculated either based on the pre-boost levels or against the other booster regimen in the study. Fold-changes were qualified based on the WHO criteria of no to minimal change for <2-fold difference, moderate for 2-5-fold difference, and large for >5-fold change. The positivity rates of the different immunologic parameters were also considered. The difference in rates, either compared to the pre-boost levels or to the rates of the other booster regimen in the study. A minimum 20% difference in rates is considered significant. Safety outcomes from both RCTs and observational studies were included. These included local and systemic adverse reactions, any adverse event, serious adverse events and deaths.

The studies were classified according to the populations included, either as studies on the general population or on the immunocompromised population. For this review, the immunocompromised population include transplant recipients, cancer patients, dialysis patients, and patients on immunosuppressive therapy. The results are presented according to the population included in the study.

For studies reporting on the effects of different doses of the vaccine, only the results with the use of approved vaccine doses, at any dosing interval between the last dose and the booster dose, were considered in this review.

General Search Results

As of November 12, fifty-one (51) studies were identified providing information regarding the effect of booster vaccination for COVID-19. Eight (8) were randomized

controlled trials, 11 were prospective cohort studies, six were retrospective cohort studies, 21 were single cohort, self-controlled and four were case reports. Thirty-five involved the general population of which five included only healthcare workers. Sixteen studies included the immunocompromised population. Ten studies investigated on both homologous and heterologous booster vaccination, ten on heterologous vaccination and 31 on homologous vaccination. Five studies reported clinical outcomes, 44 had immunogenicity outcomes and 31 studies reported safety data.

The following vaccines were used as booster in the different studies: BNT162b2 (28 studies), mRNA-1273 (11 studies), ChAdOx1 (6 studies), CoronaVac (8 studies), Ad26.CoV2.S (8 studies), BBIBP-CorV (1 study). Three studies involved a booster using an unspecified inactivated viral vaccine. One study used Ad5-nCoV and another used VO1 as booster. No study was identified that reported on using Gam-COVID-Vac, BBV152, or NVX-Cor2373 as a booster.

The search strategy is in Appendix B.

Risk of Bias Assessment
The results of the risk of bias assessment are presented in Appendix Table 1.

RESULTS

GENERAL POPULATION, HOMOLOGOUS BOOSTER VACCINATION

BNT162b2 homologous booster

Clinical Efficacy / Effectiveness

Three retrospective cohort studies, all conducted in Israel, provided information on the clinical effectiveness of BNT162b2 as a booster after at least 5 months of BNT162b2 primary vaccination.[1-3] All studies showed that booster vaccination provided additional short-term protection. The first study conducted among persons older than 60-year-olds showed that those receiving the booster were 11.4x more protected against COVID-19 infection and 15.5x more protected against severe COVID-19 infection compared to those without a booster. The follow up period in this study was less than 12 days.[1] The second study was a test negative case control study, also from Israel, conducted among the 40 years and older population. It showed increasing marginal protection associated with the booster from 3% to 48% and to 79% at 0 to 6, 7 to 13 and 14 to 20 days, respectively, after the booster.[2] The third study was a matched cohort study involving persons aged 12 years and older after a follow up of 13 days post-boost which showed vaccine effectiveness rates of >90% against symptomatic COVID infection (91%), hospitalization (93%), and severe disease (92%). VE for COVID-related death was estimated at 81% (95% CI 59-97).[3]

Immunogenicity

One US-FDA report provided the results of a booster dose in a subset of the Ph2/3 trial population after a median of six to eight months of the primary vaccination. It demonstrated a 3.3-fold rise in the antibody titers.[4]

A retrospective cohort study compared the cycle-threshold (CT) values over time of over 16,000 adult infections consisting of unvaccinated, vaccinated with BNT162b2, and boosted with BNT162b2 subgroups. The study showed a decline in CT values

over time from primary vaccination to values similar to the unvaccinated at 6 months post vaccination. This decline was overturned after a booster, which translated to a 5-fold reduction in viral load post-boost.[5]

Safety
The US-FDA report indicated that generally the same adverse event rates were reported after the booster dose as those after the second dose, after a follow up of 2.6 months.[4] Another study observed a similar and greater extent of systemic reactions 48 hours after booster compared to those given second and first dose, respectively.[6] A large retrospective study of 38,094 adults who received the BNT162b2 booster more than 6 months after primary vaccination revealed increased reporting of fatigue, lymphadenopathy, nausea, headache, arthralgia myalgia, diarrhea, fever and vomiting after the booster compared to the second dose. More emergency department visits within 2 days of the vaccination with the booster was also observed compared to the other doses.[7]

mRNA-1273 homologous booster
Clinical Efficacy / Effectiveness
No study was identified that provided information on the clinical efficacy/effectiveness of mRNA-1273 booster dose after a mRNA-1273 primary vaccination.

Immunogenicity
Two RCTs investigated the immunogenicity of a homologous mRNA-1273 booster. The first RCT had two arms of different doses of the primary series (50ug and 100ug) boosted with the 50ug dose compared to a historical control or self (i.e. after two doses only). Higher titers 28 days after the booster dose compared to 28 days after the second dose, regardless of dose, were observed in three different antibody assays.[8] The second RCT compared a modified vaccine against the beta variant (mRNA-1273.351) with the original formulation as booster given at a median of 5.9-7.5 months and 5.6-6.6 months, respectively. Two weeks after booster, significant fold-increases in neutralizing antibodies against wild type, beta variant, and gamma variants were observed after booster vaccination. Higher fold-rises were observed with the .351 version compared with the original mRNA-1273.[9]

A subgroup of a clinical trial population who received two doses of 100ug mRNA-1273 were given six month later either a lower dose (50ug) boost, or different variations of mRNA-1273 (mRNA-1273.351 at 50 or 20ug dose, mRNA-1273.211 at 50ug dose). Neutralization titers 29 days after the booster showed significantly higher levels compared to titers after the first dose. All boosters increased neutralization against all variants of concern to levels equivalent to the wild-type. The .211 version showed the greatest increase in titers against the VOCs.[10]

Safety
The above studies reported similar local and systemic reactogenicity of the booster vaccines compared to primary series alone. Majority were mild to moderate with injection site pain, fatigue, headache, myalgia, and arthralgia as the most common local and systemic adverse events. All three studies did not report serious adverse events.[8-10]

A retrospective study of almost 10,000 adults who received a booster mRNA-1273 after a mean interval of 173 days from the primary vaccination reported increased reporting of the following adverse events after the booster compared to the second dose: fatigue, lymphadenopathy, nausea, headache, arthralgia, myalgia, fever and vomiting. The study also revealed more emergency room visits after the booster vaccination compared to the other doses.[7]

ChAdOx1 homologous booster

Clinical Efficacy / Effectiveness

No study was identified that provided information on the clinical efficacy/effectiveness of ChAdOx1 booster dose after a ChAdOx1 primary vaccination.

Immunogenicity

One study was among the subset of patients in the clinical trial, who received a booster dose of the ChAdOx1 vaccine 44 to 45 weeks after the primary vaccination. It reported two-fold rise in neutralizing antibody titers and IFN-γ counts post boost.[11]

Safety

The above study also reported less reactogenicity with the booster dose compared to the first dose.[11] No safety information is available beyond 28 days post homologous ChAdOx1 boost.

Ad26CoV2.S homologous booster

Clinical Efficacy / Effectiveness

No study was identified that provided information on the clinical efficacy/effectiveness of the Ad26.COV2.S homologous booster.

Immunogenicity

One study involving a subgroup of the Ph1/2 trial population reported on the rise in the anti-spike IgG of patients who received a second dose of Ad26.COV2.S after 6 months. It showed a 4.7-fold rise in the titers.[12]

Safety

The above study reported similar reactogenicity rates pre- and post-boost.[12] No safety information is available beyond 28 days post homologous Ad26.COV.2 boost.

CoronaVac homologous booster

Clinical Efficacy / Effectiveness

No study was identified that provided information on the clinical efficacy/effectiveness of the CoronaVac homologous booster.

Immunogenicity

Six studies studied varying doses and intervals of CoronaVac homologous booster vaccination.[13-18] One RCT compared two different doses of CoronaVac boosting 8 months after a primary CoronaVac of different doses (1.5ug or 3.0ug). Both dosing regimens showed significant fold-rise in antibody titers after the boost compared to prior.[15] Another RCT compared early boosting (28 days) and late boosting (6 months) after two different dosing regimen of CoronaVac. All arms of the trial showed significant rise in antibody titers after boosting. Late booster showed higher titers compared to early boosting.[13] In the RCT comparing homologous and heterologous boosting with Ad5-nCoV, 3 to 6 months after a primary CoronaVac vaccination,

homologous boosting resulted in a 32-fold rise in neutralizing antibody titers post-boost, but still lower than the 6-fold rise with heterologous boosting.[14] The fourth RCT compared homologous CoronaVac boosting and heterologous boosting with BNT162b2 after a mean of 115 days, among adults who had <60% sVNT seropositivity one month after primary vaccination with CoronaVac. The study showed significant increase in seropositivity post boost. However, seropositivity for the Beta, Gamma, and Delta variants were significantly reduced even with homologous CoronaVac boosting.[17] In the self-controlled cohort study where a booster dose of CoronaVac was given six months after primary vaccination, one to two-fold increases in the different immunologic parameters were noted.[16] Another single cohort, self-controlled study found a 3-fold increase in neutralizing antibody titers 1 month after the booster dose.[18]

Safety

The RCTs on CoronaVac homologous booster vaccination consistently showed no difference in the adverse reaction and adverse event rates associated after the booster dose and in the earlier doses. Severe adverse reactions were rare and were not vaccine-related.[13-15,17] One study reported 14 serious adverse events within 6 months after the booster dose, all of which were assessed to be unrelated to the vaccination.[13]

Inactivated virus vaccine homologous booster

Clinical Efficacy / Effectiveness

No study was identified on inactivated virus vaccine homologous booster.

Immunogenicity

Three observational single cohort studies from China reported on the immunogenicity results of an inactivated virus vaccine homologous booster, with the make/brand not specified. All studies showed high seropositivity rates for neutralizing antibodies post boost,[19-21] and increased cellular response after the boost from a decline in levels just before the boost.[21]

Safety

No study reported on the safety of an inactivated virus vaccine homologous booster (apart from the CoronaVac studies).

VO1 homologous booster

Clinical Efficacy / Effectiveness

No study was identified on VO1 homologous booster.

Immunogenicity

One study from China included previously primed Phase 1 trial participants who received a third dose of VO1, a recombinant fusion protein vaccine, four to five months after. It showed slightly higher RBD-binding antibody titers 28 days after the boost compared to pre-boost. Greater amplification in titers was seen in the younger subgroup, and in the neutralizing titers against the variants of concern, despite reduced levels compared to the reference strain.[22]

Safety
The above study showed adverse reaction rates in the range of 5-10%, with no reported severe or vaccine-related adverse event.[22]

Gam-COVID-Vac, BBV152 and NVX-CoV2373 homologous booster
No study was identified which investigated these vaccines in a homologous booster regimen.

GENERAL POPULATION, HETEROLOGOUS BOOSTER VACCINATION
Primary BNT16b2, boosting with mRNA-1273
Clinical Efficacy / Effectiveness
No study providing clinical outcomes with this heterologous booster regimen was identified.

Immunogenicity
One multi-arm cohort study was identified with one arm involving 50 participants receiving mRNA-1273 booster after a primary BNT162b2 vaccination. This study showed significantly higher IgG and neutralizing antibody titers after this booster regimen compared to pre-boost, and to the homologous BNT162b2 booster and heterologous Ad26.CoV2.S booster regimens. It also showed higher titers against the Beta and Delta variants compared to pre-boost.[23]

Safety
The above-mentioned study noted similar reactogenicity across all treatment groups and of the booster regimen with the primary series. The most common local adverse reaction was pain or tenderness at the injection site and the most common systematic reactions were malaise or fatigue, myalgia, and headache. Twenty-two (43%) of participants reported at least one unsolicited adverse event.[23]

Primary BNT16b2, boosting with Ad26.COV2.S
Clinical Efficacy / Effectiveness
No study providing clinical outcomes with this heterologous booster regimen was identified.

Immunogenicity
Two studies were identified which investigated boosting primary BNT162b2 vaccination with Ad26.CoV2.S. One was a multi-arm adaptive trial, which compared homologous and heterologous booster regimen using BNT162b2, mRNA-1273 and Ad26.CoV2.S. This study found that the BNT162b2/Ad26.COV2.S combination provided significant IgG and NAB titer elevations post boost, but 2- to 3-fold lower titers compared with homologous BNT162b2 or heterologous booster with mRNA-1273. The study also showed increased titers against the Beta and Delta variants with booster, except for two participants.[23]

A case report of four individuals who received the Ad26CoV2.S as a booster four months after a primary BNT162b2 vaccination reported similar results with heightened titers of neutralizing antibodies following the booster that could neutralize nearly all the variants tested.[24]

Safety
The cohort study mentioned above showed similar reactogenicity with the booster vaccination as the primary series. One related adverse event of special interest was reported in a patient with severe vomiting after the booster vaccination. No serious AE was reported.[23]

Primary mRNA-1273, boosting with BNT162b2
Clinical Efficacy / Effectiveness
No study providing clinical outcomes with this heterologous booster regimen was identified.

Immunogenicity
One prospective multi-arm cohort study included one arm with 51 participants who received BNT162b2 as a booster after a primary mRNA-1273 vaccination. This study showed significant rise in IgG and neutralizing antibody titers post-boost compared to pre-boost, and higher rises when compared to titers reached after a homologous mRNA-1273 boost or a heterologous Ad26.CoV2.S boost.[23]

Safety
The above-mentioned study reported similar reactogenicity rates with booster vaccinations as with the primary series in general. For this specific regimen, local reactogenicity rates after the booster was reported at 9-14%. Systemic adverse events were at 10-60% with malaise, myalgia and headache being the most common, mostly mild in severity. At least one unsolicited adverse event was reported by seventeen individuals in the group (24/51, 47.0%). No serious or severe adverse event was noted.[23]

Primary mRNA-1273, boosting with Ad26.COV2.S
Clinical Efficacy / Effectiveness
No study providing clinical outcomes with this heterologous booster regimen was identified.

Immunogenicity
One prospective multi-arm cohort study included one arm with 49 participants receiving Ad26.CoV2.S booster after a primary mRNA-1273 vaccination. This study showed significant rise in IgG and neutralizing antibody titers post-boost compared to pre-boost, but lower rises when compared to titers reached after a homologous mRNA-1273 boost or a heterologous BNT162b2 boost.[23]

Safety
The above-mentioned study reported similar reactogenicity rates with booster vaccinations as with the primary series in general. For this specific regimen, there was a low local reactogenicity rate after the booster at 4-8%. Systemic adverse events were at 20-60% with malaise, myalgia and headache being the most common, mostly mild in severity. At least one unsolicited adverse event was reported by seventeen individuals in the group (17/49, 34.7%). No serious or severe adverse event was noted.[23]

Primary ChAdOx1, boosting with BNT162b2

Clinical Efficacy / Effectiveness

No study providing clinical outcomes with this heterologous booster regimen was identified.

Immunogenicity

One small single cohort study described the immunologic response of 20 patients who received a BNT162b2 boost after primary ChAdOx1 vaccination. It showed significantly lower CRP levels post-boost and higher titers of anti-S1-RBD IgG 14 days after the boost compared to pre-boost.[25]

Safety

No safety outcome has been reported with this combination.

Primary Ad26.COV2.S, boosting with BNT162b2

Clinical Efficacy / Effectiveness

No study providing clinical outcomes with this heterologous booster regimen was identified.

Immunogenicity

Four studies provided immunogenicity outcomes with heterologous vaccination with BNT162b2 after an Ad16.Cov2.S primary vaccination. One RCT was among healthcare workers (details reported in the section below). One prospective cohort study comparing no boost, homologous boost and BNT162b2 single and two-dose regimen, included one group of 14 persons who received BNT162b2/Ad28CoV2.S combination. This combination showed higher anti-spike IgG, IgA and neutralizing antibody titers after the heterologous than the homologous booster vaccination. No or minimal increase in the spike-specific memory B cell levels were observed. Higher spike-specific T-cells were seen after heterologous compared to homologous boosting.[26] Another multi-arm cohort study showed similar results in terms of higher titers observed with heterologous compared to homologous boosting. In addition, this study showed significant rise in titers post boost compared to pre-boost but lower titers of this combination compared with mRNA-1273 boosting after an Ad26.CoV2.S primary.[23] A single-cohort, self-controlled study involving 15 individuals who received BNT162b2 16 weeks after Ad26CoV2.S vaccination showed significant rises in IgG and neutralizing antibody titers post-boost with all participants reaching seropositivity for these parameters. It also reported significant increase in the spike-specific CD4 T-cell levels and seropositivity rates.[27]

Safety

One comparative cohort and one single cohort study provided safety outcomes after this heterologous combination. Both reported similar reactogenicity rates with the booster vaccination compared to the primary vaccination.[23,27]

Primary Ad26.COV2.S, boosting with mRNA-1273

Clinical Efficacy / Effectiveness

No study providing clinical outcomes with this heterologous booster regimen was identified.

Immunogenicity
Two studies investigated the immunogenicity of this combination. One RCT involving healthcare workers is detailed in the section below. One multi-arm study showed significantly higher IgG and neutralizing antibody titers post-boost compared to pre-boost and when compared to titers after homologous boosting and heterologous boosting with BNT162b2.[23]

Safety
The above-mentioned multi-arm study reported similar reactogenicity rates across all the vaccine combinations in the trial. Local reactogenicity rate was highest at 24% for pain or tenderness at the injection site. Most common systemic adverse reactions were myalgia and malaise (40-60%). Unsolicited adverse events were noted in 21 of the 53 participants (39.6%). No severe or serious adverse events were reported.[23]

Primary CoronaVac, boosting with BNT162b2
Clinical Efficacy / Effectiveness
No study providing clinical outcomes with this heterologous booster regimen was identified.

Immunogenicity
Three studies described the immunogenicity of this combination among the health population. One was a prospective cohort study among healthcare workers detailed in the section below. One RCT compared homologous CoronaVac booster vaccination with heterologous booster with BNT162b2 given around 4 months after the primary series. This study showed a 96.6% inhibition after heterologous boosting compared with 57.8% with homologous boosting. This significantly higher inhibition rates with heterologous boosters were seen for Beta, Gamma, and Delta variants, when compared to the homologous booster. Titers of the RBT, NTD and S2 antibodies were significantly higher in the those who received BNT162b2 as booster.[17] A single cohort study showed significantly higher anti-spike RBD IgG titers and seropositivity rates post-boost compared to pre-boost. This rise was seen regardless of age group.[18]

Safety
The RCT comparing homologous and heterologous booster vaccination reported generally similar overall reactogenicity rates. However, higher rates of injection site pain, fatigue and muscle pain were observed in the heterologous compared to the homologous group.[17]

Primary CoronaVac, boosting with ChAdOx1
Clinical Efficacy / Effectiveness
No study providing clinical outcomes with this heterologous booster regimen was identified.

Immunogenicity
Three studies reported on the immunogenicity of this combination among healthcare workers, detailed below.

Safety
The safety outcomes of this combination are described in the section covering healthcare workers.

Primary CoronaVac, boosting with Ad5-nCoV
Clinical Efficacy / Effectiveness
No study providing clinical outcomes with this heterologous booster regimen was identified.

Immunogenicity
One RCT compared immunogenicity and safety outcomes of patients who received homologous CoronaVac and heterologous Ad5-nCoV booster vaccination three to six months after a primary CoronaVac series. Heterologous vaccination resulted in significantly higher titers of neutralizing antibodies and of RBD-binding IgG compared with homologous boosting. Increased levels of Th1-biased cytokine IFN-gamma were also seen post-boost with higher levels after heterologous compared to homologous boosting.[14]

Safety
The above-mentioned RCT reported that significantly more patients receiving the heterologous booster had more solicited injection site and systemic reactions that those who received a homogenous dose (29.2% vs 2.9% and 13.5% vs 2.9%). No serious adverse event was seen in the study.[14]

Primary BBIBP-CorV, boosting with BNT162b2
Clinical Efficacy / Effectiveness
One prospective cohort study compared the immunogenicity among primary BNT162b2 vaccine recipients and those who received BNT162b2 as a booster at least three months after primary BBIBP-CorV vaccination. It reported two breakthrough infections (4%) in the booster group within one week after the booster administration, whereas none of the patients in the non-boosted group develop COVID-19 during the study. Follow up period was unclear in the report.[28]

Immunogenicity
The above study showed very a significant rise in the anti-S IgG titers after a BNT162b2 booster (6 vs. 8040 BAU/ml). This post-boost titer level was higher than the infection-naïve patients who received a primary BNT162b2 vaccination (1384 BAU/ml) but lower than those who had COVID-19 prior to the BNT162b2 vaccination (22536 BAU/ml).[28]

Safety
Safety outcomes in the above-mentioned study included a 62% adverse event rate among those who received the booster, mainly from pain at the injection site (60%). Systemic adverse event rates ranged from 2-10%, with lethargy as the most common. No severe or serious adverse event was reported.[28]

HEALTHCARE WORKERS
Five reports were identified involving healthcare workers receiving booster vaccination. Two were on homologous and three on heterologous booster vaccination.

BNT162b2 homologous booster

Clinical Efficacy / Effectiveness

No study was identified that provided information on the clinical efficacy/effectiveness of BNT162b2 booster dose after a BNT162b2 primary vaccination.

Immunogenicity

One single cohort, self-controlled study involved healthcare workers with or without a history of SARS-CoV-2 infection given a booster at a median of 166 days. At 21-28 days after booster, there was a 1.3- to 2.2-fold increase in anti-S1/S2 IgG compared to pre-boost.[29]

Safety

The above study reported less total number of adverse events after the booster vaccination compared to the primary series with pain at injection site as the most common adverse event. However, more systemic adverse events such as tiredness, myalgia, arthralgia, fever, and adenopathy were reported after the booster.[29]

BBIBP-CorV homologous booster

Clinical Efficacy / Effectiveness

No study was identified that provided information on the clinical efficacy/effectiveness of BBIBP-CorV booster dose after a BBIBP-CorV primary vaccination.

Immunogenicity

A study on volunteers for a third dose 6 months after the primary series showed a 7.2-fold increase in neutralizing antibodies, almost 2-fold increase in spike-specific and RBD-specific memory B- cells, 2.3-fold increase in T-cell response, 2.7-fold increase in SARS-CoV-2-specific CD8+ T-cell, and 5.9-fold increase in SARS-CoV-2 specific CD4+ T-cell at 1 week after booster.[30]

Safety

The above study reported no severe side effects related to vaccination.[30]

Primary Ad26.COV2.S, boosting with BNT162b2

Clinical Efficacy / Effectiveness

No study providing clinical outcomes with this heterologous booster regimen was identified.

Immunogenicity

One RCT involving HCWs who received primary Ad26.COV2.S compared no boost, heterologous boost, and boosting with either BNT162b2 or mRNA-1273 3 months after the primary vaccination. This study showed higher anti-S and neutralizing antibody titers and seropositivity rates was well as rises in T-cell counts associated with BNT162b2 booster compared to homologous booster vaccination, but lower responses when compared to the mRNA-1273 booster vaccination.[31]

Safety

The above trial reported similar local and systemic adverse reaction rates with homologous booster vaccination but lower rates when compared with the mRNA-1273 heterologous booster.[31]

Primary Coronavac, boosting with BNT162b2

Clinical Efficacy / Effectiveness

No study providing clinical outcomes with this heterologous booster regimen was identified.

Immunogenicity

One prospective cohort study compared boosting with BNT162b2 and with ChAdOx1 among healthcare workers who received two doses of CoronaVac. It showed significant rise in anti-S RBD titer post-BNT162b2 boost compared to pre-boost (37.46 vs. 22558 U/mL), with titers significantly higher than after receiving a ChAdOx1 boost (5159 U/mL). The %sVNT inhibition levels versus the Delta variant were similarly high between the two booster groups.[32]

Safety

Comparison of adverse event rates between the two heterologous vaccination regimen in the above-mentioned study showed no difference. The most common reported adverse event was pain at the injection site.[32]

Primary Coronavac, boosting with ChAdOx1

Clinical Efficacy / Effectiveness

No study providing clinical outcomes with this heterologous booster regimen was identified.

Immunogenicity

Three studies reported on immunogenicity outcomes with heterologous ChAdOx1 booster after a primary CoronaVac series on healthcare workers. One was a comparative cohort that compared this regimen with a heterologous booster with BNT162b2. This study revealed significant rise in anti-S RBD titers post-boost compared to pre-boost (106.8 vs 3647.8 U/mL), but lower titers when compared to heterologous booster with BNT162b2 (22558 U/mL). Similar %sVNT inhibition of the Delta variant was seen between the two groups.[32] Another comparative cohort study compared immunologic outcomes after a primary CoronaVac vaccination with a primary ChAdOx1 vaccination and a heterologous booster vaccination regimen using ChAdOx1 after a CoronaVac primary series. This study showed significantly better response in all immunologic parameters with the heterologous booster regimen.[33] One case report of a 52-year-old healthcare professional who received the heterologous booster combination reported significant rise in anti-spike IgG titer and neutralizing antibody seropositivity rate post boost.[34]

Safety

The comparison of adverse event rates was found to be similar between heterologous booster vaccination with BNT162b2 or with ChAdOx1 after a primary CoronaVac series in the above-mentioned study. The most common reported adverse event was pain at the injection site.[32] In the case report, the patient developed palpitations after the booster needing propranolol to control symptoms and weight loss. An increase in the dose of methimazole to 5 mg/d resolved his symptoms.[34]

IMMUNOCOMPROMISED POPULATION, HOMOLOGOUS BOOSTER

BNT162b2 homologous booster

Clinical Efficacy / Effectiveness

Three studies provided clinical outcomes after BNT162b2 homologous booster administration among the immunocompromised population. Two were single cohort (self-controlled) studies on solid organ transplant recipients[35,36] and one was a single cohort (self-controlled) study on patients on dialysis.[37] In patients on dialysis who received a BNT162b2 booster at least 3 weeks after primary BNT162b2 vaccination, no breakthrough infection was observed after a median follow-up of 30 days, compared to four symptomatic COVID-19 infections after the second dose.[37] Among the transplant recipients, one study reported one patient (out of 35) who developed RT-PCR confirmed COVID-19 infection 6 days after a third dose of BNT162b2 after a median interval of 69 days.[35] The other study reported no post-boost COVID-19 infection with the third dose given 60-62 days after the primary vaccination.[36] The pre-boost infection rate was not established in these studies.

Immunogenicity

Seven studies described immunologic responses of immunocompromised patients to the homologous BNT162b2 booster. Three reported on the change in antibody titers [37-39] and three reported on seroconversion[35,40-41] and one study reported both.[36] Consistent in these studies was the rise in the antibody titers noted after the third dose compared to the second. The two studies that compared the seropositivity rates before and after the third dose reported significant increases. In contrast, a study reported very low proportion (6.4%) of kidney transplant patient on belatacept developing detectable levels of anti-SARS-COV-2 antibodies after the third dose.[35]

Safety

Five studies reported on the safety of BNT162b2 homologous booster in the immunocompromised. Generally, they all noted similar adverse event rates with the second dose and no severe adverse events were reported after the third dose.[35-37,40,42] No safety data are available beyond 44 days after the third dose.

mRNA-1273 homologous booster

Clinical Efficacy / Effectiveness

No study was identified providing clinical efficacy/effectiveness of mRNA-1273 homologous booster vaccination on the immunocompromised population.

Immunogenicity

One RCT compared the booster dose of mRNA-1273 two months after the primary vaccination, with placebo, in transplant recipients.[43] Results showed significant increases in seropositivity rates for anti-RBD IgG (3-fold) and for neutralizing antibodies (2.4-fold) post-boost compared to placebo. T-cell titers post-boost were also noted to be 6.4x higher than placebo. A single self-controlled cohort study among kidney transplant patients who were all seronegative for anti-RBD-IgG after the two doses of mRNA-1273 showed that 49% of the booster recipients seroconverted.[44]

Safety

When compared with placebo and to the second dose in one RCT, the mRNA-1273 homologous booster dose was associated with slightly higher local and systemic

adverse reaction rates.[43] No safety information is available beyond 28 days post homologous mRNA-1273 boost.

ChAdOx1, CoronaVac, Ad26.CoV2.S, Gam-COVID-Vac, BBV152 and NVX-COV2373 homologous booster

No study was identified that investigated the above vaccines as homologous boosters among the immunocompromised.

IMMUNOCOMPROMISED POPULATION, HETEROLOGOUS BOOSTER

Primary BNT162b2, boosting with Ad26.COV2.S

Clinical Efficacy / Effectiveness

No study providing clinical outcomes with this heterologous booster regimen among the immunocompromised population was identified.

Immunogenicity

Three studies provided immunogenicity data after heterologous boosting with Ad26.CoV2.S after a primary BNT162b2 vaccination among the immunocompromised. The first was a retrospective cohort study among patients with B-cell malignancy who received different combinations of vaccines.[45] Another similar study involved 30 solid organ transplant patients who had suboptimal response to the standard vaccination. Seven of these patients received the BNT162b2/Ad26.COV2.S heterologous booster regimen, of whom four seroconverted post-boost.[46] The third study was a case report of two female chronic lymphocytic leukemia patients who received this heterologous booster regimen.[47] All three studies showed differences in the responses of the patients with some showing significant immunologic response after the booster compared to pre boost while others remained non-responsive.

Safety

Only the study involving solid organ transplant patients reported safety data after booster vaccination, but without providing outcomes by vaccine-booster regimen. Of the 30 patients, 15 had mild to moderate local and/or systemic adverse reaction. One antibody-mediated transplant rejection 7 days after the booster was reported in the study.[46]

Primary BNT162b2, boosting with mRNA-1273

Clinical Efficacy / Effectiveness

No study providing clinical outcomes with this heterologous booster regimen among the immunocompromised population was identified.

Immunogenicity

Two studies on immunocompromised patients reported on immunogenicity outcomes of different combinations of homologous and heterologous booster vaccinations. One study involved 30 solid organ transplant patients who had suboptimal response to the standard vaccination and received booster doses after a primary series. Seven patients received the BNT162b2/mRNA-1273 heterologous booster regimen. Five of these patients seroconverted post-boost.[46] The other study was on patients with B-cell malignancies where seven patients received this heterologous booster regimen. Two patients remained non-responsive while five seroconverted.[45]

Safety
The above-mentioned study reported safety data after booster vaccination, but without providing outcomes by vaccine-booster regimen. Of the 30 patients in the study, 15 had mild to moderate local and/or systemic adverse reaction. One antibody-mediated transplant rejection 7 days after the booster was reported in the study.[46]

Primary mRNA-1273, boosting with Ad26.COV2.S
Clinical Efficacy / Effectiveness
No study providing clinical outcomes with this heterologous booster regimen among the immunocompromised population was identified.

Immunogenicity
Three studies provided immunogenicity outcomes after a heterologous Ad26.COV2.S booster with a mRNA-1273 primary vaccination. The first study involved 30 solid organ transplant patients who had suboptimal response to the standard vaccination, of which eight patients received the BNT162b2/Ad26.COV2.S heterologous booster regimen. Only one patient seroconverted after the booster.[46] The study was a case report of a 74-year old male with rheumatoid arthritis on treatment who received the said heterologous vaccination regimen. Significant rise in anti-RBD IgG titers was seen post-boost, achieving seroconversion.[48] The third study was on patients with B-cell malignancy where 14 patients received this regimen. Seven remained seronegative, five seroconverted, and two showed enhanced response from initial low but detectable titers.[45]

Safety
The above-mentioned study reported safety data after booster vaccination, but without providing outcomes by vaccine-booster regimen. Of the 30 patients in the study, 15 had mild to moderate local and/or systemic adverse reaction. One antibody-mediated transplant rejection 7 days after the booster was reported in the study.[46]

Primary mRNA vaccine, boosting with ChAdOx1
Clinical Efficacy / Effectiveness
No study providing clinical outcomes with this heterologous booster regimen among the immunocompromised population was identified.

Immunogenicity
One RCT involving patients on rituximab treatment who had been immunized with two doses of mRNA vaccine compared boosting with the same mRNA vaccine or with a ChAdOx1. This study showed higher seroconversion rates with the homologous booster vaccination, a non-significant higher anti-RBD titers, T-cell response expressed as median spot forming cell counts and positivity rates with the heterologous vaccination.[49]

Safety
The above trial reported that most side effects were similar between the homologous and heterologous booster. Higher rates of arthralgia, myalgia and fatigue, and lower rates for injection site pain were noted after ChAdOx1 booster. No case of thrombocytopenia, anaphylactoid reactions or neurologic complications were reported.[49]

Primary mRNA vaccine, boosting with another mRNA

Clinical Efficacy / Effectiveness

No study providing clinical outcomes with this heterologous booster regimen among the immunocompromised population was identified.

Immunogenicity

One study including 82 kidney transplant patients reported significantly increased anti-spike IgG titers after receiving a fourth dose of an mRNA vaccine (16.6 vs. 146.2 BAU/mL). No separate analysis for the two vaccines was made. The study noted that most patients who did not achieve detectable levels of antibodies after the third dose remained seronegative after the fourth.[50]

Safety

The above-mentioned study only noted no safety concerns with the administration of the fourth dose without further elaboration.[50]

The detailed characteristics and the results of these trials are in Appendix Tables 3-8.

The summary of findings table is in Appendix C.

RECOMMENDATIONS FROM OTHER GROUPS ON BOOSTER VACCINATION

The World Health Organization, in its statement on October 4, 2021 maintained that the primary focus is to increase global vaccination coverage with the primary series. Evidence to support a widespread booster program is inconclusive. This is particularly in the context of limited global vaccine supply.[51] No update of this statement has been released as of November 16, 2021.

The US Centers for Disease Control and Prevention, in its November 9, 2021 update, recommended that the following populations should receive a COVID-19 booster shot [52]:

- Who received a primary mRNA COVID-19 vaccine and are 65 years and older, 50 to 64 years with underlying medical conditions, or 18 years and older who live in long-term care settings
- Who received the Johnson&Johnson/Janssen COVID-19 vaccine and are 18 years and older

In addition, the agency recommended that those who received a primary mRNA COVID-19 vaccine and are 18 to 49 years old with underlying medical conditions, or 18 years and older who work or live in high-risk settings may receive a booster shot.

The UK Joint Committee on Vaccination and Immunisation (JCVI) updated its previous advice on booster vaccination for all adults aged 50 years and older and those in a COVID-19 at-risk group to also include 40- to 49-year olds beginning November 15, 2021.[53]

ONGOING TRIALS

Search of ClinicalTrials.gov registry on November 16, 2021 yielded 44 trials on COVID-19 booster vaccination. See Appendix Table 9 for details.

RESEARCH GAPS

Additional and better certainty of evidence is needed in the following areas to inform practice on the implementation of a booster vaccination program against COVID-19:

1. Duration of protection (based on breakthrough infection rates over time or long-term vaccine efficacy/effectiveness data)
2. Correlates of protection
3. Clinical efficacy / effectiveness of booster vaccination
4. Optimum timing (interval from primary series) of booster administration
5. Optimum dose of booster for the different vaccines
6. Benefit/harm ratio of homologous versus heterologous booster vaccination
7. Cost-effectiveness of booster vaccination versus expansion of primary vaccination program

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Appendix A. Evidence to Decision

Table 1. Summary of initial judgements prior to the panel discussion (N=10)

FACTORS	JUDGEMENT						RESEARCH EVIDENCE/ADDITIONAL CONSIDERATIONS
Problem	No	Yes (10)					
Benefits	Large (5)	Moderate (4)	Small	Uncertain (1)			HOMOLOGOUS BOOSTERS General Population • BNT162b2/BNT162b2 showed increasing marginal protection • -fold rise in neutralizing antibody titers and IFN-γ counts post boost for ChAdOx1. • CoronaVac showed increases in antibody titers post-boost. • 4.7 fold rise in titers after Ad26CoV2.S homologous booster. Immunocompromised Population • Low to no cases of infection/hospitalization, as well as increased titers post boost using BNT162b2/BNT162b2 • Increased seropositivity and titers post boost using mRNA-1273/mRNA-1273 HETEROLOGOUS BOOSTERS • General Population: High titers post boost with heterologous than homologous for CoronaVac/Ad5-nCoV2 • Immunocompromised: Increased seropositivity post-boost using mRna/mRNA-1273 or BNT1662b2 or Ad26.CoV2.S
Harm	Large	Small (10)	Uncertain				HOMOLOGOUS General Population • BNT162b2/BNT162b2 and Coronavac showed same adverse event rates. • Less reactogenicity was documented with ChAdOx1 booster dose • similar reactogenicity rates for Ad26CoV2.S. Immunocompromised Population • Similar adverse event reaction rates as primary using boost pattern of BNT162b2/BNT162b2 • More reactogenic than no boost, similar serious adverse event rate for mRNA-1273/mRNA-1273 HETEROLOGOUS BOOSTERS General Population • CoronaVac/Ad5-nCov2: More adverse reaction, but no serious AE Immunocompromised Population • Similar adverse event rates pre-boost using mRna/mRNA-1273 or BNT1662b2 or Ad26.CoV2.S or mRNA/ChAdOx1
Certainty of evidence	High	Moderate (1)	Low (9)	Very low			• Low to very low
Balance of effects	Favors intervention (7)	Does not favor vaccine	Uncertain (3)				• Current evidence favors booster vaccination, if based solely on immunologic effectiveness versus clinical harm. The benefit is more significant in the immunocompromised population.

Values	Important uncertainty or variability (3)	Possibly important uncertainty or variability (4)	Possibly no important uncertainty or variability (3)	No important uncertainty or variability			• The survey conducted by the DOH among the general population and among healthcare workers indicated that majority would avail of boosters if they are made available and when recommended by the experts.
Resources required	Uncertain (2)	Large cost (4)	Moderate cost (4)	Negligible cost or savings	Moderate savings	Large savings	• Differs per vaccine combination used
Certainty of evidence of resources required	No included studies (8)	Very low (1)	Low (1)	Moderate	High		
Cost effectiveness	No included studies (8)	Favors the comparison (1)	Does not favor either the intervention or the comparison	Favors the intervention (1)			
Equity	Uncertain (4)	Reduced	Probably no impact (1)	Increased (5)			• Addresses the issues of poor immunologic response among immunocompromised patients, declining antibody titers over time, and reduced vaccine effectiveness against SARS-CoV-2 variants of concern. • Fully-vaccinated senior citizens per region: 34.2% MIMAROPA; 28.3% in BARMM.
Acceptability	Uncertain (3)	No	Yes (7)				• Based on the DOH Survey (September 2021), majority of the general population and healthcare workers would avail of a booster vaccine. Vaccines mentioned have been approved for EUA by the Philippine FDA on varying dates.
Feasibility	Uncertain (2)	No (1)	Yes (7)				• Varies per vaccine

Appendix B. Search Strategy

The COVID-19 Living OVerview of the Evidence (L·OVE) platform, the COVID-NMA, and www.metaEvidence.org were searched for both randomized and non-randomized studies on adults investigating the efficacy, effectiveness, and safety of a booster dose to any COVID-19 vaccine. For the COVID-19 L·OVE platform, the search was by PICO with the following filters in order: "prevention or treatment", “public health”, "vaccination", and “SARS-CoV-2 vaccines”. Only systematic reviews and primary studies were included with the latter's yield further filtered to include all study designs but only those reporting data; the reference lists of systematic reviews were examined for eligible studies. For the COVID-NMA, the living evidence synthesis of RCTs related to vaccines was examined. For the database of www.metaEvidence.org, the search filters were the following: “vaccines”,”COVID-19 prophylaxis”, “all patients”, “all studies (RCT and observational)”. The reference lists of the weekly situational (epidemiological) reports published by the World Health Organization (WHO), and the VIEW-Hub Resource Library COVID-19 Vaccine Effectiveness Reports were searched for relevant studies. The WHO COVID-19 literature on coronavirus disease database was also searched using “booster” as a search term. Relevant reports from major global regulatory agencies including the US Food and Drug Authority (US FDA), the US Center for Disease Control (CDC), the European Medicines Agency (EMA), the United Kingdom Medicines and Healthcare Products Regulatory Agency (UK-MHRA), the WHO, and the Philippine Food and Drug Association (PH FDA) including their reference lists were also reviewed for relevant studies.

Appendix 1. Risk of Bias of Included Studies

STUDY ID	STUDY DESIGN	RANDOMIZA-TION	ALLOCATION CONCEALMENT	BLINDING OF PARTICIPANTS	BLINDING OF INVESTIGATORS	BLINDING OF ASSESSORS	MISSING OUTCOMES / FOLLOW UP	SELECTIVE REPORTING	ASSESSMENT OF CONFOUNDING FACTORS												OVERALL for CONTROL OF COUNFOUNDERS	OVERALL RISK
									AGE			EXPOSURE RISK			COMORBIDITIES			VARIANT PREVALENCE				
									A	B	C	A	B	C	A	B	C	A	B	C		
Atmar	Prospective cohort	HIGH	HIGH	HIGH	HIGH	UNCLEAR	UNCLEAR	LOW	Y	U	Y	N	U	N	N	U	N	N	U	N	HIGH	VERY SERIOUS
Baker	case report (n=1)	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	VERY SERIOUS
Bar-On	Retrospective cohort	HIGH	HIGH	HIGH	HIGH	UNCLEAR	UNCLEAR	UNCLEAR	Y	U	Y	Y	U	Y	U	U	N	U	U	N	LOW	SERIOUS
Barda	matched cohort	HIGH	HIGH	HIGH	HIGH	HIGH	UNCLEAR	UNCLEAR	Y	Y	NA	Y	Y	NA	Y	Y	NA	Y	Y	NA	LOW	SERIOUS
Barin	prospective cohort	HIGH	HIGH	HIGH	HIGH	UNCLEAR	UNCLEAR	UNCLEAR	Y	U	N	Y	U	N	Y	Y	NA	N	U	N	HIGH	VERY SERIOUS
Benotmane	Single cohort, self-controlled	HIGH	HIGH	HIGH	HIGH	UNCLEAR	UNCLEAR	UNCLEAR	NA	NA	NA	NA	NA	NA	NA	NA	NA	N	U	N	HIGH	VERY SERIOUS
Bensouna	Single cohort, self-controlled	HIGH	HIGH	HIGH	HIGH	HIGH	UNCLEAR	UNCLEAR	NA	NA	NA	NA	NA	NA	NA	NA	NA	N	U	N	HIGH	VERY SERIOUS
Bonelli	RCT	UNCLEAR	UNCLEAR	UNCLEAR	UNCLEAR	UNCLEAR	LOW	LOW	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	SERIOUS
Caillard	Single cohort, self-controlled	HIGH	HIGH	HIGH	HIGH	UNCLEAR	UNCLEAR	UNCLEAR	N	U	N	N	U	N	N	U	N	N	U	N	HIGH	VERY SERIOUS
Chavarot	Single cohort, self-controlled	HIGH	HIGH	HIGH	HIGH	UNCLEAR	UNCLEAR	UNCLEAR	NA	NA	NA	NA	NA	NA	NA	NA	NA	N	U	N	HIGH	VERY SERIOUS
Choi	prospective cohort	HIGH	HIGH	HIGH	HIGH	UNCLEAR	UNCLEAR	UNCLEAR	Y	N	N	N	U	N	N	U	N	N	U	N	HIGH	VERY SERIOUS
Chu	RCT																					
David	retrospective cohort	HIGH	HIGH	HIGH	HIGH	HIGH	UNCLEAR	UNCLEAR	N	U	N	N	U	N	Y	N	N	N	U	N	HIGH	VERY SERIOUS
Del Bello	Single cohort, self-controlled	HIGH	HIGH	HIGH	HIGH	UNCLEAR	UNCLEAR	HIGH	NA	NA	NA	NA	NA	NA	NA	NA	NA	N	U	N	HIGH	VERY SERIOUS
Ducloux	Single cohort, self-controlled	HIGH	HIGH	HIGH	UNCLEAR	UNCLEAR	UNCLEAR	UNCLEAR	NA	NA	NA	NA	NA	NA	NA	NA	NA	N	U	N	HIGH	VERY SERIOUS
FDA report	Single cohort, self-controlled	HIGH	HIGH	HIGH	HIGH	UNCLEAR	UNCLEAR	UNCLEAR	N	U	N	N	U	N	N	U	N	N	U	N	HIGH	VERY SERIOUS
Flaxman	Single cohort, self-controlled	HIGH	HIGH	UNCLEAR	UNCLEAR	UNCLEAR	UNCLEAR	UNCLEAR	NA	NA	NA	NA	NA	NA	NA	NA	NA	N	U	N	HIGH	VERY SERIOUS
Greenberger	Prospective cohort	HIGH	HIGH	HIGH	HIGH	HIGH	UNCLEAR	UNCLEAR	N	U	N	N	U	N	N	U	N	N	U	N	HIGH	VERY SERIOUS
Hall	RCT	LOW	LOW	LOW	LOW	LOW	LOW	LOW	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NOT SERIOUS
Hoque	single cohort, self-controlled	HIGH	HIGH	HIGH	HIGH	HIGH	UNCLEAR	UNCLEAR	N	U	N	N	U	N	N	U	N	N	U	N	HIGH	VERY SERIOUS
Huat	Retrospective cohort	HIGH	HIGH	HIGH	HIGH	N	U	N	N	U	N	N	U	N	N	U	N	HIGH	Y SERIO	N	HIGH	VERY SERIOUS
Romero-	single cohort, self-controlled	HIGH	HIGH	HIGH	HIGH	HIGH	UNCLEAR	UNCLEAR	N	U	N	N	U	N	N	U	N	N	U	N	HIGH	VERY SERIOUS
Iketani	case report (n=4)	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	VERY SERIOUS
Kamar	Single cohort, self-controlled	HIGH	HIGH	HIGH	HIGH	UNCLEAR	UNCLEAR	UNCLEAR	NA	NA	NA	NA	NA	NA	NA	NA	NA	N	U	N	HIGH	VERY SERIOUS
Li J	RCT	LOW	LOW	LOW	LOW	LOW	LOW	LOW	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NOT SERIOUS
Li M	RCT (Phase 1 and 2)	LOW	LOW	LOW	LOW	LOW	HIGH	LOW	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NOT SERIOUS
Li Y	Single cohort, self-controlled	HIGH	HIGH	HIGH	HIGH	HIGH	UNCLEAR	UNCLEAR	N	U	N	N	U	N	N	U	N	N	U	N	HIGH	VERY SERIOUS
Liao	Single cohort, self-controlled	HIGH	HIGH	HIGH	HIGH	UNCLEAR	UNCLEAR	UNCLEAR	N	U	N	N	U	N	N	U	N	N	U	N	HIGH	VERY SERIOUS
LiuY	prospective cohort	HIGH	HIGH	HIGH	HIGH	HIGH	UNCLEAR	UNCLEAR	N	U	N	N	U	N	N	U	N	N	U	N	HIGH	VERY SERIOUS
Lyski	case report (n=2)	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	VERY SERIOUS
Masset	Single cohort, self-controlled	HIGH	HIGH	HIGH	HIGH	UNCLEAR	UNCLEAR	UNCLEAR	N	U	N	N	U	N	N	U	N	N	U	N	HIGH	VERY SERIOUS
Mofaz	prospective cohort	HIGH	HIGH	HIGH	HIGH	UNCLEAR	UNCLEAR	UNCLEAR	Y	Y	NA	N	U	N	Y	N	N	N	U	N	HIGH	VERY SERIOUS
Moghnieh	Prospective cohort	HIGH	HIGH	HIGH	HIGH	HIGH	HIGH	UNCLEAR	Y	N	N	N	U	N	N	U	N	N	U	N	HIGH	VERY SERIOUS
Mok	RCT	UNCLEAR	UNCLEAR	UNCLEAR	UNCLEAR	UNCLEAR	UNCLEAR	UNCLEAR	Y	Y	NA	N	U	N	Y	Y	NA	N	U	N	LOW	SERIOUS
Niesen	retrospective cohort	HIGH	HIGH	HIGH	HIGH	HIGH	UNCLEAR	UNCLEAR	N	U	N	N	U	N	N	U	N	N	U	N	HIGH	VERY SERIOUS
Pan	RCT	LOW	LOW	LOW	LOW	LOW	HIGH	LOW	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NOT SERIOUS
Patalon	Test-negative case control	HIGH	HIGH	HIGH	HIGH	UNCLEAR	UNCLEAR	UNCLEAR	Y	U	Y	Y	U	Y	U	U	N	U	U	N	LOW	SERIOUS
Patamatamkul	Prospective cohort	HIGH	HIGH	HIGH	HIGH	UNCLEAR	UNCLEAR	UNCLEAR	Y	Y	NA	N	U	N	N	U	N	N	U	N	HIGH	VERY SERIOUS
Peled	single cohort, self-controlled	HIGH	HIGH	HIGH	HIGH	HIGH	HIGH	UNCLEAR	N	U	N	N	U	N	N	U	N	N	U	N	HIGH	VERY SERIOUS
Sablerolles	RCT	LOW	LOW	LOW	HIGH	HIGH	HIGH	UNCLEAR	Y	Y	NA	N	U	N	Y	Y	NA	N	U	N	LOW	NOT SERIOUS*
Sadoff	Single cohort, self-controlled	HIGH	HIGH	HIGH	HIGH	UNCLEAR	UNCLEAR	UNCLEAR	N	U	N	N	U	N	N	U	N	N	U	N	HIGH	VERY SERIOUS
Sester	Single cohort, self-controlled	HIGH	HIGH	HIGH	HIGH	HIGH	UNCLEAR	UNCLEAR	N	U	N	N	U	N	N	U	N	N	U	N	HIGH	VERY SERIOUS
Singhatiraj	case report (n=1)	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	VERY SERIOUS
Sriphrapradang	case report (n=1)	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	VERY SERIOUS
Levine-Tiefenbrun	retrospective cohort	HIGH	HIGH	HIGH	HIGH	UNCLEAR	UNCLEAR	UNCLEAR	Y	U	Y	N	U	N	N	U	N	Y	Y	NA	LOW	SERIOUS
Wang	Single cohort, self-controlled	HIGH	HIGH	HIGH	HIGH	UNCLEAR	UNCLEAR	UNCLEAR	N	U	N	N	U	N	N	U	N	N	U	N	HIGH	VERY SERIOUS
Werbel	Single cohort, self-controlled	HIGH	HIGH	HIGH	HIGH	UNCLEAR	UNCLEAR	UNCLEAR	N	U	N	N	U	N	N	U	N	N	U	N	HIGH	VERY SERIOUS
Wu (also CHu?)	prospective cohort	HIGH	HIGH	HIGH	HIGH	HIGH	UNCLEAR	UNCLEAR	Y	U	N	N	U	N	Y	U	N	N	U	N	HIGH	VERY SERIOUS
Yorsaeng	Prospective cohort	HIGH	HIGH	HIGH	HIGH	UNCLEAR	UNCLEAR	UNCLEAR	Y	N	N	N	U	N	N	U	N	N	U	N	HIGH	VERY SERIOUS
Yue1	Single cohort, self-controlled	HIGH	HIGH	HIGH	HIGH	HIGH	UNCLEAR	UNCLEAR	N	U	N	N	U	N	N	U	N	N	U	N	HIGH	VERY SERIOUS
Yue2	Single cohort, self-controlled	HIGH	HIGH	HIGH	HIGH	HIGH	UNCLEAR	UNCLEAR	N	U	N	N	U	N	N	U	N	N	U	N	HIGH	VERY SERIOUS
				LOW	UNCLEAR	HIGH	NOT APPLICABLE			Y	YES	N	NO	U	UNCLEAR		NA	NOT APPLICABLE				

Appendix 2. General Characteristics of Included Studies

STUDY ID	Design	DESN	POPN	HET/HOM	BNT	MOD	CHA	SV	JJ	BBI	MRNA	INAC	OTH	CLIN	IMM	SAFE
Atmar	Prospective cohort	PC	GEN	BOTH	Y	Y			Y						Y	Y
Baker	case report (n=1)	CR	IMM	HET					Y						Y	
Bar-On	Retrospective cohort	RC	GEN	HOM	Y									Y		
Barda	matched cohort	PC	GEN	HOM	Y									Y		
Barin	prospective cohort	PC	GEN	BOTH	Y			Y							Y	
Benotmane	Single cohort, self-controlled	SC	IMM	HOM		Y									Y	
Bensouna	Single cohort, self-controlled	SC	IMM	HOM	Y										Y	Y
Bonelli	RCT	RCT	IMM	BOTH	Y	Y	Y								Y	Y
Caillard	Single cohort, self-controlled	SC	IMM	BOT	Y	Y									Y	Y
Chavarot	Single cohort, self-controlled	SC	IMM	HOM	Y										Y	Y
Choi	prospective cohort	PC	GEN	HOM		Y									Y	Y
Chu	RCT	RCT	GEN	HOM		Y									Y	Y
David	retrospective cohort	RC	IMM	HOM	Y											Y
Del Bello	Single cohort, self-controlled	SC	IMM	HOM	Y										Y	Y
Ducloux	Single cohort, self-controlled	SC	IMM	HOM	Y										Y	
FDA report	Single cohort, self-controlled	SC	GEN	HOM	Y										Y	Y
Flaxman	Single cohort, self-controlled	SC	GEN	HOM			Y								Y	Y
Greenberger	Prospective cohort	PC	IMM	BOTH	Y	Y			Y						Y	
Hall	RCT	RCT	IMM	HOM		Y									Y	Y
Hoque	single cohort, self-controlled	SC	GEN	HET	Y										Y	
Huat	Retrospective cohort	RC	GEN	BOTH	Y				Y						Y	
Romero-	single cohort, self-controlled	SC	HCW	HOM	Y										Y	Y
Iketani	case report (n=4)	CR	GEN	HET					Y						Y	
Kamar	Single cohort, self-controlled	SC	IMM	HOM	Y										Y	Y
Li J	RCT	RCT	GEN	BOTH				Y					Y		Y	Y
Li M	RCT (Phase 1 and 2)	RCT	GEN	HOM				Y							Y	Y
Li Y	Single cohort, self-controlled	SC	GEN	HOM									Y		Y	Y
Liao	Single cohort, self-controlled	SC	GEN	HOM								Y			Y	
LiuY	prospective cohort	PC	HCW	HOM						Y					Y	Y
Lyski	case report (n=2)	CR	IMM	HET				Y							Y	
Masset	Single cohort, self-controlled	SC	IMM	HOM	Y										Y	
Mofaz	prospective cohort	PC	GEN	HOM	Y											Y
Moghnieh	Prospective cohort	PC	GEN	HET	Y									Y	Y	Y
Mok	RCT	RCT	GEN	BOTH	Y			Y							Y	Y
Niesen	retrospective cohort	RC	GEN	HOM	Y											Y
Pan	RCT	RCT	GEN	HOM				Y							y	Y
Patalon	Test-negative case control	RC	GEN	HOM	Y									Y		
Patamatamku	Prospective cohort	PC	GEN	HET	Y		Y								Y	Y
Peled	single cohort, self-controlled	SC	IMM	HOM	Y										Y	
Sablerolles	RCT	RCT	GEN	HET	Y	Y									Y	Y
Sadoff	Single cohort, self-controlled	SC	GEN	HOM					Y						Y	Y
Sester	Single cohort, self-controlled	SC	GEN	HET					Y						Y	Y
Singhatiraj	case report (n=1)	CR	HCW	HET			Y								Y	Y
Sriphrapradan	case report (n=1)	CR	GEN	HET			Y									Y
Levine-	retrospective cohort	RC	GEN	HOM	Y										Y	
Wang	Single cohort, self-controlled	SC	GEN	HOM				Y							Y	
Werbel	Single cohort, self-controlled	SC	IMM	BOTH	Y	Y			Y					Y	Y	Y
Wu (also	prospective cohort	PC	GEN	HOM		Y									Y	Y
Yorsaeng	Prospective cohort	PC	HCW	BOTH			Y	Y							Y	
Yue1	Single cohort, self-controlled	SC	GEN	HOM								Y			Y	
Yue2	Single cohort, self-controlled	SC	GEN	HOM								Y			Y	

POPN: Population: General, Immunocompromised, Healthcare Workers; **HET/HOM**: heterologous/homologous vaccination; **BNT**: Pfizer; **MOD**: Moderna; **CHA**: AstraZeneca; **SV**: Sinovac; **JJ**: Janssen/JnJ; **BBI**: BBIBP-CoRV; **MRNA**: mRNA vaccine; **INAC**: inactivated vaccine; **OTH**: others; **CLIN**: clinical outcome; **IMM**: Immunologic outcome; **SAFE**: safety outcome

Appendix 3. Characteristics and detailed outcomes of studies on homologous booster vaccination involving the general population

BNT162b2								
Study author (country)	**Study design**	**Population**	**Primary series**	**Booster (interval from V2)**	**Comparator**	**Follow-up**	**Outcomes**	**Comments**
Clinical efficacy/effectiveness								
Bar-On (Israel) Preprint (August 2021)	Retrospective cohort	Israeli residents > 60 y.o., fully vaccinated at least 5 months and still alive by July 30, 2021 N= 1,144,690 booster : at least 12 days pV3 n = 3,351,598 person-days at risk no booster : none or <12 days pV3 n = 4,018,929 person-days at risk	BNT162b2 2 doses 21 day interval	BNT162b2 (at least 5 months)	no booster	1-12 days (1 week after 12 day post V3) July 30 - August 22, 2021	Incidence of confirmed infection : No booster : 3,473 / 4.0M Booster : 313 / 3.4M Incidence of severe COVID-19 No booster : 330/ 4.0M Booster : 32 / 3.4M OR protection (decreased risk of infection) by comparative cohort : **11.4x** (10,12.2) by matched cohort : 13.4x (8.2,21.4) by matched cohort, by daty : 9.6 (8.1,11.4) OR protection for severe disease by comparative cohort : 15.5 (10.5, 22.8) by match cohort by day : 9.5 (5,19.6) protection is a function of time, stabilizing after 12 days to 10-12x	Adjusted for age, gender, demographic status (risk), date of V2 alternative analysis: matched cohort
Patalon (Israel)	Test-negative case control	HMO members, 40 years and above excluded prior infection, postive RT PCR before start of ffup period; disengaged from health system prior to March 2020 Case : (+) RT PCR Control : (-) RT PCR	BNT162b2 2 doses 21 day interval	BNT162b2 (~5 months)		0-6 days 7-13 days 14-20days	Odd of a positive test No Booster : 8285 / 149,379 (5.5%) Booster : 1,188 / 32,697 (3.6%) Marginal effectivenss compared to dose 2 TNCC analysis 0-7 days : 3% (95%CI -5, 10) 7-13d : 48% (42, 54) 14-20d : 79% (72, 84) Matched case-control 0-7 days : 39% (95%CI 34, 44) 7-13d : 53% (48, 58) 14-20d : 79% (72,76)	covariates : age, sex, time since receipt of vaccine, comorbidities, no. of postitive tests, socioeconomic status alternative analysis : matched case-control matching by : age, residential socioeconomic status, biological sex, month of administration of the 2nd dose
Barda (Israel) Publication (October 2021)	Retrospective matched cohort Serious observational controlled for age, risk of exposure, comorbidities, time of vaccination	members of a healthcare organization, aged 12 years and older excludd immunocompromised, healthcare workers, residents of longterm care facilities and those medically confined to their home	21 days	BNT162b2 (~5 months)	no booster unvaccinated	13 days from booster	VE hospitalization 93% (95%CI 88-97); 231 vs 29 events VE severe disease : 92% (95%CI 82-97); 157 vs 17 events VE COVID-related death : 81% (95%CI 59-97); 44 vs 7 events VE symptomatic infection : 91% (89-92); 3345 vs 514 events VE any COVID infection : 88% (87-90); 6131 vs 1135 events	

Immunogenicity									
							HUMORAL	***CELLLAR***	
FDA Report (US) Regulatory report (September 2021)	single cohort, self-controlled Very Serious observational	Phase 2/3 trial subpopulation, adults 18-55 y.o. (N = 210)	BNT162b2 2 doses 21 days	BNT162b2 (median 6.8 mos)	self, 2nd dose	1 mo	GMT (95%CI) neutralizing antibodies (plaque neutralization assay) V2+1mo : 753.7 (658.2, 863.1) V3+1mo : 2476.4 (2210.1, 2774.9) ***3.3fold higher*** Seropositivity V2+1mo : 97.8 (94.4,99.4) V3+1mo : 93.9 (89.3, 96.9) ***minimal difference in %***		
Levine-Tiefenbrun (Israel) Correspondence (June to Sep 2021)	retrospective cohort Serious observational some control of confounders	Cycle threshold values of all recorded adult infections (n=16,553) from June 28 to Sep 9, 2021 unvaccinated : 3,100 vaccinated : 12, 934 boosted : 519	BNT162b2	BNT162b2	unvaccinated unboosted	at time of infection	CT values of RdRp, N and E genes, compared with unvacinated, over time Noted decline in difference in CT between groups from 4.6 at 7-30days post vaccination, to 0.5 after 2 months, and to insignificant values at 6 months; overturned to 2.4 after boost. translates to a 5-fold reduction in viral load post boost		
Safety									
FDA Report (US) Regulatory report (September 2021)	Single cohort, self-controlled	Phase 1 and 2/3 trial subpopulation, adults 18-55 y.o., N = 317; 65-85 y.o., N = 12)	BNT162b2 2 doses 21 days	BNT162b2 (median 6.8mos)	2nd dose	median 2.6 mo	85% with local reaction 77.2% with systemic reaction unsolicited AE = 14.4% 1 serious AE (acute MI), unrelated to the booster dose generally same AE rates as with second dose injection site pain is most common (83%), fatigue (63.7%), headache (48.4) higher rates of lymphadenopathy (5.2%) than reported after primary series (0.4%) no reported myocarditis/pericarditis post boost		Phase 1 and Phase 2/3 trial subpopulation who received BNT162b2 adults 18-55 yo (n =306(Ph2) + 11 (Ph1)) 65 to 85 yo (n = 12)
Mofaz (Israel) Preprint (September 2021)	Single cohort, self-controlled	N = 1,609 n (third dose) = 1,344	BNT162b2 (not specified)	BNT162b2 (not specified)	Self	48 hrs after booster	Did not report systemic reaction: % (90% CI) After first dose: 86.5 (81.9, 91) After second dose: 63.3 (59.1, 67.8) After third dose: 60.4 (57.9, 62.9) Similar extent of systemic reactions with third dose vs. following second dose ($p < 0.305$), greater than vs. following first dose ($p < 0.001$)		
Niesen (US) Preprint (Dec 2020 to Oct 2021)	Retrospective cohort Very Serious observational non-control of confounders	adults who received BNT162b2 doses 21 days apart n=38,094	BNT162b2	BNT162b2 mean interval : 202d	self, 2nd dose and baseline	28 days postboost	most common local AR : local swelling most common systemtic AR : fatigue, lymphadenopathy, nausea, headache, arthralgia, myalgia increased adverse event reporting after booster compared to 2nd dose, including : fatigue, lymphadenopathy, nausea, headache, arthralgia, myalgia, diarrhea, fever and vomiting more emergency department visits within 2 days of vaccination with booster compared to other doses		

ChAdOx1									
Study author (country)	**Study design**	**Population**	**Primary series**	**Booster (interval from V2)**	**Comparator**	**Follow-up**	**Outcomes**		**Comments**
Clinical efficacy/effectiveness									
None									
Immunogenicity									
							HUMORAL	***CELLULAR***	
Flaxman (UK) Full publication (September 2021)	Single cohort, self-controlled	Participants 18-55 years old to the Ph1/2/3 trial who had received 1 or 2 doses of ChAdOx1 invited to receive a delayed second dose or a third dose. n=90 n= 80 for reactogenicity n = 75 for antibody levels n = 45 for antibody levels against variance n = 15 for T cell response	ChAdOx1 2 doses variable interval	ChAdOx1 (44-45 weeks)	(control participants for reactogenicity) n = 40 self, 2nd dose (for immunogenicity)	28days	Compared titers D28 after 2nd dose and titers after 3rd dose (FRNT50 for Nab antibody levels to SARS-Cov2 Victoria spike, measured by Single dilutional total IgG ELISA), compared to 28days after V2 V2+28d : 1792 (IQR 899-4634) V3+28d: 3746 (IQR 2047-6420) ***** 2.09 fold increase*** NAb vs variants (V2 vs V3) Alpha, Beta , Delta presented as graphs, generally increased after V3	Spike specific cellular immune response (IFN-γ by ELISpot, in SFUx10 PBMC) V2+28 : 200 (IQR 127, 389) V3+14 : 264 (IQR 131, 452) V3+28 : 399 (IQR 314, 662) *****1.99 fold increase***	Cohort with historical control for reactogenicity data
Safety									
Flaxman (UK) Full publication (September 2021)	Single cohort, self-controlled	Participants 18-55 years old to the Ph1/2/3 trial who had received 1 or 2 doses of ChAdOx1 invited to receive a delayed second dose or a third dose. n=90	ChAdOx1 2 doses variable interval	ChAdOx1 (44-45 weeks)	(control participants for reactogenicity) n = 40 self control (vs V2) for immunogenicity outcomes	28days	Third dose vaccinations were less reactogenic than first doses 5% (4) reported more than 2 moderate to severe symptoms		

CoronaVac									
Study author (country)	**Study design**	**Population**	**Primary series**	**Booster (interval from V2)**	**Comparator**	**Follow-up**	**Outcomes**		**Comments**
Clinical efficacy/effectiveness									
None									
Immunogenicity									
							HUMORAL	***CELLULAR***	
Li J (China) Preprint (September 2021)	RCT	18-59 yo, healthy received two doses of CoronaVac in the past 3-6 months or one dose of CoronaVac in the past 1-2 months 2 dose : N - 200 boost with CoronaVac : boost with Ad5 : Excluded previous clinical or virologic COVID-19 diagnosis or infection, pregnant women	CoronaVac 2 doses	CoronaVac (3-6months)	Ad5 (3-6 months)	28 days for AE 14 and 28 days for immunologic outcomes	neutralizing antibody titers (live viral assay) 14 days (pre to post boost) Ad5 : 2.5 (2.3, 2.7) to 197.4 (167.7, 232.4) CoronaVac : 1.1 (2.1, 2.3) to 33.6 (28.3, 39.8) 28 days Ad5 : 150.3 (128, 175.7) Coronavac : 35.3 (29.4, 42.4) Fold-rise : 14-days vs 28 days ad5 : **78-fold / 60-fold** CoronaVac : **15.2-fold / 32-fold** anti-RBD titers (ELISA) Ad5 : 3090.1 (2636.1, 3622.3) CoronaVac : 369 (304.2, 447.5) anti-N titers (ELISA) only CoronaVac showed increases to N protein antibodies, Ad5 showed no increase post boost T-cell response (ELISpot) (N= 50) 14 days : per 10 PBMC Ad5 : 100 (IQR 60, 165) CoronaVac : 90 (40, 230)		IWRS randomization participants, investigators, lab and outcome assessors blinded to treatment but not to the 3 or 2 dose regimen
Li M (China) Preprint (August 2021)	RCT	Healthy adults >=60 years old, participants in the Ph2 trial who completed the 6 month follow up after the 2nd dosen N = 303 1.5 ug : 85 3.0 ug : 90 6.0 ug : 81 placebo : 47	CoronaVac at 1.5, 3.0 or 6.0 ug dose, 28 day interval	CoronaVac at same dose as primary vaccinations (8 months or more)	placebo	Serology : 7 or 14 days and 28 days Safety : 7 days for reactogenicity, 28 days for any AE	GMT of NAb to live SARS-CoV-2 7, 14, 28 days after V3 (pre, 7, 14, 28 days post boost) 1.5ug : 3.1, 179.01, 206.9, 184.6 3 ug : 3.4 (2.9, 4.1) to 305 (215.3, 432), 318.3, 342.8 6.0ug : 4.1, 418.18, 689.1, 437.7 ***** 342 vs 3.4 = 100.6-fold rise for 3.0ug at V3+28x*** Seropositivity rate (cut off at 1/8) (7, 14 , 28 days post boost) 1.5ug : 100%, 97.5, 98,8 3.0ug : 100% for all 6ug : 100% for all		Phase 1 and 2 computer-generated randomization participants, investigators and lab personnel blinded only half of the participants were tested for antibodies post booster

Pan (China) Preprint (July 2021)	RCT	Healthy adults 18-59 years old, N= 540	CoronaVac 3.0 or 6.0 ug dose 14 or 28 day interval	CoronaVac (28 or 180 days)	Placebo, 14 or 28 day interval, Placebo V3 at 6mos after V2	immuno : 14 days safety : 7 days, 28 days, 6 months	3.0ug dose GMT of NAbs to live SARS CoV 2 V2+28 / V3+28 (Sched 1: 0, 14, 42 d) V2 at 14d, V3 at 1mo : 22.2 / 45.8 ***2.1x*** (Sched 2: 0, 14, 194 d) V2 at 14d, V3 at 6mo : 25.6 / 137.9 ***5.4x*** (Sched 3: 0, 28, 56 d) V2 at 28d, V3 at 1mo : 39.6 / 49.7 ***1.26*** (Sched 4: 0, 28, 208 d) V3 at 28d, V3 at 6mo : 49.1 / 143.1 ***2.91*** Seropositivity / seroconversion V2+28 / V3+28 V2 at 14d, V3 at 1mo : 93.2 / 98.1 V2 at 14d, V3 at 6mo : 94.9 / 100 V2 at 28d, V3 at 1mo : 94.9/ 98.1 V3 at 28d, V3 at 6mo : 100 / 100 data also available for 6.0ug group no difference in seroconversion between 3.0ug and 6.0ug groups		multi-arm (4 arms vs placebo) different regimen vs placebo computer generated randomization allocation concealed participant, investigator and assessor blinded 3-10 patients per arm lost : withdrawal, dissent, ineligble for dose 3, lost to ffup to end of trial
Wang (China) Preprint (September 2021)	single cohort, self-controlled	subgroup of a clinical trial population, 16-69 years who received a third dose of CoronaVac	CoronaVac (0,14 or 0.28 regimen)	CoronaVac (6 months)	self, 2nd dose	1.3 months	Endpoint binding titer (V2 vs V3) anti-N IgG : 869 vs 1850 ***2.1-fold*** anit-S igG : 5039 vs 7677 ***1.5 fold*** anti- RBD : 4279 vs 4326 ***1.01 fold*** **Effectiveness of booster against variants** : (Neutralizing antibody titer fold reduction of 2 vs 3 doses, using live viral assay, compared to WT Alpha : 2.2 vs 1.7 Beta : 5.7 vs 3.0 Gamma : 4.3 vs 3.1 Delta : 3.7 vs 2.3 titers for anti-S, anti RBD, anti NTD also available for each variant		extension of the regulatory Ph1/Ph2 trial (published by Zhang)
Barin (Cyprus) Preprint (September 2021)	Single cohort, self-controlled	General population (some HCWs, with chronic condition, EXCLUDED those on chemotherapy and steroids), analyzed cohort given with booster CoronaVac/CoronaVac booster N = 13 (< 60 y.o. = 1, > 60 y.o. = 12)	CoronaVac (4 wks)	CoronaVac (6 mo after V2)	Self, 1 mo after V2	1 mo after booster	In > 60 y.o. anti-spike RBD IgG (post-boost vs. self): median 8.4 (IQR 4.3, 16.3) vs. median 3.2 (IQR 0.9, 8.6) GMR 2.8 (95% CI 1.6, 5) seropositivity rate (post-boost vs. self): 100% vs. 75%		Confusing use of terms on post-first dose vs. post-primary vaccination

Mok (HongKong) Preprint (Mar-Aug 2021)	RCT Serious unclear domains	healthy adults received 2 doses of CoronaVac with sVNT results below 60% at one month after second dose homologous : 40 heterologous : 40	CoronaVac	BNT162b2 (mean 115 days)	CoronaVac	1 month after booster	% sVNT inhibition pre and post boost +BNT : 96.85% (SD 2.4%) +CoronaVac : 57.75% (SD 24.68) ***>20% more with hetero*** % sVNT for Beta, Gamma, Delta +BNT : 92.3%, 92.5%, 95.3% +CoronaVac: 38.9%, 32.2%, 48.9% Titers for RBD, NTD and S2 antibodies were higher in those who received BNT162b2 as booster		
Safety									
Li J (China) Preprint (September 2021)	RCT	18-59 yo, healthy received two doses of CoronaVac in the past 3-6 months or one dose of CoronaVac in the past 1-2 months 2 dose : N - 200 boost with CoronaVac : boost with Ad5 : Excluded previous clinical or virologic COVID-19 diagnosis or infection, pregnant women	CoronaVac 2 doses	CoronaVac vs Ad5 (3-6months)	Ad5	28 days for AE 14 and 28 days for immunologic outcomes	Ad5 patients - reported more adverse reactions (Table 2) - had more solicited injection-site reactions (20.2% vs 2.9%) - had more solicited systemic reactions (13.5% vs 2.9%) reactions generally mild and moderate, resolved within 1-2 days injection site pain most common severe injection-site pain reported in 2.1% of Ad5 recipients Fever and fatigue most common systemic reactions NO thromboses or vaccine-related anaphylaxis or SAE seen in any of the cohorts	IWRS randomization participants, investigators, lab and outcome assessors blinded to treatment but not to th 3 or 2 dose regimen
Li M (China) Preprint (August 2021)	RCT	Healthy adults >=60 years old, participants in the Ph2 trial who completed the 6 month follow up after the 2nd dose 1.5 ug : 85 3.0 ug : 90 6.0 ug : 81 placebo : 47	CoronaVac at 1.5, 3.0 or 6.0 ug dose, 28 day interval	CoronaVac at same dose as primary vaccinations (8 months or more)	placebo	Serology : 7 or 14 days and 28 days Safety : 7 days for reactogenicity, 28 days for any AE	Safety : local and systemic adverse event rates(days 0-7), spontaneous recording of adverse event rate till day 28 Adverse reaction rates 1.5ug : 4.71% 3.0ug : 5.56% 6.0 ug: 6.17% placebo : 4.26% most common reaction was injection-site pain Serious adverse events 5 SAEs among 4 participants, none considered as vaccine -related	(Phase 1 and 2) computer-generated randomization participants, investigators and lab personnel blinded only half of the participants were tested for antibodies post booster

Pan (China) Preprint (July 2021)	RCT	Adults 18-59 years old N= 504	CoronaVac 3.0 or 6.0 ug dose 14 or 28 day interval	CoronaVac (28 or 180 days)	Placebo, 14 or 28 day interval, Placebo V3 at 6mos after V2	immuno : 14 days safety : 7 days, 28 days, 6 months	incidence of adverse reactions after the 3rd dose was lower than the highest incidence during the study Rates with 28 days of 3rd dose Schedule 2 : 0, 14, 42 3.0ug group/ placebo total : 18.18% /19.86 local : 14.55% / 14.18 systemic : 5.45 / 6.38 solicited : 16.36 / 17.73 uncolicited : 1.82 / 2.84 8-28 days : 0 / 0 ** Results also available for sched 1 : 0, 14, 194 sched 3 : 0, 28, 56 Sched 4 : 0, 28, 208 generally, no difference with placebo	multi-arm (4 arms vs placebo) different regimen vs placebo computer generated randomization allocation concealed participant, investigator and assessor blinded 3-10 patients per arm lost : withdrawal, dissent, ineligble for dose 3, lost to ffup to end of trial
Mok (HongKong) Preprint (Mar-Aug 2021)	RCT Serious unclear domains	healthy individuals, 19-77 years received 2 doses of CoronaVac with sVNT results below 60% at one month after second dose homologous : 40 heterologous : 40	CoronaVac	BNT162b2	CoronaVac	1 week after booster	similar adverse reactions as with homologous more pain and swelling at injection site compared to homologous group more fatigue and muscle pain compared to homologous	

Ad26.COV2.S									
Study author (country)	**Study design**	**Population**	**Primary series**	**Booster (interval from V2)**	**Comparator**	**Follow-up**	**Outcomes**		**Comments**
Clinical efficacy/effectiveness									
None									
Immunogenicity									
Sadoff (Belgium, US) Preprint (August 2021)	single cohort, self-controlled	Participants from ongoing Phase 1/2a study (COV1001) and Phase 2 study (COV2001) 2 groups: 18-55 yo, N = 17 >=65 yo, N = 73	Ad26.COV2.S 5 x 10 vp 1 dose	Ad26.COV2.S 5 or 1.25 x 10vp (6 months)	Self as control, single dose of Ad26.COV2.S	6-9 months after prime up to 28 days after boost	Anti-spike IgG after prime and boost dose, neutralizing antibody after prime dose: boost with 5x10 x 10vp (N=17, 18-55yo) D7 post boost titers : 3779 (2741-4243), ***4.7fold*** increase from pre-boost boost with 1.25 x10vp(N=44 (18-55) + 29 (>65) D7 post boost titers : 1719 (1321-2236), ***3.6fold*** rise from preboost D28 post boost : 2444 (1855-3219), ***6.4 fold rise*** slower rise in the >=65 yo but titers similar by D28		extension of the ongoing trial
Safety									
Sadoff (Belgium, US) Preprint (August 2021)	single cohort, self-controlled	Participants from ongoing Phase 1/2a study (COV1001) and Phase 2 study (COV2001) 2 groups : 18-55 yo and >=65 yo	Ad26.COV2.S 5 x 10 vp 1 dose	Ad26.COV2.S 5 or 1.25 x 10vp (6 months)	Self, single dose of Ad26.COV2.S	6-9 months after prime up to 28 days after boost	N = 81 patients solicited AE(primary vs boost) : 67.9% vs 54% grade 3 or more solicited AE : 1.2% vs 0% solicited local AE : 51.9% vs 47% grade 3 or more solicited local AE : 0 vs 0 solicited systemic AE : 66.7% vs 28% grade 3 or more solicited AE : 1.2 vs 0 Similar post=primary and post-booster reactogenicity in the 17 patients in Cohort2 ** results for serious AE and AE of special interest not mentioned in the report		extension of the ongoing trial

Inactivated virus vaccine									
Study author (country)	**Study design**	**Population**	**Primary series**	**Booster (interval from V2)**	**Comparator**	**Follow-up**	**Outcomes**		**Comments**
Clinical efficacy/effectiveness									
None									
Immunogenicity									
Yue 2 (China) Correspondence (September 2021)	single cohort, self-controlled	volunteers who received 2 doses of inactivated virus vaccine N = 67	inactivated vaccines 14 or 28 day interval	inactivated vaccine (8 months)	self, 2nd dose (8m	28 days	neutralizing antibody seroconversion Pre-boost (8 mos after V2) : 65.7% post-boost : 95.5% postboost seroconversion between those who received the 0,14 and 0,28 were similar Note : Titers presented as graphs, no values presented		
Liao (China) Correspondence (May 2021)	single cohort, self-controlled	adult volunteers (18-59 years) received two doses with a 14 or 28 day interval n= 76	inactivated virus vaccine 2 doses	inactivated virus vaccine (not mentioned but stated that it was after knowing of the low antibodies post V2, hence at least 7 months from V2)	self, 2nd dose	28 days	seroconversion 14d int : 100% 28d int : 100% GMT 14d : 57.9 28d: 36.8		
Yue 1 (China) Proof of correspondence (2021)	Single cohort, self controlled Very Serious observational non-control of confounders	Sera from 53 volunteers	Inactivated viral vaccine 2 doses (interval not mentioned)	Inactivated viral vaccine (8 months)	(versus reference strain)	14 days post boost	neutralzing antibody titers pre and post-boost : significant rise from immediately pre-boost, similar/slightly higher than 28days after 2nd dose (results shown in a graph) neutralizing antibody seropositivity and titer (fold-reduction) vs VOC : alpha : 98%, 1.9 fold decrease beta : 92%, 5.4-fold decrease delta : 94%, 4.2-fold decrease	SFC (PBMC) levels increased to post vaccination levels, from a decline (but still detectable) at just before boost (results presented in a graph)	
Safety									
None									

mRNA-1273									
Study author (country)	**Study design**	**Population**	**Primary series (interval)**	**Booster (timing of testing after V2)**	**Comparator**	**Timing of testing/follow-up**	**Outcomes**		**Comments**
Clinical efficacy/effectiveness									
None									
Immunogenicity									
							HUMORAL	***CELLULAR***	
Chu (US)	RCT	Healthy population Safety set N (50 ug) = 173 N (100 ug) = 171 Per protocol set (i.e. actually received booster) N (50 ug) = 146 N (100 ug) = 149	mRNA-1273 50 ug or 100 ug (28 d)	mRNA-1273 50 ug (mean 7.2 mos)	self, 28 d after V2 historical control (100 ug primary series)	28 d after booster	NAb (post-boost vs. self): 1951.7 (95% CI 1729.6, 2202.4) vs. 1268 (95% CI 1087.9, 1477.8) GMR 1.5 (95% CI 1.3, 1.8) NAb (post-boost vs. historical control): 1767.9 (95% CI 1586.4, 1970.2) vs. 1032.7 (95% CI 974.2, 1094.7) GMR 1.7 (95% CI 1.5, 1.9) NAb against Delta (post-boost vs. historical control): 743.9 (95% CI 663.7, 833.7) vs. 354 (95% CI 325, 385.5) GMR 2.1 (95% CI 1.8, 2.4) Seroresponse rate (post-boost vs. historical control): 93.5% (95% CI 90.1, 96.1) vs. 98.9% (95% CI 98, 99.4) Difference -5.3 (9% CI -8.8, -2.9) Anti-spike ELISA (post-boost vs. historical control): 1074.7 (95% CI 1024.1, 1127.8) vs. 694.8 (95% CI 664.8, 726.1) **1.5-fold** Seroresponse rate (post-boost vs. historical control): 94.7 (95% CI 91.4, 97) vs. 99.6 (95% CI 99, 99.9) Difference -4.9 (95% CI -8.2, -2.8)		Part of a Ph 2 trial For "Nab" and "spike-binding IgG", results for 100 ug group only. Assays againt D614G unless otherwise stated. Seroresponse rate per assay-specific definition shown.
Wu (US)	RCT	Healthy adults (≥ 18 y.o.) N = 40 n (mRNA-1273) = 20 n (mRNA-1273.351) = 20	mRNA-1273	mRNA-1273 (5.9 - 7.5 mos) mRNA-1273.351, 50 ug (5.6 - 6.6 mos)	Self, 1 day pre-boost	2 wks after booster	mRNA-1273 Nab titer (ID50) against wild type (post-boost vs. pre-boost) 4588 vs. 198 (23x) NAb titer (ID50) against Beta (post-boost vs. pre-boost) 864 vs. 27 (32x) NAb titer (ID50) against Gamma (post-boost vs. pre-boost) 1308 vs. 30 (44x) mRNA-1273.351 Nab titer (ID50) against wild type (post-boost vs. pre-boost) 3703 vs. 304 (12x) NAb titer (ID50) against Beta (post-boost vs. pre-boost) 1400 vs. 40 (35x) NAb titer (ID50) against Gamma (post-boost vs. pre-boost) 1272 vs. 47 (27x)		

Choi (US) Publication	Prospective cohort (subgroup of an RCT)	healthy participants in a trial	mRNA-1273 100ug 2 doses	mRNA-1273 50ug (n=20) 6.7mos mRNA-1273.351 50ug (n=20) 6.2mos mRNA-1273.211 50ug (n=20) 6.2mos mRNA-1273.351 20ug (n=19) 6.2mos	Self, pre-boost	day 29 after booster	Neutralization titers (D614G) at d29 compared to d1 : mRNA-1273 50ug : 16.7x higher mRNA-1273.351 50ug : 11.3 mRNA-1273.211 50ug: 46.4 mRNA-1273.351 20ug : 9.2 Neutralization titers (Beta) mRNA-1273 50ug : na mRNA-1273.351 50ug : 34.9x higher mRNA-1273.211 50ug: 61.6 mRNA-1273.351 20ug : 33.7 all boosters increased neutralization against VOCs to levels that were equivalent to the wild-type benchmarks; x.211 had the greatest increase		
Safety									
Chu Preprint (October 2021)	RCT	Healthy population Safety set N (50 ug) = 173 N (100 ug) = 171 Per protocol set (i.e. actually received booster) N (50 ug) = 146	mRNA-1273 50 ug or 100 ug (28 d)	mRNA-1273 50 ug (for 50 and 100 ug primary series), mean 7.2 mos)	self, 28 d after V2 historical control (100 ug primary series)	Local and systemic AE: 7 d SAE: 28 d	Similar local and systemic AE rates, majority are mild to moderate Most common systemic AE: fatigue, headache, myalgia Treatment-emergent AE: 13 in booster group No SAE.	Part of a Ph 2 trial	
Wu (US) Preprint (May 2021)	RCT	Healthy adults (≥ 18 y.o.) N = 40 n (mRNA-1273) = 20 n (mRNA-1273.351) = 20	mRNA-1273	mRNA-1273 (5.9 - 7.5 mos) mRNA-1273.351, 50 ug (5.6 - 6.6 mos)	Self, 1 day pre-boost	Not specified. Mentioned that safety assessed every 4 wks	Similar solicited local and systemic AEs between mRNA-1273 booster and mRNA-1273.351 Most common solicited local AE: injection site pain Most common solicited systemic AE: fatigue, headache, myalgia, arthralgia No SAEs reported.		
Choi (US) Publication	Prospective cohort (subgroup of an RCT)	healthy participants in a trial	mRNA-1273 100ug 2 doses	mRNA-1273 50ug (n=20) 6.7mos mRNA-1273.351 50ug (n=20) 6.2mos mRNA-1273.211 50ug (n=20) 6.2mos mRNA-1273.351 20ug (n=19)	Self, pre-boost	day 29 after booster	percentages of partcipants with solicited local and systemic Ars were similar across booster groups any grade 3 AR ranged from 10-15% no grade 4 local or systemic AR most common local AR : injection site pain most common systemtic AR : fatigue, heachache, arthralgia, myalgia no serious AE		
Niesen (US) Preprint (Dec 2020 to Oct 2021)	Retrospective cohort Very Serious observational non-control of confounders	adults who received 2 mRNA-1273 doses 25-35 days apart n=9905	mRNA-1273	mRNA-1273 mean interval : 173d	self, 2nd dose and baseline	14 days after booster	most common local AR : local pain most common systemic AR : fatigue, lymphadenopahty, nausea, headache, arthralgia increased adverse event reporting after booster compared to 2nd dose, including : fatigue, lymphadenopathy, nausea, headache, arthralgia, myalgia, fever and vomiting more emergency department visits within 2 days of vaccination with booster compared to other doses		

VO1									
Study author (country)	**Study design**	**Population**	**Primary series (interval)**	**Booster (timing of testing after V2)**	**Comparator**	**Timing of testing/follow-up**	**Outcomes**		**Comments**
Clinical efficacy/effectiveness									
None									
Immunogenicity									
							HUMORAL	***CELLULAR***	
Li Y (China) Preprint (Nov2021)	Single cohort, self controlled	previously primed from Ph1 trial	V-O1 10ug 2 doses 21 days	V-01 4-5mos	Self-pre boost	28 days post boost	RBD-binding antibody titers pre : 3651 (2769-4815) 28d : 4060 (2890-5702) noted silimar degree of rise regardless of age group noted greater amplification in titers in younger adults , and in neutralizing titers against VOC postboost despite reduced compared to reference strain		
Safety									
Li Y (China) Preprint (Nov2021)	Single cohort, self controlled	previously primed from Ph1 trial n=43	V-O1 10ug 2 doses 21 days	V-01 4-5mos	Self-pre boost	7 days post boost 30 days for AE	acceptable adverse reaction rates (5-10%, all in older subgroup) unsolicited AE rate <10%, more in younger no vaccine-related AE no grade 4		

Appendix 4. Characteristics and detailed outcomes of studies on heterologous booster vaccination involving the general population

Primary BNT162b2/Ad26.COV2.S booster										
Study author (country) Publication (date)	**Study design (Risk of Bias**	**Population**	**Primary series (interval)**	**Booster (interval from V2)**	**Comparator**	**Follow-up**	**Outcomes**		**Certainty of evidence**	**Comments**
Clinical efficacy/effectiveness										
None										
Immunogenicity										
							HUMORAL	***CELLULAR***		
Atmar (US) Preprint (October 2021)	RCT	Adults with no prior history of SARS-CoV-2 infection or monoclonocal antibody infusion N = 458 (two age groups: 18-55 y.o., ≥ 56 y.o.) n (mRNA-1273) = 154 n (Ad26.COV2.S) = 150 n (BNT162b2) = 154	mRNA-1273/BNT162b2/Ad26.COV.2S	mRNA-1273/BNT162b2/Ad26.COV.2S (at least 12 wks)	Self (1 d pre-boost)	15 d	IgG against wild type in BAU/mL (95% CI), GMR (95% CI); pre vs post boost BNT162b2/Ad26COV2.S: 1904.7 (1497.8, 24222.2), ***GMR 6.2 (4.7, 8.1)*** BNT162b2/mRNA-1273: 6155.0 (4895.4, 7738.7), GMR 17.3 (13.3, 22.4) ***3.2-fold lower*** BNT162b2/BNT162b2: 3409.1 (2760.6, 4209.8), GMR 14.9 (11.8, 18.9) ***1.8-fold lower*** NAb against D614G in IU/mL (95% CI), GMR BNT162b2/Ad26COV2.S: 216.4 (157.8, 296.9), ***GMR 12.5 (8.7, 17.9)*** BNT162b2/mRNA-1273: 785.8 (596.4, 1035.2), GMR 31.7 (23.8, 42.2) ***1.1 fold lower*** BNT162b2/BNT162b2: 446.7 (340.3, 586.3), GMR 14.6, 27.4) ***2.1 fold lower*** All but 4 participants (2 Ad26.COV2.S, 2 mRNA-1273) had ≥ four-fold increase in ID50 titers against Delta variants All but 2 participants (1 Ad26.COV2.S, 1 mRNA-1273) had > four-fold increase in ID50 titers against Beta variants		Moderate	Trial 1/2 adapative design, open-label in sequential stages at 10 clinical sites; did not screen for past or current evidence of SARS-CoV-2 infection. Data at 28 d also available
Iketaine (US) Preprint (August 2021)	Single cohort, self-controlled	4 healthy individuals who received two doses of BNT162b2	BNT162b2 (3 wks)	Ad26.COV2.S (4 mos)	Self, 3 and 16 wks after V2	2 wks after booster	"All had heighted NAb titer following booster vaccination and could neutralize nearly all variants tested…Robust increases in titer were observed following a third vaccination, greater than that achieved after two vaccine doses…The increases in plasma neutralization titers (ID50) ranged from 10.9 to 21.1-fold in the pseudovirus neutralization assay and 14.8 to 32.4-fold in the authentic virus neutralization assay."*		Very low	*Results in graphs only.
Safety										
Atmar (US) Preprint (October 2021)	RCT	Adults with no prior history of SARS-CoV-2 infection or monoclonocal antibody infusion N = 458 (two age groups: 18-55 y.o., ≥ 56 y.o.) n (mRNA-1273) = 154 n (Ad26.COV2.S) = 150 n (BNT162b2) = 154	mRNA-1273/BNT162b2/Ad26.COV.2S	mRNA-1273/BNT162b2/Ad26.COV.2S (at least 12 wks)	Self (1 d pre-boost)	7 d for local and systemic AEs, 28 d for unsolicited Aes, 28 d (planned 12 mos) for SAEs, new onset chronic medical conditions (NOCMCs), adverse events of special interests (AESIs), related medically attended adverse events (MAAEs)	Similar reactogenicity with primary series. No related SAEs. No NOCMCs One related AESI in Ad26.COV2.S boost group Unsolicited AEs: mRNA-1273: 24/154 (15.6%) Ad26.COV2.S 18/150 (12%) BNT162b2: 22/154 (14.3%) Most related AEs with Grade 2 severity at most. Injection site AEs, malaise, myalagia, headache as common AEs		High	

Primary BNT162b2/mRNA-1273 booster										
Study author (country)	**Study design**	**Population**	**Primary series (interval)**	**Booster (interval from V2)**	**Comparator**	**Follow-up**	**Outcomes**		**Certainty of evidence**	**Comments**
Clinical efficacy/effectiveness										
None										
Immunogenicity										
							HUMORAL	***CELLULAR***		
Atmar (US) Preprint (October 2021)	Prospective cohort	Adults with no prior history of SARS-CoV-2 infection or monoclonocal antibody infusion N = 458 (two age groups: 18-55 y.o., ≥ 56 y.o.) mRNA-1273 booster) = 154 Ad26.COV2.S booster) = 150 BNT162b2 booster) = 154	mRNA-1273/BNT162b2/Ad26.COV.2S	mRNA-1273/BNT162b2/Ad26.COV.2S (at least 12 wks)	Self (1 d pre-boost)	15 d	IgG against wild type in BAU/mL (95% CI), GMR (95% CI) BNT162b2/mRNA-1273: 6155.0 (4895.4, 7738.7), ***GMR 17.3 (13.3, 22.4)*** BNT162b2/Ad26COV2.S: 1904.7 (1497.8, 24222.2), GMR 6.2 (4.7, 8.1) ****3.2-fold higher*** BNT162b2/BNT162b2: 3409.1 (2760.6, 4209.8), GMR 14.9 (11.8, 18.9) ****1.8-fold higher*** NAb against D614G in IU/mL (95% CI), GMR BNT162b2/mRNA-1273: 785.8 (596.4, 1035.2), ***GMR 31.7 (23.8, 42.2)*** BNT162b2/Ad26COV2.S: 216.4 (157.8, 296.9), GMR 12.5 (8.7, 17.9) *TO COMPUTE BNT162b2/BNT162b2: 446.7 (340.3, 586.3), GMR 14.6, 27.4) *TO COMPUTE All but 4 participants (2 Ad26.COV2.S, 2 mRNA-1273) had ≥ four-fold increase in ID50 titers against Delta variants All but 2 participants (1 Ad26.COV2.S, 1 mRNA-1273) had > four-fold increase in ID50 titers against Beta variants		Moderate	Trial 1/2 adapative design, open-label in sequential stages at 10 clinical sites; did not screen for past or current evidence of SARS-CoV-2 infection. Data at 28 d also available.
Safety										
Atmar (US) Preprint (October 2021)	prospective cohort	Adults with no prior history of SARS-CoV-2 infection or monoclonocal antibody infusion N = 458 (two age groups: 18-55 y.o., ≥ 56 y.o.) n (mRNA-1273) = 154 n (Ad26.COV2.S) = 150 n (BNT162b2) = 154	mRNA-1273/BNT162b2/Ad26.COV.2S	mRNA-1273/BNT162b2/Ad26.COV.2S (at least 12 wks)	Self (1 d pre-boost)	7 d for local and systemic AEs, 28 d for unsolicited Aes, 28 d (planned 12 mos) for SAEs, new onset chronic medical conditions (NOCMCs), adverse events of special interests (AESIs), related medically attended adverse events (MAAEs)	Similar reactogenicity with primary series. No related SAEs. No NOCMCs One related AESI in Ad26.COV2.S boost group Unsolicited AEs: mRNA-1273: 24/154 (15.6%) Ad26.COV2.S 18/150 (12%) BNT162b2: 22/154 (14.3%) Most related AEs with Grade 2 severity at most. Injection site AEs, malaise, myalagia, headache as common AEs		High	

Primary mRNA-1273/Ad26.COV2.S booster										
Study author (country)	**Study design**	**Population**	**Primary series (interval)**	**Booster (interval from V2)**	**Comparator**	**Follow-up**	**Outcomes**		**Certainty of evidence**	**Comments**
Clinical efficacy/effectiveness										
None										
Immunogenicity										
							HUMORAL	***CELLULAR***		
Atmar (US) Preprint (October 2021)	Prospective cohort	Adults with no prior history of SARS-CoV-2 infection or monoclonocal antibody infusion N = 458 (two age groups: 18-55 y.o., ≥ 56 y.o.) n (mRNA-1273) = 154 n (Ad26.COV2.S) = 150 n (BNT162b2) = 154	mRNA-1273/BNT162b2/Ad26.COV.2S	/Ad26.COV.2S (at least 12 wks)	Self (1 d pre-boost) mRNA-1273/ BNT162b2	15 d	IgG against wild type in BAU/mL (95% CI), GMR (95% CI) mRNA-1273/Ad26COV2.S: 3029.4 (2433.2, 3771.7), ***GMR 4.7 (3.6, 6.2)*** mRNA-1273/BNT162b2: 5195.6 (4433.1, 6089.3), GMR 9.7 (8.0, 11.8) mRNA-1273/mRNA-1273: 6799.8 (5771.8, 8010.9), GMR 7.9 (6.2, 10.1) NAb against D614G in IU/mL (95% CI), GMR mRNA-1273/Ad26COV2.S: 382.1 (290.5, 502.5), ***GMR 6.2 (4.5, 8.5)*** mRNA-1273/mRNA-1273: 901.8 (727.5, 1117.8), GMR 10.2 (8.0, 12.8) mRNA-1273/BNT162b2: 677.9 (559.4, 821.3), GMR 11.5 (9.0, 14.8) All but 4 participants (2 Ad26.COV2.S, 2 mRNA-1273) had ≥ four-fold increase in ID50 titers against Delta variants All but 2 participants (1 Ad26.COV2.S, 1 mRNA-1273) had > four-fold increase in ID50 titers against Beta variants		Moderate	Trial 1/2 adapative design, open-label in sequential stages at 10 clinical sites; did not screen for past or current evidence of SARS-CoV-2 infection. Data at 28 d also available.
Safety										
Atmar (US) Preprint (October 2021)	Prospective cohort	Adults with no prior history of SARS-CoV-2 infection or monoclonocal antibody infusion N = 458 (two age groups: 18-55 y.o., ≥ 56 y.o.) n (mRNA-1273) = 154 n (Ad26.COV2.S) = 150 n (BNT162b2) = 154	mRNA-1273/BNT162b2/Ad26.COV.2S	mRNA-1273/BNT162b2/Ad26.COV.2S (at least 12 wks)	Self (1 d pre-boost)	7 d for local and systemic AEs, 28 d for unsolicited Aes, 28 d (planned 12 mos) for SAEs, new onset chronic medical conditions (NOCMCs), adverse events of special interests (AESIs), related medically attended adverse events (MAAEs)	Similar reactogenicity with primary series. No related SAEs. No NOCMCs One related AESI in Ad26.COV2.S boost group Unsolicited AEs: mRNA-1273: 24/154 (15.6%) Ad26.COV2.S 18/150 (12%) BNT162b2: 22/154 (14.3%) Most related AEs with Grade 2 severity at most. Injection site AEs, malaise, myalagia, headache as common AEs		High	

Primary mRNA-1273/BNT162b2 booster										
Study author (country)	**Study design**	**Population**	**Primary series (interval)**	**Booster (interval from V2)**	**Comparator**	**Follow-up**	**Outcomes**		**Certainty of evidence**	**Comments**
Clinical efficacy/effectiveness										
None										
Immunogenicity										
							HUMORAL	***CELLULAR***		
Atmar (US) Preprint (October 2021)	Prospective cohort	Adults with no prior history of SARS-CoV-2 infection or monoclonocal antibody infusion N = 458 (two age groups: 18-55 y.o., ≥ 56 y.o.) n (mRNA-1273) = 154 n (Ad26.COV2.S) = 150 n (BNT162b2) = 154	mRNA-1273	BNT162b2 (at least 12 wks)	Self (1 d pre-boost) mRNA-1273 Ad26.Cov2.S	15 d	IgG against wild type in BAU/mL (95% CI), GMR (95% CI) mRNA-1273/BNT162b2: 5195.6 (4433.1, 6089.3), ***GMR 9.7 (8.0, 11.8)*** mRNA-1273/mRNA-1273: 6799.8 (5771.8, 8010.9), GMR 7.9 (6.2, 10.1) mRNA-1273/Ad26COV2.S: 3029.4 (2433.2, 3771.7), GMR 4.7 (3.6, 6.2) NAb against D614G in IU/mL (95% CI), GMR mRNA-1273/BNT162b2: 677.9 (559.4, 821.3), ***GMR 11.5 (9.0, 14.8)*** mRNA-1273/mRNA-1273: 901.8 (727.5, 1117.8), GMR 10.2 (8.0, 12.8) mRNA-1273/Ad26COV2.S: 382.1 (290.5, 502.5), GMR 6.2 (4.5, 8.5) All but 4 participants (2 Ad26.COV2.S, 2 mRNA-1273) had ≥ four-fold increase in ID50 titers against Delta variants All but 2 participants (1 Ad26.COV2.S, 1 mRNA-1273) had > four-fold increase in ID50 titers against Beta variants		Moderate	Trial 1/2 adapative design, open-label in sequential stages at 10 clinical sites; did not screen for past or current evidence of SARS-CoV-2 infection. Data at 28 d also available.
Safety										
Atmar (US) Preprint (October 2021)	RCT	Adults with no prior history of SARS-CoV-2 infection or monoclonocal antibody infusion N = 458 (two age groups: 18-55 y.o., ≥ 56 y.o.) n (mRNA-1273) = 154 n (Ad26.COV2.S) = 150 n (BNT162b2) = 154	mRNA-1273/BNT162b2/Ad26.COV.2S	mRNA-1273/BNT162b2/Ad26.COV.2S (at least 12 wks)	Self (1 d pre-boost)	7 d for local and systemic AEs, 28 d for unsolicited Aes, 28 d (planned 12 mos) for SAEs, new onset chronic medical conditions (NOCMCs), adverse events of special interests (AESIs), related medically attended adverse events (MAAEs)	Similar reactogenicity with primary series. No related SAEs. No NOCMCs One related AESI in Ad26.COV2.S boost group Unsolicited AEs: mRNA-1273: 24/154 (15.6%) Ad26.COV2.S 18/150 (12%) BNT162b2: 22/154 (14.3%) Most related AEs with Grade 2 severity at most. Injection site AEs, malaise, myalagia, headache as common AEs		High	
Werbel (US) Correspondence (June 2021)	Single cohort, self-controlled	Solid organ transplant recipients who had suboptimal response to standard vaccination and subsequently received third dose 25/30 on immunosuppression N = 30	BNT162b2 (57%) mRNA-1273 (43% standard dosing?	Mix of homologous and heterologous 3rd dose BNT162b2 (6 pxs) Ad26.COV.2 (15 pxs), mRNA-1273 (9pxs) (median 67 days (IQR 54 to 81d)	Self as control, 2 doses	Median 7 days for safety outcomes	local and systemic reactions, (N=23) 15 with mild to moderate local reaction most frequent systemic reaction - mild to moderate fatigue in 14 pxz 1 severe myalgia 1 severe headache 1 antibody-mediated rejection 7 days after V3		Low	

Primary Ad26.COV2.S/BNT162b2 booster										
Study author (country)	**Study design**	**Population**	**Primary series (interval)**	**Booster (interval from V1)**	**Comparator**	**Follow-up**	**Outcomes**		**Certainty of evidence**	**Comments**
Clinical efficacy/effectiveness										
None										
Immunogenicity										
							HUMORAL	***CELLULAR***		
Sablerolles (The Netherlands) Preprint (October 2021)	RCT	HCWs (18-65 y.o.) without severe comorbidities, no known history of SARS-CoV-2 infection who received single Ad26.COV2.S N randomized = 461 N per protocol analysis = 434 n (Ad26.COV2.S/no boost) = 105 n (Ad26.COV2.S/Ad26.COV.2.S) = 106 n (Ad26.COV2.S/mRNA-1273) = 112 n (Ad26.COV2.S/BNT16b2) = 111	Ad26.COV2.S	BNT162b2 (median 89 d)	No boost Ad26.COV.2.S (median 95 d) mRNA-1273 (median 96 d)	28 d after booster	anti-S: significant increase after boosting vs. no boosting ($p < 0.001$) higher in heterologous vs. homologous ($p < 0.001$) higher in mRNA-1273 boost vs. BNT162b2 boost ($p = 0.01$) response rate (heterologous vs. homologous): 100% vs. 97% NAb: Significant increase after boosting vs. baseline ($p < 0.001$), those without detectable pre-boost neutralization increased to above detection level except for 1 in the homologous boost group. 100% response response rate (heterologous vs. homologous): 100% vs. 95.2%	T-cell: significant increase after boosting vs. no boosting ($p < 0.001$) higher T-cell response with mRNA-1273 vs. homologous boost ($p < 0.001$) same T-cell response with BNT162b2 vs. homologous boost response rate (mRNA-1273 vs. BNT162b2 vs. homologous): 91.7% vs. 91.5% vs. 72.7%	Low	Single-(participant blinded. No boost group did not receive placebo injection. Unblinded 8 days after vaccination
Huat (Singapore, UK) Preprint (October 2021)	Prospective cohort	N = 115 n (Ad26.COV2.S/-) = 13 n (Ad26.COV2.S/Ad26.COV2.S) = 28 n (Ad26.COV2.S/BNT162b2) = 14 n (BNT162b2/-) = 16 n (BNT162b2/BNT162b2) = 44	Ad26.COV2.S	Ad26.COV2.S/BNT162b2 (median 31 d)	BNT16b2/BNT162b2 (median 21 d); Ad26.COV2.S/Ad26.COV2.S (median 56 d)	Ad26.COV2.S/- (median 80 d) Ad26.COV2.S/Ad26.COV2.S (median 49.5 d) Ad26.COV2.S/BNT162b2 (median 32 d) BNT162b2/- (median 60 d) BNT162b2/BNT162b2 (median 94 d)	Anti-spike IgG and IgA: higher in heterologous vs. homologous Ad26.COV2.S NAb: higher in heterologous vs. homologous Ad26.COV2.S % inhibition via SVNT: all heterologous achieved more than 80%, 7/21 homologous Ad26.COV2.S below 50% Spike-specific memory B cells: no or minimal increase in both groups (although with higher	Spike-specific T cells in SFC/10^6 PBMC (heterologous vs. homologous): 347.5 vs. 152 Homologous Ad26.COV2.S lower than single dose Ad26COV2.S and single dose BNT162b2	Very low	
Atmar (US) Preprint (October 2021)	Prospective cohort	Adults with no prior history of SARS-CoV-2 infection or monoclonocal antibody infusion N = 458 (two age groups: 18-55 y.o., ≥ 56 y.o.) n (mRNA-1273) = 154 n (Ad26.COV2.S) = 150 n (BNT162b2) = 154	Ad26.COV.2S	BNT162b2(at least 12 wks)	Self (1 d pre-boost) mRNA-1273 Ad26.COV.2S	15 d	IgG against wild type in BAU/mL (95% CI), GMR (95% CI) Ad26.COV2.S/BNT162b2: 2549.5 (2038.1, 3189.3), ***GMR 32.8 (24.6, 43.8)*** Ad26.COV2.S/mRNA-1273: 3203.1 (2499.5, 4104.9), GMR 56.1 (40.7, 77.2) Ad26.COV2.S/Ad26COV2.S: 326.0 (235.8, 450.7), GMR 4.6 (3.7, 5.7) NAb against D614G in IU/mL (95% CI), GMR Ad26.COV2.S/BNT162b2: 341.3 (239.6, 486.3), ***GMR 35.1 (23.9, 51.6)*** Ad26.COV2.S/mRNA-1273: 676.1 (517.5, 883.3), GMR 75.9 (55.0, 104.8) Ad26.COV2.S/Ad26COV2.S: 31.42 (22.3, 44.3), GMR 4.2 (3.0, 5.8) All but 4 participants (2 Ad26.COV2.S, 2 mRNA-1273) had ≥ four-fold increase in ID50 titers against Delta variants All but 2 participants (1 Ad26.COV2.S, 1 mRNA-1273) had > four-fold increase in ID50 titers against Beta variants		Moderate	Trial 1/2 adapative design, open-label in sequential stages at 10 clinical sites; did not screen for past or current evidence of SARS-CoV-2 infection. Data at 28 d also available.

Sester Preprint (Oct 2021)	Single cohort, self controlled	fifteen(15) individuals	Ad26.COV2.S	BNT162b2 (16.1 weeks, IQR 13-19.3)	self, 21d after D1	16d (14-23) after booster	IgG (BAU/ml) : pre and post-boost Pre : 62 (47-11), Post : 3168 (1896-4986) IgG seropositivity : pre and post boost Pre : 95% , Post : 100% Neutralizing activity, %inhibition: median (IQR), Pre, Post Pre : 29.5 (12.7-47.9), Post : 100.2 (100-100.6) NAB seropositivity : pre and postboost Pre : 13% , Post : 100%	Spike-specific CD4 Tcell(%) median [IQR) Pre : 0.032 (0.019-0.051) Post : 0.070 (0.049-0.157) CD4Tcell seropositivity Pre : 53% Post : 93%		
Safety										
Sablerolles (The Netherlands) Preprint (October 2021)	RCT	HCWs (18-65 y.o.) without severe comorbidities, no known history of SARS-CoV-2 infection who received single Ad26.COV2.S N randomized = 461 N per protocol analysis = 434 n (Ad26.COV.2.S/no boost) = 105 n (Ad26.COV.2.S/Ad26.COV.2.S) = 106 n (Ad26.COV.2.S/mRNA-1273) = 112 n (Ad26.COV.2.S/BNT162b2) = 111	Ad26.COV.2.S	Ad26.COV.2.S (median 95 d) mRNA-1273 (median 96 d) BNT162b2 (median 89 d)	No boost	7 d after booster	Increased severity of local and systemic reactions with mRNA-1273 boost ($p < 0.01$) All AEs mild to moderate. No hospitalization. Resolved with 48 hrs.		Low	Single-(participant blinded. No boost group did not receive placebo injection. Unblinded 8 days after vaccination
Atmar (US) Preprint (October 2021)	Prospective cohort	Adults with no prior history of SARS-CoV-2 infection or monoclonocal antibody infusion N = 458 (two age groups: 18-55 y.o., >_ 56 y.o.) n (mRNA-1273) = 154 n (Ad26.COV2.S) = 150 n (BNT162b2) = 154	mRNA-1273/BNT162b2/Ad26.COV.2S	mRNA-1273/BNT162b2/Ad26.COV.2S (at least 12 wks)	Self (1 d pre-boost)	7 d for local and systemic AEs, 28 d for unsolicited Aes, 28 d (planned 12 mos) for SAEs, new onset chronic medical conditions (NOCMCs), adverse events of special interests (AESIs), related medically attended adverse events (MAAEs)	Similar reactogenicity with primary series. No related SAEs. No NOCMCs One related AESI in Ad26.COV2.S boost group Unsolicited AEs: mRNA-1273: 24/154 (15.6%) Ad26.COV2.S 18/150 (12%) BNT162b2: 22/154 (14.3%) Most related AEs with Grade 2 severity at most. Injection site AEs, malaise, myalagia, headache as common AEs		High	
Sester Preprint (Oct 2021)	Single cohort, self controlled	fifteen(15) individuals	Ad26.COV2.S	BNT162b2 (16.1 weeks, IQR 13-19.3)	self, 21d after D1	within 7 days of booster 16d (14-23) after booster	self reported reactogenicity local and systemtic adverse reaction rates were generally the same or slightly lower afte the boost compared to the primary series			

Primary Ad26.COV2.S/mRNA-1273 booster										
Study author (country)	**Study design**	**Population**	**Primary series (interval)**	**Booster (interval from V1)**	**Comparator**	**Follow-up**	**Outcomes**		**Certainty of evidence**	**Comments**
Clinical efficacy/effectiveness										
None										
Immunogenicity										
Sablerolles (The Netherlands) Preprint (October 2021)	RCT	HCWs (18-65 y.o.) without severe comorbidities, no known history of SARS-CoV-2 infection who received single Ad26.COV2.S N randomized = 461 N per protocol analysis = 434 n (Ad26.COV2.S/no boost) = 105 n (Ad26.COV2.S/Ad26.COV.2.S) = 106 n (Ad26.COV2.S/mRNA-1273) = 112 n (Ad26.COV2.S/BNT16b2) = 111	Ad26.COV2.S	BNT162b2 (median 89 d)	No boost Ad26.COV.2.S (median 95 d) mRNA-1273 (median 96 d)	28 d after booster	anti-S: significant increase after boosting vs. no boosting ($p < 0.001$) higher in heterologous vs. homologous ($p < 0.001$) higher in mRNA-1273 boost vs. BNT162b2 boost ($p = 0.01$) response rate (heterologous vs. homologous): 100% vs. 97% NAb: Significant increase after boosting vs. baseline ($p < 0.001$), those without detectable pre-boost neutralization increased to above detection level except for 1 in the homologous boost group. 100% response response rate (heterologous vs. homologous): 100% vs. 95.2%	T-cell: significant increase after boosting vs. no boosting ($p < 0.001$) higher T-cell response with mRNA-1273 vs. homologous boost ($p < 0.001$) same T-cell response with BNT162b2 vs. homologous boost response rate (mRNA-1273 vs. BNT162b2 vs. homologous): 91.7% vs. 91.5% vs. 72.7%	Low	Single-(participant blinded. No boost group did not receive placebo injection. Unblinded 8 days after vaccination
Atmar (US) Preprint (October 2021)	Prospective cohort	Adults with no prior history of SARS-CoV-2 infection or monoclonocal antibody infusion N = 458 (two age groups: 18-55 y.o., ≥ 56 y.o.) n (mRNA-1273) = 154 n (Ad26.COV2.S) = 150 n (BNT162b2) = 154	Ad26.COV.2S	mRNA-1273(at least 12 wks)	Self (1 d pre-boost) BNT162b2 Ad26.COV.2S	15 d	IgG against wild type in BAU/mL (95% CI), GMR (95% CI) Ad26.COV2.S/mRNA-1273: 3203.1 (2499.5, 4104.9), ***GMR 56.1 (40.7, 77.2)*** Ad26.COV2.S/Ad26COV2.S: 326.0 (235.8, 450.7), GMR 4.6 (3.7, 5.7) Ad26.COV2.S/BNT162b2: 2549.5 (2038.1, 3189.3), GMR 32.8 (24.6, 43.8) NAb against D614G in IU/mL (95% CI), GMR Ad26.COV2.S/mRNA-1273: 676.1 (517.5, 883.3), ***GMR 75.9 (55.0, 104.8***) Ad26.COV2.S/Ad26COV2.S: 31.42 (22.3, 44.3), GMR 4.2 (3.0, 5.8) Ad26.COV2.S/BNT162b2: 341.3 (239.6, 486.3), GMR 35.1 (23.9, 51.6) All but 4 participants (2 Ad26.COV2.S, 2 mRNA-1273) had ≥ four-fold increase in ID50 titers against Delta variants All but 2 participants (1 Ad26.COV2.S, 1 mRNA-1273) had > four-fold increase in ID50 titers against Beta variants		Moderate	Trial 1/2 adapative design, open-label in sequential stages at 10 clinical sites; did not screen for past or current evidence of SARS-CoV-2 infection. Data at 28 d also available.

Safety										
Sablerolles (The Netherlands) Preprint (October 2021)	RCT	HCWs (18-65 y.o.) without severe comorbidities, no known history of SARS-CoV-2 infection who received single Ad26.COV2.S N randomized = 461 N per protocol analysis = 434 n (Ad26.COV.2.S/no boost) = 105 n (Ad26.COV.2.S/Ad26.COV.2.S) = 106 n (Ad26.COV.2.S/mRNA-1273) = 112 n (Ad26.COV.2.S/BNT16b2) = 111	Ad26.COV.2.S	Ad26.COV.2.S (median 95 d) mRNA-1273 (median 96 d) BNT162b2 (median 89 d)	No boost	7 d after booster	Increased severity of local and systemic reactions with mRNA-1273 boost ($p < 0.01$) All AEs mild to moderate. No hospitalization. Resolved with 48 hrs.		Low	Single-(participant blinded. No boost group did not receive placebo injection. Unblinded 8 days after vaccination
Atmar (US) Preprint (October 2021)	RCT	Adults with no prior history of SARS-CoV-2 infection or monoclonocal antibody infusion N = 458 (two age groups: 18-55 y.o., ≥ 56 y.o.) n (mRNA-1273) = 154 n (Ad26.COV2.S) = 150 n (BNT162b2) = 154	mRNA-1273/BNT162b2/Ad26.COV.2S	mRNA-1273/BNT162b2/Ad26.COV.2S (at least 12 wks)	Self (1 d pre-boost)	7 d for local and systemic AEs, 28 d for unsolicited Aes, 28 d (planned 12 mos) for SAEs, new onset chronic medical conditions (NOCMCs), adverse events of special interests (AESIs), related medically attended adverse events (MAAEs)	Similar reactogenicity with primary series. No related SAEs. No NOCMCs One related AESI in Ad26.COV2.S boost group Unsolicited AEs: mRNA-1273: 24/154 (15.6%) Ad26.COV2.S 18/150 (12%) BNT162b2: 22/154 (14.3%) Most related AEs with Grade 2 severity at most. Injection site AEs, malaise, myalagia, headache as common AEs		High	

Primary CoronaVac/BNT162b2 booster										
Study author (country)	**Study design**	**Population**	**Primary series (interval)**	**Booster (interval from V2)**	**Comparator**	**Follow-up**	**Outcomes**		**Certainty of evidence**	**Comments**
Clinical efficacy/effectiveness										
None										
Immunogenicity										
Barin (Cyprus) Preprint (September 2021)	Single cohort, self-controlled	General population (some HCWs, with chronic condition, EXCLUDED those on chemotherapy and steroids), analyzed cohort given with booster CoronoVac/BNT16b2 or CoronaVac booster N = 85 < 60 y.o. = 33 > 60 y.o. = 52	CoronaVac (4 wks)	BNT162b2 (6 mos)	Self, 1 mo after V2	1 mo after booster	In < 60 y.o anti-spike RBD IgG in median AU log (IQR) (post-boost vs. self): 44 (40.4, 44.9) vs. 11 (6.7, 20.7) GMR 4.7 (95% CI, 3.2, 6.9) seropositivity rate (post-boost vs. self): 100% vs. 90.9% In > 60 y.o. anti-spike RBD IgG in median AU log (IQR) (post-boost vs. self): 36.7 (33, 39.3) vs. 5 (1.8, 13.9) GMR 7.9 (95% CI 5.8, 10.8) seropositivity rate (post-boost vs. self): 100% vs. 86.5%		Very low	
Patamatamkul (Thailand) Preprint (September 2021)	Prospective cohort	Healthcare personnel, N = 41 n = 23 (BNT162b2) n = 18 (ChAdOx1)	CoronaVac	ChAdOx1 (not specified), BNT162b2 (not specified)	Post-boost (ChAdOx1 vs. BNT162b2); self	Pre-boost: 4 wks before ChAdOx1 booster; 12 weeks before BNT162b2 booster Post-boost: 3 wks after ChAdOx1 booster; 2 wks after BNT162b2 booster	anti-S RBD in U/mL (IQR) (pre-BNT16b2 boost vs. post-BNT162b2 boost): 37.46 (23.39, 51.60) vs. 22558 (15956, 25000), p < 0.001 anti-S RBD in U/mL (IQR) (pre-ChAdOx1 boost vs. post-ChAdOx1 boost): 106.8 (49.89, 151.7) vs. 5159 (3647.75, 9196.75), p < 0.001 anti-S RBD in U/mL (IQR) (post-BNT162b2 boost vs. post-ChAdOx1 boost): 22558 (15956, 25000) vs. 5159 (3647.75, 9196.75), p <0.001 sVNT ≥ 30% inhibition against Delta variant (IQR) (post-BNT162b2 boost vs. post-ChAdOx1 boost): 97.76% (97.5, 98.29) vs. 97.02% (93.8, 97.64), p < 0.001		Very low	
Mok (HongKong) Preprint (Mar-Aug 2021)	RCT Serious unclear domains	healthy adults received 2 doses of CoronaVac with sVNT results below 60% at one month after second dose homologous : 40 heterologous : 40	CoronaVac	BNT162b2 (mean 115 days)	CoronaVac	1 month after booster	% sVNT inhibition pre and post boost +BNT : 96.85% (SD 2.4%) +CoronaVac : 57.75% (SD 24.68) ***>20% more with hetero*** % sVNT for Beta, Gamma, Delta +BNT : 92.3%, 92.5%, 95.3% +CoronaVac: 38.9%, 32.2%, 48.9% Titers for RBD, NTD and S2 antibodies were higher in those who received BNT162b2 as booster			
Safety										
Patamatamkul (Thailand) Preprint (September 2021)	Prospective cohort	Healthcare personnel, N = 41 n = 23 (BNT162b2) n = 18 (ChAdOx1)	CoronaVac	ChAdOx1 (not specified), BNT162b2 (not specified)	Post-boost (ChAdOx1 vs. BNT162b2); pre-vs. post-boost	Not specified	All participants had at least 1 symptom after booster (most common: pain at injection site). No significant difference between post-ChAdOx1 boost and post-BNT16b2 boost		Very low	
Mok (HongKong) Preprint (Mar-Aug 2021)	RCT Serious unclear domains	healthy individuals, 19-77 years received 2 doses of CoronaVac with sVNT results below 60% at one month after second dose homologous : 40 heterologous : 40	CoronaVac	BNT162b2	CoronaVac	1 week after booster	similar adverse reactions as with homologous more pain and swelling at injection site compared to homologous group more fatigue and muscle pain compared to homologous			

Primary CoronaVac/ChAdOx1 booster										
Study author (country)	**Study design**	**Population**	**Primary series (interval)**	**Booster (interval from V2)**	**Comparator**	**Follow-up**	**Outcomes**		**Certainty of evidence**	**Comments**
Clinical efficacy/effectiveness										
None										
Immunogenicity										
							HUMORAL	***CELLULAR***		
Patamatamkul (Thailand) Preprint (September 2021)	Prospective cohort	Healthcare personnel, N = 41 n = 23 (BNT162b2) n = 18 (ChAdOx1)	CoronaVac	ChAdOx1 (not specified), BNT162b2 (not specified)	Post-boost (ChAdOx1 vs. BNT162b2); self	Pre-boost: 4 wks before ChAdOx1 booster; 12 weeks before BNT162b2 booster Post-boost: 3 wks after ChAdOx1 booster; 2 wks after BNT162b2 booster	anti-S RBD in U/mL (IQR) (pre-BNT16b2 boost vs. post-BNT162b2 boost): 37.46 (23.39, 51.60) vs. 22558 (15956, 25000), p < 0.001 anti-S RBD in U/mL (IQR) (pre-ChAdOx1 boost vs. post-ChAdOx1 boost): 106.8 (49.89, 151.7) vs. 5159 (3647.75, 9196.75), p < 0.001 anti-S RBD in U/mL (IQR) (post-BNT162b2 boost vs. post-ChAdOx1 boost): 22558 (15956, 25000) vs. 5159 (3647.75, 9196.75), p <0.001 sVNT ≥ 30% inhibition against Delta variant (IQR) (post-BNT162b2 boost vs. post-ChAdOx1 boost): 97.76% (97.5, 98.29) vs. 97.02% (93.8, 97.64), p < 0.001		Very low	
Singhatiraj (Thailand) Publication (September 2021)	Case report	52/M, healthcare professional	CoronaVac (~1 mo)	Intradermal ChAdOx1 (~1 mo)	Self	2 wks after booster	anti-spike IgG in AU/mL (pre-boost vs post-boost): 853.6 vs. 10465.20 Nab (pre-boost vs. post-boost): 66.7% vs. 99.6% PVNT against wild type, alpha, beta, delta in	SARS-CoV-2-specific T cells detected	Very low	
Yorsaeng (Thailand) Preprint (September 2021)	Prospective cohort	HCWs N = 549 n (CoronaVac/CoronaVac) = 170 n (ChAdOx1/ChAdOx1) = 169 n (CoronaVac/CoronoVac + ChAdOx1 booster) = 210	CoronaVac/CoronaVac median 23 d)	ChAdOx1 (median 70 d)	CoronaVac/CoronaVac,	CoronaVac/CoronaVac: 21-49 d after V2 ChAdOx1/ChAdOx1: 21-35 d after V2 14-35 d after booster	Total Anti-RBD in U/mL (95% CI) (ChAdOx1 booster group vs. CoronaVac/CoronaVac vs. ChAdOx1/ChAdOx1): 7947 (7277, 8679) vs. 97.9 (82.6, 116.1) vs. 877.1 (763.5, 1008) anti-RBD IgG in BAU/mL (95% CI) (ChAdOx1 booster group vs. CoronaVac/CoronaVac vs. ChAdOx1/ChAdOx1): 1492 (1367, 1629) vs. 128 (113.7, 144.1) vs. 178 (155.5, 203.8) Anti-S1 IgA in OD/CO (IQR) (ChAdOx1 booster group vs. CoronaVac/CoronaVac vs. ChAdOx1/ChAdOx1): 5.25 (3.94, 9) vs. 0.88 (0.55, 1.79) vs. 1 (0.53, 1.73) NAb percent inhibition (IQR) (ChAdOx1 booster group vs. CoronaVac/CoronaVac vs. ChAdOx1/ChAdOx1): 99.49 (99.18, 99.62) vs. 76.52 (53.10, 87.97) vs. 51.56 (33.43, 72.98) NAb percent inhibition against wild type (IQR) (ChAdOx1 booster group vs. CoronaVac/CoronaVac vs. ChAdOx1/ChAdOx1): 97.75 (96.98, 97.83) vs. 66.60 (48.86, 79.41) vs. 88.86 (75.65, 96.35) NAb percent inhibition against alpha (IQR) (ChAdOx1 booster group vs. CoronaVac/CoronaVac vs. ChAdOx1/ChAdOx1): 97.24 (94.71, 97.65) vs. 42.11 (28.97, 58.31) vs. 75.94 (61.48, 88.36)		Very low	
Safety										
Patamatamkul (Thailand) Preprint (September 2021)	Prospective cohort	Healthcare personnel, N = 41 n = 23 (BNT162b2) n = 18 (ChAdOx1)	CoronaVac	ChAdOx1 (not specified), BNT162b2 (not specified)	Post-boost (ChAdOx1 vs. BNT162b2); pre- vs. post-boost	Not specified	All participants had at least 1 symptom after booster (most common: pain at injection site). No significant difference between post-ChAdOx1 boost and post-BNT16b2 boost		Very low	
Singhatiraj (Thailand) Publication (September	Case report	30/F, physician, with Graves' disease, on methimazole 2.5 mg/d	CoronaVac (< 1 mo)	ChAdOx1 (~ 3 mos)	Self	4 d after booster	With palpitations needing propranolol to control symptoms and weight loss. Increased methimazole to 5 mg/d with improvement of symptoms.		Very low	

Primary CoronaVac/Ad5-nCoV booster										
Study author (country)	**Study design**	**Population**	**Primary series (interval)**	**Booster (interval from V2)**	**Comparator**	**Follow-up**	**Outcomes**		**Certainty of evidence**	**Comments**
Clinical efficacy/effectiveness										
None										
Immunogenicity										
Li J (China) Preprint (September 2021)	RCT	18-59 yo, healthy received two doses of CoronaVac in the past 3-6 months or one dose of CoronaVac in the past 1-2 months 2 dose : N - 200 boost with CoronaVac : boost with Ad5 : Excluded previous clinical or virologic COVID-19 diagnosis or infection, pregnant women	CoronaVac 2 doses	CoronaVac (3-6months)	Ad5-nCoV (3-6 months)	28 days for AE 14 and 28 days for immunologic outcomes	neutralizing antibody titers (live viral assay) 14 days (pre to post boost) Ad5 : 2.5 (2.3, 2.7) to 197.4 (167.7, 232.4) CoronaVac : 1.1 (2.1, 2.3) to 33.6 (28.3, 39.8) 28 days Ad5 : 150.3 (128, 175.7) Coronavac : 35.3 (29.4, 42.4) Fold-rise : 14-days vs 28 days ad5 : 78-fold / 60-fold CoronaVac : 15.2-fold / 32-fold anti-RBD titers (ELISA) Ad5 : 3090.1 (2636.1, 3622.3) CoronaVac : 369 (304.2, 447.5) anti-N titers (ELISA) only CoronaVac showed increases to N protein antibodies, Ad5 showed no increase post boost T-cell response (ELISpot) (N= 50) 14 days : per 10 PBMC Ad5 : 100 (IQR 60, 165) CoronaVac : 90 (40, 230)		Moderate	IWRS randomization participants, investigators, lab and outcome assessors blinded to treatment but not to the 3 or 2 dose regimen
Safety										
Li J (China) Preprint (September 2021)	RCT	18-59 yo, healthy received two doses of CoronaVac in the past 3-6 months or one dose of CoronaVac in the past 1-2 months 2 dose : N - 200 boost with CoronaVac : boost with Ad5 : Excluded previous clinical or virologic COVID-19 diagnosis or infection, pregnant women	CoronaVac 2 doses	CoronaVac vs Ad5-nCoV (3-6months)	Ad5-nCoV (3-6 months)	28 days for AE 14 and 28 days for immunologic outcomes	Ad5 patients - reported more adverse reactions (Table 2) - had more solicited injection-site reactions (20.2% vs 2.9%) - had more solicited systemic reactions (13.5% vs 2.9%) reactions generally mild and moderate, resolved within 1-2 days injection site pain most common severe injection-site pain reported in 2.1% of Ad5 recipients Fever and fatigue most common systemic reactions NO thromboses or vaccine-related anaphylaxis or SAE seen in any of the cohorts		Moderate	IWRS randomization participants, investigators, lab and outcome assessors blinded to treatment but not to the 3 or 2 dose regimen

Primary ChAdOx1/BNT162b2 booster										
Study author (country)	**Study design**	**Population**	**Primary series (interval)**	**Booster (interval from V2)**	**Comparator**	**Follow-up**	**Outcomes**		**Certainty of evidence**	**Comments**
Clinical efficacy/effectiveness										
Immunogenicity										
							HUMORAL	***CELLULAR***		
Hoque (Bangladesh) Preprint (Feb to Oct 2021)	Single cohort, self controlled	20 ChAdOx1 recipients who developed breakthrough infection with the month and had long COVID	ChAdOx1-nCoV-19 2 doses interval not mentioned	BNT162b2	self, pre	14 days post boost	significantly lower CRP levels post boost significantly higher titers of anti-S1-RBD IgG (note : no values given, results shown in figures)			
Safety										

Primary BBIBP/BNT162b2 booster										
Study author (country)	**Study design**	**Population**	**Primary series (interval)**	**Booster (interval from V2)**	**Comparator**	**Follow-up**	**Outcomes**		**Certainty of evidence**	**Comments**
Clinical efficacy/effectiveness										
Moghnieh (Lebanon) Correspondence (Feb-Jun 2021)	Prospective Cohort Very Serious observational no control of confounders	18years and older gr 1 : BNT, COVID naïve (50) gr 2 : BNT, with previous infect (25) gr 3 : BBIBP, COVID naïve (50)	BBIBP-CorV	BNT162b2 at least 3 months after	Self, BNT primary no boost	14d after D2 14d after boost	2 (4%) patients developed COVID-19 (positive RT PCR) one week after the booster, one was asymptomatic and the other with mild symptoms none of the patients in the other groups developed COVID			
Immunogenicity										
Moghnieh (Lebanon) Correspondence (Feb-Jun 2021)	Prospective Cohort Very Serious observational no control of confounders	18years and older gr 1 : BNT, COVID naïve (50) gr 2 : BNT, with previous infect (25) gr 3 : BBIBP, COVID naïve (50)	BBIBP-CorV	BNT162b2 at least 3 months after	Self, BNT primary no boost	14d after D2 14d after boost	anti-S IgG (GMT) BAU/ml (95%CI) Gr1 BNT162b2 : 1384 (1063-1801) Gr2 BNT162b1 : 22536 (13550-37482) Gr3 preboost : 9 (6-13), post boost : 8040 (4612-14016) *****893-fold rise***			
Safety										
Moghnieh (Lebanon) Correspondence (Feb-Jun 2021)	Prospective Cohort Very Serious observational no control of confounders	18years and older gr 1 : BNT, COVID naïve (50) gr 2 : BNT, with previous infect (25) gr 3 : BBIBP, COVID naïve (50)	BBIBP-CorV	BNT162b2 at least 3 months after	Self, BNT primary no boost	14d after D2 14d after boost	62% with any side effect 60% with pain at injection site systemic adverse events : 2-10%, most common is lethargy (10%) younger patients reporting more side effects			

Appendix 5. Characteristics and detailed outcomes of studies on homologous booster vaccination involving healthcare workers

BNT162b2									
Study author (country)	**Study design**	**Population**	**Primary series (interval)**	**Booster (interval from V2)**	**Comparator**	**Follow-up**	**Outcomes**	**Certainty of evidence**	**Comments**
Clinical efficacy/effectiveness									
None									
Immunogenicity									
Romero-Ibarguengoitia (Mexico) Preprint (October 2021)	Single cohort, self-controlled	HCWs N = 168 n (with history of SARS-CoV-2 infection) = 95 n (without history of SARS-CoV-2 infection) = 73	BNT162b2 (median 31 d)	BNT162b2 (median 166 d)	Self	21-28 days after V2; 21-28 days after booster	Without history of SARS-CoV-2 infection anti-S1/S2 IgG in AU/mL (IQR) (post-boost vs. pre-boost): 2960 (2010) vs. 1350 (1224), **2.2-fold** With history of SARS-CoV-2 infection anti-S1/S2 IgG in AU/mL (IQR) (post-boost vs. pre-boost): 3090 (2080) vs. 2390 (2540), **1.3-fold**	Very low	
Safety									
Romero-Ibarguengoitia (Mexico) Preprint (October 2021)	Single cohort, self-controlled	HCWs N = 168 n (with history of SARS-CoV-2 infection) = 95 n (without history of SARS-CoV-2 infection) = 73	BNT162b2 (median 31 d)	BNT162b2 (median 166 d)	Self	Not specified.	Less total number of side effects with booster group compared to primary series Most common AE: pain at injection site Higher tiredness, myalgias, arthralgias, fever, and adenopathy after booster compared to primary series ($p < 0.05$)	Very low	

BBIBP-CorV									
Study author (country)	**Study design**	**Population**	**Primary series (interval)**	**Booster (interval from V2)**	**Comparator**	**Follow-up**	**Outcomes**	**Certainty of evidence**	**Comments**
Clinical efficacy/effectiveness									
None									
Immunogenicity									
Liu (China) Preprint (September 2021)	Single cohort, self-controlled	HCWs volunteered to receive third booster shot of inactivated vaccine 6 mos after prime vaccination N = 50	BBIBP-CorV (28 d)	BBIBP-CorV (6 mos)	Self	On day of booster, 1 wk after booster	NAb in AU/mL (pre-boost vs. post-boost): 9.3 vs. 66.9 (7.2-fold) spike-specific memory B cells in s.f.u./10^6 PBMCs (pre-boost vs. post-boost): 8 vs. 17 (1.7-fold) RBD-specific memory B cells in s.f.u./10^6 PBMCs (pre-boost vs. post-boost): 4 vs. 10.7 (2-fold) T cell response: increased 2.3-fold SARS-CoV-2-specific CD8+ T cell: increased 2.7-fold SARS-CoV-2-specific CD4+ T cell: increased 5.9-fold		Part of a previous prospective cohort
Safety									
Liu (China) Preprint (September 2021)	Single cohort, self-controlled	HCWs volunteered to receive third booster shot of inactivated vaccine 6 mos after prime vaccination N = 50	BBIBP-CorV (28 d)	BBIBP-CorV (6 mos)	Self	On day of booster, 1 wk after booster	No severe side effects related to vaccination.		Part of a previous prospective cohort

Appendix 6. Characteristics and detailed outcomes of studies on heterologous booster vaccination involving the healthcare workers

Primary Ad26.COV2.S/BNT162b2 booster										
Study author (country)	**Study design**	**Population**	**Primary series (interval)**	**Booster (interval from V1)**	**Comparator**	**Follow-up**	**Outcomes**		**Certainty of evidence**	**Comments**
Clinical efficacy/effectiveness										
None										
Immunogenicity										
							HUMORAL	***CELLULAR***		
Sablerolles (The Netherlands) Preprint (October 2021)	RCT	HCWs (18-65 y.o.) without severe comorbidities, no known history of SARS-CoV-2 infection who received single Ad26.COV2.S N randomized = 461 N per protocol analysis = 434 n (Ad26.COV2.S/no boost) = 105 n (Ad26.COV2.S/Ad26.COV.2.S) = 106 n (Ad26.COV2.S/mRNA-1273) = 112 n (Ad26.COV2.S/BNT16b2) = 111	Ad26.COV2.S	BNT162b2 (median 89 d)	No boost Ad26.COV.2.S (median 95 d) mRNA-1273 (median 96 d)	28 d after booster	anti-S: significant increase after boosting vs. no boosting ($p < 0.001$) higher in heterologous vs. homologous ($p < 0.001$) higher in mRNA-1273 boost vs. BNT162b2 boost ($p = 0.01$) response rate (heterologous vs. homologous): 100% vs. 97% NAb: Significant increase after boosting vs. baseline ($p < 0.001$), those without detectable pre-boost neutralization increased to above detection level except for 1 in the homologous boost group. 100% response response rate (heterologous vs. homologous): 100% vs. 95.2%	T-cell: significant increase after boosting vs. no boosting ($p < 0.001$) higher T-cell response with mRNA-1273 vs. homologous boost ($p < 0.001$) same T-cell response with BNT162b2 vs. homologous boost response rate (mRNA-1273 vs. BNT162b2 vs. homologous): 91.7% vs. 91.5% vs. 72.7%	Low	Single-(participant blinded. No boost group did not receive placebo injection. Unblinded 8 days after vaccination
Safety										
Sablerolles (The Netherlands) Preprint (October 2021)	RCT	HCWs (18-65 y.o.) without severe comorbidities, no known history of SARS-CoV-2 infection who received single Ad26.COV2.S N randomized = 461 N per protocol analysis = 434 n (Ad26.COV.2.S/no boost) = 105 n (Ad26.COV.2.S/Ad26.COV.2.S) = 106 n (Ad26.COV.2.S/mRNA-1273) = 112	Ad26.COV.2.S	Ad26.COV.2.S (median 95 d) mRNA-1273 (median 96 d) BNT162b2 (median 89 d)	No boost	7 d after booster	Increased severity of local and systemic reactions with mRNA-1273 boost ($p < 0.01$) All AEs mild to moderate. No hospitalization. Resolved with 48 hrs.		Low	Single-(participant blinded. No boost group did not receive placebo injection. Unblinded 8 days after vaccination

Primary Ad26.COV2.S/mRNA-1273 booster										
Study author (country)	**Study design**	**Population**	**Primary series (interval)**	**Booster (interval from V1)**	**Comparator**	**Follow-up**	**Outcomes**		**Certainty of evidence**	**Comments**
Clinical efficacy/effectiveness										
None										
Immunogenicity										
Sablerolles (The Netherlands) Preprint (October 2021)	RCT	HCWs (18-65 y.o.) without severe comorbidities, no known history of SARS-CoV-2 infection who received single Ad26.COV2.S N randomized = 461 N per protocol analysis = 434 n (Ad26.COV2.S/no boost) = 105 n (Ad26.COV2.S/Ad26.COV.2.S) = 106 n (Ad26.COV2.S/mRNA-1273) = 112 n (Ad26.COV2.S/BNT16b2) = 111	Ad26.COV2.S	BNT162b2 (median 89 d)	No boost Ad26.COV.2.S (median 95 d) mRNA-1273 (median 96 d)	28 d after booster	anti-S: significant increase after boosting vs. no boosting ($p < 0.001$) higher in heterologous vs. homologous ($p < 0.001$) higher in mRNA-1273 boost vs. BNT162b2 boost ($p = 0.01$) response rate (heterologous vs. homologous): 100% vs. 97% NAb: Significant increase after boosting vs. baseline ($p < 0.001$), those without detectable pre-boost neutralization increased to above detection level except for 1 in the homologous boost group. 100% response response rate (heterologous vs. homologous): 100% vs. 95.2%	T-cell: significant increase after boosting vs. no boosting ($p < 0.001$) higher T-cell response with mRNA-1273 vs. homologous boost ($p < 0.001$) same T-cell response with BNT162b2 vs. homologous boost response rate (mRNA-1273 vs. BNT162b2 vs. homologous): 91.7% vs. 91.5% vs. 72.7%	Low	Single-(participant blinded. No boost group did not receive placebo injection. Unblinded 8 days after vaccination
Safety										
Sablerolles (The Netherlands) Preprint (October 2021)	RCT	HCWs (18-65 y.o.) without severe comorbidities, no known history of SARS-CoV-2 infection who received single Ad26.COV2.S N randomized = 461 N per protocol analysis = 434 n (Ad26.COV.2.S/no boost) = 105 n (Ad26.COV.2.S/Ad26.COV.2.S) = 106 n (Ad26.COV.2.S/mRNA-1273) = 112 n (Ad26.COV.2.S/BNT16b2) = 111	Ad26.COV.2.S	Ad26.COV.2.S (median 95 d) mRNA-1273 (median 96 d) BNT162b2 (median 89 d)	No boost	7 d after booster	Increased severity of local and systemic reactions with mRNA-1273 boost ($p < 0.01$) All AEs mild to moderate. No hospitalization. Resolved with 48 hrs.		Low	Single-(participant blinded. No boost group did not receive placebo injection. Unblinded 8 days after vaccination

Primary CoronaVac/BNT162b2 booster										
Study author (country)	**Study design**	**Population**	**Primary series (interval)**	**Booster (interval from V2)**	**Comparator**	**Follow-up**	**Outcomes**		**Certainty of evidence**	**Comments**
Clinical efficacy/effectiveness										
None										
Immunogenicity										
Patamatamkul (Thailand) Preprint (September 2021)	Prospective cohort	Healthcare personnel, N = 41 n = 23 (BNT162b2) n = 18 (ChAdOx1)	CoronaVac	ChAdOx1 (not specified), BNT162b2 (not specified)	Post-boost (ChAdOx1 vs. BNT162b2); self	Pre-boost: 4 wks before ChAdOx1 booster; 12 weeks before BNT162b2 booster Post-boost: 3 wks after ChAdOx1 booster; 2 wks after BNT162b2 booster	anti-S RBD in U/mL (IQR) (pre-BNT16b2 boost vs. post-BNT162b2 boost): 37.46 (23.39, 51.60) vs. 22558 (15956, 25000), p < 0.001 anti-S RBD in U/mL (IQR) (pre-ChAdOx1 boost vs. post-ChAdOx1 boost): 106.8 (49.89, 151.7) vs. 5159 (3647.75, 9196.75), p < 0.001 anti-S RBD in U/mL (IQR) (post-BNT162b2 boost vs. post-ChAdOx1 boost): 22558 (15956, 25000) vs. 5159 (3647.75, 9196.75), p <0.001 sVNT ≥ 30% inhibition against Delta variant (IQR) (post-BNT162b2 boost vs. post-ChAdOx1 boost): 97.76% (97.5, 98.29) vs. 97.02% (93.8, 97.64), p < 0.001		Very low	
Safety										
Patamatamkul (Thailand) Preprint (September 2021)	Prospective cohort	Healthcare personnel, N = 41 n = 23 (BNT162b2) n = 18 (ChAdOx1)	CoronaVac	ChAdOx1 (not specified), BNT162b2 (not specified)	Post-boost (ChAdOx1 vs. BNT162b2); pre- vs. post-boost	Not specified	All participants had at least 1 symptom after booster (most common: pain at injection site). No significant difference between post-ChAdOx1 boost and post-BNT16b2 boost		Very low	

Primary CoronaVac/ChAdOx1 booster										
Study author (country)	**Study design**	**Population**	**Primary series (interval)**	**Booster (interval from V2)**	**Comparator**	**Follow-up**	**Outcomes**		**Certainty of evidence**	**Comments**
Clinical efficacy/effectiveness										
None										
Immunogenicity										
							HUMORAL	***CELLULAR***		
Patamatamkul (Thailand) Preprint (September 2021)	Prospective cohort	Healthcare personnel, N = 41 n = 23 (BNT162b2) n = 18 (ChAdOx1)	CoronaVac	ChAdOx1 (not specified), BNT162b2 (not specified)	Post-boost (ChAdOx1 vs. BNT162b2); self	Pre-boost: 4 wks before ChAdOx1 booster; 12 weeks before BNT162b2 booster Post-boost: 3 wks after ChAdOx1 booster; 2 wks after BNT162b2 booster	anti-S RBD in U/mL (IQR) (pre-BNT16b2 boost vs. post-BNT162b2 boost): 37.46 (23.39, 51.60) vs. 22558 (15956, 25000), p < 0.001 anti-S RBD in U/mL (IQR) (pre-ChAdOx1 boost vs. post-ChAdOx1 boost): 106.8 (49.89, 151.7) vs. 5159 (3647.75, 9196.75), p < 0.001 anti-S RBD in U/mL (IQR) (post-BNT162b2 boost vs. post-ChAdOx1 boost): 22558 (15956, 25000) vs. 5159 (3647.75, 9196.75), p <0.001 sVNT ≥ 30% inhibition against Delta variant (IQR) (post-BNT162b2 boost vs. post-ChAdOx1 boost): 97.76% (97.5, 98.29) vs. 97.02% (93.8, 97.64), p < 0.001		Very low	
Singhatiraj (Thailand) Publication (September 2021)	Case report	52/M, healthcare professional	CoronaVac (~1 mo)	Intradermal ChAdOx1 (~1 mo)	Self	2 wks after booster	anti-spike IgG in AU/mL (pre-boost vs post-boost): 853.6 vs. 10465.20 Nab (pre-boost vs. post-boost): 66.7% vs. 99.6% PVNT against wild type, alpha, beta, delta in AU/mL : 1812.42, 882.99, 1025.42, 1347.13)	SARS-CoV-2-specific T cells detected	Very low	
Yorsaeng (Thailand) Preprint (September 2021)	Prospective cohort	HCWs N = 549 n (CoronaVac/CoronaVac) = 170 n (ChAdOx1/ChAdOx1) = 169 n (CoronaVac/CoronoVac + ChAdOx1 booster) = 210	CoronaVac/CoronaVac median 23 d)	ChAdOx1 (median 70 d)	CoronaVac/CoronaVac,	CoronaVac/CoronaVac: 21-49 d after V2 ChAdOx1/ChAdOx1: 21-35 d after V2 14-35 d after booster	Total Anti-RBD in U/mL (95% CI) (ChAdOx1 booster group vs. CoronaVac/CoronaVac vs. ChAdOx1/ChAdOx1): 7947 (7277, 8679) vs. 97.9 (82.6, 116.1) vs. 877.1 (763.5, 1008) anti-RBD IgG in BAU/mL (95% CI) (ChAdOx1 booster group vs. CoronaVac/CoronaVac vs. ChAdOx1/ChAdOx1): 1492 (1367, 1629) vs. 128 (113.7, 144.1) vs. 178 (155.5, 203.8) Anti-S1 IgA in OD/CO (IQR) (ChAdOx1 booster group vs. CoronaVac/CoronaVac vs. ChAdOx1/ChAdOx1): 5.25 (3.94, 9) vs. 0.88 (0.55, 1.79) vs. 1 (0.53, 1.73) NAb percent inhibition (IQR) (ChAdOx1 booster group vs. CoronaVac/CoronaVac vs. ChAdOx1/ChAdOx1): 99.49 (99.18, 99.62) vs. 76.52 (53.10, 87.97) vs. 51.56 (33.43, 72.98) NAb percent inhibition against wild type (IQR) (ChAdOx1 booster group vs. CoronaVac/CoronaVac vs. ChAdOx1/ChAdOx1): 97.75 (96.98, 97.83) vs. 66.60 (48.86, 79.41) vs. 88.86 (75.65, 96.35) NAb percent inhibition against alpha (IQR) (ChAdOx1 booster group vs. CoronaVac/CoronaVac vs. ChAdOx1/ChAdOx1): 97.24 (94.71, 97.65) vs. 42.11 (28.97, 58.31) vs. 75.94 (61.48, 88.36)		Very low	
Safety										
Patamatamkul (Thailand) Preprint (September 2021)	Prospective cohort	Healthcare personnel, N = 41 n = 23 (BNT162b2) n = 18 (ChAdOx1)	CoronaVac	ChAdOx1 (not specified), BNT162b2 (not specified)	Post-boost (ChAdOx1 vs. BNT162b2); pre- vs. post-boost	Not specified	All participants had at least 1 symptom after booster (most common: pain at injection site). No significant difference between post-ChAdOx1 boost and post-BNT16b2 boost		Very low	
Singhatiraj (Thailand) Publication (September	Case report	30/F, physician, with Graves' disease, on methimazole 2.5 mg/d	CoronaVac (< 1 mo)	ChAdOx1 (~ 3 mos)	Self	4 d after booster	With palpitations needing propranolol to control symptoms and weight loss. Increased methimazole to 5 mg/d with improvement of symptoms.		Very low	

Appendix 7. Characteristics and detailed outcomes of studies on homologous booster vaccination involving the immunocompromised

BNT162b2									
Study author (country) (Publication) (date)	**Study design (Risk of Bias)**	**Population**	**Primary series**	**Booster (timing of testing after V2)**	**Comparator**	**Follow-up**	**Outcomes**		**Comments**
Clinical efficacy/effectiveness									
Bensouna (France) Pre-proof (August 2021)	single cohort, self-controlled Very Serious (observational; uncontrolled confounders)	patients receiving maintenance hemodialysis or peritoneal dialysis n = 69 (38 + 31)	BNT162b2 2 doses 21 day interval	BNT162b2 (at least 3 weeks)	self, 2nd dose	post V2 : immediate post V3 : 30 d	hospitalizations after V3 6 patients - 3 bacterial peritonitis, 1 aseptic peritonitis, 1 pulmo embolism, 1 osteitis visit to the ER after V3 2 patients : 1 chest pain, 1 fatigue breakthrough after V3 : none, median ffup of 30 days		
Kamar (France) Correspondence (August 2021)	single cohort, self-controlled Very Serious (observational; uncontrolled confounders)	Solid organ transplant recipients under immunosuppresion given 3 doses of BNT162b2 n = 101 only 99 patients with titers before and after V3	BNT162b2 2 doses 21 day interval	BNT162b2 (61+1 days)	Self as control before first, second, and third dose	1 month	COVID-19 infection: none of those who received 3rd dose developed infection		
Chavarot (France) Full publication (August 2021)	single cohort, self-controlled Very Serious (observational; uncontrolled confounders)	Kidney transplant recipients, treated with belatacept, who received 3 doses of BNT162b2 n = 62 non-belacept treated : 35	BNT162b2 2 doses 28 day interval	BNT162b2 (median 69.5d (40-84))	self, 2nd dose non-belatacept-treated n = 35	Median 44 (40-49) for overall ffup	RT-PCR confirmed or IgG antibody-confirmed COVID-19 infection : 1 patient developed infection 6 days after 3rd dose		significant difference in timing of serology, interval of booster between responders and non-responders, interval between transplant and vaccination, belacept conversion
Immunogenicity									
							HUMORAL	***CELLULAR***	
Bensouna (France) Pre-proof (August 2021)	single cohort, self-controlled Very Serious (observational; uncontrolled confounders)	patients receiving maintenance hemodialysis or peritoneal dialysis n = 69 (38 + 31)	BNT162b2 2 doses 21 day interval	BNT162b2 (at least 3 weeks)		post V2 : immediate post V3 : 30 d	seropositivity V2 : 3 (96%) V3 : 2 (97%) ***Minimal rise*** anti-S IgG V2 : 284 (IQR : 83,1190) V3 : 7554 (IQR 2268 to 11736) *** 26.6 fold rise***		
Ducloux (France) Correspondence (September 2021)	single cohort, self-controlled Very Serious (observational; uncontrolled confounders)	Hemodialysis patients, COVID-19 naive, who received 2 doses of BNT162b2 N= 45	BNT162b2 2 doses 21 day interval	BNT162b2 (unspecified)	self, 2nd dose	1 month pV2 1 month pV3	No. of patients with antibody titer >50 arbitrary units pV2 : 89% pV3 : 93% ***<20% rise*** GMT 1 month after 3rd dose (AU/ml) pV2 : 672 (IQR 213-2528) pV3 : 6435 (IQR 2790 to 17014) * *9.76-fold rise* Median increase in Ab titers = 580%		
Del Bello (France) Correspondence (July 2021)	single cohort, self-controlled Very Serious (observational; uncontrolled confounders)	Solid organ transplant recipients given 3 doses of BNT162b2 N = 396	BNT162b2 2 doses 1 month interval	BNT162b2 (59 d, IQR 47-67)	self, 2nd dose	1 month	Prevalence of anti-SARS-CoV-2 antibodies pre V3 : 41.4% (95%CI, 36.5 to 46.3) post V3 : 67.9% (63.3 to 72.6) ***>20% rise***		not all patients were examined at the different follow up dates

Kamar (France) Correspondence (August 2021)	single cohort, self-controlled Very Serious (observational; uncontrolled confounders)	Solid organ transplant recipients under immunosuppresion given 3 doses of BNT162b2 n = 101 only 99 patients with titers before and after V3	BNT162b2 2 doses 21 day interval	BNT162b2 (61+1 days)	self, 2nd dose	1 month	Seroconversion : post V2 : 40/99 = 40% (95%CI 31 to 51) post V3 : 67/99 = 68% (95%CI 58 to 77) ***>20% rise*** Titers (among the seropositive before booster) : preV3 : 36+/- 12 post V3 : 2676+/-350 *** 74 fold rise***		
Masset (France) Pre-proof correspondence (August 2021)	single cohort, self-controlled Very Serious (observational; uncontrolled confounders)	Kidney and pancreas transplant recipients without previous COVID-19 infection, who received BNT162b2 n = 456 antispike titers above threshold = 227 below threshold - 229	BNT162b2 2 doses 21 day interval	BNT162b2 (mean = 50 days)	self, 2nd dose	1 month post V2 1 month post V3	Seropositivity post V2 : 49.7% post V3 : 69.2% ***20% rise***		Not all patients had serological assessments, different patients in the different assessment periods
Chavarot (France) Full publication (August 2021)	single cohort, self-controlled Very Serious (observational; uncontrolled confounders)	Kidney transplant recipients, treated with belatacept, who received 3 doses of BNT162b2 n = 62 non-belacept treated : 35	BNT162b2 2 doses 28 day interval	BNT162b2 (median 69.5d (40-84))	3rd dose BNT162b2, non-belatacept-treated n = 35	Median 28 days (28-33) for antibody testing Median 44 (40-49) for overall ffup	median anti-spike IgG 298 (209-409) AU/ml anti-S positivity : non-belacept treatted positive : 4 (6.4%) belacept treated positive : 13/35 (37.1%)		Significant difference in timing of serology, interval of booster between responders and non-responders, interval between transplant and vaccination, belacept conversion
Peled (Israel) Pubilcation (August 2021)	single cohort, self-controlled Very Serious (observational; uncontrolled confounders)	Adult heart transplant patients. None were treated for rejection or with T-cell depleting agents or specific B cell depletion agents during the 9 months prior to vaccination N = 96	BNT162b2 (not specified)	BNT162b2 (168 d)	Self	2-3 wks after booster	NAb (pre- vs. post-boost): 3.05 vs. 27.25 ***>9-fold increase*** IgG anti-RBD (pre vs. post-boost): 0.49 vs. 1.58 ***>3-fold increase***	T-cell response: induced T-cell immunity in 80% of patients	
Safety									
Bensouna (France) Pre-proof (August 2021)	single cohort, self-controlled Very Serious (observational; uncontrolled confounders)	patients receiving maintenance hemodialysis or peritoneal dialysis n = 69 (38 + 31)	BNT162b2 2 doses 21 day interval	BNT162b2 (at least 3 weeks)	self, 2nd dose	post V2 : immediate post V3 : 30 d	most frequent self-reported reaction was pain at injection site (27%) self reported global tolerance of the 3rd vs the 2nd dose : similar ~78%		
Del Bello (France) Correspondence (July 2021)	single cohort, self-controlled Very Serious (observational; uncontrolled confounders)	Solid organ transplant recipients given 3 doses of BNT162b2 N = 396	BNT162b2 2 doses 1 month interval	BNT162b2 (59 d, IQR 47-67)	Self as control before first, second, and third dose	1 month	no serious adverse event or acute rejection episode after the 3rd dose		Not all patients were examined at the different follow up dates
Kamar (France) Correspondence (August 2021)	single cohort, self-controlled Very Serious (observational; uncontrolled confounders)	Solid organ transplant recipients under immunosuppresion given 3 doses of BNT162b2 n = 101 only 99 patients with titers before and after V3	BNT162b2 2 doses 21 day interval	BNT162b2 (61+1 days)	Self as control before first, second, and third dose	1 month	serious adverse events : none reported after 3rd dose, no acute rejection 10 patients presented with fatigue and myalgia 5 patients with transient fever		

Chavarot (France) Full publication (August 2021)	single cohort, self-controlled Very Serious (observational; uncontrolled confounders)	Kidney transplant recipients, treated with belatacept, who received 3 doses of BNT162b2 n = 62 non-belacept treated : 35	BNT162b2 2 doses 28 day interval	BNT162b2 (median 69.5d (40-84))	3rd dose BNT162b2, non-belatacept-treated n = 35	Median 28 days (28-33) for antibody testing Median 44 (40-49) for overall ffup	no patient presented severe systemic events	Significant difference in timing of serology, interval of booster between responders and non-responders, interval between transplant and vaccination, belacept conversion
David (Israel) Publication (September 2021)	Retrospective cohort Nationwide survey Very Serious (observational; uncontrolled confounders)	Citizens of Israel, immunocompromised and ≥ 60 y.o. N = 17,820	BNT162b2 (not specified)	BNT162b2 (5 months)	self, at 2nd dose	7 d after booster	Most frequent systemic side effects in the immunocompromised: fatigue, myalgia, fever Similar and local systemic reactions compared to second dose	July 20, 2021 - August 10, 2021

mRNA-1273								
Study author (country) Publication status (date)	**Study design Risk of Bias**	**Population**	**Primary series**	**Booster (timing of testing after V2)**	**Comparator**	**Follow-up**	**Outcomes**	**Comments**
Clinical efficacy/effectiveness								
None								
Immunogenicity								
							HUMORAL	***CELLULAR***
Benotmane (France) Correspondence (July 2021)	Retrospective cohort Nationwide survey Very Serious (observational; uncontrolled confounders)	Kidney transplant recipients who did not respond to 2 doses of mRNA-1273 and received a third dose of mRNA-1273, no history of COVID-19 infection and SARS-CoV-2 anti-spike IgG < 50 AU/mL n=159	mRNA-1273 2 doses ? day interval	mRNA-1273 (median 51 days, IQR 48-59)	self, 2nd dose	28 days (IQR 27-33)	Anti-RBD IgG titers, median titer : 586 AU/ml (IQR 197.2-1920.1) seropositivity rate post boost : 49% (from 0%) ***>20% rise***	
Hall (Canada) Correspondence (September 2021)	RCT Not serious all domains low risk	Transplant recipients who had received 2 doases of mRNA-1273 vaccine 1 month apart mRNA booster : 60 saline booster : safety : 59 (1 withdrawal) immuno : 57 (2 without bloodwork) excluded within 1 month of transplant; with febrile illness, confirmed COVID 19, active CMV infection, intravenous Ig in 4 weeks prior, on rituximab in last 6 months, had treatment for acute rejection in 30 days prior, allergy to mRNA-1273	mRNA-1273 2 doses 28 day interval	mRNA-1273 (2 months) vs saline (2 months)	saline 2 months after 2nd dose	2 months	Anti-RBD IgG level of at least 100U/ml at month 4 (2 months) mRNA : 55% saline : 18% **(RR =3.1, 1.7, 5.8)** Median percent virus neutralization post V3 : mRNA : 71% saline : 13% **(95% CI for between group difference 11 to 76)** Positivitiy for neutralizing antibody post V3 mRNA : 60% saline : 25% (RR 2.4, 1.5 to 4.0) ***all parameters with >20% rise***	SARS CoV2 specific Tcell mRNA : 432 saline : 67 *****6.4 fold rise***	Computer-generated schedule by someone outside the study allocation concealed, syringe prepared by person outside the study patient, study team, assessor blinded

Safety								
Hall (Canada) Correspondence (September 2021)	RCT Not serious all domains low risk	Transplant recipients who had received 2 doases of mRNA-1273 vaccine 1 month apart mRNA booster : 60 saline booster : safety : 59 (1 withdrawal) immuno : 57 (2 without bloodwork) excluded within 1 month of transplant; with febrile illness, confirmed COVID 19, active CMV infection, intravenous Ig in 4 weeks prior, on rituximab in last 6 months, had treatment for acute rejection in 30 days prior, allergy to mRNA-1273	mRNA-1273 2 doses 28 day interval	mRNA-1273 (2 months) vs saline (2 months)	saline 2 months after 2nd dose	2 months	slightly more common local and systemic events with booster than placebo mRNA vs saline pain : 76.7 vs 10.2 chills : 21.7 vs 10.2 fatigue : 43.3 vs 27.1 myalgia : 18.3 vs 8.5 headache : 18.3 vs 8.5 no grade 3 or 4 events no case of acute rejection	Computer-generated schedule by someone outside the study allocation concealed, syringe prepared by person outside the study patient, study team, assessor blinded

Appendix 8. Characteristics and detailed outcomes of studies on heterologous booster vaccination involving the immunocompromised

Primary BNT162b2/Ad26.COV2.S booster										
Study author (country) Publication (date)	**Study design (Risk of Bias**	**Population**	**Primary series (interval)**	**Booster (interval from V2)**	**Comparator**	**Follow-up**	**Outcomes**		**Certainty of evidence**	**Comments**
Clinical efficacy/effectiveness										
None										
Immunogenicity										
							HUMORAL	***CELLULAR***		
Lyski (US) Preprint (September 2021)	Case report	2 female CLL patients (60s and 80s y.o.) vaccinated with BNT162b2 who self-referred to outside pharmacies for additional Ad26.COV2.S. Subject 1: treatment-naïve Subject 2: previously on obinutuzumab, currently on ibrutinib	BNT162b2 (not specified)	Ad26.COV2.S (Subject 1: 104 d, Subject 2: 81 d)	Self	Subject 1: 30 d after booster Subject 2: 27 d after booster	Subject 1 anti-RBD (pre-boost vs. post-boost): undetectable vs. 625 RBD-specific MBC: undetectable vs. 3.6/10^6 Subject 2 anti-RBD (pre-boost vs. post-boost): undetectable vs. undetectable RBD-specific MBC: undetectable vs. undetectable	Subject 1 spike-specific CD4+ T cells/10^6: undetectable vs. 166 spike-specific CD8+ T cell/10^6: stable, did not boost Subject 2 : spike-specific CD4+ T cells/10^6: did not boost spike-specific CD8+ T cell/10^6: boosted*	Very low	*no value given
Werbel (US) Correspondence (June 2021)	Single cohort, self-controlled	Solid organ transplant recipients who had suboptimal response to standard vaccination and subsequently received third dose 25/30 on immunosuppression N = 30	BNT162b2 (57%) mRNA-1273 (43% standard dosing?	Mix of homologous and heterologous 3rd dose BNT162b2 (6 pxs) Ad26.COV.2 (15 pxs), mRNA-1273 (9pxs) (median 67 days (IQR 54 to 81d)	self, 2nd dose	Median 14 days	anti-spike IgG seropositivity/ conversion : low positive preV3 titers (6) : all had high titers post V3 negative preV3 titers (24) : 25%(6) with high positive titers, 8%(2) had low positive titers, 67% (16) remained negative BNT/JJ (n=7) : 4/7 seroconverted BNT/Mod (n=7) : 5/7 seroconverted Mod/JJ (n=8) : 1/8 seroconverted		Very low	
Greenberger (USA) Correspondence (Oct 2021)	Retrospective cohort	Patients with B cell malignancy N = 49 BNT162b2 + mRNA1273 + Ad26Cov2S +		mixed homo/het	self, pre boost		No change / seroconverted / enhanced response BNT/Mod : 2/ 5 / 0 BNT/JJ : 7/ 5 / 2 Mod/BNT : 1/ 1 / 3 Mod/JJ : 1/ 4 / 1 JJ/BNT: 0 / 1/ 0 JJ/Mod: 0 / 0 / 0			
Safety										
Werbel (US) Correspondence (June 2021)	Single cohort, self-controlled	Solid organ transplant recipients who had suboptimal response to standard vaccination and subsequently received third dose 25/30 on immunosuppression N = 30	BNT162b2 (57%) mRNA-1273 (43% standard dosing?	Mix of homologous and heterologous 3rd dose BNT162b2 (6 pxs) Ad26.COV.2 (15 pxs), mRNA-1273 (9pxs) (median 67 days (IQR 54 to 81d)	Self as control, 2 doses	Median 7 days for safety outcomes	**NO breakdown by vaccine-boost regimen local and systemic reactions, (N=23) 15 with mild to moderate local reaction most frequent systemic reaction - mild to moderate fatigue in 14 pxz 1 severe myalgia 1 severe headache 1 antibody-mediated rejection 7 days after V3		Low	

Primary BNT162b2/mRNA-1273 booster										
Study author (country)	**Study design**	**Population**	**Primary series (interval)**	**Booster (interval from V2)**	**Comparator**	**Follow-up**	**Outcomes**		**Certainty of evidence**	**Comments**
Clinical efficacy/effectiveness										
None										
Immunogenicity										
							HUMORAL	***CELLULAR***		
Greenberger (USA) Correspondence (Oct 2021)	Retrospective cohort	Patients with B cell malignancy N = 49 BNT162b2 + mRNA1273 + Ad26Cov2S +		mixed homo/het	self, pre boost		No change / seroconverted / enhanced response BNT/Mod : 2/ 5 / 0 BNT/JJ : 7/ 5 / 2 Mod/BNT : 1/ 1 / 3 Mod/JJ : 1/ 4 / 1 JJ/BNT: 0 / 1/ 0 JJ/Mod: 0 / 0 / 0			
Werbel (US) Correspondence (June 2021)	Single cohort, self controlled	Solid organ transplant recipients who had suboptimal response to standard vaccination and subsequently received third dose 25/30 on immunosuppression N = 30	BNT162b2 (57%) mRNA-1273 (43% standard dosing?	Mix of homologous and heterologous 3rd dose BNT162b2 (6 pxs) Ad26.COV.2 (15 pxs), mRNA-1273 (9pxs) (median 67 days (IQR 54 to 81d)	self, 2nd dose	Median 14 days	anti-spike IgG seropositivity/ conversion : low positive preV3 titers (6) : all had high titers post V3 negative preV3 titers (24) : 25%(6) with high positive titers, 8%(2) had low positive titers, 67% (16) remained negative BNT/JJ (n=7) : 4/7 seroconverted BNT/Mod (n=7) : 5/7 seroconverted Mod/JJ (n=8) : 1/8 seroconverted		Very low	
Safety										
Werbel (US) Correspondence (June 2021)	Single cohort, self controlled	Solid organ transplant recipients who had suboptimal response to standard vaccination and subsequently received third dose 25/30 on immunosuppression N = 30	BNT162b2 (57%) mRNA-1273 (43% standard dosing?	Mix of homologous and heterologous 3rd dose BNT162b2 (6 pxs) Ad26.COV.2 (15 pxs), mRNA-1273 (9pxs) (median 67 days (IQR 54 to 81d)	Self as control, 2 doses	Median 7 days for safety outcomes	local and systemic reactions, (N=23) 15 with mild to moderate local reaction most frequent systemic reaction - mild to moderate fatigue in 14 pxz 1 severe myalgia 1 severe headache 1 antibody-mediated rejection 7 days after V3		Low	

Primary mRNA-1273/Ad26.COV2.S booster										
Study author (country)	**Study design**	**Population**	**Primary series (interval)**	**Booster (interval from V2)**	**Comparator**	**Follow-up**	**Outcomes**		**Certainty of evidence**	**Comments**
Clinical efficacy/effectiveness										
None										
Immunogenicity										
							HUMORAL	***CELLULAR***		
Baker (US) Letter to the editor, accepted article (September 2021)	Case report	74/M with rheumatoid arthritis on hydroxychloroquine, etanercept, leflunodmide	mRNA-1273 (not specified)	Ad26.COV2.S (~4 mos)	Self	< 1 mo	anti-RBD (pre-boost vs. post-boost): 53.9 U/mL vs. 2455 U/mL anti-spike IgG (pre-boost vs. post-boost): negative vs. positive ACE2 blocking assay (pre-boost vs. post-boost): <10% vs. 90-100%		Very low	
Greenberger (USA) Correspondence (Oct 2021)	Retrospective cohort	Patients with B cell malignancy N = 49 BNT162b2 + mRNA1273 + Ad26Cov2S +		mixed homo/het	self, pre boost		No change / seroconverted / enhanced response BNT/Mod : 2/ 5 / 0 BNT/JJ : 7/ 5 / 2 Mod/BNT : 1/ 1 / 3 Mod/JJ : 1/ 4 / 1 JJ/BNT: 0 / 1/ 0 JJ/Mod: 0 / 0 / 0			
Werbel (US) Correspondence (June 2021)	Single cohort, self controlled	Solid organ transplant recipients who had suboptimal response to standard vaccination and subsequently received third dose 25/30 on immunosuppression N = 30	BNT162b2 (57%) mRNA-1273 (43% standard dosing?	Mix of homologous and heterologous 3rd dose BNT162b2 (6 pxs) Ad26.COV.2 (15 pxs), mRNA-1273 (9pxs) (median 67 days (IQR 54 to 81d)	self, 2nd dose	Median 14 days	anti-spike IgG seropositivity/ conversion : low positive preV3 titers (6) : all had high titers post V3 negative preV3 titers (24) : 25%(6) with high positive titers, 8%(2) had low positive titers, 67% (16) remained negative BNT/JJ (n=7) : 4/7 seroconverted BNT/Mod (n=7) : 5/7 seroconverted Mod/JJ (n=8) : 1/8 seroconverted		Very low	
Safety										
Werbel (US) Correspondence (June 2021)	Single cohort, self controlled	Solid organ transplant recipients who had suboptimal response to standard vaccination and subsequently received third dose 25/30 on immunosuppression N = 30	BNT162b2 (57%) mRNA-1273 (43% standard dosing?	Mix of homologous and heterologous 3rd dose BNT162b2 (6 pxs) Ad26.COV.2 (15 pxs), mRNA-1273 (9pxs) (median 67 days (IQR 54 to 81d)	Self as control, 2 doses	Median 7 days for safety outcomes	local and systemic reactions, (N=23) 15 with mild to moderate local reaction most frequent systemic reaction - mild to moderate fatigue in 14 pxz 1 severe myalgia 1 severe headache 1 antibody-mediated rejection 7 days after V3		Low	

Primary mRNA-1273/BNT162b2 booster										
Study author (country)	**Study design**	**Population**	**Primary series (interval)**	**Booster (interval from V2)**	**Comparator**	**Follow-up**	**Outcomes**		**Certainty of evidence**	**Comments**
Clinical efficacy/effectiveness										
None										
Immunogenicity										
							HUMORAL	***CELLULAR***		
Greenberger (USA) Correspondence (Oct 2021)	Retrospective cohort	Patients with B cell malignancy N = 49 BNT162b2 + mRNA1273 + Ad26Cov2S +		mixed homo/het	self, pre boost		No change / seroconverted / enhanced response BNT/Mod : 2/ 5 / 0 BNT/JJ : 7/ 5 / 2 Mod/BNT : 1/ 1 / 3 Mod/JJ : 1/ 4 / 1 JJ/BNT: 0 / 1/ 0 JJ/Mod: 0 / 0 / 0			
Safety										

Primary Ad26.COV2.S/BNT162b2 booster										
Study author (country)	**Study design**	**Population**	**Primary series (interval)**	**Booster (interval from V1)**	**Comparator**	**Follow-up**	**Outcomes**		**Certainty of evidence**	**Comments**
Clinical efficacy/effectiveness										
None										
Immunogenicity										
							HUMORAL	***CELLULAR***		
Greenberger (USA) Correspondence (Oct 2021)	Retrospective cohort	Patients with B cell malignancy N = 49 BNT162b2 + mRNA1273 + Ad26Cov2S +		mixed homo/het	self, pre boost		No change / seroconverted / enhanced response BNT/Mod : 2/ 5 / 0 BNT/JJ : 7/ 5 / 2 Mod/BNT : 1/ 1 / 3 Mod/JJ : 1/ 4 / 1 JJ/BNT: 0 / 1/ 0 JJ/Mod: 0 / 0 / 0			
None										
Safety										
None										

Primary mRNA-1273/vector vaccine booster										
Study author (country)	**Study design**	**Population**	**Primary series (interval)**	**Booster (interval from V2)**	**Comparator**	**Follow-up**	**Outcomes**		**Certainty of evidence**	**Comments**
Clinical efficacy/effectiveness										
Werbel (US) Correspondence (June 2021)	Single cohort, self-controlled	Solid organ transplant recipients who had suboptimal response to standard vaccination and subsequently received third dose 25/30 on immunosuppression N = 30	BNT162b2 (57%) mRNA-1273 (43% standard dosing?	Mix of homologous and heterologous 3rd dose BNT162b2 (6 pxs) Ad26.COV.2 (15 pxs), mRNA-1273 (9pxs) (median 67 days (IQR 54 to 81d)	Self, 2nd dose	Median 14 days	RT-PCR confirmed COVID-19 infection none developed infection		Very low	
Immunogenicity										
							HUMORAL	***CELLULAR***		
Bonelli (Austria) Preprint (September 2021)	RCT	patients under rituximab treatment who had been immunized with two doses of mRNA vaccine excluded those with detectable SARS-Cov antibodies vector vaccine : 30 , 3 withdrawals preTx mRNA vaccine : 30, 2 withdrawals	BNT162b2 or mRNA-1273	vector vaccine (ChAdOx1) (N=27) same mRNA vaccine N = 28)		4 weeks for safety : 7 days for reactogenicity 28 days for Aes	seroconversion vector : 22% mRNA : 32% (p.=0.6) anti-RBD median titer vector : 19.4 (IQR 8.2, 114.8) mRNA : 12.4 (IQR 3.8, 17.8)	T-cell response by ELISpot (done in 36 patients) vector : 75% to 100% mRNA : 63% to 81% Tcell response, median spot forming cells vector : 459, IQR (133, 722) mRNA : 305 IQR (171, 416)	Moderate	no method of randomization or concealment "blinded" but no details complete ffup / no missing data, withdrawals
Safety										
Werbel (US) Correspondence (June 2021)	Single cohort, self-controlled	Solid organ transplant recipients who had suboptimal response to standard vaccination and subsequently received third dose 25/30 on immunosuppression N = 30	BNT162b2 (57%) mRNA-1273 (43% standard dosing?	Mix of homologous and heterologous 3rd dose BNT162b2 (6 pxs) Ad26.COV.2 (15 pxs), mRNA-1273 (9pxs) (median 67 days (IQR 54 to 81d)	Self as control, 2 doses	Median 7 days for safety outcomes	local and systemic reactions, (N=23) 15 with mild to moderate local reaction most frequent systemic reaction - mild to moderate fatigue in 14 pxz 1 severe myalgia 1 severe headache 1 antibody-mediated rejection 7 days after V3		Low	
Bonelli (Austria) Preprint (September 2021)	RCT	patients under rituximab treatment who had been immunized with two doses of mRNA vaccine excluded those with detectable SARS-Cov antibodies vector vaccine : 30 , 3 withdrawals preTx mRNA vaccine : 30, 2 withdrawals	BNT162b2 or mRNA-1273	vector vaccine (ChAdOx1) (N=27) or same mRNA vaccine (n=28)		4 weeks for safety : 7 days for reactogenicity 28 days for Aes	most side effects were similar between vector and mRNA booster numerically higher AEs arthralgia : 48% vector, 29% mRNA Myalgia : 56% vector, 32% mRNA fatigue : 78%vector vs 46% mRNA local pain : 30% vector vs 57% mRNA no thrombocytopenia, no anti PF4 no analphylactoid, no neuro complications		Moderate	no method of randomization or concealment "blinded" but no details complete ffup / no missing data, withdrawals preTx for both groups

Primary mRNA/another mRNA booster										
Study author (country)	**Study design**	**Population**	**Primary series (interval)**	**Booster (interval from V2)**	**Comparator**	**Follow-up**	**Outcomes**		**Certainty of evidence**	**Comments**
Clinical efficacy/effectiveness										
Immunogenicity										
Caillard (France) Preprint (September 2021)	Single cohort, self-controlled	Kidney transplant recipients with anti-spike IgG titer below 143 BAU/mL who already received booster mRNA-based vaccines, N = 92 n (fourth dose BNT162b2) = 34 n (fourth dose mRNA-1273) = 58	mRNA-1273 or BNT 162b2	Not specified	Self	median 29 d	anti-spike IgG in BAU/mL (IQR) (pre-boost vs. post-boost): 16.6 (6.5, 70.1) vs. 146.2 (28.5, 243), p < 0.001 54.3% reaching threshold of 143 BAU/mL post-boost		Very low	
Safety										
Caillard (France) Preprint (September 2021)	Single cohort, self-controlled	Kidney transplant recipients with anti-spike IgG titer below 143 BAU/mL who already received booster mRNA-based vaccines, N = 92 n (fourth dose BNT162b2) = 34 n (fourth dose mRNA-1273) = 58	mRNA-1273 or BNT 162b2	Not specified	Self	Not specified	No safety concerns		Very low	

Appendix 9. List of ongoing trials registered at Clinicaltrials.gov on booster vaccination as of November 16, 2021

NCT Number	Title	Status	Interventions	Outcome Measures	Age	Phases	Study Type	Study Designs	Completion Date
NCT05081271	COVID-19 Booster Vaccination in Persons With Multiple Sclerosis	Not yet recruiting	Biological: Homologous booster|Biological: Heterologous booster	COVID-19 spike protein antibodies	18 Years and older åÊ (Adult, Older Adult)	Not Applicable	Interventional	Allocation: Randomized|Intervention Model: Parallel Assignment|Masking: Single (Outcomes Assessor)|Primary Purpose: Basic Science	22-Oct
NCT04568811	The Phase I Clinical Trial of Booster Vaccination of Adenovirus Type-5 Vectored COVID-19 Vaccine	Active, not recruiting	Biological: Adenovirus Type-5 Vectored COVID-19 Vaccine	Occurrence of adverse reactions within 14 days after booster vaccination|Occurrence of adverse events within 14 days after booster vaccination|Occurrence of adverse events within 28 days after booster vaccination|Occurrence of serious adverse events within 28	Child, Adult, Older Adult	Phase 1	Interventional	Allocation: N/A|Intervention Model: Single Group Assignment|Masking: None (Open Label)|Primary Purpose: Prevention	27-Sep-21
NCT04992182	Reactogenicity, Safety, and Immunogenicity of Covid-19 Vaccine Booster	Active, not recruiting	Biological: Placebo|Biological: Inactivated vaccine booster|Biological: mRNA vaccine booster|Drug: Viral vector vaccine booster	Early humoral response|Immunogenicity|Reactogenicity|Safety of booster dose	18 Years and older åÊ (Adult, Older Adult)	Phase 2	Interventional	Allocation: Randomized|Intervention Model: Parallel Assignment|Masking: Double (Participant, Investigator)|Primary Purpose: Treatment	30-Jun-22

NCT05077176	Phase 3 Booster Vaccination Against SARS-CoV-2	Recruiting	Biological: CoronaVac|Biological: Turkovac	Protection rates of Turkovac and CoronaVac vaccines against symptomatic COVID-19|Incidence of Adverse Events (AE) and Serious Adverse Events (SAE)|To Evaluate the Immunogenicity|To determine the seropositivity rate of SARS-CoV2 specific binding	18 Years to 59 Years åÊ (Adult)	Phase 3	Interventional	Allocation: Non-Randomized|Intervention Model: Parallel Assignment|Masking: None (Open Label)|Primary Purpose: Prevention	05-Oct-22
NCT05096832	Recombinant SARS-CoV-2 Fusion Protein Vaccine (V-01) Booster Study	Not yet recruiting	Biological: Recombinant SARS-CoV-2 Fusion Protein Vaccine (V-01)|Biological: Blank Preparation of Recombinant SARS-CoV-2 Fusion Protein Vaccine (V-01)	the relative efficacy of recombinant SARS-CoV-2 fusion protein vaccine (V-01) as a booster to prevent symptomatic and RT-PCR positive COVID-19 (mild or above severity)|The incidence of adverse events (AEs)|The relative vaccine efficacy of V-01 as a booster to	18 Years and older åÊ (Adult, Older Adult)	Phase 3	Interventional	Allocation: Randomized|Intervention Model: Parallel Assignment|Masking: Quadruple (Participant, Care Provider, Investigator, Outcomes Assessor)|Primary Purpose: Prevention	14-Mar-23

NCT04762680	Study of Recombinant Protein Vaccines With Adjuvant as a Primary Series and as a Booster Dose Against COVID-19 in Adults 18 Years of Age and Older	Recruiting	Biological: SARS-CoV-2 recombinant protein vaccine Phase 2 Formulation 1|Biological: SARS-CoV-2 recombinant protein vaccine Phase 2 Formulation 2|Biological: SARS-CoV-2 recombinant protein vaccine Phase 2 Formulation 3|Biological: SARS-CoV-2 adjuvanted recombinant protein	Presence of immediate adverse events|Presence of solicited injection site or systemic reactions|Presence of unsolicited adverse events|Presence of serious adverse events|Presence of adverse events of special interest|Presence of medically-attended	18 Years and older åÊ (Adult, Older Adult)	Phase 2|Phase 3	Interventional	Allocation: Randomized|Intervention Model: Parallel Assignment|Masking: Quadruple (Participant, Care Provider, Investigator, Outcomes Assessor)|Primary Purpose: Prevention	11-Jan-23
NCT05057169	Randomized Trial of COVID-19 Booster Vaccinations (Cobovax Study)	Not yet recruiting	Biological: BNT162b2|Biological: CoronaVac	Geometric mean titer (GMT) of SARS-CoV-2 serum neutralizing antibodies|Geometric mean fold rise of SARS-CoV-2 serum neutralizing antibodies|T-cell responses to vaccination|Reactogenicity|Hospitalizations from any cause	18 Years and older åÊ (Adult, Older Adult)	Phase 4	Interventional	Allocation: Randomized|Intervention Model: Parallel Assignment|Masking: Triple (Participant, Investigator, Outcomes Assessor)|Primary Purpose: Prevention	31-Mar-24

NCT05104437	Evaluation of Immunogenicity, Safety and Antibody Persistence of COVID-19 Booster Vaccine (Produced in Wuhan) in Patients With Hypertension and/or Diabetes	Not yet recruiting	Biological: Covid-19 vaccine (0-1-4 schedule)|Biological: Covid-19 vaccine (0-1-6 schedule)	Seroconversion rate|Neutralizing antibody level|Adverse events following vaccination	60 Years and older âÊ (Adult, Older Adult)	Phase 4	Interventional	Allocation: Non-Randomized|Intervention Model: Parallel Assignment|Masking: Single (Outcomes Assessor)|Primary Purpose: Prevention	22-Dec
NCT05104333	Evaluation of Immunogenicity, Safety and Antibody Persistence of COVID-19 Booster Vaccine (Produced in Beijing) in Patients With Hypertension and/or Diabetes	Not yet recruiting	Biological: Covid-19 vaccine (0-1-4 schedule)|Biological: Covid-19 vaccine (0-1-6 schedule)	Seroconversion rate|Neutralizing antibody level|Adverse events following vaccination	60 Years and older âÊ (Adult, Older Adult)	Phase 4	Interventional	Allocation: Non-Randomized|Intervention Model: Parallel Assignment|Masking: Single (Outcomes Assessor)|Primary Purpose: Prevention	22-Dec
NCT05050474	Booster Immunization Study of Recombinant SARS-CoV-2 Fusion Protein Vaccine (V-01)	Active, not recruiting	Biological: Recombinant SARS-CoV-2 Fusion Protein Vaccine	Immunogenicity Endpoints|Safety Endpoints	18 Years and older âÊ (Adult, Older Adult)	Phase 1	Interventional	Allocation: N/A|Intervention Model: Single Group Assignment|Masking: None (Open Label)|Primary Purpose: Prevention	03-Feb-22
NCT05104359	COVID-19 Quantitative Antibody Titers & Booster Vaccinations	Active, not recruiting	Other: Observational	Vaccine Response	18 Years and older âÊ (Adult, Older Adult)		Observational	Observational Model: Cohort|Time Perspective: Retrospective	15-Nov-21

NCT04979949	Booster Vaccination Against SARS-CoV-2	Recruiting	Biological: CoronaVac|Biological: Turkovac	Incidence of adverse reactions|Incidence of Serious Adverse Events (SAE)|Neutralizing antibody and anti-spike protein immunoglobulin G	18 Years to 60 Years åÊ (Adult)	Phase 2	Interventional	Allocation: Randomized|Intervention Model: Parallel Assignment|Masking: Triple (Participant, Care Provider, Investigator)|Primary Purpose: Prevention	12-Jul-22
NCT05079217	Safety and Immunogenicity Study of Booster Vaccination With Medium-dosage or High-dosage SARS-CoV-2 Inactivated Vaccine for Prevention of COVID-19	Not yet recruiting	Biological: High-dosage SARS-CoV-2 vaccine|Biological: Medium-dosage SARS-CoV-2 vaccine	Immunogenicity index-GMT of neutralizing antibodies•_öCZ02 strain•_ä|Immunogenicity index-seropositive rate of neutralizing antibodies•_öCZ02 strain•_ä|Immunogenicity index-seroconversion rate of neutralizing antibodies•_öCZ02 strain•_ä|Immunogenicity index-GMI of	18 Years and older åÊ (Adult, Older Adult)	Phase 4	Interventional	Allocation: Randomized|Intervention Model: Parallel Assignment|Masking: Double (Participant, Investigator)|Primary Purpose: Prevention	01-Jun-22

NCT05022329	COVID-19 Vaccine Boosters in Patients With CKD	Recruiting	Biological: Pfizer-BioNTech COVID-19 Vaccine|Biological: MODERNA SARS-CoV-2 Vaccine	Serum Level of Anti-RBD (Anti Receptor Binding Domain)|Serum Level of SARS-CoV-2 Antibodies (Spike, RBD-Receptor Binding Domain, NP-nucleocapsid protein)|Proportion of B and T-cell lymphocyte subsets in peripheral blood mononuclear cells (PBMC) in a	18 Years and older åÊ (Adult, Older Adult)	Phase 2|Phase 3	Interventional	Allocation: Randomized|Intervention Model: Parallel Assignment|Masking: Triple (Participant, Care Provider, Investigator)|Primary Purpose: Prevention	30-Sep-23	
NCT05109559	Ad26.COV2.S as a Heterologous Booster in Adults After Single- or Two-Dose of Inactivated COVID-19 Vaccine	Not yet recruiting	Biological: Full dose of Ad26.COV2.|Biological: Half dose of Ad26.COV2.	Frequency of solicited reportable local adverse event after vaccination|Frequency of solicited reportable systemic adverse event after vaccination|Frequency of all unsolicited AEs|GMT Anti-S IgG at baseline|GMT Anti-S IgG at 7 days after vaccination in subset subjects|G	18 Years and older åÊ (Adult, Older Adult)	Phase 1|Phase 2	Interventional	Allocation: Randomized|Intervention Model: Parallel Assignment|Masking: Triple (Care Provider, Investigator, Outcomes Assessor)|Primary Purpose: Prevention	23-May	

NCT04952727	Study on Sequential Immunization of Inactivated COVID-19 Vaccine and Recombinant COVID-19 Vaccine (Ad5 Vector) in Elderly Adults	Recruiting	Biological: Recombinant SARS-CoV-2 Ad5 vectored vaccine|Biological: Inactive SARS-CoV-2 vaccine (Vero cell)	Incidence of adverse reactions within 28 days after the booster dose.|GMT of neutralizing antibodies against live SARS-CoV-2 virus on day 14 after the booster dose.|Incidence of solicited AE within 14 days after the booster dose|Incidence of unsolicited AE within 28 days after	60 Years and older âÊ (Adult, Older Adult)	Phase 4	Interventional	Allocation: Randomized|Intervention Model: Parallel Assignment|Masking: Triple (Participant, Investigator, Outcomes Assessor)|Primary Purpose: Prevention	26-May-22
NCT05095298	Reactogenicity and Immunogenicity of Third Dose Vaccine Booster Following Two Doses of Inactivated Vaccines	Recruiting	Drug: Vaccine, COVID19	Immunogenicity of Third Dose Vaccine Booster Following Two Doses of Inactivated Vaccines|Reactogenicity of Third Dose Vaccine Booster Following Two Doses of Inactivated Vaccines|The seropositive rate of neutralizing antibodies|GMT of	18 Years and older âÊ (Adult, Older Adult)	Phase 4	Interventional	Allocation: Randomized|Intervention Model: Parallel Assignment|Masking: None (Open Label)|Primary Purpose: Prevention	01-Aug-22

NCT04961229	Booster Dose of COVID-19 Vaccine for Kidney Transplant Recipients Without Adequate Humoral Response	Not yet recruiting	Biological: The Pfizer mRNA-based BNT162b2 vaccine	anti-spike protein titer above 50 AU/ml 2 weeks post vaccination|anti-spike protein titer above 50 AU/ml 3-, 6-, and 12-months post vaccination|Log transformed titer of anti-spike protein weeks and 3, 6, and 12 months post vaccination|Adverse events to booster dose using	18 Years and older åÊ (Adult, Older Adult)	Phase 4	Interventional	Allocation: Randomized|Intervention Model: Parallel Assignment|Masking: None (Open Label)|Primary Purpose: Prevention	22-Jul
NCT04892459	Study on Sequential Immunization of Inactivated SARS-CoV-2 Vaccine and Recombinant SARS-CoV-2 Vaccine (Ad5 Vector)	Active, not recruiting	Biological: Recombinant SARS-CoV-2 Ad5 vectored vaccine|Biological: Inactive SARS-CoV-2 vaccine (Vero cell)	Incidence of adverse reactions within 28 days after the booster dose.|GMT of neutralizing antibodies against live SARS-CoV-2 virus on day 14 after the booster dose.|Incidence of solicited AE within 14 days after the booster dose|Incidence of unsolicited AE within 28 days after	18 Years to 59 Years åÊ (Adult)	Phase 4	Interventional	Allocation: Randomized|Intervention Model: Parallel Assignment|Masking: Triple (Participant, Investigator, Outcomes Assessor)|Primary Purpose: Prevention	25-Dec-21

NCT05047640	COVID-19 3rd Dose Vaccine in Transplant Patients	Recruiting	Biological: BNT162b2 vaccine|Biological: JNJ-78436735 Vaccine	Anti-spike protein of SARS-CoV-2 virus IgG positive rate|Incidence of COVID-19 infection|Number of participants with COVID-19 symptom severity as measured by the WHO scale|Incidence of vaccine-related adverse events	18 Years and older âÊ (Adult, Older Adult)	Phase 3	Interventional	Allocation: Randomized|Intervention Model: Parallel Assignment|Masking: Single (Participant)|Primary Purpose: Prevention	30-Dec-21
NCT05043259	Heterologous Prime-boost Immunization With an Aerosolised Adenovirus Type-5 Vector-based COVID-19 Vaccine (Ad5-nCoV) After Priming With an Inactivated SARS-CoV-2 Vaccine	Recruiting	Biological: inactive SARS-CoV-2 vaccine (Vero cell)|Biological: Low dose aerosolized Ad5-nCoV|Biological: High dose aerosolized Ad5-nCoV	Incidence of adverse reactions within 14 days after the booster dose.|GMT of neutralizing antibodies against live SARS-CoV-2 virus on day 14 after the booster dose.|Incidence of adverse events within 0-28 days after the booster dose.|Incidence of serious adverse	18 Years and older âÊ (Adult, Older Adult)	Phase 1|Phase 2	Interventional	Allocation: Randomized|Intervention Model: Parallel Assignment|Masking: None (Open Label)|Primary Purpose: Prevention	01-May-22

NCT04955626	Study to Evaluate the Safety and Efficacy of a Booster Dose of BNT162b2 Against COVID-19 in Participants ‰ä´16 Years of Age.	Recruiting	Biological: BNT162b2|Other: Placebo	Confirmed COVID-19 incidence in participants without evidence of past SARS-CoV-2 infection|Confirmed COVID-19 incidence in participants with and without evidence of past SARS-CoV-2 infection|Percentage of participants reporting adverse events|Percentage of participants	16 Years and older åÊ (Child, Adult, Older Adult)	Phase 3	Interventional	Allocation: Randomized|Intervention Model: Parallel Assignment|Masking: Triple (Participant, Care Provider, Investigator)|Primary Purpose: Prevention	09-Aug-22
NCT05030974	RECOVAC Booster Vaccination Study	Not yet recruiting	Biological: mRNA-1273|Biological: Ad26.COV2.S vaccine	Positive SARS-CoV-2 seroresponse|SARS-CoV-2 antibody concentration|Virus-neutralizing capacity of SARS-CoV-2 antibodies|Mucosal SARS-CoV-2 antibodies|SARS-CoV-2 specific T cell response|Acute rejection|Solicited local and systemic adverse events|Serious adverse	18 Years and older åÊ (Adult, Older Adult)	Phase 4	Interventional	Allocation: Randomized|Intervention Model: Parallel Assignment|Masking: None (Open Label)|Primary Purpose: Prevention	23-Jan

NCT05028374	COVID-19 VAX Booster Dosing in Patients With Hematologic Malignancies	Recruiting	Drug: A single "booster" dose of the Moderna mRNA COVID-19 vaccine	Observed response rate of anti-SARS-CoV2 antibody seroconversion.|Observed AEs and SAEs|Observed rate of STRONG POSITIVE anti-SARS-CoV2 antibody response	18 Years and older åÊ (Adult, Older Adult)	Phase 2	Interventional	Allocation: N/A|Intervention Model: Single Group Assignment|Masking: None (Open Label)|Primary Purpose: Treatment	31-Jan-23
NCT05000216	COVID-19 Booster Vaccine in Autoimmune Disease Non-Responders	Recruiting	Biological: Moderna mRNA-1273|Biological: BNT162b2|Biological: Ad26.COV2.S|Drug: IS (MMF or MPA)|Drug: IS (MTX)|Biological: IS (B cell depletion therapy)	Proportion of participants who have a protective antibody response at Week 4|Percentage of Subset Participants Who Seroconverted|Fold increase in anti-COVID-19 antibody levels at Week 4, following participant receipt of a booster dose of COVID-19 vaccine|Cha	18 Years and older åÊ (Adult, Older Adult)	Phase 2	Interventional	Allocation: Randomized|Intervention Model: Parallel Assignment|Masking: None (Open Label)|Primary Purpose: Prevention	22-Dec

NCT04887948	Safety and Immunogenicity Study of 20vPnC When Coadministered With a Booster Dose of BNT162b2	Active, not recruiting	Biological: 20-valent pneumococcal conjugate vaccine (20vPnC)|Biological: BNT162b2|Other: Saline	Percentage of participants reporting prompted local reactions within 10 days after vaccination|Percentage of participants reporting prompted systemic events within 7 days after vaccination|Percentage of participants reporting Adverse Events (AEs)	65 Years and older âÊ (Older Adult)	Phase 3	Interventional	Allocation: Randomized|Intervention Model: Parallel Assignment|Masking: Triple (Participant, Investigator, Outcomes Assessor)|Primary Purpose: Prevention	29-Nov-21
NCT04833101	Study on Heterologous Prime-boost of Recombinant COVID-19 Vaccine (Ad5 Vector) and RBD-based Protein Subunit Vaccine	Active, not recruiting	Biological: recombinant Ad5 vectored COVID-19 vaccine|Biological: RBD-based protein subunit vaccine (ZF2001) against COVID-19|Biological: trivalent split influenza vaccine	Incidence of solicited adverse events within 7 days after vaccination.|GMT of neutralizing antibodies against live SARS-CoV-2 virus at Day 14 after the booster vaccination.|Incidence of adverse reactions within 28 days after vaccination.|Incidence of adverse events within 28	18 Years and older âÊ (Adult, Older Adult)	Phase 4	Interventional	Allocation: Randomized|Intervention Model: Parallel Assignment|Masking: Triple (Participant, Investigator, Outcomes Assessor)|Primary Purpose: Prevention	15-Dec-21

NCT04927065	A Study to Evaluate the Immunogenicity and Safety of mRNA-1273.211 Vaccine for COVID-19 Variants	Recruiting	Biological: mRNA-1273.211|Biological: mRNA-1273|Biological: mRNA-1273.617.2|Biological: mRNA-1273.213	Geometric Mean Titer (GMT) of Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2)-Specific Antibody|Seroresponse Rate of Vaccine Recipients|Number of Participants with Solicited Local and Systemic Reactogenicity Adverse Reactions (ARs)|Number of	18 Years and older åÊ (Adult, Older Adult)	Phase 2|Phase 3	Interventional	Allocation: Non-Randomized|Intervention Model: Sequential Assignment|Masking: None (Open Label)|Primary Purpose: Prevention	30-Nov-22
NCT05119738	Immune Response to Third Dose of SARS-CoV-2 Vaccine in a Cohort of Cancer Patients on Active Treatment	Recruiting	Biological: Three doses of BNT162b2 (observational)|Biological: Two doses of Coronavac and one dose BNT162b2 (observational)	Proportion of positive neutralizing antibodies 8 to 12 weeks after third dose BNT162b2 (booster vaccine).|Neutralizing geometric mean titers 8 to 12 weeks after third dose BNT162b2 (booster vaccine)	18 Years and older åÊ (Adult, Older Adult)		Observational	Observational Model: Cohort|Time Perspective: Prospective	01-Jan-22

NCT04927936	A Trial Among HealthCare Workers (HCW) Vaccinated With Janssen Vaccine: the SWITCH Trial	Recruiting	Biological: Vaccination once with Janssen vaccine (only priming)|Biological: Vaccination with Janssen vaccine followed with Janssen vaccine (homologous boosting).|Biological: Vaccination with Janssen vaccine followed with Moderna vaccine (heterologou	Determination of antibodies by a quantitative IgG assay (LIAISON SARS-CoV-2 TrimericS IgG essay) 28 days after booster	18 Years to 65 Years åÊ (Adult, Older Adult)	Not Applicable	Interventional	Allocation: Randomized|Intervention Model: Parallel Assignment|Masking: Single (Participant)|Primary Purpose: Prevention	22-Sep
NCT05087368	Immunogenicity and Safety of Heterologous and Homologous Boosting With ChAdOx1-S and CoronaVac or a Formulation of SCB-2019 (COVID-19)	Not yet recruiting	Biological: ChAdOx1-S COVID-19 Vaccine(Fiocruz/Oxford-AstraZeneca)|Biological: CoronaVac (Sinovac Biotech)|Biological: Adjuvanted Recombinant SARS-CoV-2 TrimericS-protein Subunit Vaccine (SCB-2019 - Clover)	Immunogenicity - Stage 1|Immunogenicity - Stage 2|Reactogenicity	18 Years and older åÊ (Adult, Older Adult)	Phase 2	Interventional	Allocation: Randomized|Intervention Model: Parallel Assignment|Masking: Quadruple (Participant, Care Provider, Investigator, Outcomes Assessor)|Primary Purpose: Prevention	01-Apr-22

NCT05080218	COVID-19 VaccinE Response in Rheumatology Patients	Not yet recruiting	Drug: Upadacitinib |Drug: Abatacept|Drug: Secukinumab|Drug: Tofacitinib|Drug: TNF Inhibitor|Drug: Canakinumab Injection	Quantitative ratio post booster vs. pre-booster of IgG against SARS-CoV-2 using electrochemiluminescent (ECL) technology against the receptor binding domain (RBD) of spike protein, stratified by treatment arm|Number of patients with score change beyond the	18 Years to 85 Years åÊ (Adult, Older Adult)	Phase 4	Interventional	Allocation: Randomized|Intervention Model: Parallel Assignment|Masking: None (Open Label)|Primary Purpose: Prevention	22-Dec
NCT05054621	Immunogenicity of COVID-19 Vaccine on Heterologous Schedule	Recruiting	Biological: Heterologous prime-boost schedule with AZD1222 and MVC-COV1901|Biological: Homologous prime-boost schedule with two doses of AZD1222	Immunogenicity: Neutralizing antibody against SARS-CoV-2|Immunogenicity•__Anti-SARS-CoV-2 Spike antibody|Adverse events|Immunogenicity: Anti-SARS-CoV-2 Nucleocapsid antibody|Immunogenicity: T cell immunity	20 Years to 70 Years åÊ (Adult, Older Adult)	Phase 2	Interventional	Allocation: Randomized|Intervention Model: Parallel Assignment|Masking: Single (Participant)|Primary Purpose: Prevention	31-Aug-22

NCT05047770	A Study on the Immune Response and Safety of the Shingles Vaccine and the Influenza Vaccine When Either is Given to Healthy Adults at the Same Time or Following a COVID-19 Booster Vaccine	Recruiting	Biological: HZ/su|Combination Product: Flu D-QIV|Biological: mRNA-1273	Anti-glycoprotein E (gE) antibody concentrations expressed as Geometric Mean Concentrations (GMCs) in HZ/suSeq and HZ/suCoAd groups, and between-group ratios|Anti-S protein antibody concentrations expressed as GMCs in HZ/suSeq	18 Years and older åÊ (Adult, Older Adult)	Phase 3	Interventional	Allocation: Randomized|Intervention Model: Parallel Assignment|Masking: None (Open Label)|Primary Purpose: Prevention	21-Jul-22
NCT05057182	Third Dose of mRNA Vaccination to Boost COVID-19 Immunity	Recruiting	Biological: BNT162b2	Geometric Mean Titer of SARS-CoV-2 serum neutralizing antibodies|The geometric mean fold rise (GMFR) of SARS-CoV-2 serum neutralizing antibody titers from baseline to each post-vaccination timepoint measured.|Reactogenicity|Hospitalizations from any cause	30 Years and older åÊ (Adult, Older Adult)	Phase 4	Interventional	Allocation: N/A|Intervention Model: Single Group Assignment|Masking: None (Open Label)|Primary Purpose: Prevention	31-Dec-23

NCT04889209	Delayed Heterologous SARS-CoV-2 Vaccine Dosing (Boost) After Receipt of EUA Vaccines	Recruiting	Biological: Ad26.COV2.S|Biological: BNT162b2|Biological: mRNA-1273|Biological: mRNA-1273.211	Magnitude of SARS-CoV-2 specific antibody binding and neutralization titers|Occurrence of adverse events (AEs)|Occurrence of Adverse Events of Special Interest (AESIs).|Occurrence of New-Onset Chronic Medical Condition (NOCMCs).|Occurrence of Related	18 Years to 99 Years åÊ (Adult, Older Adult)	Phase 1|Phase 2	Interventional	Allocation: Non-Randomized|Intervention Model: Parallel Assignment|Masking: None (Open Label)|Primary Purpose: Prevention	01-Dec-22
NCT05033847	Clinical Trial on Sequential Immunization of Recombinant COVID-19 Vaccine (CHO Cells) and Inactivated COVID-19 Vaccine (Vero Cells) in Population Aged 18 Years and Above	Recruiting	Biological: Recombinant COVID-19 Vaccine (CHO cell)|Biological: COVID-19 vaccine (Vero cells)	The incidence and serverity of any adverse reactions|The incidence and serverity of solicited adverse events|The incidence and serverity of solicited adverse reactions|The incidence and severity of unsolicited adverse reactions|The incidence of SAE	18 Years and older åÊ (Adult, Older Adult)	Phase 3	Interventional	Allocation: Randomized|Intervention Model: Parallel Assignment|Masking: Double (Participant, Investigator)|Primary Purpose: Prevention	24-Jan

NCT05069129	Clinical Trial on Sequential Immunization of Recombinant COVID-19 Vaccine (CHO Cells,NVSI-06-08) and Inactivated COVID-19 Vaccine (Vero Cells) in Population Aged 18 Years and Above	Recruiting	Biological: Recombinant COVID-19 Vaccine (CHO cell•_ÎNVSI-06-08)|Biological: Inactivated COVID-19 vaccine (Vero cells)|Biological: 3 doses Recombinant COVID-19 Vaccine (CHO cell•_ÎNVSI-06-08)	The incidence and serverity of any adverse reactions|The incidence and serverity of solicited adverse events|The incidence and serverity of solicited adverse reactions|The incidence and severity of unsolicited adverse reactions|The incidence of SAE	18 Years and older åÊ (Adult, Older Adult)	Phase 1|Phase 2	Interventional	Allocation: Randomized|Intervention Model: Parallel Assignment|Masking: Double (Participant, Investigator)|Primary Purpose: Prevention	24-Feb
NCT04998240	Mix and Match Heterologous Prime-Boost Study Using Approved COVID-19 Vaccines in Mozambique	Not yet recruiting	Biological: BBIBP-CorV - Inactivated SARS-CoV-2 vaccine (Vero cell)|Biological: AZD1222 (replication-deficient Ad type 5 vector expressing full-length spike protein)	Geometric Mean Titers (GMTs) of anti-SARS-CoV-2 neutralizing antibodies|Incidence of SAEs and AESI observed at any time point during the entire study period|Incidence of solicited reactions within 7 days (local reactions) and 14 days (systemic reactions)|Incidence of	18 Years to 65 Years åÊ (Adult, Older Adult)	Phase 2	Interventional	Allocation: Randomized|Intervention Model: Parallel Assignment|Masking: Single (Outcomes Assessor)|Primary Purpose: Prevention	30-Oct-22

NCT04969276	Study of a Quadrivalent High-Dose Influenza Vaccine and a Moderna COVID-19 Vaccine Administered Either Concomitantly or Singly in Participants 65 Years of Age and Older Previously Vaccinated With a 2-dose Schedule of Moderna COVID-19 Vaccine	Recruiting	Biological: Quadrivalent Inactivated Influenza High Dose|Biological: COVID-19 mRNA Vaccine (nucleoside modified)	Number of participants with immediate adverse events (AEs)|Number of participants with solicited injection site reactions or systemic reactions|Number of participants with unsolicited AEs|Number of participants with serious adverse events	65 Years and older åÊ (Older Adult)	Phase 2	Interventional	Allocation: Randomized|Intervention Model: Parallel Assignment|Masking: None (Open Label)|Primary Purpose: Prevention	02-Feb-22
NCT04949490	A Trial Investigating the Safety and Effects of One or Two Additional Doses of Comirnaty or One Dose of BNT162b2s01 in BNT162-01 or BNT162-04 Trial Subjects	Recruiting	Biological: BNT162b2s01|Biological: BNT162b2	The proportion of participants in each treatment group with at least one serious adverse event (SAE) or the proportion of adverse events of special interest (AESIs)|The frequency of solicited local reactions (pain, tenderness, erythema/redness,	18 Years and older åÊ (Adult, Older Adult)	Phase 2	Interventional	Allocation: Randomized|Intervention Model: Sequential Assignment|Masking: None (Open Label)|Primary Purpose: Prevention	23-Jul

NCT05077254	COVID Protection After Transplant-Immunosuppression Reduction	Not yet recruiting	Biological: Pfizer-BioNTech COVID-19 Vaccine Booster|Biological: Moderna COVID-19 Vaccine Booster|Drug: SOC IS Regimen|Drug: SOC IS Reduction	Proportion of Participants Who Achieve an Antibody Response >50 U/mL|Frequency of Solicited Local Reactogenicity Adverse Events (AEs) to the mRNA-Based COVID-19 Vaccine|Frequency of Solicited Local Allergic Reaction Adverse Events (AEs)	18 Years and older åÊ (Adult, Older Adult)	Phase 2	Interventional	Allocation: Randomized|Intervention Model: Parallel Assignment|Masking: None (Open Label)|Primary Purpose: Treatment	23-Mar
NCT05016622	Booster Dose Trial	Recruiting	Biological: BNT162b2 vaccine	Rates of seroconversion for SARS-CoV-2 spike antibody	18 Years and older åÊ (Adult, Older Adult)	Phase 2	Interventional	Allocation: N/A|Intervention Model: Single Group Assignment|Masking: None (Open Label)|Primary Purpose: Prevention	24-Sep

Appendix C. Summary of Findings

	N	RoB	Indirectness	Inconsistency	Imprecision	Others	Effect	Certainty
GENERAL POPULATION								
BNT162b2 Homologous booster								
Prevention of COVID-19 infection	3 Obs	Serious (observational, short ffup)	Not serious	Not serious	Not serious	Not assessed	OR (protection) – 11.4 OR (test positive) = 79% reduction VE symptomatic COVID infection: 91%	Low
Prevention of severe infection / hospitalization / death	2 Obs	Serious (observational, short ffup)	Not serious	Not assessed	Not serious	Not serious	OR (protection) : 15.5 VE hospitalization: 93% VE severe disease: 92% VE COVID-related death: 81 % (59-97)	Low
Immunogenicity (Humoral)	2 Obs	Serious (observational, uncontrolled confounders)	Not serious	Not assessed	Not assessed	Not serious	Increased antibody titers Decreased viral load	Very Low
Immunogenicity (Cellular)	0	Not assessed	Not assessed	Not assessed	Not assessed	Not assessed	na	na
Reactogenicity	1 Obs	Serious (observational)	Not serious	Not assessed	Not assessed	Not serious	Similar reactogenicity as 2nd dose	Low
Adverse events	3 Obs	Serious (observational short ffup)	Not serious	Serious	Not assessed	Not serious	Similar adverse event rates as 2nd dose 1 report of higher ER visits and some forms of adverse events with the booster dose	Very low
Serious adverse events / Death	0	Not assessed	Not assessed	Not assessed	Not assessed	Not assessed	na	na
mRNA-1273 Homologous booster								
Prevention of COVID-19 infection	0	Not assessed	Not assessed	Not assessed	Not assessed	Not assessed	na	na
Prevention of severe infection / hospitalization / death	0	Not assessed	Not assessed	Not assessed	Not assessed	Not assessed	na	na
Immunogenicity	2 RCT	Not serious	Not serious	Not serious	Not serious	Not serious	Significant rise in titers compared to pre-boost/no boost; including titers against VOCs	Low
Immunogenicity (Cellular)	0	Not assessed	Not assessed	Not assessed	Not assessed	Not assessed	na	na
Reactogenicity	2 RCT 2 Obs	Serious (observational)	Not serious	Serious (conflicting results)	Not serious	Not serious	Less reactogenic than 1st dose // More ER visits with booster More reports of certain adverse events	Very Low
Adverse events	2 RCT 1 Obs	Serious (observational, short ffup)	Not serious	Not serious	Not serious	Not serious	Low event rates	Low
Serious adverse events / Death	2 RCT 1 Obs	Serious (observational, short ffup)	Not serious	Not serious	Not assessed	Not assessed	No events reported	Very Low
ChAdOx1 Homologous booster								
Prevention of COVID-19 infection	0	Not assessed	Not assessed	Not assessed	Not assessed	Not assessed	na	na
Prevention of severe infection / hospitalization / death	0	Not assessed	Not assessed	Not assessed	Not assessed	Not assessed	na	na

	N	RoB	Indirectness	Inconsistency	Imprecision	Others	Effect	Certainty
GENERAL POPULATION								
ChAdOx1 Homologous booster								
Immunogenicity	1 Obs	Serious (observational, uncontrolled confounders)	Not serious	Not assessed	Not assessed	Not serious	2-fold rise in titers post boost	Very Low
Immunogenicity (Cellular)	1 Obs	Serious (observational, uncontrolled confounders)	Not serious	Not assessed	Not serious	Not assessed	2-fold rise in counts post boost	Very Low
Reactogenicity	1 Obs	Serious (observational, uncontrolled confounders)	Not serious	Not assessed	Not serious	Not serious	Less reactogenic than 1st dose	Low
Adverse events	1 Obs	Serious (observational, short ffup)	Not serious	Not assessed	Not serious	Not serious	Low event rates	Low
Serious adverse events / Death	0	Not assessed	Not assessed	Not assessed	Not assessed	Not assessed	na	na
CoronaVac Homologous booster								
Prevention of COVID-19 infection	0	Not assessed	Not assessed	Not assessed	Not assessed	Not assessed	na	na
Prevention of severe infection / hospitalization / death	0	Not assessed	Not assessed	Not assessed	Not assessed	Not assessed	na	na
Immunogenicity (Humoral)	4 RCT 2 Obs	Serious (missing data)	Not serious	Not serious	Not serious	Not serious	Minimal to significant rise in titers post-boost (vs pre-boost) Lower titers compared to heterologous boosting	Low
Immunogenicity (Cellular)	0	Not assessed	Not assessed	Not assessed	Not assessed	Not assessed	na	na
Reactogenicity	4 RCT	Not serious	Not serious	Not serious	Not assessed	Not serious	Low rates, no difference with placebo	Moderate
Adverse events	4 RCT	Serious (Short ffup)	Not serious	Not serious	Not assessed	Not serious	Low rates, no difference with placebo	Moderate
Serious adverse events / Death	0	Not assessed	Not assessed	Not assessed	Not assessed	Not assessed	na	na
Ad26.CoV2.S Homologous booster								
Prevention of COVID-19 infection	0	Not assessed	Not assessed	Not assessed	Not assessed	Not assessed	na	na
Prevention of severe infection / hospitalization / death	0	Not assessed	Not assessed	Not assessed	Not assessed	Not assessed	na	na
Immunogenicity (Humoral)	1 Obs	serious (observational, uncontrolled confounders)	Not serious	Not assessed	Not serious	Not serious	4.7-fold rise in titers post-boost (vs. pre-boost)	Low
Immunogenicity (Cellular)	0	Not assessed	Not assessed	Not assessed	Not assessed	Not assessed	na	na

	N	RoB	Indirectness	Inconsistency	Imprecision	Others	Effect	Certainty
GENERAL POPULATION								
Ad26.CoV2.S Homologous booster								
Reactogenicity	1 Obs	Serious (observational, uncontrolled confounders)	Not serious	Not assessed	Not serious	Not serious	Similar reactogenicity rates with preboost	Low
Adverse events	1 Obs	Serious (observational, short ffup)	Not serious	Not assessed	Not serious	Not serious	Similar / Low adverse event rates	Low
Serious adverse events / Death	0	Not assessed	Not assessed	Not assessed	Not assessed	Not assessed	na	na
Inactivated virus vaccine homologous booster								
Prevention of COVID-19 infection	0	Not assessed	Not assessed	Not assessed	Not assessed	Not assessed	na	na
Prevention of severe infection / hospitalization / death	0	Not assessed	Not assessed	Not assessed	Not assessed	Not assessed	na	na
Immunogenicity (Humoral)	3 Obs	Serious (observational, uncontrolled confounders)	Not serious	Not serious	Not serious	Not serious	Increase seropositivity rates post boost (vs. pre-boost)	Low
Immunogenicity (Cellular)	1 Obs	Serious (observational, uncontrolled confounders)	Not serious	Not assessed	Not serious	Not serious	Increased levels post-boost (vs. pre-boost)	Low
Reactogenicity	0	Not assessed	Not assessed	Not assessed	Not assessed	Not assessed	na	na
Adverse events	0	Not assessed	Not assessed	Not assessed	Not assessed	Not assessed	na	na
Serious adverse events / Death	0	Not assessed	Not assessed	Not assessed	Not assessed	Not assessed	na	na
VO1 homologous booster								
Prevention of COVID-19 infection	0	Not assessed	Not assessed	Not assessed	Not assessed	Not assessed	na	na
Prevention of severe infection / hospitalization / death	0	Not assessed	Not assessed	Not assessed	Not assessed	Not assessed	na	na
Immunogenicity (Humoral)	1 Obs	serious (observational, uncontrolled confounders)	Not serious	Not assessed	Serious	Not assessed	Slightly higher RBD-binding antibodies post boost (vs. pre-boost)	Low
Immunogenicity (Cellular)	0	Not assessed	Not assessed	Not assessed	Not assessed	Not assessed	na	na
Reactogenicity	0	Not assessed	Not assessed	Not assessed	Not assessed	Not assessed	na	na
Adverse events	0	Not assessed	Not assessed	Not assessed	Not assessed	Not assessed	na	na
Serious adverse events / Death	0	Not assessed	Not assessed	Not assessed	Not assessed	Not assessed	na	na

	N	RoB	Indirectness	Inconsistency	Imprecision	Others	Effect	Certainty
GENERAL POPULATION								
BNT162b2/mRNA-1273 heterologous booster								
Prevention of COVID-19 infection	0	Not assessed	Not assessed	Not assessed	Not assessed	Not assessed	na	na
Prevention of severe infection / hospitalization / death	0	Not assessed	Not assessed	Not assessed	Not assessed	Not assessed	na	na
Immunogenicity (Humoral)	1 Obs	Serious (observational, non-controlled confounders)	Not serious	Not assessed	Not assessed	Not assessed	Significant rise in IgG and NAB titers post-boost (vs pre-boost, vs. homologous BNT162b2 and vs heterologous with Ad26.COV2.s	Low
Immunogenicity (Cellular)	0	Not assessed	Not assessed	Not assessed	Not assessed	Not assessed	na	na
Reactogenicity	1 Obs	Serious (no subgroup analysis)	Serious (no subgroup analysis)	Not assessed	Not assessed	Not assessed	Similar reactogenicity with other booster combinations	Very Low
Adverse events	1 Obs	Serious (missing data, short ffup)	Serious (no subgroup analysis)	Not assessed	Not assessed	Not assessed	43% with unsolicited AE	Very Low
Serious adverse events / Death	0	Not assessed	Not assessed	Not assessed	Not assessed	Not assessed	na	Na
BNT162b2/Ad26.COV2.S heterologous booster								
Prevention of COVID-19 infection	0	Not assessed	Not assessed	Not assessed	Not assessed	Not assessed	na	na
Prevention of severe infection / hospitalization / death	0	Not assessed	Not assessed	Not assessed	Not assessed	Not assessed	na	na
Immunogenicity (Humoral)	2 Obs	Serious (observational, non-controlled confounders)	Not serious	Not serious	Not assessed	Not assessed	Significant rise in IgG and NAB titers post-boost (vs pre-boost,) but lower titers vs. homologous BNT162b2 and vs heterologous with mRNA-1273	Low
Immunogenicity (Cellular)	0	Not assessed	Not assessed	Not assessed	Not assessed	Not assessed	na	na
Reactogenicity	1 Obs	Serious (no subgroup analysis)	Serious (no subgroup analysis)	Not assessed	Not assessed	Not assessed	Similar reactogenicity with other booster combinations	Very Low
Adverse events	1 Obs	Serious (missing data, short ffup)	Serious (no subgroup analysis)	Not assessed	Not assessed	Not assessed	One related adverse event of severe vomiting post booster reported	Very Low
Serious adverse events / Death	0	Not assessed	Not assessed	Not assessed	Not assessed	Not assessed	No events reported	Na
mRNA-1273/BNT162b2 heterologous booster								
Prevention of COVID-19 infection	0	Not assessed	Not assessed	Not assessed	Not assessed	Not assessed	na	na
Prevention of severe infection / hospitalization / death	0	Not assessed	Not assessed	Not assessed	Not assessed	Not assessed	Na	na

	N	RoB	Indirectness	Inconsistency	Imprecision	Others	Effect	Certainty
GENERAL POPULATION								
mRNA-1273/BNT162b2 heterologous booster								
Immunogenicity (Humoral)	1 Obs	Serious (observational, non-controlled confounders)	Not serious	Not serious	Not assessed	Not assessed	Significant rise in IgG and NAB titers post-boost (vs pre-boost, vs. homologous mRNA-1273 and vs heterologous with Ad26.COV2.S	Low
Immunogenicity (Cellular)	0	Not assessed	Not assessed	Not assessed	Not assessed	Not assessed	na	na
Reactogenicity	1 Obs	Serious (observational)	Not serious	Not assessed	Not assessed	Not assessed	Similar reactogenicity with other booster combinations	Low
Adverse events	1 Obs	Serious (observational short ffup)	Not serious	Not assessed	Not assessed	Not assessed	47% reported unsolicited AE	Low
Serious adverse events / Death	0	Not assessed	Not assessed	Not assessed	Not assessed	Not assessed	No events reported	na
mRNA-1273/Ad16.COV2.S heterologous booster								
Prevention of COVID-19 infection	0	Not assessed	Not assessed	Not assessed	Not assessed	Not assessed	na	na
Prevention of severe infection / hospitalization / death	0	Not assessed	Not assessed	Not assessed	Not assessed	Not assessed	na	na
Immunogenicity (Humoral)	1 Obs	Serious (observational, non-controlled confounders)	Not serious	Not serious	Not assessed	Not assessed	Significant rise in IgG and NAB titers post-boost (vs pre-boost) but lower titers vs. homologous mRNA-1273 and vs heterologous with BNT162b2	Low
Immunogenicity (Cellular)	0	Not assessed	Not assessed	Not assessed	Not assessed	Not assessed	na	na
Reactogenicity	1 Obs	Serious (observational)	Not serious	Not assessed	Not assessed	Not assessed	Similar reactogenicity with other booster combinations	Low
Adverse events	1 Obs	Serious (observational short ffup)	Not serious	Not assessed	Not assessed	Not assessed	34.7 % reported unsolicited AE	Low
Serious adverse events / Death	0	Not assessed	Not assessed	Not assessed	Not assessed	Not assessed	No events reported	na
ChAdOx1/BNT162b2 heterologous booster								
Prevention of COVID-19 infection	0	Not assessed	Not assessed	Not assessed	Not assessed	Not assessed	na	na
Prevention of severe infection / hospitalization / death	0	Not assessed	Not assessed	Not assessed	Not assessed	Not assessed	na	na
Immunogenicity (Humoral)	1 Obs	Serious (observational, non-controlled confounders)	Not serious	Not assessed	Not assessed	Not assessed	Higher anti-S RBD IgG post-boost (vs. pre-boost)	Low
Immunogenicity (Cellular)	0	Not assessed	Not assessed	Not assessed	Not assessed	Not assessed	na	na
Reactogenicity	0	Not assessed	Not assessed	Not assessed	Not assessed	Not assessed	na	na
Adverse events	0	Not assessed	Not assessed	Not assessed	Not assessed	Not assessed	na	na
Serious adverse events / Death	0	Not assessed	Not assessed	Not assessed	Not assessed	Not assessed	No events reported	na

	N	RoB	Indirectness	Inconsistency	Imprecision	Others	Effect	Certainty
GENERAL POPULATION								
Ad26.COV2.S/BNT162b2 heterologous booster								
Prevention of COVID-19 infection	0	Not assessed	Not assessed	Not assessed	Not assessed	Not assessed	na	na
Prevention of severe infection / hospitalization / death	0	Not assessed	Not assessed	Not assessed	Not assessed	Not assessed	na	na
Immunogenicity (Humoral)	1 RCT 3 Obs	Not serious	Not serious	Not serious	Not assessed	Not assessed	Higher antibody titers post-boost vs. pre-boost and vs homologous boost but lower titers vs heterologous boost with mRNA-1273	Low
Immunogenicity (Cellular)	1 RCT 1 Obs	Not serious	Not serious	Not serious	Not serious	Not assessed	Significant increase in T-cell response post boost	Low
Reactogenicity	2 Obs	Serious (observational)	Not serious	Not serious	Not serious	Not assessed	Similar reactogenicity rates compared to primary vaccination	Low
Adverse events	0	Not assessed	Not assessed	Not assessed	Not assessed	Not assessed	na	na
Serious adverse events / Death	0	Not assessed	Not assessed	Not assessed	Not assessed	Not assessed	na	na
Ad26.COV2.S/mRNA-1273 heterologous booster								
Prevention of COVID-19 infection	0	Not assessed	Not assessed	Not assessed	Not assessed	Not assessed	na	na
Prevention of severe infection / hospitalization / death	0	Not assessed	Not assessed	Not assessed	Not assessed	Not assessed	na	na
Immunogenicity (Humoral)	1 RCT 1 Obs	Not serious	Not serious	Not serious	Not assessed	Not assessed	Higher antibody titers post-boost vs. pre-boost vs homologous boost and vs heterologous boost with BNT162b2	Low
Immunogenicity (Cellular)	0	Not assessed	Not serious	Not assessed	Not assessed	Not assessed	na	na
Reactogenicity	1 Obs	Serious (observational)	Not serious	Not assessed	Not assessed	Not assessed	Similar reactogenicity rates compared to primary vaccination	Low
Adverse events	1 Obs	Serious (observational)	Not serious	Not assessed	Not assessed	Not assessed	39.6% unsolicited AE rate	Low
Serious adverse events / Death	0	Not assessed	Not assessed	Not assessed	Not assessed	Not assessed	na	Na
CoronaVac/BNT162b2 heterologous booster								
Prevention of COVID-19 infection	0	Not assessed	Not assessed	Not assessed	Not assessed	Not assessed	na	na
Prevention of severe infection / hospitalization / death	0	Not assessed	Not assessed	Not assessed	Not assessed	Not assessed	na	na
Immunogenicity (Humoral)	1 RCT 2 Obs	Not serious	Not serious	Not serious	Not assessed	Not assessed	Higher antibody titers post-boost vs. pre-boost vs homologous boost	Low
Immunogenicity (Cellular)	0	Not assessed	Not serious	Not assessed	Not assessed	Not assessed	na	na
Reactogenicity	1 RCT	Not serious	Not serious	Not assessed	Not assessed	Not assessed	Similar reactogenicity rates overall but higher injection site pain, fatigue and muscle pain with heterologous (vs homologous)	Moderate

	N	RoB	Indirectness	Inconsistency	Imprecision	Others	Effect	Certainty
GENERAL POPULATION								
CoronaVac/BNT162b2 heterologous booster								
Adverse events	1 RCT	Not serious	Not serious	Not assessed	Serious (low event count)	Not assessed	Low adverse event rates	Low
Serious adverse events / Death	0	Not assessed	Not assessed	Not assessed	Not assessed	Not assessed	na	na
CoronaVac/ChAdOx1 heterologous booster								
Prevention of COVID-19 infection	0	Not assessed	Not assessed	Not assessed	Not assessed	Not assessed	na	na
Prevention of severe infection / hospitalization / death	0	Not assessed	Not assessed	Not assessed	Not assessed	Not assessed	na	na
Immunogenicity (Humoral)	3 Obs	Serious (observational, non-controlled confounders)	Not serious	Not serious	Not assessed	Not assessed	Significant rise in antibody titers post boost vs. pre-boost, vs. homologous boost	Low
Immunogenicity (Cellular)	0	Not assessed	Not serious	Not assessed	Not assessed	Not assessed	na	na
Reactogenicity	2 Obs	Not serious	Not serious	Not assessed	Not assessed	Not assessed	Similar reactogenicity rates overall but higher injection site pain, fatigue and muscle pain with heterologous (vs homologous)	Moderate
Adverse events	2 Obs	Not serious	Not serious	Not assessed	Serious (low event count)	Not assessed	Low adverse event rates	Low
Serious adverse events / Death	0	Not assessed	Not assessed	Not assessed	Not assessed	Not assessed	na	Na
BBIBP-CorV/BNT162b2 heterologous booster								
Prevention of COVID-19 infection	1 Obs	Serious (observational)	Not assessed	Not assessed	Not assessed	Not assessed	4% breakthrough infections observed	Low
Prevention of severe infection / hospitalization / death	0	Not assessed	Not assessed	Not assessed	Not assessed	Not assessed	na	na
Immunogenicity (Humoral)	1 Obs	Serious (observational, non-controlled confounders)	Not serious	Not assessed	Not assessed	Not assessed	Higher titers post boost (ve pre-boost) but lower vs primary BNT162b2 vaccination on patients with prior COVID	Low
Immunogenicity (Cellular)	0	Not assessed	Not serious	Not assessed	Not assessed	Not assessed	na	na
Reactogenicity	1 Obs	Serious (observational, non-controlled confounders)	Not serious	Not assessed	Not assessed	Not assessed	60% injection site pain	Low

	N	RoB	Indirectness	Inconsistency	Imprecision	Others	Effect	Certainty
GENERAL POPULATION								
BBIBP-CorV/BNT162b2 heterologous booster								
Adverse events	1 Obs	Serious (observational, non-controlled confounders)	Not serious	Not assessed	Not assessed	Not assessed	62% AE rate, mostly local reactogenicity	Low
Serious adverse events / Death	0	Not assessed	Not assessed	Not assessed	Not assessed	Not assessed	No event reported	na
CoronaVac-Ad5 heterologous booster								
d	0	Not assessed	Not assessed	Not assessed	Not assessed	Not assessed	na	na
Prevention of severe infection / hospitalization / death	0	Not assessed	Not assessed	Not assessed	Not assessed	Not assessed	na	na
Immunogenicity	1 RCT	Not serious	Serious	Not assessed	Not assessed	Not assessed	60-fold rise in Nab titers post-boost, significantly higher titers compared to homologous booster	Moderate
Reactogenicity	1 RCT	Serious (missing data)	Not serious	Not assessed	Not assessed	Not assessed	More adverse reactions with Ad5-nCOV; no serious AEs reported	Moderate
Adverse events	1 RCT	Serious (missing data, short ffup)	Not serious	Not assessed	Not assessed	Not assessed	Similar rates	Moderate
Serious adverse events / Death	1 RCT	Serious (missing data, short ffup)	Not serious	Not assessed	Serious (no events)	Not assessed	No SAEs reported	Low

	N	RoB	Indirectness	Inconsistency	Imprecision	Others	Effect	Certainty
IMMUNOCOMPROMISED POPULATION								
BNT162b2 Homologous booster								
Prevention of COVID-19 infection	3 Obs	serious (observational, uncontrolled confounders)	Not serious	Not serious	Serious (low event rates, non-comparative)	Not serious	No breakthrough infections post boost in 2 studies 1 case in one study 6 days post boost	Very Low
Prevention of severe infection / hospitalization / death	0	Not assessed	Not assessed	Not assessed	Not assessed	Not assessed	na	na
Immunogenicity (Humoral)	7 Obs	serious (observational)	Not serious	Not serious	Serious	Not assessed	General increase in titers and seropositivity; one study reported low seroconversion post boost	Very low
Immunogenicity (Cellular)	0	Not assessed	Not assessed	Not assessed	Not assessed	Not assessed	na	na
Reactogenicity	5 Obs	serious (observational)	Not serious	Not serious	Not assessed	Not assessed	Similar reactogenicity rates pre and post boost	Low
Adverse events	5 Obs	serious (observational short ffup)	Not serious	Not serious	Not assessed	Not assessed	Similar AE rates	Low
Serious adverse events / Death	5 Obs	serious (observational short ffup)	Not serious	Not serious	Not assessed	Not assessed	No SAEs reported	Low

	N	RoB	Indirectness	Inconsistency	Imprecision	Others	Effect	Certainty
IMMUNOCOMPROMISED POPULATION								
mRNA-1273 Homologous booster								
Prevention of COVID-19 infection	0	Not assessed	Not assessed	Not assessed	Not assessed	Not assessed	na	na
Prevention of severe infection / hospitalization / death	0	Not assessed	Not assessed	Not assessed	Not assessed	Not assessed	na	na
Immunogenicity (Humoral)	1 RCT 1 Obs	Not serious	Serious	Not serious	Not assessed	Not assessed	Increased antibody and cellular titers post boost / vs no boost Increased seropositivity post boost	Moderate to Low
Immunogenicity (Cellular)	1 RCT	Not serious	Not serious	Not assessed	Not assessed	Not assessed	Increased T-cell titers post boost / vs no boost and vs placebo	Moderate
Reactogenicity	1 RCT	Not serious	Not serious	Not assessed	Not assessed	Not assessed	Slightly more common local and systemic reactions with booster than placebo, no severe reactions	Moderate
Adverse events	1 RCT	Serious (short ffup)	Not serious	Not assessed	Not assessed	Not assessed	Slightly more common local and systemic reactions with booster than placebo, no severe reactions	Moderate
BNT162b2 /Ad26.CoV2.S heterologous booster								
Prevention of COVID-19 infection	0	Not assessed	Not assessed	Not assessed	Not assessed	Not assessed	na	na
Prevention of severe infection / hospitalization / death	0	Not assessed	Not assessed	Not assessed	Not assessed	Not assessed	na	na
Immunogenicity (Humoral)	3 Obs	Serious (observational non-controlled confounders)	Not serious	Not serious	Not assessed	Not assessed	Inconsistent response to boosting	Low
Immunogenicity (Cellular)	0	Not assessed	Not assessed	Not assessed	Not assessed	Not assessed	na	na
Reactogenicity	1 obs	Serious (observational)	Serious (no subgroup analysis)	Not assessed	Not assessed	Not assessed	Acceptable reaction rates	Very Low
Adverse events	1 obs	Serious (observational)	Serious (no subgroup analysis)	Not assessed	Not assessed	Not assessed	Low adverse event rates	Very Low
Serious adverse events / Death	1 obs	Serious (observational)	Serious (no subgroup analysis)	Not assessed	Serious (no events)	Not assessed	No SAEs / deaths	Very Low
BNT162b2 /mRNA-1273 heterologous booster								
Prevention of COVID-19 infection	0	Not assessed	Not assessed	Not assessed	Not assessed	Not assessed	na	na
Prevention of severe infection / hospitalization / death	0	Not assessed	Not assessed	Not assessed	Not assessed	Not assessed	na	na

	N	RoB	Indirectness	Inconsistency	Imprecision	Others	Effect	Certainty
IMMUNOCOMPROMISED POPULATION								
mRNA-1273 Homologous booster								
Immunogenicity (Humoral)	2 Obs	Serious (observational)	Not serious	Not serious	Not assessed	Not assessed	Inconsistent response to boosting	Low
Immunogenicity (Cellular)	0	Not assessed	Not assessed	Not assessed	Not assessed	Not assessed	na	na
Reactogenicity	1 obs	Serious (observational)	Serious (no subgroup analysis)	Not assessed	Not assessed	Not assessed	Acceptable reaction rates	Very Low
Adverse events	1 obs	Serious (observational)	Serious (no subgroup analysis)	Not assessed	Not assessed	Not assessed	Low adverse event rates	Very Low
Serious adverse events / Death	1 obs	Serious (observational)	Serious (no subgroup analysis)	Not assessed	Serious (no events)	Not assessed	No SAEs / deaths	Very Low
mRNA-1273/Ad26.CoV2.S heterologous booster								
Prevention of COVID-19 infection	0	Not assessed	Not assessed	Not assessed	Not assessed	Not assessed	na	na
Prevention of severe infection / hospitalization / death	0	Not assessed	Not assessed	Not assessed	Not assessed	Not assessed	na	na
Immunogenicity (Humoral)	3 Obs	Serious (observational non-controlled confounders)	Not serious	Not serious	Not assessed	Not assessed	Inconsistent response to boosting	Low
Immunogenicity (Cellular)	0	Not assessed	Not assessed	Not assessed	Not assessed	Not assessed	na	na
Reactogenicity	1 obs	Serious (observational)	Serious (no subgroup analysis)	Not assessed	Not assessed	Not assessed	Acceptable reaction rates	Very Low
Adverse events	1 obs	Serious (observational)	Serious (no subgroup analysis)	Not assessed	Not assessed	Not assessed	Low adverse event rates	Very Low
Serious adverse events / Death	1 obs	Serious (observational)	Serious (no subgroup analysis)	Not assessed	Serious (no events)	Not assessed	No SAEs / deaths	Very Low
mRNA/ChAdOx1 Heterologous booster								
Prevention of COVID-19 infection	0	Not assessed	Not assessed	Not assessed	Not assessed	Not assessed	na	na
Prevention of severe infection / hospitalization / death	0	Not assessed	Not assessed	Not assessed	Not assessed	Not assessed	na	na
Immunogenicity (Humoral)	1 RCT	Not serious	Not serious	Not assessed	Not assessed	Not assessed	Lower seroconversion, higher antibody titers with heterologous	Moderate
Immunogenicity (Cellular)	1 RCT	Not serious	Not serious	Not assessed	Not assessed	Not assessed	Lower seroconversion, higher T cell response with heterologous	Moderate
Reactogenicity	1 RCT	Not serious	Not serious	Not assessed	Not assessed	Not assessed	Similar reactogenicity rates overall but with some events with higher rates with ChAdOx1 boost	Moderate

	N	RoB	Indirectness	Inconsistency	Imprecision	Others	Effect	Certainty
IMMUNOCOMPROMISED POPULATION								
mRNA/ChAdOx1 Heterologous booster								
Adverse events	1 RCT	Serious (short ffup)	Not serious	Not assessed	Not assessed	Not assessed	Similar adverse event rates	Moderate
Serious adverse events / Death	1 RCT	Serious (short ffup)	Not serious	Not assessed	Not assessed	Not assessed	No serious adverse events	Moderate

	N	RoB	Indirectness	Inconsistency	Imprecision	Others	Effect	Certainty
IMMUNOCOMPROMISED POPULATION								
mRNA vaccine/another mRNA vaccine heterologous booster								
Prevention of COVID-19 infection	0	Not assessed	Not assessed	Not assessed	Not assessed	Not assessed	na	na
Prevention of severe infection / hospitalization / death	0	Not assessed	Not assessed	Not assessed	Not assessed	Not assessed	na	na
Immunogenicity (Humoral)	1 Obs	Serious (observational)	Not serious	Not assessed	Not assessed	Not assessed	Higher IgG titers post boost	Low
Immunogenicity (Cellular)	0	Not assessed	Not assessed	Not assessed	Not assessed	Not assessed	na	na
Reactogenicity	0	Not assessed	Not assessed	Not assessed	Not assessed	Not assessed	na	na
Adverse events	0	Not assessed	Not assessed	Not assessed	Not assessed	Not assessed	na	na

Q8. Among adults, what is the clinical and immunologic efficacy and effectiveness and safety of heterologous COVID-19 vaccination compared to standard homologous COVID-19 vaccination in preventing COVID-19 infection?

As of 22 October 2021

RECOMMENDATIONS

We recommend the use of heterologous COVID-19 vaccination for those with serious adverse event to the first dose. *(Very low certainty of evidence; Strong recommendation)*

We suggest the use of heterologous COVID-19 vaccination in the event of the unavailability of the second dose in the recommended schedule. *(Very low certainty of evidence; Weak recommendation)*

Consensus Issues

The panel decided to give a strong recommendation, despite the very low certainty of evidence, on the use of heterologous vaccination among those with serious adverse event to the first dose. This is because of the need to provide the sufficient protection afforded by the second dose, especially for the vulnerable and at-risk populations. The importance of informed consent was emphasized by the panel, particularly on the benefits and harms of the administration of heterologous vaccination versus delayed administration of the second dose in the context of vaccine unavailability.

KEY FINDINGS

3 RCTs, 18 observational studies, and 1 case report investigated the use of heterologous vaccination using the following vaccines: BNT162b2, ChAdOx1, mRNA1273, CoronaVac, BBV152, Ad5-nCoV. No study was found using Gam-COVID-Vac, NVX-CoV2373, and BBIBP-CorV as a component of the vaccination regimen.

The overall certainty of evidence for efficacy/effectiveness is very low due to the study design (i.e. observational studies with a lack of control for confounding factors), the use of surrogate outcomes (immunogenicity), missing outcomes, and short follow up. The overall certainty of evidence for safety is low because of the study design (i.e. observational studies), unclear to lack of blinding, and the short follow-up.

Only one retrospective population-based cohort study with ChAdOx1/BNT162b2 or mRNA-1273 as the heterologous regimen showed clinical efficacy against SARS-CoV-2 infection, hospitalization, and death.

Current evidence shows that heterologous primary vaccination is immunogenic and results in acceptable adverse reaction rates. Different combinations and regimen perform differently.

INTRODUCTION

Vaccines are one of the key tools to curb the COVID-19 pandemic. However, with the suspension of the use of the ChAdOx1 (AstraZeneca) vaccine in some European countries due to reports of vaccine induced thrombotic thrombocytopenia (VITT) or thrombosis with thrombocytopenia syndrome (TTS), some have recommended to have an mRNA-based vaccine as a second dose.[1,2] Furthermore, with the decreased effectiveness of existing homologous combination vaccines against variants of concern, there is a need to determine if heterologous prime-boost regimens will induce comparable or more robust immune responses.[3-6] Vaccines also cost differently and determining a cost-effective and safe combination is important especially in resource-limited settings. Finally, with the inconsistent and erratic vaccine supplies, a heterologous vaccination may allow programmatic flexibility in the dosing regimen.

REVIEW METHODS

In this review, heterologous vaccine was operationally defined as a combination of different types of vaccines originally developed as part of a homologous multiple-dose or single-dose vaccine. The COVID-19 Living OVerview of the Evidence (L·OVE) platform, the COVID-NMA, and www.metaEvidence.org were searched for both randomized and non-randomized studies on adults investigating the efficacy, effectiveness, and safety of a heterologous combination of any COVID-19 vaccine last September 30, 2021. The weekly situational reports published by the World Health Organization (WHO) and relevant reports from major global regulatory agencies including the US Food and Drug Authority (US FDA), the US Center for Disease Control (CDC), the European Medicines Agency (EMA), the United Kingdom Medicines and Healthcare Products Regulatory Agency (UK-MHRA), the WHO, and the Philippine Food and Drug Association (PH FDA) including their reference lists were also reviewed for relevant studies. The search strategies are detailed in Appendix 2.

This review excluded multidose vaccination in which different types of vaccines were specifically developed to be part of the dosing regimen (e.g. Gam-COVID-Vac) and heterologous booster vaccination.

Randomized controlled trials (RCTs) were primarily sought for efficacy outcomes. Studies providing vaccine efficacy against COVID-19 infection of all severity, hospitalization, and deaths were preferred. In the absence of such, observational studies and studies providing immunogenicity results were also considered. Immunogenicity outcomes included geometric mean titers and seropositivity rates of neutralizing antibodies, anti-S, anti-RBD, and IFN-gamma. Geometric mean ratios and differences between seropositivity rates of homologous and heterologous vaccination were computed. The 28-day post-second dose results were used in the review when multiple timings of serologic assessment were done within a study. Both RCTs and observational studies were included for the safety outcomes, namely local and systemic adverse reactions, any adverse event, serious adverse events, and deaths after the second dose.

RESULTS

Characteristics of studies

As of September 17, 2021, a total of 21 studies composed of 3 RCTs and 18 observational studies were included in this review. Of these studies, 13 used ChAdOx1/BNT162b2, two used BNT162b2/ChAdOx1[7,8], two used ChAdOx1/mRNA1273[9,24], one used ChAdOx1/BBV152[10], one used mRNA-1273/BNT162b2[27], one used CoronaVac/ ChAdOx1[11], and one used CoronaVac/Ad5-nCoV.[12] Three studies used a ChAdOx1/BNT162b2 or mRNA-1273.[13-15] No study was found on the use of Gam-COVID-Vac, NVX-CoV2373, or BBIBP-CorV in the regimen.

Eight of the studies were on healthcare workers, two on immunocompromised populations, and the rest were on the general population. Three were RCTs, one of which compared heterologous ChAdOx1/BNT162b2 vaccination with a single dose ChAdOx1/observation[16], one was a four-arm trial comparing ChAdOx1/BNT162b2, BNT162b2/ChAdOx1, ChAdOx1/ChAdOx1, and BNT162b2/BNT162b2 regimens[7], and one compared CoronaVac/Ad5 with the homologous CoronaVac vaccination.[12] The rest were observational cohort studies. Only one study reported clinical effectiveness.[15] Nine studies provided information on the safety of heterologous vaccination. Majority reported on reactogenicity within the first seven days. Six studies reported heterologous vaccination against the variants of concern.

In general, heterologous vaccinations had longer dosing intervals (8 to 12 weeks), regardless of the regimen. On the other hand, most of the homologous vaccinations had dosing intervals of 21 to 28 days, except for the ChAdOx1/ChAdOx1 regimen which had dosing intervals ranging from 4 to 12 weeks across the studies.

The characteristics of included studies are detailed in Appendix 5.

Risk of bias assessment

Two of the three randomized controlled trials were assessed to have low risk of bias.[12,16] Although one of these was open label, the domains for blinding were assessed to be low risk given the objective outcomes.[16] The third RCT was assessed to have serious risk of bias due to missing data and non-blinding of clinical assessors.[7] All the observational studies were assessed to have serious risk of bias due to the non-randomized nature of the study design, with majority further downgraded to very serious risk due to non-blinding, missing outcomes, and lack of control for confounding factors, and short follow up. The detailed risk of bias assessment is presented in Appendix 4.

Clinical efficacy and effectiveness

ChAdOx1/BNT162b2 or mRNA-1273

One retrospective population-based cohort study from Denmark reported the vaccine effectiveness rate of the ChAdOx1/mRNA-based vaccination regimen against any COVID-19 infection at 66% (95% CI 59-72) within 13 days of the second dose and at 88% (95% CI 83-92) after 14 days of a ChAdOx1/mRNA-based vaccination regimen. Vaccine effectiveness against all-cause hospitalization was 43% (95% CI 36-49) within 13 days and 50% (95% CI 45-55) after 14 days. The adjusted VE against COVID-19-related hospitalization after 14 days of vaccination was at 93% (95% CI 80-98). No deaths were reported after vaccination.[15]

Immunogenicity
Across the studies, heterologous primary vaccination resulted in higher humoral and cellular immune response compared with homologous vaccination.

ChAdOx1/BNT162b2 or mRNA-1273
One prospective cohort looked at immunocompetent individuals receiving ChAdOx as a first dose followed by either BNT162b2 or mRNA-1273 as the second dose. The immunocompetent controls from this study were used in another matched cohort study of solid organ transplant recipients. Both studies mirrored the response of the ChaAdOx1/BNT162b2 regimen described above, with at least similar to higher immunogenicity seen in the heterologous vaccination compared to the homologous regimen.[13,14]

ChAdOx1/BNT162b2
One randomized placebo-controlled trial demonstrated significantly higher antibody titers as well as cellular responses 14 days after ChAdOx1/BNT162b2 vaccination.[16] Another RCT compared the outcomes after ChAdOx1/BNT162b2 vaccination with the homologous vaccinations of either vaccine and with the reverse sequence (BNT162b2/ChAdOx1). It showed no significant difference in the antibody seropositivity rates across the groups. However, significantly higher antibody titers (>2-fold rise or GMR > 2.0) after ChAdOx1/BNT162b2 than homologous ChAdOx1 vaccination or the BNT162b2/ChAdOx1 combination. Similar levels of antibody titers were seen with the homologous BNT162b2 vaccination.[7]

The above findings were also seen in the observational studies which had the same vaccination regimen in the patient cohorts investigated.[13,14,17-22] Differences in seropositivity rates across the vaccination regimen were not significant with differences of 10%.

ChAdOx1/mRNA 1273
One report from an ongoing clinical study assessed 51 healthcare workers who received mRNA-1273 9 to 12 weeks after a first dose of ChAdOx1, and compared their immunologic response to 37 healthcare workers who chose a homologous ChAdOx1 second dose. Those who received mRNA-1273 as a second dose showed a greater increase in neutralization titer at 7-10 days post boost, which was sustained at 30 days. Moreover, heterologous vaccination induced neutralizing antibodies against the Beta variant whereas homologous ChAdOx1 did not.[9]

Another study compared the post-boost anti-S and anti-RBD antibody titers among vaccinees who received either a heterologous ChAdOx1/mRNA-1273 or ChAdOx1/BNT162b2, or a homologous ChAdOx1 or BNT162b2 regimen. Heterologous vaccination was found to result in higher antibody titers.[17]

BNT162b2/ChAdOx1
In the randomized controlled study that used BNT162b2/ChAdOx1 in one of its arms, such combination demonstrated higher and equivalent seropositivity rates and geometric mean titers compared to homologous ChAdOx1 and homologous BNT162b2, respectively. However, in terms of T cell responses, results showed higher GMT's for the heterologous combinations, but with lower seropositivity for the

BNT162b2/ChAdOx1 combination, compared to both homologous combinations and the ChAdOx1/BNT162b2 combination.[7] The observational study which compared BNT162b2/ChAdOx1 to homologous vaccination of either component consistently showed the same results with higher immunologic responses with the heterologous vaccination.[17]

ChAdOx1/BBV152

One prospective study compared the heterologous ChAdOx1/BBV152 vaccination with homologous vaccination with either of the two components. It showed higher titers after heterologous vaccination than both homologous preparations. It also showed higher titers against variants of concern compared to either homologous vaccination.[10]

mRNA-1273/BNT162b2

One prospective study compared heterologous mRNA-1273/BNT162b2 vaccination with homologous vaccination with either of the two components. It showed no difference in the IgG levels among all groups.[23]

CoronaVac/ChAdOx1

One retrospective study used CoronaVac in combination with ChAdOx1. The ChAdOx1/CoronaVac regimen resulted in higher humoral titers compared to both homologous vaccinations. However, the CoronaVac/ChAdOx1 regimen showed equivalent anti-S IgG titers with the homologous ChAdOx1 regimen, but still with higher titers compared with the homologous CoronaVac vaccination.[11]

CoronaVac/Ad5-nCoV

One randomized controlled trial compared CoronaVac/Ad5 vaccination with homologous CoronaVac vaccination.[12] It showed higher humoral titers, and higher humoral and cellular seropositivity rates after heterologous vaccination. Adverse event rates, both local and systemic reactogenicity, was significantly higher after heterologous compared to homologous vaccination. No severe adverse events were recorded in both groups in this trial.

Effectiveness against Variants of Concern

Six observational studies reported on the immunogenicity responses to heterologous vaccination in relation to the variants of concern (Alpha, Beta and Delta). Five studies used ChAdOx1/BNT162b2 [9,21,22,24,25] and one used CoronaVac/ChAdOx1.[10] All studies consistently demonstrated significantly higher humoral titers and seropositivity rates after heterologous vaccinations compared to homologous vaccination. No study was identified on heterologous vaccination against the Gamma variant.

Safety

While generally well-tolerated with mostly mild to moderate adverse reactions, heterologous vaccination was consistently shown to have higher (but not statistically significant) local and systemic reactogenicity rates when compared with homologous vaccination, regardless of the combination.[9,10,13,16,19,22,26,27] The most commonly reported events with higher rates included pain at injection site, fever, headache, myalgia, and fatigue. Only two studies reported severe adverse reactions,

which included headache and myalgia. No long-term safety information is available at this time.

The summary of findings are in Appendix 3.

ONGOING STUDIES

Search of *clinicaltrials.gov* registry last October 2, 2021 yielded 19 trials on heterologous COVID-19 vaccination with the earliest trial completion on October 2021.

RECOMMENDATIONS FROM OTHER GROUPS

Table 1. Summary of Recommendations from Other Groups

Regulatory Agency	Recommendation
World Health Organization (WHO) as of August 10, 2021	For COVID-19 vaccines with a 2-dose primary series schedule, the same vaccine product should be used for both doses. If different COVID-19 vaccine products are inadvertently administered in the two doses, no additional doses of either vaccine are recommended. At present, mix and match schedules constitute off-label use of respective vaccines and as such should only be used if benefits outweigh the risks such as in situations of interrupted vaccine supply.[28]
Australian Technical Advisory Group on Immunization (ATAGI) as of September 23, 2021	Recommends use of heterologous vaccination for special circumstances such as serious vaccine-attributable adverse events after the first dose, precautionary conditions for which the use of BNT162b2 (Cominarty) or mRNA-1273 (Spikevax) are recommended instead of ChAdOx1 (AstraZeneca), and in those given an incomplete course of a COVID-19 vaccine brand not available in Australia.[29]
US Centers for Disease Control – Advisory Committee on Immunization (ACIP), UK-Joint Committee on Vaccination and Immunization (UK-JCVI), and European Medicines Agency (EMA)	No specific recommendation on heterologous primary vaccination

RESEARCH GAPS

The following are the identified knowledge and information gaps regarding heterologous primary vaccination:

1. Clinical efficacy and effectiveness of heterologous vaccination compared with homologous vaccination
    a. short-term and long-term outcomes
    b. in special populations (children, immunocompromised persons, the elderly, pregnant and lactating women)
    c. against variants of concern
2. Comparative efficacy and effectiveness of the different heterologous vaccination regimens
3. Duration of protection of heterologous vaccination, including comparison across the possible different regimens
4. Long-term safety of heterologous vaccination
5. Comparative safety of the different heterologous vaccination regimens

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Appendix 1. Evidence to Decision

Table 1. Summary of Initial Judgements Prior to Panel Discussion (N = 10)

FACTORS	JUDGEMENT						RESEARCH EVIDENCE/ADDITIONAL CONSIDERATIONS
Problem	No (1)	Yes (9)					
Benefits	Large (2)	Moderate (5)	Small (2)	Uncertain (1)			• ChAdOx1/mRNA-based paradigm showed prevention of SARS-CoV-2 infection 66% (95% CI 59-72) at 0-13 days follow-up; 88% (95% CI 83-92) at 14 days follow-up; no reported hospitalization and deaths. • Immunologic profiles showed similar to increased titers for varying combinations.
Harm	Large (1)	Small (5)	Uncertain (4)				• Varies per combination used, from similar to higher local and systemic reactogenicity.
Certainty of evidence	High	Moderate (4)	Low (4)	Very low (2)			• Very low to moderate
Balance of effects	Favors intervention (6)	Does not favor vaccine	Uncertain (4)				
Values	Important uncertainty or variability (3)	Possibly important uncertainty or variability (6)	Possibly no important uncertainty or variability (1)	No important uncertainty or variability			• WHO Recommendation: Mix and match schedules constitute off-label use and that benefits should outweigh risks such as in situations of interrupted vaccine supply. • ATAGI Recommendation: Heterologous vaccination be used conditionally.
Resources required	Uncertain (4)	Large cost (2)	Moderate cost (4)	Negligible cost or savings	Moderate savings	Large savings	• Varies per vaccine combination used
Certainty of evidence of resources required	No included studies (9)	Very low (1)	Low	Moderate	High		
Cost effectiveness	No included studies (9)	Favors the comparison	Does not favor either the intervention or the comparison	Favors the intervention (1)			
Equity	Uncertain (4)	Reduced (1)	Probably no impact	Increased (5)			• Addresses issues of limitation and unpredictability of supplies, programmatic flexibility in dosing regimen, and special needs of immunocompromised patients and other selected populations. • Addresses wide disparity in vaccine coverage: 85.1% fully-vaccinated senior citizens in NCR; only 28.3% in BARMM.
Acceptability	Uncertain (5)	No	Yes (5)				• No Philippine guidelines yet
Feasibility	Uncertain (5)	No	Yes (5)				

Appendix 2. Search Strategy

The COVID-19 Living Overview of the Evidence (L·OVE) platform, the COVID-NMA, and www.metaEvidence.org were searched for both randomized and non-randomized studies on adults investigating the efficacy, effectiveness, and safety of a heterologous COVID-19 vaccine. For the COVID-19 L·OVE platform, the search was by PICO with the following filters in order: "prevention or treatment", “public health”, "vaccination", and “SARS-CoV-2 vaccines”. Only systematic reviews and primary studies were included with the latter's yield further filtered to include all study designs but only those reporting data; the reference lists of systematic reviews were examined for eligible studies. For the COVID-NMA, the living evidence synthesis of RCTs related to vaccines was examined. For the database of www.metaEvidence.org, the search filters were the following: “vaccines”,”COVID-19 prophylaxis”, “all patients”, “all studies (RCT and observational)”. The reference lists of the weekly situational (epidemiological) reports published by the World Health Organization (WHO), and the VIEW-Hub Resource Library COVID-19 Vaccine Effectiveness Reports were searched for relevant studies. The WHO COVID-19 literature on coronavirus disease database was also searched using “heterologous” as a search term. Relevant reports from major global regulatory agencies including the US Food and Drug Authority (US FDA), the US Center for Disease Control (CDC), the European Medicines Agency (EMA), the United Kingdom Medicines and Healthcare Products Regulatory Agency (UK-MHRA), the WHO, and the Philippine Food and Drug Association (PH FDA) including their reference lists were also reviewed for relevant studies.

Appendix 3. Summary of Findings

	N	Risk of Bias	Indirectness	Inconsistency	Imprecision	Others	Effect	Certainty
ChAdOx1/mRNA-based vaccine								
Prevention of COVID-19 infection	1 Obs	Serious (observational, uncontrolled confounders)	Not serious	Not assessed	Not serious	Not assessed	VE at 0-13d: 66% (95% CI 59-72) VE at ≥14d: 88% (95% CI 83-92)	Low
Prevention of severe infection / hospitalization / death	1 Obs	Serious (observational, uncontrolled confounders)	Not serious	Not assessed	Not serious	Not assessed	No death or hospitalization	Low
Immunogenicity	0	Not assessed	Not assessed	Not assessed	Not assessed	Not assessed	na	na
Reactogenicity	0	Not assessed	Not assessed	Not assessed	Not assessed	Not assessed	na	na
Adverse events	0	Not assessed	Not assessed	Not assessed	Not assessed	Not assessed	na	na
Serious adverse events / Death	0	Not assessed	Not assessed	Not assessed	Not assessed	Not assessed	na	na
ChAdOx1/mRNA-1273								
Prevention of COVID-19 infection	0	Not assessed	Not assessed	Not assessed	Not assessed	Not assessed	na	na
Prevention of severe infection / hospitalization / death	0	Not assessed	Not assessed	Not assessed	Not assessed	Not assessed	na	na
Immunogenicity	2 Obs	Serious (observational, uncontrolled confounders)	Serious (surrogate outcomes)	Not serious	Not serious	Not serious	Similar to significant rise in antibody titers	Very low
Reactogenicity	1 Obs	Serious (observational, short follow-up)	Not serious	Not serious	Not serious	Not serious	Higher reactogenicity	na
Adverse events	0	Not assessed	Not assessed	Not assessed	Not assessed	Not assessed	na	na
Serious adverse events / Death	0	Not assessed	Not assessed	Not assessed	Not assessed	Not assessed	na	na
ChAdOx1/BNT162b2								
Prevention of COVID-19 infection	0	Not assessed	Not assessed	Not assessed	Not assessed	Not assessed	na	na
Prevention of severe infection / hospitalization / death	0	Not assessed	Not assessed	Not assessed	Not assessed	Not assessed	na	na

	N	Risk of Bias	Indirectness	Inconsistency	Imprecision	Others	Effect	Certainty
ChAdOx1/BNT162b2								
Immunogenicity	3 Obs	Very serious (observational, uncontrolled confounders, missing outcomes)	Serious (surrogate outcomes)	Not serious	Not serious	Not serious	Increased titers more vs. homologous ChAdOx1 than homologous BNT162b2 Anti-spike IgG: 0.92 to 175-fold Anti-RBD: 77.7 to 175-fold NAb: 0.9 to 62.95-fold IFN-γ: 2.3 to 4.25-fold	Very low
Reactogenicity	2 RCT, 4 Obs	Serious (observational, short follow-up)	Not serious	Not serious	Not serious	Not serious	Similar to higher reactogenicity than homologous regimen	Low
Adverse events	2 RCT, 2 Obs	Serious (observational, short follow-up)	Not serious	Not serious	Not serious	Not serious	Mixed reports of lower, similar, or higher adverse events than the homologous regimen	Low
Serious adverse events / Death	2 RCT	Serious (short follow-up)	Not serious	Not serious	Not serious	Not serious	No vaccine-related severe adverse events reported	Moderate
ChAdOx1/mRNA vaccine or vector vaccine/mRNA vaccine								
Prevention of COVID-19 infection	0	Not assessed	Not assessed	Not assessed	Not assessed	Not assessed	na	na
Prevention of severe infection / hospitalization / death	0	Not assessed	Not assessed	Not assessed	Not assessed	Not assessed	na	na
Immunogenicity	2 Obs	Serious (observational, uncontrolled confounders)	Serious (surrogate outcomes)	Not serious	Not serious	Not serious	Similar to significant rise in antibody titers	Very low
Reactogenicity	1 Obs	Serious (observational, short follow-up)	Not serious	Not serious	Not serious	Not serious	More reactogenic than homologous regimen	Low
Adverse events	1 Obs	Serious (observational, short follow-up)	Not serious	Not serious	Not serious	Not serious	Similar adverse events	Low
Serious adverse events / Death	1 Obs	Not assessed	Not assessed	Not assessed	Not assessed	Not assessed	na	na
BNT162b2/ChAdOx1								
Prevention of COVID-19 infection	0	Not assessed	Not assessed	Not assessed	Not assessed	Not assessed	na	na
Prevention of severe infection / hospitalization / death	0	Not assessed	Not assessed	Not assessed	Not assessed	Not assessed	na	na
Immunogenicity	1 RCT	Serious (lack of blinding of assessors)	Serious (surrogate outcomes)	Not serious	Not serious	Not serious	Similar to minimal rise in antibody titers vs. homologous BNT162b2 Significant rise in antibody titers vs. homologous ChAdOx1	Low
Reactogenicity	1 RCT 1 obs	Serious (lack of blinding of assessors, observational, short follow-up)	Not serious	Not serious	Not serious	Not serious	Higher reactogenicity than homologous regimen	Moderate

BNT162b2/ChAdOx1								
Adverse events	1 RCT	Serious (lack of blinding of assessors, short follow-up)	Not serious	Not serious	Not serious	Not serious	No significant difference	Moderate
Serious adverse events / Death	1 RCT 1 obs	Serious (lack of blinding of assessors, observational short follow-up)	Not serious	Not serious	Not serious	Not serious	None related to vaccination	Moderate
ChAdOx1/BBV152								
Prevention of COVID-19 infection	0	Not assessed	Not assessed	Not assessed	Not assessed	Not assessed	na	na
Prevention of severe infection / hospitalization / death	0	Not assessed	Not assessed	Not assessed	Not assessed	Not assessed	na	na
Immunogenicity	1 Obs	Very serious (observational, uncontrolled confounders, missing outcomes)	Serious (surrogate outcomes)	Not serious	Not serious	Not serious	Minimal rise in antibody titers	Very low
Reactogenicity	1 Obs	Serious (observational, short follow-up)	Not serious	Not serious	Not serious	Not serious	Similar to homologous regimen	Low
Adverse events	1 Obs	Serious (observational, short follow-up)	Not serious	Not serious	Not serious	Not serious	Similar to homologous regimen	Low
Serious adverse events / Death	0	Not assessed	Not assessed	Not assessed	Not assessed	Not assessed	na	Na
mRNA-1273/BNT162b2								
Prevention of COVID-19 infection	0	Not assessed	Not assessed	Not assessed	Not assessed	Not assessed	na	na
Prevention of severe infection / hospitalization / death	0	Not assessed	Not assessed	Not assessed	Not assessed	Not assessed	na	na
Immunogenicity	1 Obs	Very serious (observational, uncontrolled confounders, missing outcomes)	Serious (surrogate outcomes)	Not serious	Not serious	Not serious	No difference in antibody titers	Very low
Reactogenicity	0	Not assessed	Not assessed	Not assessed	Not assessed	Not assessed	na	na
Adverse events	0	Not assessed	Not assessed	Not assessed	Not assessed	Not assessed	na	na
Serious adverse events / Death	0	Not assessed	Not assessed	Not assessed	Not assessed	Not assessed	na	na
CoronaVac/ChAdOx1								
Prevention of COVID-19 infection	0	Not assessed	Not assessed	Not assessed	Not assessed	Not assessed	na	na
Prevention of severe infection / hospitalization / death	0	Not assessed	Not assessed	Not assessed	Not assessed	Not assessed	na	na
Immunogenicity	1 Obs	Very serious (observational, uncontrolled confounders, missing outcomes)	Serious (surrogate outcomes)	Not serious	Not serious	Not serious	Significant rise in antibody titers vs. homologous CoronoVac Similar rise in antibody titers vs. homologous ChAdOx1	Very low

CoronaVac/ChAdOx1								
Reactogenicity	0	Not assessed	Not assessed	Not assessed	Not assessed	Not assessed	na	na
Adverse events	0	Not assessed	Not assessed	Not assessed	Not assessed	Not assessed	na	na
Serious adverse events / Death	0	Not assessed	Not assessed	Not assessed	Not assessed	Not assessed	na	na
CoronaVac/Ad5								
Prevention of COVID-19 infection	0	Not assessed	Not assessed	Not assessed	Not assessed	Not assessed	na	na
Prevention of severe infection / hospitalization / death	0	Not assessed	Not assessed	Not assessed	Not assessed	Not assessed	na	na
Immunogenicity	1 RCT	Not serious	Serious (surrogate outcomes)	Not serious	Not serious	Not serious	Significant rise in antibody titers vs. homologous CoronaVac	Low
Reactogenicity	1 RCT	Serious (short follow-up)	Not serious	Not serious	Not serious	Not serious	Higher local reactogenicity, similar systemic reactogenicity	Moderate
Adverse events	1 RCT	Serious (short follow-up)	Not serious	Not serious	Not serious	Not serious	Low incidence in both groups	Moderate
Serious adverse events / Death	1 RCT	Serious (short follow-up)	Not serious	Not serious	Not serious	Not serious	None reported	Moderate

Appendix 4. Risk of Bias Assessment

STUDY ID	STUDY DESIGN	RANDOMIZATION	ALLOCATION CONCEALMENT	BLINDING OF PARTICIPANTS	BLINDING OF INVESTIGATORS	BLINDING OF ASSESSORS	MISSING OUTCOMES / FOLLOW UP	SELECTIVE REPORTING	ASSESSMENT OF CONFOUNDING FACTORS												OVERALL for CONTROL OF COUNFOUNDERS	OVERALL RISK
									AGE			EXPOSURE RISK			COMORBIDITIES			VARIANT PREVALENCE				
									A	B	C	A	B	C	A	B	C	A	B	C		
Barros-Martin	Retrospective Cohort	HIGH	HIGH	HIGH	UNCLEAR	UNCLEAR	HIGH	UNCLEAR	Y	U	N	N	U	N	N	U	N	N	U	N	HIGH	VERY SERIOUS
Behrens	Retrospective Cohort	HIGH	HIGH	HIGH	UNCLEAR	UNCLEAR	UNCLEAR	UNCLEAR	Y	Y	NA	N	U	N	N	U	N	N	U	N	HIGH	VERY SERIOUS
Benning	Prospective cohort	HIGH	HIGH	HIGH	UNCLEAR	UNCLEAR	HIGH	UNCLEAR	Y	U	N	N	U	N	N	U	N	N	U	N	HIGH	VERY SERIOUS
Borobia	RCT (Ph2)	LOW	LOW	LOW	LOW	LOW	LOW	LOW	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NOT SERIOUS
Dimeglio	Prospective cohort	HIGH	HIGH	HIGH	UNCLEAR	UNCLEAR	UNCLEAR	UNCLEAR	Y	U	Y	N	U	N	N	U	N	N	U	N	HIGH	VERY SERIOUS
Gram	Retrospective cohort	HIGH	HIGH	HIGH	UNCLEAR	UNCLEAR	UNCLEAR	UNCLEAR	Y	U	Y	Y	U	Y	Y	U	Y	Y	U	Y	LOW	SERIOUS
GroB	Single cohort	HIGH	HIGH	HIGH	HIGH	HIGH	UNCLEAR	UNCLEAR	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	SERIOUS
Hammerschmidt	Prospective cohort	HIGH	HIGH	HIGH	HIGH	HIGH	UNCLEAR	UNCLEAR	Y	U	N	N	U	N	N	U	N	N	U	N	HIGH	VERY SERIOUS
Hillus	Prospective cohort	HIGH	HIGH	UNCLEAR	UNCLEAR	UNCLEAR	HIGH	UNCLEAR	Y	N	N	N	U	N	N	U	N	N	U	N	HIGH	VERY SERIOUS
Kant	Prospective cohort	HIGH	HIGH	HIGH	HIGH	HIGH	UNCLEAR	UNCLEAR	Y	N	N	N	U	N	Y	Y	NA	N	U	N	HIGH	VERY SERIOUS
Li J	RCT	LOW	LOW	LOW	LOW	LOW	LOW	LOW	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NOT SERIOUS
Liu / Shaw	RCT	LOW	LOW	LOW	LOW	HIGH	HIGH	LOW	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	SERIOUS
Normark	Prospective cohort	HIGH	HIGH	HIGH	UNCLEAR	UNCLEAR	UNCLEAR	UNCLEAR	Y	N	N	N	U	N	Y	N	N	N	U	N	HIGH	VERY SERIOUS
Powell	Retrospective cohort	HIGH	HIGH	HIGH	UNCLEAR	UNCLEAR	HIGH	UNCLEAR	Y	N	N	N	U	N	N	U	N	N	U	N	HIGH	VERY SERIOUS
Rose	Retrospective cohort	HIGH	HIGH	HIGH	UNCLEAR	UNCLEAR	UNCLEAR	UNCLEAR	Y	N	N	N	U	N	N	U	N	N	U	N	HIGH	VERY SERIOUS
Schmidt	Prospective cohort	HIGH	HIGH	HIGH	UNCLEAR	UNCLEAR	UNCLEAR	UNCLEAR	Y	N	N	N	U	N	N	U	N	N	U	N	HIGH	VERY SERIOUS
Schmidt2	Retrospective cohort	HIGH	HIGH	UNCLEAR	UNCLEAR	UNCLEAR	UNCLEAR	UNCLEAR	Y	U	N	N	U	N	N	U	N	N	U	N	HIGH	VERY SERIOUS
Tenbusch	Retrospective cohort	HIGH	HIGH	HIGH	UNCLEAR	UNCLEAR	UNCLEAR	UNCLEAR	Y	N	N	N	U	N	N	U	N	N	U	N	HIGH	VERY SERIOUS
Vallee	Retrospective cohort	HIGH	HIGH	UNCLEAR	UNCLEAR	UNCLEAR	UNCLEAR	UNCLEAR	Y	U	Y	N	U	N	N	U	N	N	U	N	HIGH	VERY SERIOUS
Vinh	Prospective cohort	HIGH	HIGH	HIGH	UNCLEAR	UNCLEAR	UNCLEAR	UNCLEAR	Y	U	N	N	U	N	Y	U	N	N	U	N	HIGH	VERY SERIOUS
Yorsaeng	Prospective cohort	HIGH	HIGH	HIGH	UNCLEAR	UNCLEAR	UNCLEAR	UNCLEAR	Y	N	N	N	U	N	N	U	N	N	U	N	HIGH	VERY SERIOUS

LOW	UNCLEAR	HIGH	NOT APPLICABLE

Y	YES	N	NO	U	UNCLEAR	NA	NOT APPLICABLE

Appendix 5. Characteristics of Studies

ChAdOx1/BNT162b2									
Study author (country)	**Type of study (date)**	**Study design**	**Population**	**Heterologous regimen (dosing interval)**	**Homologous regimen/comparator (dosing interval)**	**Follow-up**	**Outcomes**	**Certainty of evidence**	**Comments**
Clinical efficacy/effectiveness									
None									
Immunogenicity									
Borobia (Spain)	Full publication (July 2021)	RCT (Ph2)	Healthy, 18-60yo, received prim ChAdOx1 8-12 weeks prior to screening N = 676 Excluded clinically significant acute illness, T' at least 38'C, COVID-19 disease; pregnancy 2 withdrawals in vaccine group, 1 in control 7 exclusions from vaccine and 3 in control	ChAdOx1/BNT162b2 (8-12 weeks) (n = 441) 2 withdrew consent, 7excluded 1 lost to follow up	no second dose or ChAdOx (i.e. maintain observation) (n = 222) 1 withdrew consent 3 excluded	14 d after V2	Anti-spike IgG(GMT) ***3684.87 vs 101.2*** ***GMR : 37 fold increase*** () anti-RBD* GMT (pseudovirusneutralization) ***7756.63 vs 99.84*** ***GMR = 77.69 (59.57 -101.32)*** NAb† (% neutralizing capacity) ***100% vs 100%*** (GMT) ***1905.69 vs 41.81*** ***GMR : 45 time increase*** IFN-γ cytokine production against SARS-CoV-2 spike peptide‡ (GMT) ***521.22 vs 122.67***	Very low	Open label Randomization list centrally generated by SAS, balanced wirhtdrawals and exclusions

Liu (UK)	Preprint/correspondence (July 2021)	RCT (Ph2)	Adults > 50 y.o, with no or well-controlled, mild-moderate comorbidities (N=463) Excluded Previous lab-confirmed SARS-CoV-2 infection, history of anaphylaxis, history of allergy fo a vaccine ingredient, pregnancy, breastfeeding, intent to conceive, current use of anticoagulants	ChAdOx1/BNT162b2 28-day interval (n = 90) (n= 24, immuno) BNT162b2/ChAdOx1 28-day interval (n = 90) (n = 25, immuno)	ChAdOx1/ChAdOx1, 28-day interval (n = 90) (n = 25, immuno) BNT162b2/BNT162b2 28-day interval (n = 93) (n = 26, immuno)	28 d after V2	ELISA) Anti-spike IgG* - *see tables* Anti-spike binding IgG† (IFN-γ ELISpot) Cellular responses IFN-γ Pseudotype virus neutralization assay (PNA)) NAb	Low	Participant-blind non-inferiority trial, IWRS clinical assessors unmasked only a sample of population with immunologic studies
GroB (Germany)	Preprint (July 2021)	Single cohort, self-controlled	Received ChAdOx1 as first dose (n = 26)	ChAdOx1/BNT162b2 56 days (n = 26)	(no comparison) boost compared to prime	6-11 d after V2 14-19 d after V2	% positivity IgG % positivity IgA Anti-spike-IgM titer Anti-spike-IgG titer (Surrogate virus neutralization test (sVNT) % positivity Anti spike RBD (Vesicular stomatits virus- based pseudovirus) IgG% ***6-11 days post boost : 100%*** ***14-19 days post : 100%*** ***IgA%*** ***6-11 days post boost : 92%*** ***14-19 days post : 100%*** Nab (B.1.1.7 ***2 fold lower potency for Beta (vs Alpha)***	Very low	

Rose (Germany)	Preprint (July 2021)	Prospective cohort	not described	ChAdOx1/BNT162b (n=41) ChAdOx1/mRNA=1273 (n=1)	ChAdOx1/ChAdOx1 (n = 9) BNT162b2 / BNT162b2 (n=8)	15 d after V2	IgG% ***all groups reached 100%*** IgG titers (anti-S and Anti RBD) ***titers in the heterologous groups 7-10x higher than the homologous ChAd and 10 to 175 times higher that the homologous BNT162b2*** Neutralization titers ***homologous ChA had 13 to 11 fold lower GMTs compared to heterologous or homo BNT*** Neutralization % ***similar across groups***	Very low	with missing samples post-D2
Tenbusch (Germany)	Preprint (July 2021)	Retrospective cohort	sera from assessed in 2 different laboratories	ChAdOx1/BNT162b2 (n = 232) ChAdOx1/BNT162b2 (n=250)	BNT162b2/BNT162b2 (n= 410) BNT162b2/BNT162b2 (n= 127) ChAdOx1/ChAdOx1 (n=250)	14 d after V2	Neutralizing antibody titers ***(results in table)***	Very low	sample selection not clarified

Barros-Martins (Germany)	Correspondence (June 2021)	Retrospective cohort	healthcare workers primed with ChAdOx, offered a choice of boost additional BNT homo group included in study	ChAdOx1/BNT162b2 74 days (n=55)	ChAdOx1/ChAdOx1 73 days (n=32) BNT162b2/BNT162b2 21 day interval (n=46)	16-17 d after V2	anti-S spike IgG titers (fold increase from preboost), for wild strain ***(11.5 fold inc vs 2.9)***, Alpha, Beta and Gamma neutralizing Ab titers post boost, for all strains for Wuhan ***: increased in both groups but higher titers in hetero*** for VOCs :***hetero with higher titers in all strains while ChA homo only had increase in Alpha but not in Beta and Gamma*** spike specific B cell positivity spike specific CD4 positivity ***increased in both groups but higher in hetero*** spike specific CD8	Very low	self-chosen 2nd dose comparison group BNT/BNT chosen by investigator without details with missing data in all groups
Behrens (Germany)	Correspondence (August 2021)	prospective cohort	Healthcare professionals and individuals with potential contact to SARS-CoV-2 (from CoCo study)	ChAdOx1/BNT162b2, mean 73.5 (71-85) days n = 11	ChAdOx1/ChAdOx1 mean 73.5 (71-85) days n = 12	15-17 d after V2	IgG (ELISA) 50% neutralization titer (VSV-pseudoviral assay) activity vs variants ***all heterologous indiviruals achieved NT50 = 25 against all variants with NT50>100 in 85% of vaccinees, unlike those who had homologous vaccination where a proportion of patients did not reach the 25***	Very low	balanced age no control of confounding factors

Benning (Germany)	Full publication (August 2021)	Prospective cohort	Health care workers (N= 166) heterologous group younger homologous ChA older than homologous BNT	ChAdOx1/BNT162b2 median 83d (77-94) interval (n=35)	ChAdOx1/ChAdOx1 median 82d (82-83) interval (n=17) BNT162b2/BNT162b2 median interval 20d (20-20) (n=82)	20 d (IQR 19-21) after V2	***(results in table)*** TiTers - Full spike - S1 - RBD - S2 - nucleocapside Neutralizing antibodies Seropositivity - full spike - S1 - RBD - S2	Very low	only a small sample of were subjected to some of the immunologic studies
Dimeglio (France)	Preprint/correspondence (July 2021)	Prospective cohort	Healthcare workers with COVID-19 negative antibodies pre-vaccination >55yo with choice of homologous or hetero; those <55 all given BNT booster	ChAdOx1/BNT162b2	ChAdOx1/ChAdOx1 BNT162b2/BNT162b2	1 m after V2	NAb titers (Live virus-based assay) Nab seropositivity ***in table*** Nab titers ***noted as not statistitcally significant across groups***	Very low	matched by age and gender for those >55 years old
Hammerschmidt (Germany)	Correspondence (August 2021)	Retrospective cohort	Healthcare professionals and individuals with potential contact to SARS-CoV-2	ChAdOx1/BNT162b2 2-3 months interval (n = 54)	BNT162b2/BNT162b2, 21 days interval (n = 30) ChAdOx1/ChAdOx1, 21 days interval (n = 31)	mean 17 (13-23) d after homologous ChAdOx1 prime-boost or heterologous BNT prime-boost mean 30 (15-65) d after homologous BNT162b2 prime-boost	NAb against Delta variant (sVNT, pVNT) ***ChA/BNT with higher Nabs vs Alpha, beta and Gamma compared to BNT/BNT*** ***BNT/BNT higher Nabs vs Delta vs hetero...***	Very low	

Hillus (Germany)	Full publication (August 2021)	Prospective, observational cohort	health care workers in a tertiary care center (N=380 enrolled, excluded 26)) Excluded seropositive (PCR-confiremd or IgG detectable) only 30 selected samples tested for T-cell response	ChAdOx1/BNT162b2 71 d (IQR 70-73) (n = 104)	BNT162b2/BNT162b2 21 d (IQR 21-21) (n = 174) ChAdOx1/ChAdOx1 (n = 38)	3 weeks after V2	(Microarray-based immunoassay surrogate virus neutralization test (sVNT) and IGRA and ELISA) ***see tables for results*** Anti-full spike Anti-spike S1 reactivity Anti-spike RBD-IgG anti - N RBD binding inhibition (surrogate nutralization asssay) (pseudoneutralizatio n assay) ID50 for Alpha and Beta T cell response ((IFN-gamma release assay)	Very low	use of electronic questionnaire for AEs Interim missing data, less samples with immunogenicity in homoBNT multivariate matching for sex and age between vaccine groups
Vallee (France)	Full publication (August 2021)	Retrospective crosssectional study	healthcare workers with not previous COVID infection BNT homo - younger	ChAdOx1/BNT162b2 12 weeks interval (n=130)	BNT162b2/BNT162b2 4 weeks interval (n=67)	30 and 60 d after V2	***IgG antibodies significantly higher with HETERO but no significant difference after adjustment for time between doses***	Very low	adjusted titers based on dosing interval

ChAdOx1/BNT162b2									
Study author (country)	**Type of study (date)**	**Study design**	**Population**	**Heterologous regimen (dosing interval)**	**Homologous regimen/comparator (dosing interval)**	**Follow-up**	**Outcomes**	**Certainty of evidence**	**Comments**
Safety									
Borobia (Spain)	Full publication (July 2021)	RCT (Ph2)	Healthy, 18-60yo, received prim ChAdOx1 8-12 weeks prior to screening N = 676 Excluded clinically significant acute illness, T' at least 38'C, COVID-19 disease; pregnancy 2 withdrawals in vaccine group, 1 in control 7 exclusions from vaccine and 3 in control	ChAdOx1/BNT162b2 8-12 weeks (n = 441) 2 withdrew consent, 7excluded 1 lost to follow up	no second dose or ChAdOx (i.e. maintain observation) (n = 222) 1 withdrew consent 3 excluded	7 d reactogenicity 14 d after V2 planned 1 year	Solicited local and systemic adverse events Unsolicited adverse events ***31 with severe adverse events (malaise 23%, myalgia 19% and headcahe 16%***	Low	Open label Randomization list centrally generated by SAS, balanced wirhtdrawals and exclusions
GroB (Germany)	Preprint (July 2021)	Single cohort, self-controlled	Received ChAdOx1 as first dose (n = 26)	ChAdOx1/BNT162b2 56 days Interval (n = 26)	(no comparison) boost compared to prime	Not stated	Solicited local adverse events ***80.4%(23/26) with at least 1 mild or moderate symptoms*** most common AE : ***pain at injection site (84.6%), fatigue (84.6), chills (19.2)*** ***similar AE reports in prime and boost*** ***milder reaction to boost than prime*** Severe symptoms of fatigue (7.7) and headache (15.4%) Solicited systemtic adverse events	Low	

Liu (UK)	Preprint/correspondence (July 2021)	RCT (Ph2)	Adults > 50 y.o, with no or well-controlled, mild-moderate comorbidities (N=463) Excluded Previous lab-confirmed SARS-CoV-2 infection, history of anaphylaxis, history of allergy fo a vaccine ingredient, pregnancy, breastfeeding, intent to conceive, current use of anticoagulants	ChAdOx1/BNT162b2 28-day interval (n = 90) (n= 24, immuno) BNT162b2/ChAdOx1 28-day interval (n = 90) (n = 25, immuno)	ChAdOx1/ChAdOx1, 28-day interval (n = 90) (n = 25, immuno) BNT162b2/BNT162b2 28-day interval (n = 93) (n = 26, immuno)	7 d after immunization 28 d after immunization	Solicited local and systemic events Unsolicited adverse events Medically attended adverse events Blood biochemistry and hematology assessments ***both heterologous regimen had higher systemic reactions than homologous*** ***higher proportions of paracetamol use in the heterologous*** ***no thrombocytopenia***	Low	Participant-blind non-inferiority trial, IWRS clinical assessors unmasked only a sample of population with immunologic studies
Powell (UK)	RWE (August 2021)	Retrospective cohort	Adults aged 18-75 recorded to have received vaccination in the NIMS,who had received their second dose 21 days prior, with recorded mobile numbers, invited to the survey (n = 1313) Excluded ncomplete information, those who responded"not known" when asked about prior COVID 19 symptoms	ChAdOx1/BNT162b2 med 76d (n = 572) BNT162b2/ChAdOx1 med 76d (n = 167)	ChAdOx1/ChAdOx1 med 69d (n = 461) BNT162b2/BNT162b2 med 69d (n = 133)	Within 21 d from V2	Overall AE rates ***ChAd/BNT : 60.5%*** ***BNT/ChAd : 58.8%*** ***ChAd/ ChAd : 35.2%*** ***BNT/BNT : 29.3%*** Local reactogenicity ***ChAd/BNT : 51%*** ***BNT/ChAd : 54.4%*** ***ChAd/ ChAd : 32%*** ***BNT/BNT : 26.3%*** Systemic reactogenicity ***ChAd/BNT : 51.9%*** ***BNT/ChAd : 44.3%*** ***ChAd/ ChAd : 25.9%*** ***BNT/BNT : 25.6%*** ***HETERO more likely to report more severe AEs***	Low	database review Online survey questionnaire (response rate of 18.7%) (no protocol/ no clear methods) subgrouped by age, sex, previous infection, severe AR on prime

Benning (Germany)	Full publication (August 2021)	Prospective cohort	Health care workers (N= 166) heterologous group younger homologous ChA older than homologous BNT	ChAdOx1/BNT162b2 median 83d (77-94) interval (n=35)	ChAdOx1/ChAdOx1 median 82d (82-83) interval (n=17) BNT162b2/BNT162b2 median interval 20d (20-20) (n=82)	Not stated	Any reaction ***BNT/BNT = 83%*** ***Cha/BNT = 72%*** ***Cha/Cha = 29%*** Local reactogenicity ***Cha/Cha = 7%*** ***Cha/BNT = 52%*** ***BNT/BNT = 53%*** Systemic reactogenicity ***BNT/BNT = 76%*** ***Cha/BNT = 52%*** ***Cha/Cha = 29%***	Low	only a small sample of were subjected to some of the immunologic studies
Hillus (Germany)	Full publication (August 2021)	Prospective, observational cohort	health care workers in a tertiary care center (N=380 enrolled, excluded 26)) Excluded seropositive (PCR-confiremd or IgG detectable) only 30 selected samples tested for T-cell response	ChAdOx1/BNT162b2 71 d (IQR 70-73) (n = 104)	BNT162b2/BNT162b2 21 d (IQR 21-21) (n = 174) ChAdOx1/ChAdOx1 (n = 38)	1 d, 3 d, 5 d, 7 d after V1 and V2	Local Reactogenicity ***ChA/BNT : 80%*** ***BNT/BNT : 75%*** ***ChA/ChA : 60%*** Systemic Reaction rate: ***ChA/BNT : 49%*** ***BNT/BNT : 65%*** ***ChA/ChA : 39%*** ***fatigue, myalgia, headache and chills, and fever more common in HOMO vs hetero*** ***Severe AEs least common after hetero*** ***no lifethreateaning reactions***	Low	use of electronic questionnaire for AEs Interim missing data, less samples with immunogenicity in homoBNT multivariate matching for sex and age between vaccine groups

BNT162b2/ChAdOx1									
Study author (country)	**Type of study (date)**	**Study design**	**Population**	**Heterologous regimen (dosing interval)**	**Homologous regimen (dosing interval)**	**Follow-up**	**Outcomes**	**Certainty of evidence**	**Comments**
Clinical efficacy/effectiveness									
None									
Immunogenicity									
Liu (UK)	Preprint/correspondence (July 2021)	RCT (Ph2)	Adults > 50 y.o, with no or well-controlled, mild-moderate comorbidities (N=463) Excluded Previous lab-confirmed SARS-CoV-2 infection, history of anaphylaxis, history of allergy fo a vaccine ingredient, pregnancy, breastfeeding, intent to conceive, current use of anticoagulants	ChAdOx1/BNT162b2 28-day interval (n = 90) (n= 24, immuno) BNT162b2/ChAdOx1 28-day interval (n = 90) (n = 25, immuno)	ChAdOx1/ChAdOx1, 28-day interval (n = 90) (n = 25, immuno) BNT162b2/BNT162b2 28-day interval (n = 93) (n = 26, immuno)	28 d after V2	ELISA) Anti-spike IgG* - *see tables* Anti-spike binding IgG† (IFN-γ ELISpot) Cellular responses IFN-γ Pseudotype virus neutralization assay (PNA)) NAb	Very low	Participant-blind non-inferiority trial, IWRS clinical assessors unmasked only a sample of population with immunologic studies
Safety									
Liu (UK)	Preprint/correspondence (July 2021)	RCT (Ph2)	Adults > 50 y.o, with no or well-controlled, mild-moderate comorbidities (N=463) Excluded Previous lab-confirmed SARS-CoV-2 infection, history of anaphylaxis, history of allergy fo a vaccine ingredient, pregnancy, breastfeeding, intent to conceive, current use of anticoagulants	ChAdOx1/BNT162b2 28-day interval (n = 90) (n= 24, immuno) BNT162b2/ChAdOx1 28-day interval (n = 90) (n = 25, immuno)	ChAdOx1/ChAdOx1, 28-day interval (n = 90) (n = 25, immuno) BNT162b2/BNT162b2 28-day interval (n = 93) (n = 26, immuno)	7 d after immunization 28 d after immunization	Solicited local and systemic events Unsolicited adverse events Medically attended adverse events Blood biochemistry and hematology assessments ***both heterologous regimen had higher systemic reactions than homologous*** ***higher proportions of paracetamol use in the heterologous*** ***no thrombocytopenia***	Low to moderate	Participant-blind non-inferiority trial, IWRS clinical assessors unmasked only a sample of population with immunologic studies

Powell (UK)	RWE (August 2021)	Retrospective cohort	Adults aged 18-75 recorded to have received vaccination in the NIMS,who had received their second dose 21 days prior, with recorded mobile numbers, invited to the survey (n = 1313) Excluded ncomplete information, those who responded"not known" when asked about prior COVID 19 symptoms	ChAdOx1/BNT162b2 med 76d (n = 572) BNT162b2/ChAdOx1 med 76d (n = 167)	ChAdOx1/ChAdOx1 med 69d (n = 461) BNT162b2/BNT162b2 med 69d (n = 133)	Within 21 d from V2	Overall AE rates ***ChAd/BNT : 60.5%*** ***BNT/ChAd : 58.8%*** ***ChAd/ ChAd : 35.2%*** ***BNT/BNT : 29.3%*** Local reactogenicity ***ChAd/BNT : 51%*** ***BNT/ChAd : 54.4%*** ***ChAd/ ChAd : 32%*** ***BNT/BNT : 26.3%*** Systemic reactogenicity ***ChAd/BNT : 51.9%*** ***BNT/ChAd : 44.3%*** ***ChAd/ ChAd : 25.9%*** ***BNT/BNT : 25.6%*** ***HETERO more likely to report more severe AEs***	Low to moderate	database review Online survey questionnaire (response rate of 18.7%) (no protocol/ no clear methods) subgrouped by age, sex, previous infection, severe AR on prime

ChAdOx1/mRNA-1273									
Study author (country)	**Type of study (date)**	**Study design**	**Population**	**Heterologous regimen (dosing interval)**	**Homologous regimen (dosing interval)**	**Follow-up**	**Outcomes**	**Certainty of evidence**	**Comments**
Clinical efficacy/effectiveness									
None									
Immunogenicity									
Rose (Germany)	Preprint (July 2021)	Prospective cohort	not described	ChAdOx1/BNT162b (n=41) ChAdOx1/mRNA-1273 (n=1)	ChAdOx1/ChAdOx1 (n = 9) BNT162b2 / BNT162b2 (n=8)	15 d post V2	IgG% ***all groups reached 100%*** IgG titers (anti-S and Anti RBD) ***titers in the heterologous groups 7-10x higher than the homologous ChAd and 10 to 175 times higher that the homologous BNT162b2*** Neutralization titers ***homologous ChA had 13 to 11 fold lower GMTs compared to heterologous or homo BNT*** Neutralization % ***similar across groups***	Very low	with missing samples post-D2
Normark (US)	Correspondence (September 2021)	prospective cohort	healthcare workers (n=88) excluded 5 who had COVID prior	ChAdOx1/mRNA-1273 84 (IQR 82-86) (n=48)	ChAdOx1/ChAdOx1 70d (IQR 67-76) (n=35)	7 - 10 and 30 d after V2 (extracted 30 days)	***results in tables*** S-binding and RBD binding titers ***decreased neutralization of Beta, but HETERO significantly higher titers than HOMO***	Very low	interim report of ongoing study sl younger Homo Homo with more allergy and comorbid dosing interval longer in HOMO
Safety									
Normark (US)	Correspondence (September 2021)	prospective cohort	healthcare workers (n=88) excluded 5 who had COVID prior	ChAdOx1/mRNA-1273 84 (IQR 82-86) (n=48)	ChAdOx1/ChAdOx1 70d (IQR 67-76) (n=35)	7-10 d after V2	***higher pain with HETERO*** ***more systemic events with HETERO : Fever, fatigue, headcache, chills, other***	Low	interim report of ongoing study sl younger Homo Homo with more allergy and comorbid dosing interval longer in HOMO

ChAdOx1/BBV152									
Study author (country)	**Type of study (date)**	**Study design**	**Population**	**Heterologous regimen (dosing interval)**	**Homologous regimen (dosing interval)**	**Follow-up**	**Outcomes**	**Certainty of evidence**	**Comments**
Clinical efficacy/effectiveness									
None									
Immunogenicity									
Kant (India)	Preprint (August 2021)	Prospective cohort	individuals under the national vaccination program	ChAdOx1/BBV152 (n = 18)	ChAdOX1/ChAdOx1 (n = 40) BBV152/BBV152 (n = 40)	60-70 d after V1	PRNT50 assay - ***see tables*** ELISA) Anti-RBD, anti-spike, N protein titers NAb titers against B.1, Alpha, Beta, and Delta strains	Very low	unclear on selection of the homologous groups
Safety									
Kant (India)	Preprint (August 2021)	Prospective cohort	individuals under the national vaccination program	ChAdOx1/BBV152 (n = 18)	ChAdOX1/ChAdOx1 (n = 40) BBV152/BBV152 (n = 40)	7 d after V2	Solicited local and systemic Aes (Cha/Cha vs Cov/Cov vs Cha/Cov) ***pain : 5 vs 7.5 vs 11.1 pyrexia : 15 vs 15 vs 11.1 malaise : 5 vs 15 vs. 5.5 paracetamol use : 7.5 vs 17.5 vs 11.1 overall frequency of AE in hetero similar to homo***	Low	unclear on selection of the homologous groups

mRNA-1273/BNT162b2									
Study author (country)	**Type of study (date)**	**Study design**	**Population**	**Heterologous regimen (dosing interval)**	**Homologous regimen (dosing interval)**	**Follow-up**	**Outcomes**	**Certainty of evidence**	**Comments**
Clinical efficacy/effectivenss									
None									
Immunogenicity									
Vinh (Canada)	Preprint (September 2021)	Prospective cohort	>=65 year old, in long term care facility	mRNA-1273/BNT162b2	BNT162b2/BNT162b2 mRNA1273/mRNA1273	4 weeks	***similar levels of IgG were observed with no difference between HOMO and HETERO***	Very low	
Safety									
None									

CoronaVac/ChAdOx1									
Study author (country)	**Type of study (date)**	**Study design**	**Population**	**Heterologous regimen (dosing interval)**	**Homologous regimen (dosing interval)**	**Follow-up**	**Outcomes**	**Certainty of evidence**	**Comments**
Clinical efficacy/effectiveness									
None									
Immunogenicity									
Yorsaeng (Thailand)	Preprint (September 2021)	Retrospective cohort	general population? Not described	CoronaVac/ChAdOx1 4 weeks (n=54)	CoronaVac/CoronaVac 3 weeks (n=80) ChAdOx1/ChAdOx1 10 weeks (n=80)	not specified	anti-S antibody titers	Very low	
Safety									
None									

CoronaVac/Ad5-nCoV									
Study author (country)	**Type of study (date)**	**Study design**	**Population**	**Heterologous regimen (dosing interval)**	**Homologous regimen (dosing interval)**	**Follow-up**	**Outcomes**	**Certainty of evidence**	**Comments**
Clinical efficacy/effectiveness									
None									
Immunogenicity									
Li (China)	Preprint (September 2021)	RCT	18-59 yo, healthy received two doses of CoronaVac in the past 3-6 months or one dose of CoronaVac in the past 1-2 months Excluded previous clinical or virologic COVID-19 diagnosis or infection, pregnant women	CoronaVac/Ad5 1-2 months (n=49) 2 patients discontinued	CoronaVac/CoronaVac 1-2 months (n=49) 1 patient discontinued	14 and 28 d after V2	neutralizing antibody titers (live viral assay) - seroconversion- ***see table*** - GMT-***see table*** - Geometric mean fold increase ***23.4 vs 5.2*** IFN-Gamma titers - ***see table*** anti-RBD binding titer - ***see table***	Low	IWRS randomization participants, investigators, lab and outcome assessors blinded to treatment but not to th 3 or 2 dose regimen; (4-arm trial, 2 arms on booster after 2 doses of Coronavac)
Safety									
Li (China)	Preprint (September 2021)	RCT	18-59 yo, healthy received two doses of CoronaVac in the past 3-6 months or one dose of CoronaVac in the past 1-2 months Excluded previous clinical or virologic COVID-19 diagnosis or infection, pregnant women	CoronaVac/Ad5 1-2 months (n=49) 2 patients discontinued	CoronaVac/CoronaVac 1-2 months (n=49) 1 patient discontinued	28 days after V2	(Hetero vs Homo) ***any AE :25.5% vs 8.0%*** ***Inj site AE : 23.5 vs 2.0*** ***Pain at inj : 19.6 vs 2.0*** ***Any systemic : 11.8 vs 6.0*** ***Fever : 5.9 vs 2.0*** ***Fatigue : 7.8 vs 4.0*** ***low incidence of unsolicited adverse reactions*** ***no severe AE in both groups***	Low	IWRS randomization participants, investigators, lab and outcome assessors blinded to treatment but not to th 3 or 2 dose regimen; (4-arm trial, 2 arms on booster after 2 doses of Coronavac)

ChAdOx1/BNT162b2 or mRNA-1273									
Study author (country)	**Type of study (date)**	**Study design**	**Population**	**Heterologous regimen (dosing interval)**	**Homologous regimen (dosing interval)**	**Follow-up**	**Outcomes**	**Certainty of evidence**	**Comments**
Clinical efficacy/effectiveness									
Gram (Denmark)	Preprint (July 2021)	Retrospective population-based cohort study	Vaccinated residents in Denmark N = 5,542,079	ChAdOx1/BNT162b2 (n = 88,050) ChAdOx1/mRNA-1273 (n = 48,501) results presented as ChAdOx1 / mRNA vaccine	ChAdOx1/- (n = 144,360) or no vaccination	Immediately after vaccination up to emigration, death, or June 23, 2021 whichever comes first 0-13 d and =/> 14 d after V2	VE against SARS-CoV-2 infection, *(0-13d)* *ChA/mRNA : 66% (59,72)* *(>=14d)* *ChA/mRNA : 88% (83,92)* COVID-19 related hospitalization *none* COVID 19 related death all cause hospitalization *(0-13d)* *Cha/mRNA :43% (36,49)* *(>=14d)* *Cha/mRNA : 50% (45,55)* all cause death *none occurred*	Low	controlled for calendar time, age, sex, heritage, comorbidity, and hospitaliation (for death)
Immunogenicity									
Schmidt (Germany)	Correspondence (July 2021)	Prospective cohort	216 immunocompetent individuals	ChAdOx1/mRNA-based (n = 97)	ChAdOx1/ChAdOx1 (n = 55) mRNA-based/mRNA-based (n = 64)	Median 14 d after vaccination after V2	***results in table*** Spike specfic IgG level (BAU/ml) Surrogate neutralization test (inhibitory activity) Cytokines interferon (IFN)-y Spike-specific CD4 , CD8	Very low	Homologous vector group older than other groups
Schmidt2 (Germany)	Full publication (August 2021)	Prospective cohort	40 solid transplant recipients 70 immunocompetent controls	ChAdOx1/mRNA-based (n = 20)	ChAdOx1/ChAdOx1 (n=9) mRNA-based/mRNA-based (n = 9)	Median 14 d after V2	***CD4 T cell levels after HOMO were lower than HETERO*** ***CD8 higher in hetero but not signifcant*** ***IgG and netrualizing Ab higher in Hetero and HomomRNA, thatn Homo vec***	Very low	matching across transplant vs immunocompetent, not based on vaccination
Safety									
Schmidt (Germany)	Correspondence (July 2021)	Prospective cohort	216 immunocompetent individuals	Vector vaccine/mRNA vaccine (n = 97)	Vector vaccine/Vector vaccine (n = 55) mRNA vaccine/mRNA vaccine (n = 64)	Within first week after D1 and D2	Local and systemic adverse events ***mRNA-boosted regimen less tolerated***	Low	Homologous vector group older than other groups

Appendix 6. Seropositivity

STUDY ID	Immunologic study (Test Used) (Time of Assessment)	HETERO Regimen (N) post-boost Seropositivity	HOMO Regimen (N) post-boost Seropositivity	Difference between Regimen after D2 (95% CI)
Benning	AntiS1 IgG positivity 20 days	ChAd/BNT (35) 97.0	ChAd/ChAd (17) 93.5	3.3% (-9.8 to 16.4)
		ChAd/BNT (35) 96.8	BNT/BNT (82) 97.0	-2.0% (-7.1 to 6.7)
	Full spike	ChAd/BNT (15) 100%	BNT/BNT (15) 100%	0.00%
	S1	ChAd/BNT (15) 100%	BNT/BNT (15) 100%	0.00%
	RBD	ChAd/BNT (15) 100%	BNT/BNT (15) 100%	0.00%
	S2	ChAd/BNT (15) 93%	BNT/BNT (15) 100%	-7.0% (-20 to 5.91)
Dimeglio	Nab (live virus based) (1 month) <55 y/o	ChAd/BNT (33) 75.7%	BNT/BNT (33) 87.8%	-12.1% (-31to 6.3)
	Nab (live virus based) (1 month) >55 y/o	ChAd/BNT (22) 95.4%	BNT/BNT (22) 68.2%	27.2% (5.86-48.5)
	Nab (live virus based) (1 month) >55 y/o	ChAd/BNT (22) 95.4%	ChAd/ChAd (22) 63.6%	31.8% (9.9-53.7)
Liu	Anti-spike (28days)	ChAd/BNT (108) 96%	ChAd/ChAd (105) 95%	1.0% (-4.6 to 6.6)
	Anti-spike (28days)	ChAd/BNT (108) 96%	BNT/BNT (110) 100%	-4.0% (-7.7 to -0.3)
	Anti-spike (28days)	BNT/ChAd (109) 100%	ChAd/ChAd (105) 95%	5.0% (8.3-9.2)
	Anti-spike (28days)	BNT/ChAd (109) 100%	BNT/BNT (110) 100%	0.00%
	Cellular Response (28 days)	ChAd/BNT (107) 100%	ChAd/ChAd (103) 98%	2.0% (-0.7 to 4.7)
	Cellular Response (28 days)	ChAd/BNT (107) 96%	BNT/BNT (109) 94%	7.0% (2.21-11.8)
	Cellular Response (28 days)	BNT/ChAd (108) 90%	ChAd/ChAd (103) 98%	- 8.0% (-14.2 to -1.73)
	Cellular Response (28 days)	BNT/ChAd (108) 90%	BNT/BNT (109) 94%	-3.0% (-10.4 to 4.4)
Hillus	RBD reactivity	ChAd/BNT (94) 100%	BNT/BNT (101) 99%	1.0% (-0.9 to 2.94)
	RBD reactivity	ChAd/BNT (94) 100%	ChAd/ChAd (36) 100%	0
	Nab (surrogate virus neutralization)	ChAd/BNT (94) 100%	ChAd/ChAd (36) 100%	0
	Nab (surrogate virus neutralization)	ChAd/BNT (94) 100%	BNT/BNT (101) 99%	1.0% (-0.9 to 2.94)

	Anti-S1	ChAd/BNT (94) 100%	ChAd/ChAd (36) 97%	3% (-2.57 to 8.57)
	Anti-S1	ChAd/BNT (94) 100%	BNT/BNT (101) 99%	1.0% (-0.9 to 2.94)
	Nab (surrogate virus neutralization)	ChAd/BNT (104) 97.1%	ChAd/ChAd (38) 92.4%	4.7% (-4.3 to 13.7)
	Nab (surrogate virus neutralization)	ChAd/BNT (104) 97.1%	BNT/BNT (174) 96.6%	0.5% (-3.7 to 4.7)
Li J	Neutralizing Antibody	CoV/Ad5 (50) 100%	CoV/CoV (50) 93.9%	6.1% (-0.5. to 12.73)
Schmidt	IFN gamma CD4	vector/mRNA (97) 0.17	mRNA/mRNA (55) 0.16	Median percentages, not GMTs
	IFN gamma CD4	vector/mRNA (97) 0.17	vector/vector (64) 0.04	Median percentages, not GMTs
	IFN gamma CD8	vector/mRNA (97) 0.28	mRNA/mRNA (55) 0.06	Median percentages, not GMTs
	IFN gamma CD8	vector/mRNA (97) 0.28	vector/vector (64) 0.04	Median percentages, not GMTs

Appendix 8. Titer Levels

STUDY ID	Immunologic study (Test Used) (Time of Assessment)	HETERO Regimen (N) GMT (95% CI)	HOMO Regimen (N) GMT (95% CI)	GMR (Hetero:Homo) (95% CI)
Bennings	Anti-S1 IgG levels	ChAd/BNT (n =) 116.2 (IQR 61.8-170)	BNT/BNT (n =) 145.5 (100.0-291.1)	0.8
		ChAd/BNT (n =) 116.2 (61.8-170)	ChAd/ChAd (n =) 13.1 (7.0-29.0)	8.87
	Full spike MFI values	ChAd/BNT 24243	BNT/BNT 23849	1.02
	S1 MFI values	ChAd/BNT 19332	BNT/BNT 16955	1.14
	S2 MFI values	ChA/BNT 13138	BNT/BNT 9696	1.35
Liu	Anti-spike IgG	ChA/BNT (104) 12906	Cha/Cha (104) 1392	9.27
	Anti-spike IgG	BNT/ChA (109) 7133	BNT/BNT (109) 14080	0.51
	Anti-spike IgG	ChA/BNT (104) 12906	BNT/BNT (109) 14080	0.92
	Anti-spike IgG	BNT/ChA (109) 7133	Cha/Cha (104) 1392	5.12
	Neutralizing Antibodies (pseudotype assay NT50)	ChA/BNT (101) 515	Cha/ChAd (101) 61	8.5 (6.5-11)
	Neutralizing Antibodies (pseudotype assay NT50)	BNT/ChA (104) 383	BNT/BNT (102) 574	0.67 (0.51-0.88)
	Neutralizing Antibodies (pseudotype assay NT50)	ChA/BNT (101) 515	BNT/BNT (102) 574	0.9
	Neutralizing Antibodies (pseudotype assay NT50)	BNT/ChA (104) 383	Cha/ChAd (101) 61	6.3
	IFN-Gamma (ELISpot) 28 days after	ChAd/BNT (108) 184	ChAd/ChAd (104) 48	3.9 (2.9-5.3)
	IFN-Gamma (ELISpot) 28 days after	ChAd/BNT (108) 184	BNT/BNT (110) 80	2.3
	IFN-Gamma (ELISpot) 28 days after	BNT/ChAd (109) 97	ChAd/ChAd (104) 48	2.02
	IFN-Gamma (ELISpot) 28 days after	BNT/ChAd (109) 97	BNT/BNT (110) 80	1.2 (0.87-1.7)
Behrens	Anti-spike IgG (Quantivac) 16 days after	ChAd/BNT (11) 611.0	ChAd/ChAd (12) 171.9	3.55
Kant	Anti S1-RBD (Elisa) 9 weeks later	ChAd/CoV (18) 1866	ChAd/ChAd (40) 2260	0.83
	Anti S1-RBD (Elisa) 9 weeks later	ChAd/CoV (18) 1866	CoV/CoV (40) 710	2.63
	N-protein 9 weeks	ChAd/CoV (18) 1145	ChAd/ChAd (40) 353.7	3.24
	N-protein 9 weeks	ChAd/CoV (18) 1145	CoV/CoV (40) 742.4	1.54
	IgG titers (whole virus) 9 weeks	ChAd/CoV (18) 171.4	ChAd/ChAd (40) 111	1.54
	IgG (whole virus) 9 weeks	ChAd/CoV (18) 171.4	CoV/CoV (40) 86	1.99

	Neutralzing Antibodies (PRNT50) 9 weeks	ChAd/CoV (18) 539.4	ChAd/ChAd (40) 162	3.33
	Neutralzing Antibodies (PRNT50) 9 weeks	ChAd/CoV (18) 539.4	CoV/CoV (40) 156.6	3.44
Schmidt	Spike-specific IgG 14 days	vector/mRNA (97) 3630	mRNA/mRNA (55) 4932	0.74
	Spike-specific IgG 14 days	vector/mRNA (97) 3630	vector/vector (64) 404	8.99
Tenbusch	Neutralizing antibody (surrogate neutralization assay) 14 days	ChAd/BNT (232) 2798	BNT/BNT (410) 1730	1.62
	neutralizing antibody (surrogate neutralization assay) 14 days	ChAd/BNT (250) 6673	BNT/BNT (127) 2583	2.58
	neutralizing antibody (surrogate neutralization assay) 14 days	ChAd/BNT (250) 6673	ChAd/ChAd (66) 106	62.95
Hillus	Anti-spike IgG 3 weeks	ChAd/BNT () 5.6	BNT/BNT () 5.6	1.03
	Anti-spike IgG 3 weeks	ChAd/BNT () 5.6	ChAd/ChAd ( ) 4.9	1.14
	IFN-gamma (IGRA) 3 weeks	ChAd/BNT (91) 4762	BNT/BNT (66) 2026	2.35
	IFN- gamma (IGRA) 3weeks	ChAd/BNT (91) 4726	ChAd/ChAd (34) 1061	4.45
Normark	S-Binding 1 month	ChAd/Mod (48) 104083	ChAd/ChAd (35) 7381	14.1
	RBD-binding 7-10days	ChAd/Mod (48) 41680	ChAd/ChAd (35) 1224	34.05
Vallee	Anti-IgG 30-60 days	ChAd/BNT (130) 7268.6	BNT/BNT (67) 10,734.9	0.68
Yorsaeng	Anti-S IgG unspecified	CoV/ChAd (54) 797	CoV/CoV (80) 96.4	8.27
	Anti-S IgG unspecified	CoV/ChAd (54) 797	ChAd/ChAd (80) 818	0.97
Li J	Neutralizing antibodies (live viral netrualization assa) 28 days	CoV/Ad5 (50) 49.6	CoV/CoV (50) 10.6	4.68
	IFN-gamma 14 days	CoV/Ad5 (50) 65	CoV/CoV (50) 40	1.66
	Anti RBD-binding IgG 14 days	CoV/Ad5 (50) 941.8	CoV/CoV (50) 154.1	6.11

Appendix 9. Characteristics of Ongoing Studies

NCT Number	Title	Status	Study Results	Interventions	Outcome Measures	Sponsor/Collaborators	URL
NCT04988048	Collaborative Study to Evaluate Heterologous Vaccination Against Covid-19 in Argentina	Recruiting	No Results Available	Biological: COVID-19 vaccines	Antibody against Spike protein measurement by ELISA test|Incidence of adverse events by measurement of the number of reactions after vaccination|Neutralising Antibody against Spike protein and cellular immune response	Ministry of Public Health, Argentina|Russian Direct Investment Fund	https://ClinicalTrials.gov/show/NCT04988048
NCT04889209	Delayed Heterologous SARS-CoV-2 Vaccine Dosing (Boost) After Receipt of EUA Vaccines	Recruiting	No Results Available	Biological: Ad26.COV2.S|Biological: BNT162b2|Biological: mRNA-1273|Biological: mRNA-1273.211	Magnitude of SARS-CoV-2 specific antibody binding and neutralization titers|Occurrence of adverse events (AEs)|Occurrence of Adverse Events of Special Interest (AESIs).|Occurrence of New-Onset Chronic Medical Condition (NOCMCs).|Occurrence of Related Medically attended adverse events (MAAEs).|Occurrence of Serious Adverse Events (SAEs).|Occurrence of solicited reactogenicity adverse events (AEs)|Response rate of SARS-CoV-2 specific antibody binding and neutralization titers	National Institute of Allergy and Infectious Diseases (NIAID)	https://ClinicalTrials.gov/show/NCT04889209
NCT04833101	Study on Heterologous Prime-boost of Recombinant COVID-19 Vaccine (Ad5 Vector) and RBD-based Protein Subunit Vaccine	Active, not recruiting	No Results Available	Biological: recombinant Ad5 vectored COVID-19 vaccine|Biological: RBD-based protein subunit vaccine (ZF2001) against COVID-19|Biological: trivalent split influenza vaccine	Incidence of solicited adverse events within 7 days after vaccination.|GMT of neutralizing antibodies against live SARS-CoV-2 virus at Day 14 after the booster vaccination.|Incidence of adverse reactions within 28 days after vaccination.|Incidence of adverse events within 28 days after vaccination.|Incidence of unsolicited AE within 28 days after vaccination.|Incidence of serious adverse events(SAE) from the first dose to the 6 months after completing the last dose of vaccination.|GMT of binding antibodies against SARS-CoV-2 S and RBD protein measured by ELISA at day 14, day 28 after the second vaccination, and day 14, month 6 after the third vaccination.|Proportion of the participants with at least a four-fold increase of the binding antibodies against SARS-CoV-2 S and RBD protein at day 14, day 28 after the second vaccination, and day 14, month 6 after the third vaccination.|Fold increase of binding antibodies against SARS-CoV-2 S and RBD protein at day 14, day 28 after the second vaccination, and day 14, month 6 after the third vaccination.|GMT of neutralizing antibodies against live SARS-CoV-2 virus at day 28 after the second vaccination, and day 14, month 6 after the third vaccination|Proportion of the participants with at least a four-fold increase of neutralizing antibodies against live SARS-CoV-2 virus at day 14, day 28 after the second vaccination, and day 14, month 6 after the	Jiangsu Province Centers for Disease Control and Prevention	https://ClinicalTrials.gov/show/NCT04833101

					third vaccination.|Fold increase of neutralizing antibodies against live SARS-CoV-2 virus at day 14, day 28 after the second vaccination and day 14, month 6 after the third vaccination.		
NCT05043259	Heterologous Prime-boost Immunization With an Aerosolised Adenovirus Type-5 Vector-based COVID-19 Vaccine (Ad5-nCoV) After Priming With an Inactivated SARS-CoV-2 Vaccine	Recruiting	No Results Available	Biological: inactive SARS-CoV-2 vaccine (Vero cell)|Biological: Low dose aerosolized Ad5-nCoV|Biological: High dose aerosolized Ad5-nCoV	Incidence of adverse reactions within 14 days after the booster dose.|GMT of neutralizing antibodies against live SARS-CoV-2 virus on day 14 after the booster dose.|Incidence of adverse events within 0-28 days after the booster dose.|Incidence of serious adverse events (SAE) till the 12 months after the booster dose.|GMT of neutralizing antibodies against live SARS-CoV-2 virus on day 7 and 28 after the booster dose.|Fold increase and seroconversion of neutralizing antibodies against live SARS-CoV-2 virus on day 14 after the booster vaccination.|GMT, fold increase and seroconversion of neutralizing antibodies against live SARS-CoV-2 virus at month 3, 6, and 12 after the booster dose.|GMT, fold increase and seroconversion of binding antibodies against SARS-CoV-2 RBD on day 7, day 14, day 28 after the booster dose.|GMT, fold increase and seroconversion of binding antibodies against SARS-CoV-2 RBD at month 3, 6, and 12 after the booster dose.|The levels of IFN- Î³â€• IL-2 and IL-13 secreted by specific T cells on day 7 and 14 after the booster vaccination.	Jiangsu Province Centers for Disease Control and Prevention	https://ClinicalTrials.gov/show/NCT05043259
NCT05054621	Immunogenicity of COVID-19 Vaccine on Heterologous Schedule	Not yet recruiting	No Results Available	Biological: Heterologous prime-boost schedule with AZD1222 and MVC-COV1901|Biological: Homologous prime-boost schedule with two doses of AZD1222	Immunogenicity: Neutralizing antibody against SARS-CoV-2|Immunogenicityï¼šAnti-SARS-CoV-2 Spike antibody|Adverse events|Immunogenicity: Anti-SARS-CoV-2 Nucleocapsid antibody|Immunogenicity: T cell immunity	Chang Gung Memorial Hospital	https://ClinicalTrials.gov/show/NCT05054621
NCT04998240	Mix and Match Heterologous Prime-Boost Study Using Approved COVID-19 Vaccines in Mozambique	Not yet recruiting	No Results Available	Biological: BBIBP-CorV - Inactivated SARS-CoV-2 vaccine (Vero cell)|Biological: AZD1222 (replication-deficient Ad type 5 vector expressing full-length spike protein)	Geometric Mean Titers (GMTs) of anti-SARS-CoV-2 neutralizing antibodies|Incidence of SAEs and AESI observed at any time point during the entire study period|Incidence of solicited reactions within 7 days (local reactions) and 14 days (systemic reactions)|Incidence of unsolicited adverse events that are within 28 days after each vaccination|Incidence of changes in laboratory safety measures from baseline to day 28 after each vaccination|Geometric Mean Titers (GMTs) and Geometric Mean Fold Rise (GMFR)	International Vaccine Institute|The Coalition for Epidemic Preparedness Innovations (CEPI)|Instituto Nacional de SaÃºde (INS), Mozambique|University of Antananarivo|International Centre for Diarrhoeal Disease Research, Bangladesh|Harvard University|Heidelberg University	https://ClinicalTrials.gov/show/NCT04998240

NCT04760730	Safety and Immunogenicity Study in Adults of AZD1222 and rAd26-S Administered as Heterologous Prime Boost Regimen for the Prevention of Coronavirus Disease 2019 (COVID-19)	Not yet recruiting	No Results Available	Biological: AZD1222|Biological: rAd26-S	Antibody seroconversion rate (â‰¥ 4 fold increase from baseline) against SARS-CoV-2 Spike protein 29 days post second vaccination|Incidence of local and systemic solicited Adverse Events (AEs) for 7 days following each vaccination (Day 1 through Day 7 for first vaccination and Day 29 through Day 35 for second vaccination)|Incidence of unsolicited AEs, Serious Adverse Events (SAEs) and Adverse Events of Special Interest (AESIs) through 29 days post each vaccination|Incidence of SAEs and AESIs after first vaccination until study end (Day 180)|Antibody seroconversion rate (â‰¥ 4 fold increase from baseline) against SARS-CoV-2 Spike protein 29 days post first vaccination|Antibody seroconversion rate (â‰¥ 4 fold increase from baseline) against Receptor Binding Domain (RBD) antigen|Geometric Mean Titre (GMT) and Geometric Mean Fold Rise (GMFR) of immunogenicity against Spike and RBD antigens at the day of vaccination (baseline), Day 15, 29 days post each vaccination and at study end (Day 180).|Antibody seroconversion rate (â‰¥ 4 fold increase from baseline) SARS-CoV-2 neutralising antibodies|GMT and GMFR of immunogenicity as measured by SARS-CoV-2 neutralising antibodies at day of vaccination (baseline), Day 15, 29 days post each vaccination and at study end (Day 180)	R-Pharm|AstraZeneca	https://ClinicalTrials.gov/show/NCT04760730
NCT05048940	Efficacy, Safety, and Immunogenicity of Vaccine Reimmunization With a Third Homologous Versus Heterologous Dose Against SARS-CoV-2 in Patients Undergoing Solid Organ Transplantation.	Not yet recruiting	No Results Available	Biological: Janssen vaccine|Biological: Spikevax (Moderna) vaccine	Changes in the production of anti-S1-RBD IgG antibodies.|Change in the presence of activated T cells specific for SARS-CoV-2 (Sprotein).|Changes in the phenotype of effector/memory/virgin B and T cell populations and subtypes of Th and NK cell populations.|Incidence of symptomatic/asymptomatic COVID infection after revaccination.|Number of patients with hospital admissions and/or visits to the emergency department for severe symptoms related to COVID-19 infection.	Instituto de InvestigaciÃ³n MarquÃ©s de Valdecilla	https://ClinicalTrials.gov/show/NCT05048940
NCT04684446	Study in Adults of AZD1222 and rAd26-S Administered as Heterologous Prime-Boost Regimen for the	Recruiting	No Results Available	Biological: AZD1222|Biological: rAd26-S	Antibody seroconversion rate (â‰¥ 4-fold increase from baseline) against SARS-CoV-2 neutralising antibodies 29 days post second vaccination.|Incidence of local and systemic solicited AEs for 7 days following each vaccination (Day 1 through Day 7 for first vaccination and Day 29 through Day 35 for second vaccination).|Incidence of unsolicited AEs, SAEs and	R-Pharm|AstraZeneca|Russian Direct Investment Fund|The Gamaleya National Center of Epidemiology & Microbiology	https://ClinicalTrials.gov/show/NCT04684446

	Prevention of COVID-19				AESIs through 29 days post each vaccination (ie, until Day 29 following the first vaccination and Day 57 following the second vaccination).|Incidence of SAEs and AESIs after first vaccination until study end (Day 180).|Antibody seroconversion rate (â‰¥ 4-fold increase from baseline) against SARS-CoV-2 Spike protein|Antibody seroconversion rate (â‰¥ 4-fold increase from baseline) against RBD antigen.|GMT and GMFR of immunogenicity against Spike and RBD antigens (MSD serology assay) at the day of vaccination (baseline), Day 15, 29 days post each vaccination and at study end (Day 180).|Antibody seroconversion rate (â‰¥ 4-fold increase from baseline) SARS-CoV-2 neutralising antibodies 29 days post first vaccination|GMT and GMFR of immunogenicity as measured by SARS-CoV-2 neutralising antibodies at day of vaccination (baseline), Day 15, 29 days post each vaccination and at study end (Day 180).|Intracellular cytokine staining, including quantification of Th1/Th2 responses, and flow cytometry for B- and T-cell responses from day of dosing baseline to 29 days post each vaccination and until study end|A binary response, whereby a participant is defined as a COVID-19 case if their illness (virologically confirmed [RT-PCR positive] and symptomatic) occurs		
NCT04907331	Heterologous SARS-CoV-2 Vaccination With ChAdOx-1 and BNT162b2	Recruiting	No Results Available	Biological: Vaxzevria|Biological: Comirnaty	Neutralizing antibodies|T cells|vaccine failures	Medical University Innsbruck|Medical University of Graz|Medical University of Vienna	https://ClinicalTrials.gov/show/NCT04907331
NCT05027672	Strategies for Combining the First Component of Sputnik V With Other Adenoviral or mRNA-based Vaccines.	Active, not recruiting	No Results Available	Drug: Gam-COVID-Vac (rAd26) / Gam-COVID-Vac (rAd5)	ELISA assessment of concentration of IgG anti Spike (UI/ml) at 28 days.|Serious adverse events Adverse events of special interest|Neutralising antibodies against SARS-CoV-2	Ministerio de Salud de Ciudad AutÃ³noma de Buenos Aires	https://ClinicalTrials.gov/show/NCT05027672
NCT04569383	Safety and Immunogenicity of the Candidate Vaccine MVA-SARS-2-S and a Booster Vaccination	Active, not recruiting	No Results Available	Biological: MVA-SARS-2-S vaccinations (days 0 & 28)|Biological: Comirnaty	Percentage of Participants Experiencing Solicited Local or Systemic Reactogenicity as Defined by the Study Protocol|Immunogenicity. Number of participants who seroconverted	UniversitÃ¤tsklinikum Hamburg-Eppendorf|German Center for Infection Research|Philipps University Marburg Medical Center|Ludwig-	https://ClinicalTrials.gov/show/NCT04569383

	With a Licensed Vaccine Against COVID-19					Maximilians - University of Munich	
NCT04993560	Safety and Efficacy of COVID-19 Prime-boost Vaccine in Bahrain	Recruiting	No Results Available	Biological: BBIBP-CorV|Biological: BNT162b2	Change from Baseline Immunogenicity at 8 weeks|Reactogenicity	Royal College of Surgeons in Ireland - Medical University of Bahrain|The National Taskforce for Combatting COVID-19- Kingdom of Bahrain|Bahrain Defence Force Royal Medical Services|Ministry of Health, Bahrain|Bahrain International Exhibition & Convention Centre	https://ClinicalTrials.gov/show/NCT04993560
NCT04776317	Chimpanzee Adenovirus and Self-Amplifying mRNA Prime-Boost Prophylactic Vaccines Against SARS-CoV-2 in Healthy Adults	Recruiting	No Results Available	Biological: ChAdV68-S|Biological: ChAdV68-S-TCE|Biological: SAM-LNP-S|Biological: SAM-LNP-S-TCE|Other: Sodium Chloride, 0.9%	Occurrence of Adverse Events of Special Interest (AESIs)|Occurrence of clinical safety laboratory adverse events by severity grade|Occurrence of Serious Adverse Events (SAEs)|Occurrence of solicited local reactogenicity adverse events (AEs)|Occurrence of solicited systemic reactogenicity adverse events (AEs)|Occurrence of unsolicited adverse events (AEs)|Geometric mean fold rise from baseline in titer measured by a SARS-CoV-2 neutralization assay|Geometric mean fold rise from baseline in titer of receptor-binding domain (RBD) specific Immunoglobulin G (IgG)|Geometric mean fold rise from baseline in titer of Spike-specific Immunoglobulin G (IgG)|Geometric mean titer measured by a SARS-CoV-2 neutralization assay|Geometric mean titer of receptor-binding domain (RBD) specific Immunoglobulin G (IgG)|Geometric mean titer of Spike-specific Immunoglobulin G (IgG)|Percent of cells expressing a cytokine by cell type (CD4+ or CD8+), cytokine set (Th1 or Th2 cytokine for CD4+ and CD8+ cytokine for CD8+ or other combinations of interest) and peptide pool (covering spike and T cell epitope regions)|Percentage of subjects who seroconverted for RBD from wild-type virus and emergent viral strains|Percentage of subjects who seroconverted for spike protein from wild-type virus and emergent viral strains|Percentage of subjects who seroconverted for wild-type virus and emergent viral strains|Rate of spot-forming cell per million cells by peptide pool|Responder status, derived from the intracellular cytokine staining (ICS) cell counts for each set of applicable cytokines and	National Institute of Allergy and Infectious Diseases (NIAID)|Gritstone Oncology, Inc.	https://ClinicalTrials.gov/show/NCT04776317

					each peptide pool|Responder status, determined by interferon (IFN) gamma Enzyme Linked Immunospot Assay (ELISpot) for each peptide pool|Th1/Th2 cytokine balance of T cell response		
NCT04927936	A Trial Among HealthCare Workers (HCW) Vaccinated With Janssen Vaccine: the SWITCH Trial	Recruiting	No Results Available	Biological: Vaccination once with Janssen vaccine (only priming)|Biological: Vaccination with Janssen vaccine followed with Janssen vaccine (homologous boosting).|Biological: Vaccination with Janssen vaccine followed with Moderna vaccine (heterologous boosting).|Biological: Vaccination with Janssen vaccine followed with Pfizer vaccine (heterologous boosting).	Determination of antibodies by a quantitative IgG assay (LIAISON SARS-CoV-2 TrimericS IgG essay) 28 days after booster	Erasmus Medical Center|Leiden University Medical Center|University Medical Center Groningen|Academisch Medisch Centrum - Universiteit van Amsterdam (AMC-UvA)	https://ClinicalTrials.gov/show/NCT04927936
NCT04860739	Vaccination With COMIRNATY in Subjects With a VAXZEVRIA First Dose	Active, not recruiting	No Results Available	Drug: COMIRNATY	To assess the humoral immune response against SARS-CoV-2, 14 days after a vaccination with COMIRNATY in subjects that received a previous single dose of VAXZEVRIA, as compared with no dosing.|To assess the humoral immune response against SARS-CoV-2, 28 days after a vaccination with COMIRNATY in subjects that received a previous single dose of VAXZEVRIA (antibodies)|To assess the humoral immune response against SARS-CoV-2, 28 days after a vaccination with COMIRNATY in subjects that received a previous single dose of VAXZEVRIA (Virus neutralization)|To assess the occurrence of symptomatic molecularly confirmed COVID-19 and severity of COVID-19 signs and symptoms after the administration of a dose of COMIRNATY in subjects that received a prior single dose of VAXZEVRIA|To evaluate the safety of a dose of COMIRNATY in subjects that received a previous single dose of VAXZEVRIA (solicited adverse events)|To evaluate the safety of a dose of COMIRNATY in subjects that received a previous single dose of VAXZEVRIA (unsolicited adverse events)|To evaluate the safety of a dose of COMIRNATY in subjects that received a previous single dose of VAXZEVRIA (serious adverse events)|To evaluate the safety of a dose of COMIRNATY in subjects that	Spanish Clinical Research Network - SCReN|Instituto de Salud Carlos III	https://ClinicalTrials.gov/show/NCT04860739

					received a previous single dose of VAXZEVRIA (Medically-attended adverse events)|To assess the humoral immune response against viral variants of SARS-CoV-2, 14 and 28 days after a dose of COMIRNATY in subjects that received a previous single dose of VAXZEVRIA		
NCT04952727	Study on Sequential Immunization of Inactivated COVID-19 Vaccine and Recombinant COVID-19 Vaccine (Ad5 Vector) in Elderly Adults	Recruiting	No Results Available	Biological: Recombinant SARS-CoV-2 Ad5 vectored vaccine|Biological: Inactive SARS-CoV-2 vaccine (Vero cell)	Incidence of adverse reactions within 28 days after the booster dose.|GMT of neutralizing antibodies against live SARS-CoV-2 virus on day 14 after the booster dose.|Incidence of solicited AE within 14 days after the booster dose|Incidence of unsolicited AE within 28 days after the booster dose.|Incidence of serious adverse events (SAE) till the 6 months after the booster dose.|GMT of binding antibodies against SARS-CoV-2 S and N protein on day 14, day 28 and month 6 after the booster dose.|GMT of neutralizing antibodies against live SARS-CoV-2 virus on day 28 and month 6 after the booster dose.|Fold increase of binding antibodies against SARS-CoV-2 S and N protein on day 14, day 28 and month 6 after the booster vaccination.|Fold increase of neutralizing antibodies against live SARS-CoV-2 virus on day 14, day 28 and month 6 after the booster vaccination.|Proportion of the participants with at least a four-fold increase of the binding antibodies against SARS-CoV-2 S and N protein on day 14, day 28 and month 6 after the booster vaccination.|Proportion of the participants with at least a four-fold increase of neutralizing antibodies against live SARS-CoV-2virus on day 14, day 28 and month 6 after the booster vaccination.|Specific T cell responses on day 14 after the booster vaccination.	Jiangsu Province Centers for Disease Control and Prevention|CanSino Biologics Inc.	https://ClinicalTrials.gov/show/NCT04952727
NCT04892459	Study on Sequential Immunization of Inactivated SARS-CoV-2 Vaccine and Recombinant SARS-CoV-2 Vaccine (Ad5 Vector)	Active, not recruiting	No Results Available	Biological: Recombinant SARS-CoV-2 Ad5 vectored vaccine|Biological: Inactive SARS-CoV-2 vaccine (Vero cell)	Incidence of adverse reactions within 28 days after the booster dose.|GMT of neutralizing antibodies against live SARS-CoV-2 virus on day 14 after the booster dose.|Incidence of solicited AE within 14 days after the booster dose|Incidence of unsolicited AE within 28 days after the booster dose.|Incidence of serious adverse events (SAE) till the 6 months after the booster dose.|GMT of binding antibodies against SARS-CoV-2 S and N protein on day 14, day 28 and month 6 after the booster dose.|GMT of neutralizing antibodies against live SARS-CoV-2 virus on day 28 and month 6 after the booster dose.|Fold increase of binding antibodies against SARS-CoV-2 S and N protein on day 14, day 28 and month 6 after the booster vaccination.|Fold increase of neutralizing antibodies against live SARS-CoV-2 virus on day 14, day 28 and month 6 after the booster vaccination.|Proportion of the participants with at least a	Jiangsu Province Centers for Disease Control and Prevention|CanSino Biologics Inc.	https://ClinicalTrials.gov/show/NCT04892459

					four-fold increase of the binding antibodies against SARS-CoV-2 S and N protein on day 14, day 28 and month 6 after the booster vaccination.|Proportion of the participants with at least a four-fold increase of neutralizing antibodies against live SARS-CoV-2 virus on day 14, day 28 and month 6 after the booster vaccination.|Specific T cell responses on day 14 after the booster vaccination.		
NCT04894435	Mix and Match of the Second COVID-19 Vaccine Dose for Safety and Immunogenicity	Recruiting	No Results Available	Biological: mRNA-1273 SARS-CoV-2 vaccine|Biological: BNT162b2|Biological: ChAdOx1-S [recombinant]|Other: 0, 28 day schedule|Other: 0, 112 day schedule	Antibody response to SARS-CoV-2 S protein|Durability of antibody response to SARS-CoV-2 S over 12 months|Pseudoneutralization assay, T cell testing, Antibody dependent cellular cytotoxicity (ADCC), Antibody avidity, RNA seq|Incidence of grade 3 solicited local and systemic adverse events, SAEs, AEFIs, MAAEs, AESIs in the 7 days following vaccine receipt.|Acceptability of vaccines as determined by participant-completed questionnaire.	Canadian Immunization Research Network|Canadian Center for Vaccinology|BC Children's Hospital Research Institute|Children's Hospital Research Institute of Manitoba|CHU de Quebec-Universite Laval|Ottawa Hospital Research Institute|Ontario Agency for Health Protection and Promotion|University of Toronto|Massachusetts General Hospital|Interior Health	https://ClinicalTrials.gov/show/NCT04894435

Q9. Are COVID-19 vaccines efficacious in preventing COVID-19 infections caused by the B.1.617.2 (Delta) Variant?

As of 28 October 2021

RECOMMENDATIONS

In areas where the Delta variant is the predominant circulating variant, we recommend for the use of the following vaccine to prevent symptomatic and severe COVID-19:

a. 2 doses of BBV152 (Covaxin/Bharat)
   (Moderate certainty of evidence; Strong recommendation)
b. 2 doses of BNT162b2 (Pfizer)
   (Low certainty of evidence; Strong recommendation)
c. 2 doses of mRNA-1273 (Moderna)
   (Low certainty of evidence; Strong recommendation)
d. 2 doses of ChAdOx1 (Astra Zeneca)
   (Low certainty of evidence; Strong recommendation)
e. 2 doses of CoronaVac (Sinovac)
   (Very low certainty of evidence; Strong recommendation)

In areas where the Delta variant is the predominant circulating variant, we suggest the use of the following vaccines to prevent symptomatic and severe COVID-19:

a. Ad26.CoV2 (Janssen)
   (Low certainty of evidence; Weak recommendation)
b. Gam-COVID-Vac (Sputnik V)
   (Low certainty of evidence; Weak recommendation

Consensus Issues

The panel agreed that all vaccines may be used in for protection against the infections caused by the Delta variant, despite some reduction in vaccine effectiveness. The panel's decisions on the strength of recommendation were based mainly on the certainty of evidence supporting the effectiveness. Vaccines with clinical evidence of effectiveness were given strong recommendations for use, whereas vaccines with only immunologic evidence of effectiveness were given weak recommendations.

INTRODUCTION

Earliest detection of the B.1.617.2 (Delta) variant was in October 2020 in India. As of writing, the Delta variant has already caused COVID-19 surges in several countries including the US, India, and Indonesia. It is the fourth variant of concern (VOC) identified by the WHO.[1] The Delta variant is characterized by the spike protein mutations T19R, Δ157-158, L452R, T478K, D614G, P681R, and D950N.1. Current literature suggests that the Delta variant may have increased transmission and replication.[2] As with previous VOC's, there are concerns surrounding the ability of available vaccines to protect against infection with the Delta variant. Findings on the ability of vaccines to protect against COVID-19 caused by the Delta variant will have implications on vaccine procurement, distribution, and administration policies.

REVIEW METHODS

Two types of studies on vaccine protection against the Delta variant were considered for this review. First were studies that provided clinical outcomes of efficacy or effectiveness. These included randomized controlled trials on COVID-19 vaccination efficacy or cohort studies comparing infection rates among vaccinated and unvaccinated populations that were conducted during a period where the Delta strain was known to be the prevalent strain or where genomic sequencing of the cases were confirmed as caused by the Delta variant. Test negative case control studies were also included. The second type of studies considered were immunologic studies wherein the capacity of sera from vaccinated persons to neutralize B.1.617.2 and a reference strain was compared. Both antibody and T-cell responses were considered.

In the overall assessment of vaccine performance, this review utilized the rating system by the WHO in its epidemiological update reports. In terms of vaccine efficacy/effectiveness, <10% decline in VE values (compared to non-Delta) or VE of at least 90% is assessed as no significant change (symbolized by ↔); a 10-20% decline is symbolized by ↓ and >20% decline is symbolized by ↓↓. In terms of reduction in immunologic response, less than 2-fold reduction is symbolized by ↔, a 2 to <5-fold reduction by ↓ and a 5 to <10-fold reduction by ↓↓.

No pooling of results was planned for this review.

Search Results

As of October 5, 2021, 28 studies were included in the review. Three (3) studies reported on both clinical and immunologic outcomes,[3,4,5] 11 studies reported only clinical outcomes [2,6-15] and 13 studies were immunogenicity studies.[16-28] One systematic review was included.[29]

Of the studies reporting clinical outcomes, only one (1) was a randomized controlled trial [12] and the rest were observational studies. Most of the observational studies were of the test negative case control design and three (3) were retrospective cohort studies.

Six (6) vaccines were investigated, with six (6) studies reporting results of more than one vaccine: BNT162b2 (7 studies), mRNA-1273 (3 studies), ChAdOx1 (9 studies), Ad26.CoV2.S (2 studies), CoronaVac (4 studies), BBV152 (1 study) and Gam-COVID-Vac (1 study). One (1) study reported the results of mRNA-type vaccines without providing separate results for BNT162b2 and mRNA-1273.

The search failed to identify studies that reported on the performance of NVX-CoV2373 or BBIBP-CorV on the Delta variant.

The characteristics of the included studies are presented in Appendix 2.

Risk of Bias Assessment

Only the studies reporting clinical outcomes were assessed for risk of bias. The lone RCT was assessed as low risk of bias with only the domains of complete follow-up and selective reporting assessed as uncertain.[12] The rest of the studies, being observational, were assessed to be at high risk of bias providing low certainty

evidence. Two (2) studies controlled for all three confounders [2,6] and another two (2) studies controlled for two confounders.[5,7]

Appendix 3 details the risk of bias assessment for the clinical studies.

RESULTS

mRNA Vaccines (mRNA-1273 and BNT162b2)

The mRNA vaccines will be discussed together in this review because most of the studies included both types of mRNA vaccines in their investigation. Both studies on measurement of neutralization ability from sera and vaccine effectiveness were available for review. A total of eleven studies (11) were included in this review.

A systematic review by Noori, et al., included five (5) immunologic studies investigating the neutralization of vaccinated sera by mRNA vaccines against the Delta variant. All the studies included in the systematic review were already included in the search of this review and detailed in the succeeding paragraphs.[29]

Studies measuring antibody reactivity of sera from mRNA vaccinees against the Delta variant show reduced levels (minimal to mild reductions) when compared to the reference strains. For example, in a study by Edara, et al., the GMT among the mRNA-1237 samples (n = 15, 35 to 51 days after second dose) against the Delta variant was 350 (95% CI 229-535) compared with 1062 (95% CI 773-1460) against WA1/2020. The GMT of BNT162b2 (n = 10, 7 to 27 days after second dose) against the Delta variant was 235 (95% CI 164-338), as compared with 776 (95% CI 571-1056) against WA1/2020. The Delta variant was also shown to be 2.9x less susceptible to neutralization (compared to neutralization of WA1/2020) by sera from mRNA vaccine recipients and recovered patients. However, the study pointed out that all samples from vaccinated participants have detectable neutralizing activity.[19] Likewise, the study by Choi, et al., noted that sera from fully vaccinated recipients of mRNA-1273 resulted in 2.1-fold to 8.4-fold reduced neutralization against VOCs (including the Delta variant) but all remained susceptible to mRNA-1273-elicited neutralization.[21] One study investigated neutralization ability of sera from vaccinated individuals with mRNA-1273 at 209 days after administration.[22] At 2 weeks after the second dose, all antibody reactivity of sera across age groups neutralized all pseudoviruses; however, this ability was noted to wane over time. At day 209 (6 months), all sera neutralized D614G and B.1.429 variants. However, using a pseudovirus assay, only 96% of sera were able to neutralize the Delta variant. There was a trend towards lower titers against SARS-CoV-2 spike variants in the oldest individuals at day 209. However, the authors concluded that although mRNA-1273-elicited antibody activity against variants decreased (compared to WA1 and D614G), they persisted at 6 months after the second dose.

Studies on vaccine effectiveness of mRNA vaccines against the Delta variant were also reviewed. Compared to the VEs found in the clinical trials, four (4) studies demonstrated that protection provided by the mRNA vaccines is maintained with only minimal reductions in the VEs (<20% difference). Data from one study demonstrated that protection against severe disease did not change.

The study by Lopez Bernal also investigated how BNT162b2 vaccines protected against the Delta variant. The calculated vaccine effectiveness of BNT162b2 against

symptomatic disease from the Delta variant is 88% (95% CI 85.3-90.1) after completion of 2 doses of the vaccine. The authors concluded that there were only modest differences in vaccine effectiveness with the Delta variant as compared to the Alpha variant.[2] Nasreen, et al., also concluded that full vaccination with BNT162b2 increased protection against the Delta variant to levels comparable to the Alpha and Beta/Gamma variants. Their study showed that the calculated vaccine effectiveness of BNT162b2 (at least 7 days after second dose) against symptomatic disease was 87% for the Delta variant. Effectiveness against severe outcomes for those fully vaccinated (with BNT162b2, mRNA-1273, and ChAdOx1) could not be reliably elicited for the Delta variant due to low numbers or absence of fully vaccinated test positive cases.[6] Test negative case control studies by Buxvoort, et al., and Tang, et al., showed a 97.6% (95% CI 92.8-99.2) and 100% efficacy against severe infection for the mRNA-1273 vaccine.[9,10]

ChAdOx1 (Astra Zeneca)

Ten (10) studies investigated protection by ChAdOx1 (AstraZeneca and Covishield) against the Delta variant. Five (5) studies assessed vaccine effectiveness through mostly test-negative case control design studies, while the other five (5) studies assessed the neutralization ability of vaccinated sera against the Delta variant.

The study by Davis, et al., measured neutralizing antibody titers from sera in recipients of BNT162b2 and ChAdOx1. A total of 18 participants in this study received two doses of AstraZeneca. Results showed that the sera from these recipients showed 1.48-fold lower neutralization ability versus the Delta variant as compared to that of the Wuhan-Hu-1 strain. The study also noted that sera from recipients of 2 doses of the BNT162b2 vaccine showed higher neutralizing ability compared to that of ChAdOx1. However, the authors noted that those vaccinated with ChAdOx1 were among older age groups than those vaccinated with BNT162b2.[16] Other studies that measured antibody response or neutralization ability showed reduced antibody titers in sera vaccinated with ChAdOx1 as compared to the antibody response to earlier variants, particularly the Alpha and wild type virus. Data from Sapkal et. al., showed that 16.1% of sera (5/31) from recipients of ChAdOx1 vaccine (4 weeks after second dose) were negative for neutralizing antibody titers against the Delta variant. This percentage increased to 58.1% in participants who only received 1 dose of the vaccine. Furthermore, neutralizing antibody titers of patients against B.1.617.2 relative to B.1 were also noted to be decreased to 69% in those who received 2 doses of the vaccine.[23]

Several studies investigating vaccine effectiveness against the Delta variant were also found. A study by Lopez Bernal et al., calculated the vaccine effectiveness of 2 doses of ChAdOx1 for symptomatic disease at 74.5% for the Alpha variant (95% CI 68.4-79.4) and 67% against the Delta variant (95% CI 61.3-71.8). The authors concluded that there are only modest differences in vaccines effectiveness noted with the Delta variant as compared to the Alpha variant.[2] Another study conducted in Canada among 421,073 individuals (40,828 of which were positive for variants of concern, with more than 14,000 hospitalizations or deaths) showed that ChAdOx1 was 67% effective at preventing symptomatic disease at least 14 days after one dose. This was comparable to effectiveness against the Alpha variant after partial vaccination (64%). However, the effectiveness of ChAdOx1 could not be estimated for those already fully vaccinated since there were no individuals who were fully vaccinated with this vaccine that presented with Delta symptomatic disease. Against severe outcomes, partial

vaccination with ChAdOx1 had a vaccine effectiveness of 88% (95% CI 60-96) and again couldn't be estimated for full vaccination because of very low numbers or absence of vaccinated test positive cases.[6] Another study in India involving 2,766 confirmed COVID-19 cases calculated vaccine effectiveness at 63.1% against symptomatic disease by the Delta variant, and a VE of 81.5% against moderate to severe disease.[4]

Despite findings from studies measuring neutralizing antibodies from sera of ChAdOx1 vaccinees showing reduced titers against Delta as compared with other variants, vaccine effectiveness studies still show that ChAdOx1 protects against symptomatic disease from the Delta variant, with the authors concluding only modest differences compared to previous variants.

Ad26.CoV2 (Janssen)
Two (2) studies specifically on Janssen vaccines are included in the review. The study by Jongeleen, et al., used sera from 8 participants 47 to 91 years old. Sera was collected 71 days after receiving the single-dose vaccine. Using a recombinant lentivirus-based pseudotyped virus neutralization assay, they determined antibody neutralization of the Delta variant compared to the Wuhan-Hu-1 strain. Results showed a 1.6-fold reduction in neutralization against Delta (3.6-fold reduction against Beta and 3.4-fold reduction against Gamma). The authors noted that the geometric mean neutralization titers (GMT) were observed to be decreased against all variants.[24]

Another study involving 60 Ad26.COV2.s vaccine recipients showed that the degree of antibody response to the variants of concern depended on the history of previous infection. It demonstrated reduction in the neutralizing antibody titers against the Delta variant compared to the ancestral strain (D614G), from 2.6- to 6.3-fold, with greater reductions in those previously infected during the Beta-predominant wave.[27]

CoronaVac (Sinovac)
Four (4) studies investigating CoronaVac protection against the Delta variant were found during the search. Two (2) studies were immunologic studies, while the other two (2) provided clinical outcomes.

The study by Jie Hu et al., included sera from 20 individuals who had received their second CoronaVac dose 7 to 14 days prior. In this study, 19 out of the 20 sera had substantial serum neutralizing activity against D614G spiked pseudotyped viruses. Compared with activity against D614G, 65% (13/20) of sera from the CoronaVac recipients was decreased below the threshold of serum neutralizing ability for the B.1.617 variant. The average neutralization potency of CoronaVac recipients was also decreased 2.5-fold (GMT 36) as compared to D614G (GMT 89).[25] Another immunologic study conducted in Thailand by Vacharathit et al., investigated the effect of SARS-CoV-2 variants of concerns to vaccine and infection-induced antibodies.[26] In this study, sera from 60 vaccinated (2 doses of CoronaVac) healthcare workers were used. Neutralizing antibodies against the wild type, Alpha, Beta, and Delta variants were measured. The study found out that relatively low neutralizing antibody titers were elicited by CoronaVac compared to natural infection. Results also showed that quantifiable antibody titers against Delta were present in only 69.17% of vaccinated sera as compared to 99.17% against the wild type. Furthermore, only

48.33% of vaccinated participants had neutralizing antibody titers of at least 20 (the cutoff for neutralizing antibody positivity) against the Delta variant, as compared to 98.33% against the wild type. It was noted in the study that natural infection consistently produced a greater percentage of antibody positivity as compared to CoronaVac recipients across all the tested variants. The authors stated that despite a robust S1-RBD-binding IgG and 100% seropositivity sera from CoronaVac and previously infected recipients, they had significantly reduced neutralizing capacities against all the three VOCs tested. The authors concluded that relatively low neutralizing antibody titers were elicited by CoronaVac compared to natural infection. They further recommended the use of booster doses, heterologous or otherwise, to maintain long-term anamnestic response.

Observational studies providing clinical effectiveness data were conducted in China. [13,14] Both studies showed no change in the vaccine effectiveness of CoronaVac against the Delta variant, although breaching the cutoff of 30% for the lower border of the 95% CI was noted in one study. The study by Li et al., which included participants 18 to 59 years old, showed 59% (95% CI 16-81.6) vaccine efficacy against mild COVID-19 infection from the Delta variant and 70.2% (95% CI 29.6-89.3) against moderate infection. No severe infection was noted among the vaccinees. The study by Kang et al., which involved close contacts of Delta variant cases in China, showed a 69.5% vaccine efficacy (95% CI 42.8-96.3) against pneumonia. No severe COVID-19 infection from the Delta variant was noted in the vaccinees.

BBV152 (Covaxin/Bharat)

The only RCT included in this review is the Phase 3 trial of the BBV152 (Covaxin/Bharat) COVID-19 vaccine. The trial, which involved more than 25,000 participants, had 50 cases of COVID-19 infection due to the Delta variant. The study calculated that the vaccine efficacy against Delta infection is 65.2% (95% CI 33.1-83.1) as compared to the overall vaccine efficacy of 77.8%.[12]

Gam-COVID-Vac (Sputnik V)

Only one (1) immunologic study investigating antibody neutralization of the Delta variant involving the Gam-COVID-Vac was found. Data from sera of 27 participants showed a 2.5-fold reduction of neutralizing antibody titers compared to the B.1.1.1.[28]

Appendix 4 presents the summary results on the clinical (4A) and immunologic outcomes (4B).

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Appendix 1. Evidence to Decision

Table 1. Summary of Initial Judgements Prior to Panel Discussion (N = 12)

FACTORS	JUDGEMENT						RESEARCH EVIDENCE/ADDITIONAL CONSIDERATIONS
Problem	No	Yes (12)					
Benefits	Large (5)	Moderate (7)	Small	Uncertain			• 4 studies demonstrated that protection provided by the mRNA vaccines is maintained with only minimal reductions in the VEs (<20% difference).
Harm	Large (2)	Small (3)	Uncertain (7)				• Studies measuring antibody reactivity of sera from mRNA vaccinees against the Delta variant show reduced levels (minimal to mild reductions) when compared to the reference strains
Certainty of evidence	High	Moderate (2)	Low (9)	Very low (1)			• Low to very low
Balance of effects	Favors vaccine (11)	Does not favor vaccine	Uncertain (1)				
Values	Important uncertainty or variability	Possibly important uncertainty or variability (10)	Possibly no important uncertainty or variability (2)	No important uncertainty or variability			
Resources required	Uncertain (3)	Large cost (4)	Moderate cost (5)	Negligible cost or savings	Moderate savings	Large savings	• Differs per vaccine combination used
Certainty of evidence of resources required	No included studies (4)	Very low (4)	Low (3)	Moderate (1)	High		• Differs per vaccine brand
Cost effectiveness	No included studies (9)	Favors the comparison (1)	Does not favor either the intervention or the comparison	Favors the intervention (2)			
Equity	Uncertain (3)	Reduced (2)	Probably no impact (1)	Increased (6)			• Varies per vaccine • Addresses wide disparity in vaccine coverage: 85.1% fully-vaccinated senior citizens in NCR; while only 28.3% in BARMM.
Acceptability	Uncertain	No	Yes (12)				• Vaccines mentioned have been approved for EUA by the Philippine FDA on varying dates.
Feasibility	Uncertain (1)	No	Yes (11)				• Varies per vaccine

Appendix 2. Characteristics of Included Studies

A. Clinical Studies

STUDY ID	STUDY SITE/PERIOD	STUDY DESIGN	STUDY POPULATION	INTERVENTION / EXPOSURE	CONTROL	FOLLOW-UP	OUTCOMES
BNT162b2 (Pfizer)							
Lopez Bernal 2021	England Infections from October 2020 to March 21 2021, extracted May 2021 (Immunologic testing from April 5, 2021 onwards)	Test-negative case control Case = PCR positive and with symptoms Control = with symptoms but PCR negative Vaccination status at time of infection defn: D1: symptom onset 21 days or more from D1 to day before D2 D2: symptom onset 14 days or more after D2 Covariates: age, sex, index of multiple deprivation, ethnicity, care home status, history of foreign travel, region, period, health and social care worker status, history of infection Logistic regression used	Persons >/=16 years old as of March 21, 2021 reporting symptoms and tested within 10 days of symptom onset vaccinated with either BNT or AZ N = 14,837 N sequenced = 12, 675 Delta = 1,054	Vaccinated			Vaccine effectiveness (at D1 and D2) (Table 2) Proportion of Delta in the vaccinated and unvaccinated cases (Odds of a Delta infection vs B.11.7 between vaccinated and unvaccinated)
Nasreen 2021	Canada Dec 14 2020 to May 30 2021 (April 2021 for Delta)	Test-negative case control Linked databases including centralized COVID-19 vaccine information system, laboratory information system and Public Health case and contact management system Covariates: age, sex, no. of tests (proxy for risk of exposure), comorbidities, influenza vaccination status, household income of neighborhood Multiple logistic regression	Community dwelling, >/= 16-year-old with symptoms or severe outcome attributable to COVID-19 tested for SARS-COv-2 N = 421,073 infections Cases / positive for non-VOC = 28,705 Cases / positive for VOC = 40,828 Delta = 991 - Symptomatic infection = 991 - Severe = 165	Measurement of Delta based on predicted probability (not direct genome sequencing) of those with N501-/E484K- Case = symptomatic and positive forSARS-Cov-2 in OLIS (Delta = 991) BNT D1: 50 BNT D2: <5 Mod D1: <5 Mod D2: <5	Control: RT-PCR negative for SARS-CoV-2 Symptomatic Severe N = 351,540 BNT D1: 34,747 BNT D2: 6,910 Mod D1: 7,806 Mod D2: 1,520 AZ D1: 5,916 AZ D2: 25		Vaccine effectiveness against symptomatic disease at least 7 days after 2nd dose (Table 3) VE for severe COVID (hospitalization and death) (Table 3) VE at >/=14 and at 21 days after first dose for partially vaccinated VE at >/= 7 and at 14 days for those fully vaccinated Subgroup: By vaccine By age By timing

				AZ D1: <5 AZ D2 :0 Severe case = hospitalized or dead with positive SARS-Cov-2, regardless of symptoms at time of testing) (Delta = 165)			
Sheikh 2021	Scotland April 1 to June 6, 2021	Test-negative case control S-gene positive considered Delta variant Adjustment made for age, temporal trend when the swabs done, no. of previous tests, sex, deprivation	EAVEII surveillance database All hospitalized patients 19,543 positives 377 hospitalized	BNT; AZ	Unvaccinated = 117,263		D1 0-27, D1 28+, D2 0-13, D2 14+ VE for COVID infection (positive test, regardless of symptoms) VE for symptomatic COVID infection (Appendix 4)
Stowe 2021	England April 12 – June 4, 2021	Test-negative case control Linked databases	Hospitalized patients within 14 days of a positive COVID test 14,019 symptomatic cases with Delta 166 hospitalized	BNT AZ	Unvaccinated		VE for hospitalization after D1 and D2
Mlcochova 2021	India	Cross-sectional Comparing proportion of Delta vs. non-Delta Confounders: age, sex, hospital Calendar time not used as a confounder because of short duration of the study Multivariable logistic regression	Healthcare workers who developed COVID-19 infection in April and May 2021	Delta infection	Non-Delta infection		Breakthrough infection rate CT values at diagnosis Proportion of Delta vs non-Delta infection (Odds ratio of testing positive with Delta vs non-Delta in vaccinated relative to unvaccinated)
mRNA-1273 (Moderna)							
Nasreen 2021	Canada Dec 14 2020 to May 30 2021 (April 2021 for Delta)	Test-negative case control Linked databases including centralized COVID-19 vaccine information system, laboratory information system and Public Health case and contact management system	Community dwelling, >/= 16-year-old with symptoms or severe outcome attributable to COVID-19 tested for SARS-COv-2 N = 421,073 infections	Measurement of Delta based on predicted probability (not direct genome sequencing) of those with N501-/E484K-	Control: RT-PCR negative for SARS-CoV-2 Symptomatic Severe N = 351,540		Vaccine effectiveness against symptomatic disease at least 7 days after 2nd dose (Table 3) VE for severe COVID (hospitalization and death) (Table 3)

		Covariates: age, sex, no. of tests (proxy for risk of exposure), comorbidities, influenza vaccination status, household income of neighborhood Multiple logistic regression	Cases / positive for non-VOC = 28, 705 Cases / positive for VOC = 40, 828 Delta = 991 - Symptomatic infection = 991 - Severe = 165	Case = symptomatic and positive forSARS-Cov-2 in OLIS (Delta = 991) BNT D1: 50 BNT D2: <5 Mod D1: <5 Mod D2: <5 AZ D1: <5 AZ D2 :0 Severe case = hospitalized or dead with positive SARS-Cov-2, regardless of symptoms at time of testing) (Delta = 165)	BNT D1: 34,747 BNT D2: 6,910 Mod D1: 7,806 Mod D2: 1,520 AZ D1: 5,916 AZ D2: 25		VE at >/=14 and at 21 days after first dose for partially vaccinated VE at >/= 7 and at 14 days for those fully vaccinated Subgroup: By vaccine By age By timing
ChAdOx1 (Astra Zeneca)							
Lopez Bernal 2021	England Infections from October 2020 to March 21 2021, extracted May 2021 (Immunologic testing from April 5, 2021 onwards)	Test-negative case control Case = PCR positive and with symptoms Control = with symptoms but PCR negative Vaccination status at time of infection defn : D1: symptom onset 21 days or more from D1 to day before D2 D2: symptom onset 14 days or more after D2 Covariates: age, sex, index of multiple deprivation, ethnicity, care home status, history of foreign travel, region, period, health and social care worker status, history of infection Logistic regression used	Persons >/=16 years old as of March 21, 2021 reporting symptoms and tested within 10 days of symptom onset vaccinated with either BNT or AZ N = 14, 837 N sequenced = 12, 675 Delta = 1,054	Vaccinated			Vaccine effectiveness (at D1 and D2) (Table 2) Proportion of Delta in the vaccinated and unvaccinated cases (Odds of a Delta infection vs B.11.7 between vaccinated and unvaccinated)
Nasreen 2021	Canada Dec 14 2020 to May 30 2021	Test-negative case control Linked databases including centralized COVID-19 vaccine information system, laboratory	Community dwelling, >/= 16-year-old with symptoms or severe outcome attributable to COVID-19 tested for SARS-COv-2	Measurement of Delta based on predicted probability (not direct genome	Control: RT-PCR negative for SARS-CoV-2 Symptomatic		Vaccine effectiveness against symptomatic disease at least 7 days after 2nd dose (table 3)

	(April 2021 for Delta)	information system and Public Health case and contact management system Covariates: age, sex, no. of tests (proxy for risk of exposure), comorbidities, influenza vaccination status, household income of neighborhood Multiple logistic regression	N = 421,073 infections Cases / positive for non-VOC = 28, 705 Cases / positive for VOC = 40, 828 Delta = 991 - Symptomatic infection = 991 - Severe = 165	sequencing) of those with N501-/E484K- Case = symptomatic and positive forSARS-Cov-2 in OLIS (Delta = 991) BNT D1: 50 BNT D2: <5 Mod D1: <5 Mod D2: <5 AZ D1: <5 AZ D2 :0 Severe case = hospitalized or dead with positive SARS-Cov-2, regardless of symptoms at time of testing) (Delta = 165)	Severe N = 351,540 BNT D1: 34,747 BNT D2: 6,910 Mod D1: 7,806 Mod D2: 1,520 AZ D1: 5,916 AZ D2: 25		VE for severe COVID (hospitalization and death) (Table 3) VE at >/=14 and at 21 days after first dose for partially vaccinated VE at >/= 7 and at 14 days for those fully vaccinated Subgroup: By vaccine By age By timing
Sheik 2021	Scotland April 1 to June 6, 2021	Test-negative case control S-gene positive considered Delta variant Adjustment for age, temporal trend when the swabs done, no. of previous tests, sex, deprivation by generalized additive logistic regression model	EAVEII surveillance database All hospitalized patients 19,543 positives 377 hospitalized	BNT; AZ	Unvaccinated = 117,263		D1 0-27, D1 28+, D2 0-13, D2 14+ VE for COVID infection (positive test, regardless of symptoms) VE for symptomatic COVID infection (appendix 4)
Stowe 2021	England April 12 – June 4, 2021	Test-negative case control Linked databases	Hospitalized patients within 14 days of a positive COVID test 14,019 symptomatic cases with Delta 166 hospitalized	BNT AZ	Unvaccinated		VE for hospitalization after D1, and D2
Thiruvengadam 2021	India April 1- May 31, 2021	Test negative case control Adjustment for age, sex, risk of exposure to COVID-19 positive individuals (balanced)	Those who tested positive for RT-PCR SARS-CoV-2 2766 confirmed cases 3.1% fully vaccinated	Case = RT-PCR positive for SARS-Cov-2 infection (2,776)	Control = randomly selected from a computer program from individuals who		VE for COVID-19 infection (table 2) VE for moderate to severe disease (Table 3)

				Not all genome sequenced, sample of 150 done with 90% with Delta	tested negative, matched for each calendar week of testing during study period 2,377 individuals who tested negative during the same week		After full and single dose vaccination
Ad26-Cov-2 (Janssen)							
(None)							
Coronavac (Sinovac)							
Li	China Guangzhou	Test negative case control	628 participants including 475 close contacts of Delta cases	Inactivated vaccine (CoronaVac or CNBG)		14 to 21 days	VE for mild, moderate, severe infection
Kang	China Guangdong	Retrospective cohort	12,501 close contacts of Delta cases	Inactivated vaccine (Sinovac, Sinopharm, BICV)			VE against pneumonia and severe/critical illness
Gam-COVID-Vac (Sputnik V)							
(None)							

BNT = BNT162b2; **AZ** = ChAdOx1; **Mod** = mRNA-1273; **D1** = first dose; **D2** = second dose; **VOC** = variant of concern

B. Immunologic Studies

STUDY ID	STUDY SITE/PERIOD	STUDY POPULATION	TIMING OF EXTRACTION	CONTROL STRAIN	OUTCOMES (Test Used)
BNT162b2 (Pfizer)					
Davis 2021	UK	Healthy individuals who have received: BNT D1 = 37 BNT D2 = 50 Note: outcomes assessed compared with ChAdOx	Not specified	WT	Reactivity by ELISA - anti S1, - anti RBD - anti N Neutralizing antibody titers Table S1 (HIV-pseudotype-based system) Reductions in mean titers / fold reduction Table S1
Mlcochova 2021	India	Live virus assay BNT = 10 Pseudovirus assay BNT = 32	Not mentioned	WT	Fold reduction (Live virus neutralization assay) Fold reduction (vs. WT) Pseudovirus assay (Figure 1e, Table e1) GMT (vs. WT vs. other vaccine) Pseudovirus assay (Figure 1e, Table e1)
Lustig 2021	Israel	Healthy HCWs N = 19	1 month after D2 (Delta-S1 and S2 substrains tested separately)	B.1	Neutralising antibody activity (micro-neutralisation assay TCID50): 1. GMT 2. fold-reduction
Planas 2021	France	Randomly selected 59 vaccinees Pfizer = 16 AZ 1 dose = 23 AZ 2 doses = 20	Pfizer: W3, W8 W16 after vaccination (W13 after D2) AZ D1: W10 AZ D2: W16	D614G	Fold reduction in neutralization titers (p279) % positivity (Fig 7)
Chia 2021	Singapore April 1- June 14, 2021	Retrospective cohort Vaccinated with serology (N = 69) Unvaccinated with serology (N = 45)	Week 1, 2 from diagnosis *Not all sequenced, for those not sequenced, lineage inferred based on epidemiologic investigations and likely B.1.617.2 included	WT (Comparison available for 36 vaccinated individuals)	Vaccinated vs unvaccinated: Seropositivity for - anti N (CLIA) - anti-spike protein (CLIA) Inhibition rate (week 1, week 2) - Nab anti RBD (surrogate virologic neutralization test) WT vs. B.1.617.2 % inhibition of NaB relative to WT using multiplex-sVNT assay using Luminex platform

			For sVNT inhibition % against WT, median day of sample collection from infection onset 6 days (IQD 3-7)		
Edara 2021	USA	Serum samples from infected/convalescent and vaccinated persons N = 10 (post BNT)	7 to 27 days after 2nd dose	WA1/2020	Neutralizing antibody response (live virus focus reduction neutralization test on a Vero E6 cell line): 1. GMT 2. Fold reduction (Fig 1)
Liu C 2021	UK	Serum from vaccinated individuals BNT = 25 Dosing interval = 3 weeks	4 to 14 days post D2 Also studied after D1 only at D28 and D70	Victoria (VIC01/2020)	GMT (Fig 7) (Focus Reduction neutralization test) Fold reduction (Fig 7) GMT, fold reduction, % neutralization after D1 at D28 and D70 (Fig 7)
mRNA-1273 (Moderna)					
Choi 2021	USA	Participants immunized with mRNA-1273 (prime-boost) N = 8	7 days post boost	Wildtype (Wuhan-Hu-1 with D614G)	Neutralization antibody titer (VSV-Based pseudotype assay % neutralization Fold reduction in neutralization titers relative to control Relative decline in GMTs
Pegu 2021	USA	Random samples of sera from 24 volunteers	4 time points: 4 weeks after D1, 2 wks, 3 mo, 6 mo after D2	Wuhan-Hu-1 D614G	Fold reduction by pseudovirus neutralization assay and cell-surface spike binding (Fig 2G) % positivity (number with detectable antibody titers) using pseudovirus neutralization assay and cell surface spike binding (Fig 3) at the 4 time points
Edara 2021	USA	Serum samples from infected/convalescent and vaccinated persons N = 15 (post mRNA-1273)	35 to 51 days after 2nd dose	WA1/2020	Neutralizing antibody response (live virus focus reduction neutralization test (FRNT) live virus assay on a Vero E6 cell line): 1. GMT difference 2. Mean Fold reduction (Fig 1)
ChAdOx1 (Astra Zeneca)					
Sapkal 2021	India	Covishield vaccinated individuals D1 only (31) D2 (31) Covid-recovered + D1 (15) Cvoid-recovered +D2 (19) Breakthrough COVID 19 (20)	Not mentioned	B.1	% positivity Neutralizing antibodies (plaque reduction neutralization assay) Fold - reduction in Nab titers relative to B.1 GMT NaB titers
Davis 2021	UK	Healthy individuals who have received: ChAdox D1 = 50 ChAdOx D2 = 18	Not specified	WT	Reactivity by ELISA - anti S1, - anti RBD - anti N

		Note: outcomes assessed compared with BNT162b			GMT Neutralizing antibody titers Table S1 (HIV pseudotype-based system) Reductions in mean titers Table S1
Mlcochova 2021	India	Live virus assay ChAd – 10 Pseudovirus assay Chad- 33	Not mentioned	WT	Fold reduction (live virus neutralization assay) Fold reduction (vs WT) Pseudovirus assay (Figure 1e, Table e1) GMT (vs. WT, vs other vaccine) Pseudovirus assay (Figure 1e, Table e1)
Thiruvengadem	India	Plasma from 49 fully vaccinated healthy participants	Median 61 days after D2	WT	GMT for IgG RBD (live virus neutralization) Fold reduction in neutralization – Table S3 *(but supplement not available)* Mean IFN-gamma secretion (Fig 2) % IFN responders Antigen specific CD8+ T cell (cellular granzyme B and perforin expression)
Liu 2021	UK	Serum from vaccinated individuals ChAdOx1 = 25, dosing interval 8-14 weeks	14-28 days after D2	Victoria (VIC01/2020)	GMT (Fig 7) (Focus Reduction neutralization test) Fold reduction (Fig 7)
Ad26.Cov2.S (Janssen)					
Jongeleen 2021	Brazil, USA, RSA	Sera from ph 3 ENSEMBLE trial participants		Wuhan-Hu-1 (B.1)	Anti-S Nab titers (GMT) (HIV-based lentivirus neutralization assay) fold reduction vs B.1 (Fig 3)
Keeton	South Africa	Sera from 60 healthcare workers		D614G	For infection naïve - Neutralization rate = 78% (GMT = 29) For previously infected (by D614G) - neutralization of Delta maintained but lower titers (606 to 443) = 2.7-fold reduction For previously infected with Beta 6-fold lower neutralization of Delta (GMT = 200)
Coronavac (Sinovac)					
Hu 2021	China (timing of study not mentioned)	Sera from 20 vaccinated patients	7-14 dyas post D2	D614G	Neutralizing antibody response(pseudovirus-based neutralization assay) : Neutralizing activity (positivity?) - % above threshold X-fold decline in neutralization potency compared to control
Vacharathit 2021	Thailand March 2020-May 2020	Healthworkers who received 2 doses of Coronavac (n=60)	Not mentioned	WT Sera from unvaccinated	Live virus neutralization: GMT for Nab (Table 1)

	April 2021 – May 2021			and naturally infected COVID-19 patients (Mar –May 2020 and Apr-May 2021)	% NaB positivity (table 2) GMT IgG (s-1-RBD binding IgG (table 3)
Gam-COVID-Vac (Sputnik V)					
Guschin	Russia	Sera from 16 samples	Not mentioned	B.1.1.1	VNT using live virus and spike-pseudotyped lentivirus 2.5 fold decline with Delta
BBV-152 (Covaxin)					
(None)					
NVX-CoV2373 (Novavax)					
(None)					

Appendix 3. Risk of Bias Assessment of Clinical Studies

STUDY ID	STUDY DESIGN	RANDOMIZA-TION	ALLOCATION CONCEALMENT	BLINDING OF PARTICIPANTS	BLINDING OF INVESTIGATORS	BLINDING OF ASSESSORS	MISSING OUTCOMES / FOLLOW UP	SELECTIVE REPORTING	ASSESSMENT OF CONFOUNDING FACTORS									
									AGE			EXPOSURE RISK			COMORBIDITIES			OVERALL for CONTROL OF COUNFOUNDERS
									A	B	C	A	B	C	A	B	C	
Chia	Retrospective cohort	HIGH	HIGH	HIGH	UNCLEAR	UNCLEAR	UNCLEAR	UNCLEAR	Y	N	Y	N	NA	NA	Y	N	Y	LOW
Lopez Bernal	test negative case control	HIGH	HIGH	HIGH	UNCLEAR	UNCLEAR	UNCLEAR	UNCLEAR	Y	U	Y	Y	U	Y	Y	U	Y	LOW
Micochova	Crosssectional?	HIGH	HIGH	HIGH	UNCLEAR	UNCLEAR	UNCLEAR	UNCLEAR	Y	U	Y	N	NA	NA	N	NA	NA	HIGH
Nasreen	test negative case control	HIGH	HIGH	HIGH	UNCLEAR	UNCLEAR	UNCLEAR	UNCLEAR	Y	N	Y	Y	N	Y	Y	N	Y	LOW
Sheikh	test negative case control	HIGH	HIGH	HIGH	UNCLEAR	UNCLEAR	UNCLEAR	UNCLEAR	Y	U	Y	Y	N	Y	N	NA	NA	LOW
Stowe	test negative case control	HIGH	HIGH	HIGH	UNCLEAR	UNCLEAR	UNCLEAR	UNCLEAR	U	U	U	U	U	U	U	U	U	HIGH
Thiruvengadam	test negative case control	HIGH	HIGH	HIGH	UNCLEAR	UNCLEAR	UNCLEAR	UNCLEAR	Y	Y	Y	Y	Y	Y	N	U	N	LOW
Li	test negative case control	HIGH	HIGH	HIGH	UNCLEAR	UNCLEAR	UNCLEAR	UNCLEAR	U	U	U	U	U	U	U	U	U	HIGH
Kang	retrospective cohort	HIGH	HIGH	HIGH	UNCLEAR	UNCLEAR	UNCLEAR	UNCLEAR	U	U	U	U	U	U	U	U	U	HIGH
Nanduri		HIGH	HIGH	HIGH	UNCLEAR	UNCLEAR	UNCLEAR	UNCLEAR	U	U	U	Y	Y	Y	U	U	U	HIGH
Buxvoort	test negative case control	HIGH	HIGH	HIGH	UNCLEAR	UNCLEAR	UNCLEAR	UNCLEAR	Y	Y	Y	U	U	U	Y	Y	Y	LOW
Tang	test negative case control	HIGH	HIGH	HIGH	UNCLEAR	UNCLEAR	UNCLEAR	UNCLEAR	Y	Y	Y	U	U	U	Y	Y	Y	LOW
Tartoff	retrospective cohort	HIGH	HIGH	HIGH	UNCLEAR	UNCLEAR	UNCLEAR	UNCLEAR	Y	Y	Y	N	N	N	Y	Y	Y	LOW
Ella	RCT	LOW	LOW	LOW	LOW	LOW	UNCLEAR	UNCLEAR	NA	NA	NA	NA	NA	NA	NA	NA	NA	LOW
			LOW	UNCLEAR	HIGH	NOT APPLICABLE			Y	YES	N	NO	U	UNCLEAR		NA	NOT APPLICABLE	

Appendix 4. Summary of COVID-19 vaccines performance against COVID-19 infection due to the Delta Variant

A. Clinical Outcomes

	BNT162b2 (Comirnaty/ Pfizer)	mRNA-1273 (Moderna/ USNIH)	ChAdOx1 (Vaxzevria/ AstraZeneca)	Ad26.COV2.S (J&J)	CoronaVac (Vero Cell / Sinovac)	Gam-COVID-Vac	Bharat
B.1.617.2							
VE against symptomatic COVID-19 infection	↔ 88% (95% CI 85.3-90.1%) after 2 doses (Lopez Bernal) VE 87% after 2 doses (Nasreen)		↔ 67% (61.3-71.8%) after 2 doses (Lopez Bernal)		↔ 69.5% (95% CI 42.8-96.3) against pneumonia (calculated with sinopharm) (Kang) 59% (16-81.6) mild, Li 70.2% (29.6-89.3) moderate, Li		↓ 65.2 (33.1, 83.1) (Ella)
VE against severe COVID-19 infection	↔ 96% (CI 86-99%) after 2 doses (Stowe) 97.3 (84.4-99.5) (Tang) 93% (84-96) hospitalization (Tartof)	97.6% (92.8, 99.2) Buxvoort 100% Tang	↔ To ↓ 92% (75-97%) after 2 doses (Stowe) Full vaccination prevented moderate to severe COVID in 81.5% (95% CI 9.9, 99) (Thiruvengadem)		↔ 100% (Li, Kang)		
VE against any COVID-19 infection	↓ 79% (95% CI 75-82%) at least 14 days after 2nd dose (Skeih) 52.4% (95% CI 48.0-56.4) including asymptomatic (Naduri) 59.6 (50.7-66.9) (Tang) 75% (71-78) (Tartoff)	50.6% (95% CI 45-55.7) including asymptomatic (Naduri) 86.1 (78.0-91.3) (Tang) 86.7% (84.3-88.7) Buxvoort	↓ 60% (95% CI 52-66%) at least 14 days after 2nd dose (Skeih) aOR of 3.81 (95% CI 1.11-13) 63.1% (51.5, 72.1) Thirivengadem				

B. Immunologic Outcomes

B.1. Fold reductions per vaccine

	Pfizer	Moderna	AstraZeneca	Janssen	Sinovac	Gam-COVID-Vac
Antibody neutralization	↓ to ↓↓	↓	↓ to ↓↓	↓	↓	↓
	11.3, 8.4 fold reduction vs WT (Davis, Mlchova) 2.1 fold reduction vs B.1 (Lustig) 3.3 fold reduction vs WA1 Edara) 2.5 fold reduction vs Victoria (Liu, C) 3.6 fold reduction (Tada)	2.1, 0.7-2.4 fold reduction vs Wuhan-Hu-1 with D614G (Choi, Pegu) 3-fold reduction vs WA1/2020 (edara) 4.0 fold reduction (Tada)	4.01, 6.8, 9-fold reduction vs WT (Davis, Thiruvegadem, Mlchova) 3.2 fold reduction vs B.1 (Sapkal) 4.3 fold reduction vs Victoria (Liu) 2.5 fold reduction (Wall)	1.6 fold reduction in neutralization (Jongoleen) 7.4 fold reduction (Tada)	Neutralization potency decreased 2.5-fold (Hu) Quantifiable antibody titers present in 69% with 48% having titers above the threshold (Vacharathit)	2.5 fold reduction (Guschin)

B.2. Fold Reduction in Neutralizing Capacity of COVID-19 vaccines against B.1.617.2 (Delta Variant)

Study ID	n	Test Used	Timing of Extraction	Reference Strain	Fold-reduction	Comments
BNT162b2						
Davis	D1 = 37 D2 = 50	HIV pseudotype-based system	not specified	WT	1.92 11.2	excluding seropositive at baseline
Mlcochova	10	live virus neutralization assay	not specified	WT	8.4	
Lustig	19	micro-netrualization assay	1 month after D2	B.1	2.1	
Planas	16	not described	week 13 after D2	D614G	3	
Edara	10	live virus focus reduction neutralization	7-27 days after D2	WA1/2020	3.3	
Liu C	25	Focus reduction neutralization test	4-14, 28d and 70d after D2	Victoria	2.5	
Liu J	20	plaque reduction neutralization test	2-4 weeks after D2	USA/WA1/2020	not available	
Tada	9	lentivirus pseudovirus-based neutralization	90 days	D614G	3.6	
mRNA-1273						
Choi	8	VSV-based pseurotype assay	7 days after D2	Wuhan-Hu-1 with D614G	2.1	
Pegu	24	pseudovirus neutralization assay	4 wks after D1, 2 weeks,3 mos,6 mos after D2	Wuhan-Hu-1 D614G	0.7 2.4	
Edara	15	live virus focse reduction neutralization	35 to 51 days after D2	WA1/2020	3	
Tada	8	lentivirus pseudovirus-based neutralization	80 days	D614G	4	
ChAdOx1						
Sapkal	D1 - 31 D2 - 31	plaque reduction neutralization test	not specified	B.1	3.2	
Davis	D1 - 50 D2 - 18	HIV-pseudotype-based system	not specified	WT	4.01 3.14	excluding seropositive at baseline
Mlcochova`	10 33	live virus neutralization assay pseudovirus neutralization assay	not specified	WT	9	
Thiruvengadem	49	live virus neutralization	median 61 days after D2	WT	6.8	
Liu	25	focus reduction neutralization test	14-28 days after D2	Victoria	4.3	
Wall	D1 - 60 D2 - 63	live virus neutralization assay	D1 : median 41d (IQR 30-51) D2 : median 31d (IQR 19.5-46)	D614G (after 2 doses BNT162b2)	2.5	relative to 2 doses of BNT162b2
Ad26.CoV.2						
Jongeleen	8	HIV-based lentivirus neutralization assay	not mentioned	Wuhan-Hu-1 (B.1)	1.6	
Tada	10	lentivirus pseudovirus-based neutralization	82 days after vaccination	D614G	7.4	
Coronavac						
Hu	20	pseudovirus-based neutralization assay	71-4 days after D2	D614G	2.5	
Vacharathit	60	live virus neutralization assya	not mentioned	WT	3	
Gam-COVID-Vac						
Gushchin	27	live virus neutralization assay spike-pseudotyped lentivirus	one month after D2	B.1.1.1	2.5	

Q10. Among children <18 years old, what is the efficacy/effectiveness and safety of COVID-19 vaccines compared to placebo in preventing COVID-19?

As of 21 October 2021

RECOMMENDATIONS

We recommend the use of the BNT162b2 (Pfizer/BioNTech) vaccine, [given as 0.3 mL (30 ug) intramuscular injections, in 2 doses, 21 days apart] for children 12-15 years old to prevent symptomatic SARS-CoV-2 infection. *(Moderate certainty of evidence; Strong recommendation)*

We suggest the use of the mRNA-1273 (Moderna) vaccine, [given as 0.5 mL (100 ug) intramuscular injections, in 2 doses, 28 days apart] for children 12-17 years old to prevent symptomatic SARS-CoV-2 infection. *(Low certainty of evidence; Weak recommendation)*

We suggest against the use of Coronavac (Sinovac), [given as 0.5 mL (600 SU) intramuscular injection, in 2 doses, 28 days apart] for children 3-17 years old to prevent symptomatic SARS-CoV-2 infection. *(No evidence; Weak recommendation)*

Consensus Issues

The issue of myocarditis associated with the mRNA vaccines in children was a major consideration in the recommendation, particularly with the mRNA-1273 (Moderna) vaccine. Despite the low incidence of post-vaccination myocarditis, some Panel members considered it significant enough, especially when normal children are concerned, to weigh heavily on the benefit risk ratio. The suspension of the use of mRNA-1273 among children in some countries due to the myocarditis issue was also raised, resulting in the cautious recommendation given for this vaccine. The Panel emphasized that warnings should be given to the parents and caregivers of the vaccine recipients to consult immediately in case of symptoms occurring after vaccination, which may suggest the development of myocarditis.

KEY FINDINGS

This review provides the evidence on the use of COVID-19 vaccines in children based on one (1) systematic review, three (3) randomized controlled trials (RCTs), two (2) real world effectiveness studies, five (5) case series/reports, and six (6) regulatory agency reports. Findings show that BNT162b2 (Pfizer/BioNTech) and mRNA-1273 (Moderna) provide sufficient protection against COVID-19 infection among adolescents who are at least 12 years old. More reactogenicity events were noted but adverse events were generally non-severe. Higher immunogenicity responses were also seen with children compared to adults. CoronaVac (Sinovac) was found to be immunogenic among children aged 3-17 years old.

Real world evidence on the use of mRNA vaccines in children supported the findings in the clinical trials. Myocarditis was detected among children after mRNA vaccination, although rare.

INTRODUCTION

COVID-19 affects more children than adults.[1] In the USA, children comprised 16.2% of the total cumulative cases of COVID-19.[2] In the recent months, adolescents already represent a growing proportion of new COVID-19 cases.[3] Some of these cases can become severe or develop into the Multisystem Inflammatory Syndrome in Children (MIS-C).[1]

Aside from directly getting infected, children have also been affected because of the continued closure of face-to-face classes. Once children start going back to school, the risk of transmission among themselves as well as the possibility of bringing home the virus and causing household transmission is a concern to most parents, especially when there are households who are at risk of developing severe COVID-19, such as the elderly. Vaccinating these children may be one way of protecting these children as well as their household members. There is thus a need for a safe and effective vaccine for children.

REVIEW METHODS

The search of the literature performed on September 17, 2021 identified 18 reports on the use of COVID-19 vaccines in children and adolescents. One systematic review included two RCTs, two case series and four case reports.[4] All studies cited in this systematic review are included here, save for two case reports, which involved adults as well. Three randomized controlled trials were identified, one using BNT162b2 (Pfizer) [5], one mRNA-1273 (Moderna) [6], and one CoronaVac (Sinovac).[7] Five reports presented real-world evidence on the effectiveness and safety of BNT162b2(Pfizer) in children.[8-12] Seven reports on post-COVID-19 vaccination myocarditis were identified.[13-19] Search of the regulatory sites identified assessment reports providing vaccine efficacy and safety information on the pediatric use of BNT162b2 (Pfizer) [20] and mRNA1273 (Moderna).[21]

Six regulatory sites (WHO, US-CDC, NACI-Canada, UK-JCVI, EMA, and Singapore MOH) provided specific recommendations on COVID-19 vaccination in children.[21-26] One local recommendation from the Philippine Pediatric Society (PPS)-Philippine Infectious Disease Society of the Philippines (PIDSP) is also included.[27]

Search of the *clinicaltrials.gov* identified 21 active intervention trials on COVID-19 vaccination in the pediatric population.

RESULTS

BNT162b2 (Pfizer)

Clinical Efficacy

One randomized placebo-controlled trial investigated the efficacy and safety of BNT162b2 (Pfizer) in the prevention of COVID-19 infection.[5,20] The trial randomized 2,264 children (vaccine group = 1,134; control group = 1,129). The overall quality of evidence of the RCT for BNT162b2 was downgraded to moderate because this was an interim report; for safety the quality of evidence was further downgraded to low because of imprecision.

The study reported a vaccine efficacy of 100% (95% CI 78.0-100.0) at least 7 days after the second dose, after a median follow up of 2 months, as no cases of COVID-

19 infection occurred in the vaccine group. It also suggests potential sufficient protection after the single dose (VE = 75.1%, 95% CI 7.6-95.5). Efficacy against severe COVID-19 infection or COVID-19-related deaths could not be assessed since there were no cases reported during the study period.

Immunogenicity

The above study also demonstrated that BNT162b2 is highly immunogenic in children aged 12 to 15 years old, generating a GMT of 1283.0 at 1 month after dose 2, compared to a GMT of 15.1 in the placebo group and 730.8 in the 16 to 25 years old treatment group. It also compared immune responses to that of adults aged 16 to 26 years old and results showed that their responses were non-inferior with a neutralizing antibody geometric mean titer ratio (GMR) of 1.76 (95% CI 1.47–2.10). Non-inferiority criteria was set at a lower boundary of the two-sided confidence interval for the GMR of greater than 0.67.

Real World Evidence - Effectiveness

A retrospective case series of 31 long-term pediatric care facility residents with patients aged 16 to 25 years old showed that none among the vaccinated patients (all of which received BNT162b2) developed COVID-19, resulting in a vaccine effectiveness of 100%. Majority (83.9% and 74.2% after dose 1 and dose 2, respectively) did not have any adverse reactions to the vaccine after the first and second doses.[8]

A case series of 13 patients with solid tumors, 9 of which were aged 16 to 17 years old looked at the immunogenicity of BNT162b2 among patients with solid tumor under treatment or had completed their treatment within 6 months. Seroconversion rate after dose 1 was 60% and 90% after dose 2.[9]

One study looked at the US Coronavirus Disease 2019–Associated Hospitalization Surveillance Network (COVID-NET) data and reported that hospitalization rate among the unvaccinated adolescents were 10.1 times higher than those who were vaccinated in the US, where the only vaccine with an emergency use authorization (EUA) for adolescents aged 12 to 15 years old is BNT162b2.[10] A US-CDC study that looked at hospitalization and emergency department visits using the National Syndromic Surveillance Program and CDC data reported that emergency department visits and hospitalization rates were higher (3.4 and 3.7 times higher, respectively) in the states with lowest vaccination coverage compared to the states with the highest vaccination coverage.[11]

Safety, Clinical trial

In the randomized clinical trial on BNT162b2 among children aged 12 to 15 years old, patients who received BNT162b2 reported more local and systemic events than those who received placebo.[5,20] Most resolved within 1 to 2 days. The most common local adverse event reported by the vaccine group was pain at injection site (post D1 = 86%, D2 = 79%). The most common systemic adverse events were headache (post D1 = 55%, post D2 = 65%) and fatigue (post D1 = 60%, post D2 = 66%). Systemic events were reported more often after the second dose of BNT162b2 than the first dose. There were no deaths, hypersensitivity, myocarditis, thrombosis, or multisystem inflammatory syndrome in children (MIS-C) reported. One discontinuation from the

study due to adverse event was in a patient with fever of greater than 40°C and was assessed as a vaccine-related event.

The US–FDA regulatory review reported the following rates of adverse events after administration of BNT162b2 in children: pain at injection site (90.5%), fatigue (77%), headache (75.5%), chills (49.2%), muscle pain (42.2%), fever (24.3%), joint pain (20.2%), injection site swelling (9.2%), injection site redness (8.6%), lymphadenopathy (0.8%), and nausea (0.4%). Apart from the significantly higher reactogenicity rates compared with placebo, the BNT162b2 group also presented with higher numbers of patients developing lymphadenopathy.[20]

Safety, Real World Evidence

One retrospective case series described the adverse events reported by 31 patients aged 16 to 25 years old (mean age 21) admitted to a long-term pediatric care facility after vaccination with BNT162b2.[8] Majority did not report any side effects (83.9% post D1, 74.2% post D2). The most commonly reported adverse events were agitation and discomfort (9.7% post D1, 12.9% post D2)**,** nausea (6.5% post D1, 3.2% post D2), and fever (0% post D1, 6.5% post D2). The study also reported that none of the patients tested positive for COVID-19 nor developed any COVID-19 symptoms post-vaccination. The study, however, did not mention the duration of the follow-up after vaccination.

In the case series of 13 patients with solid tumors who received BNT162b2 vaccine, 5 did not report any adverse event. The most common reported adverse event was mild to moderate pain at the injection site, relieved after 1 to 2 days.[9]

A review of the reports to the Vaccine Adverse Event Reporting System (VAERS) and adverse events and health impact assessments reported in v-safe, which is a smartphone-based safety surveillance system showed that as of July 16, 2021, VAERS had received 9,246 reports for the Pfizer/BioNTech vaccine out of approximately 8.9 million adolescents vaccinated. Most were non-serious (90.7%) while 9.3% were serious adverse events including 4.3% for myocarditis. There were 63.4% local and 48.9% systemic reactions. For serious adverse events, the following were the common conditions or findings: chest pain (56.4%), increased troponin levels (41.7%), myocarditis (40.3%), increased C-reactive protein (30.6%), and negative SARS-CoV-2 test results (29.4%). There were 14 reports of death, all reviewed by CDC physicians. Causes of death were pulmonary embolism (2), suicide (2), intracranial hemorrhage (2), heart failure (1), hemophagocytic lymphohistiocytosis, and disseminated *Mycobacterium chelonae* infection (1), and unknown or pending further records (6). From the v-safe data, among 62,709 enrolled 12 to 15 year old children, there were 63.9% local reactions and 48.9% systemic reactions after the 1st dose. For the 2nd dose, systemic reactions were more common (63.4%). For ages 16 to 17 years old, systemic reactions were 55.7% after the 1st dose and 69.9% after the 2nd dose. The most frequently reported reactions for both age groups after either dose were injection site pain, fatigue, headache, and myalgia. Less than 1% required medical care with 56 (0.04%) needing hospitalization.[12]

mRNA-1273 (Moderna)

One Phase 2/3 randomized placebo-controlled trial was performed to assess the efficacy, immunogenicity, and safety of mRNA-1273 (Moderna) in the prevention of

COVID-19 infection among adolescents aged 12 to <18 years old. The interim report has been published with additional information available from the EMA regulatory review report.[6,21] The characteristics of the study are presented in Appendix 2. The methodological assessment is presented in Appendix 3.

Clinical Efficacy
The study provided several measures of clinical efficacy for mRNA1273 (Moderna) against COVID-19 for adolescents aged 12 to 17 years. Point estimates of vaccine efficacy for symptomatic COVID-19 disease (VE = 92.7%, 95% CI 67.8-99.2), SARS-CoV-2 infection (VE = 69.8%, 95% CI 49.9-82.1), and asymptomatic SARS-CoV-2 infection(VE = 59.5%, 95% CI 28.4-77.3), showed sufficient protection. No severe cases nor deaths occurred in the study.

Immunogenicity
Non-inferiority for neutralizing and binding antibody level and seroresponse using the pseudovirus neutralization assay (both at ID50 and ID80), the spike IgG antibody ELISA, and the MSD Multiplex assay was demonstrated. A slightly lower seroresponse rate in the 12 to <16 year old subgroup was observed.

Safety, Clinical Trial
The incidence of local adverse reactions (ARs) was higher in the mRNA-1273 group compared with the placebo group after any and after each dose. The most frequently reported local solicited AR in the mRNA-1273 was injection site pain reported by 97.2% (93.1% post D1, 92.4% post D2). Majority of solicited local ARs were mild to moderate. The incidence of systemic ARs was higher in the mRNA-1273 group compared with the placebo group after any and after each dose. The most frequently reported systemic solicited adverse reaction in the mRNA-1273 group after any dose was headache. The incidence of solicited systemic adverse reactions was notably higher after dose 2 compared with dose 1. The majority of systemic solicited ARs was mild to moderate. Severity of systemic adverse events increased from dose 1 to dose 2. Grade 4 solicited systemic ARs were recorded for three (3) subjects in the mRNA-1273 group (fever, headache, and nausea/vomiting).

At the time of the report, no anaphylactic reaction, serious adverse events (SAEs) with fatal outcomes or deaths were reported. No cases of myocarditis have been reported, although three (3) participants who received the vaccine reported symptoms that could be consistent with myocarditis or pericarditis.

Coronavac (Sinovac)
A Phase 1/2 randomized controlled trial for CoronaVac in children aged 3 to 17 years old compared the reactogenicity and adverse reactions for the 1.5ug dose and the 3ug dose. The 3ug dose, which is the preparation currently available, resulted in higher neutralizing antibody titers and seropositivity rate compared to the 1.5ug and placebo groups. No clinical outcomes of efficacy was reported. Adverse reactions were similar in both the vaccine and placebo (alum) groups and were generally mild to moderate.[7]

ChAdOx1 (Astra Zeneca), Ad26-CoV2-S (Janssen/ Johnson&Johnson), Gam-COVID-Vac (Sputnik V)

The search failed to identify any study reporting on outcomes of the use of these vaccines in children or adolescents.

Adverse Events of Interest in Children : Myocarditis
Myocarditis was found to be an adverse event of special interest for mRNA vaccines, particularly in children.

One article reviewed four reports of myocarditis, including two on adolescents, which are included in this review.[16] Four case series of myocarditis included in this review which support the database review findings. The clinical presentation of the mRNA vaccine-associated myocarditis/pericarditis in children and adolescents is consistent across the available reports [17-19,28]. Majority of which were in males (>90%). Nearly all presented after the second dose, commonly within 7 days of the vaccination. The common symptoms included chest pain, fever, palpitation, shortness of breath, fatigue, nausea, and vomiting, often transient and self limiting. Median interval of the symptoms was 2 days.[14] All reported cases had elevated troponin and C-reactive protein levels. The most common abnormal ECG changes included ST-segment elevation and diffuse ST changes. On echocardiography, left ventricular function was normal. The clinical course was mild and all patients recovered and were discharged home in less than a week.

A study looked specifically at the VAERS reports for myocarditis among persons less than 30 years old vaccinated with either BNT162b2 or mRNA-1273. There were 62.8 cases per million second doses among males 12 to 17 years old. More than 90% of cases were males, majority (76%) occurring after the second dose and within 7 days of vaccination. Most would present with chest pain, fever, palpitations, and shortness of breath and these were generally mild. No deaths were reported.[14] Two more studies looked at database reports of myocarditis in different countries where mRNA vaccines are given to adolescents. Incidence of myocarditis in most of these countries showed that myocarditis is rare with less than 10 cases per million vaccinees, except for Israel and Australia, which had slightly higher cases.[15,29]

The CDC estimated the rate of mRNA-vaccine-associated myocarditis at 40.6 cases per million second doses for males aged 12 to 29 years old and 4.2 for females. The highest rate was found with males aged 12 to 17 years old at 62.8 cases per million.[14] The ACIP concluded that the benefit of vaccination still outweigh the risks, including the risk of myocarditis after vaccination for all age groups, given the benefit of preventing 5,700 cases of COVID-19, 215 hospitalizations, 71 ICU admisssions and 2 deaths over the risk of 56 to 69 cases of myocarditis with vaccination among males. Greater benefit / harm ratio was seen in women with the prevention of 8,500 COVID-19 cases, 183 hospitalizations, 38 ICU admissions, 1 death prevented over the risk of 8 to 10 cases of myocarditis with vaccination.[14,23]

RECOMMENDATIONS FROM OTHER ORGANIZATIONS

The following are recommendations / guidelines from regulatory agencies on the use of COVID-19 vaccines in children:

Table 1. Summary of Recommendations from other Organizations on the use of COVID-19 vaccines in children

Regulatory Agency	Recommendation
World Health Organization (WHO) as of September 2, 2021 [22,30]	• Consider COVID-19 in children aged 12 to 15 years of age only when high vaccine coverage with 2 doses has been achieved in the high priority groups • Children 12 to 15 years of age with comorbidities may be vaccinated
Advisory Committee on Immunization Practices (ACIP) US CDC as of May 12, 2021 [3, 20,23]	• Children ≥12 years with high risk medical conditions in Phase 1c priority • Children ≥12 years without medical conditions in Phase 2 priority
National Advisory Committee on Immunization (NACI) Canada as of August 27, 2021 [24]	• A complete series with an mRNA COVID-19 vaccine should be offered to adolescents 12 to 17 years of age who do not have contraindications to the vaccine. *(Strong NACI Recommendation)*
Joint Committee on Vaccination and Immunization (JCVI)-UK Medicines and Health products Regulatory Agency (MHRA) as of September 16, 2021 [25]	• Children 12 to 15 years old can receive their first dose of COVID-19 vaccine • Second dose is pending further evidence on the safety • Children 12 to 17 years old who are at risk should receive their second dose at an interval of at least 8 weeks • Children ≥12 years old who live with immunosuppressed individuals should be offered two doses of vaccine, 8 weeks apart
European Medicines Agency (EMA) [21]	• Extended indication for mRNA-1273 to include use in children aged 12 to 17 years old as of July 23, 2021 • Extended indication for BNT162b2 to include use in children aged 12 to 15 years old as of May 28, 2021
Singapore Ministry of Health [26]	• Pfizer-BioNTech/Comirnaty COVID-19 vaccine is safe for use on adolescents aged 12 to 15 years old • While there is a small increased risk of myocarditis or pericarditis following the administration of the vaccines, the local incidence rate remains low at 0.48 per 100,000 doses administered • As a precaution, all vaccine recipients, especially adolescents and younger men, should avoid strenuous physical activity for one week following each dose of the vaccine
Philippine Pediatric (PPS)-Philippine Infectious Diseases Society of the Philippines (PIDSP) as of September 6, 2021 [27]	• Children ≥12 years old may be considered for vaccination with any duly approved COVID-19 vaccine • However, due to the limited vaccine supply, the older and more vulnerable age groups be prioritized. • Once the country will have adequate vaccine supply, the roll out can be initiated in high transmission areas and should prioritize the adolescents that are qualified in the A3 (children with comorbidities) and A1 (children of healthcare frontliners) category

ONGOING TRIALS

As of October 7, 2021, 21 vaccine trials involving children and an additional 11 trials involving both children and adults were registered in *clinicaltrials.gov*.

RESEARCH GAPS

The evidence to inform practice on the use of COVID-19 vaccines in children is still lacking :

1. Clinical efficacy and safety of ChAdOx1, Ad26.CoV2.S, Gam-COVID-Vac, CoronaVac, BBV152, BBIBP in children
2. Long term efficacy, effectiveness and safety of all COVID-19 vaccines in children
3. Clinical efficacy and safety of COVID-19 vaccines in children younger than 3 years old
4. Duration of protection in children
5. Efficacy, effectiveness and safety of booster vaccination in children

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Appendix 1. Evidence to Decision

Table 1. Summary of Initial Judgements Prior to Panel Discussion (N = 10)

FACTORS	JUDGEMENT						RESEARCH EVIDENCE/ADDITIONAL CONSIDERATIONS
Problem	No	Yes (10)					
Benefits	Large (3)	Moderate (6)	Small	Uncertain (1)			• BNT162b2 (Pfizer) vaccine efficacy of 100% (95% CI 78.0-100.0) at least 7 days after the second dose.
Harm	Large (2)	Small (4)	Uncertain (4)				• Local and systemic adverse events were reported. • Myocarditis: adverse event of special interest for mRNA vaccines, particularly in children.
Certainty of evidence	High	Moderate (6)	Low (4)	Very Low			• Very low to moderate
Balance of effects	Favors vaccine (9)	Does not favor vaccine	Uncertain (1)				• Benefit of vaccination still outweigh risks, including the risk of myocarditis after vaccination, for all age groups.
Values	Important uncertainty or variability (2)	Possibly important uncertainty or variability (8)	Possibly no important uncertainty or variability	No important uncertainty or variability			• Vaccination coverage in the Philippines (as of October 11, 2021): 26,486,522 have had 1 dose; 23,186,969 have completed 2nd dose & single-dose vaccines.
Resources required	Uncertain	Large cost (5)	Moderate cost (5)	Negligible cost or savings	Moderate savings	Large savings	• Average composite cost of around PHP 1,300.00 per person for the vaccination program. • The mRNA vaccines require ultra-low freezer (between -90°C and -60°C for BNT162b2; -50°C and -15°C for mRNA-1273). • For the CoronaVac vaccine, it can be stored at 2° to 8°C for 6 months.
Certainty of evidence of resources required	No included studies (7)	Very low (1)	Low (1)	Moderate (1)	High		
Cost effectiveness	No included studies (9)	Favors the comparison (1)	Does not favor either the intervention or the comparison	Favors the intervention			
Equity	Uncertain (2)	Reduced (3)	Probably no impact	Increased (5)			• Available through the designated hospitals / local government units (LGUs).
Acceptability	Uncertain (2)	No	Yes (8)				• DOH confirmed that pediatric vaccination using Pfizer and Moderna will start among 12 to 17 year olds with comorbidities as part of Priority Group A3 (9/30/21) • Issues surrounding vaccine hesitancy are due to exposure to negative media information (related to the dengue vaccine) and concerns about vaccine safety.
Feasibility	Uncertain (2)	No	Yes (8)				

Appendix 2. Characteristics of Randomized Clinical Trials on COVID-19 in Children

Study ID	Population	Intervention	Comparator	Outcomes
Frenck et al.[5] Ph. 3	12 to 15 years old, healthy or had stable preexisting disease (N = 2,264)	BNT162b2 30 ug in 0.3 mL x 2 doses, 3 weeks apart (N = 1,134)	0.9 NSS 0.5 mL x 2 doses (N = 1,130)	Efficacy - VE against confirmed COVID-19, 7 days or more after dose 2 Immunogenicity (1 month after dose 2) - SARS-CoV-2 serum neutralization assay - Receptor-binding domain [RBD]–binding or S1-binding IgG - GMT rise from baseline to 1 month after dose 2 Safety - Local and systemic reactogenicity events 7 days after each dose - Serious adverse events 1 month and 6 months after dose 2
Ali et al.[6] Ph. 3	12 to <18 years old, in good health (N = 3,732)	mRNA-1273 100 ug in 0.5 mL x 2 doses, 28 days apart (N = 2,139)	0.9 NSS 0.5 mL (N = 1,243)	Efficacy - VE against confirmed COVID-19 14 days after dose 2 - VE against asymptomatic SARS-CoV-2 infection Immunogenicity - Neutralizing antibody titer - SARS-CoV-2 spike protein antibody - GMT, seroresponse rate 28 days after dose 2 Safety - Local and systemic adverse reactions 7 days after each dose - Unsolicited adverse events (AEs) from days 1 to 28 - Medically attended adverse events, adverse events leading to withdrawal, serious adverse events, data on MIS-C collected until end of the trial
Han et al.[7] Ph. 1, 2	3-17 years old, healthy (Ph 1: 72, Ph 2: 480)	CoronaVac 1.5 ug / 3.0 ug in 0.5 mL x 2 doses, 28 days apart (Ph1: 36; Ph 2: 1.5 ug = 192; 3.0 ug = 192)	Aluminum hydroxide only (Ph 1: 36; Ph 2: 96)	Immunogenicity - Seroconversion rate (for neutralizing antibodies at day 28 after D2) - GMT of neutralizing antibodies to live SARS-CoV-2 - Seropositive rates - Geometric mean increase Safety - Solicited adverse events within 7 days - Unsolicited adverse events within 28 days, follow up until 12 months - Serious AE Abnormal changes in labs at day 3 after each dose

Appendix 3. Detailed Study Appraisals of RCTs

Risk of Bias Assessment for Frenck et al.

Parameter	Basis	Assessment
Random sequence generation	Interactive web-based response system	Low
Allocation concealment	Interactive web-based response system	Low
Blinding of participants and personnel	Yes (triple-blinded)	Low
Blinding of outcome assessment	Yes (triple-blinded)	Low
Incomplete outcome data (efficacy)	Interim report, 2 month median follow up data reported (planned 1 year assessment)	High / unclear*
Incomplete outcome data (safety)	Interim report, 2 month median follow up data reported (planned 1 year assessment)	High / unclear*
Selective reporting	All planned outcomes reported	Low

Risk of Bias Assessment for Ali et al.

Parameter	Basis	Assessment
Random sequence generation	Centralized interactive response technology	Low
Allocation concealment	Access to code controlled at pharmacy level	Low
Blinding of participants and personnel	Yes	Low
Blinding of outcome assessment	Yes	Low
Incomplete outcome data (efficacy)	Interim report, 2 month median follow up data reported	High / unclear*
Incomplete outcome data (safety)	Interim report, 2 month median follow up data reported	High / unclear*
Selective reporting	All planned outcomes reported	Low

Risk of Bias Assessment for Han et al.

Parameter	Basis	Assessment
Random sequence generation	Randomization codes generated by the randomization statistician using SAS software	Low
Allocation concealment	Randomization code assigned to each participant in sequence in the order of enrollment	Unclear
Blinding of participants and personnel	Participants and investigators masked	Low
Blinding of outcome assessment	Investigators and laboratory staff masked	Low
Incomplete outcome data (efficacy)	Interim analysis, planned follow up to 12 months after dose 2	High / unclear*
Incomplete outcome data (safety)	Interim analysis, planned follow up to 12 months after dose 2	High / unclear*
Selective reporting	All planned outcomes reported	Low

Appendix 4. Summary of Findings and GRADE Tables

1. BNT162b2 (Pfizer)

COMPARISON : BNT162b2 (Pfizer) vs placebo in Children (12-15 years)

Efficacy Outcome (at >7 days after dose 2)	Quality Assessment					Summary of Findings			Certainty
	Risk of Bias	Inconsistency	Indirectness	Imprecision	Overall Assessment	Vaccine	Control	Vaccine Efficacy	
1.1. Symptomatic COVID-19 infection *without evidence of previous infection*	With concerns (interim report)	Not assessed	Not serious	Not serious	With concerns	0/1005	16/978	100% (75.3,100.0)	+++ Moderate
1.2. Symptomatic COVID-19 infection *with or without evidence of previous infection*	With concerns (interim report)	Not assessed	Not serious	Not serious	With concerns	0/1119	18/1110	100% (78.1, 100)	+++ Moderate
2. Severe COVID-19 infection	With concerns (interim report)	Not assessed	Not assessed	Not assessed	Not assessed	Na	Na	Na	Na
3. COVID-19 infection, postD1, preD2	With concerns (interim report)	Not assessed	Not assessed	Not assessed	Not assessed	Na	Na	Na	Na
4. Asymptomatic COVID-19 infection	With concerns (interim report)	Not assessed	Not assessed	Not assessed	Not assessed	Na	Na	Na	Na
5. Hospitalization	With concerns (interim report)	Not assessed	Not assessed	Not assessed	Not assessed	Na	Na	Na	Na
6. ICU Admission	With concerns (interim report)	Not assessed	Not assessed	Not assessed	Not assessed	Na	Na	Na	Na
7. Death due to COVID-19	With concerns (interim report)	Not assessed	Not assessed	Not assessed	Not assessed	Na	Na	Na	Na
Safety Outcome	Risk of Bias	Inconsistency	Indirectness	Imprecision	Overall Assessment	Vaccine	Control	Vaccine Efficacy	Certainty
8. Adverse reaction	Not serious	Not assessed	Not assessed	Not assessed	Not serious	na	na	na	na
9. Local adverse reaction	Not serious	Not assessed	Not assessed	Not assessed					++++ High
10. Systemic adverse reaction	Not serious	Not assessed	Not assessed	Not assessed					++++ High
11. Adverse event	With concerns (interim report)	Not assessed	Not assessed	Serious	Serious	68/1131	67/1129	1.01 (0.73 1.41)	++ Low
12. Severe adverse event	With concerns (interim report)	Not assessed	Not assessed	Serious	Serious	7/1131	2/1129	3.49 (0.73, 16.78)	++ Low
13. Serious adverse event	With concerns (interim report)	Not assessed	Not assessed	Serious	Serious	4/1131	1/1129	3.99 (0.45, 35.67)	++ Low
14. Related serious adverse event	With concerns (interim report)	Not assessed	Not assessed	No cases	Not assessed	0	0	0	na
15. Withdrawals due to adverse event	With concerns (interim report)	Not assessed	Not assessed	Serious	Serious	2/1131	0/1129	4.99 (0.24, 103.85)	++ Low
16. Death	With concerns (interim report)	Not assessed	Not assessed	No cases	Not assessed	0	0	0	na

2. mRNA-1273 (Moderna)

COMPARISON : mRNA-1273 vs placebo in Children (12 to <18years old)

Efficacy Outcome (at >14 days after dose 2)	Quality Assessment					Summary of Findings			Certainty
	Risk of Bias	Inconsistency	Indirectness	Imprecision	Overall Assessment	Vaccine	Control	Vaccine Efficacy	
1.1. Symptomatic COVID-19 infection *without evidence of previous infection*	With concerns (interim report)	Not assessed	Not serious	Serious (wide CI)	Serious	0/2163	4/1073	100 (28.9, NE)	++ Low
1.2. Symptomatic COVID-19 infection *with or without evidence of previous infection*	With concerns (interim report)	Not assessed	Not serious	No cases	Not assessed	Na	Na	Na	Na
2. Severe COVID-19 infection	With concerns (interim report)	Not assessed	Not serious	No cases	Not assessed	Na	Na	Na	Na
3. COVID-19 infection, postD1, preD2	With concerns (interim report)	Not assessed	Not serious	Serious (wide CI)	Serious	25/2163	29/1073	59.5% (28.4, 77.3)	++ Low
4. Asymptomatic COVID-19 infection	With concerns (interim report)	Not assessed	Not assessed	No event	Not assessed	Na	Na	Na	Na
5. Hospitalization	With concerns (interim report)	Not assessed	Not assessed	No event	Not assessed	Na	Na	Na	Na
6. ICU Admission	With concerns (interim report)	Not assessed	Not assessed	No event	Not assessed	Na	Na	Na	Na
7. Death due to COVID-19	With concerns (interim report)	Not assessed	Not serious	Serious (wide CI)	Serious	0/2163	4/1073	100 (28.9, NE)	++ Low
Safety Outcome	Risk of Bias	Inconsistency	Indirectness	Imprecision	Overall Assessment	Vaccine	Control	Vaccine Efficacy	Certainty
8. Adverse reaction	Not reported	Not assessed	Not serious	Not reported	Not assessed	na	na	na	na
9. Local adverse reaction	Not serious	Not assessed	Not serious	Not serious	Not serious	2339/2482	455/1238	2.56 (2.38, 2.76)	++++ High
10. Systemic adverse reaction	Not serious	Not assessed	Not serious	Not serious	Not serious	2314/2478	398/1220	2.86 (2.64, 3.11)	++++ High
11. Adverse event	Not serious	Not assessed	Not serious	Not serious	Not serious	1701/2482	687/1238	1.24 (1.17, 1.31)	++++ High
12. Severe adverse event	Not serious	Not assessed	Not serious	Not serious	Not serious	2134/2478	561/1220	1.90 (1.78, 2.02)	++++ High
13. Serious adverse event	With concerns (interim report)	Not assessed	Not serious	Not serious	Serious	510/2485	197/1240	1.17 (1.12, 1.22)	+++ Moderate
14. Related serious adverse event	With concerns (interim report)	Not assessed	Not serious	Serious	Serious	4/2486	1/1240	2.0 (0.22, 17.83)	++ Low
15. Withdrawals due to adverse event	With concerns (interim report)	Not assessed	Not serious	Serious	Serious	2/2485	1/1240	0.54 (0.03, 8.67	++ Low
16. Death	With concerns (interim report)	Not assessed	Not serious	No cases	With concerns	0	0	na	na

3. Coronavac (Sinovac)

COMPARISON : Coronavac (Sinovac) vs placebo in Children (3 to 17 years old) using 0.3ug

Safety Outcome	Quality Assessment					Summary of Findings			Certainty
	Risk of Bias	Inconsistency	Indirectness	Imprecision	Overall Assessment	Vaccine	Control	Vaccine Efficacy	
1. Adverse reaction	Serious (unclear concealment)	Not assessed	Not serious	Serious	Serious	59/217	22/114	1.41 (0.91, 2.17)	++ Low
2. Local adverse reaction	Not reported	Not assessed	Not assessed	Not assessed	Not assessed	na	na	na	na
3. Systemic adverse reaction	Not reported	Not assessed	Not assessed	Not assessed	Not assessed	na	na	na	na
4. Adverse event	Very Serious (unclear concealment) (interim report)	Not assessed	Not serious	Serious	Very Serious	15/217	9/114	0.88 (0.40, 1.94)	+ Very Low
5. Severe adverse event	Not reported	Not assessed	Not assessed	Not assessed	Not assessed	na	na	na	na
6. Serious adverse event	Not reported	Not assessed	Not assessed	Not assessed	Not assessed	na	na	na	na
7. Related serious adverse event	Not reported	Not assessed	Not assessed	Not assessed	Not assessed	na	na	na	na
8. Withdrawals due to adverse event	Not reported	Not assessed	Not assessed	Not assessed	Not assessed	na	na	na	na
9. Death	Not reported	Not assessed	Not assessed	Not assessed	Not assessed	na	na	na	na
1. Adverse reaction	Serious (unclear concealment)	Not assessed	Not serious	Serious	Serious	59/217	22/114	1.41 (0.91, 2.17)	++ Low

Q11. Is COVID-19 vaccination effective and safe among pregnant and lactating individuals and their infants in the prevention of COVID-19 infections?

As of 27 Decermber 2021

RECOMMENDATIONS

We suggest the use of following vaccines, after the first trimester, for the prevention of COVID-19 infection in pregnant and lactating women.

a. **BNT162b2 (Pfizer)** *(Low certainty of evidence; Weak recommendation)*
b. **mRNA-1273 (Moderna)** *(Low certainty of evidence; Weak recommendation)*
c. **ChAdOx1 (AstraZeneca)** *(No direct evidence; Weak recommendation)*
d. **Ad26.CoV2.S (Janssen/Johnson&Johnson)** *(No direct evidence; Weak recommendation)*
e. **CoronaVac (Sinovac)** *(No direct evidence; Weak recommendation)*
f. **BBIBP-CorV (Sinopharm)** *(No direct evidence; Weak recommendation)*
g. **BBV152 (Covaxin)** *(No direct evidence; Weak recommendation)*

We suggest <u>against</u> the use of the following vaccines for the prevention of COVID-19 infection in pregnant and lactating women:

a. **Gam-CoV-Vac (Sputnik V)** *(No direct evidence; Weak recommendation)*
b. **NVX-2373 (Novavax)** *(No direct evidence; Weak recommendation)*

Consensus Issues

The Panel took into consideration that pregnant and lactating women are at a higher risk for severe COVID infection and are a particularly vulnerable population to recommend COVID-19 vaccination for them. Despite the absence of direct evidence of the efficacy of some vaccines for this population, the Panel still recommended their use using indirect evidence of efficacy and safety from the other vaccines and from the general adult population. The decision to recommend against the use of Gam-COVID-Vac (Sputnik V) was made based on the manufacturer's restriction of their product among pregnant women, in the absence of direct evidence of its effect. On the other hand, the decision to recommend against the use of NVX-2373 for pregnant women was mainly due to its low efficacy seen in the immunocompromised population and a higher risk of adverse reaction.

KEY FINDINGS

The current evidence base includes forty-two reports that investigated the effectiveness, immunogenicity, and safety of COVID-19 vaccination among pregnant and lactating women and their infants. Three were systematic reviews and 39 were observational studies. Available evidence demonstrates that COVID-19 vaccination provides sufficient protection against COVID-19 disease for pregnant and lactating women, with transfer of antibody protection to the newborn, without significant increase in the risk of maternal and neonatal adverse events nor adverse pregnancy and delivery outcomes.

INTRODUCTION

Pregnancy has been designated as a risk factor for severe COVID-19 infection by the Centers for Disease Control and Prevention (CDC) and the American College of Obstetricians and Gynecologists (ACOG). Physiologic changes in pregnancy such as

increased metabolic and cardiovascular demands, reduced lung capacity and immune modulation contribute to increased hospital and intensive care unit admission, and mortality in pregnant individuals with COVID-19 related illness. Subsequently, maternal infection in pregnancy correlates with increased neonatal respiratory distress and hospitalization, supporting the need for COVID-19 prevention.

As of July 30, 2021, the ACOG recommends that both pregnant and lactating individuals, as well as eligible people who consider any future pregnancy, be vaccinated against COVID-19. However, only one randomized clinical trial on the use of a COVID-19 vaccine versus placebo in pregnant women has been reported and Pfizer-N-Biotech is still in the recruitment phase as of October 28, 2021. Subsequently, there has been vaccine hesitancy among pregnant and lactating individuals. This review thus aims to synthesize existing real-world data on the effectiveness, immunogenicity and safety of COVID-19 vaccines in pregnancy and lactation.

REVIEW METHODS

Search Results

As of December 8, 2021, forty-two studies, including three systematic reviews were identified by the search. All studies in these systematic reviews, apart from case reports reporting on efficacy outcomes with sample sizes less than 10, were included in this review.

Characteristics of Included Studies

This review involves information provided by 39 observational studies. Twenty of these involved pregnant women, 15 involved lactating women and 4 involved both. No completed randomized controlled trial (RCT) comparing the efficacy of a COVID-19 vaccine to placebo/no vaccination in pregnant or lactating women was found.

Of the 24 studies included in the vaccinated pregnant women review, 13 were comparative cohort studies, three were case control studies, and the rest were cross-sectional or single cohort studies. Eleven studies compared the outcomes of the vaccinated with the unvaccinated pregnant women, of which one was a matched cohort study. Four of the studies specifically included previously infected pregnant women in the unvaccinated control group. One study included only vaccinated pregnant women and compared the outcomes across the three vaccines used. Four studies compared the outcomes of the vaccinated pregnant women with vaccinated non-pregnant and/or lactating women.

Seventeen studies used BNT162b2 vaccine, seven used mRNA-1273, four mentioned using mRNA vaccines, two included pregnant women vaccinated with Ad26.CoV2.S and another with ChAdOx1, and two studies did not specify the vaccine used. No study reported on the outcomes of vaccination among pregnant women with CoronaVac, Gam-COVID-Vac, BBV152, BBIBP-CorV or NVX2373.

Of the 19 studies included in the vaccinated lactating women review, nine were comparative cohort studies, one was a cross sectional study and the rest were single cohort non-comparative studies. Comparisons were among unvaccinated lactating women, unvaccinated pregnant women, non-lactating healthy women or vaccinated pregnant women.

Seventeen studies included women who received the BNT162b2, eight included those who received mRNA-1273, one included those who had CoronaVac and one included women who received ChAdOx1. One study did not specify the vaccine received by the participants. No study among vaccinated lactating women received Gam-COVID-Vac, BBV152, BBIBP-CorV or NVX-2373.

Details of the studies are in Appendix 2.

Methodological Quality Assessment of Included Studies

All available primary studies included in this review were observational studies. Majority of the comparative studies failed to control for confounders, and nearly all had missing data and short follow up. Thus, methodological assessment of the studies uniformly showed serious risk of bias. In addition, studies on efficacy were mostly immunologic studies, and those on safety were cross-sectional, non-comparative. Hence, the certainty of evidence for this review is generally low.

Details of the methodological quality assessment are in Appendix 3.

COVID-19 VACCINATION IN PREGNANT WOMEN AND THEIR CHILDREN

Results of Efficacy

Real World Evidence: Effectiveness

Four studies provided information on infection rates after vaccination among pregnant women.[1-4] All studies reported significantly lower COVID-19 infection rates associated with vaccination, with two studies reporting vaccine effectiveness rates that reflect sufficient to excellent protection.

A test-negative case-control study of pregnant women in Qatar matched three RT-PCR negative controls for every woman who tested positive. The vaccinated group received either BNT162b2 or mRNA-1273. Vaccine effectiveness was at 40.3% (95% CI 0.0-80.4) 14 days or more after being given the first dose but prior to second dose administration. At 14 days or more after the second dose was given, vaccine effectiveness was at 67.7% (95% CI 30.5-86.9).[1]

Another case-control study of pregnant women with no prior SARS-CoV-2 infection was done in Israel where 10,861 pregnant women given BNT162b2 were matched to unvaccinated pregnant controls. Median age of the participants was 30 years with majority in their third trimester at 48%, while 26% were in their first and second trimesters. With a follow-up of 7 to 56 days after the second dose, estimated vaccine effectiveness for any documented SARS-CoV-2 infection was 96% (95% CI 89-100). For symptomatic COVID-19 infection, vaccine effectiveness was 97% (95% CI 91-100), while for COVID-19 related hospitalization it was 89% (95% CI 43-100). During a longer follow up, estimated vaccine effectiveness for documented COVID-19 infection was at 93% with narrower confidence interval of 91-94% and 96% for symptomatic infection with a more precise CI of 94-97%. Cumulative incidences of documented COVID-19 infections were similar in both vaccinated and unvaccinated groups until day 14 after the first dose when incidence in the vaccinated group started to have a steep decline. No deaths were observed in both groups and only one case of severe illness was noted in the unvaccinated group. Due to low incidence of severe

outcomes, vaccine effectiveness was not estimated for severe infection and mortality.[2]

In a sequential questionnaire survey from among 326 pregnant women, the unvaccinated were 4.5 times more likely to report testing positive for COVID-19 since the survey one month prior (OR=4.5 [95% CI 1.19-17.6]) compared to those who received at least one dose of vaccine.[3]

A comprehensive vaccine registry from Mayo Clinic showed that vaccinated pregnant women were significantly less likely to have COVID-19 infection before delivery compared to unvaccinated pregnant women, (2/140, 1.4% vs 210/1862, 11.3%, p<0.001, computed VE 87.3% [95% CI 49.6-96.8]). No maternal COVID-19 infections occurred after vaccination during the pregnancy (both cases occurred prior to vaccination).[4]

Immunogenicity

Maternal Immune Response

Thirteen studies provided information on the maternal immune response to COVID-19 vaccination. Six studies showed significant rise in antibody titers (IgM, IgG and IgA) after vaccination compared to baseline.[5-10] Two cohort studies comparing vaccinated and unvaccinated pregnant women showed higher antibody IgM and IgG titers in the vaccinated group.[5,11] Four studies were consistent in showing higher antibody titers among vaccinated pregnant women when compared with titers from those who were unvaccinated previously infected.[5-6,12-13] Four studies compared the maternal antibody responses of pregnant, non-pregnant and lactating women after vaccination. Two comparative cohort studies showed similar titers across the three groups[6,12] while one showed lower titers in the pregnant women when compared to the lactating mothers.[14] A matched cohort study found lower serum IgG signal to cutoff ratio in pregnant compared to non-pregnant vaccinees.[15]

One study compared antibody titers at delivery after early versus late trimester vaccination. It showed lower titers in the early trimester vaccination group.[8]

Three studies compared responses to the different vaccines. Two studies showed higher rises in antibody titers after mRNA-1273 vaccination compared to BNT162b2.[12,14] Similar higher titers for anti-spike IgG2 with mRNA-1273 were seen.[16] This study also showed significantly lower antibody titers among those who received Ad26.CoV2.S compared to those who received the mRNA vaccine.

The mRNA COVID-19 vaccines were seen to produce maternal antibodies as early as 5 days after the first dose while transplacental transfer occurred as early as 16 days.[10] The follow up study by Rottenstreich et al. showed a significantly negative association between maternal IgG concentrations and time elapsed since immunization.[8]

Two cohort studies showed that immunologic response was rapid after vaccination in contrast to a more gradual response during COVID-19 infection,[5,12] producing higher anti-spike IgG titers.[12] Collier et al. also reported median IgG levels to the Receptor Binding Domain (RBD) of the S protein of SARS-CoV-2 as a useful tool to estimate individual protection against infection.[6] Similar to the other studies,

vaccinated pregnant women had higher anti-RBD IgG titers and neutralizing antibody titer than infected pregnant women. Gray et al. also showed that anti-spike and anti-RBD IgG titers both significantly increased after the first dose. This was followed by a further significant increase in both titers after the second dose.[12]

T-cell response to COVID-19 vaccination was evaluated in peripheral blood mononuclear cells by comparative cohort study.[6] Pregnant, lactating, and non-pregnant participants were seen to have similar spike-specific IFN-gamma production by CD4 T-cells, CD4 central memory T-cells, CD8 T-cells, and CD8 central memory T-cells post-vaccination.

Antibody response to the variants of concern by BNT162b2 vaccination was compared among non-pregnant, pregnant, and lactating women in a study from Israel.[6] Serum anti-RBD IgG binding and neutralizing antibody titers to the wildtype USA-WA1/2020 and B.1.1.7 (Alpha) RBD proteins were similar in all three groups but less to the B.1.351 (Beta) RBD protein. Median neutralizing antibody titers across all groups were 3.5-fold lower for the Alpha variant and 6-fold lower for the Beta variant than for the USA-WA1/2020 variant.

Antibody Transfer to the Fetus/Newborn (Via Placenta or Cord Blood)
Twelve observational studies investigated the potential transfer of immunity/protection of maternal vaccination during pregnancy to the child, through the identification of binding and neutralizing antibodies in the placenta or cord blood. Consistent findings across the studies were presence of antibodies in the cord blood, albeit at a lower level with a positive correlation between the maternal and cord blood antibody titers. Prabhu et al. showed that 44% of cord blood samples after the first vaccination dose had IgG detected which then increased to 99% of samples after both vaccine doses. Higher titers in the cord blood at the time of delivery were seen in those who received the vaccination earlier in the pregnancy.[8] Significantly higher IgG levels were seen in maternal serum and cord blood of vaccinated women as compared to recovered COVID-19 pregnant women. Significantly greater antibody persistence was also seen at 6 months among infants of vaccinated women compared to those with natural infection.[13]

Binding and neutralizing antibodies (IgG RBD) were analyzed in nine paired maternal and cord blood samples by Collier et al. and it was found that vaccinated maternal-infant dyads had a more robust response compared to non-vaccinated dyads.[6] Prabhu et al. showed that 44% of cord blood samples after the first vaccination dose had IgG detected which then increased to 99% of samples after both vaccine doses.[10] Cord blood IgG levels were seen to increase as maternal IgG levels increased, with positive correlation seen only after the second dose. Rottenstreich et al. showed that all 20 maternal-infant dyads in their study had detectable anti-S and anti-RBD specific IgG levels with significant positive correlations between maternal sera and cord blood concentrations, a finding replicated in 33 maternal-infant pairs in their follow-up cohort.[8] Similarly, the prospective cohort observed by Nir et al. showed a significant positive correlation between maternal serum levels of SARS-CoV-2 and cord blood IgG. Also, significantly higher IgG levels were seen in maternal serum and cord blood of vaccinated women as compared to recovered COVID-19 patients.[17] In a prospective case series by Mithal et al., IgG was higher than IgM, and only IgG was seen in cord blood among pregnant, vaccinated women.[7] Further

support is seen in the study by Zdanowski et al. where high anti-S total IgG antibody titers were seen in cord serum at birth in 16 analyzed mother-infant pairs post-vaccination with BNT162b2.[9] Significant positive correlation was seen between week of gestation of first dose and week of gestation for second dose and the respective cord-to-maternal ratio. The follow-up cohort by Rottenstreich et al. showed significantly higher anti-RBD-specific IgG concentrations in neonatal sera and placental transfer ratios among mothers vaccinated early in the third trimester compared with those vaccinated later on.[8] These data show that there is efficient maternal antibody transplacental transfer.

Shook et al. further compared the durability of anti-Spike IgG antibodies in the infants of vaccinated and infected women. Significantly higher maternal and cord titers were seen at delivery and significantly greater antibody persistence was seen at 6 months among infants of vaccinated women compared to those with natural infection.[13]

Results of Safety

Maternal Reactogenicity and Adverse Events

Eight observational studies reported maternal reactogenicity and adverse events post-vaccination. Shimabukuro and Kadali reported injection site pain as the most common adverse event after receiving either mRNA vaccines.[18-19] This was seen more in pregnant patients while non-pregnant patients had more systemic symptoms such as fatigue, myalgia, chills, fever, and nausea. All occurred more commonly after the second dose for both mRNA vaccines in the study by Shimabukuro. Meanwhile, the online survey questionnaire conducted by Kadali et al. on female healthcare workers showed no differences between pregnant and non-pregnant populations for adverse events reported. Similarly, rates of rash, fever, and severe fatigue were similar after vaccination in pregnant and non-pregnant women in the study by Peretz et al.[15] Timing of vaccine administration during pregnancy also did not significantly affect rate of side effects.

Incidences of post-vaccine symptoms were similar across pregnant, lactating, and non-pregnant women in the study by Gray et al.[12]

Collier et al. reported no severe adverse events or any complications in both mothers and neonates post-vaccination in pregnancy.[6]

In a prospective observational cohort, composite pregnancy complications in the short term were not increased following vaccination using BNT162b2, in comparison to the non-vaccinated group.[3] Another large retrospective cohort showed no differences in the incidence of pregnancy related hypertensive disorder and cesarean delivery rates in the vaccinated versus unvaccinated groups.[22] A composite of adverse maternal pregnancy-related events (eclampsia/pre-eclampsia, gestational hypertension, thromboembolism) and delivery outcomes such as uterine rupture, hemorrhage with transfusion, mode of delivery and stillbirth were also not significantly different between the vaccinated and unvaccinated groups in a delivery database registry.[4] Pregnancy or delivery outcomes were not significantly affected among the vaccinated as seen in the study by Beharier.[5] Obstetric complications (uterine contractions, vaginal bleeding, pre-labor rupture of membranes) were seen by Peretz et al. to be very low after vaccination.[15]

In the largest cohort by Shimabukuro et al., spontaneous abortion, stillbirth, preterm birth, small size for gestational age, congenital anomalies and neonatal death were all seen to be similar to or lower than published incidences.[18] In a study by Magnus et al. based on Norwegian registries, among 13,956 pregnant women (5.5% vaccinated) and 4521 women with miscarriages (5.1% vaccinated), no evidence was found of an increased risk for early pregnancy loss after COVID-19 vaccination.[21] Zauche et al. showed from v-safe registry data that there is no increased risk of spontaneous abortion (SAB) following mRNA COVID-19 vaccination and that the cumulative risk of SAB from 6-19 weeks' gestation is within the expected range based on previous SAB studies.[23]

Neonatal Outcomes

Seven studies provided neonatal outcomes after maternal vaccination during pregnancy.[12,15,18,20,22] Reported congenital anomaly rates ranged from 2.2 to 4.5%, and NICU admission rates from 1.5 to 15.1%. No neonatal deaths were reported by any study. The studies were consistent in their observation that outcomes were comparable known rates for the unvaccinated.

Gray et al. found that post-vaccination, 15% of neonates required NICU admission, 8% had transient tachypnea of the newborn (TTN), and 8% required supplemental oxygenation.[12] From the V-safe data set analysis, small size for gestational age, congenital anomalies and neonatal death were all seen to be similar to or lower than published incidences.[18] Similar results were seen in the cross-sectional study by Trostle et al. where rates of small for gestational age neonates and NICU admission rates were within expected rates for the general pregnant population.[20] Peretz et al. had no cases of preterm birth, fetal or neonatal death, and only 3.5% of cases needing NICU admission for respiratory support.(15) In the large retrospective cohort observed by Wainstock et al., slightly higher gestational age and birthweight was noted in women who received 2 doses of BNT162b2 but no differences in newborn characteristics and complications were found between vaccinated and unvaccinated women. There was even a lower risk of meconium stained amniotic fluid and non-reassuring fetal monitoring in the vaccinated group.[22]

Detailed outcomes are in Appendix 2b. The summary of findings tables for efficacy and safety are in Appendix 4.

COVID-19 VACCINATION IN LACTATING WOMEN AND THEIR CHILDREN

Results of Efficacy

Real World Evidence: Effectiveness

No study was identified reporting clinical effectiveness of COVID-19 vaccination among lactating women.

Immunogenicity

Maternal Immune Response

Six studies recorded antibody response among vaccinated lactating women. IgG was the dominant antibody noted in the maternal sera for all observational studies. Vaccinated lactating women had similar levels of antibody response with vaccinated pregnant women in the cohort study by Atyeo et al.[14] After their booster dose, the antibody response of lactating women increased more effectively than pregnant

women, as seen in higher IgG and NK-cell activating antibodies, but with lower FcR binding levels.

Both lactating and non-lactating vaccinated women had increased sera IgG in the cohort study by Charepe et al., with lower detectable IgM and IgA levels.[24] Among lactating women, serum IgM and IgG both increased after the second dose but with slight reduction of IgA levels. Higher IgG levels were seen by Valcarce et al. in individuals given BNT162b2 than those given mRNA-1273.[25]

Peak antibody titers in lactating, vaccinated individuals were seen to appear as early as 7 days and lasted as long as 28 days after the second dose in the cohort by Esteve-Paula et al. Juncker et al. and Friedman et al. also looked at trends of IgG titers in lactating individuals at multiple timepoints, with a trend towards gradual increase without any declines.[26-28]

Antibody Transfer to the Breastmilk

Thirteen studies reported on detected antibody levels in the breastmilk of vaccinated lactating individuals. Similar to maternal sera, IgG was consistently seen as the predominant antibody while results on IgA detection were varied.

Majority (96.4%) of breast milk samples obtained from vaccinated women after birth were positive for IgG in the study by Nir et al.[17] Similarly, IgG levels in breast milk of vaccinated lactating women were positively correlated with maternal IgG serum levels as seen by Esteves-Paula et al and Schwartz et al.[26,29]

Fox et al. and Gray et al. both detected IgA, IgM and IgG titers in breast milk after the first dose, with significantly increasing IgG after both vaccine doses.[12,30] This trend was also present in the cohort seen by Charepe et al. where IgG levels noted in breastmilk after the first dose of BNT162b2 increased further after the second dose. Moreover, a positive correlation was seen between duration of breastfeeding and milk IgG levels after the second dose of BNT162b2, implying that higher IgG titers are seen with longer breastfeeding time.[24]

Fox et al. and Gray et al. both detected IgA, IgM and IgG titers in breast milk after the first dose, with significantly increasing IgG after both vaccine doses.[12,30] This trend was also present in the cohort seen by Charepe et al. where IgG levels noted in breastmilk after the first dose of BNT162b2 increased further after the second dose. Moreover, a positive correlation was seen between duration of breastfeeding and milk IgG levels after the second dose of BNT162b2, implying that higher IgG titers are seen with longer breastfeeding time.[24]

Meanwhile, IgA was also present after the first dose but decreased after the second dose in the same cohort by Charepe et al.[24] Binding and neutralizing antibodies were noted in lactating women post vaccination but IgA responses were also low compared to infected lactating individuals in both studies by Collier et al. and Selma-Royo et al.[6,31] No differences were noted by Golan et al. in the IgA levels of vaccinated and infected lactating individuals.[32] In contrast, higher IgA levels were found in lactating individuals post- vaccination in the studies by Low et al. and Perl et al.[33-34] Furthermore, Perl et al. saw that SARS-CoV-2 specific IgA and IgG antibodies in breast milk remained elevated for 6 weeks post-vaccination and that IgA was secreted as early as two weeks after completion of doses. IgG levels only spiked

four weeks from the second dose.[34] Valcarce et al. also showed that a predominant IgA response was seen in human milk with a significantly increasing trend from pre-vaccination, post-first dose and post- second dose. This was positively correlated with increased IgA in maternal plasma seen 7-10 days after vaccination completion. IgG also significantly increased throughout the three time points as seen in human milk samples.[25]

All studies previously mentioned reported findings from individuals given mRNA vaccines, with the exception of Selma-Royo et al. who included 24 lactating women given ChAdOx1.[31] A single Israeli cohort by Calil et al. observed 20 lactating employees given CoronaVac vaccine where an increase in mean anti SARS-CoV-2 specific IgA was seen in the first two weeks after the first dose, but with significantly higher mean values only 5 and 6 weeks after.[35] However, four months after the first dose, only 5 out of 20 mothers still had high specific IgA levels. Future studies should have larger sample sizes and matched controls for more definitive conclusions on effect of the different vaccines in breast milk antibody titers.

Antibody Transfer to the Newborn

Two studies examined antibody levels in the newborn of pregnant and lactating women.[17,29] In a study of 64 vaccinated parturients, 94% of the neonatal blood spots were found to have SARS-CoV-2 IgG, with titers correlated with the maternal serum levels.[17] In contrast, a study of 61 vaccinated lactating women showed that none of the neonatal blood spots had any detectable IgG but 60% of the saliva of infants did.[29]

Results of Safety

Reactogenicity and Adverse Events

Low et al. reported that among vaccinated lactating women, 6% had axillary or neck lymphadenitis with 3% experiencing mastitis. Pain/redness/swelling at injection site was the most common side effect in lactating vaccinated women but no serious adverse events were noted.[36]

Mclaurin-Jiang et al. saw that symptoms were more commonly reported after the second dose of mRNA vaccination for lactating individuals, with mRNA-1273 being the more common cause of fatigue, headache, pain at injection site, muscle pain, chills, fever and allergic reactions than BNT162b2. In contrast, Perl et al. saw that lactating individuals had a higher incidence of vaccine-related adverse events after the first dose instead of the second dose, but still had pain at injection site as the most reported symptom.[37] Selma-Royo et al. included lactating women who received ChAdOx1 and it was seen that more symptoms such as fever and headache were reported as opposed to those who had mRNA vaccines.[31] More than 85% of the vaccinated lactating women presented with local or systemic symptoms after either first or second dose of mRNA vaccines in the study by Bertrand et al., again with more frequent occurrence after the second dose.[38] No significant adverse reactions were reported by either lactating mothers or babies in the small cohort given CoronaVac vaccine in the study by Calil et al.[35]

Changes in Lactation / Breastmilk

No changes were noted to milk supply post-vaccination in the studies by Low et al.[36] and McLaurin-Jiang et al.[37] No adverse events were also noted in children who were

breastfed by their mothers post-vaccination. Peretz et al. found reduced milk supply in a few of the population but production in all cases became normal within 72 hours.[15]

In summary, the available data shows an acceptable safety profile for vaccination in pregnant and lactating women, with majority of the data on mRNA vaccines.

Detailed outcomes are in Appendix 2c. The summary of findings tables for efficacy and safety are in Appendix 5.

RECOMMENDATIONS FROM OTHER GROUPS

As of June 2, 2021, in the interim, the World Health Organization (WHO) currently recommends vaccination in pregnant women when the benefits of vaccination to the pregnant women outweigh the potential risks, i.e. those with high risk of exposure to COVID-19 and those with comorbidities that place them in a high risk group for severe COVID-19.

The American College of Obstetrics and Gynecology (ACOG), as of July 30, 2021, recommends that pregnant and lactating individuals be vaccinated against COVID-19, including all eligible people who may consider future pregnancy. Pregnancy testing is not required prior to receiving any EUA-approved COVID-19 vaccine. In its updated recommendations on December 3, 2021, booster vaccination was also advised for pregnant individuals.[39]

The United Kingdom's Joint Committee on Vaccination and Immunisation (JCVI) has advised that pregnant women should be offered COVID-19 vaccines at the same time as people of the same age or risk group.

In its March 30, 2021 health update, the Department of Health stated that pregnancy is not a contraindication to COVID-19 vaccination and women are advised to get the vaccine after the first trimester of pregnancy. However, it stated that Gam-COVID-Vac should not be administered to pregnant women. Breastfeeding women may be vaccinated if they belong to the priority group by the WHO.[40] As of August 13, 2021, pregnant women were included in the national vaccination priority list.

The Philippine Obstetrical and Gynecological Society (POGS) practice bulletin updated on August 9, 2021 stated that COVID-19 vaccination is recommended for pregnant women, who should be given information about the risks of COVID-19 in pregnancy, the benefits of vaccination in the local epidemiologic context, and the current limitations of safety data in pregnant women. The POGS likewise recommended COVID-19 vaccination among breastfeeding women, noting that there is no need to avoid initiation or discontinue breastfeeding in those who receive the vaccine.[41]

RESEARCH GAPS

The following are identified research gaps regarding COVID-19 vaccination for pregnant and lactating women:

1. Efficacy and long-term safety for both mRNA vaccines and non-mRNA vaccines
2. Clinical efficacy / effectiveness and safety of heterologous vaccination
3. Clinical efficacy / effectiveness against infection with variants of concern

ONGOING TRIALS

The search performed on November 18, 2021 of the Clinicaltrials.gov registry showed one ongoing randomized, placebo-controlled trial on the safety, tolerability and immunogenicity of SARS CoV-2 RNA Vaccine Candidate (BNT162b2). It is currently in the recruitment phase.

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Appendix 1. Evidence to Decision

Table 1. Summary of initial judgements prior to the panel discussion (N=6)

FACTORS	JUDGEMENT						RESEARCH EVIDENCE/ADDITIONAL CONSIDERATIONS
Problem	No	Yes (6)					
Benefits	Large (5)	Moderate	Small	Uncertain	Varies (1)		• VE COVID-19 infection: 96% (89-100) • VE symptomatic COVID-19: 97% (91,100) • VE hospitalization: 89% (43,100) OR COVID-19 infection: 4.5 (1.19-17.9) for unvaccinated
Harm	Large	Moderate	Small (5)	Trivial	Varies (1)	Uncertain	• No serious adverse events reported. Adverse reaction and event rates general similar to vaccinated non-pregnant women. • Pain at injection site as most common side effect • Symptoms more common after second dose of mRNA vaccines; higher incidence of fever and headache in those given ChAdOx1 versus mRNA vaccines.
Certainty of evidence	High	Moderate	Low (6)	Very low			• Low
Balance of effects	Favors vaccine (4)	Probably favors vaccine (2)	Does not favor diagnostic/treatment or no diagnostic/treatment	Probably favors no diagnostic/treatment	Favors no diagnostic/treatment	Don't know	
Values	Important uncertainty or variability (1)	Possibly important uncertainty or variability (3)	Possibly NO important uncertainty or variability (2)	No important uncertainty or variability			
Resources required	Varies (5)	Large cost	Moderate Cost	Negligible cost	Moderate savings / Large savings	Uncertain/Don't know (1)	• Varies per vaccine
Certainty of evidence of resources required	No included studies (5)	Very low	Low (1)	Moderate	High		
Equity	Uncertain (2)	Reduced	Probably no impact	Probably increased (3)	Increased	Varies (1)	
Acceptability	Uncertain (1)	No	Probably no	Probably yes (3)	Yes (2)	Varies	• Varies per vaccine
Feasibility	Uncertain (2)	No	Probably no	Probably yes (2)	Yes (2)	Varies	• Varies per vaccine

Appendix 2a: Characteristics of Included Studies

Author/Study ID	Country	Study design	Vaccine type	No. of doses administered before analysis	Timing of vaccination	N	Sample collection	Population type	Outcomes reported
PREGNANT WOMEN REVIEW									
Atyeo	USA	Observational cohort	Pfizer, Moderna	One and two	Unspecified but mentioned that participants who gave birth were all immunized in 3rd trimester	131	Serum antibody of pregnant/lactating women and non-pregnant women	Vaccinated pregnant, lactating women and non-pregnant women	Serum antibody titers, Fc-receptor (FCR) binding capacity, IgG subclass response, Fc-effector profiles, NK cell activation ability of antibodies
Atyeo2	USA	Observational cohort	Johnson, Moderna. Pfizer	One or two	First trimester: n=18 (11%), Second trimester: n=88 (56%), Third trimester: n=52 (33%)	158	Maternal serum antibodies, cord blood samples	Vaccinated pregnant, lactating women and non-pregnant women	Maternal serum antibody (Spike specific antibody, Fc-receptor (FCR) binding), Umbilical cord serum (spike specific antibody titers, Fc-receptor binding, functional antibody responses, absolute anti-Spike IgG titer), Transfer ratio
Beharier	Israel	Case-control	Pfizer	One and two, numbers not specified	Mean gestational age at first vaccine dose: 34.5 +/- 7.5 weeks (third trimester)	213	Maternal and fetal blood samples: sera: IgG and IgM titers	Pregnant, vaccinated (n=86) Pregnant, unvaccinated, infected (n=65). Pregnant, unvaccinated, non-infected (n=62)	Temporal dependence in pregnant women, temporal dependence in neonates, maternal IgG between vaccinated vs PCR-positive, and Maternal-fetal IgG response to infection and vaccination correlation
Bleicher	Israel	Prospective Observational cohort	Pfizer	Unspecified	First trimester: n=24 (30%), Second trimester: n=37 (46%), Third trimester: n=18 (24%)	313	Two subsequent questionnaires	Pregnant vaccinated, and pregnant non-vaccinated women	Composite pregnancy complications, vaccine side effects, COVID-19 infection incidence, prevalence of vaccinated participants, refusal to be vaccinated
Butt	Qatar	Case-control matched, unbalanced to nationality	Pfizer, Moderna (unspecified)	One and two	Not reported	1255	Pregnant women identified from the centralized hospital electronic medical records. RT-PCR	Pregnant, vaccinated; Pregnant, unvaccinated; Pregnant, PCR positive; Pregnant, PCR negative	Vaccine effectiveness
Collier	USA	Observational cohort	Pfizer and Moderna	Not reported	<14 weeks: n=5 (17%); 14-28 weeks: n=15 (50%); >= 28 weeks: n=10 (33%)	131	Participants recruited in hospital wide prospective data and tissue biorepository	Non-pregnant, nonlactating, vaccinated (n=57) Pregnant, vaccinated (n=30) Lactating, vaccinated (n=16) Non-pregnant, unvaccinated, infected (n=6) Pregnant, unvaccinated, infected (n=22)	Adverse events, Serum binding and functional antibody responses, Binding and Neutralizing Antibodies in cord blood, Binding and Neutralizing Antibodies in Breast milk, T cell Responses in peripheral blood, Humoral and Cellular Immune Responses to SARS-COV-2 Variants of Concern
Dagan	Israel	Case-control	Pfizer	One (14-20 days after, 21-27 days after); Two (7-56 days after)	First trimester: n=2814 (26%), Second trimester: n=5242 (48%), Third trimester: n=2805 (26%)	21722	Pregnant vaccinated women identified from Clalit Health Services matched to unvaccinated pregnant controls	Pregnant, vaccinated; Pregnant, unvaccinated	Vaccine effectiveness

Gray	USA	Cohort	Pfizer and Moderna	One and Two	Mean gestational age at first vaccine dose: 23.2 weeks (second trimester)	131	Antibodies in umbilical cord blood, maternal sera and breastmilk measured using ELISA, Adverse events measured using questionnaire	Pregnant and non pregnant vaccinated women	Maternal antibody titer, local and systemic adverse events, adverse pregnancy outcomes, composite infant morbidity
Kadali	USA	Cross-sectional study	Pfizer and Moderna	Two	Not reported	1029	Online survey questionnaire	Pregnant and non pregnant vaccinated women	Local and systemic adverse events
Mithal	USA	Prospective case series	Pfizer, Moderna, unspecified	One and Two	Mean gestational age at first vaccine dose: 33 +/- 2 weeks (third trimester)	27	Maternal and umbilical cord blood	Pregnant, vaccinated	Maternal antibody titer, positive IgM rate, positive IgG rate, IgG transfer outcomes, Infant IgG outcomes
Nir	Israel	Prospective Observational cohort	Pfizer	Two	All women in third trimester, mean age of 33.5+/-3 weeks	75	Maternal and cord blood samples, breastmilk	Pregnant vaccinated and COVID-19 recovered women	Maternal serum IgG, Neonatal cord blood IgG, Breastmilk IgG
Peretz	Israel	Observational case-control	Pfizer	One and Two	1ST DOSE First trimester: n=76 (19%), Second trimester: n=193 (50%), Third trimester: n=121 (31%); 2ND DOSE First trimester: n=52 (13%), Second trimester: n=154 (40%), Third trimester: n=184 (47%)	650	Pregnant women vaccinated between 2-40 weeks of gestation, recruited via social media and matched to a control group of non pregnant vaccinated females at Sheba Medical Center, Tel Hashomer	Pregnant and non pregnant vaccinated women	Adverse events, Serum binding and functional antibody responses, Binding and Neutralizing Antibodies in cord blood, Binding and Neutralizing Antibodies in Breast milk, T cell Responses in peripheral blood, Humoral and Cellular Immune Responses to SARS-COV
Prabhu	USA	Cohort	Pfizer and Moderna	One and Two	Not reported	122	Semi quantitative testing of maternal peripheral blood and neonatal cord blood	Pregnant vaccinated women	Maternal antibody, Neonatal IgG, Placental transfer ratio
Rotteinstrech	Israel	Cohort	Pfizer	One or Two	Interval from first vaccine to delivery (median): 33 (30-37 days) *(third trimester)*	20	Antibody in maternal and cord blood sera samples	Pregnant vaccinated women	Maternal igG, cord blood IgG and placental transfer ratio
Rottenstreich2	Israel	Cohort	Pfizer	One and two	Interval from first vaccine to delivery (median): 33 (30-37 days) *(third trimester)*	171	Maternal and cord blood samples	Pregnant vaccinated women	Maternal IgG, Neonatal IgG, Placental transfer ratio
Shanes	USA	Cohort	mRNA vaccines	Two	Interval from first vaccine to delivery (mean): 45.96 +/- 24.3 days, *(second to third*	200	Antibody testing from plasma	Pregnant vaccinated and non vaccinated women	Maternal antibody titer, placental findings
Shimabukuro	USA	Observational cohort	Pfizer (n=19252), Moderna (n=16439)	One (n=16982), Two (n=12273)	Not reported	35961	Data from "v-safe and VAERS.	Pregnant, vaccinated	Infection rate, local adverse events, systemic adverse events, pregnancy loss, and neonatal outcomes
Shook	USA	Prospective cohort	Johnson (n=7), Moderna (n=28), Pfizer (n=55)	One or Two, unspecified	Interval from first vaccine to delivery (mean): 91 days (54 SD), *(second to*	102	Maternal and Neonatal blood samples	Pregnant women, COVID-19 recovered women, neonates of vaccinated women, neonates of women with recovered COVID-19 infection	Maternal and umbilical cord titers at birth, infant titer at 2 then 6 months, proportion of infants with detectable antibody after 2 or after 6 months

Theiler	USA	Case-control	Johnson (n=1), Moderna (n=12), Pfizer (n=127)	One (n=37), Two (n=103)	Mean gestational age at first vaccine dose: 32 (13.9 - 40.6) weeks, *(first to third*	2002	Medical records from Mayo Clinic	Pregnant, unvaccinated (n=1862), Pregnant, vaccinated (n=140)	Infection rate, Maternal and delivery outcome, length of hospital stay
Trostle	USA	Cross-sectional study	Pfizer, Moderna	One or Two	First trimester or <14 weeks: n=0, Second trimester or 14-27 weeks: n=14 (16.5%), Third trimester or >28 weeks: n=71 (83.5%)	424	Medical records	Pregnant, vaccinated	Fetal or neonatal demise, Gestational age at delivery, preterm delivery, mode of delivery, obstetrical complications, NICU admission, small for gestational age, congenital anomalies
Magnus 1	Norway	Case-control	Pfizer, Moderna, Astra Zeneca	One or Two	All women in first trimester	13956	Norwegian registry	Pregnant vaccinated and unvaccinated	
Wainstock	Israel	Retrospective observational cohort	Pfizer	One or Two	All women in third trimester, mean age of 30.6 +/- 5.3 weeks, *(third*	4860	HMO database	Pregnant vaccinated and pregnant unvaccinated	
Zauche	USA	Observational cohort	Pfizer, Moderna	One, Two	1ST DOSE Preconceptio n: n=380 (15.5%), First trimester or >=2 weeks and <14 weeks: n=1230 (50.1%), Second trimester or >=14 weeks and <20 weeks: n=846 (34.4%), 2ND DOSE Preconceptio n: n=188 (8.5%), First trimester or >=2 weeks and <14 weeks: n=885	2456	V-safe pregnancy registry	Pregnant, vaccinated	Self reported spontaneous abortion rates
Zdanowski	Poland	Observational cohort	Pfizer	One, Two	All women in third trimester, mean age of 31.75 +/- 2.05 weeks at first dose, mean age of 35.13 +/- 2.13	16	Maternal and cord blood samples	Pregnant vaccinated women	Anti-S total IgG antibody titers in maternal and cord serum

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Atyeo	USA	Observational cohort	Pfizer, Moderna	One and two	Unspecified but mentioned that participants who gave birth were all immunized in 3rd trimester	131	Serum antibody of pregnant/lactating women and non-pregnant women	Vaccinated pregnant Lactating women and non-pregnant women	Serum antibody titers, Fc-receptor (FCR) binding capacity, IgG subclass response, Fc-effector profiles, NK cell activation ability of antibodies
Bertrand	USA	Observational cohort	Moderna (n=52), Pfizer (n=128)	Moderna: both doses (n=52), Pfizer not clear	Post delivery	180	Records from Mommy's Human Milk Human Milk Research Biorepository at the University of California, San Diego	Lactating, vaccinated	Maternal symptoms and child events after vaccination
Caliil	Sao Paulo, Brazil	Observational cohort	Coronavac	One, Two	Post delivery	20	Human milk samples obtained from employee volunteers during immunization process in HC-FMUSP	Lactating, vaccinated	Anti-SARS-Cov-2 IgA Ratio
Charepe	Portugal	Observational cohort	Pfizer	One, Two	Unspecified	24	Maternal serum and breast milk	Lactating and non lactating vaccinated women	Maternal and breastmilk IgM, IgA and IgA antibodies
Collier	USA	Observational cohort	Pfizer and Moderna	Not reported	<14 weeks: n=5 (17%); 14-28 weeks: n=15 (50%); >= 28 weeks: n=10 (332%)	131	Participants recruited in hospital wide prospective data and tissue biorepository	Non-pregnant nonlactating vaccinated (n=57) Pregnant vaccinated (n=30) Lactating vaccinated (n=16) Non-pregnant unvaccinated infected (n=6) Pregnant unvaccinated infected (n=22)	Adverse events, Serum binding and functional antibody responses, Binding and Neutralizing Antibodies in cord blood, Binding and Neutralizing Antibodies in Breast milk, T cell Responses in peripheral blood, Humoral and Cellular Immune Responses to SARS-COV-2 Variants of Concern
Esteve-Palau	Spain	Observational cohort	Pfizer	Two	Post delivery	18	Breastmilk and maternal antibodies	Lactating, vaccinated	Antibodies in breast milk, seropositivity in maternal blood
Fox	USA	Observational cohort	Pfizer (n=6), Moderna (n=4)	Two	Post delivery	10	Breastmilk antibodies	Lactating vaccinated	Breastmilk SARS-CoV-2 Spike-specific IgA, SC, IgG reactivity
Friedman	Israel	Observational cohort	Pfizer	Two	5 months postpartum (mean 154 days, range 68-382)	10	Maternal serum and breast milk	Lactating vaccinated	Vaccine specific IgG/IgA ratio in breastmilk and serum
Golan	USA	Observational cohort	Moderna (n=9), Pfizer (n=14)	Two	Post delivery	23	Maternal serum and breast milk	Lactating vaccinated Lactating infected	anti-SARS-CoV2 IgG and IgM antibodies in maternal plasma, anti SARS-CoV2 IgA in human milk
Gray	USA	Cohort	Pfizer and Moderna	One and Two	Mean gestational age at first vaccine dose: 23.2 weeks, *(second to third*	131	Umbilical cord blood, maternal sera and breastmilk measured using ELISA, Adverse events measured using questionnaire	Pregnant and non pregnant vaccinated women Lactating vaccinated	Maternal antibody titer, local and systemic adverse events, adverse pregnancy outcomes, composite infant morbidity
Juncker	Netherlands	Observational cohort	Pfizer	One (n=6), Two (n=20)	Post delivery	26	Maternal serum and breast milk	Lactating vaccinated	Antibodies in breast milk, seropositivity in maternal blood
Low 1	Singapore	Observational cohort	Pfizer	Two	Post delivery	25	Breastmilk	Lactating vaccinated Lactating infected unvaccinated Lactatin unvaccinated	Antibodies in breast milk
Low 2 (singapore)	Singapore	Observational cohort	Pfizer	Two	Post delivery	88	Questionnaire	Lactating vaccinated	Maternal-child local, systemic and/or serious adverse events
McLaurin-Jiang	USA	Cross-sectional study	Pfizer (n=2702) Moderna	One (n=2627) Two (n=1828)	Post delivery	4455	Survey	Lactating vaccinated	Local and systemic maternal adverse events
Nir	Israel	Prospective Observational cohort	Pfizer	Two	All women in third trimester, mean age of 33.5+/-3 weeks	75	Maternal and cord blood samples, breastmilk	Pregnant vaccinated and COVID-19 recovered women	Maternal serum IgG, Neonatal cord blood IgG, Breastmilk IgG
Perl	Israel	Observational cohort	Pfizer	Two	Post delivery	84	Breastmilk	Lactatingvaccinated	Antibodies in breast milk

Schwartz	Israel	Observational cohort	Pfizer	Unspecified	Post delivery	61	Maternal sera and breastmilk	Lactating vaccinated women	SARS-CoV-2 IgG and IgA in serum and breastmilk
Selma-Royo	Spain	Observational cohort	Pfizer (n=30) Moderna (n=21) Astra Zeneca (n=24)	One, Two	Post delivery	131	Breastmilk	Lactating vaccinated (n=75) Lactating infected unvaccinated (n=19)	IgG, IgA antibodies in breast milk, maternal adverse events
Valcarce	USA	Observational cohort	Pfizer (n=14) Moderna (n=7)	Two	Post delivery	21	Maternal sera and breastmilk	Lactating vaccinated	Antibodies in breast milk, seropositivity in maternal blood

Appendix 2b. Detailed Data Extraction Tables for Pregnancy Reviews

STUDY ID	DESIGN	POPULATION	INTERVENTION (Vaccine) (Timing) (n)	CONTROL/S Population (n)	INFECTION RATE / VE	MATERNAL ANTIBODIES (Titers / %)	NEONATAL ANTIBODIES (Titers / %)	PREGNANCY OUTCOMES	DELIVERY OUTCOMES	NEONATAL OUTCOMES	LOCAL AR	SYSTEMIC AR	ADVERSE EVENTS
Atyeo (USA) **Preprint**	Comparative cohort Pregnant vs nonpregnant vs lactating Pfizer vs Moderna Age matched	Vaccinated women: Pregnant women Non pregnant Lactating	Pfizer and Moderna: unspecified (Timing not specified, implied that all participants who gave birth were all immunized in the third trimester) Pregnant vaccinated (n=84)	Non-pregnant vaccinated (n=16) Lactating vaccinated (n=31)	na	Differences in titers among pregnant, non-pregnant and lactating women post vac : higher titers pD1 in non-pregnant vs pregnant and lactating; higher pD2 titers in lactating vs pregnant Higher post D2 after Moderna vs Pfizer : ADNP, IgA, IgG2, IgG3, and NK cell activating antibodies Higher IgG1 and FC-binding titers after Pfizer vs Moderna Lower antibody titers & FcR binding in P & L after dose 1 but no significant difference after dose 2 After dose 2, lactating had higher IgG titer & NK cell activity (similar to non-pregnant but still with lower FcR binding)	(cord blood) (+) variable transfer of IgG to cord blood: equivalent for IgGS1 but lower for IgGS3 Higher levels of antibodies were observed in maternal blood compared to cord blood	na	na	na	na	na	na
Atyeo2 (USA) preprint	Comparative cohort (across vaccines) not all participants contributed to the outcomes	Vaccinated pregnant womencomparable by vaccination to sampling, maternal age, gravidity, parity, BMI, race, insurance status, obesity, autoimmune disorder	Pfizer = 69 [86]Moderna = 61[62]JnJ = 28 [27]Timing:First trimester: n=18 (11%), Second trimester: n=88 (56%), Third trimester: n=52 (33%)maternal infant dyads = 175 : 123 with titers, +52 dyads who delivered	Across platforms	na	Antibody titers and functions were significantly lower in those who received JnJ compared to mRNAshigher IgG2 and anti-S2 anti-spike response in those vaccinated with mRNA_1273 vs BNT162b2no trimester-specific differences in anti-Spike antibodies or FcR-binding, but 1st	Cord blood titers significantly higher in mRNA recipients compared to JnJ correlating with maternal levels spike-specific antibody response and response to variants mirrored maternal response IgG2 against Spike was significantly	na	na	na	na	na	na

						& 3rd trimester had higher functional antibody responsetime interval of extraction:mRNA: 62 [27-91] BNT162b2: 42 [22-74]Ad26.COV2.S: 58 [38-85]	higher in the cord blood of mRNA 1273 recipients compared to either Ad26.COV2.S or BNT162b2 recipients Functional antibody responses were lower in the cord blood of Ad26.COV2.S recipients compared to mRNA-1273 or BNT162b2 ***Similar maternal and cord blood antibody titers and functions*** *Higher TRs generated by first and second trimester vaccination (median TR = 1.5 and 1.3) compared to third trimester vaccination (median TR = 1.0)- highest TRs for first trimester vaccination but lower absolute titers in cords of mothers vaccinated in the first trimester (waning maternal titers by delivery)*						
Beharier et al. (Israel)	Comparative cohort (vac vs unvac)younger infectedsimilar comorbidities	Pregnant women 213 dyads	BNT162b2(n=86) Timing: Mean gestational age at first vaccine dose: 34.5 +/- 7.5 weeks (third trimester)	Pregnant unvaccinated, infected(n=65)Pregnant unvaccinated, non-infected(n=62)	na	IgG, IgMsignificant rise in anti-S1, anti-S2, and anti-RBD IgG from baseline to at least 15 days after D2 compared to unvacsimilar pattern for IgMlevels and pattern similar to infected unvaccinated; (but anti-N levels also rise; low seropositivity for anti-N-IgG for the vaccinated N-group)	IgG, IgM (fetal / cord blood)significant rise in anti-S1, anti-S2, and anti-RBD IgG from baseline to at least 15 days after D2, titers similar to maternal IgM levels significantly lower than maternal levels	na	Preterm delivery:Vaccinated: 4/92 (4.3%)UnVac noninfec: 5/66 (7.6%)UnVac Infec: 8/74 (10.8%)	NICU admission:Vac: 4/92 (4.3%)UnVac noninf: 1/66 (1.6%)UnVac Infec: 1/74 (1.6%)	na	na	na

Bleicher (Israel)	Comparative cohort (online questionnaire, 2 instances) (vacc vs Unvac) Vaccinated group more with flu vaccine, more were medical workers, less had no risk factors, less had previous pregnancy loss	Pregnant women who completed 2 online questionnaires n = 313	Pfizer Timing First trimester: n=24 (30%), Second trimester: n=37 (46%), Third trimester: n=18 (24%)	Unvaccinated	COVID-19 positive since the last questionnaire (Vaccinated vs unvac): 3/202 (1.5%) vs 8/124 (6.5%) OR = 4.5 (95%CI 1.19-17.6)	na	na	No difference in composite pregnancy complications (15.8% vs 20.2%) Vaccinated vs Unvac : fetal grown restriction : 3/202 (1.5%) vs) (0.0), ns	First trim pregnancy loss = 2/202 0.9%) vs 1/124 (0.8%) ns No preterm births in either group	Anomaly on anatomy scan: 9 (4.5%) vs 6 (4,8%) ns	66% with local reaction at injection site	16.8% weakness 16.8% headache	na
Butt (Qatar) **preprint**	TNCC matched by age and reason for testing	2020 pregnant women with RT-PCR results PCR (+) : 393 PCR (-) : 1074	pregnant, vaccinated mRNA vaccine unspecified (Timing not specified) PCR (+) = 23 PCR (-) = 109	unvaccinated PCR (+) = 370 PCR (-) = 753	VE at least 14 days after D2: 67.7% (30.5, 86.9) VE at least 14 days after D1, before D2 : 40.3% (0, 80.4)	na	na	na	na				
Collier (USA)	Comparative Cohort(vaccinated pregnant/nonpregnant/lactating vs nonvaccinated nonpregnant infected, vs nonvaccinated pregnant infected)	Pregnant, lactating and nonpregnant vaccinated, non-pregnant infected unvaccinated, pregnant-infected unvaccinated	Pfizer (n=56)Moderna (n=47)Vaccinated nonpregnant : 57Vaccinated pregnant : 30Vaccinated lactating : 16Timing <14 weeks: n=5 (17%); 14-28 weeks: n=15 (50%); >= 28 weeks: n=10 (33%)	Unvaccinated, pregnant, infectedunvaccinated, non-pregnant, infected	na	Significant increase in RBD IgG and neutralizing antibody titers; equivalent between non-pregnant and lactating vaccinated, higher than infected unvaccinated Median RBD-IgG binding antibody titer:pregnant, vaccinated: 27 601 Pregnant, infected: 1321 Non-pregnant, vaccinated: 37839	(cord blood) among vaccinated :similar RBD IgG titers between maternal sera and cord blood RBD IgG: maternal: 14 953 cord blood: 19 873 Lower NABs in cord blood vs maternal sera NT50 (NAB): Maternal: 1016 cord blood: 324 Among unvaccinated infected:similar levels of RBD and NABs between maternal sera and cord blood	No pregnancy complications	na	No neonatal complications	na	Fever was reported in 27/52 nonpregnant (52%, SD; 7%), 4/29 pregnant (14%; SD, 6%), and 7/16 lactating (44%; SD, 12%) women	No severe adverse events

						Non-pregnant, infected: 771 Pseudovirus NT50:pregnant: 910 Non-pregnant: 901 Functional assays: ADNP:pregnant: 27 non-pregnant: 58 ADCD:pregnant: 402 non-pregnant: 376 ADCP:pregnant: 282 non-pregnant: 277 Cellular response comparable in pregnant, lactating and nonpregnant vaccinated womenT cell responses (per million PBMCs): Pregnant: 270 Non-pregnant: 435 Spike-specific IFN-γ production by CD4 T cells,CD4 central memory T cells, CD8 T cells, and CD8 central memory T cells were comparable in pregnant, lactating, and non-pregnant women Anti RBD IgG comparable with Alpha but lower with Beta strain, but NABs lower for both alpha (3.5-fold lower) and beta strain (6-fold lower) for pregnant and lactating, as with non-pregnant; No differences in ELISPOT response, CD4 T-cell responses, CD4 central memory T-cell responses, CD8 T-cell responses, or	RBD IgG: Maternal: 1342 Cord blood: 635 NT50 (NAB): Maternal: 151 cord Blood: 164						

						CD8central memory T-cell responses across these variants							
Dagan (Israel) Communication	Matched cohortby age, pregnancy trimester, population sector, CDC risk factorcovariates: age, sex, pregnancy trimester, place of residence, health care worker, long-term care facility resident, influenza vaccination, comorbidities	Vaccinated pregnant 16 years and older, matched with unvaccinated pregnant	BNT162b2 (n = 10, 861) Timing First trimester: n=2814 (26%), Second trimester: n=5242 (48%), Third trimester: n=2805 (26%)	Unvaccinated (n = 10,861)	7 days after D2 (56 days ffup) VE any infection : 96% (89-100) : 1 vs 37 VE symptomatic infection : 97 (91-100) : 1 vs 26 Hospitalization : 89% (43-100) 1 vs 7 Severe disease: 1 in unvaccinated vs 0 in vaccinated Death : no events for both	na	na	na	na	na	na	na	na
Gray (USA)	Comparative cohort (Pregnant vs lactating vs nonpregnant)	Vaccinated women Pregnant, lactating and nonpregnant vaccinated	Pregnant (N=84) Pfizer: n=41 (49%), Moderna: n=43 (51%) First dose given at mean gestational age of 23.2 weeks, 46% in 2nd trimester, 40% in 3rd trimester	Non-pregnant vaccinated (N=16) Pfizer: n=8 (50%) Moderna: n=8 (50%) pregnant infected 4-12weeks prior (37)	na	Antibody titers similar between pregnant, lactating and nonpregnant vaccinated, all higher than infected; did not differ by trimester of vaccination Higher S- and RBD-specific IgA responses were noted in Moderna vaccinees than Pfizer/BioNTech vaccinees IgG predominant by 2 weeks after dose 2	Slightly lower NABs in the cord compared to maternal sera	na	13 deliveries: 1 spontaneous preterm delivery	13 deliveries: 1 (8%) - supplemental O2 1 (8%) - TTN 2 (15%) NICU admission 0 death 0 sepsis 0 NEC	na	na	Cumulative symptoms scores of side effects in all 3 groups were low and with no significant difference
Kadali (USA) letter	Cross sectional(Vac vs nonVac)	Pregnant HCWs	mRNA vaccine(Timing not specified)(n =	Nonpregnant HCW = 991	na	na	na	na	na	na	na	na	No significant difference in side effect

			38)Pfizer = 20Moderna = 18										profile between the 2 groups
Mithal (USA) letter	Single cohort (matched maternal and cord blood)	Vaccinated pregnant (mostly HCW)	Pfizer, Moderna, unspecified (n= 27) Timing: Mean gestational age at first vaccine dose: 33 +/- 2 weeks (third trimester) Pfizer = 18 Moderna = 6 unknown = 4	None	na	IgM: 15/27 IgG: 26/27	IgG transfer ratio : 1.0 ± 6 increased latency from vaccination to delivery associated with an increase in transfer ratio IgM: 0/28 IgG: 25/28 (2 mothers: dose 1 <3 weeks before delivery) Increased latency from vaccination to delivery (weeks): associated with an increased transfer ratio (β=0.2; 95% CI, 0.1, 0.2) Having received the second vaccine dose before delivery: significantly associated with increased infant IgG levels (β=19.0; 95% CI, 7.1, 30.8) Latency from vaccination to delivery: associated with increased infant IgG levels (β=2.9; 95% CI, 0.7, 5.1)	na	na	na	na	na	na
Nir	Comparative cohort (vaccinated vs unvac infected)	Parturients	BNT162b2(mean 21 days prior to delivery)(n=64) Timing: all women in third trimester, mean age of 33.5+/-3 weeks	Unvaccinated, had COVID during pregnancy(mean 92 days prior to delivery)(n=11)	na	na	Cord blood: IgG titers higher in vaccinated (26.1 vs 20.2)good correlation between maternal and cord blood titers	No difference in gestational diabetes, gestational hypertensive disease between vaccinated and unvaccinated	na	na	na	na	na
Peretz (Israel)	Comparative cohort (stated as case	Vaccinated women excluded those who	Pregnant Pfizer (2-40 weeks	Non-pregnant women (n=260)	na	Lower serum IgG signal to cut off ratio in pregnant compared to non-	na	Gestational diabetes = 4 (7%)	n=91 deliveries, 57 with complete data	2/57 NICU admission for respiratory support	Less local pain and swelling	Myalgia, arthralgia and headache	No significant differences in the rates

	control in study but assessed as a matched cohort study) Matched by age; comparable by BMI and comorbidities Not all outcomes available for all recruited	delivered and had an abortion before D2	AOG) (n=390) Immunogenicity (n=96) Timing: 1ST DOSE First trimester: n=76 (19%), Second trimester: n=193 (50%), Third trimester: n=121 (31%); 2ND DOSE First trimester: n=52 (13%), Second trimester: n=154 (40%), Third trimester: n=184 (47%)			pregnant (27.03 vs. 34.35)		preeclampsia = 1 (1.8%)	no preterm delivery no fetal deaths no neonatal death no miscarriage		than non-pregnant	and lymphadenopathy were less than non-pregnant Rates of rash, fever and severe fatigue comparable to non-pregnant women; paresthesia more common (after dose 2)	of side effects according to whether patients were vaccinated in the first, second or third trimester
Prabhu (USA) letter	Single cohort	Vaccinated pregnant who delivered	Pfizer or Moderna; at least 1 dose (Time not specified) (n=122)	None/self	na	Increasing maternal IgG starting 2 weeks after first vaccine; linearly associated with cord blood	Cord blood IgG linearly associated with maternal levels Placental transfer ratio correlated with the number of weeks elapsed since maternal vaccine dose 2	na	na	na	na	na	na
Rotteinstrech (Israel) Brief report	Single cohort	Vaccinated pregnant who delivered	Pfizer, two doses(n= 20) Timing: Interval from first vaccine to delivery (median): 33 (30-37 days) *(third trimester)*	Self	na	All women were positive for anti-S and Anti-RBD specific IgG; IgM in 6 mothers Anti-S: 319 [IQR 211–1033]Anti-RBD: 11 150 [IQR 6154–17 575]	All were positive for anti-S and anti-RBD IgG No IgM Anti-S: 193 [IQR 111–260] Anti-RBD: 3494 [IQR 1817–6163] Titers correlated with maternal sera; increasing titers with increased time since first dose of vaccine Median placental transfer ratios: Anti-S: 0.44 [IQR 0.25–0.61]	na	na	na	na	na	na

							Anti-RBD: 0.34 [IQR 0.27– 0.56]						
Rottenstreich2	Comparative cohort (early vs late 3rd trim vaccination)	Pregnant women vaccinated in the 3rd trim	BNT162b2 early (27-31weeks) (n= 83) Timing: Interval from first vaccine to delivery (median): 33 (30-37 days) *(third trimester)*	Late (32-36wks) n=88	na	Median anti-S and anti-RBD titers at time of delivery lower in the early vs late group (S: 200 vs 292 AU/ml) (RBD : 3980 vs 8506)	Neonatal concentrations of anti-S IgG did not differ AntiRBD IgG higher in the early vs late group (9620 vs 6697); positively correlated with increasing time since vaccination NAB titers reflected maternal activity; higher placental transfer ratio with early vs late (1.9 vs 0.8),	3rd vs 1st trim gestational DM: 7.2% vs 8.0% gestational HPN: 1.2% vs 2.3%	na	na	na	na	na
Shanes (USA)\ research letter	Comparative cohort(vac vs unvac) timing of vaccination not known for all	Pregnant	vaccine not specified(n = 84) Interval from first vaccine to delivery (mean): 45.96 +/- 24.3 days, *(second to third trimester)*	Unvaccinated (n= 116)	na	Higher IgG and IgM titers after vaccination (compared to unvaccinated)	na	na	Higher vaginal delivery in vaccinated (79% vs 65%) Placental examination of vaccinated showed no increased decidual arteriopathy, fetal vascular malperfusion, low-grade chronic vasculitis or chronic histiocytic intervillositis	na	na	na	No increased incidence of decidual arteriopathy ,fetal vascular malperfusion, low-grade chronicvilliti s, or chronic histiocytic intervillositis
Shimabukuro (USA)	Cross-sectional (historical control)	Pregnant vaccinated 16-54 yo enrolled in v-safe and in registry n = 35691 v-safe pregnant: 3958 827	Pfizer (n=19252), Moderna (n=16439) Timing not specified	Non pregnant 16 to 54yo	na	na	na	SGA = 3.2% n= 827 115 (13.9%) pregnancy losses still birth 0.1% spon abortion 12.6% (96 occurred before 13 weeks)	Preterm birth = 9.4% SGA = 3.2% Congenital anomalies = 2.2% n= 827	Major congenital anomalies = 2.2% no neonatal deaths Calculated proportions of pregnancy and neonatal outcomes	(injection-site pain was reported more frequently among pregnant persons	Overall reactogenicity profile was similar	221 pregnancy-related AEs, Most common was spontaneous abortion (46 cases)

		completed pregnancies						induced abortion/ectopic 1.2% 712 (86.1%) live births, mostly among participants vaccinated in the 3rd trim)	115 (13.9%) pregnancy losses Still birth 0.1% Spon abortion 12.6% (96 occurred before 13 weeks) Induced abortion/ectopic 1.2% 712 (86.1%) live births, mostly among participants vaccinated in the 3rd trim)	appeared similar to incidences published in literature			
Shook	Comparative cohort(vaccinated vs infected)	Deliveries	Johnson (n=7), Moderna (n=28), Pfizer (n=55) Timing: Interval from first vaccine to delivery (mean): 91 days (54 SD), *(second to third trimester)*	Previously infected median 71 days from infection to delivery (n=12)	na	Maternal titers at birth significantly higher vs. infected (1.94 vs).65)	Umbilical cord titers at birth significantly higher at birth vs infected (2.06 vs 1.0) Iinfant titers at 2 months seen only in the vaccinated (1.19) at 60 months 0.33, also seen only in vaccinated antibodies detected in 94% at 2 months (vs 0) and in 60% at 6 mos (vs 8%)	na	na	na	na	na	na
Theiler (USA) **Preprint**	Comparative cohort (vaccinated vs infected)	Deliveries	Johnson (n=1), Moderna (n=12), Pfizer (n=127) (N=140) Timing: Mean gestational age at first vaccine dose: 32 (13.9 - 40.6) weeks, *(first to third trimester)*	Unvaccinated, infected (n=212)	Infection prior to delivery: vac: 2/140 (1.4%) unvac : 210/1862 (11.3%) - 26 in first trim, 84 in 2n, 100 in 3rd No maternal COVID-19 infections after	na	na	No difference in gestational hypertension, eclampsia	No difference in preterm births, still births,	No difference in early neonatal deaths No difference in NICU admission, APGAR <7, low birth wight	na	na	Adverse outcomes index not different between groups: 5.0% (7/140) vs 4.9% (91/1862) No maternal or early neonatal deaths

					vaccination during pregnancy								
v	Cross-sectional	Pregnant vaccinated; at least 1 dose of mRNA vaccine	Pfizer: n = 332 (78.3%); Moderna: n = 92 (21.7%), N= 424 348 (82%) two doses 76 (17.1%) one dose Timing: First trimester or <14 weeks: n=0, Second trimester or 14-27 weeks: n=14 (16.5%), Third trimester or >28 weeks: n=71 (83.5%)	none	na	na	na	18.8% hypertensive disorder of pregnancy2 (0.6%) intrauterine growth restriction	5.9% preterm birth 9 spontaneous abortions, 8 in the first trim (6.5%)3 terminated pregnancies85 liveborn infantsno stillbirths	2 (0.6%) intrauterine growth restriction5 (1.5%) with anomalies15.5 % admission to NICU	na	na	na
Magnus	Case control Adjusted for age, country of birth, marital status, educational level, household income, number of children, employment as healthcare prof, underlying risk conditions for COVID, previous test positive for SARSCOV, calendar month	First trimester registrants Cases: miscarriages control: continued pregnancy	Pfizer Moderna AstraZeneca unspecified N = 13956 Timing: all women in first trimester	none	na	na	na	na	OR for miscarriages for vaccination : 0.91 (0.75, 1.10) for vaccination in the previous 3 weeks, 0.81 (0.69 , 0.95) for vaccination in the previous 5 weeks 5-week window Pfizer : 0.80 (0.67, 0.96) Moderna : 0.84 (0.56, 1.25) AZ : 0.84 (0.48, 1.48)	na	na	na	na

Wainstock	Comparative cohort(vaccinated vs unvaccinated)vaccinated older, conceived following fertility treatments, had sufficient prenatal care, higher socioeconomic positionadjusted for age, fertility treatment, socioeconomic score	Women who delivered, excluded women diagnosed with COVID-19 in the past, multiple gestation or unknown vaccination statusn = 4399	BNT162b2Timing: All women in third trimester, mean age of 30.6 +/- 5.3 weeks, *(third trimester)*	Unvaccinated	na	na	na	No difference in pregnancy complications except for meconium stained amniotic fluid, aOR 0.52 (0.32-0.83) for vaccinated	No difference in delivery outcomes (age at delivery, CS, placental abruption, postpartum hemorrhage)	No difference in APGAR <7 at 5 mins, birthweight, SGA, newborn respiratory complications, new born fever, length of newborn hospitalization compared to unvaccinated	na	na	na
Zauche	Cross sectional / single cohortwith lost patients	V-safe pregnancy registry participants who received at least one dose of mRNA vaccine preconception or prior to 20 weeks AOG, and who did not report pregnancy loss before 6 weeks gestation	(N=2456) Pfizer: n=1294 (52.7%), Moderna: n=1162 (47.3%)(prior to 20 weeks AOG) Timing: 1ST DOSE Preconception: n=380 (15.5%), First trimester or >=2 weeks and <14 weeks: n=1230 (50.1%), Second trimester or >=14 weeks and <20 weeks: n=846 (34.4%), 2ND DOSE Preconception: n=188 (8.5%), First trimester or >=2 weeks and <14 weeks: n=885 (40%),	none	na	na	na	na	Cumulative risk of spontaneous abortion from 6-19 weeks = 14.1% (95%CI 12.1-16.1%), risk increasing with age	na	na	na	na

			Second trimester or >=14 weeks and <28 weeks: n=1125 (50.9%)										
Zdanowski (Poland)	Single cohort	Vaccinated mothers who delivered	BNT162b2,2 dosesn = 16Timing: All women in third trimester, mean age of 31.75 +/- 2.05 weeks at first dose, mean age of 35.13 +/- 2.13 weeks at second dose	None	na	Anti-S = 100%, 984.37 U/mL	Anti-S = 100% in umbilical blood, 1062.51 U/mlcord/materna: 1.28positive correlation between weeks from first vaccine dose to delivery and antiS antibody titer in cord blood	na	na	na	na	na	na

Appendix 2c. Detailed Data Extraction Tables Lactating Women Reviews

STUDY ID	DESIGN	POPULATION	INTERVENTION (Vaccine) (Timing) (n)	CONTROL/S Population (n)	INFECTION RATE / VE	MATERNAL ANTIBODIES (Titers / %)	NEONATAL ANTIBODIES (Titers / %)	BREASTMILK ANTIBODIES	OVERALL AR	LOCAL AR	SYSTEMIC AR	ADVERSE EVENTS
Atyeo	Comparative cohort (lactating vs nonpregnant)	Vaccinated pregnant (n=84) vs Vaccinated lactating (n=31)	Pfizer and Moderna: unspecified (Timing not specified, implied that all participants who gave birth were all immunized in the third trimester) Vaccinated lactating (n=31)	Non-pregnant (n=16)	na	Lower antibody titers & FcR binding in P & L after dose 1 but no significant difference after dose 2 After dose 2, lactating had higher IgG titer & NK cell activity (similar to non-pregnant) Lactating women induced significantly higher NK cell activating antibodies after boosting	Higher levels of antibodies were observed in maternal blood compared to cord blood	Robust transfer of FCR binding antibodies after the second dose; also with enriched transfer of IgM IgG and IgA to breast milk higher transfer with Moderna vs Pfizer	na	na	na	na
Bertrand	Comparative cohort (across vaccines)	Vaccinated lactating women	BNT162b2 = 128 mRNA-1273 = 52 Timing: post delivery	None (with each other)	na	na	na	na	After D1: 89.4% Pfizer; 98.1% Moderna After D2 : 98.3 Pfizer, 100% Moderna	After D1: 86.8% Pfizer, 96.2% Moderna After D2: 87.9% Pfizer, 98% after moderna Significantly higher with moderna at dose 2	After D1: 41.5% Pfizer, 53.8 Moderna After D2: 87.1% Pfizer, 96.0% Moderna Significantly higher with Moderna at dose 2	Reported significant reduction in mild production for both vaccines, but normalized after 72 hours; 5 women reported change in color of breast milk post vaccination Few events for children reported post vaccination, including irritability, poor sleep
Caliil	Single cohort	Vaccinated lactating women (N = 20)	CoronaVac N=20 Timing: post delivery	Self	na	na	na	Siginificant rise in IgA titers in the first 2 weeks after the	na	na	na	na

		(n = 10 with 4-month sample)						first dose, significantly higher mean values at weeks 5 and 6 (21 days after the second dose) All determinations, including at 4 months showed levels above the cut off				
Charepe	Comparative cohort (lactating vs non lactating)	Healthcare workers, vaccinated	BNT162b2 N=24 (Timing not specified) Lactating	Non lactating vaccinated	na	All had positive serum antibodies after the second dose 1st dose igG levels higher in non-lactating group	IgG in 42.9% after D2 IgA in 21.4% after D2 (higher in D1) Higher correlation between IgA maternal and serum IgG titers higher with longer breastfeeding time	na	No difference in vaccination side effects	na	Most common AE was myalgia	na
Collier (USA)	Comparative cohort (pregnant, lactating vaccinated vs unvaccinated)	Pregnant, lactating and nonpregnant vaccinated, non-pregnant infected unvaccinated, pregnant-infected unvaccinated	Pfizer (n=56) Moderna (n=47) Timing: <14 weeks: n=5 (17%); 14-28 weeks: n=15 (50%); >= 28 weeks: n=10 (33%)	Unvaccinated, pregnant, infected Unvaccinated, non-pregnant, infected	na	Significant increase in RBD IgG and neutralizing antibody titers; equivalent between non-pregnant and lactating vaccinated, higher than infected unvaccinated Pseudovirus NT50: lactating: 783 non-pregnant: 901 Functional assays: ADNP: Lactating: 12 Non-pregnant: 58 ADCD: lactating: 333 Non-pregnant: 376 ADCP: lactating: 249 non-pregnant: 277 Cellular response comparable in pregnant, lactating and nonpregnant vaccinated women	na	Lower IgG titers in breast milk among vaccinated compared to infected, despite higher titers in the maternal sera of vaccinated Serum RBD IgG: vaccinated: 25 055 infected: 1593 Breastmilk RBD IgG: vaccinated: 97 infected: 203 Same pattern with IgA titers and median NT50 (lower with vaccinated compared to infected) Serum RBD IgA: vaccinated: 820 infected: 152 Breastmilk RBD IgA: vaccinated: 25	na	na	Fever was reported in 27/52 nonpregnant (52%, SD; 7%), 4/29 pregnant (14%; SD, 6%), and 7/16 lactating (44%; SD, 12%) women	No severe adverse events

						T cell responses (per million PBMCs): pregnant: 185 non-pregnant: 435 Anti RBD IgG comparable with Alpha but lower with Beta strain, but NABs lower for both alpha and beta strain for pregnant and lactating, as with non-pregnant		infected: 1940 Median breastmilk NT50: vaccinated: 75 infected: 153				
Esteve-Palau	Single cohort With missing samples	Lactating, no previous infection	Pfizer (n=18) Timing: post delivery	None/self	na	na	na	Median IgG levels for serum-milk pairs T1(14s p D1) : 410-1.7 T2(14d pD2) : 11505-52.2 T3 (28d pD2) : 8311-41.7 Breast milk IgG(S1) levels dramatically increase after the second dose and that they are positively correlated with corresponding serum levels	Adverse reactions were minor	na	na	No adverse events observed in the lactating infants
Fox	Single cohort	Lactating, no history of SARS COV infection, negative IgA titers in milk prior to vaccination	Pfize (n=6), Moderna (n=4) Timing: post delivery	None/ self at baseline	na	na	na	Spike specific IgA % = 60^ Secretory IgA = 50% Spike specific IgG = 100%	na	na	na	na
Friedman	Single cohort	Lactating	Pfizer (n=10) Timing: 5 months postpartum (mean 154 days, range 68-382)	None/self	na	na	na	IgG and IgA at D7 and D14 pD1 and D1 and D14 pD2 First significant increase in titers noted at 14d pD1 and peaked at 7d pD2 with a slight decrease at 14dpD2 Serum antibody response dominated by IgG and IgG/IgA	na	na	na	na

								was significantly higher in serum than in breast milk.				
Golan	Comparative cohort	vaccinated lactating women	Moderna (n=9), Pfizer (n=14) Timing: post delivery	Infected unvaccinated	na	Significant rise in plasma IgG, peaking at 4 weeks post D2 from baseline	na	IgA levels in milk (anti RBD) increased with vaccination but lower than levels reached post-infection	na	na	na	na
Gray (USA)	Comparative cohort	Pregnant, lactating and nonpregnant vaccinated	Lactating N=31 Pfizer: n=16 (52%), Moderna: n =15 (48%) first dose given at mean gestational age of 23.2 weeks, 46% in 2nd trimester, 40% in 3rd trimester	Non-pregnant vaccinated (16) Pregnant infected 4-12weeks prior (37)	na	na	na	2nd dose boosted maternal sera and breastmilk IgG but not IgA breastmilk titer	na	na	na	na
Juncker	Single cohort	Lactating, vaccinated	Pfizer N=26 One dose (n=6), Two doses (n=20) Timing: post delivery	None/self	na	Steep rise in IgG in first 2 weeks after D1 with continued rise. All participants showed seroconversion after D1	na	High inter-individual variability in IGA response in human milk Rise after D1, sustained until 3d after D2, then decline 2d after D2 Most had milk conversion after D1, but only some show milk conversion after D2 Spike- and RBD-specific IgG low after 1 dose in 1 mother (2 doses may be essential to optimize humoral immune transfer to the neonate)	na	na	na	na
Low 1 **(Singapore)**	Comparative cohort	Lactating vaccinated; no prior exposure to COVID-19, excluded autoimmune disease, current infection, cancer, current immunomodulatory medication	Pfizer Timing: mean 10 months post-partum (n= 10)	Convalescent (n=6) Healthy moms (n=9)	na	na	na	Strong IgA and IgG response at 3-7days after D2; higher than convalescent; no levels seen with health unvaccinated cohort Minimal transfer of BNT162b2 mRNA in milk samples of vaccinated women	na	na	na	No serious adverse events noted during the 28-day study period None of the infants breastfed within 72

												hours of vaccination had any adverse events
Low 2 **(Singapore)**	Single cohort	Lactating vaccinated and children	Pfizer Timing: post-delivery (n=88)	None/self	na	na	na	na	No serious adverse event No adverse events in children	64.8% with pain/redness/swelling at injection site	na	5/88 (5.7%) lymphadenopathy 3 (3.4%) mastitis none with change in milk supply 1 with bluish-green tinge
McLaurin-Jiang	Cross-sectional survey	Breastfeeding mothers who underwent vaccination at least 2 days prior to survey	Pfizer (n=2702) Moderna (n=1714) Timing: post delivery	none	na	na	na	na	77 (1.7%) reported negative impact on breastfeeding post vaccination - fatigue, headache, muscle pain, injection site pain, fever, allergic reactions	na	na	na
Nir	Comparative cohort	Parturients	BNT162b2 Timing: All women in third trimester, mean age of 33.5+/-3 weeks; mean 21 days prior to delivery (n=64)	Had COVID during pregnancy (mean 92 days prior to delivery) (n=11)	na	na	Cord blood: IgG titers higher in vaccinated (26.1 vs 20.2)	IgG higher in vaccinated (11.0 vs 4.9) Good correlation between neonatal blood spot samples and breast milk samples	na	na	na	na
Perl	Single cohort	Vaccinated lactating	Pfizer Timing: post-delivery (n=84)	None/self	na	na	na	Increased IgA in first 2 weeks after D1 (61.8% positive), increased to 86% at week 1 pD2, and 65% positive at week6. igG antibodies increase at week 4 (91%), and increased to 97% at week 5 and 6	55.9% at D1, 61.9% at D2	Local pain most common complaint	na	No mother had serious adverse event Four infants developed fever after maternal vaccination
Schwartz	Single cohort	Vaccinated lactating women	Pfizer Timing: post-	Self	na	All were positive for IgG, 31.7 S/Co	IgG detected in 60% of infant saliva, but none in	All were positive for IgG, 6.3 S/Co	na	na	na	na

			delivery (n=61)				the dried blood spot	Positive correlation of IgG between maternal serum and breastmilk samples Secretory IgA found in 15% of breast milk				
Selma-Royo (Spain)	Single cohort	Vaccinated lactating women	Pfizer (n=30) Moderna (n=21) Astra Zeneca (n=24) Timing: post delivery	None/ self-compared across vaccines	na	na	na	Strong reactivity for IgG and IgA after vaccination , especially after D2 IgG levels higher than convalescent group IgA levels lower than convalescent group Higher levels of IgG and IgA after first dose with mRNA vaccines vs AZ, no diff between Pfizer and Moderna except for higher IgA with Moderna	na	na	na	More adverse events in those vaccinated with AZ compared to mRNA vaccine 4 infants developed fever after maternal vaccination No serious adverse events
Valcarce	Single cohort	Lactating healthcare workers; no history of COVID,	Pfizer (n=14) Moderna (n=7) Timing: post-delivery (N=21)	None/self	na	na	na	IgA significantly increased in milk (85% positivity) and correlated with maternal serum Same with IgG. Concentration of IgA higher than IgG	na	na	na	na

Appendix 3. Risk of Bias Assessment

STUDY ID	STUDY DESIGN	RANDOMIZATION	ALLOCATION CONCEALMENT	BLINDING OF PARTICIPANTS	BLINDING OF INVESTIGATORS	BLINDING OF ASSESSORS	MISSING OUTCOMES/ FOLLOW UP	SELECTIVE REPORTING	AGE			COMORBIDITIES			EXPOSURE RISK			OVERALL RISK for CONTROL FOR CONFOUNDERS	OVERALL RISK OF BIAS
									A	B	C	A	B	C	A	B	C		
PREGNANT WOMEN REVIEW																			
Atyeo	comparative cohort	HIGH	HIGH	HIGH	HIGH	HIGH	UNCLEAR	UNCLEAR	Y	U	Y	N	U	N	N	U	N	HIGH	SERIOUS
Atyeo2	comparative cohort	HIGH	HIGH	HIGH	HIGH	HIGH	HIGH	UNCLEAR	Y	Y	NA	Y	Y	NA	N	U	N	LOW	SERIOUS
Beharier	comparative cohort	HIGH	HIGH	HIGH	HIGH	HIGH	LOW	UNCLEAR	Y	N	N	Y	Y	NA	N	U	N	HIGH	SERIOUS
Bleicher	comparative cohort	HIGH	HIGH	HIGH	HIGH	HIGH	HIGH	UNCLEAR	Y	N	N	Y	Y	NA	Y	N	N	HIGH	SERIOUS
Butt	TNCC	HIGH	HIGH	HIGH	HIGH	HIGH	LOW	UNCLEAR	Y	Y	Y	N	U	N	N	U	N	HIGH	SERIOUS
Collier	Comparative Cohort	HIGH	HIGH	HIGH	HIGH	HIGH	UNCLEAR	UNCLEAR	Y	Y	NA	N	U	N	N	U	N	HIGH	SERIOUS
Dagan	Matched cohort	HIGH	HIGH	HIGH	HIGH	HIGH	LOW	UNCLEAR	Y	Y	Y	Y	Y	Y	Y	Y	Y	LOW	SERIOUS
Gray	comparative cohort	HIGH	HIGH	HIGH	HIGH	HIGH	HIGH	UNCLEAR	Y	N	N	Y	N	N	N	U	N	HIGH	SERIOUS
Kadali	cross sectional	HIGH	HIGH	HIGH	HIGH	HIGH	UNCLEAR	UNCLEAR	N	U	N	N	U	N	N	U	N	HIGH	SERIOUS
Mithal	single cohort	HIGH	HIGH	HIGH	HIGH	HIGH	UNCLEAR	UNCLEAR	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	SERIOUS
Nir	comparative cohort	HIGH	HIGH	HIGH	HIGH	HIGH	LOW	UNCLEAR	Y	Y	NA	Y	Y	NA	N	U	N	LOW	SERIOUS
Peretz	comparative cohort	HIGH	HIGH	HIGH	HIGH	HIGH	HIGH	UNCLEAR	Y	N	N	Y	Y	NA	N	U	N	LOW	SERIOUS
Prabhu	single cohort	HIGH	HIGH	HIGH	HIGH	HIGH	LOW	UNCLEAR	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	SERIOUS
Rotteinstrech	single cohort	HIGH	HIGH	HIGH	HIGH	HIGH	LOW	UNCLEAR	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	SERIOUS
Rottenstreich2	comparative cohort	HIGH	HIGH	HIGH	HIGH	HIGH	LOW	UNCLEAR	Y	Y	NA	N	U	N	N	U	N	HIGH	SERIOUS
Shanes	comparative cohort	HIGH	HIGH	HIGH	HIGH	HIGH	LOW	UNCLEAR	Y	Y	NA	N	U	N	N	U	N	HIGH	SERIOUS
Shimabukuro	crossectional	HIGH	HIGH	HIGH	HIGH	HIGH	UNCLEAR	UNCLEAR	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	SERIOUS
Shook	comparative cohort	HIGH	HIGH	HIGH	HIGH	HIGH	LOW	UNCLEAR	Y	Y	NA	NA	NA	NA	NA	NA	NA	NA	SERIOUS
Theiler	comparative cohort	HIGH	HIGH	HIGH	HIGH	HIGH	LOW	UNCLEAR	Y	N	N	N	U	N	N	U	N	HIGH	SERIOUS
Trostle	crosssectional	HIGH	HIGH	HIGH	HIGH	HIGH	UNCLEAR	UNCLEAR	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	SERIOUS
Wainstock1	Case control	HIGH	HIGH	HIGH	HIGH	HIGH	UNCLEAR	UNCLEAR	Y	U	Y	Y	U	Y	Y	U	Y	LOW	SERIOUS
Wainstock2	comparative cohort	HIGH	HIGH	HIGH	HIGH	HIGH	LOW	UNCLEAR	Y	N	Y	N	U	N	N	U	N	HIGH	SERIOUS
Zauche	cross sectional /	HIGH	HIGH	HIGH	HIGH	HIGH	HIGH	UNCLEAR	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	SERIOUS
Zdanowski	single cohort	HIGH	HIGH	HIGH	HIGH	HIGH	UNCLEAR	UNCLEAR	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	SERIOUS
LACTATING WOMEN REVIEW																			
Atyeo	comparative cohort	HIGH	HIGH	HIGH	HIGH	HIGH	UNCLEAR	UNCLEAR	Y	U	Y	N	U	N	N	U	N	HIGH	SERIOUS
Bertrand	Comparative cohort	HIGH	HIGH	HIGH	HIGH	HIGH	LOW	UNCLEAR	Y	N	N	N	U	N	N	U	N	HIGH	SERIOUS
Calili	Single cohort	HIGH	HIGH	HIGH	HIGH	HIGH	HIGH	UNCLEAR	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	SERIOUS
Charepe	comparative cohort	HIGH	HIGH	HIGH	HIGH	HIGH	LOW	UNCLEAR	Y	Y	NA	Y	Y	NA	Y	Y	NA	LOW	SERIOUS
Collier	Comparative Cohort	HIGH	HIGH	HIGH	HIGH	HIGH	UNCLEAR	UNCLEAR	Y	Y	NA	N	U	N	N	U	N	HIGH	SERIOUS
Esteve-Palau	Single cohort	HIGH	HIGH	HIGH	HIGH	HIGH	LOW	UNCLEAR	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	SERIOUS
Fox	Single cohort	HIGH	HIGH	HIGH	HIGH	HIGH	LOW	UNCLEAR	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	SERIOUS
Friedman	Single cohort	HIGH	HIGH	HIGH	HIGH	HIGH	LOW	UNCLEAR	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	SERIOUS
Golan	Comparative cohort	HIGH	HIGH	HIGH	HIGH	HIGH	LOW	UNCLEAR	N	U	N	N	U	N	N	U	N	HIGH	SERIOUS
Gray	comparative cohort	HIGH	HIGH	HIGH	HIGH	HIGH	HIGH	UNCLEAR	Y	N	N	Y	N	N	N	U	N	HIGH	SERIOUS
Juncker	single cohort	HIGH	HIGH	HIGH	HIGH	HIGH	LOW	UNCLEAR	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	SERIOUS
Low 1	comparative cohort	HIGH	HIGH	HIGH	HIGH	HIGH	LOW	UNCLEAR	N	U	N	N	U	N	N	U	N	HIGH	SERIOUS
Low 2	single cohort	HIGH	HIGH	HIGH	HIGH	HIGH	LOW	UNCLEAR	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	SERIOUS
McLaurin-Jiang	crosssectional	HIGH	HIGH	HIGH	HIGH	HIGH	LOW	UNCLEAR	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	SERIOUS
Nir	comparative cohort	HIGH	HIGH	HIGH	HIGH	HIGH	LOW	UNCLEAR	Y	Y	NA	Y	Y	NA	N	U	N	LOW	SERIOUS
Perl	single cohort	HIGH	HIGH	HIGH	HIGH	HIGH	LOW	UNCLEAR	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	SERIOUS
Schwartz	single cohort	HIGH	HIGH	HIGH	HIGH	HIGH	UNCLEAR	UNCLEAR	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	SERIOUS
Selma-Royo	single cohort	HIGH	HIGH	HIGH	HIGH	HIGH	UNCLEAR	UNCLEAR	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	SERIOUS
Valcarce	single cohort	HIGH	HIGH	HIGH	HIGH	HIGH	LOW	UNCLEAR	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	SERIOUS

HIGH	UNCLEAR	LOW	NA

Y	Yes	N	No	U	Unclear	NA

Appendix 4. Summary of Findings Table of Efficacy and Safety Outcomes, Pregnant women

A. Efficacy outcomes

Efficacy Outcome	N Study design	Quality Assessment					Summary of Findings			Certainty
		Risk of Bias	Inconsistency	Indirectness	Imprecision	Overall Assessment	Vaccine	Control	Vaccine Efficacy	
1: COVID-19 infection / Breakthrough infection	4 OBS (2 TNCC 2 RC)	Serious (Observational, short ffup, uncontrolled confounders)	Not serious	Not serious	Not serious	Serious	VE COVID-19 infection: 96% (89-100) VE symptomatic COVID-19: 97% (91,100) VE hospitalization: 89% (43,100) OR COVID-19 infection: 4.5 (1.19-17.9) for unvaccinated Breakthrough infection during pregnancy: 0%			Low
2 : Maternal immunogenicity (humoral)	7 OBS	Serious (Observational, short ffup, uncontrolled confounders)	Not serious	Not serious	Not serious	Serious	Significant rise in IgA, IgG and NABs post-vaccination Higher antibody titers post vaccination versus previous infection Equivalent antibody titers between pregnant, nonpregnant and lactating vaccinees (with one study reporting lower titers in pregnant vs nonpregnant)			Low
3. Maternal immunogenicity (cellular)	1 OBS	Serious (Observational, short ffup, uncontrolled confounders)	Not serious	Not serious	Not serious	Serious	Similar T-cell response among pregnant and non-pregnant vaccinated women			
4. Neonatal immunogenicity	12 OBS	Serious (Observational, non-comparative)	Not serious	Not serious	Not serious	Serious	Evidence of placental transfer of maternal antibodies to fetus, titers correlated with maternal sera			Low

B. Safety Outcomes

Safety Outcome	N Study Design	Quality Assessment					Summary of Findings			Certainty
		Risk of Bias	Inconsistency	Indirectness	Imprecision	Overall Assessment	Vaccine	Control	Vaccine Efficacy	
1: Maternal adverse reactions / adverse events	8 OBS	Serious (Observational, short ffup, uncontrolled confounders)	Serious (1 study with more local ARs in vaccinated pregnant vs nonpregnant)	Not serious	Not serious	Serious	Adverse reaction and event rates general similar to vaccinated non-pregnant women.			Low
2: Pregnancy Outcomes										
2a. PROM	0	Not reported	Not assessed	Not assessed	Not assessed	Not assessed	Not assessed			Na
2b. Intrauterine growth retardation	1 OBS	Serious (Observational)	Not assessed	Not serious	Not assessed	Serious	0.6%, not different from non-vaccinated group			Low
3: Delivery Outcomes										
3a. Fetal Death in Utero/ Stillbirth	3 OBS	Serious (Observational, no control of confounders)	Not serious	Not serious	Not serious	Serious	0.1%; not different from published rates most studies reporting no stillbirths;			Low
3b. Preterm Delivery	3 OBS	Serious (Observational, no control of confounders)	Not serious	Not serious	Not serious	Serious	0-9.4%, no difference from non-vaccinated group or from published rates			Low
3c. Spontaneous abortion	5 OBS	Serious (Observational, no control of confounders)	Not serious	Not serious	Not serious	Serious	OR (vaccination in the previous 3 weeks) = 0.91, (95%CI 0.75, 1.10) OR (vaccination in the previous 5 weeks) = 0.81 (95%CI 0.69, 0.95) Risk for abortion from 6 to 19 weeks = 14.1% (95%CI 12.1 to 16.1%) No difference from published rates			Low
4: Neonatal Outcomes										
4a. APGAR <7	1 OBS	Serious (Observational)	Not assessed	Not serious	Not assessed	Serious	No difference in incidence of APGAR<7 at 5 mins compared with unvaccinated			Low
4b. NICU admission	3 OBS	Serious (Observational, non comparative)	Not serious	Not serious	Serious	Serious	Reported rates : 1.5%, 4.5%, 15.5%			Low
4c. Congenital anomaly	3 OBS	Serious (Observational, no control of confounders)	Not serious	Not serious	Not serious	Serious	Reported rates : 2.2%, 2.2%, 4.5% No difference from unvaccinated			Low

Appendix 5. Summary of Findings Table of Efficacy and Safety Outcomes, Lactating women

A. Efficacy outcomes

Efficacy Outcome	N Study design	Quality Assessment					Summary of Findings			Certainty
		Risk of Bias	Inconsistency	Indirectness	Imprecision	Overall Assessment	Vaccine	Control	Vaccine Efficacy	
1: COVID-19 infection / Breakthrough infection	0	Not reported	Not assessed	Not assessed	Not assessed	Not assessed	Not assessed			na
2 : Maternal immunogenicity (humoral)	6 OBS	Serious (Observational, short ffup, uncontrolled confounders)	Not serious	Not serious	Not serious	Serious	IgG as dominant antibody in maternal sera with increasing levels over time; IgM and IgA detected at lower levels Similar antibody titers with vaccinated pregnant women after prime vaccine, antibodies increased more after booster dose versus pregnant women			Low
3. Maternal immunogenicity (cellular)	0	Not reported	Not assessed	Not assessed	Not assessed	Not assessed	Not assessed			na
4. Breast milk antibody levels	13 OBS	Serious (Observational, short ffup, uncontrolled confounders)	Not serious	Not serious	Not serious	Serious	IgG as dominant antibody, positive correlation with maternal IgG serum levels and breastfeeding duration Varied IgA levels: 3 studies showed low levels, 1 study with no difference between vaccinated and infected, 2 studies with higher levels post vaccination and increasing trend			Low
5. Neonatal immunogenicity	2 OBS	Serious (Observational, short ffup, uncontrolled confounders)	Not serious	Not serious	Not serious	Serious	IgG detected in neonatal blood spot and saliva among newborns of vaccinated mothers			Low

B. Safety Outcomes

Safety Outcome	N Study Design	Quality Assessment					Summary of Findings			Certainty
		Risk of Bias	Inconsistency	Indirectness	Imprecision	Overall Assessment	Vaccine	Control	Vaccine Efficacy	
1: Maternal adverse reactions / adverse events	5 OBS	Serious (Observational, short ffup, uncontrolled confounders)	Not serious	Not serious	Not serious	Serious	No serious adverse events reported Pain at injection site as most common side effect Symptoms more common after second dose of mRNA vaccines; higher incidence of fever and headache in those given ChAdOx1 versus mRNA vaccines			Low
2 : Breastmilk changes	4 OBS	Serious (Observational, short ffup, uncontrolled confounders)	Not serious	Not serious	Not serious	Serious	No adverse events in either lactating mothers or infants breastfed post vaccination Reduced milk supply in a few cases but resolved in 72 hours			Low

Q12. Is BCG vaccination effective and safe in the prevention of COVID-19 infections?

As of 09 April 2021

RECOMMENDATION

We suggest against the use of BCG vaccine for the prevention of COVID-19 infection. *(Very low quality of evidence; Conditional recommendation)*

Consensus Issues

A conditional recommendation against the use of BCG vaccination for COVID-19 prevention was made by the Panel in consideration of the following issues. Most of the evidence included in the review are retrospective cohorts and one case control. Among the articles, the timing of BCG administration is variable or unclear and the outcomes were self-reported and not necessarily RT-PCR confirmed. Also, although an RCT was recently completed in Greece on the potential utility of BCG vaccine as prophylaxis for COVID-19, it is still a preprint and not yet included in the review. There is also clinical trial evidence in the elderly that it improves outcomes for other respiratory viral infections. Furthermore, it is relatively inexpensive and there is no evidence of serious harm. It was discussed that BCG vaccine is usually given among children to prevent disseminated or miliary tuberculosis.

It was also discussed in the panel meeting that the Philippines has a policy on birth doses for BCG within 24-hours of delivery; however, this is not fully implemented in health centers since it is available as a multi-dose vial, they do not administer this if there is only one infant. On the other hand, it was noted that there is no national policy on BCG vaccination among adults.

KEY FINDINGS

A systematic review of the literature on April 2, 2021 did not yield any completed randomized trial on the efficacy and safety of BCG vaccination in the prevention of COVID-19 infection. Five retrospective cohort studies and one case control study were included in this review and all showed high risk of bias and conflicting results. As of March 6, 2021, 22 studies that addresses this issue have been registered, 21 of which are randomized controlled trials.

INTRODUCTION

Since the COVID-19 pandemic was declared on March 11, 2020, the race to safe and effective vaccines has already started. However, their development will take years to reach the final marketing phase of clinical trials. While regulatory agencies around the world have already approved some vaccine candidates for emergency use, their safety and efficacy have yet to be evaluated long-term.

Bacille Calmette-Guerin (BCG), a live attenuated strain of *Mycobacterium bovis* and an already proven safe and effective vaccine in the prevention of tuberculosis, is being studied to be repurposed as an effective pharmacologic intervention to prevent COVD-19 infection. It is postulated that BCG provides non-specific protective effects against allergenic and pathogenic respiratory disorders by innate immunity training, induction of receptor expression of NK cells and acute induction of localized lung immunity through expansion of CD4+, CD8+ and other specific T cells, without causing a

cytokine storm.[1] An interim report of a randomized trial on the effect of BCG vaccination in preventing infections among the elderly demonstrated significant increase in the time to first infection and lower incidence of new infections among those who received the vaccine. [2] Most of the protection was against respiratory tract infections of probable viral origin. In addition, another randomized trial evaluated BCG as a potential therapy for COVID-19. Results showed that addition of BCG vaccination to standard of care resulted in significantly higher proportions of patients with favorable outcomes compared to standard of care alone.[1] The investigators of this trial suggested the possible positive impact of BCG vaccines against COVID-19.

REVIEW METHODS

Literature search

The COVID-nma living systematic review and two online living COVID evidence repositories were searched. The metaevidence.com was search using “BCG vaccination” and “COVID 19 prophylaxis” as filters. The COVID-19 Living OVerview of Evidence (L·OVE) platform (www.app.iloveevidence.com/covid19), was searched by selecting “vaccination”, “BCG”, “primary studies” and using “RCT” and “reporting data” as additional filters. To increase the yield, the search the additional filters were removed and replaced to “all” studies. Press releases, systematic reviews, and additional information from systematic reviews were excluded. Finally, the clinicaltrials.gov registry was searched using “BCG vaccine” as a search term, selecting only randomized controlled trials for inclusion in the review. The registered trials were classified as either completed or ongoing.

Study Selection

Studies considered for the review included those with the following characteristics: population: human, without restrictions; intervention: BCG vaccination given at any point before COVID infection; comparator: no BCG vaccination; outcome: positive SARS-CoV-2 PCR test or seroconversion, or COVID-19 infection (either clinical diagnosis only or PCR-confirmed diagnosis). Only randomized clinical trials were included. A priori step down to inclusion of nonrandomized comparative studies (cohort and case control studies) was planned.

Two review authors independently screened the titles and abstracts of the search results for full text retrieval and review and eventually for final inclusion. Any disagreement was resolved by a third review author.

Methodological Assessment

Two review authors independently assessed the 'risk of bias' (RoB) of each included study. Disagreements were resolved by discussion or by consulting a third review author. Risk of bias in RCTs was assessed by using the Cochrane Risk of Bias tool version 1, which included the following domains: random sequence generation; allocation concealment; blinding of participants and personnel; blinding of outcome assessment; incomplete outcome data; selective reporting.[3]

Risk of bias in non-randomized comparative studies was assessed using all domains above. Sequence generation and allocation concealment were retained as domains but were assessed by default as ‘high risk of bias’ given the non-randomized nature of these studies. An extra item to assess the risk of findings being explained by confounding was added. This is a pragmatic approach informed by methodological

literature pertaining to assessing RoB in nonrandomized studies.[4,5] A list of the most important potential confounders for harm and benefit outcomes was developed a priori with clinical content experts The potential confounding factors were: age, gender, risk of COVID exposure, and presence of comorbidities. For each study, a pragmatic approach was used to assess the risk of confounding bias. The following were considered in sequence:

- Was the prognostic confounder considered (yes/no)? If 'no', the study is at 'high' risk of bias for this confounder. If 'yes' go to question 2.
- Was the confounder balanced between the intervention(s) and control group (s) (yes/no)? If 'yes', the study is a 'low' risk of bias. If 'no', go to question 3.
- Was the confounder controlled for in the analysis, for example by statistical adjustment such as univariate or multivariate analysis or propensity score matching. If 'yes' the study was at 'low' risk of bias. If 'no' the study was 'high' risk of bias

RESULTS

Search Results

The searches were performed on April 1, 2021. The COVID-nma and the metaevidence.com evidence registries did not yield any record. The COVID-19 Living OVerview of Evidence (L·OVE) platform search yielded 3 records of randomized controlled trials. One was a press release about the interim results of the BCG-PRIME study stating the failure of the BCG vaccine to provide protection to the elderly against COVID-19 infection. No reference to the trial report or any other detail was provided. The other two trials were on the use of the BCG vaccine as treatment against COVID-19 infection. Expansion of the search to include nonrandomized studies yielded 148 records. After screening for eligibility based on titles and abstracts, 96 references were considered for inclusion in the review. After full text retrieval and review, five retrospective cohort studies and one case control studies were included. Majority of the excluded studies were epidemiologic / ecological studies comparing COVID infection rates of countries with and without BCG vaccination programs.

Search of clinicaltrials.gov yielded 27 records, of which 22 were identified as related to BCG vaccination for the prevention of COVID-19. Of the ongoing trials, 5 are active and done recruiting, 15 are recruiting, and 2 are not yet recruiting. There are six Phase 4 studies, 14 Phase 3 studies, one Phase 2 study, and one case-control study. The target number of participants ranges from 59 to 10,078 while the target population varies with 10 trials specifically on healthcare workers and 7 involving the elderly population only. Outcomes are diverse but most commonly include incidence of COVID-19 infection, hospitalization, ICU admission, use of mechanical ventilation, mortality, seroconversion, and adverse events; for studies on healthcare workers, absenteeism is included as an outcome. The sole case-control study will explore the prognosis of COVID-19 positive participants with positive tuberculin skin test (TST) compared to those with negative TST. The earliest study completion date is January 1, 2021, but none of the active trials have posted their results as of the time of the search. Details are in Appendix 3.

Characteristics of Included Studies

Five retrospective cohort studies and one case control study were included in this review. Two were population-based cohort studies, one by de Chaisemartin *et al.* from Sweden[6] and the other by Hamiel *et al.* from Israel.[7] The studies by Amirlak *et al.*[8]

and by Noval Rivas *et al.* [9] had healthcare workers as study cohorts. The study by Moorlag *et al.* recruited volunteers from another research project [10]. Among these cohort studies, two investigated the effect of childhood vaccination [6,7], two had adult or booster BCG vaccination as the intervention [8,10] while the timing of the vaccination was not specified in one study [9]. The efficacy outcomes across the studies were varied and the same outcomes were reported in different ways, precluding pooling of results. Three reported PCR-positive test results, [7,8,9] although one was based on self-reporting rather than from test results registry,(9) two had self-reported COVID symptoms or self-reported COVID diagnosis as outcomes.[9,10] One study reported hospitalization and deaths.[6]

The case control study was among individuals hospitalized for potential COVID infection based on symptoms and exposures and those with PCR-positive test results were identified as the cases and those who had negative results were classified as the controls.[11] Efficacy of BCG vaccination in the prevention of COVID infection was determined by comparing the proportions of childhood BCG vaccination between the cases and controls.
Details of the studies are in Appendix 1.

Methodological Quality Assessment of Included Studies
All but one of the studies included in the review were assessed to be with high risk of bias due to the failure to assess and to adequately control for the pre-specified confounding factors. Only the retrospective cohort study of Moorlag and coworkers assessed and controlled for age, gender, risk of COVID exposure and comorbidities and adjusted their results accordingly. Due to the serious and very serious risks of bias in the design of all the included studies, certainty of the evidence for this review is assessed as very low risk.

Details of the methodological quality assessment are in Appendix 2.

Efficacy
The results of the included studies on the efficacy of BCG vaccination for the prevention of COVID-19 infection were conflicting.

The two population-based cohort studies, which had the largest sample sizes, both did not show any protective effect from childhood BCG vaccination against COVID-19 infection. [6, 7] The Swedish study, which utilized data from its national database of over 2 million persons showed that the odds ratios (95% CI) for COVID-19 cases and COVID-19–related hospitalizations were 1.0005 (.8130–1.1881) and 1.2046 (.7532–1.6560).[6] The study from Israel including data from nearly 6,000 persons reported the COVID-19 infection incidence rates of 11.7% among BCG vaccinated population and a 10.4% among the non-vaccinated, with a risk difference of 1.3 (0.3-2.9), p=0.09.[7]

The two cohort studies reporting protection by BCG vaccination against COVD-19 infection were conducted with vaccination given as adults. In the study conducted in a hospital in United Arab Emirates, staff members were offered BCG vaccination booster doses at the start of the COVID pandemic. Regardless of BCG vaccination or not, all underwent mandatory PCR-testing at specific time periods. Three months later, none of the vaccines had a positive result while 18 (8.6%) did.[8] A study among

healthy volunteers from an ongoing research project compared the incidence of self-reported sickness between those who received BCG vaccination within the past 5 years and those who did not. It showed an odds ratio of 0.58 ($p<0.05$) after adjusting for all potential confounders. The protective effect of BCG vaccination in this study was highlighted in the context of an older BCG vaccinated population with a higher rate of exposure risk compared to the non-vaccinated group.[10]

The study among workers in a healthcare system in Los Angeles where the timing of the BCG vaccination was not specified, showed that the group with a history of BCG vaccination were less likely to report experiencing COVID-19 related symptoms in the past 6 months (75.6% vs 72.7%, p=0.017), had a lower percentage for a COVID-19 diagnosis (1.9 vs 2.9, p=0.029) or a positive PCR test (1.0 vs 1.7, p=0.062) and had a lower proportion of positive serology (IgG) test (2.7 vs 3.8, p=0.044).[9]

The case control study from India showed that the cases had a higher proportion reporting a history of BCG vaccination (49.7%) compared to the controls (9.7%).[11]

Safety

The study by Amirlak *et al.* reported that no local or systemic complications were noted in the BCG booster vaccine group.[8] None of the other studies reported on safety issues regarding BCG vaccination.

RECOMMENDATIONS FROM OTHER GROUPS

The US-CDC and the Infectious Disease Society of America have not provided any recommendation regarding the use of BCG vaccination in the prevention of COVID-19 infection. The WHO, in its statement in April 2020 In a statement from April 2020, did not recommend BCG vaccination for the prevention of COVID-19, but recommended continued neonatal vaccination in countries or settings with a high incidence of tuberculosis.[12]

RESEARCH GAPS

The efficacy and safety of BCG vaccination in the prevention of COVID-19 infection is not yet known. The results of the ongoing trials should provide information on this issue.

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Appendix 1. Characteristics of included Studies

Study ID	Study Design	Population	Timing of BCG vaccine	BCG (n)	No BCG (n)	Outcomes
Amirlak	Retrospective cohort	Hospital staff (UAE)	Booster	71	209	Mandatory PCR test result
DeChaisemartin	Retrospective cohort with regression discontinuity analysis	Total population (from national databases and records), by birth cohorts (Sweden)	Childhood	1026304	1018544	COVID infection based on positive PCR tests, hospitalization, deaths
Hamiel	Retrospective cohort	Population-based, cohorts born 3 years before and 3 years after BCG program cessation (Israel)	Childhood	3064	2869	PCR-confirmed COVID symptoms
Moorlag	Retrospective cohort. Digital survey done in 2 time periods	Healthy volunteers in the Human Functional Genomics Project,	Recent past 5 years	266	164	self-reported sickness; symptoms of COVID (fever, cough, sore throat, SoB, headache, muscle ache, extreme fatigue)
Noval Rivas	Retrospective cohort; digital survey	Healthcare workers in Cedar-Sinai Health system (USA)	Unspecified	1836	4275	COVID symptoms, self reported COVID infection, self-reported PCR (+), seropositivity
Sharma	Case control	Admitted symptomatic patients and close contacts (India)	Childhood	NA (cases, + PCR = 234)	NA (controls, - PCR = 267)	History of BCG vaccination

Appendix 2. Methodological Quality Assessment of Included Studies

2A. Cochrane Risk of Bias Assessment

STUDY ID	RANDOMIZATION	ALLOCATION CONCEALMENT	BLINDING	FOLLOW UP	SELECTIVE REPORTING	OVERALL RoB
Amirlak	High Risk	High Risk	Low Risk	Low Risk	Unclear	High Risk
DeChaismartin	High Risk	High Risk	Unclear	Low Risk	Unclear	High Risk
Hamiel	High Risk	High Risk	Low Risk	Low Risk	Unclear	High Risk
Moorlag	High Risk	High Risk	High Risk	Low Risk	Unclear	High Risk
Noval Rivas	High Risk	High Risk	High Risk	Low Risk	Unclear	High Risk
Sharma	High Risk	High Risk	Uncertain	Low Risk	Unclear	High Risk

2b. Assessment of Risk of Findings Being Influenced by Confounders

STUDY ID	AGE				GENDER				EXPOSURE RISK				COMORBIDITIES				OVERALL RoB
	A	B	C	RoB	A	B	C	RoB	A	B	C	RoB	A	B	C	RoB	
Amirlak	No	NA	NA	High	No	NA	NA	High	Yes	Yes	NA	Low	No	NA	NA	High	High
deChaisemartin	Yes	No	Yes	Low	Yes	Yes	Yes	Low	No	Unk	NA	High	No	Unk	NA	High	High
Hamiel	Yes	Yes	No	Low	Yes	Yes	No	Low	No	Unk	No	High	No	Unk	No	High	High
Moorlag	Yes	No[1]	Yes[2]	Low	Yes	Yes	NA	Low	Yes[3]	No[4]	Yes	Low	Yes	Yes	NA	Low	Low
Noval Rivas	Yes	No[5]	No	High	Yes	No[6]	No	High	No	NA	NA	High	Yes	No	No	High	High
Sharma	Yes	No[8]	No	High	No	NA	NA	High	No	NA	NA	High	Yes	No[9]	No	High	High

Unk – unknown; **na** – not applicable; **A = Assessed; B = Balanced; C = Controlled**

[1] (median age : BCG 25, no 30)
[2] (logistic regression)
[3] (recent travel history, exposure to infected individuals)
[4] (BCG more travel, HCWs)
[5] (BCG older)
[6] (BCG more females)
[7] (BCG with higher rates of hypertension, CV dis, DM, COPD)
[8] (Cases older)
[9] (cases with higher rates)

Appendix 3. Characteristics of Ongoing Trials

Trial Registry Number	Title	Status	Sponsor/ Collaborations (Country Site)	Study Characteristics
NCT04659941	Use of BCG Vaccine as a Preventive Measure for COVID-19 in Health Care Workers	Recruiting	Universidade Federal do Rio de Janeiro; Ministry of Science and Technology, Brazil (Brazil)	Phase 2 RCT
NCT04328441	Reducing Health Care Workers Absenteeism in Covid-19 Pandemic Through BCG Vaccine	Active, not recruiting	UMC Utrecht; Radboud University (Netherlands)	Phase 3 RCT Placebo controlled adults
NCT04534803	BCG Against Covid-19 for Prevention and Amelioration of Severity Trial (BAC to the PAST)	Not yet recruiting	Harvard Medical School; Texas Medical Research Associates, L.L.C. (USA)	Phase 3 RCT Placebo controlled Older adults (>70)
NCT04350931	Application of BCG Vaccine for Immune-prophylaxis Among Egyptian Healthcare Workers During the Pandemic of COVID-19	Not yet recruiting	Ain Shams University (Egypt)	Phase 3 RCT Placebo controlled Adults
NCT04417335	Reducing COVID-19 Related Hospital Admission in Elderly by BCG Vaccination	Active, not recruiting	Radboud University (Netherlands)	Phase 4 RCT Placebo controlled Older adult (60 and older)
NCT04379336	BCG Vaccination for Healthcare Workers in COVID-19 Pandemic	Recruiting	TASK Applied Science (South Africa)	PHae 3 RCT Placebo controlled Adults
NCT04537663	Prevention Of Respiratory Tract Infection And Covid-19 Through BCG Vaccination In Vulnerable Older Adults	Recruiting	UMC Utrecht (Netherlands)	Phase 4 RCT Placebo controlled Older adults (60 and older)
NCT04632537	BCG Vaccination to Prevent COVID-19	Recruiting	Henry M.Jackson Foundation for the Advancement of Military Medicine; Harvard Medical School; Uniformed Services University of the Health Sciences; United States Department of Defense; Immunization HealthCare Division, Defense Health Agency (USA)	Phase 3 RCT Placebo (saline) controlled Adults (18 to 64)
NCT04475302	BCG Vaccine in Reducing Morbidity and Mortality in Elderly Individuals in COVID-19 Hotspots	Recruiting	Tuberculosis Research Centre, India; ICMR-National Institute for Research in Tuberculosis, Chennai, Tamil Nadu; All India Institute of MedicalSciences, New Delhi; National Institute for Research in Environmental Health, Bhopal, Madhya Pradesh; National Institute of Occupational Health,	Phase 3 Observational single group assignment

			Ahmedabad, Gujarat; King Edward Memorial Hospital; National Institute for Implementation Research on Non-Communicable Disease (India)	Adults (60-80)
NCT04347876	Outcome of COVID-19 Cases Based on Tuberculin Test: Can Previous BCG Alter the Prognosis?	Recruiting	Assiut University (Egypt)	Case control 12 years to 80 years
NCT04641858	BCG to Reduce Absenteeism Among Health Care Workers During the COVID-19 Pandemic	Recruiting	University of Southern Denmark; Institute of Hygiene and Tropical Medicine, NOVA University, Lisbon, Portugal; University of Cape Verde, Praia, Cape Verde; National Institute of Public Health of Cape Verde, Praia, Cape Verde; Centro deInvestigacao em Saude de Manhica; European and Developing Countries Clinical Trials Partnership (EDCTP); Bandim Health Project, Bissau, Guinea-Bissau (Multicountry)	Phase 4 RCT Placebo (saline) controlled Adults
NCT04648800	Clinical Trial Evaluating the Effect of BCG Vaccination on the Incidence and Severity of SARS-CoV-2 Infections Among Healthcare Professionals During the COVID-19 Pandemic in Poland	Recruiting	Department of Anesthesiology and Intensive Care, University Clinical Center, School of Medicine in Katowice, Medical University of Silesia, Katowice, Poland; Stefan #eromski Specialist Hospital, Kraków, Poland; Voivodeship Hospital nr 2 iN the Name of The Saint Queen Jadwiga, University of Rzeszów, Poland, Rzeszów, Poland; Saint Jadwiga #I#ska Hospital, Trzebnica, Poland; Department of Pediatrics, Bielanski Hospital,, Warsaw, Poland; Praski Hospital, Warsaw, Poland (Poland)	Phase 3 RCT Placebo (saline) controlled Adults (25 years and older)
NCT04461379	Prevention, Efficacy and Safety of BCG Vaccine in COVID-19 Among Healthcare Workers	Active, not recruiting	Hospital Universitario Dr. Jose E. Gonzalez (Mexico)	Phase 3 RCT Placebo controlled Adults
NCT04327206	BCG Vaccination to Protect Healthcare Workers Against COVID-19	Recruiting	Murdoch Childrens Research Institute; Royal Children's Hospital (Australia)	Phase 3 RCT Placebo controlled Adults
NCT04414267	Bacillus Calmette-guérin Vaccination to Prevent COVID-19 (ACTIVATE II)	Recruiting	Hellenic Institute for the Study of Sepsis (Greece)	Phase 4 RCT Placebo controlled Older adult (50 years and older)
NCT04369794	COVID-19: BCG As Therapeutic Vaccine, Transmission Limitation, and Immunoglobulin Enhancement	Recruiting	University of Campinas, Brazil; Conselho Nacional de Desenvolvimento Científico e Tecnológico; Instituto de Infectologia Emílio Ribas; Pontifícia Universidade Católica de Campinas, PUCCampinas; Faculty of Medicine of Ribeirão Preto (FMRP-USP); Faculdade de Medicina de Botucatu, UNESP, Botucatu, Brasil Federal University of São Paulo; State Hospital Dr. Leandro Franceschini, Sumaré, Unicamp; Paulinia Municipal Hospital (BRAZIL)	Phase 4 RCT Placebo controlled Adults
NCT04373291	Using BCG Vaccine to Protect Health Care Workers in the COVID-19 Pandemic	Active, not recruiting	Bandim Health Project; University of Southern Denmark (Denmark)	Phase 3 RCT Placebo (saline) controlled Adults

NCT04542330	Using BCG to Protect Senior Citizens During the COVID-19 Pandemic	Recruiting	Bandim Health Project; Odense Patient Data Explorative Network; Odense University Hospital; Municipality of Odense (Denmark)	Phase 3 RCT Placebo controlled Older adults (65 to 110 yo)
NCT04348370	BCG Vaccine for Health Care Workers as Defense Against COVID 19	Recruiting	Texas A&M University; Baylor College of Medicine; M.D. Anderson Cancer Center; Cedars-Sinai Medical Center; Harvard University (USA)	Phase 4 RCT Placebo controlled Adults (18-75y)
NCT04384549	Efficacy of BCG Vaccination in the Prevention of COVID19 Via the Strengthening of Innate Immunity in Health Care Workers	Recruiting	Assistance Publique - Hôpitaux de Paris (France)	Phase 3 RCT Placebo-controlled Adults
NCT04439045	Efficacy and Safety of VPM1002 in Reducing SARS-CoV-2 (COVID-19) Infection Rate and Severity	Recruiting	University Health Network, Toronto; Serum Institute of India Pvt. Ltd.; Max Planck Institute for Infection Biology; Verity Pharmaceuticals (Canada)	Phase 3 RCT Placebo controlled Adults
NCT04387409	Study to Assess VPM1002 in Reducing Healthcare Professionals' Absenteeism in COVID-19 Pandemic	Active, not recruiting	Vakzine Projekt Management GmbH; FGK Clinical Research GmbH (Germany)	Phase 3 RCT Placebo-controlled Adults

Q13. Among close contacts of COVID-19 patients, should casirivimab + imdevimab cocktail be used as post-exposure prophylaxis?

As of 04 November 2021

RECOMMENDATION

We suggest the subcutaneous use of casirivimab + imdevimab as day 4 post-exposure prophylaxis for COVID-19 close contacts*, ages 12 years and above weighing at least 40 kilograms, who are at risk for severe disease or hospitalization.** *(Moderate quality of evidence; weak recommendation)*

Consensus Issues:
Despite moderate quality of evidence, the panel decided on a weak recommendation for prophylactic use of casirivimab + imdevimab cocktail given the following factors related to equity: (1) prohibitive cost (PHP 25,000-30,000), (2) potential problems with accessibility, (3) limited supply, (4) EUA mandate last October 2021 specifically allowing its use for treatment only and (5) issues on applicability.
The recommendation is based on a single multi-center, randomized controlled trial that was done in the United States. There is a very limited window to administer the drug therefore, the poor contact tracing and the delayed release of test results are issues in our setting that compromises the applicability of the results of this study. The vaccination status of the participants as well as the prevalent viral strains during the time of the trial were considerations of the panel. While neither of the two were discussed in the study, the study was implemented from June 2020 to March 2021.

*The definition of close contacts is the same as in the Living COVID CPG guidelines.
**This includes the following people: elderly; BMI >25; those with chronic diseases such as hypertension, diabetes, and chronic kidney disease; those who are not expected to mount an adequate immune response to the vaccine due to immunosuppressive therapy or those in an immunocompromised state.

KEY FINDINGS

There was 1 randomized controlled trial that investigated casirivimab + imdevimab cocktail as post-exposure prophylaxis for RT-PCR SARS-CoV-2 negative close contacts of COVID-19 patients. The results showed a significant decrease in symptomatic and asymptomatic COVID-19 infection. Among those who developed infection, casirivimab + imdevimab resulted in significant decrease in duration of infection. There was no significant difference in serious adverse events between those given casirivimab + imdevimab and placebo. The overall quality of evidence was rated moderate due to imprecision in 1 critical outcome.

INTRODUCTION

COVID-19 hypoxemia has been theorized to be related to an immune hyperresponsiveness to viral infection. With recent studies showing high viral titers among hospitalized patients with hypoxemia, it is hypothesized that treatments that effectively reduce viral load could prevent complications and death resulting from COVID-19 infection.[1,2] One such treatment that has shown favorable effects from in vitro studies is Regeneron or REGEN-COV, an antibody cocktail containing two non-competing SARS-COV-2 neutralizing human IgG1 antibodies (casirivimab

[REGN10933], imdevimab [REGN10987]). By targeting the receptor-binding domain of the SARS-CoV-2 spike protein, viral entry into human cells through the angiotensin-converting enzyme 2 (ACE2) receptor is prevented.[3,4]

REVIEW METHODS

A systematic search was done from inception until September 1, 2021 using Medline, CENTRAL, and Google Scholar with a combined MeSH and free text search using the terms coronavirus infections, COVID-19, severe acute respiratory syndrome coronavirus 2 or SARS-CoV-2, and REGEN-COV or REGN-COV2 or casirivimab. We also looked at the COVID-NMA Living Data registry and searched for ongoing studies in the NIH *clinicaltrials.gov* and various trial registries. Preprints were also searched using medrxiv, chinaxiv and biorxiv. Only randomized controlled trials that compared casirivimab + imdevimab against placebo or standard care for post-exposure prophylaxis were included in this review. No limits were placed on age, COVID-19 severity, and dosing.

RESULTS

A total of 41 related articles were found using MEDLINE but only 1 published article met our inclusion criteria. The same article was found when searching CENTRAL, COVID-NMA initiative, and Google Scholar.

The published study was a multicenter randomized, double-blind, placebo-controlled trial that evaluated the efficacy and safety of casirivimab + imdevimab in 2 parts and was implemented from June 2020 to March 2021. Part A evaluated the use of casirivimab + imdevimab as post-exposure prophylaxis among healthy, previously uninfected household contacts of patients with RT-PCR confirmed COVID-19 at least 12 years of age. They were tested via SARS-CoV-2 RT-PCR on day post-exposure and if their tests were negative, they were enrolled in the trial. Approximately 30% of the participants had at least 1 risk factor for severe COVID-19 (elderly, BMI ≥ 35, chronic kidney disease, diabetes, immunocompromised disease/treatment). 2.8% of the participants were noted to be of Asian race. The four subcutaneous doses equivalent to 600mg casirivimab and 600mg imdevimab were given to the participants on day 1. Part B included the use of casirivimab + imdevimab as treatment for asymptomatic persons with COVID-19. Only the results of part A (involving 1,505 study participants) were published in this report. The primary outcome was the development of symptomatic, RT-PCR confirmed COVID-19 infection during the 28-day assessment period. The secondary outcomes included the number of patients that developed a high viral load ($\geq 10^4$ copies/mL), duration of symptoms, duration of infection (symptomatic or asymptomatic), development of any RT-PCR confirmed infection (symptomatic or asymptomatic), and adverse events.[5]

The overall quality of evidence was rated moderate due to imprecision in 1 critical outcome (serious adverse events). Appraisal of study quality showed no serious risk of bias in this study. The risk of bias summary is in Appendix 3. The GRADE evidence profile is in Appendix 4.

Contacts of COVID-19 patients given casirivimab + imdevimab as post-exposure prophylaxis had significant decreased risks in the development of symptomatic COVID-19 infection (RR 0.19, 95% CI 0.10-0.35) and in the development of

symptomatic/asymptomatic COVID-19 infection (RR 0.34, 95% CI 0.23-0.48) compared to those given placebo. There was also a
significant reduction in the number of participants who developed high viral load (≥10^4 copies/mL) in the casirivimab + imdevimab group compared to the placebo group (RR 0.14, 95% CI 0.08-0.26). Among the study participants who developed COVID-19 infection, there was significant decrease in the duration of symptomatic infection (MD -2.0 weeks, 95% CI -2.21 to -1.79) and the duration of infection, whether symptomatic or asymptomatic (MD -1.1 weeks, 95% CI -1.18 to -1.02) in the casirivimab + imdevimab group compared to the placebo group.[5]

SAFETY

Overall, a significantly lower risk of adverse events was found with casirivimab + imdevimab compared to placebo (RR 0.31, 95% CI 0.24-0.40). The most common adverse effects mentioned were headache and injection-site reactions.

There was no significant difference in serious adverse events in the casirivimab + imdevimab group and the placebo group (RR 0.66, 95% CI 0.30-1.47). The serious adverse events reported were cardiac disorders and other infections. None of these were attributed to the treatment received.[5]

EVIDENCE TO DECISION

The price for the monoclonal antibody cocktail is said to be about USD 1250 per dose, but can reach up to USD 6000. The cost of casirivimab + imdevimab is currently being subsidized by the US federal government.[6,7] As of October 1, 2021, the Philippine FDA granted Emergency Use Authorization for casirivimab and imdevimab to be used as treatment for mild to moderate COVID-19 in patients aged 12 years and older and weighing at least 40 kg that do not require supplemental oxygen for COVID-19 and who are at high risk of progressing to severe disease. [8]

According to the US FDA EUA Fact Sheet for casirivimab + imdevimab, the drug is best administered via 4 subcutaneous injections in 1 day for post-exposure prophylaxis. The vials should be stored in the refrigerator between 2°C to 8°C (36°F to 46°F). Once the drug is for use, 4 syringes must be prepared with 25-gauge or 27-gauge needles for subcutaneous injections. The prepared syringes must be administered immediately. If immediate administration is not possible, the prepared syringes must be stored at room temperature up to 25°C for no more than a total of 4 hours. If refrigerated, the syringes must be allowed to equilibrate to room temperature for approximately 20 minutes prior to administration. The injections must be administered in 4 separate injection sites (thighs, back of the upper arms, abdomen except for 2 inches around the navel and waistline should be avoided). Patients must be monitored clinically for at least 1 hour after administration. There is a black box note indicating that the cocktail must be used with caution for pregnant women.[9]

RECOMMENDATIONS FROM OTHER GROUPS

As of 10 August 2021, the US FDA recently expanded the emergency use authorization for casirivimab + imdevimab to include not only treatment for patients with mild to moderate COVID-19 who are at high risk for progression of the disease, but also for post-exposure prophylaxis among patients at least 12 years old and 40 kg

who are considered high-risk for progression to severe COVID-19, not fully vaccinated, or not expected to mount an adequate immune response to the vaccine.[10]

As of 27 October 2021, the IDSA [11] and the Australian guidelines [12] issued a conditional recommendation for the use of casirivimab + imdevimab as post-exposure prophylaxis for those at high risk of progression to severe COVID-19, not fully vaccinated, or those with immunocompromised conditions who may not mount adequate immune responses despite being fully vaccinated. The NIH [13] issued a strong recommendation for the subcutaneous delivery of the cocktail. They also released prioritization guidelines that state that this cocktail should be given to those who will benefit most from it for post-exposure prophylaxis when there are logistical or supply constraints.

There were no recommendations from the WHO guidelines (updated March 2, 2021) on the use of casirivimab + imdevimab as post-exposure prophylaxis for COVID-19.[14]

ONGOING TRIALS

There are currently 4 ongoing randomized clinical trials on casirivimab + imdevimab, with 3 studies evaluating safety and tolerability of the drug and 1 study evaluating the efficacy and safety of the drug when used post-exposure prophylaxis for COVID-19 (Appendix 5).

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Appendix 1. Evidence to Decision

Table 1. Summary of Initial Judgements Prior to Panel Discussion (N=10)

FACTORS	JUDGEMENT						RESEARCH EVIDENCE/ADDITIONAL CONSIDERATIONS
Problem	No (1)	Yes (9)					
Benefits	Large (5)	Moderate (4)	Small	Uncertain (1)			• Contacts of COVID-19 patients given casirivimab + imdevimab as post-exposure prophylaxis had significant decrease in the development of symptomatic COVID-19 infection (RR 0.19, 95% CI 0.10-0.35) and in the development of symptomatic/asymptomatic COVID-19 infection (RR 0.34, 95% CI 0.23-0.48) compared to placebo.
Harm	Large	Small (10)	Uncertain				• There were significantly less adverse events in the casirivimab + imdevimab group versus control group (RR 0.31, 95% CI 0.24-0.40). • There was no significant difference in serious adverse events (RR 0.66, 95% CI 0.30-1.47).
Certainty of evidence	High	Moderate (9)	Low (1)	Very Low			• Moderate
Balance of effects	Favors drug (9)	Does not favor drug	Uncertain (1)				• Net potential benefit for prevention of COVID-19 and development of adverse outcomes.
Values	Important uncertainty or variability (1)	Possibly important uncertainty or variability (6)	Possibly no important uncertainty or variability (3)	No important uncertainty or variability			
Resources required	Uncertain	Large cost (10)	Moderate cost	Negligible cost or savings	Moderate savings	Large savings	• The price of 1 course of subcutaneous casirivimab + imdevimab is estimated to be $1,250-$6,000. • According to the US FDA EUA Fact Sheet for casirivimab + imdevimab, the vials should be stored in the refrigerator between 2°C to 8°C. • Using 25-gauge or 27-gauge needles, subcutaneous injections must be administered in 4 separate injection sites.
Certainty of evidence of resources required	No included studies (4)	Very low (2)	Low	Moderate (3)	High (1)		• Cost is based on news websites (Forbes, PMLive)
Cost effectiveness	No included studies (9)	Favors the comparison	Does not favor either the intervention or the comparison	Favors the intervention (1)			
Equity	Uncertain (4)	Reduced (2)	Probably no impact	Increased (4)			• The US FDA, NIH and IDSA (conditional recommendation) recommend the use of casirivimab + imdevimab as post-exposure prophylaxis for selected populations.
Acceptability	Uncertain (9)	No	Yes (1)				
Feasibility	Uncertain (7)	No (3)	Yes				

Appendix 2a. Search Yield and Results

DATABASE	SEARCH STRATEGY / SEARCH TERMS	DATE AND TIME OF SEARCH	RESULTS	
			Yield	Eligible
Medline	{"Coronavirus Infections"[Mesh] OR "Coronavirus"[Mesh] OR coronavirus OR novel coronavirus OR NCOV OR "COVID-19" [Supplementary Concept] OR covid19 OR covid 19 OR covid-19 OR "severe acute respiratory syndrome coronavirus 2" [Supplementary Concept] OR severe acute respiratory syndrome coronavirus 2 OR SARS2 OR SARS 2 OR SARS COV2 OR SARS COV 2 OR SARS-COV-2} AND (REGEN-COV) OR (REGN-COV2) OR (Casirivimab)	Sep 1, 2021 9:00 AM	41	1
CENTRAL	MeSH descriptor: [Coronaviridae Infections] explode all trees OR MeSH descriptor: [Coronavirus] explode all trees OR coronavirus OR novel coronavirus OR NCOV OR covid19 OR covid 19 OR covid-19 OR severe acute respiratory syndrome coronavirus 2 OR SARS2 OR SARS 2 OR SARS COV2 OR SARS COV 2 OR SARS-COV-2 AND (REGEN-COV) OR (REGN-COV2) OR (Casirivimab)	Sep 1, 2021 9:30 AM	11	1
Google Scholar	REGEN-COV AND COVID AND randomized trial	Sep 1, 2021 10:00 AM	74	1
COVID-NMA initiative	REGEN-COV REGN-COV2 Casirivimab	Sep 1, 2021 11:30 AM	1	1
ClinicalTrials.gov	Casirivimab OR REGEN-COV OR REGN-COV2 and COVID-19	Sep 1, 2021 1:00 PM	8	0
Chinese Clinical Trial Registry	Casirivimab OR REGEN-COV OR REGN-COV2	Sep 1, 2021 1:30 PM	0	0
EU Clinical Trials Register	Casirivimab OR REGEN-COV OR REGN-COV2 and COVID-19	Sep 1, 2021 3:00 PM	2	0
Republic of Korea - Clinical Research Information Service	Casirivimab OR REGEN-COV OR REGN-COV2	Sep 1, 2021 3:30 PM	0	0
Japan Primary Registries Network/ NIPH Clinical Trials Search	Casirivimab OR REGEN-COV OR REGN-COV2	Sep 1, 2021 4:00 PM	2	0
CenterWatch	Casirivimab OR REGEN-COV OR REGN-COV2	Sep 1, 2021 4:30 PM	4	0
chinaxiv.org	Casirivimab OR REGEN-COV OR REGN-COV2	Sep 1, 2021 8:00 PM	0	0
Medrxiv.org	Casirivimab OR REGEN-COV OR REGN-COV2	Sep 1, 2021 8:30 PM	2	0
Biorxiv.org	Casirivimab OR REGEN-COV OR REGN-COV2 AND COVID-19	Sep 1, 2021 9:00 PM	48	0

Appendix 2b. Characteristics of Included Studies

Study ID	Patients (n) & Duration of Follow-Up	Interventions	Outcomes	Study Design
Subcutaneous REGEN-COV Antibody Combination to Prevent Covid-19 *O'Brien et al. (USA, Romania, Moldova)*	RT-PCR negative close contacts of confirmed COVID-19 patients ages 12 and above (n=1505) Duration of follow-up: Approximately 28 days	EXPERIMENTAL: REGEN-COV MAB Cocktail 1200mg SC (600mg Casirivimab + 600mg Imdevimab) CONTROL: Placebo	PRIMARY: Development of symptomatic, RT-PCR confirmed COVID-19 infection within 28 days SECONDARY: Viral load >10^4 copies, duration of symptomatic RT-PCR confirmed SARS-CoV-2 infection, duration of any RT-PCR confirmed SARS-CoV-2 infection whether symptomatic or asymptomatic, development of any RT-qPCR confirmed SARS-CoV-2 infection whether symptomatic or asymptomatic	Randomized, double-blind, placebo-controlled

Appendix 3. Study Appraisal

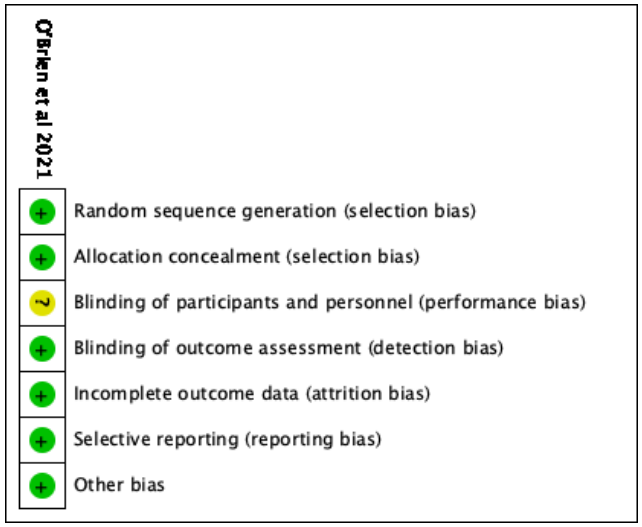

Figure 1. *Risk of bias summary table*

Appendix 4. GRADE Evidence Profile

Author(s): Isabella S. Ocampo, MD
Question: Casirivimab + Imdevimab compared to Placebo for COVID-19 post-exposure prophylaxis
Setting: Outpatient
Bibliography: O'Brien M, Forleo-Neto E, Musser B, et al. Subcutaneous REGEN-COV antibody combination for Covid-19 prevention. NEJM. 2021Aug4. doi:10.1056/NEJMoa2109682

CERTAINTY ASSESSMENT							NO. OF PATIENTS		EFFECT		CERTAINTY	IMPORTANCE
No. of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Casirivimab + imdevimab	Placebo	Relative (95% CI)	Absolute (95% CI)		
Prevention of symptomatic RT-qPCR SARS-CoV-2 infection (follow up: 28 days)												
1	Randomised trials	Not serious	Not serious	Not serious	Not serious	None	11/753 (1.5%)	59/752 (7.8%)	**RR 0.19** (0.10 to 0.35)	**64 fewer per 1,000** (from 71 fewer to 51 fewer)	⊕⊕⊕⊕ HIGH	CRITICAL
Prevention of any RT-PCR confirmed symptomatic or asymptomatic SARS-CoV-2 infection (follow up: 28 days)												
1	Randomised trials	Not serious	Not serious	Not serious	Not serious	None	36/753 (4.8%)	107/752 (14.2%)	**RR 0.34** (0.23 to 0.48)	**94 fewer per 1,000** (from 110 fewer to 74 fewer)	⊕⊕⊕⊕ HIGH	CRITICAL
Duration of symptomatic SARS-CoV-2 infection (follow up: 28 days)												
1	Randomised trials	Not serious	Not serious	Serious[a]	Serious[b]	None	6/72 (8.3%)	4/66 (6.1%)	**RR 1.37** (0.40 to 4.67)	**22 more per 1,000** (from 36 fewer to 222 more)	⊕⊕◯◯ Low	CRITICAL
Adverse events (follow up: 28 days)												
1	Randomised trials	Not serious	Not serious	Not serious	Not serious	None	753	752	-	MD **2 weeks lower** (2.21 lower to 1.79 lower)	⊕⊕⊕⊕ HIGH	CRITICAL
Serious adverse events (follow up: 28 days)												
1	Randomised trials	Not serious	Not serious	Not serious	serious [a]	none	10/1311 (0.8%)	15/1306 (1.1%)	**RR 0.66** (0.30 to 1.47)	**4 fewer per 1,000** (from 8 fewer to 6 more)	⊕⊕⊕◯ MODERATE	CRITICAL

CI: Confidence interval; **RR:** Risk ratio; **MD:** Mean difference
Explanations
[a] There is a wide confidence interval.

Appendix 5. Table of Ongoing Studies

Clinical Trial Identifier/Title	Study Design	Country	Population	Intervention	Outcome	Estimated Date of Completion
NCT04852978 **COVID-19 Study to Assess Immunogenicity Safety and Tolerability of Moderna mRNA-1273 Vaccine Administered with Casirivimab+Imdevimab in Healthy Adult Volunteers**	Randomized controlled trial	USA	Healthy adults or adults with stable, chronic medical conditions with no COVID-19	Casirivimab+imdevimab, Moderna mRNA-1273 vaccine	Extent of effect of casirivimab+imdevimab administration on vaccine-induced neutralizing antibody responses to SARS-CoV-2 Time interval required between casirivimab+imdevimab administration and Moderna mRNA-1273 vaccine to ensure no meaningful impact on vaccine-induced neutralizing antibody responses to SARS-CoV-2	Aug 30, 2022
NCT04519437 **Study Assessing the Safety, Tolerability, Pharmacokinetics, and Immunogenicity of Repeated Subcutaneous Doses of Anti-Spike (S) SARS-CoV-2 Monoclonal Antibodies (REGN10933+REGN10987) in Adult Volunteers as Related to COVID-19**	Randomized controlled trial	USA	Healthy individuals with no COVID-19	Regeneron vs placebo	Adverse events of special interests	Oct 25, 2021
NCT04452318 **COVID-19 Study Assessing the Efficacy and Safety of Anti-Spike SARS CoV-2 Monoclonal Antibodies for Prevention of SARS CoV-2Infection Asymptomatic in Healthy Adults and Adolescents Who Are Household contacts to an Individual with a Positive SARS-CoV-2 RT-PCR Assay**	Randomized controlled trial	USA	Asymptomatic patients RT PCR negative at baseline with household contact exposure to a known COVID-19 confirmed patients.	Regeneron vs placebo	Proportion of participants who have a positive SARS-CoV-2 RT-qPCR (based on central lab test) and signs and symptoms (strict-term) of SARS-CoV-2 infection during the Efficacy assessment period (EAP) Proportion of participants who have a RT-qPCR confirmed SARS-CoV-2 infection (either symptomatic or asymptomatic) during the EAP Incidence and severity of treatment-emergent adverse events (TEAEs)	June 15, 2021

jRCT2071200117 **A phase I study of casirivimab and imdevimab in Japanese adult volunteers**	Randomized controlled trial	Japan	Healthy individuals ages 20-89 years old	Single dose IV casirivimab+imdevimab vs single dose IV placebo Single dose SC casirivimab+imdesivimab vs single dose SC placebo	Adverse events, pharmacokinetics of casirivimab and imdevimab, incidence of anti-drug antibodies to casirivimab and imdevimab	Not mentioned

Q14. Should melatonin be used in the prevention of COVID-19 infection?

As of 26 February 2021

RECOMMENDATION

We recommend <u>against</u> the use of melatonin as prevention for COVID-19 infection. *(Very low quality of evidence; Strong recommendation)*

Consensus Issues

It was discussed that among the limitations of the efficacy study was the lack of information on the dose administered and the duration of intake; hence, the panel could not compare it against the usual dose used for sleep disorder, which is one (1) 3-mg capsule a day for at least a month. The cost per capsule ranges from Php 16.00 to 20.00. With regard to melatonin's adverse effects, it was noted that indirect studies were evaluated (i.e., use of 2 mg to 10 mg melatonin for different indications); hence, the observation on excessive sleepiness may be dose-related. The panel raised a concern on the potential for its misuse or overuse considering that it may be marketed as prophylaxis for COVID-19, which is an off-label indication. Likewise, its potential adverse effects from long-term use are unknown.

Considering that the quality of evidence to support the use of melatonin is very low, and in the context of potential adverse events as well as cost considerations, the panel decided to strongly recommend against its use for COVID-19 infection.

KEY FINDINGS

One observational study reported lower odds of getting a positive test result for COVID-19 among those taking melatonin compared to those who were not. The study was found to be with serious risk of bias because of absence of randomization and allocation concealment and the lack of details which precluded assessment of blinding and follow-up. For safety, one systematic review reported that overall, melatonin supplements have a good safety profile. However, there are some adverse effects that are dose- and timing-related, and one study stated that caution should be exercised in the use of melatonin in patients with hypertension.

INTRODUCTION

Melatonin (5 methoxy-N-acetyltryptamine) is a hormone produced by the pineal gland at night, which controls circadian rhythms such as the sleep-wake rhythm [1]. Melatonin supplements have been used to treat sleep orders and are reported to have potential anti-viral action through its inflammatory and antioxidant properties [2]. It was also reported that it indirectly targets human coronavirus (HCoV) cellular targets, including ACE2, BCL2L1, JUN, and IKBKB [3].

REVIEW METHODS

We conducted a literature search using PubMed and the Cochrane Library using the terms "COVID-19," "melatonin," and "systematic review" or "randomized controlled trials" and their synonyms or MESH terms. The date of the last search was December 26, 2020. We also searched the following databases: clintrials.gov, ChinaXiv.org, MedRxiv.org, BioRxiv.org, chictr.org and WHO International Clinical Trials Registry Platform (ICTRP).

Randomized controlled trials, systematic reviews, and meta-analyses that assessed the effect of melatonin supplement as prevention for COVID-19 infection were included. Observational studies or quasi-experimental studies were also included in case of lack of data. We excluded in vitro and animal studies and those that did not meet our PICO criteria (see below).

The following PICO criteria were used:

- Population: people at risk for COVID-19
- Intervention: Melatonin supplements as a prophylaxis, as a single agent, any dose, any duration
- Comparator: placebo, any active control, no intervention plus minimum health standards
- Outcomes: incidence of COVID-19, adverse events
- Study design: observational studies, quasi-experimental studies, randomized controlled trials (RCTs)

RESULTS

Efficacy

Zhou and colleagues conducted retrospective case control studies using a COVID-19 registry (N=26,779) of patients tested for COVID-19 in the Cleveland Clinic Health System in Ohio and Florida [4]. It was stated that patients were actively taking melatonin or other drugs at the time of testing. Investigators used combination network-based prediction and propensity score (PS) matching and found that the odds ratio of getting a positive test result for COVID-19 among those taking melatonin compared to those who were not was 0.72 (95% CI 0.56–0.91) after adjusting for age, sex, race, smoking history, and comorbidities such as diabetes, hypertension, coronary artery disease, and COPD [4]. The characteristics of this study are shown in Appendix 1 and 2.

Five (5) subgroup analyses were done to further observe the effect of melatonin [4]. Results showed that melatonin significantly reduced the likelihood of a positive laboratory test result for SARS-CoV-2 in black Americans (aOR = 0.48, 95% CI 0.31–0.75) after adjusting for age, sex, race, smoking, and various disease comorbidities; the same was true for patients with diabetes (aOR = 0.52, 95% CI 0.36–0.75). However, no significant differences were observed for asthma (aOR = 0.61, 95% CI 0.36–1.06), hypertension (aOR = 0.80, 95% CI 0.61–1.05), and white Americans (aOR = 0.77, 95% CI 0.57–1.04). The authors concluded that melatonin could have a potential benefit in preventing and treating COVID-19 [4].

Level of evidence was graded as very low as it was an observational study and had serious risk of bias because of absence of randomization and allocation concealment, and the lack of details which precluded assessment of blinding and follow-up. The study did not specify clinical details such as timing or duration of melatonin intake, and only stated the analysis of drug-outcome relationships from a large dataset from a COVID-19 registry. Moreover, the investigators did not clearly describe if they identified the outcome first before the exposure. In the results section, they mentioned that they used retrospective cohort analysis (Appendix 2).

Safety

We did not find any article that assessed the safety of melatonin use as prophylaxis for COVID-19. Instead, we report here the findings from one systematic review regarding the adverse events of oral supplementation of melatonin [5]. Foley and Steel reported that oral melatonin supplementation in humans has a generally good safety profile, but there are some exceptions. Out of 50 studies included in their systematic review, 24 reported at least one statistically significant adverse event. Generally minor and transient were fatigue, mood disturbance, or psychomotor and neurocognitive performance. Those pertaining to the endocrine and cardiovascular systems were often related to dose, timing, and potential interactions with antihypertensives. The systematic review found two studies which reported that melatonin could elevate blood pressure and heart rate. This is contradicted in other literature which reported that melatonin could lower blood pressure and heart rate [6].

In-vitro and animal studies suggest that melatonin may have possible drug interactions with calcium channel blockers [5]. Thus, caution in the use of melatonin would be needed in patients with hypertension [5]. The review also reported adverse events relating to endocrine function, such as reproductive parameters and glucose metabolism [5].

The most common adverse events reported were related to reduction in psychomotor and neurocognitive function or fatigue and excessive sleepiness, which may be due to melatonin's sedative and hypnotic activity [5]. Other adverse events reported were dizziness, headache, nausea and sleepiness [6].

RECOMMENDATIONS FROM OTHER GROUPS

There are no guidelines that mentioned the use of melatonin in preventing COVID-19 [7, 8, 9]. Moreover, the (National Institutes of Health (NIH) COVID-19 guidelines "recommends against the use of any agents for SARS-CoV-2 pre-exposure prophylaxis (PrEP), except in a clinical trial" [7].

RESEARCH GAPS

There is one ongoing randomized placebo-controlled trial. The MeCOVID trial aims to evaluate the efficacy of daily melatonin as a pre-exposure prophylaxis against SARS-CoV-2 infection among healthcare workers at high risk of SARS-CoV-2 exposure [10]. The eligible participants will be randomized to receive either 2 mg of melatonin or placebo orally before bedtime for 12 weeks [10]. The primary outcome to be measured is the number of confirmed COVID-19 symptomatic infections confirmed by SARS-CoV 2 infection rate (12 weeks) [10]. The completion date is supposed to be in December 2020; however, as of 16 Feb 2021, the results have not yet been published [10].

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Appendix 1: Characteristics of Included Studies

Author	Population	Intervention Group(s)	Comparison Group(s)	Outcomes
Zhou et al [4]	Patients registered in COVID-19 registry from the Cleveland Clinic Health systems in Ohio and Florida	Melatonin use before testing for COVID-19	Non-melatonin use before testing for COVID-19	Positive laboratory test result for COVID-19

Appendix 2: GRADE Evidence Profile

Melatonin compared to Non-melatonin Use for COVID-19

CERTAINTY ASSESSMENT							SUMMARY OF FINDINGS				
Participants (studies) Follow-up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty of evidence	Study event rates		Relative effect (95% CI)	Anticipated absolute effects	
							With non-melatonin use	With melatonin		Risk with non-melatonin use	Risk difference with melatonin
COVID-19 positive											
8274 cases 18505 controls (1 observational study)	Serious [a]	Not serious	Not serious	Not serious	None	⨁◯◯◯ VERY LOW	8274 cases 18505 controls	**OR 0.72** (0.56 to 0.91)	8274 cases 18505 controls (1 observational study)	**Low**	
										0 per 1,000	**0 fewer per 1,000** (from 0 fewer to 0 fewer)

CI: Confidence interval; **OR:** Odds ratio

Explanations

[a] Unclear study design/methodology: clinical details such as timing and duration of melatonin intake not given

Appendix 3: Study Characteristics of Ongoing Trials

Title/ Clinical Trial ID Number	Study design	Population	Intervention Group(s)	Comparison Group(s)	Outcomes
Efficacy of Melatonin in the Prophylaxis of Coronavirus Disease 2019 (COVID-19) Among Healthcare Workers. (MeCOVID) NCT04353128 [6]	RCT	Healthcare workers from the public and private Spanish hospital network at risk of SARS-CoV 2 infection with no previous COVID-19 infection	2 mg of melatonin orally before bedtime for 12 weeks	Identically looking placebo orally before bedtime for 12 weeks	Primary SARS-CoV 2 infection rate (12 weeks)

Q15. Should Vitamin D supplementation be used in the prevention of COVID-19 infection?

As of 18 March 2021

RECOMMENDATION

We recommend <u>against</u> the use of Vitamin D supplementation to prevent COVID-19 infection. *(Very low quality of evidence; Strong recommendation)*

Consensus Issues

It was pointed out that although the study by Jollife et al. found that Vitamin D supplementation reduced the risk of acute respiratory infection (ARI) overall, this systematic review was done prior to the COVID-19 pandemic, hence the population assessed did not include COVID-19 patients. In relation to the preventive effect of Vitamin D against ARI, it was noted that the duration of the trials in the systematic review ranged from 7 weeks to 12 months, and such a duration for effect to be seen is not deemed beneficial since vaccines will soon be available. Overall, the panel recognized that all the studies evaluated on its efficacy and safety were indirect evidence.

KEY FINDINGS

One direct evidence of very low quality was found. A retrospective cohort study on frail, elderly nursing home residents (N=66) reported that fewer patients died among those who received 80,000 IU of Vitamin D during the week following the diagnosis of COVID-19, or within one month prior to diagnosis, when compared to patients who received other medications. There was no direct evidence on the safety of Vitamin D supplementation as prevention for COVID-19.

INTRODUCTION

Vitamin D plays a significant role in muscle, bone, and immune health and supports the induction of antimicrobial peptides in response to both viral and bacterial stimuli by inducing innate antimicrobial effector mechanisms. Vitamin D lowers the risk of COVID-19 infection through the maintenance of the integrity of cellular junctions, attenuation of cytokine storm, suppression of T helper cell type 1 responses and promotion of T regulatory cell induction [1]. Vitamin D modulates the renin-angiotensin system in rat models with lipopolysaccharide-induced acute lung injury [2]. A meta-analysis of observational studies (16 studies, N = 4922) showed that 89% of COVID-19 patients had Vitamin D insufficiency (48%; 95% CI, 29%-67%) or deficiency (41%; 95% CI, 26.7%-50.1%) [3]. The meta-analysis of Jolliffe et al. (42 RCTs, N = 46,331) showed that Vitamin D supplementation reduced the risk of Acute Respiratory Infections overall (Odds Ratio [OR] 0.91, 95% CI 0.84 to 0.99; p for heterogeneity 0.01) compared to placebo [4]. In the same systematic review, a meta-analysis of adverse events reported that Vitamin D supplementation did not have a statistically significant effect on work/school absences due to ARI, hospitalizations or emergency department attendances for ARI, serious adverse events of any cause, mortality of any cause, hypercalcemia or renal stones [4]. Vitamin D supplementation has thus been investigated as a potential prevention against COVID-19.

REVIEW METHODS

We searched for existing traditional/ living systematic reviews and/or traditional/ living COVID-19 databases and CPGs, published studies (PubMed, Cochrane Library, Herdin), MedRxIV, and BioRxIV (search date up to December 15, 2020). Ongoing trials were searched in Clinicaltrials.gov Registry and EudraCT (search date up to December 15, 2020). We used the following keywords and MeSH terms: “Vitamin D,” “ergocalciferol,” “cholecalciferol,” "prevention," and COVID-19 related terms in the search strategy.

The following PICO criteria were used:

- Population: people at risk for COVID-19
- Intervention: Vitamin D supplements as a prophylaxis, as a single agent, any dose, any duration
- Comparator: placebo, any active control, no intervention
- Outcomes: incidence of COVID-19, adverse events
- Study design: observational studies, quasi-experimental studies, randomized controlled trials (RCTs)

RESULTS

We found one direct evidence on the efficacy of Vitamin D supplementation for the prevention of COVID-19. A retrospective cohort study by Annweiler et al. [5] on frail, elderly nursing home residents (N=66) reported that fewer patients died among those who received 80,000 IU of Vitamin D during the week following the diagnosis of COVID-19 or within one month prior to diagnosis (HR = 0.11, 95 % CI 0.03 to 0.48; P = 0.003) after adjustment for all potential confounders, when compared to patients who received other medications. The number of patients who received other medications was small (n = 9) compared to the Vitamin D group (n = 57). This study provided very low quality of evidence due to indirectness, i.e., the authors did not state how many patients received a Vitamin D bolus prior to the diagnosis of COVID-19 therefore we could not ascertain the preventive efficacy. Furthermore, it was an observational study, and the comparator group (no Vitamin D supplements) was small (n = 9).

We found no direct evidence on the safety of Vitamin D supplementation as a prevention of COVID-19. Indirect evidence on safety was found from two systematic reviews. High dose, long-term Vitamin D supplementation was not found to increase the risk of adverse events or deaths of any cause. Vitamin D supplementation may increase the risk for hypercalcemia and possible hypercalciuria (low quality evidence due to indirectness).

RECOMMENDATIONS FROM OTHER GROUPS

There are no recommendations for Vitamin D as a prophylaxis of COVID-19. In the UK Guideline with NICE Evidence Review (NG187), there are recommendations for Vitamin D supplementation for maintaining immune health [6].

RESEARCH GAPS

There are nine registered clinical trials investigating Vitamin D supplementation for the prevention of COVID-19 [7-15] (Appendix 3).

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15. Reducing Asymptomatic Infection With Vitamin D in Coronavirus Disease (RAID-CoV-2) [Internet]. 2020. Available from: https://clinicaltrials.gov/ct2/show/NCT04476680.

Appendix 1. Characteristics of Included studies

No.	Author (year)	Country/ Setting	Study design	Population	Intervention	Comparator	Outcomes
1	Annweiler (2020)	France	Retrospective cohort (record review)	N = 66 elderly nursing home residents (disabled, neurocognitive, psychiatric) with COVID-19 (clinical signs/ confirmed by rtPCR)	n = 57 Oral Vitamin D3 bolus (80,000 IU) in the week following suspicion or diagnosis of COVID-19 or the month prior to diagnosis	n = 9 Other medications (corticosteroids, HCQ, Antibiotics)	Mortality Ordinal Scale of Clinical Improvement (OSCI) for COVID-19

Appendix 2. GRADE Evidence Profile

Author(s): Dofitas, Belen & Eubanas, Gina
Question: Vitamin D supplements compared to placebo, other drugs, standard preventive measures for prevention of COVID-19
Setting:
Bibliography: Anweiller (2020)

CERTAINTY ASSESSMENT							NO. OF PATIENTS		EFFECT		CERTAINTY	IMPORTANCE
No. of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Vitamin D supplements	Placebo, other drugs, standard preventive measures	Relative (95% CI)	Absolute (95% CI)		
Mortality: Vit D for prevention of ARI (follow up: mean 36 days; assessed with: proportion of participants)												
1	Observational studies	Serious [a]	Not serious	Very serious [b]	Serious [c]	None	10/57 (17.5%)	5/9 (55.6%)	**HR 0.11** (0.03 to 0.48)	**470 fewer per 1,000** (from 532 fewer to 233 fewer)	⨁◯◯◯ VERY LOW	

CI: Confidence interval; **OR:** Odds ratio; **HR:** Hazard Ratio; **RR:** Risk ratio

Explanations
[a] Retrospective review of records; Vitamin D bolus given within the week of diagnosis or one month prior to diagnosis of COVID-19; comparison group had small sample size: majority of patients were given Vit D (n = 57) versus other medications (n = 9)
[b] No data on number of patients given Vitamin D prior to diagnosis of COVID-19 therefore we can not ascertain preventive efficacy
[c] small sample size of comparator group: other medication (n = 9)

Appendix 3. Registered clinical trials

	Clinical Trial ID/Titile	Country /Setting	Study design	Population	Intervention	Comparator	Outcomes
1	Efficacy of Vitamin D Supplementation to Prevent the Risk of Acquiring COVID-19 in Healthcare Workers NCT04535791	Mexico	Interventional RCT; parallel assignment	Adults,Health workers (doctors, residents, nurses, technicians, stretcher-bearers, cleaning crew)	Cholecalciferol 4000 IU daily for 30 days	Placebo	Outcome Measures: 1) No. of participants with Covid-19; 2) No. of participants with hospitalization for Covid -19; 3) Serum concentration of 25 (OH) vitamin D
2	PRevention of COVID-19 With Oral Vitamin D Supplemental Therapy in Essential healthCare Teams (PROTECT). NCT04483635	Canada	RCT parallel assignment, triple blind	2414 Health care workers 18 to 69 yrs old	Weekly bolus dose of Vitamin D 100 000 IU Vit D3 + weekly 10 000 IU	Placebo	Primary Outcome : 1) Change in incidence of laboratory-confirmed COVID-19 infection [Time Frame: 16 weeks]; 2) COVID-19 suspected/confirmed infection 3) Number of workday absences for any reason; 4) adverse reactions
3	Vitamin D Supplementation in the Prevention and Mitigation of COVID-19 Infection (VitD-COVID19) NCT04482673	United States	Randomized parallel assignment; quadruple blind; phase 4 interventional	140 adults aged 50 yrs and older	COVID-19 Negative Active : vitamin D3 (6000 IU) per day for 12 months and daily 800 IU vitamin D3. Intervention: Daily Vitamin D3. COVID-19 Positive Active Treatment bolus (20,000 IU) per day for 3 days followed by high dose vitamin D (6000 IU) per dayfor 12 months. 800 IU vitamin D3/day. Interventions: Drug: Daily Vitamin D3 Drug: Bolus vitamin D3	Placebo Comparator: COVID-19 Negative Placebo placebo for 12 months. All will receive a multivitamin 800 IU vitamin D3/day. Intervention: Drug: Daily placebo. Placebo Comparator: COVID-19 Positive Placebo placebo as a bolus followed by daily placebo for 12 months. All participants will receive a multivitamin containing 800 IU vitamin D3/day. Interventions: Drug: Daily placebo Drug: Bolus placebo	Primary outcome : 1) Change in total circulating 25(OH)D concentration [Time Frame: monthly in COVID-19 negative participants through study completion for 1 year]; 2) Change in total circulating 25(OH)D concentration in COVID-19 positives [Time Frame: baseline, 2 and 4 weeks, then months 3, 6, 9 and 12 in COVID-19 positive participants]; 3) Change in SARS-CoV-2 antibody titers; 4) intake; 5) perceived stress; 6) Charlson comorbidity index; 7) pandemic stress
4	Oral 25-hydroxyvitamin D3 and COVID-19 NCT04386850	Iran	Multicenter randomized double-blinded placebo-controlled clinical trial with parallel groups	health care providers and hospital workers with a negative test for COVID-19 and a close patient relative with a negative test for COVID-19 who lives with the infected patients	25 mcg of 25(OH)D3 once daily at bedtime for 2 months	placebo daily for 2 months	COVID-19 (SARA-Cov-2) infection [Time Frame: 60 days]; Severity of COVID-19 (SARA-Cov-2) infection [Time Frame: 60 days]

5	Trial of Vitamin D to Reduce Risk and Severity of COVID-19 and Other Acute Respiratory Infections (CORONAVIT) NCT04579640	UK	Open-label, phase 3, randomised clinical trial	UK resident ≥16 years old with sub-optimal vitamin D status	Capsules containing 800 IU (20 micrograms) or 3,200 IU (80 micrograms) cholecalciferol	standard of care (national recommendation of 400 IU/day vitamin D)	Proportion of participants experiencing at least one doctor-diagnosed or laboratory-confirmed acute respiratory infection of any cause. [Time Frame: Over 6 months]
6	Vitamin D and COVID-19 Trial (VIVID) NCT04536298	USA	Cluster-Randomized, Double-Blind, Placebo-Controlled	Household members of newly infected COVID-19 patients	Vitamin D softgel capsules; each capsule contains 3200 IU of vitamin D3. Three capsules per day (9600 IU/day) will be taken on days 1 and 2, and one capsule per day (3200 IU/day) will be taken on days 3 through 28	Placebo softgel capsules. Three capsules per day will be taken on days 1 and 2, and one capsule per day will be taken on days 3 through 28	SARS-CoV-2 infection in close household contacts [Time Frame: 4 weeks]; Self-reported disease severity in close household contacts [Time Frame: 4 weeks]
7	The Effect of D3 on Selected Cytokines Involved in Cytokine Storm in the Covid-19 Uninfected Jordanian People NCT04476745	Jordan	randomized parallel, open-label trial	Covid-19 uninfected adults with vitamin D deficiency	Vitamin D3 (50,000) IU / week for 8 weeks	No intervention	IL-1 beta, IL-6, TNF serum levels [Time Frame: 8 weeks]
8	Vitamin D3 Supplementation to Prevent Respiratory Tract Infections NCT04596657	USA	Randomized parallel, open-label trial	Hospital worker 52 years old and above	vitamin D3 supplementation (5000 IU)	Control	Respiratory tract infection (including COVID-19) [Time Frame: 9 months]; Incidence of acute respiratory tract infection
9	Reducing Asymptomatic Infection With Vitamin D in Coronavirus Disease (RAID-CoV-2) NCT04476680	UK	Randomized, double-blind, parallel group trial	18 - 30 years old w/o any previous or current COVID -19 infection	Vitamin D 1000 IU	Placebo	Seroconversion [Time Frame: 24 weeks]; asymptomatic seroconversion for SARS-CoV-2

Q16. Should zinc supplementation be used in the prevention of COVID-19 infection?

As of 18 March 2021

RECOMMENDATION

We recommend against the use of zinc supplementation to prevent COVID-19 infection. *(Very low quality of evidence; Strong recommendation)*

Consensus Issues
A concern was raised that the recommendation may be misconstrued that zinc supplementation is not needed, but it was clarified that this will be specific only for COVID-19 infection.

KEY FINDINGS

No direct published evidence was found on the use of zinc supplements in the prevention of COVID-19. Among non-COVID adult participants, zinc acetate doses of 100 to 150 mg/day taken for months had few adverse effects. Excessive intake of zinc may lead to gastrointestinal disturbances. When taken together with other supplements, zinc may reduce copper and iron levels in the body.

INTRODUCTION

Zinc is a widely-used supplement given to boost the immune system, fight infections and repair tissues. Zinc supplementation has attracted attention during the COVID-19 pandemic because of *in vitro* evidence that high intracellular zinc concentrations are able to inhibit the SARS-CoV RNA-dependent RNA polymerase Replication/Transcription Complexes (RdRp-RTC), making zinc likely to inhibit SARS-CoV-2 RdRp-RTC as well. SARS-CoV RdRp elongation was inhibited and template binding reduced, effectively blocking replication of the virus. [1] Zinc is well-absorbed in the oral mucosa and gastrointestinal tract which are primary sites of SARS-CoV-2 infection, [2] making zinc supplements a feasible prophylaxis for COVID-19.

Three systematic reviews of randomized controlled trials reported that zinc supplements may prevent pneumonia and diarrhea among children at risk for zinc deficiency. [3,4,5] Two clinical trials showed that zinc supplements significantly prevented colds and other respiratory infections among adults. [6,7] Excessive intake of zinc may lead to gastrointestinal disturbances. When taken together with other supplements, zinc may reduce copper and iron levels in the body. [8]

Zinc-deficient COVID-19 patients had higher complication rates than those with normal serum zinc levels on admission. [9] Zinc supplementation has thus been proposed as a possible prevention of COVID-19.

REVIEW METHODS

We searched for existing traditional/ living systematic reviews and/or traditional/ living COVID-19 databases and CPGs, published studies (Medline, Cochrane Library), pre-print studies, ongoing or completed studies in clinical trials registries up to December 2020. Key words were "COVID-19," "zinc," "prevention," and "prophylaxis."

Articles were selected based on the following inclusion criteria:

- **Population:** Patients at risk of exposure to COVID-19
- **Intervention:** Zinc supplements as a prevention, as a single agent, any dose, any duration
- **Comparator:** placebo, any active control, no intervention
- **Outcomes:** any clinical outcome such as prevention of COVID-19, incidence of COVID-19, adverse events
- **Study designs:** systematic reviews, randomized controlled trials (RCTs), non-randomized studies, observational studies (e.g. cohort, case-control, cross-sectional, case report, case series)

RESULTS

There was no direct evidence from available clinical trials or observational studies regarding zinc supplementation for the prevention of COVID-19.

In the systematic review by Hemilä on high dose zinc lozenges for the common cold among non-COVID participants, several included studies reported bad taste and constipation, but none of these persisted over a long-term period. The author reported that zinc acetate doses of 100 to 150 mg/day have been administered for months with few adverse effects. [10]

RECOMMENDATIONS FROM OTHER GUIDELINES

The National Institutes of Health guidelines state that there is insufficient evidence regarding zinc supplementation for the prevention of COVID-19. Zinc supplementation above the recommended daily intake should not be used for the prevention of COVID-19 if it is taken outside of a clinical trial. [11]

RESEARCH GAPS

We await the results of one completed but unpublished open-label, randomized controlled trial of Seet et al. for the prevention of COVID-19 among migrant workers in a closed dormitory in Singapore, that compared zinc with other drugs (HCQ, ivermectin, povidone-iodine throat spray) and a dietary supplement (vitamin C) in the prevention of COVID-19 among migrant workers. [12] (Appendix 1)

ONGOING STUDIES

There are no ongoing clinical trials on zinc alone for the prevention of COVID-19. There are two ongoing clinical trials investigating zinc supplements in combination with hydroxychloroquine and other nutritional supplements in the prevention of COVID 19 (Appendix 3). [13,14]

UPDATES SINCE LAST PANEL MEETING

As of April 2021, one cluster RCT (Seet et al.) has been published on the preventive efficacy of a daily intake of a combination of 64 mg elemental zinc with Vitamin C 500 mg compared to Vitamin C 500 mg alone ($N_{zinc/Vit\ C}$ = 634; $N_{Vit\ C}$ = 619). There was no significant difference between the two interventions in preventing COVID-19 among healthy migrant workers living in a dormitory (RR 0.67, 0.38 to 1.08). [15]

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Appendix 1. Characteristics of Registered/Ongoing Trials

	Clinical Trial ID / Title	Status	Start and estimated primary completion date	Study design	Country	Population	Intervention Group(s)	Comparison Group(s)	Outcomes
1	NCT04446104 A Randomized Open-label Prophylaxis Trial Among Migrant Workers at High-risk of COVID-19 (DORM Trial) Completed	Completed	May 13 to Aug 31, 2020	RCT (N=4257)	Singapore	Migrant workers in a closed dormitory	Zinc	Hydroxychloroquine Sulfate Tablets Ivermectin 3mg Tab Povidone-Iodine throat spray Vitamin C tablet	Laboratory-confirmed COVID-19 Acute respiratory illness Febrile respiratory illness Rate of hospitalization for COVID-19 and non-COVID-19 related indications Adverse events
2	NCT04377646 A Study of Hydroxychloroquine and Zinc in the Prevention of COVID-19 Infection in Military Healthcare Workers (COVID-Milit)	Not yet recruiting	May 4, 2020 - May 24, 2021	RCT (N=660)	Tunisia	military health professionals working in Tunisia and exposed to SARS CoV2 at different levels (2 levels of exposure).	Hydroxychloroquine: 400 mg at day 1 and day 2, then 400 mg weekly up to 2 months Zinc: 15 mg per day up to 2 months	Placebo of Zinc - 1 pill per day up to 2 months Placebo of HCQ - 1 pill at day 1 and day 2, then 1 pill weekly up to 2 months Double placebo (HCQ and Zinc)	Frequency of confirmed SARS CoV2 infection Any COVID-19 related symptoms (cough, fever, headache, vomiting, nausea, dyspnea, diarrhea, smell disorder,conjunctivitis, dizziness) Any adverse event or serious adverse event
3	NCT04551339 Zinc Versus Multivitamin Micronutrient Supplementation in the Setting of COVID-19 (ZnCOVID-19)	Enrolling by Invitation	September 28, 2020 - June 14, 2021	RCT (n=4500)	USA	Individuals over 50 years old or primary health care professionals over the age of 18 who have had no evidence of prior COVID-19 infection	High dose Zinc (PreserVision AREDS formulation soft gels or tablets) Two tabs taken daily for three months in combination with Copper, Vitamin C/E and beta-carotene	Multivitamin with 11mg of zinc One tab taken daily for three months	Admitted to the hospital in relations to COVID-19 illness PCR or undergo seroconversion Subjects with COVID-19 illness that are not hospitalized Require supplemental oxygen therapy during hospitalization for COVID-19 Require invasive ventilation during hospitalization for COVID-19 Deaths

Q17. Should hydroxychloroquine/chloroquine be used in the prevention of COVID-19?

As of 12 March 2021

RECOMMENDATIONS

We recommend against the use of HCQ for pre-exposure prophylaxis in adults who are at high risk of exposure to COVID-19 cases. *(Moderate quality of evidence; Strong recommendation)*

We recommend against the use of HCQ for post-exposure prophylaxis in adults who are exposed to COVID-19 cases. *(Low quality of evidence; Strong recommendation)*

Consensus Issues

For pre-exposure prophylaxis, HCQ will only have 2% benefit considering the worst-case scenario. With regard to its safety profile, there is clear harm in terms of gastrointestinal (e.g., diarrhea, abdominal cramps, nausea and vomiting) and neurological (e.g., dizziness) adverse events, which are incapacitating to health workers if they are to use this as prophylaxis.

For post exposure prophylaxis, the low-quality evidence showed no significant benefit of HCQ, and a trend toward increase in the risk of adverse events was likewise observed.

KEY FINDINGS

Two randomized controlled clinical trials (RCTs) on the use of hydroxycholoroquine (HCQ) as pre-exposure prophylaxis for COVID-19 showed tendency for reduction in the risk of developing COVID-19 infection. However, there was significant increase in the risk of adverse events.. Three RCTs were found on the use of HCQ for post-exposure prophylaxis for COVID -19 no significant reduction in the risk of developing COVID-19 infection and a trend toward increase in the risk of adverse events. Most of the studies were found to be at risk for bias with common issues in ascertainment bias and one study without blinding

INTRODUCTION

Chloroquine and its less toxic analogue, HCQ, were shown to have potential antiviral and anti-inflammatory properties against SARS CoV-2 demonstrated in-vitro: 1) inhibition of the entry of SARS-COV2 into Vero cells by increasing endosomal pH required for virus/cell fusion and interfering with the glycosylation of cellular receptors of SARS-CoV and 2) inhibition of activation and production of several cytokines that are evident in cytokine release syndrome in fulminant forms of COVID-19 [1,2]. However, two large randomized controlled trials, RECOVERY and WHO SOLIDARITY TRIALS revealed lack of benefit of HCQ as treatment for COVID-19 [3,4] and increased risk of cardiac adverse events as compared to placebo [3]. Likewise, latest systematic review and meta-analysis [5] and recommendations from US-NIH, WHO, and PSMID were against the use of HCQ for prophylaxis for COVID-19 unless in the context of a clinical trial [6,7,8].

REVIEW METHODS

We did a systematic search last February 24, 2021 using Medline, Cochrane Central Register of Controlled Trials (CENTRAL), and clinicaltrials.gov for systematic review and meta-analysis and RCTs. Eligibility criteria include population (P) of healthy adult subjects, intervention (I) CQ or HCQ used for prevention or prophylaxis and placebo as comparator (C), and COVID-19 infection and any adverse events as outcomes (O). We also searched for the Rapid Review for COVID-19 Management [9], a rapid review resource initiated by local reviewers, for the latest version of the review on the use of HCQ in COVID-19 Prophylaxis. We used the Cochrane risk of bias assessment tool [10]. Level of evidence was assessed using GRADE [11].

Results

Characteristics of Included studies

We included five RCTs in this review that met our eligibility criteria. Four of the five RCTs were the RCTs included the latest systematic review and meta-analysis [5]. There was one RCT that was added which was published last December 2020.

Two of the five included RCTs were done in the USA, two RCTs done both in the USA and some parts of Canada and one RCT was done in Spain. The five RCTs included a total of 5432 subjects who were exposed or at high risk of exposure to COVID-19 case, composed of hospital based workers (3 RCTs) and contacts, occupational or household contacts of index case (2 RCTs). They were given either pre-exposure (2 RCTs) or post exposure prophylaxis (3 RCTs) using HCQ of varying doses (400-800mg/day), frequency (daily to 3x a week) and duration (5 days to 12 weeks). No trials investigated the use of chloroquine. Four RCTs used an identical placebo while one RCT used standard of care in the control arm. The efficacy outcome was the incidence of COVID-19 infection defined by either presence of usual symptoms of COVID-19 or detection of SARS COV-2 in the RTPCR test of oropharyngeal or nasopharyngeal swabs on the follow up period specified per study. The safety outcome or incidence of adverse events included mild adverse events, hospitalization, and mortality. Observation or follow up period ranged from 2 weeks to 12 weeks [12,13,14,15,16] (Appendix - Table 1, Summary of Included Studies).

Summary of Results

For pre-exposure prophylaxis, there was significant reduction in the risk of developing COVID-19 infection (RR = 0.76; 95%CI 0.59, 0.98) (Appendix – Figure 1). However, there was significant increase in the risk of adverse events (RR = 1.59; 95%CI 1.33-1.91) (Appendix – Figure 2). Adverse events were mostly mild and include gastrointestinal symptoms such as nausea, abdominal pain, diarrhea, and vomiting and neurologic symptoms such as irritability, dizziness, vertigo, headache, tinnitus, and visual symptoms. Non-treatment related severe adverse events were noted in a few, described as hospitalization due to COVID-19 and some allergic reaction. No deaths were attributed to the study drug.

For post-exposure prophylaxis, there was no significant reduction in the risk of developing COVID-19 infection (RR = 0.95; 95%CI 0.78,1.16) (Appendix – Figure 1). However, there was a trend toward increase in the risk of adverse events (RR = 3.15; 95%CI 0.95,10.46) (Appendix – Figure 2).

Summary of Methodological Quality

For pre-exposure prophylaxis, the two studies were assessed to have risk of ascertainment bias (ascertainment of efficacy: considered COVID-19 case in the presence of COVID-19 symptoms +/- laboratory confirmation; ascertainment of safety: if adverse event is due to HCQ or due to COVID-19). Quality of evidence was downgraded to moderate certainty due to the aforementioned risk of bias.

For post-exposure prophylaxis, the three studies were assessed to have risk of ascertainment bias (as explained above) and one study with risk of performance bias (open label study) for both efficacy and safety outcome. Quality of evidence downgraded to low certainty due to aforementioned risk of bias and imprecision.

RECOMMENDATIONS FROM OTHER GROUPS

The latest recommendation was issued last February 11, 2021 by the US-NIH COVID-19 Treatment Guidelines Panel which recommended against the use of any drugs for SARS-CoV-2 for pre-exposure prophylaxis except in the context of a clinical trial. It also recommended against the use of HCQ and other drugs for post exposure prophylaxis, except in the context of clinical trials [5]. This is consistent with WHO's guideline recommendation last May 2020 [6] and with Philippine Society for Microbiology and Infectious Disease (PSMID) last July 2020 [7]. This is in contrast with the Indian Medical Council of Medical Research that recommended prophylaxis with HCQ for asymptomatic healthcare workers involved in the care of suspected or confirmed cases of COVID-19, based on observational studies done by their council, last June 2020 [17].

ONGOING STUDIES

As of February 24, 2021, there were 33 registered clinical trials on HCQ prophylaxis for COVID-19 (Appendix – Table 3). Of the 33, 18 were not recruiting, 11 were recruiting, and 4 were completed, but results were not available.

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Appendix 1. Characteristics of Included Studies (Table 1)

Study & Setting	Population	Intervention	Comparator	Outcomes
Boulware June 2020 USA, Canada N = 821	Adults with household contact, healthcare worker or occupational moderate to high-risk exposure within 4 days to a person with confirmed Covid-19	PEP HCQ 800 mg (4 tablets) once, then 600 mg (3 tablets) 6 to 8 hours later, then 3 tablets daily for 4 more days for a total course of 5 days	PEP Placebo folate tablets (4 tablets) once, then 600 mg (3 tablets) 6 to 8 hours later, then 3 tablets daily for 4 more days for a total course of 5 days	Symptomatic illness confirmed by a positive molecular assay or if testing was unavailable, Covid-19 related symptoms within 14 days 4-6 weeks follow up tests, illness, hospitalizations) Adverse events
Mitja July 2020 USA N = 2314	Adults >18yo, with a recent history of close contact exposure to a PCR-confirmed COVID-19 case (as healthcare worker, household contact, nursing home worker or resident) Asymptomatic 14 days prior to enrolment	PEP HCQ 800mg OD x 1 day then 400mg OD x 6 days	Usual care	COVID-19 infection (SARS CoV 2 PCR test and at least on the COVID-19 symptoms; COVID-19 compatible symptoms) at day 14 Serological Positivity at Day 14 Adverse events up to 4 weeks follow up
Abella Sep 2020 USA N = 125	Adult hospital-based health care workers exposed to COVID patients at ER and COVID units	PrEP HCQ 600mg per day x 8 weeks	PrEP Placebo cellulose tablets 600mg per day x 8 weeks	SARS-CoV-2 infection via RT-PCR assay of NPS at 4th and 8th week or the occurrence of COVID-19 symptoms Adverse events 8 weeks follow up
Rajasingham Oct 2020 USA and some parts of Canada N = 1405	Adult 18 y/o and above, health care workers with ongoing exposure (Considered high-risk if exposure (ED, ICU, Covid-19 hospital ward, first responder, does aerosol-generating procedures)	PrEP HCQ 400mg OD or twice weekly for 12 weeks	PrEP Placebo tablets OD or twice weekly for 12 weeks	COVID-19 infection (laboratory confirmed or symptomatic compatible illness) Adverse events 12 weeks follow up
Barnabas Dec 2020 USA (seven institutions) N = 689	Adults 18-80 y/o, had close contact with an infected person <96hrs (household contacts or other close contacts or health care workers who cared for an infected person without wearing appropriate PPE) Asymptomatic at baseline. (negative baseline RTPCR test)	PEP HCQ 400mg OD for 3 days, followed by HCQ 200mg OD for an additional 11 days	PEP Placebo ascorbic acid 500mg OD for 3 days, then 200mg OD for 11 days	(+) Sars-cov-2 by RT PCR within 14 days Adverse events 4 weeks follow up

Appendix 2. GRADE Evidence Table (Table 2)

Patient or population: COVID-19 prophylaxis
Setting: Healthy individuals exposed or at high risk of exposure to COVID-19
Intervention: HCQ Prophylaxis
Comparison: Placebo

Outcome № of participants (studies)	Relative effect (95% CI)	Anticipated absolute effects (95% CI)		Difference	Certainty	What happens
COVID-19 Infection (PrEP and PEP) № of participants: 5432 (5 RCTs)	**RR 0.87** (0.74 to 1.02)	10.6%	**9.2%** (7.8 to 10.8)	**1.4% fewer** (2.8 fewer to 0.2 more)	⊕⊕◯◯ LOW [a,b]	No significant benefit in preventing COVID-19 infection with use of HCQ prophylaxis
Adverse events (PrEP and PEP) № of participants: 5416 (5 RCTs)	**RR 2.43** (1.06 to 5.56)	11.8%	**28.8%** (12.5 to 65.8)	**16.9% more** (0.7 more to 54 more)	⊕⊕⊕⊕ HIGH [c]	Significant increase in the risk of adverse events in the HCQ prophylaxis group
COVID-19 infection (PrEP) № of participants: 1608 (2 RCTs)	**RR 0.76** (0.59 to 0.98)	23.4%	**17.8%** (13.8 to 23)	**5.6% fewer** (9.6 fewer to 0.5 fewer)	⊕⊕⊕◯ MODERATE [d]	Significant benefit in preventing COVID-19 with the use of HCQ as PrEP
COVID-19 infection (PEP) № of participants: 3824 (3 RCTs)	**RR 0.95** (0.78 to 1.16)	9.1%	**8.7%** (7.1 to 10.6)	**0.5% fewer** (2 fewer to 1.5 more)	⊕⊕◯◯ LOW [e,f]	No significant benefit in preventing COVID-19 infection with use of HCQ for PEP
Adverse Events (PrEP) № of participants: 1530 (2 RCTs)	**RR 1.59** (1.33 to 1.91)	21.9%	**34.8%** (29.1 to 41.8)	**12.9% more** (7.2 more to 19.9 more)	⊕⊕⊕◯ MODERATE [g]	Significant increase in adverse events in the use of HCQ for PrEP
Adverse Event (PEP) № of participants: 3886 (3 RCTs)	**RR 3.15** (0.95 to 10.46)	9.2%	**28.9%** (8.7 to 95.8)	**19.7% more** (0.5 fewer to 86.6 more)	⊕⊕⊕◯ MODERATE [h]	Trend towards increase in adverse events in the use of HCQ for PEP

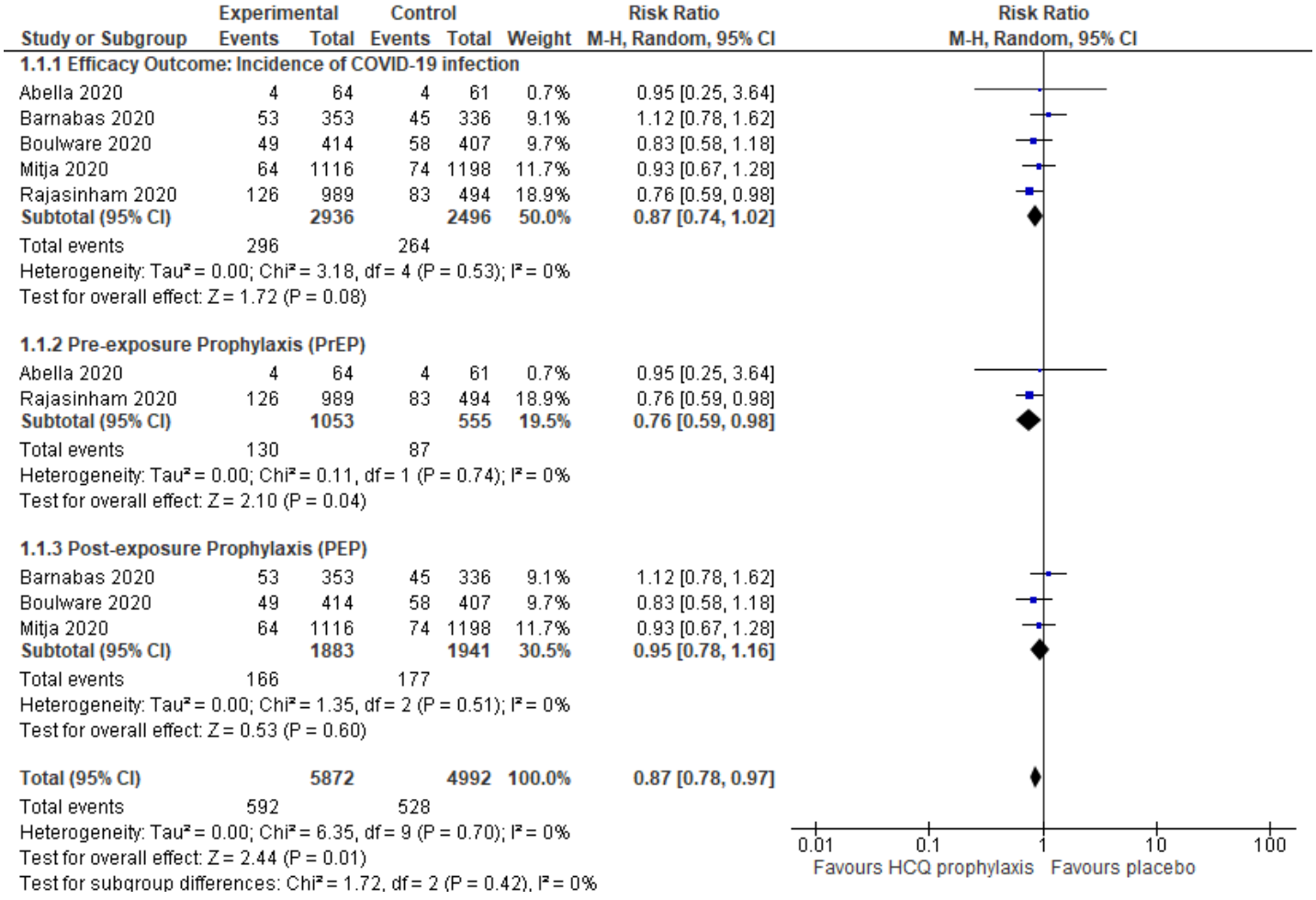
*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: Confidence interval; **RR:** Risk ratio

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

Explanations
[a] Downgraded due to moderate risk of ascertainment bias in one study (Barnabas et al) and performance bias due to lack of blinding in one study (Mitja et al).
[b] Downgraded due to imprecsion noted in 4 studies (Boulware et al, Barnabas et al, Abella et al, and Mitja et al.)
[c] Low risk of ascertainment bias was noted in deciding whether the adverse event especially gastrointestinal symptoms were drug related or COVID-related. However, despite this low risk of bias, the results showed significant increase in adverse events in the HCQ prophylaxis group compared to placebo or no prophylaxis.
[d] Risk of ascertainment bias for one study in using symptoms to identify those with COVID-19 infections
[e] Risk of performance bias due to lack of blinding in one study and risk of ascertainment bias in two studies using symptoms to identify those with COVID-19 infections
[f] Imprecision noted in all studies
[g] risk of ascertainment bias
[h] risk of ascertainment bias

Appendix 3. Forest Plots

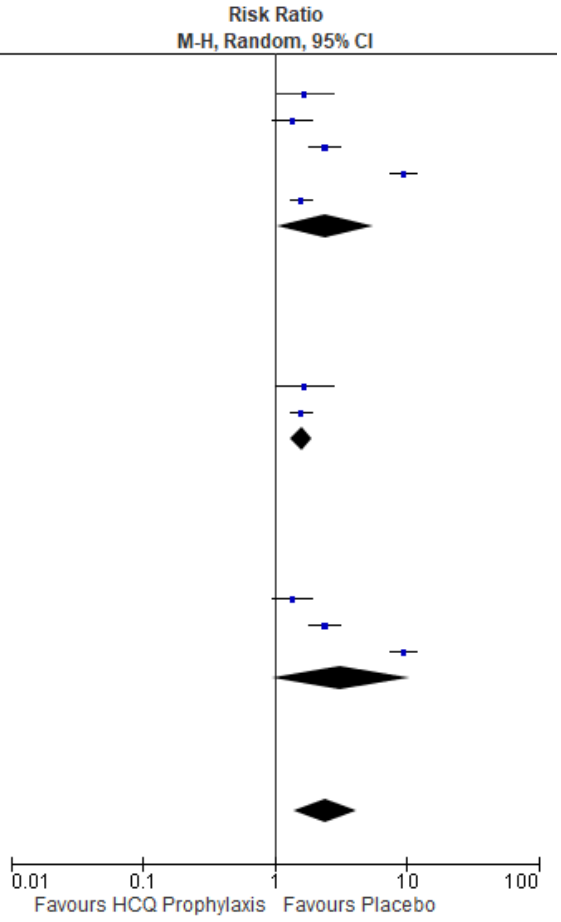
A. Efficacy Outcome: Incidence of COVID-19



Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
1.1.1 Efficacy Outcome: Incidence of COVID-19 infection						
Abella 2020	4	64	4	61	0.7%	0.95 [0.25, 3.64]
Barnabas 2020	53	353	45	336	9.1%	1.12 [0.78, 1.62]
Boulware 2020	49	414	58	407	9.7%	0.83 [0.58, 1.18]
Mitja 2020	64	1116	74	1198	11.7%	0.93 [0.67, 1.28]
Rajasinham 2020	126	989	83	494	18.9%	0.76 [0.59, 0.98]
Subtotal (95% CI)		**2936**		**2496**	**50.0%**	**0.87 [0.74, 1.02]**
Total events	296		264			
Heterogeneity: Tau² = 0.00; Chi² = 3.18, df = 4 (P = 0.53); I² = 0%						
Test for overall effect: Z = 1.72 (P = 0.08)						
1.1.2 Pre-exposure Prophylaxis (PrEP)						
Abella 2020	4	64	4	61	0.7%	0.95 [0.25, 3.64]
Rajasinham 2020	126	989	83	494	18.9%	0.76 [0.59, 0.98]
Subtotal (95% CI)		**1053**		**555**	**19.5%**	**0.76 [0.59, 0.98]**
Total events	130		87			
Heterogeneity: Tau² = 0.00; Chi² = 0.11, df = 1 (P = 0.74); I² = 0%						
Test for overall effect: Z = 2.10 (P = 0.04)						
1.1.3 Post-exposure Prophylaxis (PEP)						
Barnabas 2020	53	353	45	336	9.1%	1.12 [0.78, 1.62]
Boulware 2020	49	414	58	407	9.7%	0.83 [0.58, 1.18]
Mitja 2020	64	1116	74	1198	11.7%	0.93 [0.67, 1.28]
Subtotal (95% CI)		**1883**		**1941**	**30.5%**	**0.95 [0.78, 1.16]**
Total events	166		177			
Heterogeneity: Tau² = 0.00; Chi² = 1.35, df = 2 (P = 0.51); I² = 0%						
Test for overall effect: Z = 0.53 (P = 0.60)						
Total (95% CI)		**5872**		**4992**	**100.0%**	**0.87 [0.78, 0.97]**
Total events	592		528			
Heterogeneity: Tau² = 0.00; Chi² = 6.35, df = 9 (P = 0.70); I² = 0%						
Test for overall effect: Z = 2.44 (P = 0.01)						
Test for subgroup differences: Chi² = 1.72, df = 2 (P = 0.42), I² = 0%						

B. Safety Outcome: Adverse events

Study or Subgroup	HCQ Prophylaxis Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
2.1.1 Safety Outcome: Adverse Events						
Abella 2020	28	64	16	61	9.5%	1.67 [1.01, 2.76]
Barnabas 2020	66	353	46	336	9.9%	1.37 [0.97, 1.93]
Boulware 2020	140	349	59	351	10.1%	2.39 [1.83, 3.11]
Mitja 2020	671	1197	77	1300	10.2%	9.46 [7.58, 11.82]
Rajasinham 2020	316	936	100	469	10.2%	1.58 [1.30, 1.93]
Subtotal (95% CI)		**2899**		**2517**	**50.0%**	**2.43 [1.06, 5.56]**
Total events	1221		298			
Heterogeneity: Tau² = 0.87; Chi² = 183.55, df = 4 (P < 0.00001); I² = 98%						
Test for overall effect: Z = 2.10 (P = 0.04)						
2.1.2 Pre-exposure Prophylaxis (PrEP)						
Abella 2020	28	64	16	61	9.5%	1.67 [1.01, 2.76]
Rajasinham 2020	316	936	100	469	10.2%	1.58 [1.30, 1.93]
Subtotal (95% CI)		**1000**		**530**	**19.7%**	**1.59 [1.33, 1.91]**
Total events	344		116			
Heterogeneity: Tau² = 0.00; Chi² = 0.04, df = 1 (P = 0.85); I² = 0%						
Test for overall effect: Z = 5.01 (P < 0.00001)						
2.1.3 Post-exposure Prophylaxis (PEP)						
Barnabas 2020	66	353	46	336	9.9%	1.37 [0.97, 1.93]
Boulware 2020	140	349	59	351	10.1%	2.39 [1.83, 3.11]
Mitja 2020	671	1197	77	1300	10.2%	9.46 [7.58, 11.82]
Subtotal (95% CI)		**1899**		**1987**	**30.3%**	**3.15 [0.95, 10.46]**
Total events	877		182			
Heterogeneity: Tau² = 1.10; Chi² = 115.91, df = 2 (P < 0.00001); I² = 98%						
Test for overall effect: Z = 1.88 (P = 0.06)						
Total (95% CI)		**5798**		**5034**	**100.0%**	**2.43 [1.41, 4.17]**
Total events	2442		596			
Heterogeneity: Tau² = 0.74; Chi² = 367.10, df = 9 (P < 0.00001); I² = 98%						
Test for overall effect: Z = 3.21 (P = 0.001)						
Test for subgroup differences: Chi² = 2.09, df = 2 (P = 0.35), I² = 4.1%						



Appendix 4. Characteristics of registered studies (Table 3)

NCT Number	Title	Population	Interventions	Comparator	Outcomes
NCT04414241 (Peru) Not yet recruiting	Hydroxychloroquine to Prevent SARS-CoV-2 Infection	Healthcare workers	Drug: Hydroxychloroquine 600mg OD Day 1 400mg OD qitherday x 8 weeks	Standard measures of personal protection	Efficacy: Proportion of participants with positive molecular or serologic testing for SARS-CoV-2 [Time Frame: Eight weeks] Safety: Proportion of participants with grade 3 or more adverse events [Time Frame: Eight weeks]
NCT04410562 (Spain) Not yet recruiting	Hydroxychloroquine Efficacy and Safety in Preventing SARS-CoV-2 Infection and COVID-19 Disease Severity During Pregnancy	Pregnant women	Drug: Hydroxychloroquine 400mg OD x 3 days 200mg OD x 11 days	Placebo 2 tablets OD for 3 days 1 tablet OD x 11 days	Number of PCR confirmed cases among pregnant women [Time Frame: 21 days after intervention]
NCT04400019 (Spain) Not yet recruiting	Prevention of COVID19 Infection in Nursing Homes by Chemoprophylaxis With Hydroxychloroquine (PREVICHARM)	Nursing Home residents and healthcare professionals who provide direct care	Drug: Hydroxychloroquine 800mg OD Day 1 400mg OD x 4 days	Masked placebo	Number of secondary cases of SARS-CoV2 infection among residents at six days [Time Frame: This outcome will be evaluated at six days from the administration of chemoprophylaxis with hydroxychloroquine]
NCT04397328 (Canada) Not yet recruiting	COVID-19 PEP- High-risk Individuals in Long-term and Specialized Care - Canada	40 y/o and above with two or more high risk comorbidties	Drug: Hydroxychloroquine 400mg once, the 400mg after 8 hrs, then 200mg BID for 4 days	Placebo	Incidence of symptomatic fever >37.8, dry cough, or shortness of breath (resident/patient report or nurse observation) respiratory infection with confirmed PCR+ result for SARS-CoV-2. [Time Frame: baseline through day 90]
NCT04385264 (Switzerland) Not yet recruiting	#StayHome: Early Hydroxychloroquine to Reduce Secondary Hospitalisation and Household Transmission in COVID-19	SARS CoV 2 positive at risk for complications	Drug: Hydroxychloroquine 800mg PO OD Day 0 400mg PO OD (Day 1-5) + Mannitol	Placebo + Mannitol	Proportion of poor outcomes (in index cases) [Time Frame: During the period that the subject is considered as COVID-19-positive: Average of 11 days]
NCT04381988 (United States) Recruiting	A Study of Hydroxychloroquine vs Placebo to Prevent COVID-19 Infection in Patients Receiving Radiotherapy	Cancer patients receiving radiation therapy	Drug: Hydroxychloroquine 400mg OD daily	Placebo	cumulative incidence of SARS-CoV-2 infection [Time Frame: within 9 weeks from randomization]
NCT04377646 (Tunisia) Not yet recruiting	A Study of Hydroxychloroquine and Zinc in the Prevention of COVID-19 Infection in Military Healthcare Workers	Military Health Professionals	Drug: Hydroxychloroquine 400mg day 1, 2 400mg weekly up to 2 months	Placebo (Zinc)	SARS CoV2 infection [Time Frame: At 2 months of follow-up] Frequency of confirmed SARS CoV2 infection
NCT04374942 (Canada) Enrolling by invitation	Does Hydroxychloroquine Before & During Patient Exposure Protect Healthcare Workers From Coronavirus?	Healthcare Workers in the emergency department	Drug: Hydroxychloroquine 400mg OD x 3 months	Placebo	Microbiologically confirmed COVID-19 (SARS-CoV-2 infection) [Time Frame: Samples collected at day 0, 30, 60, 90 and 120]

NCT04372017 (United States) Active, not recruiting	Hydroxychloroquine as Post-Exposure Prophylaxis Against COVID-19 Infection	Healthcare worker	Drug: Hydroxychloroquine 800mg OD Day 1 400mg OD Day 2-5	Placebo (Vitamin D)	Percentage of COVID-19 exposed healthcare workers treated with hydroxychloroquine with a positive COVID-19 test. [Time Frame: At enrollment completion outcome 1 will be analyzed.]
NCT04371523 (Canada) Not yet recruiting	Hydroxychloroquine to Prevent COVID-19 Disease Amongst Healthcare Workers	Healthcare workers with primary practice in ICU, general medicine	Drug: Apo-Hydroxychloroquine 400mg PO BID day 1 400mg PO weekly for 8 weeks	Placebo	Positive for SARS-CoV-2 [Time Frame: 8 weeks]
NCT04363827 (Italy) Active, not recruiting	Protect: Study With Hydroxychloroquine for Prevention and Early Phase Treatment of Coronavirus Disease (COVID-19)	Healthy volunteers, exposed to COVID-19 patients (prevention arm)	Drug: Hydroxychloroquine LD 400mg OD day 1 200mg BID weekly dose day 8,15,22 for 1 month	No Intervention	the proportion of subjects of Group 1 who become symptomatic and/or swab positive in each arm within 1 month from randomization. [Time Frame: within 1 month from randomization]
NCT04363450 (United States) Recruiting	Hydroxychloroquine as Prophylaxis for COVID-19 in Healthcare Workers (HCQPreP)	Healthcare or Hospital Worker who has direct patient contact	Drug: Hydroxychloroquine 400mg (2 capsules) twice 12 hours apart followed by 200mg (1 capsule) twice weekly	Identical Placebo	Incidence of symptomatic COVID-19 infection in healthcare workers [Time Frame: 12 weeks]
NCT04359537 (Pakistan) recruting	Efficacy of Various Doses of Hydroxychloroquine in Pre-Exposure Prophylaxis for COVID 19	healthcare worker at high risk for COVID19 exposure	Drug: Hydroxychloroquine 400 mg twice a day 1,followed by 400 mg weekly for a total of 12 weeks	Placebo	COVID-19-free survival in experimental arms compared to placebo [Time Frame: 12 weeks]
NCT04354870 (United States) **COMPLETED**	COVID-19 PrEP HCW HCQ Study	Heathcare workers direct care with COVID-19 patients or doing AGP	Drug: Hydroxychloroquine (HCQ) Loading dose: 600 mg, oral, 1 day Maintenance dose: 200 mg, oral, daily, for 90 days	No intervention	Frequency of seroconversion to SARS-CoV-2 [Time Frame: baseline, 30 days, 60 days, 90 days]
NCT04354597 (Jordan) Not yet recruiting	Hydroxychloroquine and Azithromycin as Prophylaxis for Healthcare Workers Dealing With COVID19 Patients	Medical doctors, Nurses and Respiratory therapists caring for COVID-19 patients in ER and ICU and dedicated COVID19 units.	Drug: HCQ & AZ 400mg PO and AZ PO 500mg X 3 Days; weekly for 16 weeks.	No intervention	Effect of HCQ and AZ in preventing infection with COVID-19 among healthcare workers working with COVID-19 patients [Time Frame: 4 Months]
NCT04352946 (United States) Not yet recruiting	HEalth Care Worker pROphylaxis Against COVID-19: The HERO Trial	Health care worker (HCW) at the hospital who work on a "full time" basis during the study period	Drug: Hydroxychloroquine 400mg orally once for 60 days.	Placebo	Cumulative Incidence of COVID-19 Infection [Time Frame: 90 days] Incidence of symptomatic and asymptomatic COVID-19 infection in health care workers
NCT04352933 (United Kingdom) Recruiting	PROLIFIC ChemoprophylaxisTrial (COVID-19)	Work in a high-risk secondary or tertiary healthcare setting (hospitals accepting COVID-19 patients) with direct patient-facing care	Drug: Hydroxychloroquine 800mg for first 2 days; maintenance phase: 1 x 200mg tablet every day) + weekly placebo, for approximately 90 days	Placebo	Time to positive COVID-19 disease [Time Frame: Assessed up to 90 days

NCT04346329 (Colombia) Not yet recruiting	Immune Monitoring of Prophylactic Effect of Hydroxychloroquine in Healthcare Providers Highly Exposed to COVID-19	Health personnel exposed to patients with COVID-19. Not having symptoms compatible with an acute respiratory infection for the last 21 days	Drug: Hydroxychloroquine 800 mg of hydroxychloroquine the first day followed by 400 mg/week for 90 days	Placebo	Adverse effects [Time Frame: six months after administration of hydroxychloroquine or placebo]
NCT04345653 (United States) Active, not recruiting	Hydroxychloroquine as Chemoprevention for COVID-19 for High Risk Healthcare Workers	High-risk HCP's are defined as those actively working during the study duration in the Emergency Department and in the Intensive Care Setting, for the purpose of this study.	Drug: Hydroxychloroquine Sulfate (HCQ) 400mg (2x 200mg tablets) by mouth 6-12 hours apart on day 1, followed by 3 weeks of weekly 400mg (2x 200mg tablets) by mouth	No comparison group	Early feasibility as reflected on the number of participants contracting COVID-19 (10% or less) in comparison to the expected 30% as per CDC. [Time Frame: 28 day post enrollment]
NCT04340349 (Mexico) Enrolling by invitation	Low-dose Hydroxychloroquine and Bromhexine: a Novel Regimen for COVID-19 Prophylaxis in Healthcare Professionals	Health Care workers with high exposure to COVID-19 patients	Drug: Hydroxychloroquine Sulfate|Drug: Bromhexine 8 MG Hydroxychloroquine plus Bromhexine 200 mg of Hydroxychloroquine daily for 2 months 8 mg of Bromhexine every 8 hrs for 2 months	Hydroxycholoroquine only 200 mg of Hydroxycholoroquine only	Polymerase chain reaction assay (PCR) negative at day 30. [Time Frame: Day 30]
NCT04336748 (Austria) Not yet recruiting	HCQ for Primary Prophylaxis Against COVID19 in Health-care Workers	Health-care worker with frequent contact with confirmed COVID-19 patients	Drug: Hydroxychloroquine Hydroxychloroquine low dose (200mg) Hydroxychloroquine once daily for 4 weeks	Placebo	Symptomatic or asymptomatic SARS-CoV-2 infection confirmed by PCR [Time Frame: 4 weeks]
NCT04335084 (United States) Recruiting	A Study of Hydroxychloroquine, Vitamin C, Vitamin D, and Zinc for the Prevention of COVID-19 Infection	High-risk individuals are defined as all health care workers in hospitals, clinics, and emergency rooms, and medical facilities.	Drug: Hydroxychloroquine	Vitamin C, D, Zinc	Prevention of COVID-19 symptoms as recorded in a daily diary [Time Frame: 24 weeks]
NCT04334928 (Spain) Recruting	Randomized Clinical Trial for the Prevention of SARS-CoV-2 Infection (COVID-19) in Healthcare Personnel	hospital healthcare workers aged 18 to 70 years in public and private hospitals	daily single dose of tenofovir disoproxil fumarate (TDF) (245 mg)/ Emtricitabine (FTC) (200 mg), a daily single dose of hydroxychloroquine (HC) (200 mg), a daily single dose of TDF (245 mg)/FTC (200 mg) plus HC (200 mg)	Placebo	12 weeks in: (1) reducing the incidence of symptomatic disease and (2) reducing clinical severity COVID-19
NCT04334148 (United States) **COMPLETED**	Healthcare Worker Exposure Response and Outcomes of Hydroxychloroquine	Currently working in any environment in which there is a risk of exposure to patients with COVID-19 infections ("healthcare worker")	Drug: Hydroxychloroquine tablet 600mg bid loading dose on day 1 followed by 400mg on days 2-30.	Placebo	Number of participants with clinical infection with COVID-19 infection [Time Frame: 30 days]

NCT04333225 (United States) **COMPLETED**	Hydroxychloroquine in the Prevention of COVID-19 Infection in Healthcare Workers	Healthcare workers with • One day or more of exposure to suspect and/or positive COVID-19 patients, including but not limited to those working in the Emergency Department or Intensive Care Unit. OR • Unprotected exposure to a known positive COVID-19 patient within 72 hours of screening.	Drug: Oral hydroxychloroquine 400 mg twice a day (two 200 mg tabs twice a day) on day 1 followed by two 200 mg tablets once a week for a total of 7 weeks.	No intervention	Rate of COVID-19 positive conversion [Time Frame: 7 weeks]
NCT04331834 (Spain) **COMPLETED**	Pre-Exposure Prophylaxis With Hydroxychloroquine for High-Risk Healthcare Workers During the COVID-19 Pandemic	Healthcare worker at any of the trial sites	Drug: Hydroxychloroquine with the following dosage: day 0: 400 mg (2 tablets) day 1: 400 mg (2 tablets) day 2: 400 mg (2 tablets) day 3: 400 mg (2 tablets) weekly: 400 mg (2 tablets) for a period of six months	Placebo	Confirmed cases of a COVID-19 [Time Frame: Up to 6 months after start of treatment]
NCT04330495 (Spain) Not yet recruiting	Randomized, Controlled, Double-blind Clinical Trial Comparing the Efficacy and Safety of Chemoprophylaxis With Hydroxychloroquine in Patients Under Biological Treatment and / or JAK Inhibitors in the Prevention of SARS-CoV-2 Infection	patients diagnosed with an immunomediated inflammatory disease who are following a treatment with biological agents and / or Jak inhibitors	Drug: hydroxychloroquine at a dose of 200 mg twice a day for 6 months	Placebo	Incidence rate of new COVID-19 cases in both arms [Time Frame: From day 14 after start of treatment up to the end of follow-up: week 27]
NCT04330144 (Korea) Not yet recruiting	Hydroxychloroquine as Post Exposure Prophylaxis for SARS-CoV-2(HOPE Trial)	A contact person from confirmed case of SARS-CoV-2 infection Medical staff exposed from confirmed case of SARS-CoV-2 infection in hospitals Persons exposed to SARS-CoV-2 in COVID-19 outbreak situation with certain workplaces, religious groups, and military, etc.	Drug: 1day: Hydroxychloroquine 800mg Qd po 2-5dy: Hydroxychloroquine 400mg Qd po	No intervention	rate of COVID-19 [Time Frame: PCR test of COVID-19 at 14 days after the contact from confirmed case]

NCT04328285 (France) Active, not recrutiing	Chemoprophylaxis of SARS-CoV-2 Infection (COVID-19) in Exposed Healthcare Workers	HCW involved at the time of enrolment in the care and the management of patients with confirmed or suspected SARS-CoV-2 infection in hospital settings, in outpatient care settings or in geriatric long-term care facilities. These HCWs have prolonged or repeated close contact to these patients.	Drug: HCQ 200 mg : 2 tablets on the evening at Day 1 and 2 tablets on the morning at Day 2 and 1 tablet once daily afterwards	Placebo	Occurrence of an symptomatic or asymptomatic SARS-CoV-2 infection among healthcare workers (HCWs) [Time Frame: Up to 2.5 months]
NCT04326725 (Turkey) Active, not recruiting	Proflaxis Using Hydroxychloroquine Plus Vitamins-Zinc During COVID-19 Pandemia	Mainly doctors, nurses, health workers in the hospital whereby they have close contacts with possile COVID-19 infected patients were included. Their first degree relatives(spouse, child, parents)	Drug: Plaquenil 200Mg Tablet	No comparison group	Protection against COVID-19 [Time Frame: 4 months]
NCT04318444 (United States) Recruiting	Hydroxychloroquine Post Exposure Prophylaxis for Coronavirus Disease (COVID-19)	Household contact of index case: currently residing in the same household as an individual evaluated at NYP via outpatient, emergency department (ED), or inpatient services who (1) test positive for COVID-19, or (2) are defined as suspected cases, or persons under investigations (PUI), by the treating physician.	Drug: Two tablets (400mg) twice daily on day 1; for days 2-5, they will be instructed to take one tablet (200mg) twice daily. Other Name: Plaquenil	placebo	Number of participants with symptomatic, lab-confirmed COVID-19. [Time Frame: Date of enrollment to 14 days post-enrollment date]
NCT04318015 (Mexico) Recruiting	Hydroxychloroquine Chemoprophylaxis in Healthcare Personnel in Contact With COVID-19 Patients (PHYDRA Trial)	Healthcare personnel exposed to patients with COVID-19 respiratory disease: physicians, nurses, chemists, pharmacists, janitors, stretcher-bearer, administrative and respiratory therapists.	Drug: Hydroxychloroquine 200mg per day for 60 days.	Placebo	Symptomatic COVID-19 infection rate [Time Frame: From date of randomization until the appearance of symptoms or study completion 60 days after treatment start]
NCT04303507 (Thailand) Recruiting	Chloroquine/ Hydroxychloroquine Prevention of Coronavirus Disease (COVID-19) in the Healthcare Setting	Adult healthcare workers and other staff working in a facility where there are cases of either proven or suspected COVID-19	Drug: A loading dose of 10 mg base/ kg followed by 155 mg daily (250mg chloroquine phosphate salt or 200mg of or hydroxychloroquine sulphate) will be taken for 3 months	Placebo	Number of symptomatic COVID-19 infections [Time Frame: Approximately 90 days]

Q18. Should lopinavir/ritonavir be used as prophylaxis for the prevention of COVID-19?

As of 12 March 2021

RECOMMENDATION

We recommend <u>against</u> the use of lopinavir/ritonavir for chemoprophylaxis in individuals exposed to COVID-19 patients. *(Very low quality of evidence; Strong recommendation)*

Consensus Issues

The panel strongly recommends against the use of lopinavir/ritonavir for chemoprophylaxis because of very low quality of evidence. The drug combination is not commercially available and can only be availed of through the HIV program. In addition to the limited accessibility, there might also be competition with HIV patients who need it as regular regimen. Given the limited supply in the country, it is not deemed to be a feasible intervention for prophylaxis since a large quantity of lopinavir/ritonavir will be required in such cases.

KEY FINDINGS

There is currently no available direct evidence on the use of lopinavir/ritonavir in the prevention of COVID-19 among healthy individuals, particularly those exposed to confirmed COVID-19 individuals. There is very low-quality indirect evidence of lopinavir/ritonavir as post-exposure prophylaxis for an outbreak of MERS-CoV.

INTRODUCTION

Several measures on how to prevent and mitigate the spread of COVID-19 have been recommended, such as wearing of masks and personal protective equipment, social distancing, testing and contact tracing. The use of pharmacologic agents as pre-exposure and post-exposure prophylaxis as a preventive strategy in COVID-19 are still being investigated. Lopinavir/ritonavir has been utilized as post-exposure chemoprophylaxis among Korean health care workers during the outbreak of Middle East Respiratory syndrome (MERS) [1]. As such, it is one of the anti-viral agents being investigated as a potential agent for chemoprophylaxis for COVID-19.

REVIEW METHODS

We sought articles investigating the use of lopinavir/ritonavir (I) in the prevention of COVID-19 (O) among healthy individuals or health care workers exposed to COVID-19 patients (P).

We performed a systematic literature search in online databases such as MEDLINE, CENTRAL, and Google Scholar. Additional searches in MedRxiv, clinicaltrials.gov, and WHO ICTRP were also done to look for articles awaiting publication and ongoing clinical trials, respectively. We used search terms such as “lopinavir,” “ritonavir,” “kaletra,” “prevention,” “prophylaxis” and “COVID-19.” References from review articles were also manually searched for additional articles.

RESULTS

The initial search from all the databases retrieved 571 references. After removal of duplicates, letters, narrative reviews, screening of abstracts and studies not meeting the inclusion criteria, we retrieved 21 full text articles. There was one COVID clinical practice guideline that was retrieved while the rest were narrative reviews and ongoing

clinical trials. After a comprehensive and systematic search, we found no direct completed studies on the use of lopinavir/ritonavir in the prevention of COVID-19.

During the MERS-COV outbreak in Korea, a non-randomized clinical trial assessed the efficacy of lopinavir/ritonavir (with ribavirin) as post-exposure prophylaxis (PEP) among health care workers (n=43) exposed to a confirmed MERS-COV case. None of the HCW in the PEP group developed MERS compared to six (28%) in the non-PEP group (OR 0.05, CI 0.0028-1.01). No adverse events were observed in the use of lopinavir/ritonavir with ribavirin for two weeks [2].

The use of lopinavir/ritonavir as PEP was also evaluated for its associated adverse events. A randomized clinical trial evaluated the rate of discontinuation and tolerability of two PEP regimens for HIV infection: zidovudine/lamivudine plus either lopinavir/ritonavir (n=131) or atazanavir (n=124). Both arms experienced similar rates of adverse events (49% lopinavir/ritonavir vs 43% atazanavir), majority of which were mild. The use of lopinavir/ritonavir, compared to atazanavir, was not associated with increased risk of adverse events (OR 1.2 CI 0.7-2.2) [3].

RECOMMENDATIONS FROM OTHER GROUPS

A clinical practice guideline from Evidence-Based Medicine Chapter of China International Exchange and Promotive Association for Medical and Health Care (CPAM) and Chinese Research Hospital Association (CRHA) [4] found insufficient evidence for or against any agents as either pre-exposure or pre-exposure prophylaxis for COVID-19.

Clinical practice guidelines from WHO, IDSA, US NIH, UK NHS, or PSMID made no recommendation on the use of lopinavir/ritonavir in the prevention of COVID-19.

ONGOING STUDIES

Currently, there are three clinical trials being conducted in Canada, France, and Switzerland on the use of lopinavir/ritonavir as chemoprophylaxis for COVID-19 that are awaiting completion (Appendix 3).

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Appendix 1: Characteristics of Included Studies

Title/Author	Study design	Sample Size	Population	Intervention Group(s)	Control	Outcomes
Park, 2018	Non-RCT	N=43	Health care workers	Lopinavir+ritonavir+ ribavirin post exposure prophylaxis	post exposure prophylaxis	Attack rate of MERS COV
Diaz-Brito, 2012 (for adverse events)	Randomized controlled trial	N=255	Emergency room patients exposed to HIV, receiving PEP	Lopinavir/ritonavir	Atazanavir	Adverse events reported in 50/102 [49%] in the lopinavir/ritonavir arm, 42/98 [43%] in the atazanavir arm. Difference not significant (p=0.38).

Appendix 2: GRADE Evidence Profile

Author(s):
Question: Lopinavir/ritonavir compared to minimum health standards for prevention of COVID-19
Setting:
Bibliography:

CERTAINTY ASSESSMENT							NO. OF PATIENTS		EFFECT		CERTAINTY	IMPORTANCE
No. of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Lopinavir /ritonavir	Minimum health standards	Relative (95% CI)	Absolute (95% CI)		
Incidence of infection												
1	Observational studies	Serious	Not serious	Very serious	Not serious	None	0/22 (0.0%)	6/21 (28.6%)	**OR 0.0500** (0.0028 to 1.0100)	**266 fewer per 1,000** (from 285 fewer to 2 more)	⨁◯◯◯ VERY LOW	CRITICAL
Adverse events												
1	Randomised trials	Very serious	Not serious	Serious	Not serious	None	50/102 (49.0%)	42/98 (42.9%) (Control: Azatanavir)	**OR 1.2** (0.7 to 2.2)	**45 more per 1,000** (from 84 fewer to 194 more)	⨁◯◯◯ VERY LOW	CRITICAL

Appendix 3: Summary of Ongoing Studies

Registration Number	Title	Population	Interventions	Comparator	Outcome
NCT04321174 (recruiting)	COVID-19 Ring-based Prevention Trial With Lopinavir/Ritonavir (CORIPREV-LR)	High risk close contact with a confirmed COVID-19 case during their symptomatic period	Lopinavir/ ritonavir x 14 days	None	Microbiologic evidence of infection
NCT04328285 (active, not recruiting)	Chemoprophylaxis of SARS-CoV-2 Infection (COVID-19) in Exposed Healthcare Workers (COVIDAXIS)	Adult healthcare workers (HCWs) involved at the time of enrolment in the care and the management of patients with confirmed or suspected SARS-CoV-2 infection	Lopinavir/ ritonavir	Placebo	Occurrence of SARS-COV2 infection
NCT04364022 (recruiting)	Efficacy of Pragmatic Same-day COVID-19 Ring Prophylaxis for Adult Individuals Exposed to SARS-CoV-2 in Switzerland (COPEP)	Documented close contact with a PCR-confirmed SARS-CoV-2 positive individual	Lopinavir/ ritonavir	None	21-day incidence of COVID-19 in individuals exposed to SARS-CoV- 2 who are asymptomatic at baseline

Q19. Should ivermectin be used as COVID-19 prophylaxis for the general population?

As of 17 April 2021

RECOMMENDATIONS

We recommend against the use of ivermectin as COVID-19 prophylaxis for the general population. *(Very low quality of evidence; Strong recommendation)*

We recommend against the use of ivermectin for COVID-19 as post exposure prophylaxis for household contacts of confirmed COVID- 19 patients *(Very low quality of evidence; Strong recommendation)*

We recommend against the use of ivermectin for COVID-19 as prophylaxis for healthcare workers. *(Very low quality of evidence; Strong recommendation)*

Consensus Issues

The studies included in the review have very serious or high risk of bias. In particular, the study by Elgazzar et al. (2021) had a very low overall quality of evidence due to the risk of bias and serious imprecision from the wide 95% confidence interval (CI). The Shoumann et al. (2021) study also has a serious validity issue due to the premature termination of the control group, and lack of pretermination protocol, thus leading to selective reporting. Lastly, the results of the Chahla et al. (2021) study also have validity issues due to the presence of a co-intervention in the treatment arm. These methodologic limitations leads to uncertainty in the effects of ivermectin.

The panel recognized the high likelihood for its misuse or overuse and the concomitant false sense of security. The panel also stressed that there is a need to have concrete evidence on safety, as well as on the appropriate dose and dosing frequency, which the current very low-quality evidence did not provide. Another issue raised was that only a compassionate special permit (CSP) has been granted to two specific hospitals that applied for the permit, despite the current registration of ivermectin products as veterinary treatment for internal and external animal parasites. Hence, there may be legal implications when a positive recommendation to use it as a prophylaxis is issued. The human-grade ivermectin, on the other hand, is still applying for emergency use authorization (EUA) from the Philippine Food and Drug Administration. Considering the vaccine hesitancy of the public, a concern was raised by the panel that if a recommendation to an alternative to the vaccine as prophylactic agent will be made, then people may opt not to get vaccinated, undermining the national vaccination program of the government.

KEY FINDINGS

Three very low quality randomized controlled trials (RCT) were found on the use of ivermectin as COVID-19 prophylaxis. Both RCTs showed indirect evidence for the general population and were also found to have very serious risk of bias particularly on blinding, incomplete outcome, and selective reporting. One RCT showed lower rates of developing COVID-19 related symptoms. Another RCT showed lower RT-PCR-confirmed COVID-19 infection rates in ivermectin group compared to non-intervention group. Thirdly, one RCT revealed a lower rate of RT-PCR-confirmed COVID-19 in the ivermectin group, however, the administration of a co-intervention in this group poses serious validity issues in the outcome of interest. Mild adverse events were reported such as gastrointestinal upset, fatigue, sleepiness, pruritus, numbness, and burning sensation, all of which did not necessitate discontinuation of therapy.

INTRODUCTION

Ivermectin, an anti-parasitic agent used for onchocerciasis and lymphatic filariasis, is currently being investigated as treatment and prophylaxis for COVID-19 due to its potential anti-viral effect against SARS-CoV-2 [1-3]. In an *in vitro* study by Caly *et al*. [4], SARS-CoV-2 infected cells that were treated with ivermectin two hours after infection were found to have a 99.98% reduction in viral RNA load on real-time polymerase chain reaction (RT-PCR) after 48 hours. It has been hypothesized that ivermectin inhibits importin $\alpha/\beta 1$-mediated transport of viral proteins into the host's cell nucleus, which is also the proposed mechanism of action of ivermectin in other RNA viruses. Given the promising *in vitro* findings and known safety profile of ivermectin, several clinical trials are now in progress to determine if this repurposed drug may be of significant value in controlling COVID-19 transmission.

REVIEW METHODS

Literature search was conducted on electronic databases and clinical trial registries (PubMed, CENTRAL, ClinicalTrials.gov, medRxiv.org, bioRxiv.org, covid-nma.com, COAP Living Evidence on COVID-19, Chinese and EU Clinical Trial Registry), and UpToDate on March 16-18 and April 21, 2021. Terms such as "COVID-19", "ivermectin", "prophylaxis" or "prevention" were used during the search. No limitation on language was set. Further review of references of retrieved studies was also done to check for other possible articles.

Studies that involved administration of ivermectin to high-risk contacts of COVID-19 patients such as household members and healthcare workers were included. Study outcomes included were development of COVID-19 infection or symptoms, and adverse events. Any studies that solely involved administration of ivermectin as treatment for COVID-19 patients were excluded.
This search strategy yielded 49 articles in PubMed. Studies cited in meta-analyses and systematic reviews by Kory *et al.* [5], Bryant *et al.* [6] and the British Ivermectin Recommendation Development [7] were also searched. After removing duplications, eight full-text articles were retrieved. Only three RCTs were included in the review after assessing for eligibility and methodology (Appendix 1). The six articles excluded in the review were case control and cohort studies, mostly involving healthcare workers [1-3,8-10].

RESULTS

The three completed RCTs were by Elgazzar *et al.* [11], Shoumann *et al.* [12], and Chahla *et al.* [13] (Appendix 1). The multi-center double-blind study by Elgazzar *et al*. (preprint article) involved populations of COVID-19 patients (n = 400), and their household contacts and healthcare workers (n = 200), aiming on determining the efficacy and safety of ivermectin both as treatment and prevention of COVID-19 infection [11]. The household contacts and healthcare workers recruited for prophylaxis groups (ivermectin group and non-intervention group) had baseline negative RT-PCR results. Only the outcomes of these prophylaxis groups were included in this review. The study by Chahla *et al.* [13] recruited healthcare and non-healthcare (administrative) personnel from local healthcare centers (n = 234). The intervention group received a combination of ivermectin and iota-carrageenan, while the control group had no prophylaxis. COVID-19 diagnosis for each group was confirmed by RT-PCR. Lastly, the randomized open-label trial by Shoumann *et al.* [12]

recruited asymptomatic household contacts (n = 340) of RT-PCR-confirmed COVID-19 patients. Recruitment was based on normal body temperature and lack of symptoms, and not on negative RT-PCR results, unlike the two RCTs. Only four symptomatic participants in ivermectin group and 12 symptomatic participants in non-intervention group underwent RT-PCR testing, which all had positive results. The study did not discuss the reasons for participant withdrawal.

The overall risk of bias was deemed to be very serious. The study by Elgazzar *et al.* [11] had blinding issues due to absence of placebo in the control group, unclear allocation concealment, and selective reporting of results due to unavailable data on adverse events. No baseline and outcome data on the subgroups (household contacts and healthcare workers) were presented as well. Shoumann *et al.* [12] also lacked blinding and had unclear allocation concealment. Per protocol analysis was made due to exclusion of drop-outs. Furthermore, the premature termination of the control group due to perceived high protective effect of ivermectin was another source of serious bias. Chahla *et al.* [13] also had issues on blinding and allocation concealment similar to the two RCTs. Administration of a co-intervention in the ivermectin group poses a serious risk of bias as well.

All three studies determined the COVID-19 infection rate as primary outcome within 14-day follow-up period after contact [11-13]. Results were not pooled since the studies had issues on its outcome definitions (RT-PCR confirmed COVID-19 vs presence of COVID-19 symptoms). The study by Elgazzar *et al.* [11] showed that the rate of developing RT-PCR confirmed COVID-19 was 2% in ivermectin group compared to 10% in non-intervention group (RR 0.2, 95% CI 0.05 to 0.89). There were no available data on the subgroup analysis between healthcare workers and household contacts. Although with significant protection in the ivermectin group, the confidence interval was wide, and the risk of bias for this study was deemed to be very serious as mentioned above. Similarly, Chahla *et al.* [13] looked into the number of patients who tested positive with RT-PCR for COVID-19. However, since a co-intervention in the form of iota-carrageenan spray was also used in the treatment arm, we decided not to combine its results with the earlier study. The incidence of RT-PCR confirmed COVID-19 in the ivermectin plus iota-carrageenan group was 3.4% compared to 21.4% in the control group (RR 0.16, 95% CI 0.06 to 0.45). The study's very serious risk of bias may have also affected the frequency of outcomes.

The second outcome was the development of COVID-19 related symptoms as reported by Shoumann *et al.* [12] Statistically significant difference between the two groups in favor of ivermectin prophylaxis group (7.4% vs 58.4%, p <0.001) was reported (RR 0.13, 95% CI 0.08 to 0.21). Despite showing clear benefit, the results should be interpreted with caution due to its very serious risk of bias as mentioned above, and its methodological inconsistencies. The study did not use the gold standard test (RT-PCR) both as baseline and as confirmatory test for majority of participants, and prematurely terminated the control arm. The symptom-based approach in COVID-19 diagnosis of Shoumann *et al.* might have missed an unknown number of asymptomatic carriers.

In terms of adverse events, Chahla *et al.* [13] had no reported adverse events. Elgazzar *et al.* [11] did not mention results on adverse events in the preprint article. However, through email correspondence, the author revealed that only minor side

effects were observed such as upper gastrointestinal upset, insomnia, and pruritus; no major side effects developed necessitating discontinuation of the drug. Similarly, Shoumann *et al.* [12] reported mild side effects in 11 (5.4%) subjects in the ivermectin group. Symptoms included diarrhea (1.5%), nausea (1%), fatigue (1%), sleepiness (0.5%), abdominal pain (0.5%), heart burn (0.5%), numbness (0.5%), and burning sensation (0.5%). Though the side effects were mild, statistical analysis showed significant difference ($p = 0.018$) between the ivermectin group and non-intervention group. These symptoms were similar to the known adverse events from systemic administration of ivermectin as anti-parasitic agent [14].

RECOMMENDATIONS FROM OTHER GROUPS

As of this writing, certain agencies have recommended against the use of ivermectin as COVID-19 prophylaxis. In particular, the European Medicine Agency [15] has concluded that the currently available data have not been found to be sufficient to support the use of ivermectin for COVID-19 outside of clinical trials. Other groups such as Infectious Diseases Society of America [16], and Alberta Health Services COVID-19 Scientific Advisory Group [17] have expressed similar recommendations in their latest guidelines on COVID-19 management, citing presence of confounding factors and very low to low certainty of evidence. The National COVID-19 Clinical Evidence Taskforce of Australia [18] has not yet made recommendations on this topic due to insufficiency of well-designed clinical trials. The guideline development group of the World Health Organization [19] has not issued a statement on ivermectin as COVID-19 prophylaxis stating that the topic is not included in the scope of the guidelines.

The US Food and drug Administration (FDA) [20] and Philippine FDA [21] both have not approved the use of ivermectin for COVID-19 prevention. However, as of April 17, 2021, the Philippine FDA has granted a compassionate use permit to use Ivermectin as COVID-19 treatment to two unnamed hospitals [22,23]. Medical societies of the Philippines have yet to make recommendations on this matter.

RESEARCH GAPS

Majority of the nine ongoing RCTs on ivermectin as COVID-19 prophylaxis in various trial registries have started recruitment, and will be completed as early as April 2021 (Appendix 4). Additionally, two RCTs have already been completed on registry, but all have yet to publish or release their preliminary results (Appendix 3).

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Appendix 1. Table of Included Studies

Study (RCTs)	Population, n	Intervention	Control	Outcome
Elgazzar *et al.,* 2021 (preprint)	Health care and household contacts of COVID-19 patients; Age 18-80 years n = 200	Ivermectin 0.4 mg/kg BW single oral dose, and another dose after 1 week	No Ivermectin, only usual standard precautions and PPE	Primary outcome: • Prevention of COVID-19 (RT PCR confirmation) Secondary outcome: • Adverse events
Shoumann *et al.,* 2021	Asymptomatic household contacts of confirmed RT-PCR COVID-19 index case; Age ≥ 16 years n = 340	Ivermectin 0.225-0.375 mg/kg: 15 mg/day per orem for subjects 40-60 kg BW; 18 mg/day for 60-80 kg; 24 mg/day for >80 kg, given on D1 and D3 from diagnosis day	No Ivermectin, only usual standard precautions and PPE	Primary outcome • Prevention of COVID-19 by D14 of follow-up (symptom-based) Secondary outcomes: • Occurrence of disease before 14 days • Drug side effects
Chahla *et al.*, 2021	Personnel who perform patient care and administrative tasks (healthcare and non-healthcare personnel) n = 234	Ivermectin 12mg/tab PO every 7 days, + Iota-carrageenan 6 oral sprays per day, for 4 weeks	No Ivermectin or carrageenan, only usual standard precautions and PPE	Primary outcome: • Prevention of COVID-19 (RT PCR confirmation) Secondary outcome: • Adverse events

Appendix 2. GRADE Evidence Profile

CERTAINTY ASSESSMENT							NO. OF PATIENTS		EFFECT		CERTAINTY	IMPORTANCE
No. of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Ivermectin	No ivermectin	Relative (95% CI)	Absolute (95% CI)		
Development of RT-PCR confirmed COVID-19 (Elgazzar 2021)												
1	Randomised trials	Very serious [a]	Not serious	Serious [b]	Serious [c]	None	2/100 (2.0%)	10/100 (10.0%)	**RR 0.2000** (0.0450 to 0.8898)	**80 fewer per 1,000** (from 96 fewer to 11 fewer)	⨁◯◯◯ VERY LOW	
Development of RT-PCR Confirmed COVID-19 (Chahla 2021)												
1	Randomised trials	Very serious [e]	Not serious	Serious [b]	Not serious	None	4/117 (3.4%)	25/117 (21.4%)	**RR 0.1600** (0.0575 to 0.4455)	**179 fewer per 1,000** (from 201 fewer to 118 fewer)	⨁◯◯◯ VERY LOW	
Development of COVID-19 related symptoms (Shoumann 2021)												
1	Randomised trials	Very serious [d]	Not serious	Serious [b]	Not serious	None	15/203 (7.4%)	59/101 (58.4%)	**RR 0.1265** (0.0757 to 0.2115)	**510 fewer per 1,000** (from 540 fewer to 461 fewer)	⨁◯◯◯ VERY LOW	
Adverse events (follow up: 28 days)												
1	Randomised trials	Not serious	Not serious	Not serious	Not serious	None	753	752	-	MD **2 weeks lower** (2.21 lower to 1.79 lower)	⨁⨁⨁⨁ HIGH	CRITICAL
Serious adverse events (follow up: 28 days)												
1	Randomised trials	Not serious	Not serious	Not serious	serious [a]	none	10/1311 (0.8%)	15/1306 (1.1%)	**RR 0.66** (0.30 to 1.47)	**4 fewer per 1,000** (from 8 fewer to 6 more)	⨁⨁⨁◯ MODERATE	CRITICAL

CI: Confidence interval; **RR:** Risk ratio

Explanations

[a] Unclear allocation concealment, incomplete reporting of results (article was only a preprint), no data on breakdown of household contacts and healthcare workers

[b] Indirect evidence for the general population

[c] Wide confidence interval

[d] The study by Shoumann demonstrated high risk of bias in terms of blinding, selective reporting and incomplete outcome data. Subjects recruited did not undergo baseline RT-PCR tests to confirm that they were indeed COVID negative. Most participants in both groups who were diagnosed to have COVID-19 infection also did not undergo confirmatory RT-PCR tests, and were only diagnosed based on presence of symptoms. The non-intervention group was also prematurely stopped due to the perceived high protective efficacy of Ivermectin by the researchers.

[e] Lack of blinding, allocation concealment, co-intervention bias

Appendix 3. Table of Completed Unpublished Studies (no preprint available)

Study	Population/Setting	Intervention	Control	Outcomes	Status
A Preventive Treatment for Migrant Workers at High-risk of COVID-19 NCT04446104 Randomized Open-label trial Author: National University Hospital, Singapore	Men residing in dormitory Ages 21-69 years 4257 participants Singapore	Arm 1: Hydroxychloroquine Arm 2: Ivermectin Arm 3: Zinc/Vit C Arm 4: Povidone-iodine throat spray Arm 5: Vitamin C	-	Primary: Laboratory-confirmed COVID-19 Secondary: 1. Acute respiratory illness in treatment arms 2. Febrile respiratory illness in treatment arms 3. Rate of hospitalization for COVID-19 and non-COVID-19 related indications 4. Rate of O2 supplementation 5. Duration of O2 supplementation and mechanical ventilation 6. Length of hospital stay 7. Rate of laboratory-confirmed COVID-19 8. Adverse events and serious adverse events 9. Drug discontinuation due to adverse events	Completed, no available results Completion date: August 31, 2020
Evaluation of prophylaxis induced by ivermectin in populations exposed to COVID-19 patients IRCT20200408046987N3 Randomized trial Author: Gheibi	Healthy individuals exposed directly and constantly with COVID-19 patients Ages 18-65 years Iran	Ivermectin	Placebo	Primary: 1. Percentage of patients in family members 2. Duration of Illness 3. Severity of Illness Secondary: 1. Considering the drug side effects 2. IgA 3. IgM 4. IgG 5. Duration of illness with recheck of RT-PCR	Completed Completion date: December 30, 2020

Appendix 3. Table of Ongoing Studies

Study	Population/Setting	Intervention	Control	Outcomes	Status
Efficacy of Nano-Ivermectin Impregnated Masks in Prevention of Covid-19 Among Healthy Contacts and Medical Staff NCT04723459 Randomized Open-label trial	Health care personnel and family contact of confirmed COVID-19 cases Ages 18 years and older Estimated: 150 participants Egypt	Ivermectin mask	Ordinary Mask	Primary: 1. Number of persons who complain of any suspected symptoms (within 14 days after enrolment) Secondary: 1. Number of persons who are diagnosed as COVID-19 patients (within 21 days of enrolment)	Recruiting Estimated Completion Date: February 28, 2021 (not yet updated in registry)
Comparative Study of Hydroxychloroquine and Ivermectin in COVID-19 Prophylaxis NCT04384458 Randomized open-label trial	Professionals working in areas of high exposure and high risk of transmission of COVID-19 Ages 18-70 years Estimated: 400 participants Brazil	Ivermectin	Hydroxychloroquine	Primary: 1. Proportion of participants positive for COVID-19 (post-intervention at day 52) Secondary: 1. Participants who developed mild, moderate, or severe forms of COVID-19 (proportion according to severity) 2. Measurement of QT interval 3. Widening of corrected QT interval or with changes in heart rate on ECG 4. Comparison of hematological and biochemical parameters 5. Occurrence of adverse events 6. Assessment of COVID-19 symptom severity 7. Proportion of participants who discontinue study intervention 8. Proportion requiring hospital care 9. Proportion requiring mechanical ventilation	Recruiting Estimated completion date: April 2021
Exploratory Ph I Trial of the Active IMP in Healthy Volunteers in Relation to COVID-19 NCT04632706 Randomized Double-Blind, Placebo-controlled Trial	Healthy male with negative RT-PCR test for SARS-CoV 2 Ages 18-45 years Estimated: 24 participants United Kingdom	Ivermectin 50 mcg/kg, 75 mcg/kg, 100 mcg/kg doses	Placebo	Primary: 1. Maximum plasma concentration (Cmax) 2. Time to reach Cmax (Tmax) 3. Trough Plasma Concentration 4. Area under the plasma concentration-time curve from zero to 24 hrs 5. Area under the plasma concentration-time curve from zero to 48 hrs 6. Apparent Terminal Half-life Secondary: 1. Number of participants with treatment emergent adverse events 2. Number of participants with abnormal ECG 3. Number of participants with abnormal clinical neurological exam 4. Number of participants with abnormal urine and/or blood test 5. Number of participants with abnormal physical exams	Recruiting Estimated completion date: May 2021
Prevention and Treatment for COVID-19 associated severe Pneumonia in the Gambia (PaTS-COVID)	Cohort 1: -Index case ≥ 5 years with confirmed COVID-19 mild disease or moderate pneumonia	Ivermectin	Placebo	Primary: 1. Cohort 1 Index Case: Percentage of patients with COVID-19 2. Cohort 1 Household contacts: Percentage of HH members that get infected with COVID-19	Recruiting Estimated completion date: July 2022

NCT04703608 Single-Blinded Randomized Trial	-Household contacts Cohort 2: Individuals ≥ 12 years with suspected or confirmed COVID-19 associated severe pneumonia Ages ≥ 5 years Estimated: 1200 participants Gambia			3. Cohort 2: Percentage of COVID-19 associated severe pneumonia patients Secondary: 1. Days from recruitment to virological clearance 2. Days from recruitment until clinical recovery 3. IgG 4. HH contacts IgG 5. Percentage of HH members infected that develop COVID-19 symptoms	
Effectiveness and Safety of Ivermectin for the Prevention of COVID-19 Infection in Colombian Health Personnel (IveprofCovid19) NCT04527211 Randomized multi-center trial	Health care worker, with negative COVID-19 serological antibody test Age ≥ 18 years Estimated: 550 participants Colombia	Ivermectin	Placebo	Primary: Clinical development of COVID-19 Secondary: 1. Seroconversion 2. Hospitalization requirement 3. ICU Requirement 4. Safety of the intervention	Not yet recruiting Estimated completion date: December 16, 2020
Prophylactic Ivermectin in COVID 19 Contacts CTRI/2020/08/027282 Randomized Trial	Healthy contacts of COVID-19 patients Ages 18-70 years India	Ivermectin	Placebo	Primary: Episodes and severity of symptoms of respiratory tract infection Secondary: 1. Requirement of treatment for symptoms 2. Incidence of COVID-19 3. Analysis of adverse events	Not yet recruiting
Ivermectin in the prevention of COVID-19 CTRI/2020/06/026232 Randomized trial	Healthy volunteers with high chances of exposure to COVID-19 patients Age ≥ 18 years India	Ivermectin	Placebo	Primary: Clinical development of COVID-19 Secondary: 1. Seroconversion 2. Hospitalization requirement 3. ICU Requirement 4. Safety of the intervention	Recruiting Estimated completion date: July 2022
Study of the effects of using ivermectin to prevent COVID-19 in an adult population in Brazil ISRCTN90437126 Randomized trial	Healthy volunteer Ages ≥ 18 years Brazil	Ivermectin	Placebo	Primary: COVID-19 case diagnosis Secondary: 1. Clinical status of COVID-19 2. Incidence of severe COVID-19 3. Rate of adverse events 4. Hospitalization 5. Deaths	Recruiting Estimated completion date: June 30, 2021

Randomized clinical trial of ivermectin for treatment and prophylaxis of COVID-19 2020-001994-66 Randomized trial	Contacts of symptomatic COVID-19 patients Ages 18-64 years 229 participants Spain	Ivermectin	Placebo	Primary: Incidence of secondary cases of COVID-19 Secondary: 1. Morbidity and mortality at 28 days 2. Analytical values at 0, 7, 12, 21 days	Ongoing

Q20. Should saline nasal irrigation be used for the prevention of COVID-19?

As of 12 March 2021

RECOMMENDATION

There is insufficient evidence to recommend the use of saline nasal irrigation (SNI) to prevent COVID-19 in healthy individuals. *(Very low quality of evidence)*

Consensus Issues

The panel did not provide a recommendation on SNI because of the very low quality of evidence on the use of nasal spray to prevent the common cold.

KEY FINDINGS

There are no direct studies assessing the benefit or harm of saline nasal irrigation use among healthy individuals as a preventive strategy for COVID-19. Only indirect evidence from an observational study using saline spray compared to no nasal spray in the prevention of common colds showed shorter duration of symptoms of nasal blockage and discharge but no difference in number of respiratory infections.

INTRODUCTION

Saline nasal irrigation (SNI) has been recommended as an additional non-pharmacological strategy to prevent upper respiratory tract infection [1–3]. It is an adjunctive practice that has been postulated to clean the nasal cavities by removing antigens, inflammatory mediators, and microorganisms such as bacteria and viruses [4]. Since it has been shown to work in other respiratory viruses, it is being recommended as a COVID-19 preventive strategy that can help curb transmission of SARS-COV-2 because of its availability and affordability [4–8].

REVIEW METHODS

We searched for articles that included healthy individuals or health care workers exposed to COVID-19 patients (P) and compared receiving nasal saline irrigation, whether isotonic or hypertonic, (I) versus placebo or minimum health standards (C) in the prevention of COVID-19 (O).

We performed a systematic literature search in online databases such as MEDLINE, CENTRAL, and Google Scholar. Additional searches in MedRxiv and clinicaltrials.gov were also done to look for articles awaiting publication and ongoing clinical trials, respectively. We used search terms such as “nasal saline irrigation,” “saline irrigation,” “nasal lavage,” “nasal rinse” and “COVID-19.” References from review articles were also manually searched for additional articles. We did not anticipate finding many randomized controlled trials; hence, we did not set any limitation as to the type of study design during the search.

RESULTS

The initial search from all the databases retrieved 203 references. We screened the title and abstracts of 29 (out of 203) references. After removal of duplicates, letters, narrative reviews, and studies not meeting the inclusion criteria, we retrieved three full text articles. These articles were Cochrane reviews that assessed the benefits and harms of antimicrobial mouthwash and/or antimicrobial nasal spray and compared it

with either placebo or saline; hence, these also did not fulfill our inclusion criteria of saline nasal irrigation as the intervention. After a comprehensive and systematic search, we found no direct studies assessing the effect of SNI in preventing COVID-19 in healthy individuals.

We found indirect evidence from a study that investigated the use of saline nasal spray in the prevention of the common cold among 60 military men in Sweden [2]. Participants were asked to do nasal spray with physiologic saline for 10 weeks, followed by a two-week wash out period after which they were again observed without nasal spraying. The number of days with nasal secretion and/or blocked nose were shorter (mean 6 vs 11 days) when using nasal spray with physiologic saline compared to no nasal spray. No differences were observed in the number of episodes of upper respiratory tract infection and total medicine and antibiotic consumption (days).

We found no studies that investigated adverse events of SNI as prevention of COVID-19. The Sweden study did not report outcomes on adverse events [8]. The limited indirect evidence was considered to be of very low certainty.

RECOMMENDATIONS FROM OTHER GROUPS

Clinical practice guidelines from WHO, IDSA, US NIH, UK NHS, or PSMID made no recommendation on the use of SNI in the prevention of COVID-19.

RESEARCH GAPS

Since SNI is an affordable and locally available tool, randomized controlled trials on the use of SNI may be undertaken to determine its effectiveness and safety as a preventive tool for COVID-19 in healthy individuals, including health care workers exposed to COVID-19 or contacts of suspected or confirmed COVID-19 patients.

ONGOING STUDIES

There is one ongoing trial on the use of saline nasal irrigation, steam inhalation, and povidone iodine gargling among asymptomatic mild cases and their household contacts and its effect on household transmission of COVID-19. (Appendix 3)

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Appendix 1: Characteristics of Included Studies

Title/Author	Study design	Sample Size	Population	Intervention Group(s)	Control	Outcomes
Tano, 2004	Non-RCT Time interrupted series	N=60	Healthy individuals	Saline nasal spray	none	Number of episodes of upper respiratory tract infection

Appendix 2: GRADE Evidence Profile

Author(s):
Question: Saline nasal irrigation compared to minimum health standard for prevention of COVID-19
Setting:
Bibliography:

CERTAINTY ASSESSMENT							NO. OF PATIENTS		EFFECT		CERTAINTY	IMPORTANCE
No. of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Lopinavir /ritonavir	Minimum health standards	Relative (95% CI)	Absolute (95% CI)		
Number of episodes (common cold) (follow up: median 22 weeks)												
1	Observational studies	Very serious	Not serious	Very serious	Not serious	None	0.7	60	-	MD **0.3 higher** (0 to 0)	⊕◯◯◯ VERY LOW	

CI: Confidence interval; **MD**: Mean difference

Appendix 3: Summary of Ongoing Study

Registration Number	Title	Population	Interventions	Outcomes
CTRI/2020/09/027687	Assessment of effect of steam inhalation, saline gargling and povidone Iodine gargling on reduction of symptoms and prevention of spread of COVID 19	Asymptomatic mild cases of COVID-19 under home isolation and their **household contacts**	Steam inhalation, **saline gargling (hypertonic solution)** povidone iodine gargling	1. Reduction in severity of symptoms 2. Early negativity of the RT PCR in nasopharyngeal swab among the intervention group when compared to the controls 3. Reduction in transmission of infection among household members of COVID-19

Q21. Should steam inhalation be used for the prevention of COVID-19?

As of 12 March 2021

RECOMMENDATION

We recommend <u>against</u> the use of steam inhalation in the prevention of COVID-19. *(Very low quality of evidence; Strong recommendation)*

Consensus Issues
In spite of the very low quality of evidence, the panel strongly recommended against the use of steam inhalation as prevention for COVID-19 because it was recognized that the potential for harm outweighs the benefit.

KEY FINDINGS

Based on two single arm observational studies with high risk of bias, there is currently only very low quality evidence showing the possible benefit of steam inhalation in the prevention of developing symptomatic COVID-19 among exposed healthy individuals and reducing symptoms and number of days to negative SARS-COV-2 RT-PCR test of COVD-19 confirmed individuals. Meanwhile, there is indirect evidence highlighting the significant adverse effects of steam inhalation among individuals using it for symptomatic relief from colds.

INTRODUCTION

Steam inhalation is a traditional practice used as a home remedy for treating common colds. It is thought to provide relief by loosening mucus, opening up the nasal passage, reducing mucosal inflammation and inhibiting viral replication by heat inactivation. Published articles supporting its use are varying but a systematic review published in Cochrane showed no association between symptomatic relief, reduction of clinical severity and having a positive viral culture from nasal washings from the common cold and use of steam inhalation [1]. The Philippines has a diverse culture and is known for certain populations having strong beliefs in traditional medicine, sometimes choosing these over scientifically sound treatment options, hence this review.

REVIEW METHODS

We searched for articles investigating the use of steam inhalation (I) in the prevention of COVID-19 (O) among healthy individuals (P).

We performed a systematic literature search in online databases such as MEDLINE, CENTRAL, and Google Scholar. Additional searches in MedRxiv, clinicaltrials.gov, and WHO ICTRP were also done to look for articles awaiting publication and ongoing clinical trials, respectively. We used search mesh terms for “steam inhalation,” “steam treatment,” “prevention,” “prophylaxis” and “COVID-19.” References from review articles were also manually searched for additional articles.

RESULTS

We found one prospective observational study investigating steam therapy for prevention and treatment of COVID-19 and one single-arm interventional study as treatment of COVID-19 [2,3].

As prevention

An observational study investigated the role of steam inhalation for the prevention and treatment of COVID-19 [2]. In this study, one group composed of asymptomatic healthcare workers who were exposed to COVID-19 patients either through direct contact or travel were advised to take in steam at least twice daily for five minutes (n=25). None of the participants developed any symptoms throughout the follow-up duration (14 days to 2 months). There was, however, no control group in this study. There was also no mention of whether the participants were tested for COVID-19, and if they adhered to the intervention, received any other treatment, or used other personal protective equipment. The manner in which the symptoms were assessed (self-reported or with an independent assessor) was likewise not reported; hence, this study had a high risk for bias.

As treatment

In the same study, a second group of people (n=80) composed of patients and healthcare workers) were observed. These were COVID-19 confirmed cases who had mild to moderate symptoms. They were given steam inhalation for five minutes every three hours. The outcomes assessed were the regression of symptoms and the number of days to having a negative COVID-19 test. Results showed that patients having mild symptoms recovered in a mean of 3 days while those having moderate symptoms recovered in 7 to 10 days. Test for COVID-19 became negative after 10 days for 65 (81%) of the participants, and after 14 days for 78 of them (97.5%). It took a total of 18 days for all participants to obtain a negative result. Issues with this study centered on the lack of data reported on several factors; specifically, the participants' concurrent treatment, admission status, total number of days of steam inhalation, their adherence to steam inhalation, and the day of illness on which the intervention was started. It also had no control group.

Another study investigated ten asymptomatic and pauci-asymptomatic healthcare professionals who tested positive for COVID-19 (N=10) [3]. Steam inhalation was given for at least twenty minutes either by 4 cycles of 5 minutes or 5 cycles of 4 minutes within one hour. The study excluded three participants from the final pool but monitoring was continued. Among the seven, all tested negative after only one day of steam inhalation, with four patients having no symptoms after 5 days, while three had improving symptoms. This study posed a high risk of bias because there was no control and no blinding; no data on the specific day of illness the intervention was started; and no mention of the adherence of the participants to the intervention. Moreover, three of the participants did self-swabbing, which could have affected yield of the samples. Lastly, the three excluded participants also happened to be the ones who had a positive test for COVID-19 on repeat testing which adds to the bias of the results of the study.

Safety

There is no mention of safety in the two included studies. However, a published narrative report in the Lancet [4] describes an increase in incidence of scald burn among the pediatric population due to the increased use of steam inhalation for COVID-19 (from an average of two scald burns per year from steam inhalation to six cases in just one month). As indirect evidence, a meta-analysis [1] also described that those who received steam inhalation for common colds had a significant higher risk

for adverse events (N=65, OR 4.73, 95% CI 1.46-15.30) which included nasal and lip irritation, increase in congestion, lightheadedness and general discomfort.

RECOMMENDATIONS FROM OTHER GROUPS

There are no recommendations from other groups on the use of steam inhalation for COVID-19.

ONGOING STUDIES

Currently, there is one registered clinical trial that will investigate the effect of steam inhalation as a treatment for COVID-19. Recruitment of participants is ongoing and the estimated primary completion of the study is registered on October 2021.

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Appendix 1. Characteristics of included studies

Authors	Country	Population	Intervention	Control	Outcomes	Results
La Marca (Italy)	Single center open label interventional study	Asymptomatic or pauci-symptomatic (2-3 mild to moderate symptoms) healthcare professionals working at a Hospital with positive rhinopharyngeal swab Exclusion criteria for enrolment a history of pre-existing allergies and/or asthma, ongoing drug therapies against SARS-CoV-2, and individuals with multiple symptoms consistent with COVID infection.	Steam inhalation for at least 20 minutes (either 4 cycles of 5 minutes or 5 cycles of 4 minutes) within 1 hour. temperature of boiled water was maintained at 55-65 C in the first 4-5minutes after initiation of boiling	None	Reduction of viral shedding after 4 days (at least 6 cycle threshold measured with RT PCR) Complete virus elimination after 4 days	n=10 (3 patients met exclusion criteria) 1/7 asymptomatic all throughout 6/7 improvement of symptoms after end of study period - 3 improvement of all symptoms - 2 persistent anosmia and ageusia - 1 mild muscle pain and nasal congestion 7/7- tested negative on RT-PCR
Pawar	Prospective observational	Group 1: asymptomatic healthcare workers exposed to COVID-19 either through travel or direct contact (n= 25) group 2: mild or moderate COVID-19 PCR confirmed patients (n=80 patient and health care workers) Severe patients excluded	Inhalation of steam twice daily, either through ordinary steamers or by boiling of water - Grp 1: 5mins by nasal route BID (no mention of duration of treatment) - Grp 2: 5mins every 3 hours	None	RT PCR result after 5 days of steam inhalation, and until COVID was negative for two consecutive tests symptom pattern	No patients in group 1 developed symptoms (14 days to 2 months follow-up) Group 2 Regression of symptoms - For mild symptoms, mean of 3 days to return to normal - For moderate symptoms, 7-10 days to return to normal COVID-19 test - After 10 days since start: 65/80 turned negative (81%) - After 14 days since start: 78/80 turned negative (97.5%) - After 18 days since start: 80/80 turned negative (100%)

Appendix 2. GRADE Evidence Profile

Question: Should steam inhalation compared to no steam inhalation for COVID-19 treatment
Setting: COVID-19 confirmed patients

Certainty assessment							Impact	Certainty	Importance
No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations			
Recovery									
2	Observational studies	Very serious [a]	Not serious	Not serious	Not serious	Publication bias strongly suspected [b]	In one study, patients having mild symptoms recovered in a mean of 3 days while those having moderate symptoms recovered in 7 to 10 days in the other study, all seven had recovered after five days	⨁◯◯◯ VERY LOW	IMPORTANT
Time to negative RT-PCR									
2	Observational studies	Very serious [a]	Not serious	Not serious	Not serious	Publication bias strongly suspected [b]	Test for COVID-19 became negative after 10 days for 65 (81%) of the participants, 14 days for 78 of them (97.5%). in the other study, all included participants became negative after one day of steam inhalation	⨁◯◯◯ VERY LOW	IMPORTANT

CI: Confidence interval

Explanations
[a] No mention of how symptoms was monitored (self monitoring or independent assessor), no mention of participants' adherence to the protocol and at what day of ilneess the intervention was given
[b] Limited presentation of data

Appendix 3. Characteristics of ongoing studies

	Clinical Trial ID / Title	Status	Start and estimated primary completion date	Study design	Country	Population	Intervention Group(s)	Comparison Group(s)	Outcomes
1	NCT04743349 Steam Inhalations in COVID-19 Patients (Steam-COVID)	Recruiting	Study Start: January 26,2021 Primary Completion: October 31, 2021	Study Design: •Allocation: Randomized •Intervention Model: Parallel Assignment •Masking: single (Outcome Assessor) •Primary Purpose: Treatment	Italy	Adults confirmed to have SARS-Cov-2 within 48 hrs of enrolment and only have no or mild symptoms	Steam inhalation	No steam inhalation	Reduction in viral shedding, clinical outcome, negativization rate

Q22. Should aspirin be used for prophylaxis against COVID-19-induced coagulopathy in patients with COVID-19?

As of 02 June 2021

RECOMMENDATION

We suggest against the use of BCG vaccine for the prevention of COVID-19 infection. *(Very low quality of evidence; Conditional recommendation)*

Consensus Issues

A conditional recommendation against the use of BCG vaccination for COVID-19 prevention was made by the Panel in consideration of the following issues. Most of the evidence included in the review are retrospective cohorts and one case control. Among the articles, the timing of BCG administration is variable or unclear and the outcomes were self-reported and not necessarily RT-PCR confirmed. Also, although an RCT was recently completed in Greece on the potential utility of BCG vaccine as prophylaxis for COVID-19, it is still a preprint and not yet included in the review. There is also clinical trial evidence in the elderly that it improves outcomes for other respiratory viral infections. Furthermore, it is relatively inexpensive and there is no evidence of serious harm. It was discussed that BCG vaccine is usually given among children to prevent disseminated or miliary tuberculosis.

It was also discussed in the panel meeting that the Philippines has a policy on birth doses for BCG within 24-hours of delivery; however, this is not fully implemented in health centers since it is available as a multi-dose vial, they do not administer this if there is only one infant. On the other hand, it was noted that there is no national policy on BCG vaccination among adults.

KEY FINDINGS

Very low-quality evidence from one retrospective cohort study was found on the use of aspirin prophylaxis for COVID-19 induced coagulopathy among COVID-19 patients. There was a significant reduction in the risk of mortality. COVID-19 induced coagulopathy and adverse events were not examined in this study.

INTRODUCTION

COVID-19 is characterized by excessive inflammation, endothelial dysfunction, platelet activation and stasis leading to thrombotic and hemostatic complications [1]. Arterial thrombosis, microvascular thrombosis, and VTE have been reported [2-6]. Major bleeding was also reported in 2.3% [2]. Hospitalized COVID-19 patients with comorbidities have demonstrated a higher risk for VTE, with a prevalence of 14% [5,6]. Their survival is significantly reduced. Currently, the standard of care includes prophylactic anticoagulation with low molecular weight heparin (LMWH) for all hospitalized COVID-19 patients. Early use of aspirin may be beneficial due to its antiplatelet, anti-viral and anti-inflammatory properties. It irreversibly inactivates cyclooxygenase 1 (COX-1), which decreases thromboxane A2 synthesis, platelet aggregation and thrombus formation. It resulted in improved gas exchange efficiency and increased arterial oxygenation in severe COVID-19 patients with risk factors for thrombotic complications[7]. Hence, the early use of aspirin in COVID-19 patients may reduce the incidence of severe to critical cases and deaths but it may also increase

GI bleeding. The efficacy and safety of aspirin prophylaxis against COVID-19 induced coagulopathy remains unknown.

METHODS

We searched MEDLINE thru PubMed and Cochrane CENTRAL for randomized controlled trials, cohort studies, systematic reviews and meta-analysis using the following free and MeSH terms: “COVID-19” AND “aspirin” on April 26, 2021 without language, country and disease severity restrictions. We also searched ChinaXiv, MedRxiv and BioRxiv for preprints and ClinTrials.gov, the WHO International Clinical Trials Registry Platform and Chinese Clinical Trial Registry for ongoing studies. We further searched COVID-19 Open Living Evidence and Living Evidence on COVID-19 for published and ongoing studies. We included RCTs that assessed efficacy of aspirin as prophylaxis against COVID-19 induced coagulopathy in patients with COVID-19. In the absence of RCTs, we included cohort studies instead. We excluded case series and case-control studies, studies that combined aspirin with drugs other than the standard of care or compared aspirin with other drugs, and those studies that had a mix of patients with pre-existing aspirin, and aspirin started at COVID-19 diagnosis.

RESULTS

Characteristics of included studies

We found 1 preprint retrospective study that assessed the association of aspirin prophylaxis for COVID-19 induced coagulopathy to clinical outcome [8]. The study included hospitalized, adult COVID-19 patients (aspirin n=319, no aspirin n=319). They received 81 mg/day of aspirin. Severity of COVID-19 was not reported. The study reported mortality as an outcome. [Appendix Table 1].

Methodological quality

Overall quality of evidence was very low. Newcastle Ottawa Scale score was 9/9. The study was not peer-reviewed (Appendix 2).

Outcomes

The study did not report association of aspirin with COVID-19-induced coagulopathy. Aspirin was associated with a significant reduction in the risk of mortality with an aHR of 0.52(0.34-0.81).

RECOMMENDATIONS FROM OTHER GROUPS

COVID-LMIC Task Force (January 11, 2021) recommends against the use of aspirin for VTE prophylaxis in hospitalized COVID-19 in LMICs [9].

RESEARCH GAPS

One randomized controlled trial has completed recruitment with no results yet (IRCT20180205038626N7). There are 11 ongoing studies on aspirin prophylaxis in preventing mortality/progression of disease. (Appendix 3).

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Appendix 1. Characteristics of included studies

Author	Country	Design	Population Disease Severity Age	Aspirin	No aspirin	Outcome	Risk of bias (Newcastle Ottawa 9/9) Other sources of bias
Meizlish 2021	USA	Multi-center cohort	Hospitalized adult COVID-19 (with CAD, congestive heart failure, diabetes mellitus and hypertension) > 60 y/o (54%) Males - 63% CVD- 54.5%	n=319 81 mg/day	n=319 Standard of care	Mortality aHR 0.522 (0.34-0.81)	9/9 not peer-reviewed

Appendix 2. GRADE Evidence Profile

CERTAINTY ASSESSMENT							NO. OF PATIENTS		EFFECT		CERTAINTY	IMPORTANCE
No. of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Aspirin	SOC	Relative (95% CI)	Absolute (95% CI)		
Mortality												
1	Observational study	Not serious	Not serious	Not serious	Not serious	Non-peer reviewed	-	HR 0.52 (0.34 to 0.81)	1 fewer per 1,000 (from 1 fewer to 0 fewer)	⊕◯◯◯ VERY LOW	CRITICAL	

Appendix 3. Characteristics of ongoing trials.

Registry No/Country	Status	Population	n	Intervention	Comparator	Outcome	Estimated completion date
CTRI/2020/07/026791 India	Recruiting		800	Aspirin	Standard of care	Clin improvement Progression Length of Hospital Stay Mortality	July 2021
NCT04410328 USA	Recruiting	19 and older	132	Aspirin Dipyridamole	Standard of care	COVID-19 Ordinal Scale	Dec 15, 2021
NCT04498273 USA	Recruiting	40-80 outpatients	7000	Aspirin	Placebo	Hospital admission	September 2021
NCT04365309 China	Recruiting	18-85	128	Aspirin	Standard of care	Recovery Time	June 2020
NCT04808895 Italy	Not Recruiting	18-99	204	Aspirin	Placebo	Mortality Progression	August 31, 2021
NCT04363840 USA	Not recruiting updated April 2020	18 and above	1080	Aspirin Vit D	Standard of care	Clin Status Score	Dec 2020
NCT04333407 UK	Recruiting updated April 2020	18-85	3170	Aspirin Clopidogrel Rivaroxaban Atorvastatin Omeprazole	Standard of care	Mortality	March 2021
NCT04703608 UK	Recruiting	5 and above	1200	Aspirin Ivermectin	Placebo	Progression Discharge	July 2022
CTRI/2020/09/028088 India	Not Recruiting	with O2 <90% at room air	34	Aspirin Colchicine Montelukast	Standard of care	Change in CRP	3 months' duration
IRCT20180205038626N7 Iran	Recruitment complete	18 and above		Aspirin	Placebo	Stroke	No results
PACTR202101544570971 Gambia	Not Recruiting	8-12 years	1200	Aspirin	Placebo	Severe COVID-19	Dec 30, 2021
CTRI/2020/08/027503 India	Not Recruiting	18-65 O2 sat < 94%	60	Aspirin	Standard of care	SpO2/FiO2 at day 7	6 months' duration


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