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?

Evidence Reviewers: Dr. John Jefferson Besa, Dr. Mary Anne Castor, Dr. Marie Carmela Lapitan

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).

PREVIOUS RECOMMENDATIONS (October 2021)

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, Strong recommendation)*

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

3. **For immunocompromised patients who received primary vaccination of any kind, we recommend for the use of heterologous vaccination.** *(Very low certainty, Weak 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).

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

References

[1] Bar-on Y, Goldberg Y, Mandel M, Bodenheimer O, Freedman L, Kalkstein N, et al. BNT162b2 vaccine booster dose protection: A nationwide study from Israel [Internet]. medRxiv. 2021 [cited 2021 Sep 7]. Available from: https://doi.org/10.1101/2021.08.27.21262679

[2] Patalon T, Gazit S, Pitzer V, Prunas O, Warren J, Weinberger D. Short Term Reduction in the Odds of Testing Positive for SARS-CoV-2; a Comparison Between Two Doses and Three doses of the BNT162b2 Vaccine. medRxiv. 2021.

[3] Barda N, Dagan N, Cohen C, MA H, Lipsitch M, IS K, et al. Effectiveness of a third dose of the BNT162b2 mRNA COVID-19 vaccine for preventing severe outcomes in Israel: an observational study. Lancet (London, England) [Internet]. 2021; Available from: http://www.epistemonikos.org/documents/f25fb54ff2b477f94228bbe78487fa5fb81044c7

[4] VRBPAC. September 17, 2021 Meeting Briefing Document - FDA [Internet]. 2021 [cited 2021 Sep 18]. Available from: https://www.fda.gov/media/152176/download

[5] Levine-Tiefenbrun M, Yelin I, Alapi H, Katz R, Herzel E, Kuint J. Viral loads of Delta-variant SARS-CoV-2 breakthrough infections after vaccination and booster with BNT162b2 [Internet]. Nature medicine. 2021 [cited 2021 Nov 5]. Available from: https://doi.org/10.1038/s41591-021-01575-4

[6] Mofaz M, Yechezkel M, Guan G, Brandeau ML, Patalon T, Gazit S, et al. Self-reported and physiological reactions to the third BNT162b2 mRNA COVID-19 (booster) vaccine dose. medRxiv [Internet]. 2021; Available from: http://www.epistemonikos.org/documents/355d4df501c99de8986b72206b3fd258d7faf343

[7] Niesen MJM, Pawlowski C, O'Horo JC, Challener DW, Silvert E, Donadio G, et al. Three doses of COVID-19 mRNA vaccination are safe based on adverse events reported in electronic health records. medRxiv [Internet]. 2021; Available from: http://www.epistemonikos.org/documents/bccdc1587a9c07cc64ef3d633f16691c01c65f0c

[8] Chu L, Montefiori D, Huang W, Nestorova B, Chang Y, Carfi A, et al. Immune Memory Response After a Booster Injection of mRNA-1273 for Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2). medRxiv [Internet]. 2021; Available from: http://www.epistemonikos.org/documents/2ff5ae9b7641ed768b86f07f6b8beb9536aa0bb0

[9] Wu K, Choi A, Koch M, Ma L, Hill A, Nunna N, et al. Preliminary Analysis of Safety and Immunogenicity of a SARS-CoV-2 Variant Vaccine Booster. medRxiv [Internet]. 2021; Available from: http://www.epistemonikos.org/documents/9a44dd424b51cff2df60d966e00323fd3231408d

[10] Choi A, Koch M, Wu K, Chu L, Ma L, Hill A, et al. Safety and immunogenicity of SARS-CoV-2 variant mRNA vaccine boosters in healthy adults: an interim analysis. Nat Med [Internet]. 2021; Available from: http://www.epistemonikos.org/documents/b116c6d1f58f76e7d18c11aed426f5071527ee54

[11] Flaxman A, Marchevsky NG, Jenkin D, Aboagye J, Angus B, Belij-Rammerstorfer S. Tolerability and immunogenicity after a late second dose or a third dose of ChAdOx1 nCoV-19 (AZD1222) [Internet]. SSRN. 2021 [cited 2021 Aug 8]. Available from: https://papers.ssrn.com/sol3/papers.cfm?abstract_id=3873839

[12] Sadoff J, Le Gars M, Cardenas V, Shukarev G, Vaissiere N. Durability of antibody responses elicited by a single dose of Ad26.COV2.S and substantial increase following late boosting [Internet]. medRxiv. 2021 [cited 2021 Sep 7]. Available from: https://doi.org/10.1101/2021.08.25.21262569

[13] Pan H, Wu Q, Zeng Q, Zeng G, Yang J, Jiang D. Immunogenicity and safety of a third dose, and immune persistence of CoronaVac vaccine in healthy adults aged 18-59 years: interim results from a double-blind, randomized, placebo-controlled phase 2 clinical trial. MedRxiv. 2021.

[14] Li J, Hou L, Guo X, Jin P, Wu S, Zhu J. Heterologous prime-boost immunization with CoronaVac and Convidecia [Internet]. medRxiv. 2021 [cited 2021 Sep 7]. Available from: https://doi.org/10.1101/2021.09.03.21263062

[15] Li M, Yang J, Wang L, Wu Q, Wu Z, Zheng W, et al. A booster dose is immunogenic and will be needed for older adults who have completed two doses vaccination with CoronaVac: a randomised, double-blind, placebo-controlled, phase 1/2 clinical trial [Internet]. medRxiv. 2021 [cited 2021 Sep 15]. Available from: https://doi.org/10.1101/2021.08.03.21261544

[16] Wang K, Cao Y, Zhou Y, Wu J, Jia Z, Hu Y. A third dose of inactivated vaccine augments the potency, breadth, and duration of anamnestic responses against SARS-CoV-2. medRxiv. 2021.

[17] Mok CKP, Cohen CA, Cheng SMS, Chen C, Kwok K-O, Yiu K, et al. Comparison of the Immunogenicity of BNT162b2 and CoronaVac COVID-19 Vaccines in Hong Kong: An Observational Cohort Study. SSRN [Internet]. 2021; Available from: http://www.epistemonikos.org/documents/c37accfceac5098a5e1308164fffd2fdcb0e94fd

[18] Barin B, Kasap U, Selçuk F, Volkan E, Uluckan O. Longitudinal Comparison of SARS-CoV-2 Anti-Spike RBD IgG antibody Responses After CoronaVac, BNT162b2, ChAdOx1 nCoV-19 Vaccines and Evaluation of a Single Booster Dose of BNT162b2 or CoronaVac After a Primary CoronaVac Regimen. SSRN [Internet]. 2021; Available from: http://www.epistemonikos.org/documents/3e23dc8b436b4bb7973c2089d8d20f931d6faffd

[19] Yue L, Xie T, Yang T, Zhou J, Chen H, Zhu H, et al. A third booster dose may be necessary to mitigate neutralizing antibody fading after inoculation with two doses of an inactivated SARS-CoV-2 vaccine. J Med Virol [Internet]. 2021; Available from: http://www.epistemonikos.org/documents/6eeb8b98e94a24ccda3173f7e7e5d1c5106d2fda

[20] Liao Y, Zhang Y, Zhao H, Pu J, Zhao Z, Li D, et al. Intensified antibody response elicited by boost suggests immune memory in individuals administered two doses of SARS-CoV-2 inactivated vaccine. Emerg Microbes Infect [Internet]. 2021;10(1):1112–5. Available from: https://dx.doi.org/10.1080/22221751.2021.1937328

[21] Yue L, Zhou J, Zhou Y, Yang X, Xie T, Yang M, et al. Antibody response elicited by a third boost dose of inactivated SARS-CoV-2 vaccine can neutralize SARS-CoV-2 variants of concern. Emerg Microbes Infect [Internet]. 2021;1–9. Available from: http://www.epistemonikos.org/documents/44649a65700cd4060c0a3ee38e7655c046b9239d

[22] Li Y, Fang X, Pei R, Fan R, Chen S, Zeng P, et al. Immunogenicity and safety of the homogenous booster shot of a recombinant fusion protein vaccine (V-01) against COVID-19 in healthy adult participants primed with a two-dose regimen. medRxiv [Internet]. 2021; Available from: http://www.epistemonikos.org/documents/fa9ea94583e966283063d87453097e4d48385c60

[23] Atmar R, Lyke K, Deming M, Jackson L, Branche A, ElSahly H, et al. Heterologous SARS-CoV-2 Booster Vaccinations – Preliminary Report [Internet]. MedRxiv. 2021 [cited 2021 Nov 5]. Available from: https://doi.org/10.1101/2021.10.10.21264827

[24] Iketani S, Liu L, Nair M, Mohri H, Wang M, Huang Y, et al. A third COVID-19 vaccine shot markedly boosts neutralizing antibody potency and breadth [Internet]. MedRxiv. 2021 [cited 2021 Nov 5]. Available from: https://doi.org/10.1101/2021.08.11.21261670

[25] Hoque A, Rahman M, Imam H, Nahar N, Chowdhury FUH. Third dose vaccine With BNT162b2

and its response on Long COVID after Breakthrough infections. medRxiv [Internet]. 2021; Available from: http://www.epistemonikos.org/documents/fa8cdeb1c29ff1ac00821be30937544c03a5db1d

[26] Huat N, Lim J, Gill U, de Alwis R, Tan N, Toh J, et al. Differential immunogenicity of homologous versus heterologous boost in Ad26.COV2.S vaccine recipients [Internet]. MedRxiv. 2021 [cited 2021 Nov 12]. Available from: https://doi.org/10.1101/2021.10.14.21264981

[27] Sester M, Klemis V, Venhorst A, Halmans L, Schmidt T, Greiß F, et al. Immunogenicity and reactogenicity of heterologous Ad26.COV.2 and BNT162b2 vaccination. ResearchSquare [Internet]. 2021; Available from: http://www.epistemonikos.org/documents/375ea1006cb8923d3fe23a63566b9ddc0534350e

[28] Moghnieh R, Mekdashi R, El-Hassan S, Abdallah D, Jisr T, Bader M, et al. Immunogenicity and reactogenicity of BNT162b2 booster in BBIBP-CorV-vaccinated individuals compared with homologous BNT162b2 vaccination: Results of a pilot prospective cohort study from Lebanon. Vaccine [Internet]. 2021; Available from: http://www.epistemonikos.org/documents/88e5b508c75c86a8869254c1cebe4d4c79b1012f

[29] Romero-Ibarguengoitia ME, Rivera-Salinas D, Hernandez-Ruiz YG, Armendariz-Vazquez AG, Gonzalez-Cantu A, Barco-Flores IA, et al. Effect of the third dose of BNT162b2 vaccine in quantitative SARS-CoV-2 spike 1-2 IgG antibody titers in healthcare workers. medRxiv [Internet]. 2021; Available from: http://www.epistemonikos.org/documents/89e8a516684f9ff9ce614d5aa3405d3f37523787

[30] Liu Y, Zeng Q, Deng C, Li M, Li L, Liu D. Robust induction of B cell and T cell responses by a third dose of inactivated SARS-CoV-2 vaccine. medRxiv. 2021.

[31] Sablerolles R, Rietdijk W, Goorhuis B, Postma D, Visser L, Geers D, et al. Immunogenicity and reactogenicity of booster vaccinations after Ad26.COV2.S priming. medRxiv [Internet]. 2021; Available from: http://www.epistemonikos.org/documents/8c24d7d3bbe697a739407310aada45cf2920164f

[32] Patamatamkul S, Thammawat S, Buranrat B. Induction of robust neutralizing antibodies against the COVID-19 Delta variant with ChAdOx1 nCoV-19 or BNT162b2 as a booster following a primary vaccination series with CoronaVac [Internet]. MedRxiv. 2021 [cited 2021 Nov 5]. Available from: https://doi.org/10.1101/2021.09.25.21264099

[33] Yorsaeng R, Vichaiwattana P, Klinfueng S, Wongsrisang L, Sudhinaraset N, Vongpunsawad S, et al. Immune response elicited from heterologous SARS-CoV-1 2 vaccination: Sinovac (CoronaVac) followed by AstraZeneca (Vaxzevria) [Internet]. medRxiv. 2021 [cited 2021 Sep 30]. Available from: https://doi.org/10.1101/2021.09.01.21262955

[34] Singhatiraj E, Rongpirul K, Jongkaewwattana A, Hirankarn N. Intradermal ChAdOx1 Vaccine Following Two CoronaVac Shots: A Case Report. Vaccines [Internet]. 2021;9:990. Available from: https://doi.org/10.3390/%0Dvaccines9090990

[35] Chavarot N, Morel A, Leruez-Ville M, Villain E, Divard G, Burger C. Weak antibody response to 3 doses of mRNA vaccine in kidney transplant recipients treated with belatacept [Internet]. Am J Transplant. 2021. Available from: https://doi.org/10.1111/AJT.16814

[36] Kamar N, Abravanel F, Marion O, Couat C, Izopet J, Del Bello A. Three Doses of an mRNA Covid-19 Vaccine in Solid-Organ Transplant Recipients. N Engl J Med [Internet]. 2021;385(7):661–2. Available from: https://dx.doi.org/10.1056/NEJMc2108861

[37] Bensouna I, Caudwell V, Kubab S, Acquaviva S, Pardon A, Vittoz N, et al. SARS-CoV-2 Antibody

Response After a Third Dose of the BNT162b2 Vaccine in Patients Receiving Maintenance Hemodialysis or Peritoneal Dialysis. Am J Kidney Dis [Internet]. 2021; Available from: http://www.epistemonikos.org/documents/5712a0aecee60f7b858952f03a3d9d14210f5d77

[38] Ducloux D, Colladant M, Chabannes M, Yannaraki M, Courivaud C. Humoral response after 3 doses of the BNT162b2 mRNA COVID-19 vaccine in patients on hemodialysis. Kidney Int [Internet]. 2021;100(3):702–4. Available from: https://dx.doi.org/10.1016/j.kint.2021.06.025

[39] Peled Y, Ram E, Lavee J, Segev A, Matezki S, Wieder-Finesod A, et al. Third dose of the BNT162b2 vaccine in heart transplant recipients: Immunogenicity and clinical experience. J Heart Lung Transplant [Internet]. 2021; Available from: http://www.epistemonikos.org/documents/17effe940234e7478143e97a9c253071efcdbd4a

[40] Del Bello A, Abravanel F, Marion O, Couat C, Esposito L, Lavayssiere L. Efficiency of a boost with a third dose of anti–SARS-CoV-2 messenger RNA–based vaccines in solid organ transplant recipients [Internet]. Am J Transplant. 2021 [cited 2021 Sep 7]. Available from: https://doi.org/10.1111/AJT.16775

[41] Masset C, Kerleau C, Garanddeau C, Ville S, Cantarovich D, Hourmant M. A third injection of BNT162b2 mRNA Covid-19 vaccine in kidney transplant recipients improves the humoral immune response [Internet]. Kidney Int. 2021 [cited 2021 Sep 7]. Available from: https://doi.org/10.1016/j.kint.2021.08.017

[42] David S, Shamir-Stein N, Gez S, Lerner U, Rahamim-Cohen D, AE Z. Reactogenicity of a third BNT162b2 mRNA COVID-19 vaccine among immunocompromised individuals and seniors - A nationwide survey. Clin Immunol [Internet]. 2021;108860. Available from: http://www.epistemonikos.org/documents/35d4ff071a7e8669998cfe12b3ea46ac7cc20f6b

[43] Hall V, Ferreira V, Ju T, Jerullo M, Majchzrak-Kita B. Randomized Trial of a Third Dose of mRNA-1273 Vaccine in Transplant Recipients. N Engl J Med. 2021.

[44] Benotmane I, Gautier G, Perrin P, Olagne J, Cognard N, Fafi-Kremer S, et al. Antibody Response After a Third Dose of the mRNA-1273 SARS-CoV-2 Vaccine in Kidney Transplant Recipients With Minimal Serologic Response to 2 Doses [Internet]. JAMA. 2021 [cited 2021 Aug 28]. Available from: https://doi.org/10.1001/jama.2021.12339

[45] Greenberger L, Saltzman L, Senefeld J, Johnson P, DeGennaro L, Nichols G. Anti-spike antibody response to SARS-CoV-2 booster vaccination in patients with B cell-derived hematologic malignancies [Internet]. Cancer Cell. 2021 [cited 2021 Nov 5]. Available from: https://doi.org/10.1016/j.ccell.2021.09.001.

[46] Werbel W, Boyarsky B, Ou M, Massie A, Tobian A, Garonzik-Wang J. Safety and Immunogenicity of a Third Dose of SARS-CoV-2 Vaccine in Solid Organ Transplant Recipients: A Case Series [Internet]. Ann Intern Med. 2021 [cited 2021 Sep 7]. Available from: https://doi.org/10.7326/L21-0282

[47] Lyski Z, Kim S, Lee D, Sampson D, Raue H, Raghunathan V, et al. Immunogenicity of Pfizer mRNA COVID-19 vaccination followed by J&J adenovirus COVID-19 vaccination in two CLL patients [Internet]. MedRxiv. 2021 [cited 2021 Nov 5]. Available from: https://doi.org/10.1101/2021.09.02.21262146

[48] Baker M, Mallayosyula V, Davis M, Boyd S, Nadeau K, Robinson W. Effective Viral Vector SARS-CoV-2 Booster Vaccination in a Patient with Rheumatoid Arthritis after Initial Ineffective mRNA Vaccine Response [Internet]. Arthritis and Rheumatology. 2021 [cited 2021 Oct 22]. Available from: https://onlinelibrary.wiley.com/doi/abs/10.1002/art.41978

[49] Bonelli M, Mrak D, Tobudic S, Sieghart D, Koblischke M, Mandl P, et al. Additional heterologous versus homologous booster vaccination in immunosuppressed patients without SARS-CoV-2 antibody seroconversion after primary mRNA vaccination: a randomized controlled trial. medRxiv [Internet]. 2021; Available from: http://www.epistemonikos.org/documents/29ed89ed3746bcc6fc81dd6c365069b08e2a2f30

[50] Caillard S, Thaunat O, Benotmane I, Masset C, Blancho G. Antibody response to a fourth mRNA Covid-19 vaccine boost in weak responder kidney transplant recipients [Internet]. MedRxiv. 2021 [cited 2021 Oct 31]. Available from: https://doi.org/10.1101/2021.09.03.21262691

[51] WHO. Interim statement on COVID-19 vaccine booster doses. Update 4 October 2021 [Internet]. [cited 2021 Oct 7]. Available from: https://www.who.int/news/item/04-10-2021-interim-statement-on-booster-doses-for-covid-19-vaccination

[52] US CDC. COVID-19 Vaccine Booster Shots. November 9. 2021 [Internet]. [cited 2021 Nov 16]. Available from: https://www.cdc.gov/coronavirus/2019-ncov/vaccines/booster-shot.html#print

[53] UK JCVI. Update to JCVI advice on booster vaccination in adults, 15 November 2021 [Internet]. [cited 2021 Nov 16]. Available from: https://www.gov.uk/government/publications/covid-19-booster-vaccine-programme-for-winter-2021-to-2022-jcvi-statement-november-2021/update-to-jcvi-advice-on-booster-vaccination-in-adults-15-november-2021

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)			<u>HOMOLOGOUS BOOSTERS</u> 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 <u>HETEROLOGOUS BOOSTERS</u> • 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				<u>HOMOLOGOUS</u> 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 <u>HETEROLOGOUS BOOSTERS</u> 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 RISK
									AGE			EXPOSURE RISK			COMORBIDITIES			VARIANT PREVALENCE			OVERALL for CONTROL OF COUNFOUNDERS	
									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)		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, ineligible 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	<u>% sVNT inhibition pre and post boost</u> +BNT : 96.85% (SD 2.4%) +CoronaVac : 57.75% (SD 24.68) ***>20% more with hetero*** <u>% sVNT for Beta, Gamma, Delta</u> +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/follo w-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 $\geq$ 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/Corona Vac 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 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% ***<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 BNT162b2	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 BNT162b2	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 åÊ (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 åÊ (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 åÊ (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 åÊ (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 åÊ (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 åÊ (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 åÊ (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 åÊ (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 åÊ (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 åÊ (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 âÊ (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 âÊ (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	serious (observational, short ffup)	Not serious	Not serious	Not serious	Not serious	Low event rates	Low

	1 Obs							
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
	N	**RoB**	**Indirectness**	**Inconsistency**	**Imprecision**	**Others**	**Effect**	**Certainty**
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)	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
	N	**RoB**	**Indirectness**	**Inconsistency**	**Imprecision**	**Others**	**Effect**	**Certainty**
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
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	Not assessed	Not assessed	Not	Not	na	na

		assessed			assessed	assessed		
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
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
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

	N	RoB	Indirectness	Inconsistency	Imprecision	Others	Effect	Certainty
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
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	Not serious	Not assessed	Not	Not	47% reported unsolicited AE	Low

		(observational short ffup)			assessed	assessed		
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
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	Not assessed	Not assessed	Not	Not	na	na

		assessed			assessed	assessed		
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
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
	N	**RoB**	**Indirectness**	**Inconsistency**	**Imprecision**	**Others**	**Effect**	**Certainty**
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
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	Not serious	Not assessed	Not	Not	na	na

		assessed			assessed	assessed		
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

	N	RoB	Indirectness	Inconsistency	Imprecision	Others	Effect	Certainty
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
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								
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 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
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
	N	**RoB**	**Indirectness**	**Inconsistency**	**Imprecision**	**Others**	**Effect**	**Certainty**
Serious adverse events / Death	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
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

	N	RoB	Indirectness	Inconsistency	Imprecision	Others	Effect	Certainty
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
Adverse events	1	Serious	Not serious	Not assessed	Not	Not	Similar adverse event rates	Moderate

	RCT	(short ffup)			assessed	assessed		
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
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
Serious adverse events / Death	0	Not assessed	Not assessed	Not assessed	Not assessed	Not assessed	na	na