Philippine COVID-19 Living Clinical Practice Guidelines
Institute of Clinical Epidemiology, National Institutes of Health, UP Manila
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EVIDENCE SUMMARY

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 compared to no booster?

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RECOMMENDATIONS

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

2. **We suggest homologous booster vaccination in the immuno-compromised population for the following vaccines**:
   a. BNT162b2 (*Very low certainty of evidence; Weak recommendation)*
   b. mRNA-1273 (*Very low certainty of evidence; Weak recommendation)*

3. **For immunocompromised patients who received primary vaccination of any kind, we recommend for the use of heterologous vaccination**.

(Very low certainty of evidence; Strong recommendation)

NOTE: No consensus was reached on the recommendation regarding the use of homologous vaccination for immunocompromised patients who received primary vaccination with ChAdOx1 (AstraZeneca), CoronaVac (Sinovac), Gam-COVID-Vac (Sputnik) or Ad26.COV2.S (J&J/Janssen).

Consensus Issues

The panel was unanimous against recommending booster program in the current situation while the overall vaccination coverage is still low. The members believe that the focus of the vaccination program should be to vaccinate the unvaccinated first and achieve good coverage across the country, particularly in the vulnerable population. The panel believes that the provision of boosters at this time will worsen vaccine equity and will tantamount to robbing others of their first dose. Apart from the need to achieve good primary vaccination coverage, sufficient supplies for booster coverage must also be ensured prior to providing such.

The panel recognizes that the provision of boosters for healthcare workers is an important issue to consider, given that they are at a higher risk of exposure and that they were one of the first recipients of the vaccines with their protection possibly waning at this time. However, the panel still resolved to defer booster vaccinations even for the healthcare workers at this time.

For the immunocompromised, the panel members were in agreement that they are a vulnerable population that requires additional COVID-19 vaccine doses to gain sufficient protection. However, the panel members were divided and could not reach consensus

regarding homologous booster vaccination for ChAdOx1, CoronaVac, Gam-COVID-Vac, and Ad26.COV2.S. Despite three (3) 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 population 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 or 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 or 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 to provide an effective vaccination regimen to the immunocompromised, the heterologous booster vaccination may be the only available option at this time.

Key Findings

In this review, 5 RCTs, 1 comparative observational study, 1 test negative case control, and 14 single cohort self-controlled studies explored the use of either homologous or heterologous boosters after BNT162b2, CoronaVac, mRNA-1273, ChAdOx1, or Ad26.COV2.S vaccination.

The overall certainty of evidence for effectiveness in terms of clinical and immunologic outcomes is low to very low because of study design (i.e., mostly observational studies) and the lack of control for confounding factors in observational studies, the predominance of immunologic outcomes (rather than clinical effectiveness), and the short follow up.

Two (2) observational studies demonstrated sufficient protection against COVID-19 infection and hospitalization after BNT162b2 homologous vaccination in the general population. Four (4) small observational studies on the immunocompromised showed very few to no cases of COVID-19 infections after a homologous BNT162b2 booster compared to pre-boost.

Homologous or heterologous booster vaccination for BNT162b2, ChAdOx1, CoronaVac and Ad26.CoV2.S is associated with increased immunologic response against SARS-CoV-2 and is generally associated with acceptable adverse reaction rates, for both the general and immunocompromised populations.

Introduction

The need for an additional dose of a COVID-19 vaccine after completion of the standard approved dosing regimen has been raised in light of the poor response of immunocompromised patients, the findings of declining antibody titers over time, and the emergence of SARS-CoV-2 variants of concern that reduce 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.

Review Methods

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 2 for the detailed search strategy). For this review, a booster dose 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, and protection rates) were preferred. In the absence of such, observational studies and studies providing immunogenicity results were also considered. Immunologic response was presented as the fold-increase in antibody titers or T-cell counts after the booster dose compared to the primary vaccination. The positivity rates before and after the booster dose were also considered. 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 under immunosuppressive therapy. The results are presented according to the population included in the study. A subgroup analysis of the studies specifically among healthcare workers was planned but not implemented due to the absence of studies.

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.

Search Results

As of September 17, 2021, twenty (20) studies from the pre-identified electronic databases were identified as providing information on the performance of COVID-19 vaccine boosters. In addition, one regulatory agency document was identified as providing trial results that were not in the published reports.[1] Eleven (11) studies included healthy individuals, of which two provided clinical outcomes.[2,3] The remaining nine (9) studies provided only immunologic data as efficacy outcomes. Ten (10) studies were on immunocompromised patients, all presenting immunologic outcomes and four (4) with clinical outcomes. Safety data was available from 14 studies.

There were five (5) randomized controlled trials, one (1) comparative study, one (1) test negative case control, and 14 single cohort, self-controlled studies.

Nine (9) studies used BNT162b2, four (4) used CoronaVac, two (2) used mRNA-1273, two (2) used ChAdOx1, and one (1) Ad26.COV2, as homologous booster. Two (2) studies used an inactivated viral vaccine without specifying the make. One (1) randomized trial used Ad5 as a heterologous booster to CoronaVac in one of the treatment arms. One (1) study used

BNT162b2, mRNA-1273, and Ad26COV2S as either homologous or heterologous booster to a primary mRNA vaccination.

No study was identified that reported on the outcomes of using Gam-COVID-Vac, BBV152, BBIBP or NVX as a booster.

Risk of Bias Assessment
All but one of the randomized controlled trials were assessed to have an overall risk of bias of not serious; the remaining one study was deemed to have serious risk of bias because of unclear risk of bias in several domains. All but two observational studies were assessed to have an overall risk of bias of very serious because of lack of control for confounding factors, missing outcomes and incomplete testing of the study population. The two other studies that controlled for confounding factors were deemed to have serious risk of bias.

The results of the risk of bias assessment are presented in Appendix 3.

Results

General Population

BNT162b2 homologous booster

Clinical Efficacy / Effectiveness
Two (2) retrospective cohort studies, both conducted in Israel, provided information on the clinical effectiveness of BNT162b2 as a booster after at least 5 months of BNT162b2 primary vaccination.[2,3] The first study conducted among persons older than 60 years old 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.[2] 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.[3]

Immunogenicity
One (1) US-FDA report provided the results of a booster dose in a subset of the Phase 2/3 trial population after a median of 6 to 8 months of the primary vaccination. It demonstrated a 3.3-fold rise in the antibody titers.[1]

Safety
The above 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.[1]

ChAdOx1 homologous booster

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

Immunogenicity
One (1) 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 a two-fold rise in neutralizing antibody titers and IFN-γ counts post booster dose.[4]

Safety

The above study also reported less reactogenicity with the booster dose compared to the first dose.[4] No safety information is available beyond 28 days post homologous ChAdOx1 booster dose.

CoronaVac homologous booster

Clinical Efficacy / Effectiveness

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

Immunogenicity

Four (4) studies studied varying doses and intervals of the CoronaVac homologous booster vaccination.[5-8] One (1) RCT compared two different doses of CoronaVac booster 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.[7] Another RCT compared early boosting (28 days) and late boosting (6 months) after two different dosing regimens of CoronaVac. All arms of the trial showed a significant rise in antibody titers after receiving booster doses. Late boosting showed higher titers compared to early boosting.[5] In the RCT comparing homologous and heterologous boosting 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 heterologous boosting.[6] In the self-controlled cohort study where a booster dose of CoronaVac was given 6 months after primary vaccination, one to two-fold increases in the different immunologic parameters were noted.[8]

Safety

The RCTs on the CoronaVac booster 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.[5-7] One (1) study reported 14 serious adverse events within 6 months after the booster dose, all of which were assessed to be unrelated to the vaccination.[5]

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 (1) study involving a subgroup of the Phase 1/2 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.[9]

Safety

The above study reported similar reactogenicity rates pre and post boost.[9] No safety information is available beyond 28 days post homologous Ad26.COV.2 booster dose.

Inactivated virus vaccine homologous booster

Clinical Efficacy / Effectiveness

No study was identified on inactivated virus vaccine homologous booster.

Immunogenicity

Two (2) observational studies from China reported on the immunogenicity results of an inactivated virus vaccine homologous booster, with the make/brand not specified. Both studies showed high seropositivity rates for neutralizing antibodies post-boost, with one (1) study showing a significant increase in the rates from pre-boost levels.[10,11]

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

mRNA-1273, Gam-COVID-Vac, and BBV124 homologous booster
No study was identified which investigated these vaccines in a homologous booster regimen.

Healthcare Workers
No study was identified that involved healthcare workers and COVID-19 vaccine booster administration.

Immunocompromised Population

BNT162b2 homologous booster
Clinical Efficacy /Effectiveness
Three (3) studies provided clinical outcomes after BNT162b2 homologous booster administration among the immunocompromised population. Two (2) were single cohort (self-controlled) studies on solid organ transplant recipients [12,13] and one (1) was a single cohort (self-controlled) study on patients on dialysis.[14] For 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.[14] Among the transplant recipients, one (1) study reported 1 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.[12] The other study reported no post-boost COVID-19 infection with the third dose given 60 to 62 days after the primary vaccination.[13] The pre-boost infection rate was not established in these studies.

Immunogenicity
Six (6) studies described immunologic responses of immunocompromised patients to the homologous BNT162b2 booster. Two (2) reported on the change in antibody titers [14,15] and three (3) reported on seroconversion [12,16,17] and one (1) study reported both.[13] Consistent in the three 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, one (1) 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.[12]

Safety
Four (4) studies reported on the safety of BNT162b2 homologous booster in the immunocompromised population. Generally, they all noted similar adverse event rates with the second dose and no severe adverse events were reported after the third dose.[12-14,16] No safety data is available beyond 44 days after the third dose.

mRNA-127 homologous booster vaccination
Clinical Efficacy /Effectiveness
No study was identified providing clinical efficacy or effectiveness of mRNA-1273 homologous booster vaccination on the immunocompromised population.

Immunogenicity
One (1) randomized controlled trial compared the booster dose of mRNA-1273 two months after the primary vaccination, with placebo, in transplant recipients.[18] 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.[19].

Safety

When compared with placebo and to the second dose in one (1) RCT, the mRNA-1273 homologous booster dose was associated with slightly higher local and systemic adverse reaction rates.[18] No safety information is available beyond 28 days post homologous mRNA-1273 booster dose.

ChAdOx1, CoronaVac, Ad26.CoV2.S, Gam-COVID-Vac, BBV125 homologous booster

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

Heterologous Booster Vaccination

One (1) study provided a clinical outcome on the use of BNT162b2 or mRNA-1273 or Ad26.COV2.S after a median of 67 days of primary mRNA (either BNT162b2 or mRNA-1273) vaccination. No RT-PCR confirmed COVID-19 infection was reported after a median follow-up of 14 days. No information was provided on the infection rate prior to the third dose.[20]

Three (3) studies provided immunogenicity results of heterologous booster vaccination; one used ChAdOx1 two months after a primary mRNA vaccination in patients on rituximab [21], one used Ad5-nCOV booster after 3 to 6 months of a CoronaVac primary vaccination on healthy adults [6], and one had BNT162b2, or mRNA-1273 or Ad26.COV2.S after an mRNA-based primary vaccination in transplant patients.[20] Generally, heterologous booster vaccination was more immunogenic than homologous vaccination. Safety outcomes were inconsistent, with some studies reporting more adverse events and some stating similar adverse event rates to those after primary vaccination.

The detailed characteristics and results of these trials are in Appendix 4

The summary of findings table is in Appendix 5

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Recommendations from Other Groups

Table 1. Summary of Recommendations from Other Groups

Regulatory Agency	Recommendation
World Health Organization (WHO) as of 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.[22]
US Food and Drug Administration (US-FDA) as of September 22, 2021	Recommends a booster of BNT162b2 of at least 6 months in the following populations: individuals who are 65 years old or older, 18 to 64 years old at high risk of severe COVID-19, and 18 to 64 years old with frequent institutional or occupational exposure to SARS-CoV-2.[23]
Centers for Disease Prevention Advisory Committee on Immunization Practices (CDC-ACIP) as of September 2021	Recommends a booster shot of BNT162b2 after at least 6 months in the following populations: individuals 65 years or older and residents in long-term care settings and 50 to 64 years old with underlying medical conditions. It also recommended that the following populations may have a booster shot: 18 to 49 years old with underlying medical conditions and 18 to 64 years old at increased risk of COVID-19 due to occupational or institutional settings.[24]

Ongoing Trials

Search of *clinicaltrials.gov* registry on September 23, 2021 yielded 17 ongoing trials on COVID-19 booster vaccination with the earliest trial completion noted in December 2021.

Research Gaps

Additional and better quality 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 of booster administration
5. Optimum dose of booster administration
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 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 (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 BOOSTERS 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 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 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 3. Risk of Bias Assessment

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		
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
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
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
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
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
Hall 2021	RCT	LOW	LOW	LOW	LOW	LOW	LOW	LOW	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NOT 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														NOT 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
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
Pan	RCT	LOW	LOW	LOW	LOW	LOW	HIGH	LOW														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
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
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
Yue	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
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
				LOW	UNCLEAR	HIGH	NOT APPLICABLE			Y	YES	N	NO	U	UNCLEAR		NA	NOT APPLICABLE				

Appendix 4. Characteristics of Included Studies

A. Homologous Vaccination in the General Population

BNT162b2									
Study author (country)	**Study design**	**Population**	**Primary series**	**Booster (interval from V2)**	**Comparator**	**Follow-up**	**Outcomes**	**Certainty of evidence**	**Comments**
Clinical efficacy/effectiveness									
Bar-On (Israel)	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 reduction in risk	Low	Preprint 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 : 70% (62,76)	Low	Preprint 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

Immunogenicity									
FDA Report (US)	single cohort, self-controlled	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*** Seropositivity V2+1mo : 97.8 (94.4,99.4) V3+1mo : 93.9 (89.3, 96.9)	Very low	regulatory report
Safety									
FDA Report (US)	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	Moderate	regulatory report 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)

ChAdOx1									
Study author (country)	**Study design**	**Population**	**Primary series**	**Booster (timing of testing after V2)**	**Comparator**	**Follow-up**	**Outcomes**	**Certainty of evidence**	**Comments**
Clinical efficacy/effectiveness									
None									
Immunogenicity									
Flaxman (UK)	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***	Very low	preprint Cohort with historical control for reactogenicity data
Safety									
Flaxman (UK)	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	Moderate	preprint

CoronaVac									
Study author (country)	**Study design**	**Population**	**Primary series**	**Booster (interval from V2)**	**Comparator**	**Follow-up**	**Outcomes**	**Certainty of evidence**	**Comments**
Clinical efficacy/effectiveness									
None									
Immunogenicity									
Li J (China)	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=	Moderate	preprint IWRS randomization participants, investigators, lab and outcome assessors blinded to treatment but not to the 3 or 2 dose regimen
Li M 2021 (China)	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	Moderate	preprint 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)	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	Moderate	preprint 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	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 boosterr 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	Very low	preprint trial extension of the regulatory Ph1/Ph2 trial (published by Zhang)

Safety									
Li J (China)	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	Moderate	preprint IWRS randomization participants, investigators, lab and outcome assessors blinded to treatment but not to th 3 or 2 dose regimen
Li M (China)	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	Moderate	preprint (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)	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 serious adverse events not related to vaccine	Moderate	preprint 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

Ad26.COV2.S									
Study author (country)	**Study design**	**Population**	**Primary series**	**Booster (timing of testing after V2)**	**Comparator**	**Follow-up**	**Outcomes**	**Certainty of evidence**	**Comments**
Clinical efficacy/effectiveness									
None									
Immunogenicity									
Sadoff (Belgium, US)	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	Very low	preprint extension of the ongoing trial
Safety									
Sadoff (Belgium, US)	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	Moderate	preprint extension of the ongoing trial

Inactivated virus vaccine									
Study author (country)	**Study design**	**Population**	**Primary series**	**Booster (timing of testing after V2)**	**Comparator**	**Follow-up**	**Outcomes**	**Certainty of evidence**	**Comments**
Clinical efficacy/effectiveness									
None									
Immunogenicity									
Yue (China)	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 (8	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	Very low	proof correspondence
Liao (China)	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	Very low	correspondence
Safety									
None									

B. **Homologous Vaccination in the Immunocompromised Population**

Immunogenicity									
Bensouna (France)	single cohort, self-controlled	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	anti-S IgG V2 : 284 (IQR : 83,1190) V3 : 7554 (IQR 2268 to 11736) ***** 26.6 fold rise*** seropositivity V2 : 3 (96%) V3 : 2 (97%)	Very low	Pre-proof
Ducloux (France)	single cohort, self-controlled	Hemodialysis patients, COVID-19 naïve, 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% 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%	Very low	correspondence
Del Bello (France)	single cohort, self-controlled	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 V1 : 1.3% pre V2 : 5.1% pre V3 : 41.4% (95%CI, 36.5 to 46.3) post V3 : 67.9% (63.3 to 72.6)	Very low	Pre-print correspondence not all patients were examined at the different follow up dates

Kamar (France)	single cohort, self-controlled	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) Titers (among the seropositive before booster) : preV3 : 36+/- 12 post V3 : 2676+/- 350 ***** 74 fold rise***	Very low	correspondence
Masset (France)	single cohort, self-controlled	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%	Very low	pre-proof correspondence Not all patients had serological assessments, different patients in the different assessment periods
Chavarot (France)	single cohort, self-controlled	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%)	Very low	proof NOTE : significant difference in timing of serology, interval of booster between responders and non-responders, interval between transplant and vaccination, belacept conversion

Safety									
Bensouna (France)	single cohort, self-controlled	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	adverse events most frequent self-reported reaction was pain at injection site (27%) self reported global tolerance of the 3rd vs the 2nd dose : similar ~78%	Moderate	pre-proof
Del Bello (France)	single cohort, self-controlled	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	Moderate	Pre-print correspondence not all patients were examined at the different follow up dates
Kamar (France)	single cohort, self-controlled	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	Moderate	correspondence
Chavarot (France)	single cohort, self-controlled	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	Moderate	proof NOTE : significant difference in timing of serology, interval of booster between responders and non-responders, interval between transplant and vaccination, belacept conversion

mRNA-1273									
Study author (country)	**Study design**	**Population**	**Primary series**	**Booster (timing of testing after V2)**	**Comparator**	**Follow-up**	**Outcomes**	**Certainty of evidence**	**Comments**
Clinical efficacy/effectiveness									
None									
Immunogenicity									
Benotmane (France)	single cohort, self-controlled	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%)	Very low	correspondence
Hall (Canada)	RCT	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) SARS CoV2 specific Tcell mRNA : 432 saline : 67 ***6.4 fold rise**	Moderate	correspondence 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)	RCT	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	Moderate	correspondence computer-generated schedule by someone outside the study allocation concealed, syringe prepared by person outside the study patient, study team, assessor blinded

C. Heterologous Vaccination in the Immunocompromised Population

Primary BNT162b2 or mRNA-1273									
Study author (country)	**Study design**	**Population**	**Primary series**	**Booster (timing of testing after V2)**	**Comparator**	**Follow-up**	**Outcomes**	**Certainty of evidence**	**Comments**
Clinical efficacy/effectiveness									
Werbel (US)	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	Low	correspondence
Immunogenicity									
Werbel (US)	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	Very low	correspondence
Bonelli (Austria)	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	preprint no method of randomization or concealment "blinded" but no details complete ffup / no missing data, withdrawals preTx for both groups

Safety									
Werbel (US)	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	Moderate	correspondence
Bonelli (Austria)	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	preprint no method of randomization or concealment "blinded" but no details complete ffup / no missing data, withdrawals preTx for both groups

Appendix 4. Summary of Findings

	N	RoB	Indirectness	Inconsistency	Imprecision	Others	Effect	Certainty
GENERAL POPULATION								
BNT162b2 Homologous booster								
Prevention of COVID-19 infection	2 Obs	Serious (Observational short ff-up)	Not serious	Not serious	Not serious	Not assessed	OR (protection) – 11.4 OR (test positive) = 79% reduction	Low
Prevention of severe infection / hospitalization / death	1 Obs	Serious (Observational short ff-up)	Not serious	Not assessed	Not serious	Not serious	OR (protection): 15.5	Low
Immunogenicity	1 Obs	Serious (Observational uncontrolled confounders)	Not serious	Not assessed	Not assessed	Not serious	Increased antibody titers	Very
Reactogenicity	1 Obs	Serious (Observational)	Not serious	Not assessed	Not assessed	Not serious	Similar reactogenicity as 2nd dose	Low
Adverse events	1 Obs	Serious (Observational short ff-up)	Not serious	Not assessed	Not assessed	Not serious	Similar adverse event rates as 2nd dose	Very low
Serious adverse events / Death	0	Not assessed	Not assessed	Not assessed	Not assessed	Not assessed	na	na
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
Immunogenicity	1 Obs	Serious (Observational uncontrolled confounders)	Serious	Not assessed	Not assessed	Not serious	2-fold rise in titers	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 ff-up)	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

	N	RoB	Indirectness	Inconsistency	Imprecision	Others	Effect	Certainty
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	3 RCT 1 Obs	Serious (Missing data)	Serious	Not serious	Not serious	Not serious	Minimal to significant rise in titers	Low
Reactogenicity	3 RCT	Not serious	Not serious	Not serious	Not assessed	Not serious	Low rates, no difference with placebo	Moderate
Adverse events	3 RCT	Serious (Short ff-up)	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	1 Obs	Serious (Observational uncontrolled confounders)	Serious	Not assessed	Not serious	Not serious	4.7-fold rise in titers	Very Low
Reactogenicity	1 Obs	Serious (Observational uncontrolled confounders)	Not serious	Not assessed	Not serious	Not serious	Similar reactogenicity rates with pre-boost	Low
Adverse events	1 Obs	Serious (Observational short ff-up)	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

	N	RoB	Indirectness	Inconsistency	Imprecision	Others	Effect	Certainty
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	2 Obs	Serious (Observational uncontrolled confounders)	Serious	Not serious	Not serious	Not serious	Increase seropositiity post-boost	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-Ad5 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	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 ff-up)	Not serious	Not assessed	Not assessed	Not assessed	Similar rates	Moderate
Serious adverse events / Death	1 RCT	Serious (Missing data, short ff-up)	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	Low
Prevention of severe infection / hospitalization / death	1 Obs	Serious (Observational uncontrolled confounders)	Not serious	Not assessed	Not assessed	Not assessed	6/69 post boost	Low
Immunogenicity	6 Obs	Serious (Observational)	Serious	Not assessed	Not assessed	Not assessed	Increased titers post-boost Increased seropositive rates post-boost	Very low
Reactogenicity	4 Obs	Serious (Observational)	Not serious	Not serious	Not assessed	Not assessed	Similar reactogenicity rates pre and post boost	Low
Adverse events	4 Obs	Serious (Observational short ff-up)	Not serious	Not serious	Not assessed	Not assessed	Similar AE rates	Low
Serious adverse events / Death	4 Obs	Serious (Observational short ff-up)	Not serious	Not serious	Not assessed	Not assessed	No SAEs reported	Low
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	1 RCT 1Obs	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
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 ff-up)	Not serious	Not assessed	Not assessed	Not assessed	Slightly more common local and systemic reactions with booster than placebo, no severe reactions	Moderate
Serious adverse events / Death	1 RCT	Serious (Short ff-up)	Not serious	Not assessed	Not assessed	Not assessed	Slightly more common local and systemic reactions with booster than placebo, no severe reactions	Moderate

	N	RoB	Indirectness	Inconsistency	Imprecision	Others	Effect	Certainty
BNT162b2 or mRNA-1273 or Ad26.CoV2.S Heterologous booster (after an mRNA primary)								
Prevention of COVID-19 infection	1 obs	Very serious (Observational, unclear allocation and assessment, short ff-up)	Not serious	Not assessed	Serious (Very small sample size and no events)	Not Assessed	No infection post boost	Very low
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, unclear allocation and assessment, short ff-up)	Serious	Not assessed	Not assessed	Not assessed	Increase in seropositivity post boost	Very low
Reactogenicity	1 obs	Very serious (Observational)	Not serious	Not assessed	Not assessed	Not assessed	Acceptable reaction rates	Low
Adverse events	1 obs	Very serious (Observational, short ff-up)	Not serious	Not assessed	Not assessed	Not assessed	Low adverse event rates	Low
Serious adverse events / Death	1 obs	Very serious (Observational, short ff-up)	Not serious	Not assessed	Not assessed	Not assessed	No SAEs / deaths	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	1 RCT	Not serious	Serious	Not assessed	Not assessed	Not assessed	Lower seroconversion, higher antibody titers and T cell response with heterologous	Moderate
Reactogenicity	1 RCT	Not serious	Not serious	Not assessed	Not assessed	Not assessed	Lower seroconversion, higher antibody titers and T cell response with heterologous	Moderate
Adverse events	1 RCT	Serious (Short ff-up)	Not serious	Not assessed	Not assessed	Not assessed	Similar adverse event rates	Moderate
Serious adverse events / Death	1 RCT	Serious (Short ff-up)	Not serious	Not assessed	Not assessed	Not assessed	No serious adverse events	Moderate