EVIDENCE SUMMARY

RESEARCH QUESTION: Among persons of high-risk, what is the clinical and immunologic efficacy, effectiveness, and safety of a first booster (third) dose?

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RECOMMENDATIONS

Recommendations	Certainty of Evidence	Strength of Recommendation
Among the **immunocompromised**, we suggest the use of the following COVID-19 vaccines as **homologous** booster at least two months after the primary series. a. monovalent BNT162b2 (Pfizer-BioNTech) b. monovalent mRNA-1273 (Moderna)	 Very low Low	 Weak Weak
Among the **elderly**, we suggest the use of the following COVID-19 vaccines as **homologous** booster at least two months after the primary series: a. monovalent BNT162b2 (Pfizer-BioNTech) b. AdCOV2.S (Janssen)/ AdCOV2.S (Janssen)	 Very low Very low	 Weak Weak
Among **immunocompromised population** we suggest the following heterologous booster vaccination regimen: a. mRNA-based / mRNA-based b. mRNA-based / ChAdOx1 **(AstraZeneca) booster** c. BNT162b2 (Pfizer-BioNTech) / **monovalent mRNA-1273 (Moderna) booster** d. mRNA-based / Ad26.CoV2.S (**J&J) booster** e. AstraZeneca first dose, CoronaVac second dose / **monovalent Moderna or Pfizer booster** f. **AstraZeneca / monovalent Moderna or Pfizer booster** g. CoronaVac / **monovalent Pfizer booster** Among the **immunocompromised population, there is insufficient evidence to recommend** the following heterologous booster vaccination regimen due to insufficient evidence: a. Janssen / **monovalent Moderna or Pfizer booster** b. CoronaVac primary **/ monovalent *Moderna***	 Very low Very low Very low Very low Very low Very low Very low Very low Very low	 Weak Weak Weak Weak Weak Weak Weak Weak Weak
Among the **elderly population**, we suggest the following heterologous COVID-19 booster vaccination regimen: a. ChAdOX (AstraZeneca) Primary / **mRNA-based** b. BNT162b2 (Pfizer BioNTech) or mRNA1273 (Moderna) or ChAdOx1Oxford-AstraZeneca or Ad26CoV2 (J&J) / **mRNA-based** c. mRNA-based vaccine / **mRNA-based booster** d. CoronaVac Primary / **monovalent BNT162b2 (Pfizer-BioNTech)** e. CoronaVac Primary / **ChAdOX (AstraZeneca)**	 Very low Low Very low Very low Very low	 Weak Weak Weak Weak Weak

Consensus Issues

The Panel only considered the monovalent version of the Pfizer vaccine in this updated recommendation. This was due to the limited evidence available for bivalent Pfizer vaccine as a first booster (third dose).

KEY FINDINGS

Homologous vaccine booster in the immunocompromised

- In immunocompromised adults, there were 34 observational studies (five from the previous update) on the effectiveness, immunogenicity, and safety of homologous **monovalent BNT162b2 (Pfizer-BioNTech)** vaccine as booster. It showed reduced incidence of confirmed symptomatic COVID-19, COVID-19-related hospitalization, severe COVID-19, and COVID-19-related mortality compared with those not given a booster. Humoral response, but not cellular response, was observed to increase after a booster dose. Reported serious adverse events (SAEs) were not increased after a booster dose.
- For homologous **monovalent mRNA-1273 (Moderna**) booster in immunocompromised adults, there was one RCT and four observational studies that investigated its efficacy or effectiveness, immunogenicity, and safety. It resulted in reduced incidence of severe or critical COVID-19, COVID-19 infection, and increased immunogenicity compared with no booster. It also showed increased risk of local, mild adverse events (pain and swelling) with no interference in daily activities.
- Immunocompromising conditions included hematologic, oncologic and breast malignancies, liver cirrhosis, chronic kidney disease requiring dialysis, HIV and organ transplant.
- Overall certainty of evidence was very low for monovalent BNT162b2 (Pfizer-BioNTech) due to serious risk of bias from confounding and outcome measurement biases, indirectness, inconsistency in immunogenicity outcomes across studies, and imprecision. For mRNA-1273 (Moderna), overall certainty of evidence was low due to imprecision and indirectness.

Homologous vaccine booster in the elderly

- There were five (2 cohort and 3 before-after studies) on **monovalent BNT162b2 (Pfizer-BioNTech**) as first booster in the elderly population, some with underlying chronic medical conditions and living in nursing homes. It showed reduced incidence of COVID-19 infection, severe COVID-19, COVID-19-associated hospitalization and COVID-19-related mortality compared to no booster. It also showed increased humoral and cellular responses, except in COVID-19-recovered elderly. There were no SAEs nor adverse events reported. Overall certainty of evidence was very low due to risk of bias, inconsistency, indirectness, and imprecision.
- One RCT (ENSEMBLE2) on **Ad26.COV2.S (Janssen)** as a booster included adults and elderly, Data were not available for subgroup analysis of the elderly and immunocompromised. It showed no difference in incidence of moderate to severe-critical COVID-19, and severe to critical COVID-19 compared to no booster. It also showed increased antibody response and reduced risk of hypersensitivity reaction and unsolicited vaccine-related adverse events compared to no booster but no differences in SAEs, hemorrhagic, embolic and thromboembolic adverse events compared to no booster. Overall certainty of evidence was low due to attrition bias, indirectness, and imprecision.

Heterologous vaccine booster in the immunocompromised

- All studies found on the **mRNA-based vaccine** for this population used the monovalent vaccine. It was used as heterologous booster to the following:
    - **ChAdOx1 (AstraZeneca) or CoronaVac as primary series** did not show any difference in the risk for COVID-19 mortality and COVID-19-related pneumonia compared to no booster. It reduced the risk of COVID-19-related hospitalization but increased the risk of requiring mechanical ventilation during COVID-19 infection. It enhanced humoral immune response, with increased anti-Receptor Binding Domain (anti-RBD) IgG titer and SARS-

CoV2 Spike-1 IgG response as well as the cellular immune response. The risk for adverse events increased compared to no booster. Pain and tenderness on the injection site, myalgia and fatigue were the most common adverse events.
    - **ChAdOx1 (AstraZeneca) as primary vaccine** had no reported COVID-19-related deaths but with mild COVID-19 infection in observational studies. It increased immunogenicity responses and increased incidence of adverse events compared to no booster.
    - **CoronaVac as a primary series**, based on an observational study had no reported cases of COVID-19 infection.
    - **Ad26.COV2.S (Janssen) primary series** had pain on injection site and fatigue as the most commonly reported adverse events.
    - **viral vector (ChADOx1 AstraZeneca or Ad26.COV2.S Janssen) primary series** had increased neutralizing antibodies based on a preprint cohort study.
- Monovalent mRNA1273 (Moderna) was heterologous booster to the following:
    - **BNT162b2 (Pfizer-BioNTech) primary series**, wherein there were cases of COVID-19 infection reported in an observational study. It increased humoral response: anti-RBD IgG titer, seroconversion, neutralizing antibody against COVID-19, and SARS-CoV2 Spike-1 antibody compared to no booster.
    - **Ad26.COV2.S (Janssen) or BNT162b2 (Pfizer-BioNTech) as primary series** and had no SAEs reported by an observational study.
- The monovalent BNT162b2 (Pfizer-BioNTech) was heterologous booster to the following:
    - **ChAdOx1 primary series**, wherein observational studies reported to have increased seroconversion from pre- to post-booster. The detection of neutralizing antibodies also increased specifically against the SARS-CoV2 Omicron variant compared to no booster.
    - **CoronaVac primary series** increased the neutralizing antibodies against SARS-CoV2 compared to no booster.
- Ad26.COV2.S (Janssen) was studied as heterologous booster to the following:
    - **BNT162b2 primary series**, had no reported COVID-19 infection in observational studies. It increased seroconversion and neutralizing antibodies against SARS-CoV2 but not the SARS-CoV2 Spike-1 antibody response compared to no booster.
    - **mRNA-based primary series** increased the anti-RBD IgG titer. It did not increase the risk for adverse events compared to no booster.
- ChAdOX1 recombinant (AstraZeneca) booster with mRNA-based primary vaccines increased humoral and cellular response compared to no booster.
- For the viral vector booster and mRNA-based vaccine combination, anti-RBD IgG titer increased as reported in an observational study.
- Studies included immunocompromised populations with varying conditions: autoimmune diseases on immunosuppressants, solid organ and oncohematological malignancies, chronic kidney disease with on-going dialysis, and those solid organ transplant (heart, lung, hepatic) recipients. There were several studies that described the presence of co-morbidities or underlying chronic illnesses such as diabetes, hypertension, cardiovascular disease, stroke, heart failure, renal disease or failure, respiratory illness, and liver disease. However, no subgroup analysis was done for the presence of these comorbidities.
- Overall certainty of evidence was very low to low due to serious risk of bias, indirectness, and imprecision. The sole RCT was rated to have moderate certainty of evidence.
- There was no evidence on the use of the following vaccines as first booster in high-risk population: bivalent mRNA-based vaccines, Sinopharm BBIBP, Bharat, Biotech BBV152 COVAXIN/BBV152, Cansino Biologics Ad5-nCoV-S (recombinant), Novavax NVX-CoV2373, NVX-CoV2372 Nuvaxovid, and Sputnik V vaccine/Gamaleya/Gam-COVID-Vac as booster.

Heterologous vaccine booster in the elderly

- All studies found on the **mRNA-based vaccine** [BNT162b2 (Pfizer-BioNTech) or mRNA-1273 (Moderna)] for the elderly population used the monovalent vaccine. It was used as heterologous booster for the following:
    - **ChAdOx1-S (AstraZeneca) primary series**, one cohort study showed reduced risk for COVID19-related mortality, severe COVID-19 infection and COVID19 infection of any degree. There were no immunogenicity and safety studies.
    - **BNT162b2 (Pfizer-BioNTech) or mRNA-1273 (Moderna) or ChAdOx1 (AstraZeneca) or Ad26.COV.2 (Janssen) as primary series**, one cohort study showed increased risk of COVID-19 infection, but reduced risk of COVID-related hospitalization and ICU-admission. The elderly population in this study all had chronic heart failure. There were no immunogenicity and safety studies.
- For mRNA-1273 (Moderna) booster following the first dose mRNA-1273 (Moderna) and second dose BNT162b2 (Pfizer-BioNTech) vaccine as primary. There was no reported SAE although systemic adverse events were described to occur in one-third of patients after a booster in one before-after study. There were no effectiveness and immunogenicity studies.
- With monovalent BNT162b2 (Pfizer-BioNTech) as the heterologous booster to CoronaVac primary vaccine, one before-after study showed rise in anti-RBD IgG titer and neutralizing antibodies.
- For ChAdOx-1 (AstraZeneca) as a booster following CoronaVac primary series, the anti-RBD IgG titer and neutralizing antibodies inhibiting SARS-CoV2 increased. No effectiveness and safety outcomes were available.
- The certainty of evidence was very low due to serious risk of bias, and indirectness except for one cohort study on mRNA-based booster with varying combinations of primary vaccine series rated as low.

Heterologous or Homologous mRNA-based booster

- For monovalent mRNA-based vaccine booster with unspecified mRNA-based primary, it demonstrated reduced likelihood of COVID-19 associated hospitalization compared to no booster (VISION study).

WHAT'S NEW IN THIS VERSION?

Homologous booster

There were 38 new studies included in this review. Out of the 10 studies from the previous evidence summary (December 2021), three were excluded because they assessed immunogenicity studies earlier than two months after the primary series or participants were included in another study (duplication). There was one published conference abstract only on the efficacy and safety of Novavax COVID-19 vaccine as homologous booster (NVX-CoV2373) which could not be retrieved (Anez et al.)

In the immunocompromised, new studies on monovalent mRNA-1273 (Moderna) and BNT162b2 (Pfizer-BioNTech) as a booster still showed reduced risk of COVID-19, and safety of the vaccines, with low and very low certainty of evidence, respectively.

In the elderly population, five studies on monovalent BNT162b2 (Pfizer-BioNTech) (two cohort and three before-after studies) showed reduced risk of COVID-19 mortality, hospitalization, severe COVID-19, increased immunogenicity, and without reported serious adverse events. One RCT (ENSEMBLE2) on Ad26.COV2.S (Janssen) showed increased immunogenicity with decreased risks of adverse events. There were no studies in the elderly in the previous update. Certainty of evidence for these studies were rated very low.

There are additional recommendations for the use of monovalent BNT162b2 (Pfizer-BioNTech) and Ad26.COV2.S (Janssen) as booster vaccines in the elderly population with and without underlying medical conditions.

Heterologous booster

There were 25 new studies included in this review, conducted from 2021 to 2022. Out of the six studies from the previous evidence summary, five were excluded because they were case series and one wherein the fourth dose was considered as the booster. The review now includes studies on the elderly population (n=4 studies). For the immunocompromised population, there are 22 studies. Previous evidence presented on immunocompromised population was on immunogenicity alone (1 RCT), whereas currently there are eight studies added on clinical efficacy and effectiveness with very low certainty of evidence. These studies presented evidence on (1) monovalent mRNA-based booster with ChAdOx1 or CoronaVac or Ad26.COV2.S (Janssen) primary vaccine; (2) monovalent mRNA-1273 booster with mRNA-1273 (first dose) BNT162b2 (second dose) as primary vaccine; (3) monovalent mRNA1273 booster with BNT162b2 as primary vaccine; and (4) Ad26.COV2.S or ChAdOx-1 recombinant booster with mRNA-based primary vaccine.

There are additional three recommendations on other primary and heterologous booster vaccination regimens for the immunocompromised population. These include mRNA-based heterologous booster to the following primary vaccines: (1) ChAdOx1 (AstraZeneca) first dose and CoronaVac second dose; (2) ChAdOx1 (AstraZeneca); (3) CoronaVac primary, Pfizer-BioNTech booster; and (4) mRNA-based primary with mRNA-based booster.

There are now recommendations on the elderly population based on new studies with effectiveness, safety, and immunogenicity outcomes.

Heterologous or Homologous mRNA-based booster

One new case-control study (VISION) with monovalent mRNA-based as a booster and mRNA-based vaccines as primary series provided data for effectiveness in the immunocompromised and elderly.

PREVIOUS RECOMMENDATION
27 December 2021

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).

INTRODUCTION

Immunocompromised individuals, older adults, and those with certain underlying medical conditions like diabetes mellitus, lung and heart diseases, are at highest risk of severe COVID-19, prolonged hospitalization, complications, and death [1-3]. Due to either the primary disease or the immunosuppressive treatments, immunocompromised patients are more likely to show a weak or suboptimal immune response to COVID-19 vaccines. More than 81% of COVID-19 deaths occur in people over age 65 [4]. Furthermore, a person's risk of severe illness from COVID-19 increases as the number of underlying medical conditions they have increases [4]. The need for additional doses of a COVID-19 vaccine after completion of the standard approved dosing regimen has been raised in the light of 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.

This gives an update on the previous recommendation on the first booster vaccination for immunocompromised as of December 2021. The first booster in this review is referred to as the third dose

of any COVID-19 vaccine for the high-risk population, except if Janssen vaccine was given, where the second dose is considered the first booster.

REVIEW METHODS

Search Strategy

A systematic search was done until December 31, 2022 without language restrictions in PubMed, Cochrane Central Register of Controlled Trials, Cochrane COVID-19 Study Register, Living Overview of the Evidence platform for COVID-19, Chinese Clinical Trial Registry, medRxiv.org, and COVID-NMA. The advanced search facility of the databases with the following keywords was used: “COVID-19”, “third", “booster”, “vaccine”, “efficacy”, and “effectiveness. Cross-referencing of relevant articles was also done.

RCTs and observational studies evaluating the efficacy, effectiveness, and safety of any COVID-19 vaccine as a booster dose in high-risk individuals were included. High-risk adults, as defined by WHO, are those older than 60 years or who have health conditions like lung or heart disease, diabetes or condition that affect their immune system. A booster dose was defined as the third dose of any COVID-19 vaccine given at least two months after the second dose, except for Janssen or J&J vaccine where the second dose is considered as the booster. The comparator was placebo or no booster. Outcomes assessed were confirmed symptomatic COVID-19, severe or critical COVID-19, COVID-19 hospitalization, COVID-19-related mortality, all-cause mortality, immunogenicity, and safety. Studies that determined immunologic effects just prior to booster vaccination and at least two weeks after a booster dose were included. Case series and studies that used another COVID-19 vaccine as comparator were excluded.

Risk of bias assessment

Two authors independently evaluated the risk of bias of included studies. Studies were assessed with the Risk of Bias in observational studies (ROBINS-I) tool and Risk of Bias tool from RevMan for randomized trials.

Statistical Analysis

Descriptive statistics were used for the characteristics of the included studies. Meta-analysis was planned. The range of adjusted effect estimates, and pooled effect estimates, when possible, and its 95% CI were reported. Sensitivity analysis was planned for studies with low risk of bias and excluding studies with high missing rate. The I2 statistic was used to estimate the level of heterogeneity, if applicable. Outcome measures were planned to be stratified by type of booster vaccine, and prior COVID-19 status. For immunogenicity results, a positive neutralizing antibody was detected when there was 30% or more inhibition of SARS-CoV-2. Safety outcomes were summarized using descriptive statistics, if applicable.

RESULTS

Characteristics of included studies

Homologous Booster Vaccine

In the immunocompromised population (n=133,904), 34 observational studies on monovalent BNT162b2 (Pfizer-BioNTech) [5-39], five (5) studies on monovalent mRNA-1273 (Moderna) [5, 13, 28, 40, 41] and one (1) RCT on Ad26.COV2.S (Janssen) [47] as a booster were included in the review. Immunocompromising conditions included hematologic, oncologic and breast malignancies, liver cirrhosis, chronic kidney disease requiring dialysis, HIV and organ transplant. Booster dose was given at least two months to six months after the second dose.

For monovalent BNT162b2 (Pfizer-BioNTech) as a booster in immunocompromised, all studies were observational: majority of studies (30) were on immunogenicity, ten (seven before-after and three cohort) on effectiveness, and 16 (one cohort study, one cross-sectional and 14 before-after) on safety outcomes.

For monovalent mRNA-1273 (Moderna) as a booster in immunocompromised, there was one RCT on efficacy, one cohort on effectiveness; four on immunogenicity (three before-after studies and one RCT), and two on safety (one before-after study and one RCT). Efficacy and effectiveness were observed from 21 days until a median of 66 days post-booster vaccination while immunogenicity was assessed up to 150 days post-booster.

For the elderly population, there were five observational studies on monovalent BNT162b2 (Pfizer-BioNTech) [42-46] and one placebo-controlled RCT on Ad26.COV2.S (Janssen) as a booster in the elderly population (n=1,342,547) [47]. There were two before-after studies on elderly in nursing homes, of whom the majority had hypertension and coronary heart diseases (n=18,717). Other comorbidities reported among elderly were dyslipidemia, diabetes, and obesity. Immunocompromised individuals included those with autoimmune diseases. Booster vaccine was given at least two months after the primary series. Outcomes were moderate to severe-critical COVID-19, severe to critical COVID-19, immunogenicity, and adverse events for both Ad26.COV2.S (Janssen) and monovalent BNT162b2 (Pfizer-BioNTech).

Heterologous Booster Vaccine

Among high-risk adult populations, 25 studies investigated varying heterologous booster-primary vaccine combinations. The studies looked into monovalent mRNA-based vaccines (n=21 studies) [3, 48-67], Oxford/AstraZeneca (ChAdOx1-S recombinant) (n=3 studies) [56, 68, 69], and Ad26.COV.2 (Janssen) (n=3 studies) [50, 70, 71], as heterologous booster.

The sample size of the studies were generally small ranging from 20 (RCT) to 245 [68], and another studied more than 7 million records of elderly individuals. For the elderly population, four studies were included in the review: the large retrospective cohort [69], two cohort studies (one cohort on elderly living in long-term care facility [67], and those having chronic heart failure [3]), and a before-after study among elderly healthcare workers and those residing in long-term care facilities [56]. The rest were studies on immunocompromised populations with varying conditions: solid organ transplant recipients and on autoimmune diseases on immunosuppressants, with malignancy, and those undergoing dialysis. There were 7 studies that described the presence of co-morbidities or underlying chronic illnesses such as diabetes, hypertension, cardiovascular disease, stroke, heart failure, renal disease or failure, respiratory illness, and liver disease. However, no subgroup analysis was done for the presence of these comorbidities.

Clinical and immunologic efficacy as well as safety after administration of the first heterologous booster were assessed. The heterologous booster was administered 2 to 9 months after the second dose of the primary series. The reported clinical outcomes among the elderly population were from two cohort studies [3, 69] and which include COVID-19-related deaths, severe and any degree of COVID-19 infection. For the immunocompromised group, 3 cohort [51, 52, 65] and 2 before-after [49, 61] studies reported on clinical outcomes: COVID-19-related deaths, hospitalization, and need for mechanical ventilation, severe and any degree of COVID-19 infection. The evidence on safety of the heterologous booster was also presented by one cohort study for the elderly [67], and 4 cohort [50, 57, 60, 70] studies among immunocompromised individuals. There was one study [56] in the elderly populations that measured immunogenicity against COVID-19 through humoral response. For the immunocompromised population there were 13 studies that measured humoral response and 4 reported cellular responses. These outcomes were compared with pre-booster, and no booster groups. Follow up period after the third dose or first heterologous booster was until 150 days for clinical and safety outcomes, and 360 days for immunogenicity outcomes.

Homologous or Heterologous monovalent mRNA-based booster

One case-control study on monovalent mRNA-based booster with unspecified mRNA-based vaccine as primary included 16,310 (10,256 cases and 6,054 control) elderly and any individual likely to have an immunocompromising condition (VISION) [72]. The study reported on COVID-19-associated hospitalization. Follow up period after the booster was 12 months.

Homologous Booster Vaccine

Immunocompromised Adult Population

BNT162b2 homologous booster in Immunocompromised population

Effectiveness Outcomes

BNT162b2 homologous booster reduced the risk for mortality (RR 0.01, 95% CI 00-0.17) and hospitalization (RR 0.23, 95% CI 0.16-0.32) in patients with autoimmune disease compared to no booster (1 cohort, n=76,842) [10].

Among those with liver cirrhosis, reduced incidence of severe COVID-19 disease was noted compared to no booster (aHR 0.0, 95% CI 0.0-0.08) (one cohort, n=12,978) [28].

It reduced risk for COVID-19 infection among those with autoimmune disease (RR 0.15, 95% CI 0.14-0.16) and in those with liver cirrhosis compared to no booster (aHR 0.19, 95% CI 0.09-0.39) (2 cohort, n=89,820) [10, 28].

Immunogenicity Outcomes

An increase in anti-spike Ab (MD 2,077, 95% CI 1,718-2,436) was reported but no difference in neutralizing antibodies post-booster compared with pre-booster levels (MD 184, 95% CI 130-4980) (11 before after studies, n=1,336) [8, 9, 12-14, 16, 20, 22-24, 31].

Safety Outcomes

SAEs were reported in 0% to 10% of immunocompromised individuals after a booster dose of BNT162b2 during a follow-up period of 116 days. These were suspected unexpected severe adverse reaction (SUSAR): transverse myelitis [14], one sensorineural hearing loss [23] and ten hospitalizations (peritonitis in PD patients, pulmonary embolism, and osteitis) [12], 2 AML relapse, 1 catheter infection and 1 for surgery for gastric cancer [14]. (1 cohort [38], 1 cross-sectional [37], 16 before-after studies [11-12, 14-15, 17-19, 21, 23, 26-27, 29-30, 32-33, 36], n=5349)]. Adverse events were reported in 0% to 80% post-booster (1 cohort [38], 10 before-after studies [1, 12, 15, 21, 23, 27, 29, 32-33, 37], n=4,125).

mRNA-1273 homologous booster in immunocompromised adults

Efficacy Outcomes

One cohort study showed reduced incidence of severe or critical COVID-19 (aHR 0.0, 95% CI 0.00-0.08) and symptomatic COVID-19 (aHR 0.19, 95% CI 0.09-0.39) compared to no booster in patients with liver cirrhosis (n=13,104) [28].

One RCT demonstrated no difference in incidence of COVID-19 between the mRNA-1273 vaccine (RR 0.34, 95% CI 0.01-8.15) and placebo in COVID-19–naive, transplant recipients (n=119) [40].

Immunogenicity Outcomes

One placebo-controlled randomized study showed that it increased anti-spike Ab positivity (RR 3.13, 95% CI 1.71-5.76) and surrogate virus neutralization positivity (RR 2.44, 95% CI 1.48-4.03) (n=119) [40].

Two before-after studies showed increased seroconversion rate post-booster (range, 63% to 96%) (n=105) [5, 13].

Safety Outcomes

One RCT showed that there was almost 6 times increased risk for adverse events after a booster dose of mRNA-1273 compared to placebo (RR 6.46, 95% CI 3.18-13.13) among transplant recipients. (n=119) [40].

One before-after study showed that 27% of patients with autoimmune disease reported local (pain at injection site) and systemic (fatigue) adverse events after a booster dose (n= 27) [41].

Certainty of Evidence

For homologous BNT162b2, two cohort studies did not adjust analysis for confounders. There was measurement outcome bias in three observational studies due to a short follow up period of 14 to 21 days post-booster and a low response rate of 30%. There was also inconsistency due to non-overlapping 95% Confidence Intervals across some studies. There was also imprecision due to the wide confidence intervals. Hence, the overall certainty of evidence was downgraded to very low.

For homologous mRNA-1273, there was imprecision for its efficacy, with observational study on effectiveness. Indirectness was also observed for immunogenicity outcomes and imprecision in the safety outcomes with wide 95% CI. Hence, overall certainty of evidence was low.

Elderly Population

BNT162b2 (Pfizer-BioNTech) homologous booster in elderly population with underlying medical conditions

Efficacy Outcomes

One cohort study reported that BNT162b2 reduced the incidence of COVID-19-related mortality (aHR 0.04, 95% CI 0.009-0.16) and COVID-19-associated hospitalization compared to no booster (aHR 0.10, 95% CI 0.04-0.24) (n=18,611) [45].

Another cohort study showed a reduction in the incidence of severe COVID-19 compared to no booster (aRR 0.07, 95% CI 0.05-0.11) (n=1,312,057) [43].

Two cohort studies showed that a booster dose reduced incidence of COVID-19 compared to no booster [(aRR 0.103, 95% CI 0.096-0.11) [45] and (aHR 0.11, 95% CI 0.07-0.15) [43]] (n= 1,330,908).

Immunogenicity Outcomes

Three before-after studies (n=201) [42, 44, 46] demonstrated increase in anti-spike antibodies after a booster shot among both COVID-naive and COVID-recovered elderly [(MD 25,028BAU/ml, 95% CI 23,912-26,144) and (MD 180BAU/ml, 95% CI 104-256), respectively]. No difference in cellular response compared to pre-booster levels (MD 2.50, 95% CI 0.65-4.35) was noted. (one before-after study, n= 47) [42].

Safety Outcomes

There were no reported serious adverse events after a homologous booster dose with BNT162b2 (2 before-after, n=203) [42, 44].

Ad26.COV2.S (Janssen) homologous booster in elderly population with underlying medical conditions

Efficacy Outcomes

An RCT compared Ad26.COV.2S (Janssen) [47] with placebo and showed no effect in the incidence of [RR 0.74 (95% CI 0.41-1.32)] and incidence of severe to critical COVID-19 [RR 0.32 (95% CI 0.02-6.23)].

Immunogenicity Outcomes

In the same study, homologous booster of Ad26.COV2.S (Janssen) showed increased anti-spike Ab GMC titer (MD 1853, 95% CI 1820-1887) compared to placebo but only a minimal increase in immunogenicity response rate (RR 1.08, 95% CI 1.02-1.15) with anti-spike Ab from baseline to post vaccination between booster vs no booster [47].

Safety Outcomes

A reduced incidence of unsolicited vaccine-related adverse events (RR 0.54, 95% CI 0.42-0.69) and hypersensitivity (RR 0.49, 95% CI 0.28-0.86) was noted [47].

Certainty of Evidence

The two studies on BNT162b2 (Pfizer-BioNTech) homologous booster did not adjust analysis for confounders, namely care-seeking behavior and comorbidities. There was also imprecision in the effect estimates of one cohort and one before-after studies. Inconsistency was also observed in immunogenicity outcomes. Indirectness was rated for immunogenicity outcomes. The resulting overall certainty of evidence was downgraded to very low.

All the outcomes from the RCT on Ad26.COV2.S (Janssen) homologous booster were rated with very low certainty of evidence due to attrition bias (20% from each arm) and indirectness (elderly comprised only 25% of the total population), and imprecision.

Heterologous Booster Vaccine

Immunocompromised Adult Population

mRNA-based Heterologous Booster in Immunocompromised Population

Only two combinations with mRNA-based boosters had results on clinical effectiveness and immunogenicity: either with ChAdOx1 (AstraZeneca) alone, and ChAdOx1/CoronaVac as primary vaccines. The evidence presented for the combination of mRNA-based booster with CoronaVac was on clinical effectiveness only, while the only outcome on safety was available with Ad26.COV2.S (Janssen) as primary vaccine. Viral vectors (ChAdOx1 or Ad26.COV2.S (Janssen) as primary vaccines to mRNA-booster only had evidence for immunogenicity. Most of the studies had small sample sizes.

mRNA-based boosters with ChAdOx1 (AstraZeneca) and CoronaVac primary series

Efficacy Outcomes

With ChAdOx1 (AstraZeneca) first dose and CoronaVac second dose primary vaccines, there was no change in risk for COVID-19 mortality (RR 0.91, 95% CI 0.09-9.68) and COVID19-related pneumonia (RR 0.46, 95% CI 0.18-1.21) when given a booster of mRNA-based vaccines, among kidney transplant recipients on immunosuppressants. In the same population, there was a reduced risk of COVID19-related hospitalization (RR 0.25, 95% CI 0.12-0.52) but an increased risk of requiring mechanical ventilation during COVID-19 infection (RR 1.47, 95% CI 1.28-1.68) (retrospective cohort, n=98) [65]. This population also has chronic illnesses such as hypertension, diabetes, ischemic heart disease and obesity.

Immunogenicity Outcomes

The mRNA-based vaccines given as booster to heterologous primary vaccines CoronaVac and ChAdOX1 increased the anti-RBD IgG titer by 32-fold (MD 2258.6BAU/ml, 95% CI 1601.16-2916.04) among individuals with solid cancer breast, colorectal head and neck [57].

Safety Outcomes

With ChAdOX1 first dose and CoronaVac second dose as primary vaccines, use of mRNA-based booster increased adverse events two-fold (RR 2.10, 95% CI 1.51-2.92) among solid cancers patients such as breast, colon, head and neck. Pain and tenderness on the injection site, myalgia and fatigue were the most common adverse events (Cohort, n=44) [57].

mRNA-based booster with ChAdOx1 (AstraZeneca) primary series

Efficacy Outcomes

With ChAdOx1 (AstraZeneca) as primary vaccine, there were no reported COVID-19-related deaths within 42 days of follow-up. In the same population, 5.5% (1/16) had mild COVID-19 infection within 178 days post-booster (before-after, n=16) [49].

Immunogenicity Outcomes

The booster with ChAdOX1 alone as primary vaccine was also tested and it increased the anti-RBD IgG titer by 58-fold (MD 2321.39BAU/ml, 95% CI 2113.32-2529.46) and the positive response of SARS-CoV-2 Spike-1 Antibody against COVID-19 compared to that pre-booster (RR 1.27, 95% CI 1.05-1.54) (2 Cohort, n=124) [57, 63]. Cellular response also increased (RR 1.33, 95% CI 1.24-1.43) among adults with SLE and rheumatoid arthritis, and those immunosuppressed individuals with hematologic malignancy, solid cancers and autoimmune diseases (2 cohort studies, n=436) [57, 63].

Safety Outcomes

Risk for mild local and systemic adverse events increased with mRNA-based heterologous booster with ChAdOX1 as primary vaccine combination (RR 2.77, 95% CI 2.09-3.68) [57].

mRNA-based booster with CoronaVac alone primary series

Efficacy Outcomes

With CoronaVac as primary vaccine, no case of COVID-19 infection was reported among individuals with inflammatory arthritis receiving biologic treatments after a 30- to 90-day follow-up (cohort, n=76) [52].

Immunogenicity and Safety Outcomes

There are no studies on immunogenicity and safety.

mRNA-based boosters with Ad26.COV2.S (Janssen) primary series

Safety Outcomes

Among liver transplant recipients who received a combination of mRNA-based vaccine booster with Ad26.COV2.S (Janssen) primary vaccine, 43% (6/14) was reported to have pain on injection site and 12% (2/14) had fatigue (cohort, n=45) [50].

Efficacy and Immunogenicity Outcomes

There are no studies on clinical effectiveness and immunogenicity.

mRNA-based boosters with viral vector ChADOx1 (AstraZeneca) or Ad26.COV2.S (Janssen) as primary

Immunogenicity Outcomes

Immunogenicity was the only reported outcome of the heterologous combination. Humoral response was increased with positive neutralizing antibodies, inhibiting more than 30% of SARS-CoV2 (RR 1.74, 95% CI 1.37-2.21). For cellular response, there was a slight increase (RR 1.17, 95% CI 1.004-1.35). Study population were adults with hematologic and solid malignancy [cohort (preprint), n=89] [64].

Efficacy and Safety Outcomes

There are no studies on clinical effectiveness and safety.

mRNA-1273 (Moderna) as heterologous booster in immunocompromised population

There were two combinations for evidence on mRNA-1273 (Moderna) as heterologous booster and these include BNT162b2 (Pfizer-BioNTech) or Ad26.COV2.S (Janssen). For the combination with BNT162b2 (Pfizer-BioNTech), there was one study on clinical effectiveness, two studies for immunogenicity and one on safety outcome of BNT162b2 (Pfizer BioNTech) or Ad26.COV2.S (Janssen).

mRNA-1273 (Moderna) booster with BNT162b2 (Pfizer-BioNTech) primary series

Efficacy Outcomes

COVID-19 infection developed among 7.9% (3/38) of individuals with multiple myeloma within 4 months from the administration of mRNA-1273 heterologous booster with BNT162b2 (Pfizer-BioNTech) as primary vaccine (before-after, n=38) [61].

Immunogenicity Outcomes

Immunogenic response to this primary-booster combination was good. The anti-RBD IgG titer increased by 58-fold (MD 22,722.8BAU/ml, 95% CI 18,541.9-26,903.7) after this mRNA-1273 heterologous booster combination among those on maintenance dialysis and active immunosuppression (cohort, n=194) [55]. These antibody titers were also increased 36-fold, from 128BAU/mL (IQR 43-1027.5) pre-booster to 4560BAU/mL (IQR 646.7-7272.5) post-booster in another study among long-term dialysis patients with comorbidities (diabetes, lung and cardiovascular disease) (before-after, n=42) [59]. Increased seroconversion (RR 1.32, 95% CI 1.11-1.57), and neutralizing antibody against COVID-19 (RR 2.72, 95% CI 2.26-3.37) were noted. However, there was only a slight increase in positive antibody response to SARS-CoV-2 spike protein (RR 1.070, 95% CI 1.02-1.13) among those on maintenance dialysis and active immunosuppression (cohort, n=194) [55].

Safety Outcomes

There are no studies on safety.

mRNA-1273 (Moderna) booster with BNT162b2 (Pfizer-BioNTech) or Ad26.COV2.S (Janssen) primary series

Safety Outcomes

No SAE was reported among liver transplant recipients with this heterologous mRNA-1273 (Moderna) booster combination (cohort, n=80) [50].

Efficacy and Immunogenicity Outcomes

There are no studies on clinical effectiveness and immunogenicity.

BNT162b2 (Pfizer-BioNTech) as heterologous booster in immunocompromised population

For BNT162b2 (Pfizer-BioNTech) as heterologous booster, the studies presented evidence on its combination with ChAdOX1 (AstraZeneca) or CoronaVac with immunogenicity as the only outcome. There were four studies for ChAdOX1 (AstraZeneca) as primary series and one cohort for CoronaVac as its primary vaccine combination. All studies were of small sample size.

BNT162b2 (Pfizer-BioNTech) booster with ChAdOX1 (AstraZeneca) primary series

Immunogenicity Outcomes

With ChAdOx1 as the primary vaccine, immunogenicity results were good. It is the most common reported outcome in the studies. Neutralizing antibody increased specifically against the SARS-CoV-2 Omicron variant (RR 31.0, 95% CI 1.92-499.2) among adults with SLE and rheumatoid arthritis (cohort, n=36) [48]. Seroconversion increased from pre- to post-booster from 33% to 47% (before-after, n=81) [62], and 41.9% to 74.8% (before-after, n=31) [58] in adults with multiple sclerosis on active immunosuppression and 62.5% to 100% among individuals on hemodialysis and comorbidities such as asthma, COPD, diabetes, hypertension, heart failure, kidney and liver disease (before-after, n=85) [53].

Efficacy and Safety Outcomes

There are no studies on clinical effectiveness and safety.

BNT162b2 (Pfizer-BioNTech) booster with CoronaVac primary series

Immunogenicity Outcomes

The combination with BNT162b2 heterologous booster to CoronaVac increased the neutralizing antibodies against SARS-CoV-2 (RR 3.94, 95% CI 2.62-5.93) among those with inflammatory mediated arthritis on biologic treatment (cohort, n=76) [52].

Efficacy and Safety Outcomes

There are no studies on clinical effectiveness and safety.

Ad26COVS1 (Janssen) as heterologous booster in immunocompromised population

The evidence on Ad26COVS1 (Janssen) as a heterologous booster was in combination with mRNA-based primary vaccines. For its combination with BNT162b2 (Pfizer-BioNTech) there were two cohort studies for clinical effectiveness and one cohort for immunogenicity. For its combination with mRNA-1273 (Moderna) or BNT162b2 (Pfizer-BioNTech) as primary vaccine, there were two cohort studies for both immunogenicity and safety. All of the studies had a very small sample size.

Ad26COVS1 (Janssen) heterologous Booster with BNT162b2 (Pfizer-BioNTech) primary series

Efficacy Outcomes

Only this combination of Ad26COVS1 (Janssen) booster with BNT162b2 as primary vaccine reported clinical outcomes. No reported cases of COVID-19 infection with this combination among individuals undergoing dialysis in a chronic in-center (Cohort, n=36) [51] and among liver transplant recipients (cohort, n=80) [50].

Immunogenicity Outcomes

With Ad26.COV2.S (Janssen) as heterologous booster to BNT162b2 (Pfizer-BioNTech) increased seroconversion (RR 1.44, 95% CI 1.16-1.79) and neutralizing antibodies against SARS-CoV-2 (RR 1.57, 95% CI 1.17-2.11) among individuals undergoing dialysis in a chronic in-center. However, the SARS-CoV-2 Spike-1 antibody response did not significantly increase (RR 1.03, 95% CI 0.89-1.19) (Cohort, n=36) [51].

Safety Outcomes

There are no studies on safety.

Ad26COVS1 (Janssen) heterologous Booster with BNT162b2 (Pfizer-BioNTech) or mRNA-1273 (Moderna) primary series

Immunogenicity Outcomes

The anti-RBD IgG titer reported results showed increased titers but these were variable in degree. Titers increased (MD 1031.33BAU/ml, 95% CI 847.94-1214.73) among adults with onco-hematological malignancies (cohort, n=29) [70] and in those receiving hemodialysis in chronic-in centers (cohort, n=36) [51].

Safety Outcomes

There was no increase in the risk of adverse events (RR 17.00, 95% CI 0.99-290.95) among liver transplant recipients on active immunosuppression and those with onco-hematological malignancies (2 cohort, n=109) [50, 70].

Efficacy Outcomes

There are no studies on clinical effectiveness.

ChAdOX1 recombinant (AstraZeneca) as heterologous booster with mRNA-based primary series

For the viral vector ChAdOX1 (AstraZeneca) as heterologous booster, one RCT presented data on immunogenicity but had a very small sample size. One cohort study with small sample size presented evidence on immunogenicity and safety.

Immunogenicity Outcomes

ChAdOX1 recombinant (AstraZeneca) booster with mRNA-based primary vaccines showed increased seroconversion (RR 20.31, 95% CI 1.24-333.47) among individuals with chronic inflammatory rheumatoid arthritis under rituximab therapy (RCT, n=20) [68]. In adults with immune-mediated inflammatory disease on rituximab and chronic illness such as hypertension, diabetes, ischemic heart, and lung disease, there was increased seroconversion (RR 45, 95% CI 2.82-717.31) and neutralizing antibodies (RR 4.2, 95% CI 1.76-10.04) (Simon, cohort, n=40) [60]. However, results for cellular response were conflicting with an increase (RR 1.33, 95% CI 1.04-1.72) in the RCT but not in the cohort.

Safety Outcomes

Adverse events were reported in 42.4% among adults with immune-mediated inflammatory disease on rituximab and chronic illness such as hypertension, diabetes, ischemic heart, and lung disease who received a combination of ChAdOX1 recombinant (AstraZeneca) booster with mRNA-based primary vaccines (cohort, n=66) [60]. The common adverse events reported were fatigue, pain on injection site, headache, and myalgia.

Efficacy Outcomes

There are no studies on clinical effectiveness.

Viral Vector (ChAdOX1 recombinant AstraZeneca or Ad26COVS1 Janssen) as heterologous booster with mRNA-based primary series

Immunogenicity Outcomes

For the viral vector booster and mRNA-based vaccine combination, anti-RBD increased by 20 fold form 5.9BAU/ml to 119BAU/ml post-booster and seroconversion reported in 16.7% (8/48) among kidney transplant recipients with active immunosuppression (before-after, n=48) [54].

Efficacy and Safety Outcomes

There are no studies on clinical effectiveness and safety.

Certainty of Evidence

Among the immunocompromised population, the sample size of the studies were mostly small with 15 of these studies having a sample size of 100 or less. This resulted in imprecision in clinical outcomes such as COVID-19-related mortality, severe infection and pneumonia; for serious adverse events under safety outcomes and certain parameters for immunogenicity. Two of the studies with larger sample sizes were retrospective. There were two cohorts and one before-after study that did not indicate possible co-morbidities of the participants. One cohort gathered data on adverse effects via a questionnaire with the details on questionnaire content, validation, and manner of administration not indicated. In general, the participants of the different studies have varying co-morbidities and treatments (biologic therapy, immunosuppressants, antihypertensive and antidiabetics). There were three cohort and two before-after studies that did subgroup analysis according to co-morbidity (e.g. severity of multiple myeloma), as well as treatment and type of immunosuppressants received.

Generally, the certainty of evidence for the clinical and safety outcomes were graded as very low attributed to the serious risk of bias and imprecision. For the evidence on immunogenicity these were graded as very low due to serious risk for bias, indirectness, and imprecision. The certainty of evidence for the sole RCT on immunogenicity was rated as low for indirectness and imprecision.

mRNA-based [(BNT162b2 (Pfizer-BioNTech) or mRNA-1273 (Moderna)] homologous/heterologous booster to mRNA-based primary series in immunocompromised population

In one case-control study, mRNA-based booster showed reduction in the odds of COVID-19 associated hospitalization compared with no booster (aOR 0.40, 95% CI 0.36-0.46). Certainty of evidence was low (VISION) [72]. There were no immunogenic or safety outcome data reported in the study.

Certainty of Evidence

For this case-control study (VISION), other infectious diseases may present with COVID-19-like illness other than COVID-19 although those with clinical symptoms-related to COVID-19 infection were tested by PCR. However, PCR testing was only done among those who presented with clinical symptoms.

For homologous or heterologous monovalent mRNA booster with mRNA-based primary, certainty of evidence rated low due to indirectness.

Elderly Population

mRNA-based Heterologous Booster in elderly with underlying medical conditions

mRNA-based Booster with ChAdOX1 (AstraZeneca)

Efficacy Outcomes

The monovalent mRNA-based heterologous booster with ChAdOx1 as primary series decreased the risk for COVID-19-related mortality (RR 0.00871, 95% CI 0.007-0.011), severe COVID-19 infection (RR 0.0205, 95% CI 0.018-0.023), and COVID-19 infection (RR 0.091, 95% CI 0.090-0.093) among elderly individuals (retrospective cohort, n=7,685,672) [69].

Immunogenicity and Safety Outcomes

There are no studies on immunogenicity and safety.

mRNA-based Booster with BNT162b2 or mRNA-1273 or ChAdOx1 Oxford-AstraZeneca or Ad26CoV2.S (Janssen)

Efficacy Outcomes

In one cohort study, there was reduced risk of COVID-19-related hospitalization (RR 0.81, 95% CI 0.75-0.88) and ICU admission (RR 0.72, 95% CI 0.57-0.92) and increased risk for COVID-19 infection (RR 1.19, 95% CI 1.13-1.25) (cohort, n=165,453) [3] among adults with heart failure or having chronic illnesses compared to no booster.

Immunogenicity and Safety Outcomes

There are no studies on immunogenicity and safety.

BNT162b2 Heterologous booster in elderly with underlying medical conditions

BNT162b2 booster with CoronaVac primary series

Immunogenicity Outcomes

With BNT162b2 booster and CoronaVac primary vaccine there is a 32-fold rise in anti-RBD IgG titer. The median pre-booster concentration of anti-RBD antibodies was 77.7BAU/mL (IQR 42.9-12.3 BAU/mL) which increased to 2493.0BAU/mL (IQR 1272.3-4328.5) post-booster. Subjects were elderly healthcare workers with chronic comorbidity such as cardiovascular, metabolic, and respiratory illness. Positive neutralizing antibodies (detected as 30% or more inhibition of SARS-CoV2) at 28 days post-booster was noted in 54.5% to 100% of elderly healthcare workers with chronic illness with BNT162b2 booster from 13.7% to 53.4% pre-booster with CoronaVac as primary vaccine (before-after study, n=46) [56].

Efficacy and Safety Outcomes

There are no studies on clinical effectiveness and safety.

BNT162b2 (Pfizer-BioNTech) Booster with mRNA-1273 (Moderna) primary series

Safety Outcomes

Among individuals 70 years old and above in long-term care facilities, with BNT162b2 as booster and mRNA-1273 primary vaccine combination, no serious adverse events (SAE) was reported (cohort, n=183)

[67]. About 6% (3/52) of those who received BNT162b2 booster developed adverse effects, commonly fever and malaise.

Efficacy and Safety Outcomes
There are no studies on clinical effectiveness and immunogenicity.

mRNA-1273 Heterologous Booster in elderly with underlying medical conditions

mRNA-1273 Booster with mRNA-1273 (Moderna) 1st dose and BNT162b2 (Pfizer- BioNTech) 2nd dose
Safety Outcomes
Among individuals 70 years old and above in long-term care facilities who received monovalent mRNA-1273 (Moderna) booster with mRNA-1273 (Moderna) first dose and BNT162b2 (Pfizer-BioNTech) second dose as primary vaccine combination, there was no serious adverse events (SAE) reported post-booster (cohort, n=183) [67].

Efficacy and Safety Outcomes
There are no studies on clinical effectiveness and immunogenicity.

mRNA-1273 Booster with BNT162b2 (Pfizer-BioNTech) primary series
Safety Outcomes
Among the subjects who received monovalent mRNA-1273 (Moderna) booster and BNT162b2 (Pfizer-BioNTech) as primary vaccines, 28.96% (53/183) developed systemic adverse effects commonly fever, GI symptoms, tachycardia, and malaise [67].

Efficacy and Safety Outcomes
There are no studies on clinical effectiveness and immunogenicity.

ChAdOx-1 Heterologous Booster in elderly with underlying medical conditions

ChAdOx-1 Booster with CoronaVac primary series
Immunogenicity Outcomes
The anti-RBD IgG titer increased 10-fold among those given ChAdOx-1 booster and CoronaVac primary vaccine combination among elderly healthcare workers with chronic illness such as cardiovascular, metabolic, and respiratory disease. The median concentration of anti-RBD antibodies increased from 77.7BAU/mL (IQR 42.9-12.3 BAU/mL) prior to booster to 771.0BAU/mL (IQR 593.8-1344.8) post-booster. Neutralizing antibodies were also described to be present in 41.7% to 100% post-booster and 5.2% to 52.8% prior to booster (before-after study, n=46) [56].

Efficacy and Safety Outcomes
There are no studies on clinical effectiveness and safety.

Certainty of Evidence
In the elderly population, there were two studies that presented evidence on clinical outcomes and one on immunogenicity. For the evidence on clinical outcome, the largest is a retrospective cohort among 60 years old and above individuals who received [69]. Their data was obtained from the Korean Disease Control and Prevention Agency integrated database. The other study was a cohort which involved older adults, 70-years old and above, residing in a long-term care facility (n=183) [67]. This cohort study also did an analysis comparing the risk of adverse events among those with and without prior COVID19 infection. A cohort study among individuals with chronic heart failure (n=165,453) compared clinical effectiveness between those with and without booster [3]. In this study the participants had comparable comorbidities and chronic illness. One before-after study with small sample size (n=46) presented the evidence on immunogenicity among

healthcare workers 60 years old above [56]. For the cohort studies, comorbidities of participants were not indicated.

Generally, the certainty of evidence for the clinical outcome as well as safety outcomes were graded as low to very low attributed to the serious risk of bias and imprecision. The evidence on immunogenicity was graded as very low due to serious risk for bias, indirectness, and imprecision.

Homologous/ Heterologous mRNA-based Booster with mRNA-based primary series vaccine

Efficacy Outcomes

One case-control study [72] showed that it reduced odds of COVID-19 associated hospitalization compared to no booster (aOR 0.58, 95% CI 0.46-0.73). Certainty of evidence was low.

Immunogenicity and Safety Outcomes

There are no studies on immunogenicity and safety.

Certainty of Evidence

For the case-control study [72], other infectious diseases may present with COVID-19-like illness other than COVID-19 although those with clinical symptoms-related to COVID-19 infection were tested by PCR. However, testing was only done if clinical symptoms were present.

For homologous or heterologous monovalent mRNA booster with mRNA-based primary, certainty of evidence rated low due to indirectness.

RECOMMENDATIONS FROM OTHER GROUPS

Table 1. Summary of Recommendations from Other Groups

Group / Agency	Recommendation	Strength of Recommendation
WHO As of Aug 18, 2022 [73]	Recommends mRNA-1273 or BNT162b2 as either as homologous or heterologous booster 4 to 6 months after primary vaccination series. In line with the WHO Prioritization Roadmap, and the WHO Values Framework, older adults, health workers and immunocompromised persons should be prioritized.	Strong
DOH, HTAC As of April 21, 2022 [74]	Recommends mRNa-1273, BNT162b2, ChAdOx1-S (recombinant), AstraZeneca, CoronaVac, Sinopharm as fourth dose at least 3 months after the third dose in immunocompromised population at least 18 years of age.	Strong
WHO [73] 1. updated June 13, 2022 2. updated Sept 28, 2022	Recommends the following vaccines as homologous booster dose 4 to 6 months after primary vaccination series: 1. Oxford/AstraZeneca (ChAdOx1-S recombinant) 2. Novavax NVX-CoV2373 (Trade name in India) NVX-CoV2373 Nuvaxovid (Trade name in Europe) In line with the WHO Prioritization Roadmap, and the WHO Values Framework, older adults, health workers and immunocompromised persons should be prioritized.	Strong
WHO As of June 10, 2022 [73]	Recommends the following vaccines either as homologous or heterologous booster 4 to 6 months after primary vaccination series 1. Sinovac-Corona Vac 2. Sinopharm	Strong

	3. Bharat Biotech BBV152 COVAXIN 4. CanSino Biologics Ad5-nCoV-S (recombinant) vaccines In line with the WHO Prioritization Roadmap, and the WHO Values Framework, older adults, health workers and immunocompromised persons should be prioritized.	
US-CDC As of Dec 22, 2022 [75] European CDC and European Medicines Agency As of updated Sept 6, 2022 [76]	Recommends the following vaccines as homologous or heterologous booster at least 2 months after primary series or last booster: 1. bivalent mRNA-1273 (Moderna) 2. bivalent BNT162b2 (Pfizer-BioNTech)	Strong
US-CDC As of Jan 27, 2023 [75]	Recommends Janssen/J&J at least 2 months after primary series as homologous or heterologous booster if - with contraindication to mRNA and Novavax vaccine dose (ex. severe allergic reaction to previous dose) - with limited access to other COVID-19 vaccines - those who prefer it despite safety concerns (risk of thrombosis with thrombocytopenia syndrome)	Strong

ONGOING STUDIES AND RESEARCH GAPS

We identified 26 ongoing registered studies, evaluating the efficacy, effectiveness, and safety of COVID-19 vaccines as boosters. (Appendix 7)

ADDITIONAL CONSIDERATIONS FOR EVIDENCE TO DECISION (ETD) PHASE

COST

The government estimated that it would spend an average cost of around PHP 1,300.00 per person for the country's vaccination program, to include the 2-dose vaccine cost and ancillaries. [77]

There is no cost-effectiveness analysis on implementation of a vaccination program in the Philippines. [78]

PATIENT'S VALUES AND PREFERENCE, EQUITY, ACCEPTABILITY, AND FEASIBILITY

A survey on COVID-19 vaccine brand hesitancy [79] and other challenges to vaccination in the Philippines was conducted early during the pandemic from July to August 2021 involving 1,599 respondents 18 years and older with representation from different vaccination priority groups working in various parts of the country. They had different educational backgrounds, employment status, and vaccination attitude. Vaccine hesitancy was attributed to beliefs about vaccine safety and effectiveness, negative vaccine-related experiences, the need for other measures to protect them from COVID-19 infection, vaccines not yet being fully approved by the Food and Drug Administration (FDA), misinformation about COVID-19 vaccines.

Furthermore, inadequate supply of vaccines perceived inefficient system and logistical challenges affected feasibility of vaccination even to those who believed that the vaccine protects them from severe illness, hospitalization, and death, and that vaccines only have minimal risk [79]. In another survey of unvaccinated individuals conducted from April to May 2021 [80], mostly involving 18 to 25 years of age (n= 565, 70.3%), the majority were willing to accept COVID-19 vaccine. For those who refused, safety was their main concern. Majority (n=384, 68%) were willing to pay PHP up to 2,000 if there is such provision [80].

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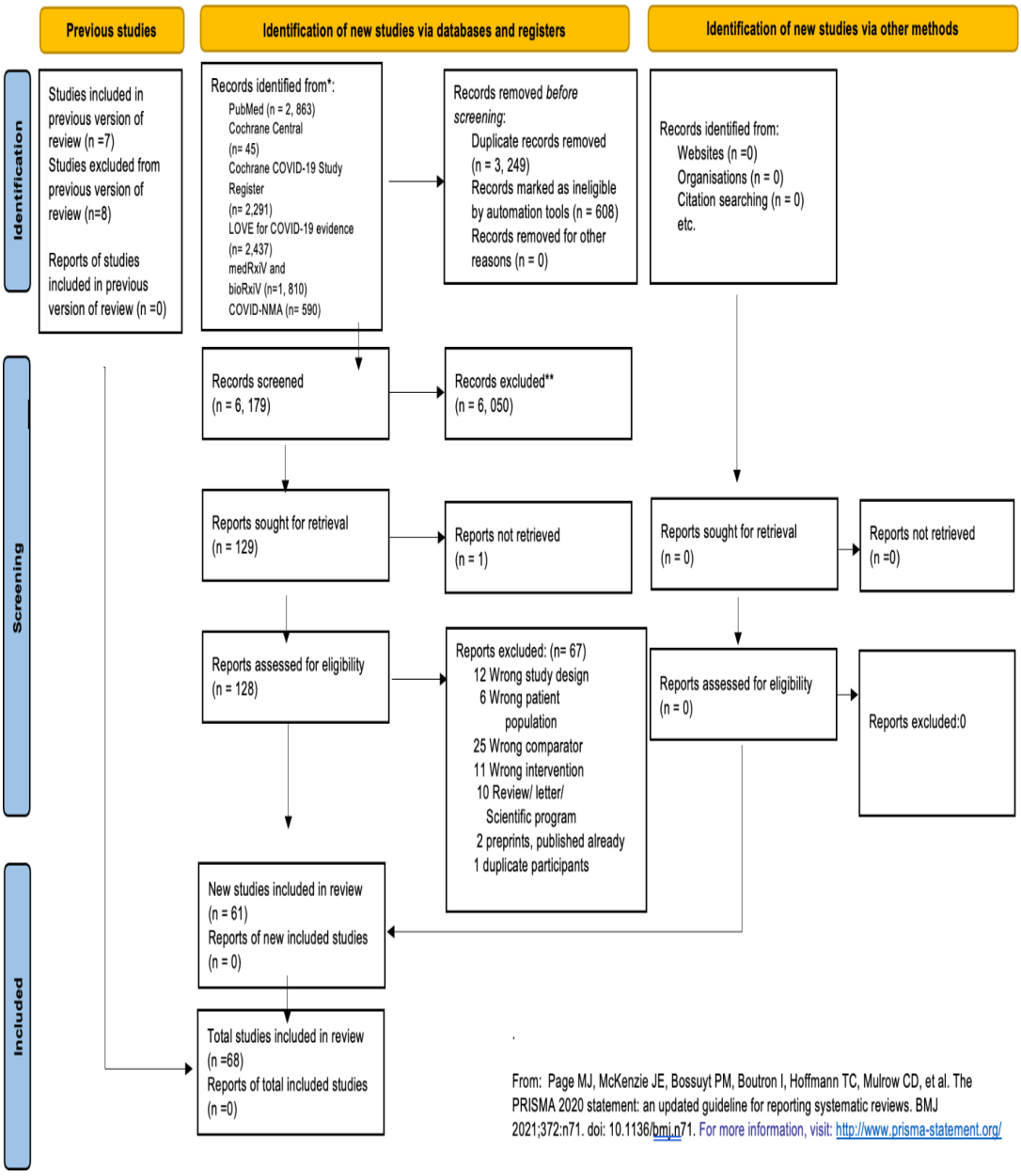
Appendix 1: Preliminary Evidence to Decision

Table 2. Summary of initial judgements prior to the panel discussion (N=7/10)

FACTORS	JUDGEMENT							RESEARCH EVIDENCE/ADDITIONAL CONSIDERATIONS
Problem	No		Yes (7)	Varies	Uncertain			
Benefits	Large (2)		Moderate (5)	Small	Trivial	Varies	Uncertain	
Harm	Large (1)		Moderate (1)	Small (5)	Trivial	Varies	Uncertain	
Certainty of Evidence	High		Moderate (1)	Low (4)	Very low (2)			
Balance of effects	Favors vaccination (2)		Probably favors vaccination (5)	Does not favor vaccination	Probably favors no vaccination	Favors no intervention	Varies	
Values	Important uncertainty or variability (1)		Possibly important uncertainty or variability (5)	Possibly NO important uncertainty or variability (1)	No important uncertainty or variability			A survey on COVID vaccine brand hesitancy [79] and other challenges to vaccination in the Philippines was conducted early during the pandemic from July to August 2021 involving 1,599 respondents 18 years and older with representation from different vaccination priority groups working in various parts of the country. Vaccine hesitancy was attributed to beliefs about vaccine safety and effectiveness, negative vaccine-related experiences, the need for other measures to protect them from COVID-19 infection, vaccines not yet being fully approved by the Food and Drug Administration (FDA), misinformation about COVID-19 vaccines.
Resources Required	Don't know (1)	Varies	Large cost (4)	Moderate cost (2)	Negligible cost or savings	Moderate savings	Large savings	Inadequate supply of vaccines perceived inefficient system and logistical challenges affected feasibility of vaccination even to those who believed that the vaccine

								protects them from severe illness, hospitalization, and death, and that vaccines only have minimal risk [79]. In another survey of unvaccinated individuals conducted from April to May 2021 [80], mostly involving 18 to 25 years of age (n= 565, 70.3%), the majority were willing to accept COVID-19 vaccine. For those who refused, safety was their main concern. Majority (n= 384, 68%) were willing to pay PHP up to 2,000 if there is such provision [80].
Certainty of evidence of required resources	No included studies (5)		Very low	Low (1)	Moderate (1)	High		
Cost effectiveness	No included studies (3)	Varies	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention (4)	Favors the intervention	The government estimated that it would spend an average cost of around PHP 1,300.00 per person for the country's vaccination program, to include the 2-dose vaccine cost and ancillaries [77]. There is no cost-effectiveness analysis on implementation of a vaccination program in the Philippines [78].
Equity	Uncertain (1)	Varies (2)	Reduced	Probably reduced (1)	Probably no impact	Probably increased (3)	Increased	
Acceptability	Don't know		Varies (2)	No (1)	Probably no	Probably yes (2)	Yes (1)	
Feasibility	Don't know		Varies (1)	No (2)	Probably no	Probably yes (1)	Yes (3)	

Appendix 2: PRISMA flow diagram



From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n71. For more information, visit: http://www.prisma-statement.org/

Appendix 3: Characteristics of Included Studies

Table 3. Characteristics of included studies (n=66)

Author	Study Design	Country	n	Population	Intervention	Control	Outcome
HOMOLOGOUS BOOSTER- IMMUNOCOMPROMISED							
Abid (A) Published April 2022	Before-after	USA	43	alloHCT (hematopoietic cell transplantation) -had not seroconverted after dose 2 per the assay cut-off 31-81 y/o	BNT162b2 booster 172 (28-296)	Self, homologous 2nd dose	Immunogenicity, humoral seroconversion rate (anti-spike-receptor-binding domain (RBD) IgG median 58 days (IQR 14-140)
Abid (B) Published April 2022	Before-after	USA	23	alloHCT (hematopoietic cell transplantation) -had not seroconverted after dose 2 per the assay cut-off 31-81 y/o	mRNA1273 booster 172 (28-296)	Self, homologous 2nd dose	Immunogenicity, humoral seroconversion rate (anti-spike-receptor-binding domain (RBD) IgG median 58 days (IQR 14-140)
Avivi Published Jan 2022	Before-after study	Israel	44	Patients with B-cell non-Hodgkin lymphoma (B-NHL) who failed to respond to two consecutive vaccine and were not currently treated with an induction/salvage chemo-immunotherapy median age 66 IQR (55-73) n=44	BNT162b2 booster 174 (168-188)	Self, BNT162b2 2nd dose	Immunogenicity, humoral Seroconversion rate (50 AU/ml) anti- spike (S) Receptor Binding Domain (RBD) IgG 61 days
Bajwa Published March 2022	Multi-center Before-after	Denmark USA	53	Multiple Sclerosis on anti-CD20 on ocrelizumab therapy median age 47 years (range 24 - 67 years)	BNT162b2 booster 150	Self, homologous 2nd dose	Immunogenicity, humoral anti-spike-RBD IgG B lymphocyte enumeration cellular T-lymphocyte enumeration 28 days
Balsby Published April 2022	Before-after	Denmark	335	Solid-organ transplant recipients median age 58.2 years (IQR, 48.0–66.9)	BNT162b2 booster 231 (201–241)	Self, homologous 2nd dose	COVID-19 Immunogenicity, humoral anti-spike S1-RBD IgG (cut-off of 7.1 BAU/mL) 52 days
Beiber Published March 2022	Cohort	Israel	100,578	Acute rheumatic disease, RA, SLE, psoriatic arthritis, systemic sclerosis >18 y/o	BNT162b2 booster (6 mo)	No booster, Received 2 homologous doses	COVID-related mortality Hospitalization 35 days
Beilhack Published June 2022	Before-after	Austria	27	Adult peritoneal dialysis (PD) patients mean age 54.3 years (range 33–76) with a median dialysis vintage of 13.4 months (IQR 5.25–30.6 months)	mRNA-1273 booster (6 months)	Self, homologous 2nd dose	Immunogenicity, humoral anti-spike RBD IgG 28 days Adverse events 7 days

Benning Published March 2022	multi-center, Before-after study	German y	84	Hemodialysis patients Median (IQR) age of hemodialysis patients was 72 (62–79) years Dialysis vintage was a median of 46.3 (14.8–89.3) months	BNT162b2 Booster [median (IQR) of 119 (109-165) days]	Self, homologous 2nd dose	Immunogenicity, humoral anti-spike RBD IgG 21 days COVID-19 Adverse Events 7 days
Bensouna Published Previous ES Sept 2021	Before-after Questionnaire	France	69	Peritoneal / hemodialysis patients median age 68 years [interquartile range (IQR), 53-76 years]	BNT162b2 booster 50 (IQR, 31-58) day	Self, BNT162b2 2nd dose	Immunogenicity, humoral anti- spike total Ig Ab (including IgG, IgM, and IgA) Immunogenicity, cellular 21 days Adverse events 30 days
Broseta Published (A) March 2022	Multicenter Before-after	Spain	71	Hemodialysis patients median age of 72.12 ± 14.44 years	BNT162b2booster (6 mo)	Self, homologous 2nd dose	Severe COVID-19 Asymptomatic COVID-19 Immunogenicity, humoral - Anti-S1-RBD IgG Immunogenicity, cellular 21 days
Broseta Published (B) March 2022	Multicenter Before-after	Spain	82	Hemodialysis patients median age of 72.12 ± 14.44 years	mRNA-1273booster (6 mo)	Self, homologous 2nd dose	Severe COVID-19 Asymptomatic COVID-19 Immunogenicity, humoral - Anti-S1-RBD IgG Immunogenicity, cellular 21 days
Bensouna Published Previous ES Sept 2021	Before-after Questionnaire	France	69	Peritoneal / hemodialysis patients median age 68 years [interquartile range (IQR), 53-76 years	BNT162b2 booster 50 (IQR, 31-58) days	Self, BNT162b2 2nd dose	Immunogenicity, humoral anti- spike total Ig Ab (including IgG, IgM, and IgA) Immunogenicity, cellular 21 days Adverse events 30 days
Chavarot Published Previous ES Aug 2021	before-after study	France	181	Kidney transplant recipients median age (63.5 years IQR [51–72] N=62	BNT162b2 booster (median 69.5 days, IQR 40-84 days)	Self, BNT162b2 2nd dose	Immunogenicity, humoral Anti-spike RBD IgG Median 28 days COVID-19 related mortality Severe COVID-19 Symptomatic COVID-19 Median 44 days
David Published 2021 Previous ES	Cross sectional descriptive	Israel	3,195	Immunocompromised Solid organ transplant/ cancer/immunosuppressive therapy	BNT162b2 booster	NA	Safety 7 days

Dekervel Published Aug 2021	Before-after study	France	66	On maintenance hemodialysis a.systematic cohort-regardless of humoral response after dose 2 (n=66) b.conditional cohort-no or low response after dose 2 (n=34)	BNT162b2 booster 60 days (IQR 55–97)	Self, homologous 2nd dose	Immunogenicity, humoral anti-S RBD IgG SAE 28 days
Del Bello Published 2022 (Previous ES)	Before-after	France	396 (101 were included in Kamar study)	Solid organ transplants (mean age 59 ± 15 years	BNT162b2 booster [59 days (IQR 25-75 47-67)]	Self, homologous 2nd dose	Immunogenicitiy, humoral Anti-SARS-spike RBD Ab SAE
Di Noia Published Feb 2022	Multi-center Before-after	Italy	407	Solid cancer- breast/ lung median age was 67 (range 24-89) years. Breast cancer (28.5%) and lung cancer (19.9%) were the most common tumor subtypes	BNT162b2 booster (4-6 months)	Self, homologous 2nd dose	Immunogenicity, humoral Anti-spike IgG GMT SAE AE 28 days
Diamantopoulos Published Oct 2022	multi-center Before-after	Greece	39	Adult patients with Chronic lymphocytic leukemia	BNT162b2 booster (median 5.6 mo (2- 7.7)	Self, homologous 2nd dose	Immunogenicity, humoral anti-spike RBD IgG 21 days
Dreyer-Alster Published Jan 2022	Before-after /Questionnaire for safety	Israel	211-safety 55-immunogenicity	Multiple sclerosis mean ± SD age 51.5 ± 13.0 years	BNT162b2 booster (>/= 6 mo)	Self, homologous 2nd dose	Immunogenicity, humoral anti-spike RBD IgG SAE Median 66 days (IQR 54-84)
Ducloux Published Previous ES June 2021	Before-after	France	45	Dialysis patients (COVID-naïve) n=45	BNT162b2booster	Self, homologous 2nd dose	Immunogenicity, humoral anti-spike RBD Ab 28 days
Gianserra Published Aug 2022	Before-after Safety passive reporting	Italy	42	HIV patients median age was 53 years (IQR: 48–61)	BNT162b2booster (median of 5.5 months)	Self, homologous 2nd dose	COVID-19 Immunogenicity, humoral anti-spike RBD IgG Immunogenicity, cellular CD4+, CD8+ 28 days SAE 14 days
Goggins Preprint May 2022	Before-after	USA	27	Dialysis patients	BNT162b2booster (6 mo)	Self, homologous 2nd dose	Immunogenicity, humoral anti-spike RBD IgG 14 days
Gressens Published March 2022	Before-after	France	78	Patients with lymphoid malignancies	BNT162b2booster (70 days (IQR 47-87)	Self, homologous 2nd dose	Immunogenicity, humoral anti-spike RBD IgG

Hall Published Previous ES Aug 2021	RCT	Canada	120	Transplant recipients, COVID-naïve median age of the patients was 66.6 years (inter- quartile range, 63.3 to 71.4)	mRNA-1273booster (2 mo)	Placebo	COVID-19 Immunogenicity, humoral anti-RBD IgG surrogate virus neutralization assay Immunogenicity, cellular T-cell response SAE 120 days
Herishanu Published Feb 2022	Multi-center, Before-after	Israel	172	Patients with chronic lymphocytic leukemia, small lymphocytic lymphoma- non-responders to. 2 doses median age was 72.1 years (IQR, 68.1-77.7),	BNT162b2booster [median 175 days (IQR 171-178)]	Self, homologous 2nd dose	COVID-19-related mortality Severe COVID-19 COVID-19 Immunogenicity, humoral anti S-RBD IgG 21 days AE 7 days
Hod Published March 2022	Before-after And Cross-Sectional descriptive	Israel	99	Renal transplant recipients Median age was 66 years (IQR, 53–73)	BNT162b2booster Median 175 days (IQR 171-178)	Self, homologous 2nd dose	COVID-19-related mortality Severe COVID-19 COVID-19 Immunogenicity, humoral geometric mean titers (GMTs) for RBD IgG and NA AE 28 days
John Published 2022	Cohort	USA	12,978 13,104	Patients with liver cirrhosis	BNT162b2booster (6 mo) mRNA1273booster (6 mo)	No booster Received 2 doses of homologous vaccine	COVID-19-related death Moderate/severe/critical Symptomatic COVID-19 14 days
Peled Published Previous ES Feb 2022	Before-after	Israel	96	Heart transplant recipients aged 61.0 [49.8, 68.0] years	BNT162b2Booster 168 (+/- 18 days)	Self, homologous 2nd dose	COVId-19 Immunogenicity, humoral anti (RBD) IgG neutralizing antibodies Immunogenicity, cellular T-cell AE 18 days
Re Preprint Feb 2022	Before-after	France	43	Patients with hematological (lymphoid)malignancies Median 77 years [range: 37-92]	BNT162b2 booster 78 days [range: 47-114]	Self, homologous 2nd dose	Immunogenicity, humoral Anti-S Ab Immunogenicity, cellular T-cell responses AE 35 days

Saiag Published Feb 2022	Before-after	Israel	279	Immunosuppressed 124 (44.4%) had hematological malignancies, 57 (20.4%) had rheumatologic diseases, and 98 (35.1%) were solid organ-transplant recipients. median age was 69 years	BNT162b2booster	Self, homologous 2nd dose	Immunogenicity, humoral Anti-S RBD IgG 28 days
Shashar Published April 2022	Cohort	Israel	88	Patients on maintenance hemodialysis median age 72.7 years (range 24.8–94.3) years.	BNT162b2booster (6 mo)	No booster, Received 2 doses of homologous vaccine	Immunogenicity, humoral IgG AE
Shaul Published Feb 2022	Before-after	Israel	42	Heart transplant recipients On standard immunosuppressive therapy median age was 65 years [interquartile range (IQR) 58–70]	BNT162b2booster (6 mo)	Self, homologous 2nd dose	COVID-19 Immunogenicity, humoral anti-spike IgG AE 28 days
Shehab Published July 2022	Cohort	Kuwait	162	Patients with Inflammatory Bowel Disease on immunosuppressive therapies (infliximab combination) Mean age-35 y/o	BNT162b2Booster (6 mo)	No booster, Received 2 doses of BNT162b2	Immunogenicity, humoral IgG Neutralizing Ab Safety 91 days
Speer Published April 2022	Multi-center Before-after	Germany	21	antineutrophil cytoplasmic antibodies (ANCA)-associated vasculitis (AAV) on immunosuppressive maintenance therapy median age 71 (59-74)???	BNT162b2booster (median (IQR) of 103 (72–126) days)	Self, homologous 2nd dose	Immunogenicity, humoral anti-Spike IgG surrogate neutralizing Ab Safety 21 days
Suso Publishel Jan 2022	Before-after study	Czech Republic	80	With hematological malignancies, COVID-naïve, low responders or non-responders after dose 2, without active treatment	BNT162b2booster (3 mo)	Self, homologous 2nd dose	Immunogenicity, humoral IgG, IgM and IgA anti-S1/S2 Ab neutralizing antibodies 21 days
Terpos Published March 2022	Before-after	Greece	167	Patients with active Multiple Myeloma Dexamethasone administration was held from 2 weeks before until 1 week after each vaccine injection. -receiving anti-myeloma treatment median age, 68 years; IQR, 60-75 years	BNT162b2booster	Self, homoloogus 2nd dose	Immunogenicity, humoral Neutralizing Ab 28 days

Verdier Published 2022	Before-after	Fran ce	97	Hemodialysis patients Mean 71.1 y/o n=124 COVID negative	BNT162b2bo oster (2 mo) n=97	Self, homologou s 2nd dose n=111	Immunogenicity, humoral Anti–spike (S1) IgG AE 35 days
HOMOLOGOUS BOOSTER- ELDERLY							
Alidjinou Published June 2022	Before-after study	Franc e	106	Nursing home residents, majority with hypertension, coronary heart disease 68-98 y/o median IQR 86.5 (81-91)	BNT162b2 booster >/= 180	Self, homologous 2nd dose	COVID-19 Immunogenicity, humoral - Anti spike SARS-CoV-2 IgG - Serum neutralizing Ab against delta and omicron variants cellular -S1 domain reactive T cell counts Safety 150 days
Bar-on Published Dec 2021	Cohort	Israel		>/= 60 y/o	BNT162b2 booster (>/= 5 months)	No booster, Received 2 homologous doses	COVID-19- related mortality Severe COVID-19 42 days
Eliakim-Raz Published Dec 2021	Before-after	Israel	97	>/=60 y/o median age was 70 years (IQR, 67-74)	BNT162b2boos ter >/= 6 mo	Self,homolo gous 2nd dose	Immunogenicity, humoral anti-spike RBD IgG SAE
Muhsen Published July 2022	Cohort	Israel	18, 611	Residents of long-term care facilities 60 years and older mean (SD) age was 81.1 (9.2) years	BNT162b2bo oster (5 mo)	No booster, Received 2 doses of homologous vaccine	COVID-19-related mortality COVID-19 hospitalization COVID-19 Median 66 days (IQR 60-70)
Vanshylla Published April 2022	Before-after	Germa ny	37	Older adults median age of 82 years (range 76–96)	BNT162b2bo oster[(media n 209 days [IQR 189–228]	Self,homolo gous 2nd dose	Immunogenicity, humoral neutralising Ab geometric mean 50% inhibitory serum dilutions (ID50) against the Wu01 vaccine strain as well as the delta (B.1.617.2) and omicron variants (BA.1) median 106 days (IQR 86-125)
Hardt Published 2022 (ENSEM BLE2)	RCT	Belgium, Brazil, Colombi a, France, Germany, the Philippin es, South Africa, Spain, the UK, and the USA	n=11, 639	COVID-naïve from public and private hospitals -healthy or with stable and well-controlled comorbidities -well controlled HIV Median age 50 (IQR 40, 60) 25% were >/= 60 y/o 25% had BMI >/= 30 (obese) 36.7% had 1 or more baseline comorbidities	Ad26.COV2.S as a primary dose plus a booster dose at 2 months n=7,484 per protocol n=6,024 assessed not assessed= 1,460 (19.50%)	two placebo injections 2 months apart n=7,008 per protocol n=5615 assessed not assessed=1, 393 (19.88%)	RT-PCR-confirmed moderate to severe-critical COVID-19 (onset at least 14 days after booster vaccination) Asymptomatic COVID-19 COVID-19 requiring medical intervention Mild COVID-19 Safety Reactogenicity: solicited local and systemic AE (n=6,067

							randomly selected)-7days Unsolicited AE- 28 days ffup Medically attended adverse events (6 mo ff up) Immunogenicity (200 from vaccine and 200 from placebo) -spike specific GM concentrations
HETEROLOGOUS BOOSTER							
Bonelli Published (Sept 2021) Included in the previous LCPG2	RCT	Vienna, Austria	41	adults (18 years) with chronic-inflammatory rheumatic or neurologic diseases under current rituximab therapy and without detectable SARS-CoV-2 spike protein antibodies with concomitant DMARDs and anti-inflammatory agent	vector COVID-19 vaccine (ChAdOx1 nCoV-19) possibly > 2 months from 2nd primary dose n = 21 BNT162b2(Primary)/ vector COVID-19 vaccine (ChAdOx1 nCoV-19) (booster) n = 6 mRNA-12730 (Primary)/ ChAdOx1 nCoV-19) (booster))	mRNA vaccine (BNT162b2 or mRNA-12730 2 doses given 28 days apart	PRIMARY STUDY ENDPOINT: difference in antibody seroconversion rates between the vector and mRNA vaccinated groups SECONDARY ENDPOINTS: (1) serocon-version rate (2) SARS- CoV-2 antibody levels at week 4 overall - stratified for patients with and without detectable peripheral B cells as well as cellular immune response defined by T lymphocyte restimulation potential before and 1week after vaccination (3) adverse events
Chauhan Published (January 2022)	Prospective cohort	Baltimore, USA	80	Liver transplant (LT) patients (n = 45) those with chronic liver disease (CLD) with (n = 18) or without cirrhosis (n = 17) who had poor antibody response to SARS-CoV-2 spike protein Patients were on varying immunos-uppressants mean (± SD) age = 64.1 (10.6) Liver transplant n = 45 Cirrhosis n = 18 Other liver etiologies n = 17	mRNA (Pfizer/Moderna) or Johnson & Johnson (JnJ) vaccine given at median of 138.5 days after completion of standard regimen Booster vaccine received: 47/80 (59%) with Pfizer 27/80 (34%) Moderna 6/80 (7%) JnJ vaccine	Self, 2nd dose Pfizer(I)/Moderna (n = 9) Pfizer/JnJ (n =1) Moderna/Pfizer (n = 6) Moderna/JnJ (n = 4) JnJ/Pfizer (n =10) JnJ/Moderna (n =4)	PRIMARY OUTCOME Receptor binding domain IgG to SAR-CoV-2 spike protein measured after a median of 28 days from booster vaccination. Titers ≥250 U/mL -positive; <0.8 U/mL - negative SECONDARY OUTCOME report of adverse events

Davidovic Published (June 2022)	Prospective Cohort	Austria	36	Chronic in-center hemodialysis patients mean age (SD) 66.9 (15.9) years Females 12 (33%) Males 24 (66.7%) with a median dialysis vintage of 35 months (IQR 17.3–62.0 months)	Janssen vector vaccine Ad26COVS1 given 8 months after 2nd dose	Self after mRNA – BNT162b2 2nd dose given 4 weeks apart	PRIMARY OUTCOME humoral response assessed by quantifying anti-SARS-COV-2 spike IgG antibody and neutralizing antibody concentrations Cellular immune response evaluated by SARS-COV-2 spike specific interferon-gamma release assay SECONDARY OUTCOME: incidence COVID19 infection confirmed by symptoms and PCR
Duran Published (April 2022)	Prospective cohort	Chile	76	inflammatory arthritis (IA) patients with biologic treatments anti-TNF, anti-IL6 or anti-IL17 Mean age was 51.9 (SD 11.3) Mean years since diagnosis were 6.2 years (SD 7.4) 74% rheumatoid arthritis (RA) 24% psoriatic arthritis 1% juvenile idiopathic arthritis 1% ankylosing spondylitis all had RA, received steroids and four of them used methotrexate.	mRNA (BNT162b2) administered after 2nd dose of Coronavac with a median (IQR) number of days 157 (143-170)	CoronaVac 2nd dose	PRIMARY OUTCOME Humoral response was assessed by measuring IgG SARS-CoV-2 total antibody (Tab) and neutralising antibody (Nab) within 7days and 4weeks after the booster SECONDARY OUTOME Occurrence of COVID-19 infection monitored on follow-up 1–3 months) Reported adverse events
Faustini Published (2021)	Observational before-after multicenter	Birmingham, UK	90	hemodialysis under renal care at University Hospitals of Birmingham	Pfizer-BioNtech COVID-19 vaccine	Self after 2nd dose of AstraZeneca ChAdOx1 nCoV-19 2nd dose	Anti-IgG/A/M SARS-CoV-2 ELISA to measure IgG antibodies specific for spike protein from the original Wuhan strain
Ferdinands (2022) Published	Case-control	USA	elderly-41, 917 immunocompromised 16, 310	elderly subgroup >/= 60 y/o subgroup on those with any likely immunocompromising condition	monovalent mRNA based COVID-19 vaccine	no booster	COVID-19 associated hospitalization
Kantauskaite (2022) Publsihed	Observational before-after multicenter	Düsseldorf, Germany	245	Kidney transplant recipients 18 y/o and above on immune-suppressants	BNT162b2 (Pfizer-BioNTech) Interval between 2nd and 3rd dose (first boater) 76 ± 25 days	Self after 2nd dose of mRNA-1273 (Moderna)	IgG antibodies against SARS-CoV-2 spike S1 subunit using Anti-SARS-CoV-2-QuantiVac-ELISA and SARS-CoV-2 neutralization efficacy (NT)

Kim (2022) Published	retrospective cohort nationwide via Korean Disease Control and Prevention Agency integrated database multicenter	South Korea	elderly 60 y/o and above N = 10,999,292	given at least 5 months from 2nd dose of primary vaccine mRNA - mRNA n = 3,110,923 Viral vector – mRNA n = 7,055,573 heterologous – mRNA n = 203,332	ChAdOx1 nCoV-19 (AstraZeneca) n = 202,688	ChAdOx1 nCoV-19 (AstraZeneca) n = 202,688 BNT162b2 mRNA (Pfizer BioNTech) n = 422,319 vaccines heterologous n = 4457 2nd dose	SARS-CoV2 Infection rate as documented by PCR; SARS-CoV2 infection status death rate
Kohmer (January 2022) Published	Prospective Cohort Single center	Frankfurt, Germany	194	Patients on maintenance dialysis in 2021 in the nephrology OPD of Grünstadt (Apherese und Dialysezentrum) andWorms (Nierenzentrum), Germany ≥ 18 y/o on immuno-suppressants (corticosteroids, mycophenolate, rituximab) hemodialysis n = 167; peritoneal dialysis n = 27 time RRT in years mean 4.2 (SD 5.6)	mRNA-1273 within 4 to 5 months after 2nd dose	Self after BNT162b2, 2nd dose	Anti-SARS-CoV-2 spike antibodies were measured with the ElecsysAnti-SARS-CoV-2 S assay ; presence of neutralizing antibodies measured by SARS-CoV-2 Surrogate Virus Neutralization Test
Liwsrisakun (2022) Published	Observational Study Before-After Single Center	Chiang Mai, Thailand	46	Health care Workers Age ≥ 60 y/o ChAdOx-1 (n = 24; mean age 70.1 ± 8.3 years) or BNT162b2 (n = 22; mean 74.6 ± 9.4 years)	Booster with mean time span after completion of primary doses: ChAdOx-1 = 50 ± 8.5 days BNT162b2 = 60.7 ± 13.6 days	Self after CoronaVac 2nd dose	HUMORAL RESPONSE Seropositivity for and titer of anti-RBD IgG antibodies median % inhibition of NAbs against the WT, Alpha, Beta, Delta, or Omicron variant CELLULAR RESPONSE Determination of expression of IL-17A, IFN-γ, and FasL in CD4 and CD8 T cells.

Luangdilok (2022) Published	Prospective Cohort 2 Centers	Thailand	131	Patients with solid cancer (breast cancers, colorectal cancers, and cancer of the head and neck) at King Chulalongkorn Memorial Hospital, Bangkok, Thailand, and Phrapokklao Hospital, Chanthaburi, Thailand ≥ 18 y/o	mRNA-based booster: BNT162b2 (Pfizer-BioNTech) n = 51) or mRNA-1273 (Moderna) n = 80 interval between 2nd and 3rd dose: CoronaVac/ ChAdOx1/ BNT162b2 (127.5 days ChAdOx1/ChAdOx1/ BNT162b2 [118 days [IQR 107–136]	Self, after 2nd dose Primary Vaccine heterologous CoronaVac followed by ChAdOx1 (n = 20/44), administered 4 weeks apart for at least 3 months ChAdOx1/ChAdOx1 = 31/87	Primary outcome: SARS-CoV2 antibody response Assessment of SARS-CoV-2 Binding Antibody (7.1 BAU/mL (equal to 50 AU/mL) was positive)and Neutralization against Omicron Variant Secondary outcome: Safety assessed 2 – 4 weeks after 3rd dose
Maglione (2022) Published	Observational study Before-after. Study Single center	Italy	31	person with multiple sclerosis (pwMS) diagnosed by Mc Donald's criteria On the following immune-suppressants 12 - ocrelizumab 12 - fingolimod 7 - cladribine	Comirnaty or Spikevax vaccine (Moderna, Moderna Biotech Spain S.L.) booster (median (IQR): 102 (57; 105) days from 2nd dose	Self after 2nd dose of BNT162b2	PRIMARY OUTCOME: measurement of anti-receptor-binding domain (RBD) lgG titers, considered as neutralizing Abs (nAb) Seroconversion SECONDARY OUTCOME: Adverse events COVID19-related hospitalization
Parenica (2022) Published	Cohort	Czech Rebulic	134, 906	Persons with chronic HF and the following comorbidities: hypertension diabetes malignancy history of stroke history of renal failure	mRNA BNT162b2 (85%) or mRNA-1273 (15%)	2nd dose mRNA BNT162b2 (65.8%), Oxford-Astra-Zeneca (18.4%), mRNA1273 (11.5%), and Janssen	COVID-19 infection, COVID-19 hospitalization, and COVID-19- ICU/ hospitalization

Patyna (February, 2022) Published	Observational Study Before-After 2 centers	Frankfurt, Germany	42	long-term dialysis patients median (IQR) age of 62 (52–72.5) years tertiary care dialysis unit at the Department of Nephrology and Dialysis at Frankfurt University Hospital (Frankfurt, Germany)	mRNA-1273 (Moderna) median (IQR) 34.5 (30.5-47.8) days from 2nd vaccination	Self, after 2nd dose of BNT162b2 (BioNTech/Pfizer)/ BNT162b2 or BNT162b2/ ChAdOx1	Levels of antibodies against SARS-CoV-2 spike receptor binding domain (S- RBD) Detection of SARS-RBD) measured by SARS- CoV-2-neutralizing antibodies using the ELISA-based GenScript SARS-CoV-2 Surrogate Virus Neutralization Test Kit T cells specific for SARS-C0V-2 using multicolor fluorescence enzyme-linked immunospot (ELISpot) assay (CoV-iSpot, AID GmbH, Strassberg, Germany) Secondary outcome: Safety assessment
Reimann (March 2022) Published	prospective cohort Single center	Feldkirch, Austria	29	Oncohematological malignancies in an Academic Teaching Hospital Feldkirch CLL n = 18 Other hema malignancies n = 8 Solid cancer n = 3	Ad26.COV2.S (J&J) administered either Median IQR 124 (124 to 167)	BNT162b2 2nd dose	OUTCOME: **efficacy** (Anti-SARS-CoV-2-S immunoassay from Roche (Basel, Switzerland) as well as the SARS-CoV-2 IgG II Quant assay from Abbott (Abbott Park, IL, USA), both of which detect S/RBD-antibodies to the SARS-CoV-2 spike (S) protein RBD; serological response we used the Elecsys Anti-SARS-CoV-2-S immunoassay from Roche (Basel, Switzerland) as well as the SARS-CoV-2 IgG II Quant assay from Abbott (Abbott Park, IL, USA); **safety** assessed by questionnaire
Simon (November 2021) Published	Prospective cohort Single Center	Germany	40	Patients with immune-mediated inflammatory disease On rituximab n = 33 Non-exposed to rituximab n=33	BNT162b2 or ChAdOx1 Timing from 2nd dose 83 (IQR: 55-112) days	2nd dose of mRNA/mRNA (BNT162b2 Pfizer Biotech) n = 58 (87.9%) ChAdOx1 (AstraZeneca)/ ChAdOx1 n = 8 (12.1%)	Humoral and cellular response Safety

Storti (2022) Published	Observational before-after Single center	Italy	38	Patients treated in a Hematology Unit with multiple myeloma (MM) heterologous monoclonal gammopathies of undetermined significance (MGUS) n = 6 smoldering MM (SMM) n = 10 Newly diagnosed MM (MMD) n=7 relapsed-refractory MM (MMR) n = 9	mRNA-1273 by Moderna, received in at least six months (>180 days) after 2nd dose	BNT162b2, mRNA vaccine by Pfizer-BioNTech 2nd dose	humoral and cellular response seropositivity rate (detectable levels of spike-IgG-Abs in patient's sera) Correlation between spike-IgG-Abs and baseline total CD4+T cells counts correlation between spike- IgG-Abs levels and neutralizing titers against Wuhan-Hu-1 spike
Stumpf (2022) Published	Observational study Before-After Multicenter	Germany	193	kidney transplant recipients ib 26 out of 36 Saxonian nephrology centers	vector vaccines (AZD1222 and 3x Ad26.COV2.S) 3rd dose given 3.5 to 5 months after the 2nd dose	Self 2nd dose BNT162b2-mRNA nRNA-1273	Seroconversion rate and IgG antibody titer
Tallantyre (June 2022) Publsihed	Observational study Before-After Multicenter	UK	81	persons with multiple sclerosis (pwMS) Fifty-eight (72%) were women, mean age 45.8 years. 55 on ocrelizumab 15 on fingolimod 9 on other immunosuppressants	mRNA- based Interval between 2nd and 3rd dose - 6 months	Self after 2nd dose of: BNT162b2 (Pfizer-BioNTech) *n* = 54 mRNA-1273 (Moderna) *n* = 2 CHAdOx1 nCoV-19 (Oxford/AstraZeneca) n = 1	Anti-SARS-CoV-2-spike IgG seroconversion post-COVID-19 vaccine 3 T-cell responses
Tanner (May 2022) Published	prospective cohort single center	Dublin, Ireland	80	Heart transplant recipient 18–70 years of age mean age 49 ± 12.6 years, 28% female, median 7.7 [3.8, 14.4] years since transplantation	BNT162b2 mRNA with median time interval from 2nd dose of 3.7 (3.3-4.1) months	ChAdOx1 nCoV-19(ADZ 1222) viral vector vaccine – 2nd dose	anti-Spike antibody response anti-RBD IgG titer
Thakkar (April 2022) (PREPRINT)	Prospective cohort Single center	Denmark	106	Cancer patients Hematologic malignancy n = 66 (62%) solid malignancy n = 40 (38%) Cancer status n = 69 (65%) Progressive n = 3(3%) Recurrent n = 3(3%) Relapse n = 7 (7%) Remission n = 24 (23%) Median age 68 (IQR 63.25-76.5)	BNT162B2 n = 78 (74%) mRNA-1273 n = 28 (26%) In the results the of mRNA booster not specified Only 100 available for testing	2nd dose of Ad26.CoV2.S	Seroconversion Anti-S titer T cell response against SARS-CoV-2

Thotsiri (Aug 2022) Published	Retrospective cohort Single center	Bangkok, Thailand	98	kidney transplant recipients at Ramathibodi Excellent Center for Organ Transplantation Mean age 47 y/o 56% males Average time after transplant = 46 months Co-morbidities: HPN (62%), DM (20%), IHD (6%), obesity (14%)	Pfizer BioNTech (BNT162b2) or Moderna COVID-19 (mRNA-1273) vaccine administered to at least 4 to 6 months after the 2nd dose	After 2 doses of ChAdOx1 nCoV-19; 7 (23%) 2 doses CoronaVac; and 5 (16%) 1st dose CoronaVac 2nd dose ChAdOx1 nCoV-19 n = **31** 50 (75%) 2 doses ChAdOx1 nCoV-19; 9 (13%) 1st dose CoronaVac an 2nd dose ChAdOx1 nCoV-19 plus mRNA booster n = **67**	COVID-related infection (Pneumonia), hospital admission and need for mechanical ventilation COVID-RELATED death
Yang (June 2022) Published	Retrospective cohort Single center	Stanford, California	496	At Stanford Health care center 54% female; median age 50 years 18 HCWs, 28 non-immunosuppressed patients (NISPs), and 427 immunosuppressed patients; Active Hematologic malignancy = 29 Inactive Hematologic malignancy = 65 Primary anemia = 9 Solid malignancy = 24 Solid organ transplant = 67 Autoimmune disease = 149 Primary immunodeficiency = 42 Multiple categories = 42	mRNA-based vaccine mRNA-1273, BNT162b2,	2nd dose of mRNA-1273, BNT162b2, or Ad26. COV2.S	anti-S1 IgG and SARS-CoV-2 interferon gamma release assay (IGRA) positivity
Zhang (2022) Published	Prospective Cohort Single Center	Italy	183	Long-term Care Center residents 70 years old and above	mRNA booster doses, BNT162b2 (Pfizer [P]), or mRNA-1273 (Moderna [M] given 5 months from 2nd dose Primary-heterologous vaccine combinations MPM without prior COVID19 infection n = 104 MPM with prior COVID19 infection n = 79 MMP n = 52	Self, after 2nd mRNA booster doses, BNT162b2 (Pfizer [P]), or mRNA-1273 (Moderna [M]	incidence of COVID19 infection Serious adverse event Adverse event

Appendix 4: Study Appraisal

Table 4a. Risk of Bias: ROBINS-I tool in non-randomized studies

Author	Confounding (Severity/ co-morbidities/ healthcare use)	Selection bias (Participants/ lost to follow-up/ outcome/ missing data)	Classification of Intervention/s Or measurement/ misclassification bias (ex. recall bias in case-control)/ detection bias	Deviations from intended interventions	Missing data	Measurement of outcome	Selection of the reported result	Overall risk
Abid Before-after study	Low	Low	Low	Low		Low	Low	Low
Alidjinou Before-after study	Low	low	Low	Low		Low	Low	low
Avivi Before-after study	Low	Low	Low	Low		Low	Low	Low
Bajwa Before-after study	Low	Low	Low	Low		Low	Low	Low
Balsby Before-after study	Serious Adjusted for age and treatment only	Low	Low	Low		Low	Low	High
Beihack Before-after study	Low	Low	Low	Low		Low	Low	Low
Benning Before-after study	Low	Low	Low	Low	Low	Low	Low	Low
Bensouna Before-after study	Low	Low	Low	Low	Low	Low	Low	Low
Broseta Before-after study	Low	Low	Low	Low		Serious Test was approved in the emergency setting and not yet validated and approved	Serious Short ff up of 2 weeks	High
Canti Before-after study	Low	Low	Low	Low		Low	Low	Low
Chavarot Before-after study	Low	Low	Low	Low		Low	Low	Low
Debie Before-after study	Low	Low	Low	Low		Low	Low	Low
Dekervel Before-after study	Low	Low	Low	Low		Low	Low	Low
Del Bello	Low	Low	Low	Low		Low	Low	Low
Di Noia Before-after study	Serious Did not control confounding variables	Low	Low	Low		Low	Low	High for immuno genicity
Diamantopoulos Before-after study	Low	Low	Low	Low		Low	Low	Low

Dreyer-Alster Before-after study	Low	Low	Low	Low		Low	Low	Low
Ducloux Before-after study	High Only History of COVID was controlled	Low	Low	Low		Low	Low	High
Eliakim-Raz Before-after study	Low	Low	Low	Low		Serious Short follow up, 14 days	Low	High for safety outcomes
Ferdinands case-control	Low	Low	Low	Low		Low	Low	Low
Gianserra Before-after study	Low	Low	Low	Low		Low	Low	Low
Goggins Preprint Before-after study	Low	Low	Low	Low		Low	Low	Low
Gressens Before-after study	Low	Low	Low	Low		Low	Low	Low
Herishanu Before-after study	Low	Low	Low	Low		Low	Low	Low
Hod Before-after study	Low	Low	Low	Low		Low	Low	Low
Peled Before-after study	NA	Low	Low	Low		Serious Short follow up of 18 days	Low	High for efficacy
Re Preprint Before-after study	Low	low	Low	Low		Low	Low	Low
Saiag Before-after study	Low	Low	Low	Low		low	Low	Low
Shaul Before-after study	Low	Low	Low	Low		Low	Low	Low
Speer Before-after study	Serious 1 subgroup only-with or without rituximab	Low	Low	Low		Low	Low	High
Susol Before-after study	Low	low	Low	Low		Low	Low	Low
Terpos Before-after study	Low	Low	Low	Low		Low	Low	Low
Vanshylla Before-after study	serious	Low	Low	Low		Low	Low	High
Verdier Before-after study	serious (sex, majority male 72%, other data not available)	Serious (only those with available date)	Low	Low		Low	Low	High
Bar-on (Cohort)	other confounders not adjusted in analysis	Low	Low	Low	Low	Short follow up of 12 days	Low	High

Beiber (Cohort)	Confounders not adjusted in analysis	Low	Low	Low	Low	Short follow up of 21 days	Low	High
David (Cross-sectional)	30% response rate	NA	Low	Low	NA	High Recall bias	Low	High
John (Cohort)	Low	Low	Low	Low	Low	short follow up- 14 days	Low	High
Muhsen (Cohort)	Low	low	Low	Low	Low	Low	Low	Low
Shashar (Cohort)	Low	Low	Low	Low	Low	low	Low	Low
Shehab (Cohort)	Low	Low	Low	Low	Low	Low	Low	Low

Table 4b. Risk of Bias tool (RevMan 5.4) for randomized trials

Author	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment (Detection bias)	Attrition bias	Reporting bias	Overall risk
Hall	Yes	Yes	Yes	Yes	No	No	Low
Hardt (ENSEMBLE2)	Yes	Yes	Yes	Yes	Yes	No	High

Appendix 5: Grade Evidence Profile

GRADE Evidence Profile for Elderly population (Homologous BNT162b2 booster vs no booster)

Author(s): Eva I. Bautista, Lylah D. Reyes, Ma. Lucila Perez
Question: Homologous BNT162b2 as first booster compared to no booster or placebo in high risk population
Setting: Hospital and Out-patient
Bibliography:

Certainty assessment							№ of patients		Effect		Certainty	Importance
No. of Studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	homologous BNT162b2 as first booster	no booster or placebo	Relative (95% CI)	Absolute (95% CI)		
COVID-19 related mortality in elderly population (homologous BNT162b2 booster) (follow-up: median 66 days)												
1[1]	observational studies	not serious	not serious	not serious	not serious	none	aHR 0.04 (95% CI 0.009, 0.16) (n=18,611)				⨁⨁◯◯ Low	CRITICAL
Severe COVID-19 in elderly population (homologous BNT162b2) (follow-up: median 66 days)												
1[2]	observational studies	serious[2,a]	not serious	not serious	not serious	none	aRR 0.07 (95% CI 0.05, 0.11) (n=1, 312, 057)				⨁◯◯◯ Very low	CRITICAL
COVID-19 associated Hospitalization in elderly population (follow-up: 70 days)												
1[1]	observational studies	not serious	not serious	not serious	not serious	none	aHR 0.10 (95% CI 0.04, 0.24) (n=18,611)				⨁⨁◯◯ Low	CRITICAL
COVID-19 in elderly population (homologous BNT162b2)												
2[1,2]	observational studies	serious[2,a]	not serious	not serious	not serious	none	aHR 0.11 (95% 0.07, 015) (n=18,611) aRR 0.103 (95% CI 0.096, 0.11) (n= 1, 312, 057)				⨁◯◯◯ Very low	CRITICAL
Immunogenicity of homologous BNT162b2 in COVID-19-naive elderly population (Humoral response: anti-spike Ab) (follow-up: 150 days)												
3[3,4]	observational studies	not serious	serious[3,4,b]	serious[3,4,c]	not serious	none	144	144	-	MD **25028 BAU/ml higher** (23912 higher to 26144 higher)	⨁◯◯◯ Very low	CRITICAL
Immunogenicity of homologous BNT162b2 in COVID-19-recovered elderly population (Humoral response: anti spike Ab) (follow-up: 150 days)												
1[3]	observational studies	not serious	not serious	serious[c]	not serious	none	57	57	-	MD **180 higher** (104 higher to 256 higher)	⨁◯◯◯ Very low	CRITICAL
Immunogenicity of homologous BNT162b2 booster in elderly (Cellular response)												
1[3]	observational studies	not serious	not serious	serious[c]	serious[3,d,e]	none	47	47	-	MD **2.5 higher** (0.53 higher to 4.47 higher)	⨁◯◯◯ Very low	CRITICAL
Serious Adverse Events in Elderly population (homologous BNT162b2) (follow-up: 150 days)												
2[3,4]	observational studies	serious[f,g]	not serious	not serious	not serious	none	There was no reported SAE. (n= 203)				⨁◯◯◯ Very low	CRITICAL

CI: confidence interval; **MD:** mean difference; **RR:** risk ratio

Explanations
a. Other confounders were not adjusted in the analysis like care-seeking behaviors and cautiousness, along with differences in coexisting illnesses that are not recorded in the national database
b. Non-overlapping 95% CI
c. Indirect measures of efficacy/effectiveness
d. 95% CI includes the no effect value = 1
e. small sample size
f. Measurement of outcome. Short follow up of 14 days.
g. passive reporting

GRADE Evidence Profile for Elderly population (Homologous AdCOV2.S booster vs placebo)

Author(s): Eva I. Bautista, MD, Lylah D. Reyes, MD, Ma. Lucila Perez, MD
Question: Homologous AdCOV2.S (Janssen) compared to no booster in high-risk population?:
Bibliography:

Certainty assessment							№ of patients		Effect		Certainty	Importance
No. of Studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	homologous AdCOV2.S (Janssen)	no booster	Relative (95% CI)	Absolute (95% CI)		
Moderate to Severe to Critical COVID-19 (follow-up: median 36 (IQR 15, 62) days)												
1[1]	randomised trials	serious[1,a]	not serious	serious[1,b]	serious[1,c]	none	15/6024 (0.2%)	46/13578 (0.3%)	**RR 0.74** (0.41 to 1.32)	**1 fewer per 1,000** (from 2 fewer to 1 more)	⨁◯◯◯ Very low	CRITICAL
Severe to Critical COVID-19 (follow-up: median 36 (IQR 15, 62) days)												
1[1]	randomised trials	serious[1,a]	not serious	serious[1,b]	serious[1,c]	none	0.5/6024.5 (0.0%)	3.5/13578.5 (0.0%)	**RR 0.32** (0.02 to 6.23)	**0 fewer per 1,000** (from 0 fewer to 1 more)	⨁◯◯◯ Very low	CRITICAL
Immunogenicity: Antibody Response Rate (follow-up: 28 days)												
1[1]	randomised trials	serious[a]	not serious	serious[b,d]	not serious	none	68.5/69 (99.3%)	113.5/124 (91.5%)	**RR 1.08** (1.02 to 1.15)	**73 more per 1,000** (from 18 more to 137 more)	⨁⨁◯◯ Low	CRITICAL
Immunogenicity: anti-spike Ab Geometric Mean Concentration (follow-up: 28 days)												
1[1]	randomised trials	serious[a]	not serious	serious[b,d]	not serious	none	68	123	-	MD **1853 EU/ml higher** (1820 higher to 1887 higher)	⨁⨁◯◯ Low	CRITICAL
Adverse Events; Solicited Grade 1-Grade 2 local and systemic AE (follow-up: 7 days)												
1[1]	randomised trials	serious[a]	not serious	serious[b]	serious[c]	none	886/1559 (56.8%)	1667/3015 (55.3%)	**RR 1.02** (0.95 to 1.08)	**11 more per 1,000** (from 28 fewer to 44 more)	⨁◯◯◯ Very low	CRITICAL
Adverse Events: Solicited Grade 3 local and systemic AE (follow-up: 7 days)												
1[1]	randomised trials	serious[a]	not serious	serious[b]	serious[c]	none	10/1559 (0.6%)	9/3015 (0.3%)	**RR 2.15** (0.88 to 5.28)	**3 more per 1,000** (from 0 fewer to 13 more)	⨁◯◯◯ Very low	CRITICAL
Adverse Events: Unsolicited Vaccine-Related AE (follow-up: 28 days)												
1[1]	randomised trials	serious[a]	not serious	serious[b]	not serious	none	79/1559 (5.1%)	283/3015 (9.4%)	**RR 0.54** (0.42 to 0.69)	**43 fewer per 1,000** (from 54 fewer to 29 fewer)	⨁⨁◯◯ Low	CRITICAL
Adverse Events: Embolic and Thrombotic Events (follow-up: 28 days)												
1[1]	randomised trials	serious[a]	not serious	serious[b]	serious[c]	none	3/8646 (0.0%)	2/15705 (0.0%)	**RR 2.75** (0.46 to 16.30)	**0 fewer per 1,000** (from 0 fewer to 2 more)	⨁◯◯◯ Very low	CRITICAL
Adverse Events: Hypersensitivity												
1[1]	randomised trials	serious[a]	not serious	serious[b]	not serious	none	15/8646 (0.2%)	56/15705 (0.4%)	**RR 0.49** (0.28 to 0.86)	**2 fewer per 1,000** (from 3 fewer to 0 fewer)	⨁⨁◯◯ Low	CRITICAL

CI: confidence interval; **MD:** mean difference; **RR:** risk ratio

Explanations
a. Attrition bias: 20% prematurely terminated or discontinued participation.
b. Elderly population comprised 25% of the population. No data for subgroup analysis.
c. 95% CI crossed equivalence value of 1.
d. Indirect Measure of Efficacy

GRADE Evidence Profile for immunocompromised adults (Homologous BNT162b2 booster vs no booster)

Author(s): Eva I. Bautista, Lylah D. Reyes, Ma. Lucila Perez
Question: Homologous BNT162b2 as first booster compared to no booster or placebo in high risk population
Setting: Hospital and Out-patient
Bibliography:

Certainty assessment							№ of patients		Effect		Certainty	Importance
No of Studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	homologous BNT162b2 as first booster	no booster or placebo	Relative (95% CI)	Absolute (95% CI)		
COVID-19 related mortality in adults with autoimmune disease (homologous BNT162b2) (follow-up: median 5 weeks)												
1[2]	observational studies[f]	serious[2,g,h]	not serious	not serious	not serious	none	0.5/45435.5 (0.0%)	32.5/3140 7.5 (0.1%)	**RR 0.01** (0.00 to 0.17)	**1 fewer per 1,000** (from 1 fewer to - -)	⨁◯◯◯ Very low	CRITICAL
Hospitalization in adults with autoimmune disease (homologous BNT162b2) (follow-up: median 5 weeks)												
1[2]	observational studies	serious[2,h,i]	not serious	not serious	not serious	none	45/45435 (0.1%)	138/31407 (0.4%)	**RR 0.23** (0.16 to 0.32)	**3 fewer per 1,000** (from 4 fewer to 3 fewer)	⨁◯◯◯ Very low	CRITICAL
Severe COVID-19 in adults with liver cirrhosis (homologous BNT162b2) (follow-up: 21 days)												
1[3]	observational studies	serious[3,4,j]	not serious	not serious	not serious	none	aHR 0.0 (95% CI 0.0, 0.08) (n= 12, 978)				⨁◯◯◯ Very low	CRITICAL
COVID-19 in adults with autoimmune disease (homologous BNT162b2) (follow-up: median 5 weeks)												
1[2]	observational studies	serious[2,g,h]	not serious	not serious	not serious	none	770/45435 (1.7%)	3498/3140 7 (11.1%)	**RR 0.15** (0.14 to 0.16)	**95 fewer per 1,000** (from 96 fewer to 94 fewer)	⨁◯◯◯ Very low	CRITICAL
COVID-19 in immunocompromised adults (with liver cirrhosis) (homologous BNT162b2) (follow-up: 21 days)												
2[3]	observational studies	serious[2,3,j]	not serious	not serious	not serious	none	aHR of 0.19 (95% CI 0.09, 0.39) (n= 12,978)				⨁◯◯◯ Very low	CRITICAL
Immunogenicity of homologous BNT162b2 in Immunocompromised Adults (Humoral response: anti-spike Ab) (follow-up: range 21 days to 154 days)												
11[5,6,7,8,9,10,11,12,13,14,15,16]	observational studies	serious[12,17,h,k]	serious[5,9,l]	serious[5,6,8,9,10,11,12,13,14,15,16,b]	not serious	none	1141	1141	-	MD **10.78 BAU/ml higher** (8.37 higher to 13.2 higher)	⨁◯◯◯ Very low	CRITICAL
Immunogenicity of homologous BNT162b2 in immunocompromised adults (Humoral response: Neutralizing Ab) (follow-up: range 14 days to 150 days)												
2[18,19]	observational studies	not serious	serious[18,19,a]	serious[18,19,b]	serious[18,19,c,d]	none	195	195	-	MD **184.33 higher** (129.79 lower to 498.46 higher)	⨁◯◯◯ Very low	CRITICAL
Serious adverse events in immunocompromised adults (homologous BNT162b2) (follow-up: range 1 to 116)												
18[4,8,9,16,18,19,20,21,22,23,24,25,26,27,28,29,30,31]	observational studies	serious[1,4,32,e,i,m]	not serious	not serious	not serious	none	It ranged from 0% to 10%.				⨁◯◯◯ Very low	CRITICAL
Adverse Events: Immunocompromised Adults												

11[9,16,18,19,20,23,24,25,29,32,33]	observational studies	serious[19,30,m,n]	not serious	not serious	not serious	none	There were 0% to 80% reported adverse events among those given booster dose.	⊕◯◯◯ Very low	CRITICAL

CI: confidence interval; **MD:** mean difference; **RR:** risk ratio

Explanations
a. Non-overlapping 95% CI
b. Indirect measures of efficacy/effectiveness
c. 95% CI includes the no effect value = 1
d. small sample size
e. Measurement of outcome. Short follow up of 14 days.
f. One of the 4 studies is before-after study.
g. Measurement of outcome. Short follow-up post-third dose up to median of 5 weeks (IQR 2-7).
h. Confounding bias. Did not adjust for confounders other than age and treatment
i. Measurement of outcome: Short follow up post third dose up to 21 days.
j. Short follow up: 21 days post booster dose
k. Test used was approved for emergency setting only, not yet validated.
l. I2 is 100%
m. 30% response rate in the survey among vaccine recipients
n. Measurement of outcome: short follow up: 18 days

GRADE Evidence Profile: Immunocompromised Adults (Homologous mRNA-1273 booster vs no booster)

Author(s): Eva I. Bautista, Lylah D. Reyes, Ma. Lucila Perez
Question: Homologous mRNA-1273 as first booster compared to no booster or placebo in high risk population
Setting: Hospital and Outpatient
Bibliography:

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	homologous mRNA-1273 as first booster	no booster or placebo	Relative (95% CI)	Absolute (95% CI)		
Severe or Critical COVID-19 (homologous mRNA-1273) (follow-up: range 14 to 60)												
1[1]	observational studies	not serious	not serious	not serious	not serious	none	Adults with liver cirrhosis: aHR 0.0 (95% CI 0.00-0.08) [n= 13, 104]				⨁⨁◯◯ Low	CRITICAL
COVID-19 (mRNA-1273) (follow-up: 120 days)												
1[2]	randomised trials	not serious	not serious	not serious	serious[2,a]	none	0.5/60.5 (0.8%)	1/59 (1.7%)	**RR 0.34** (0.01 to 8.15)	**11 fewer per 1,000** (from 17 fewer to 121 more)	⨁⨁⨁◯ Moderate	CRITICAL
COVID-19 (mRNA) (follow-up: 14-120 days)												
1	observational studies	not serious	not serious	not serious	not serious	none	aHR 0.19 (95% CI 0.09, 0.39)				⨁⨁◯◯ Low	CRITICAL
Symptomatic COVID-19 in liver cirrhosis patients (homologous mRNA-1273 (follow-up: range 14 days to 60 days)												
1[1]	observational studies	not serious	not serious	not serious	not serious	none	Adults with liver cirrhosis: aHR 0.19 (95% CI 0.09, 0.39)				⨁⨁◯◯ Low	CRITICAL
Immunogenicity (Humoral response: anti RBD positivity) (follow-up: 120 days)												
1[2]	randomised trials	not serious	not serious	serious[2,b]	not serious	none	33/60 (55.0%)	10/57 (17.5%)	**RR 3.13** (1.71 to 5.76)	**374 more per 1,000** (from 125 more to 835 more)	⨁⨁⨁◯ Moderate	CRITICAL
Immunogenicity (Humoral: surrogate virus neutralization positivity) (follow-up: 120 days)												
1	randomised trials	not serious	not serious	serious[2,b]	not serious	none	36/60 (60.0%)	14/57 (24.6%)	**RR 2.44** (1.48 to 4.03)	**354 more per 1,000** (from 118 more to 744 more)	⨁⨁⨁◯ Moderate	CRITICAL
Adverse events												
1[2]	randomised trials	not serious	not serious	not serious	serious[2,c]	none	46/60 (76.7%)	7/59 (11.9%)	**RR 6.46** (3.18 to 13.13)	**648 more per 1,000** (from 259 more to 1,000 more)	⨁⨁⨁◯ Moderate	CRITICAL

CI: confidence interval; **RR:** risk ratio
Explanations
a. 95% CI included the value=1
b. Indirect measure of efficacy/effectiveness
c. wide 95% CI

GRADE evidence profile for Heterologous first booster versus no booster for immunocompromised population

Author(s): Lylah D. Reyes, MD, Eva I. Bautista, MD, Ma Lucila Perez

Question: Heterologous first booster compared to pre booster or no booster for clinical and immunologic efficacy against COVID19 infection among the immunocompromised population

Setting: Austria, Denmark, Hungary, Ireland, Italy, Germany, Peru, Thailand, UK, USA

Bibliography:

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	heterologous first booster	pre booster or no booster	Relative (95% CI)	Absolute (95% CI)		
mRNA (Pfizer BioNTech (BNT162b2) or Moderna COVID-19 (mRNA-1273) booster with ChAdOx1 nCoV-19 or CoronaVac primary vaccine and Death due to COVID19 w (follow-up: range 88 days to 137 days)												
1[1]	observational studies	serious[a,b]	not serious	not serious	serious[1,c,d]	none	2/67 (3.0%)	1/31 (3.2%)	RR 0.91 (0.09 to 9.68)	3 fewer per 1,000 (from 29 fewer to 280 more)	⨁◯◯◯ Very low	CRITICAL 1
mRNA (Pfizer BioNTech BNT162b2 or Moderna mRNA-1273) booster with ChAdOx1 or CoronaVac primary vaccine and Pneumonia due to COVID19 (follow-up: range 88 days to 137 days)												
1[1]	observational studies	serious[1,a,b]	not serious	not serious	serious[1,c,d]	none	7/67 (10.4%)	7/31 (22.6%)	RR 0.46 (0.18 to 1.21)	122 fewer per 1,000 (from 185 fewer to 47 more)	⨁◯◯◯ Very low	CRITICAL 1
mRNA (Pfizer BioNTech BNT162b2 or Moderna mRNA-1273) booster with ChAdOx1 nCoV-19 or CoronaVac primary vaccine and Hospitalization among patients with COVID19 (follow-up: range 88 days to 137 days)												
1[1]	observational studies	serious[1,a,b]	not serious	not serious	not serious	none	8/67 (11.9%)	15/31 (48.4%)	RR 0.25 (0.12 to 0.52)	363 fewer per 1,000 (from 426 fewer to 232 fewer)	⨁◯◯◯ Very low	CRITICAL 1
mRNA (Pfizer BioNTech BNT162b2 or Moderna mRNA-1273) booster with ChAdOx1 or CoronaVac primary vaccine and need for mechanical ventilation among patient with COVID-19 disease (follow-up: range 88 days to 137 days)												
1[1]	observational studies	serious[1,a,b]	not serious	not serious	not serious	none	1/67 (1.5%)	0/31 (0.0%)	RR 1.47 (1.28 to 1.68)	0 fewer per 1,000 (from 0 fewer to 0 fewer)	⨁◯◯◯ Very low	CRITICAL 1
mRNA (BNT162b2 BioNTech/Pfizer or mRNA-1273 Moderna) Booster with CoronaVac 1st dose; ChAdOx1 (Astra Zeneca) 2nd dose Primary vaccine and anti-RBD IgG titer (BAU/ml) (follow-up: range 14 days to 28 days)												
1[2]	observational studies	serious[2,e,f]	not serious	serious[2,g]	not serious	none	2330	71.4	-	MD 2258.6 BAU/ml higher (1601.16 higher to 2916.04 higher)	⨁⨁◯◯ Low	CRITICAL 2
mRNA (Pfizer BioNTech BNT162b2 or Moderna mRNA-1273) booster with CoronaVac 1st dose ChAdOx1 2nd dose primary vaccine and adverse event (follow-up: range 14 days to 28 days)												
1[2]	observational studies	serious[2,e,f]	not serious	not serious	not serious	none	42/44 (95.5%)	20/44 (45.5%)	RR 2.10 (1.51 to 2.92)	500 more per 1,000 (from 232 more to 873 more)	⨁◯◯◯ Very low	CRITICAL 2
mRNA (Pfizer BioNTech (BNT162b2) or Moderna COVID-19 (mRNA-1273)) booster with non-mRNA ChAdOx1 (AstraZeneca) Primary vaccine and deaths due to COVID19 (follow-up: 42 days)												
1[3]	observational studies	serious[3,b]	not serious	not serious	serious[3,c]	none	16 out 41 received ChAdOx1 as primary vaccine with mRNA booster. No reported COVID-related death up to 42 days of follow up postbooster.				⨁◯◯◯ Very low	CRITICAL 3
mRNA (Pfizer BioNTech BNT162b2 or Moderna mRNA-1273) booster with non-mRNA ChAdOx1 (Astra Zeneca) (Primary) vaccine and COVID19 infection (follow-up: 178 days)												

1[3]	observational studies	serious[3,b]	not serious	not serious	serious[3,c]	none	16 out 41 received ChAdOx1 as primary vaccine with mRNA booster 1 out of 16 developed infection within 178 days from booster				⊕◯◯◯ Very low	CRITICAL 3

mRNA (BNT162b2 BioNTech/Pfizer or mRNA-1273 Moderna) Booster with Astra Zeneca (ChAdOx1) primary vaccine and anti-RBD IgG titer (BAU/ml) (follow-up: range 14 days to 28 days)

1[2]	observational studies	serious[2,e,f]	not serious	serious[2,3,g]	not serious	none	2362	40.6	-	MD 2321.39 BAU/ml higher (2113.32 higher to 2529.46 higher)	⊕◯◯◯ Very low	CRITICAL 2

mRNA-based vaccine (BNT162B2 or mRNA-1273) booster with ChAdOx1 (AstraZeneca) primary vaccine and SARS-CoV2 Spike-1 Antibody assay (follow-up: range 28 days to 30 days)

2[2,4]	observational studies	serious[2,4,e,f,h]	not serious	serious[g]	not serious	none	89/124 (71.8%)	70/124 (56.5%)	RR 1.27 (1.05 to 1.54)	152 more per 1,000 (from 28 more to 305 more)	⊕◯◯◯ Very low	CRITICAL 24

m-RNA based (Pfizer BioNTech BNT162b2 or mRNA 1273) booster with AstraZeneca viral vector primary vaccine and Cellular immune response (follow-up: range 8 days to 34 days)

2[5,6]	observational studies	serious[5,6,a,e,f]	not serious	serious[g]	not serious	none	284/307 (92.5%)	303/436 (69.5%)	RR 1.33 (1.24 to 1.43)	229 more per 1,000 (from 167 more to 299 more)	⊕◯◯◯ Very low	CRITICAL 56

mRNA-based vaccine (BNT162b2 or mRNA-1273) Booster with ChAdOX-1 recombinant (Oxford/AstraZeneca) primary and Adverse event (follow-up: range 14 days to 28 days)

1[2]	observational studies	serious[2,e,f]	not serious	not serious	not serious	none	86/87 (98.9%)	31/87 (35.6%)	RR 2.774 (2.090 to 3.680)	632 more per 1,000 (from 388 more to 955 more)	⊕◯◯◯ Very low	CRITICAL 2

mRNA-based vaccine (BNT162b2 or mRNA-1273) Booster with CoronaVac Primary vaccine and COVID19 infection (follow-up: range 30 days to 90 days)

1[7]	observational studies	serious[7,i]	not serious	not serious	not serious	none	No reported COVID19 cases (0/76)				⊕◯◯◯ Very low	CRITICAL 21

mRNA (Pfizer BioNTech BNT162b2 or Moderna mRNA-1273) booster with Ad26COVS1 Janssen primary vaccine and adverse event (follow-up: range 14 days to 28 days)

1[8]	observational studies	not serious	not serious	not serious	not serious	none	Pain on injection site 43% (6/14) Fatigue 12% (2/14)				⊕⊕◯◯ Low	CRITICAL 8

mRNA-based (BNT162b2 or mRNA-1273) Booster with AstraZeneca or Ad26.CoV2.S (Janssen) viral vector primary vaccine and positive neutralizing antibody PRERPINT (follow-up: 28 days)

1[9]	observational studies	serious[9,j]	not serious	serious[g]	not serious	none	77/100 (77.0%)	47/106 (44.3%)	RR 1.74 (1.37 to 2.21)	328 more per 1,000 (from 164 more to 537 more)	⊕◯◯◯ Very low	CRITICAL 9

m-RNA based (BNT162b2 Pfizer BioNTech or mRNA 1273 Moderna) Booster with AstraZeneca viral vector Primary vaccine and Cellular immune response PREPRINT (follow-up: 28)

1[9]	observational studies	serious[9,j,k]	not serious	serious[g]	serious[g,c]	none	76/89 (85.4%)	65/89 (73.0%)	RR 1.170 (1.004 to 1.350)	124 more per 1,000 (from 3 more to 256 more)	⊕◯◯◯ Very low	CRITICAL 9

mRNA 1273 Moderna Booster with BNT162b2 Pfizer/BioNTech primary vaccine and COVID19 infection of any degree (follow-up: range 28 days to 120 days)

1[10]	observational studies	not serious	not serious	not serious	not serious	none	7.9% (3/38) developed infection within 4 months postbooster				⊕⊕◯◯ Low	CRITICAL 10

mRNA- 1273 (Moderna) booster with BNT162b2 (BioNTech/Pfizer) primary vaccine and anti-RBD IgG titer (BAU/ml) (follow-up: 28 days)

1[11]	observational studies	serious[11,l]	not serious	serious[g]	not serious	none	23119	396.2	-	MD 22722.8 BAU/ml higher (18541.9 higher to 26903.7 higher)	⨁◯◯◯ Very low	CRITICAL 11

mRNA- 1273 (Moderna) booster with BNT162b2 (BioNTech/Pfizer) primary vaccine and anti-RBD IgG titer (BAU/ml) (follow-up: 28 days)

1[12]	observational studies	serious[e,i]	not serious	serious[g]	not serious	none	28 BAU/mL (IQR 43–1027.5) pre-booster to 4560 BAU/mL (IQR 646.7–7272.5) postbooster				⨁◯◯◯ Very low	CRITICAL 12

mRNA-1273 (Moderna) Booster with BNT162b2 (Biontech/Pfizer) primary vaccine and Seroconversion (follow-up: 28 days)

1[11]	observational studies	serious[11,l]	not serious	serious[g]	not serious	none	113/165 (68.5%)	94/181 (51.9%)	RR 1.32 (1.11 to 1.57)	166 more per 1,000 (from 57 more to 296 more)	⨁◯◯◯ Very low	CRITICAL 11

mRNA 1273 (Moderna) Booster with BNT162b2 (Pfizer BioNTech) primary vaccine and positive neutralizing antibody (follow-up: 28 days)

1[11]	observational studies	serious[11,l]	not serious	serious[g]	not serious	none	144/148 (97.3%)	64/181 (35.4%)	RR 2.72 (2.26 to 3.37)	608 more per 1,000 (from 446 more to 838 more)	⨁◯◯◯ Very low	CRITICAL 11

mRNA-1273 (Moderna) booster with BNT162b2 (Pfizer BioNTech) primary vaccine and SARS-CoV2 Spike-1 Antibody assay (follow-up: 28 days)

1[11]	observational studies	serious[11,l]	not serious	serious[g]	not serious	none	176/181 (97.2%)	164/181 (90.6%)	RR 1.070 (1.018 to 1.130)	63 more per 1,000 (from 16 more to 118 more)	⨁◯◯◯ Very low	CRITICAL 11

mRNA-1273 Moderna booster with BNT162b2 Pfizer BioNTech or Ad26COVS1 Janssen primary vaccine and Serious adverse event (SAE) (follow-up: 58 days)

1[8]	observational studies	serious[8,e]	not serious	not serious	not serious	none	No reported events				⨁◯◯◯ Very low	CRITICAL 8

BNT162b2 (Pfizer BioNTech) booster with ChAdOx1 (AstraZeneca) primary vaccine and Seroconversion (follow-up: range 28 days to 45 days)

3[13,14,15]	observational studies	serious[14,15,i,m]	not serious	serious[g]	not serious	none	Postbooster seroconversion:Maglione: partiicipants with multiple sclerosis 74.2% (23/31) Tallantyre: partiicipants with multiple sclerosis 47% (21/45) Faustini: hemodialysis patients with comorbities 100% (n = 85)				⨁◯◯◯ Very low	CRITICAL 1415

BNT162b2 (Pfizer BioNTech) Booster with AstraZeneca viral vector primary vaccine and Positive Neutralizing Antibody against Omicron variant (follow-up: 28 days)

1[6]	observational studies	serious[6,i]	not serious	serious[g]	serious[6,c,d]	none	15/36 (41.7%)	0/36 (0.0%)	RR 31.00 (1.92 to 499.24)	0 fewer per 1,000 (from 0 fewer to 0 fewer)	⨁◯◯◯ Very low	CRITICAL 23

BNT162b2 (Pfizer BioNTech) Booster with CoronoVac primary vaccine and positive neutralizing antibodies (follow-up: 28 days)

1[7]	observational studies	serious[7,e,i]	not serious	serious[g]	not serious	none	71/76 (93.4%)	18/76 (23.7%)	RR 3.94 (2.62 to 5.93)	696 more per 1,000 (from 384 more to 1,000 more)	⨁◯◯◯ Very low	CRITICAL 7

Ad26COVS1 Janssen vector booster with BNT162b2 primary vaccine and COVID19 infection (follow-up: range 28 days to 120 days)

2[8,16]	observational studies	serious[8,16,f]	not serious	not serious	serious[c]	none	No Reported COVID19 cases (0/112)				⨁◯◯◯ Very low	CRITICAL 822

Ad26COVS1 vector (Janssen) booster with BNT162b2 (Pfizer BionTech) primary vaccine and Seroconversion (follow-up: range 20 days to 120 days)

1[16]	observational studies	serious[16,f]	not serious	serious[g]	not serious	none	36/36 (100.0%)	25/36 (69.4%)	RR 1.44 (1.16 to 1.79)	306 more per 1,000 (from 111 more to 549 more)	⊕◯◯◯ Very low	CRITICAL 22

Ad26COVS1 (Janssen) vector vaccine booster with BNT162b2 Pfizer BioNTech primary vaccine and positive neutralizing antibodies (follow-up: range 21 days to 360 days)

1[16]	observational studies	serious[16,f]	not serious	serious[g]	not serious	none	33/36 (91.7%)	21/36 (58.3%)	RR 1.57 (1.17 to 2.11)	333 more per 1,000 (from 99 more to 648 more)	⊕◯◯◯ Very low	CRITICAL 22

Ad26.COVS1 (Janssen) Booster with mRNA BNT162b2 (Pfizer BioNTech) Primary vaccine and SARS-CoV2 Spike-1 Antibody assay (follow-up: 28 days)

2[5,17]	observational studies	serious[5,17,a,e,n,o,p]	not serious	serious[g]	serious[d]	none	90/147 (61.2%)	266/448 (59.4%)	RR 1.03 (0.89 to 1.19)	18 more per 1,000 (from 65 fewer to 113 more)	⊕◯◯◯ Very low	CRITICAL 517

Ad26COVS1 (Janssen) vector booster with mRNA based (BNT162b2 or mRNA- 1273) primary vaccine and anti-RBD IgG titer (BAU/ml) (follow-up: 28 days)

2[16,17]	observational studies	serious[17,e,n,o,p]	not serious	serious[g]	not serious	none	1588.495	567.16	-	MD 1031.33 BAU/ml higher (847.96 higher to 1214.73 higher)	⊕◯◯◯ Very low	CRITICAL 1722

Ad26COVS1 (Janssen) booster with mRNA-based primary vaccine and adverse events (follow-up: range 28 days to 58 days)

2[8,17]	observational studies	serious[17,e,n,o,p]	not serious	not serious	serious[d]	none	8/109 (7.3%)	0/109 (0.0%)	RR 17.00 (0.99 to 290.95)	0 fewer per 1,000 (from 0 fewer to 0 fewer)	⊕◯◯◯ Very low	CRITICAL 817

ChAdOx1 (AstraZeneca) booster with mRNA BNT162b2 (Biontech/Pfizer) or mRNA-1273 (Moderna) Primary vaccine and Seroconversion (follow-up: 28 days)

1[18]	randomised trials	not serious	not serious	serious[g]	serious[c,d]	none	9/28 (32.1%)	0/30 (0.0%)	RR 20.31 (1.24 to 333.47)	0 fewer per 1,000 (from 0 fewer to 0 fewer)	⊕⊕◯◯ Low	CRITICAL 18

ChAdOx1 (AstraZeneca) booster with mRNA BNT162b2 (Biontech/Pfizer) or mRNA-1273 (Moderna) Primary vaccine and Seroconversion (follow-up: range 15 days to 28 days)

1[19]	observational studies	serious[19,f,q]	not serious	serious[g]	serious[c,d]	none	22/40 (55.0%)	0/40 (0.0%)	RR 45.00 (2.82 to 717.31)	0 fewer per 1,000 (from 0 fewer to 0 fewer)	⊕◯◯◯ Very low	CRITICAL 19

ChAdOx1 (AstraZeneca) vector vaccine booster with m-RNA based (Pfizer BionTech BNT162b2 or mRNA 1273 Moderna) primary vaccine and neutralizing antibody (follow-up: range 8 days to 58 days)

1[19]	observational studies	serious[e,q]	not serious	serious[g]	not serious	none	21/40 (52.5%)	5/40 (12.5%)	RR 4.20 (1.76 to 10.04)	400 more per 1,000 (from 95 more to 1,000 more)	⊕◯◯◯ Very low	CRITICAL

ChAdOx1 (AstraZeneca) vector vaccine booster with m-RNA based (Pfizer BionTech BNT162b2 or mRNA 1273 Moderna) primary vaccine and Cellular immune response (follow-up: 28 days)

1[18]	randomised trials	not serious	not serious	serious[g]	not serious	none	20/20 (100.0%)	15/20 (75.0%)	RR 1.33 (1.04 to 1.72)	248 more per 1,000 (from 30 more to 540 more)	⊕⊕⊕◯ Moderate	CRITICAL 18

ChAdOx1 (AstraZeneca) vector vaccine booster with m-RNA based (Pfizer BionTech BNT162b2 or mRNA 1273 Moderna) primary vaccine and Cellular Immune repose (follow-up: range 8 days to 58 days)

1[19]	observational studies	serious[e,q]	not serious	serious[g]	serious[c,d]	none	29/40 (72.5%)	22/40 (55.0%)	RR 1.32 (0.94 to 1.85)	176 more per 1,000 (from 33 fewer to 468 more)	⊕◯◯◯ Very low	CRITICAL

ChAdOx-1 recombinant booster with mRNA-based vaccine Primary and Adverse event (follow-up: range 8 days to 58 days)

1[19]	observational studies	serious[19,e,q]	not serious	not serious	serious[c]	none	Simon et al.: ChAdOx1 nCoV-19 - overall 28/66 = 42.4%	⨁◯◯◯ Very low	CRITICAL 19

Viral vector (ChAdOx-1 (Astra Zeneca)/Ad26COVS1) booster with mRNA-based (BNT162b2/ mRNA- 1273) Primary vaccine and anti-RBD IgG titer (BAU/ml) (follow-up: 22 days)

1[19]	observational studies	serious[19,q]	not serious	not serious[g]	serious[c]	none	from 5.9 BAU/ml to 119 BAU/ml (20 fold increae in titer)	⨁◯◯◯ Very low	CRITICAL 19

Viral vector (ChAdOx-1 (Astra Zeneca)/Ad26COVS1) booster with mRNA-based (BNT162b2/ mRNA- 1273) Primary vaccine and Seroconversion (follow-up: 22 days)

1[20]	observational studies	serious[20,q]	not serious	serious[g]	serious[c]	none	Reported in 16.7% (8/48)	⨁◯◯◯ Very low	CRITICAL 20

CI: confidence interval; MD: mean difference; RR: risk ratio

Explanations

a. one study of retrospective nature of the study, hence selection bias may be possible
b. vaccines administered according to availability
c. small sample size
d. wide confidence interval
e. Short post booster follow-up
f. participants with varying co-morbidities which was not comparable between the 2 groups
g. immunogenicity is considered as an indirect measure of efficacy
h. variation in patient characteristics such as length of heart transplant and function of the graft
i. participants with varying immunosuppressive treatment
j. Varying cancer type, status and treatment
k. not all participants underwent cellular response evaluation
l. variation with age and length of renal replacement therapy (RRT)
m. included only participants willing to have their blood drawn after the booster
n. Safety assessment done through a self-administered questionnaire, hence, relied on self-reported adverse reactions felt by the respondents
o. relatively long interval between initial immunisation and booster vaccination
p. pre booster outcomes measured 124 to 167 days from 2nd dose because of prolonged interval from initial to booster vaccination
q. selection of subjects not clear

GRADE evidence profile on heterologous booster versus no booster among elderly population

Author(s): Lylah D. Reyes, MD, Eva I. Bautista, MD, Ma Lucila Perez MD
Question: Heterologous first booster compared to pre booster or no booster for clinical and immunologic efficacy against COVID19 infection among the elderly population
Setting: Korea, Thailand, Italy
Bibliography:

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	heterologous first booster	pre booster or no booster	Relative (95% CI)	Absolute (95% CI)		
mRNA-based booster with Viral Vector ChAdOx1) as primary vaccine and Death due to COVID19 among elderly 60 years old and above (follow-up: 150 days)												
1[1]	observational studies	serious[a,b,c]	not serious	not serious	not serious	none	100/7258905 (0.0%)	675/426767 (0.2%)	RR 0.00871 (0.00706 to 0.01075)	2 fewer per 1,000 (from 2 fewer to 2 fewer)	⨁◯◯◯ Very low	CRITICAL 1
mRNA-based booster with Viral Vector ChAdOx1) as primary vaccine and severe COVID19 infection among the elderly 60 years old and above (follow-up: 150 days)												
1[1]	observational studies	serious[1,a,b,c]	not serious	not serious	not serious	none	365/7258905 (0.0%)	1047/426767 (0.2%)	RR 0.02050 (0.01819 to 0.02309)	2 fewer per 1,000 (from 2 fewer to 2 fewer)	⨁◯◯◯ Very low	CRITICAL 1
mRNA-based booster with Viral Vector ChAdOx1) as primary vaccine and COVID19 infection among elderly 60 years old and above (follow-up: 150 days)												
1[1]	observational studies	serious[1,a,b,c]	not serious	not serious	not serious	none	36511/7258905 (0.5%)	23348/426767 (5.5%)	RR 0.09194 (0.09047 to 0.09343)	50 fewer per 1,000 (from 50 fewer to 50 fewer)	⨁◯◯◯ Very low	CRITICAL 1
mRNA-based heterologous BOOSTER with BNT162b2 (Pfizer BioNTech) or mRNA-1273 or ChAdOx1 or Ad26CoV2PRIMARY vaccine and COVID19 infection (follow-up: 3 months)												
1[2]	observational studies	not serious	not serious	not serious	not serious	none	5237/89.129 (5875.8%)	2260/45777 (4.9%)	RR 1.19 (1.13 to 1.25)	9 more per 1,000 (from 6 more to 12 more)	⨁⨁◯◯ Low	CRITICAL 2
mRNA-based heterologous BOOSTER with BNT162b2 (Pfizer BioNTech) or mRNA-1273 or ChAdOx1 or Ad26CoV2PRIMARY vaccine and COVID19-related hospitalization (follow-up: 3 months)												
1[2]	observational studies	not serious	not serious	not serious	not serious	none	1404/89127 (1.6%)	809/45777 (1.8%)	RR 0.81 (0.75 to 0.88)	3 fewer per 1,000 (from 4 fewer to 2 fewer)	⨁⨁◯◯ Low	CRITICAL 2
mRNA-based heterologous BOOSTER with BNT162b2 (Pfizer BioNTech) or mRNA-1273 or ChAdOx1 or Ad26CoV2PRIMARY vaccine and COVID19-related ICU admission (follow-up: 3 months)												
1[2]	observational studies	not serious	not serious	not serious	not serious	none	152/89127 (0.2%)	108/45777 (0.2%)	RR 0.72 (0.57 to 0.92)	1 fewer per 1,000 (from 1 fewer to 0 fewer)	⨁⨁◯◯ Low	CRITICAL 2
mRNA-1273 booster with mRNA-1273 1st dose and BNT162b2 2nd dose Primary or BNT162b2 booster with mRNA-1273 primary vaccine and serious adverse events (SAE) among elderly 70 years old and above on a long-term care facility (follow-up: 28 days)												
1[3]	observational studies	serious[3,c,d,e]	not serious	not serious	not serious	none	None of the participants regardless of heterologous primary-booster mRNA-based vaccine combination had SAE (n = 183)				⨁◯◯◯ Very low	CRITICAL 3

mRNA-1273 (booster) with mRNA-1273 (1st dose) BNT162b2 (2nd dose) primary vaccine and adverse events among elderly 70 years old and above in a long-term care facility

1[3]	observational studies	serious[3, c]	not serious	not serious	not serious	none	Systemic adverse events such as fever, GI symptoms, tachycardia, and malaise in 28.96% (53/183)	⊕◯◯◯ Very low	CRITICAL 3

mRNA BNT162b2 Pfizer BionTech with CoronoVac Primary vaccine and positive neutralizing antibodies among healthcare workers more than 60 years old (follow-up: 28 days)

1[4]	observational studies	serious[4,f]	not serious	serious[4, g]	not serious	none	Those positive for Nab: Prior to booster = 13.7% to 53.4% Postbooster =54.5% to 100%	⊕◯◯◯ Very low	CRITICAL 4

mRNA BNT162b2 (Pfizer BionTech) booster with CoronaVac Primary vaccine and anti-RBD IgG titer (BAU/ml) among healthcare workers more than 60 years old (follow-up: 28 days)

1[4]	observational studies	serious[4,f]	not serious	serious[4, g]	not serious	none	median concentration of anti-RBD antibodies increased by 32-fold, prior to booster = 77.7 BAU/mL (IQR 42.9–12.3 BAU/mL) vs postbooster 2493.0 BAU/mL (IQR 1272.3– 4328.5)	⊕◯◯◯ Very low	CRITICAL 4

ChAdOx-1 (Astra Zeneca) booster with CoronoVac (Primary and positive neutralizing antibodies among healthcare workers more than 60 years old (follow-up: 28 days)

1[4]	observational studies	serious[4,f]	not serious	serious[4, g]	not serious	none	Those positive for Nab: Prior to booster = 5.2% to 52.8% Postbooster = 41.7% to 100%	⊕◯◯◯ Very low	CRITICAL 4

ChAdOx-1 (Astra Zeneca) booster with CoronaVac Primary vaccine and anti-RBD IgG titer (BAU/ml) among healthcare workers more than 60 years old (follow-up: 28 days)

1[4]	observational studies	serious[4,f]	not serious	serious[4, g]	not serious	none	median concentration of anti-RBD antibodies increased by 10-fold prior to booster = 77.7 BAU/mL (IQR 42.9–12.3 BAU/mL) vs postbooster = 771.0 BAU/mL (IQR 593.8–1344.8)	⊕◯◯◯ Very low	CRITICAL 4

CI: confidence interval; RR: risk ratio

Explanations

a. retrospective nature with possible selection bias
b. Analysis was based on an integrated database from the Korea Disease Control and Prevention Agency, but other patient characteristics were not mentioned such as co-morbidities of the elderly population
c. Co-morbidities whether present or not was not indicated
d. Prior COVID19 infection status not determined
e. adverse events not compared with that after the primary vaccination
f. participants selected their own booster vaccine ChAdOX-1 or BNT162b2. Hence, selection bias is possible.
g. immunogenicity is considered an indirect measure of efficacy

GRADE evidence profile on heterologous or homologous booster versus no booster in elderly population

Author(s): Eva I. Bautista, MD, Lylah D. Reyes, MD, Ma. Lucila Perez, MD
Question: Homologous/heterologous mRNa-based COVId-19 vaccine booster compared to no booster in immunocompromised and elderly?
Setting:
Bibliography:

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	homologous/heterologous mRNa-based COVId-19 vaccine booster	no booster	Relative (95% CI)	Absolute (95% CI)		
COVID-19-associated hospitalization (follow-up: 12 months)												
1[1]	observational studies	not serious	not serious	not serious	not serious	none	2251/27654 (8.1%)	2854/14263 (20.0%)	RR 0.58 (0.46 to 0.73)	84 fewer per 1,000 (from 108 fewer to 54 fewer)	⨁⨁◯◯ Low	CRITICAL

CI: confidence interval; RR: risk ratio

GRADE evidence profile on heterologous or homologous booster versus no booster in immunocompromised population

Author(s):
Question: Homologous/heterologous COVID-19 booster compared to no booster in immunocompromised
Setting:
Bibliography:

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	homologous/heterologous COVID-19 booster	no booster	Relative (95% CI)	Absolute (95% CI)		
COVID-19 associated Hospitalization												
1[1]	observational studies	Serious[a]	not serious	not serious	not serious	none	855/8904 (9.6%)	974/5677 (17.2%)	OR 0.52 (0.46 to 0.57)	74 fewer per 1,000 (from 85 fewer to 66 fewer)	⨁◯◯◯ Very low	CRITICAL

CI: confidence interval; OR: odds ratio

Explanations
a. PCR testing was done only among those who presented with clinical symptoms which may miss those with asymptomatic COVID cases.

Appendix 6: Forest Plots

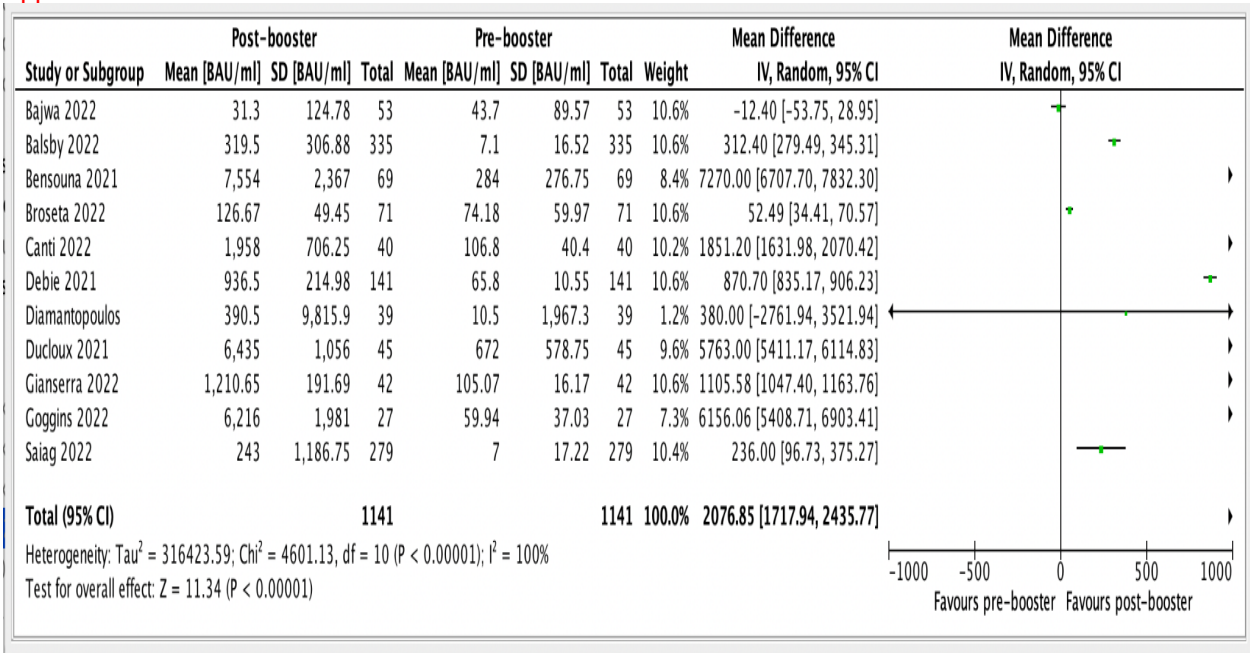


Figure 2. Immunocompromised Population: Homologous monovalent BNT162b2 (Pfizer-BioNTech) booster: ANti-spike Ab MD (SD) post-booster vs pre-booster

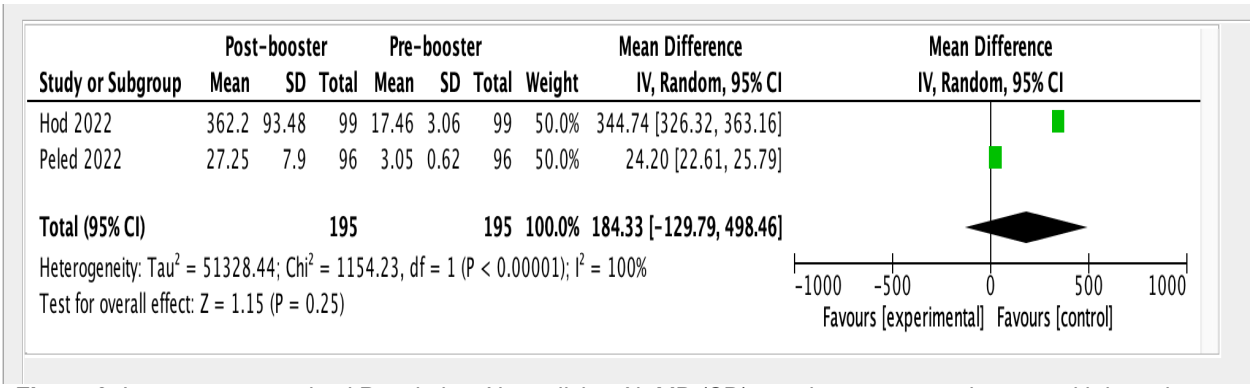


Figure 3. Immunocompromised Population: Neutralizing Ab MD (SD) post-booster vs pre-booster with homologous monovalent BNT162b2 (Pfizer-BioNTech)

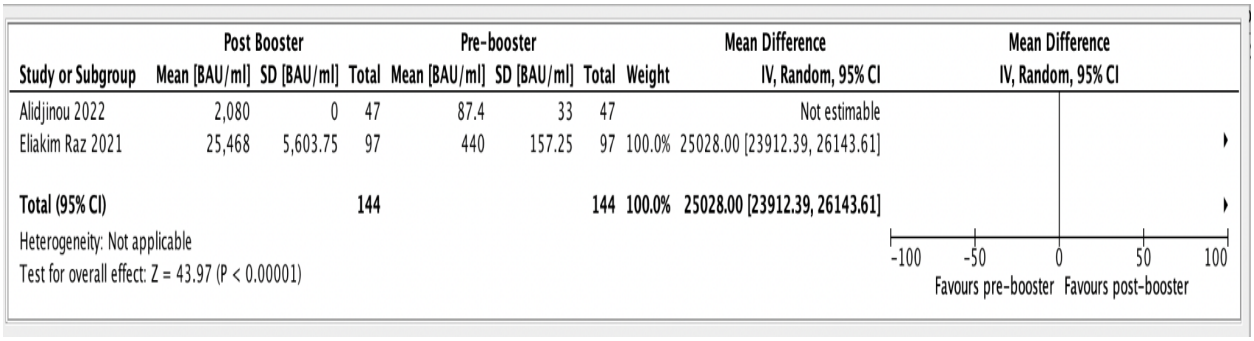


Figure 4. Elderly Population: anti-spike Ab MD (SD) post-booster vs pre-booster with homologous monovalent BNT162b2 (Pfizer-BioNTech)

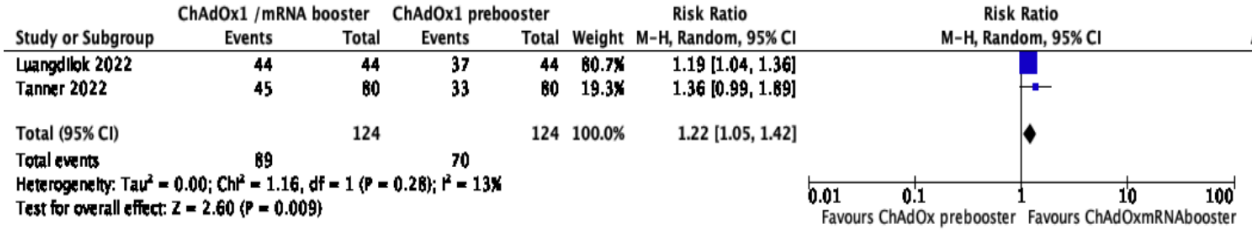


Figure 5. Immunocompromised Population: SARS-CoV2 Spike-1 Antibody assay and mRNA-based vaccine (BNT162B2 or mRNA-1273) booster withChAdOx1 (AstraZeneca) primary vaccine vs pre booster

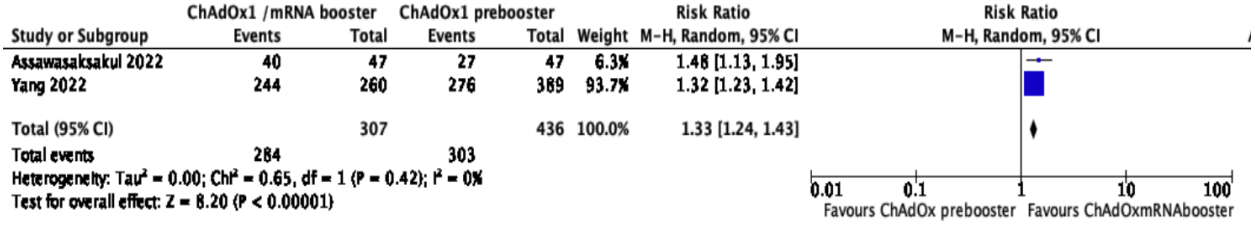


Figure 6. Immunocompromised Population: Cellular immune response and mRNA-based (Pfizer-BioNTech BNT162b2 or mRNA-1273) booster with AstraZeneca viral vector primary vaccine vs pre booster

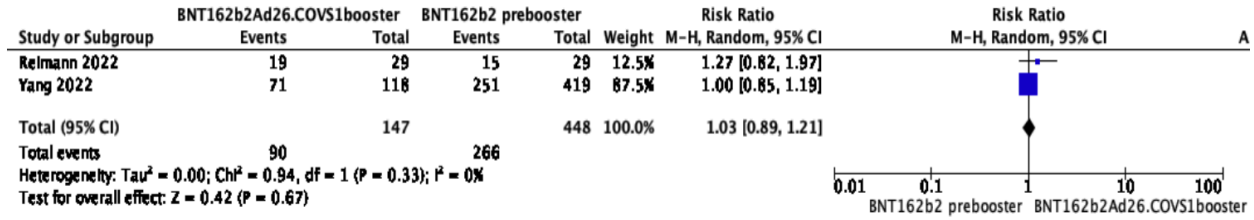


Figure 7. Immunocompromised Population: SARS-CoV2 Spike-1 Antibody assay and Ad26.COVS1 (Janssen) Booster with mRNA BNT162b2 (Pfizer-BioNTech) Primary vaccine vs pre booster

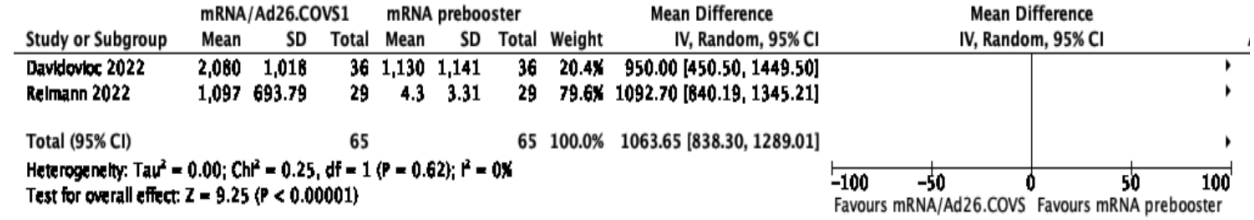


Figure 8. Immunocompromised Population: anti-RBD IgG titer (BAU/ml) and Ad26COVS1 (Janssen) vector booster with mRNA based (BNT162b2 or mRNA-1273) primary vaccine vs pre booster

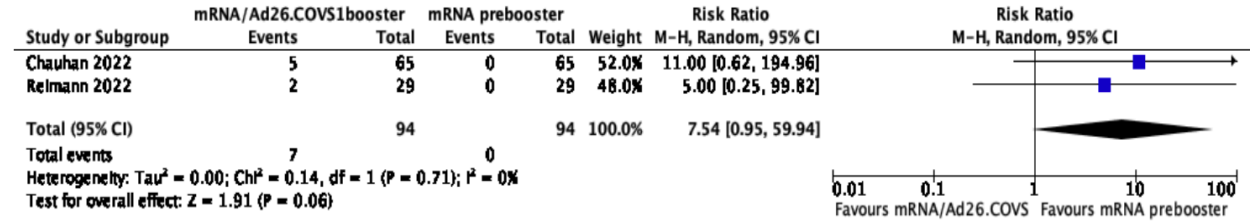


Figure 9. Immunocompromised Population: adverse events and Ad26COVS1 (Janssen) booster with mRNA-based primary vaccine vs pre booster

Appendix 7: Ongoing Studies

Table 5. Ongoing Studies

No (#26)	Title	Status	Intervention	Outcome	Start Date	Completion Date
NCT 04889209	A Phase 1/2 Study of Delayed Heterologous SARS-CoV-2 Vaccine Dosing (Boost) After Receipt of EUA Vaccines Adults and elderly	recruiting	Biological: Ad26.COV2.SBiological: BNT162b2 Biological: mRNA-1273 Biological: mRNA-1273.211Biological: mRNA-1273.222Biological: SARS-CoV-2 rS/M1	Immunogenicity AE	May 2021	Dec 2023
NCT 04927065	A Study to Evaluate the Immunogenicity and Safety of mRNA Vaccine Boosters for SARS-CoV-2 (COVID-19) Variants elderly	Active, not recruiting	mRNA-1273	Immunogenicity AE	May 2021	April 2023
NCT 04961229	Booster Dose of COVID-19 Vaccine for Kidney Transplant Recipients Without Adequate Humoral Response (WHO	Not yet recruiting	BNT162b2	Efficacy Immunogenicity AE	Oct 2021	July 2022
NCT 05000216	Booster Effects With Autoimmune Treatments in Patients With Poor Response to Initial COVID-19 Vaccine (ACV01)	recruiting	Biological: Moderna mRNA-1273Biological: BNT162b2 Biological: Ad26.COV2.S	Efficacy Immunogenicity AE	Aug 2021	Nov 2024
NCT 05016622	Safety and Efficacy of Booster Doses of BNT162b2 Vaccine in Immunocompromised Patients With a Cancer Diagnosis	recruiting	BNT162b2	Efficacy Safety	Aug 2021	Sept 2024
NCT 05022329	A Multi-Centre 12 Month Parallel-Group Randomized Control Trial of BNT162b2 Versus mRNA(Messenger Ribonucleic Acid) -1273 COVID-19 Vaccine Boosters in Chronic Kidney Disease and Dialysis Patients With Poor Humoral Response Following COVID-19 (Corona Virus Disease of 2019)Vaccination	Active, not recruiting	BNT162b2 mRNA-1273	Efficacy Immunogenicity AE	Sept 2021	Sept 2023

NCT 05028374	Phase II Trial Evaluating the Efficacy of Moderna COVID-19 Vaccine Booster Dosing in Patients With Hematologic Malignancies Who Did Not Have an Adequate Response to Prior Vaccination	Active, not recruiting	mRNA1273	Efficacy Safety	Aug 2021	July 2023
NCT 05030974	Optimal Repeated Dose Strategy for SARS-CoV-2 Vaccination in Kidney Transplant Patients A Prospective, Randomized Multicenter Study by the REnal Patients COVID-19 VACcination (RECOVAC) Consortium	Recruitment status completed no results posted	mRNA1273	Efficacy Immunogenicity AE		Last updated March 2022
NCT 05033847	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)	Efficacy Immunogenicity AE	Sept 2021	Jan 2024
NCT 05047640	A Single-Blind, Randomized, Controlled Trial Comparing BNT162b2 vs JNJ-78436735 Vaccine as a Booster Dose After Completion of BNT162b2 Vaccine in Solid Organ Transplant Recipients	Recruitment status completed, no results	Biological: BNT162b2 vaccine Vs Biological: JNJ-78436735 Vaccine	Efficacy Immunogenicity AE	Sept 2021	Last update Oct 2022
NCT 05077254	A Randomized Study to Evaluate Antibody Response to an Additional Dose of SARS-CoV-2 Vaccination With and Without Immunosuppression Reduction in Kidney and Liver Transplant Recipients	recruiting	mRNA 1273 BNT162b2	Efficacy Immunogenicity Safety	Dec 2021	June 2024
NCT 05080218	The SARS-CoV-2 Vaccine Response and Safety in Rheumatology Patients and the Influence of Temporary Interruptions in Immunomodulatory Therapy	recruiting	mRNA vaccine	Efficacy Safety Immunogenicity	Nov 2021	Sept 2023

NCT 05081271	COVID-19 Booster Vaccination in Persons With Multiple Sclerosis	Terminated (most potential participants had already received their booster vaccination outside of the study)				updated Nov 2022
NCT 05104437	A Post-marketing Clinical Study of a Third Dose of the Inactivated SARS-CoV-2 Vaccine (Vero Cells) (Produced in Wuhan): Immunogenicity, Safety and Antibody Persistence Assessments in Patients With Hypertension and/or Diabetes	Not yet recruiting (last update posted)	Inactivated SARS-CoV-2 Vaccine (Vero Cells	Immunogenicity Safety	Nov 2021	Dec 2022
NCT 05104359	Should COVID-19 Quantitative Antibody Titers be Implemented to Guide COVID-19 Booster Vaccinations Regardless of HIV Status, Immunosuppression, or Age?	Completed recruitment No results posted (last update posted July 2022	(Observational)	immunogenicity	Dec 2022	April 2022
NCT 05119738	Immune Response to Third Dose of SARS-CoV-2 Vaccine in a Cohort of Cancer Patients on Active Treatment	recruiting	Cohort (BNT162b2)	Immunogenicity	Oct 2021	June 2022
NCT05279365	Prospective open label clinical trial to administer a booster dose of pfizer/biontech or moderna covid-19 vaccine in high-risk individuals	recruiting	BNT162b2 mRNA-1273	COVID-19 titers of anti-SARS-CoV-2 IgG (Baseline/Day 0, Day 14, Week 12 and Week 24 after booster)	July 2021	Aug 2023
ChiCTR2100049770	A prospective, multicenter, clinical controlled study of COVID-19 vaccine for the elderly population	Not yet recruiting	Inactivated vaccine	Immunogenicity Safety Effectiveness	Aug 2021	June 2022 Updated March 2022

EudraCT Number: 2021-004558-44	Optimal Booster Strategy for SARS-CoV-2 Vaccination in Kidney Transplant patients	Completedno results yet			Oct 2021	
EudraCT Number: 2021-004550-33	Immunogenicity and reactogenicity following a booster dose of COVID-19 mRNA vaccine (Pfizer-BioNtech) and two adjuvanted sub-unit vaccines (SP/GSK) administered in adults who received 2 doses of Pf...	ongoing	mRNA	Immunogenicity	Nov 2021	Not stated
EudraCT Number: 2021-002356-37	Study about the response to the administration of a third dose of mRNA-1273 vaccine (COVID19 vaccine Moderna) in renal transplants with immunological failure initial to vaccination	ongoing			Sep 2021	
EudraCT Number: 2021-005094-28	Population-based prospective, clinical study on efficacy and safety of a booster COVID-19 vaccination (elderly and adults)				Oct 2021	
EudraCT Number: 2021-003573-58	Vaccination against cOvid-19 In CancEr: booster shot BNT161b2 vaccine after full vaccination with ChAdOx1-S vaccine (Tri-VOICE plus)				Aug 2021	
EudraCT Number: 2021-002693-10	A Phase II Study to Evaluate Safety and Efficacy to a Third Vaccination in Immunocompromised Patients with Inadequate Humoral Response after Primary mRNA SARS-CoV-2 (Covid-19) Vaccination	ongoing			July 2021	
EudraCT Number: 2020-003370-41	Immunogenicity and Safety of SARS-CoV-2 Recombinant Protein Vaccines with AS03 Adjuvant in Adults 18 Years of Age and Older as a Primary Series and Immunogenicity and Safety of a Booster Dose			ongoing	Aug 2021	

	of SA... (elderly and adults)					
EudraCT Number: 2021-004526-29	A MULTINATIONAL, PHASE 2, RANDOMISED, ADAPTIVE PROTOCOL TO EVALUATE IMMUNOGENICITY AND REACTOGENICITY OF DIFFERENT COVID-19 VACCINES ADMINISTRATION IN OLDER ADULTS (≥75) ALREADY VACCINATED AGAINST ...	ongoing			Oct 2022	