Philippine COVID-19 Living Clinical Practice Guidelines
Institute of Clinical Epidemiology, National Institutes of Health, UP Manila
In cooperation with the Philippine Society for Microbiology and Infectious Diseases
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EVIDENCE SUMMARY

RESEARCH QUESTION: Among the general population, what is the clinical and immunologic efficacy, effectiveness, and safety of a second booster dose in the prevention of SARS-CoV-2 infection?

Review by: Marquis Von Angelo Syquio Go Joson, MD, Giselle Anne Q. Adajar, MD, Christdianzen Grace Pena Saroca, MD, Ma. Lucila M. Perez, MD, Aileen R. Espina, MD, MPH, MHA, Rosemarie S. Arciaga, MD, MSc, Marissa M. Alejandria, MD, MSc

RECOMMENDATIONS

Recommendations	Certainty of Evidence	Strength of Recommendation
We suggest the preferential use of the following bivalent vaccines over monovalent mRNA vaccines as 2nd homologous booster among the general population: a. BNT162b2 Bivalent (Pfizer-BioNTech) b. mRNA-1273.214 (Moderna)	Very Low	Weak
We suggest the administration of the following second heterologous booster vaccination in the general population: a. BNT162b2 (Pfizer monovalent) b. mRNA-1273 (Moderna monovalent) c. ChAdOx1 (AstraZeneca)	Very Low	Weak
There is no recommendation on the use of the following vaccines as a second homologous booster vaccination in the general population due to insufficient evidence: a. CoronaVac (Sinovac) b. NVX-CoV2373 (Novavax)	Very Low Low	None

Consensus Issues

The Panel considered the benefits of increased immunogenicity and seroconversion in voting on the recommendations for both homologous and heterologous booster vaccination regimens. However, the decision to withhold a recommendation on CoronaVac and NVX-CoV2373 as second homologous booster options was due to the limited evidence available.

For populations studied, quasi-experimental studies had a small sample size. In the case-control studies, thousands were involved. However, both types of studies had low certainty of evidence. The Delta and Omicron periods were studied over a 3-month follow-up period. The Panel gave value to use of immunogenicity and clinical outcomes. The recommendation for heterologous vaccines were chosen by the Panel based on waning immunity over time for breakthrough infections and the evidence presented an increase in immunogenicity and effect on seroconversion factor. Epidemiological-wise, there are more beneficial effects. There is a desire to increase immunogenicity.

KEY FINDINGS

- The systematic search done until February 16, 2023 yielded 12 studies on the COVID-19 vaccine second booster to the general healthy adult population. Seven studies on monovalent vaccine and five studies on bivalent vaccines were found.
- There were no studies on BBIBP-CorV (Sinopharm), Ad26-CoV2-S (Janssen/Johnson&Johnson) and Gam-COVID-Vac (Sputnik V) as second booster dose for the general healthy adult population.

- There was no significant difference in the odds of a COVID-19 associated hospitalization between receiving a second monovalent mRNA (heterologous and/or homologous) booster and not receiving a second booster. (Very Low overall certainty of evidence)
- A homologous second booster vaccination with monovalent BNT162b2 (Pfizer-BioNTech) showed a large 8.5-fold increase in humoral anti-spike protein IgG antibody response with modest cellular response against wild-type, beta, and delta variant in a quasi-experimental study. No serious adverse event related to vaccination were reported in that study. (Very Low overall certainty of evidence)
- One study showed that a homologous monovalent second booster with mRNA-1273 (Moderna) significantly reduced Omicron infection, but protection against hospitalization was not consistent across the Omicron subvariants tested. (Very Low overall certainty of evidence)
- An immunogenicity study showed that CoronaVac (Sinovac) showed a moderate 2.5-fold increase in neutralization antibody response but had low seroconversion against Omicron. (Very Low overall certainty of evidence)
- There was no clinical efficacy data available for NVX-CoV2373 (Novavax) as second booster. Safety outcomes showed no significant difference in the odds of having a local, systemic, and unsolicited adverse reactions between a second booster and a first booster of NVX-CoV2373 (Novavax). Increase in anti-rS IgG titers and neutralization titers were found after the first and second booster vaccination. However, there was not enough data available for a comparison on the immunogenicity outcome. (Low overall certainty of evidence)
- Real-world evidence data of heterologous monovalent second dose booster of either monovalent mRNA-1273 (Moderna), BNT162b2 (Pfizer-BioNTech), or ChAdOX1 (AstraZeneca) showed a significant risk reduction of COVID-19 infection among those who received a second booster vaccination compared to no second booster dose but with no significant benefit against progression to severe COVID-19. An immunogenicity study with monovalent mRNA-1273 (Moderna) or BNT162b2 (Pfizer-BioNTech) as a heterologous second dose booster also showed a large-fold increase in anti-spike protein IgG antibody titers and cellular response against the wild-type strain. (Very Low overall certainty of evidence)
- For both bivalent BNT162b2 (Pfizer-BioNTech) and mRNA-1273.214 (Moderna) vaccines given as homologous second booster, one large real-world study showed that receiving a bivalent booster was significantly associated with a lower risk of COVID-19 infection and hospitalization among 18 to 64 years of age compared to no bivalent booster. (Very Low overall certainty of evidence)
- Both types of bivalent mRNA vaccine consistently showed a significantly larger increase in neutralization antibody titers against Omicron variants compared to the monovalent vaccine. (Very Low overall certainty of evidence)
- For the monovalent vaccines, no significant serious adverse events related to vaccination were reported across the studies on heterologous or homologous boosters, while for the bivalent vaccines, real-world safety data noted five reports of myocarditis and four reports of pericarditis. (Very low overall certainty of evidence)

INTRODUCTION

Vaccination is important in controlling the impact of COVID-19. However, protection from vaccination wanes over time. In addition, with the emergence of new variants, further protection is needed. Recent advances in COVID-19 vaccine technology have allowed the incorporation of the Omicron strain in the form of a bivalent mRNA vaccine. These had led to further evaluate additional booster doses [1-2].

The World Health Organization defines a second booster as the fourth dose overall in a two-dose primary series and as the third dose overall in a single dose primary series [1]. The practice of a second booster for the general adult healthy population on top of a single booster following the primary vaccination series must be based on clinical evidence supporting its efficacy, effectiveness, and safety.

REVIEW METHODS

An initial systematic search was done last September 10, 2022. An updated search focused on bivalent vaccines as second booster was done until December 30, 2022. With the growing number of evidence available, another search to update evidence on monovalent vaccine was done until February 16, 2023. The various electronic databases and registers that were searched one were as follows: MEDLINE, Cochrane CENTRAL, L.OVE Platform for COVID-19 Evidence, COVID-NMA, medRxiv.org and bioRXiv.org, www.metaEvidence.org, Cochrane COVID-19 Study Register, US Clinical Trails Registry, Chinese Trial Registry, and EU Clinical Trials Registry. The search strategies and PRISMA flowchart are seen in Appendix 2 & 3.

Clinical trials and observational studies on the clinical and immunologic efficacy, effectiveness, and safety of a second booster dose compared to a no second booster dose on top of a primary series and a first booster dose in the general adult healthy population (aged 18 to 60 years) were considered for this evidence summary. Clinical outcomes (e.g., risk of infection, disease progression, hospitalization) were prioritized. The immunologic outcomes included studies reporting antibody titers or T-cell counts. When fold changes were reported, these were qualified based on the WHO criteria of no to minimal change for <2-fold difference, moderate for 2-5-fold difference, and large for >5-fold change. Safety outcomes from all studies were also included.

Studies on the immunocompromised, the elderly, those with high-risk comorbidities, and healthcare workers were excluded in this review. In addition, articles that had no available full-text reports or with insufficient data to make comparison between the second booster dose and no second booster dose received were excluded.

Methodological quality assessment of the included studies was done with the Cochrane Risk of Bias tool version 1 for the randomized trials [3], the Newcastle – Ottawa Quality Assessment Scale for case-control and cohort studies [4], and the JBI Critical Appraisal Checklist for Quasi-Experimental Studies [5].

RESULTS

Characteristics of Included Studies

The search yielded a total of 12 studies [2,6-16]. There are seven studies on monovalent vaccines [2,6-11] and five studies on bivalent vaccines [12-16].

For the monovalent vaccines, two quasi-experimental studies [6,7], three case-control studies [2,8-9], one retrospective cohort [10] and one randomized controlled trial [11] were found. The clinical trial [11] and one of the quasi-experimental studies [6] are in pre-print.
Four studies have clinical outcomes [2,8-10]. Four studies used homologous second booster vaccines (CoronaVac n=1, BNT162b2 n=1, mRNA-1273 n=1, Novavax n=1) [6-7,9,11]. Three studies used heterologous booster combinations with a variable primary series and first booster combined with second boosters of either BNT162b2, ChAdOx1, or mRNA-1273 [2,7,10]. One case-control is on monovalent mRNA that did not specify if a heterologous or homologous vaccination was done [8]. (Appendix 4)

As of December 30, 2022, five studies on bivalent vaccines were included in this review. Two quasi-experimental studies [12-13], two population-based case-control studies [14-15], and one safety study on bivalent mRNA were found [16]. Two studies reported immunogenicity data [12-13], and two reported clinical outcomes [14-15]. All clinical outcomes with bivalent vaccination as an intervention had no 2nd booster as a comparator. The two immunologic studies [12-13] compared bivalent vaccines against the monovalent type. One study is still in pre-print publication [13]. (Appendix 4)

Methodological quality assessment showed the case-control and cohort studies were of good quality in the Newcastle-Ottawa Scale. The clinical trial had high risk of bias based on the Cochrane Risk of Bias tool. All the quasi-experimental studies were of moderate quality based on the JBI Critical Appraisal Checklist for Quasi-Experimental Studies. (Appendix 5)

As of the last search date, there were no evidences on BBIBP-CorV (Sinopharm), Ad26-CoV2-S (Janssen/ Johnson&Johnson) and Gam-COVID-Vac (Sputnik V) as second booster dose for the general healthy adult population.

Monovalent Vaccines

mRNA Vaccines [BNT162b2 (Pfizer-BioNTech) or mRNA-1273 (Moderna)]

In the United States, a test-negative case-control study showing the effectiveness of monovalent mRNA vaccine was done but no results on safety. Immunocompetent adults (aged >18 years old) admitted for COVID-19-like illness were the study participants (n=4730). Age range is 18 to ≥ 85 years with a median of 65 years old. Around 50% of the population was aged 18 to 64 years old (n=2357). Monovalent mRNA vaccines were used as the first and second booster. The primary series that the participants received were not specified if a homologous or heterologous vaccination scheme was done. Follow-up time was 7 to 120 days after each vaccination of the first and second booster. The study was done during the time when Omicron was the predominant variant. No immunologic and safety outcomes were presented [8].

Effectiveness Outcomes

Real-world effectiveness of monovalent mRNA against COVID-19 associated hospitalization showed that the odds of a COVID-19 associated hospitalization is not significantly different between a second booster dose and not receiving a second booster dose (OR 0.85, 95% CI 0.64-3.22).

Certainty of Evidence

The overall certainty of evidence is Very Low due to imprecision in an observational study.

Homologous Vaccination of BNT162b2 (Pfizer-BioNTech)

One quasi-experimental study presented only the immunogenicity and safety data of a homologous second booster vaccination of BNT162b2 (Pfizer-BioNTech) in healthy adults without clinical outcomes reported [7].

Immunogenicity outcomes

The study by Munro et al. (n=31) showed a considerable decay in anti-spike protein IgG titers by the time the second booster was given approximately seven months after the first booster. Among adults less than 70 years of age, a large eight-fold increase in SARS-Cov2 anti-spike protein IgG levels was noted after 14 days of giving the second booster of BNT162b2, 8.45 fold change (95% CI 7.83-9.11; n=12). The T-cell response measured against the wild-type and delta variants was significantly increased by four to five-fold change after 14 days of giving the second booster dose, but not for the beta variant [7].

Safety outcomes

No serious adverse events related to the monovalent BNT162b2 (Pfizer-BioNTech) vaccine were reported in the study of Munro, but there were four unspecified non-serious adverse events [7].

Certainty of Evidence

The overall certainty of evidence is Very Low due to indirectness of the immunogenicity results and imprecision in an observational study.

Homologous Vaccination of mRNA-1273 (Moderna)

A test-negative case-control study done by Tseng et al. (n=123,326) in the United States has shown the real-world effectiveness of a homologous mRNA-1273 (Moderna) second booster vaccination. The population's median age was 46 years, and 82% of the participants were aged 18 to 64 years old. Immunogenicity and safety outcomes were not reported [9].

Effectiveness Outcomes

Omicron COVID-19 Infection

In the study by Tseng et al., fourteen days after the second booster, protection from COVID-19 infection was observed. By 31 to 90 days after receiving a second booster dose, significant protection was conferred against infection for the omicron sub-variants BA.2, BA.2.12.1, BA.4, and BA.5 (pooled OR 0.67, 95% CI 0.59-0.76). Beyond 90 days, protection against BA.2 and BA.2.12.1 sub-variants waned but not for the BA.4 and BA.5 sub-variants [9].

Hospitalization

For COVID-19 hospitalization, hospital records collected over 6 months showed a significant protective effect against Omicron (pooled OR 0.46, 95% CI 0.22–0.97). Subgroup analysis showed that protection was only effective against the BA.2 sub-variant (OR 0.264, 95% CI 0.091-0.766) but not for the BA.4/BA.5 sub-variant (OR 1.23, 95% CI 0.378-4.007) [9].

Certainty of Evidence

Issues on serious risk of bias in an observational study led to a Very Low overall certainty of evidence.

Homologous Vaccination of CoronaVac (Sinovac)

A small quasi-experimental study (n=138) reported only the elicited immune response of CoronaVac (Sinovac) as second booster in the general healthy adult population [6] and no clinical and safety outcomes.

Immunogenicity outcomes

Subjects (n=138) received the CoronaVac (Sinovac) vaccine as second booster six months after the first booster [6]. There was a 2.5-fold increase in the neutralizing antibody response against the wild type (WT) SARS-CoV-2 after comparing the antibody levels taken before the homologous second booster dose and after an interval of 4 to 9 weeks from the administration (220.4 vs 549.2 GMU; $p<0.001$). Inoculation of a second booster led to a 67.8% seroconversion against the Delta variant (n=59/87) and 18.4% seroconversion (n=16/87) against the Omicron variant.

Certainty of Evidence

Serious risk of bias, indirectness and imprecision led to a Very Low overall certainty of evidence on the use of CoronaVac (Sinovac) as second booster with a homologous vaccination scheme.

Homologous Vaccination of NVX-CoV2373 (Novavax)

A preprint of an ongoing Phase 2, randomized, observer-blinded, placebo-controlled trial on NVX-CoV2373 (Novavax) in USA and Australia reported the immunogenicity and safety of the second booster dose (fourth homologous booster. Healthy adults aged 18 to 84 years old were given homologous vaccination of NVX-CoV2373 (Novavax) (N=257) and followed up to 28 days after each vaccination. However, approximately 18% received the second booster dose (n=45). Efficacy outcomes were not reported [11].

Immunogenicity outcomes

Only graphical results of the anti-rS IgG titers and neutralization titers after vaccination were presented and no data for statistical analysis was provided. An increase in both titers after the first booster dose was followed by a gradual decline. Then 14 days after the second booster, an increase in anti-rS IgG and neutralization titers were again noted [11].

Safety outcomes

The study showed no significant difference in the odds of having any local and systemic adverse reaction between the second and no second booster dose within 7 days of vaccination. [(local: OR 0.63, 95%CI 0.29-1.34); (systemic: OR 0.60, 95%CI 0.29-1.26)]. This was also seen in Grade 3 local and systemic reactions [(Gr 3 local: OR 1.53, 95%CI 0.59-4.00); (systemic: OR 1.11, 95%CI 0.42-2.93)]. Local reactions noted were tenderness, pain, swelling and erythema. Systemic reactions reported were fatigue, headache, muscle pain, malaise, joint pain, nausea or vomiting, and fever.

Odds of vaccine-related unsolicited adverse reactions within 28 days of vaccination of second booster vaccination is not significantly different from those who did not receive a second booster vaccination (OR 2.46, 95%CI 0.59-10.32). Details of the unsolicited adverse reactions were not available in the study.

Certainty of Evidence

The overall certainty of evidence for the safety of NVX-CoV2373 (Novavax) is Low due to imprecision and issues in the risk of bias as study is just a pre-print with only a small number of participants receiving the treatment group and a short duration of follow-up.

Heterologous Vaccination [ChAdOx1 (AstraZeneca), BNT162b2 (Pfizer-BioNTech), mRNA-1273 (Moderna)]

Effectiveness Outcomes

One test-negative case-control study in Thailand observed 823 subjects given a second booster in the Omicron-dominant period: 50% received BNT162b2, 44% received mRNA-1273, and 6% received ChAdOx1. Five vaccines were used as primary series and first booster: CoronaVac, ChAdOx1, Sinopharm, BNT162b2, and mRNA-1273. However, the varying combinations of these vaccines were not reported. Vaccination with a second booster compared to no second booster was significantly associated with a lower risk for COVID-19 infection (OR 0.48, 95% CI 0.40-0.57). For positive cases, the median time from the last vaccination was 44 days for those given a second booster dose and 58 days for no second booster dose. Said findings were more consistent across the 18 to 50 year age groups, with only limited data for older ages [2].

A retrospective cohort study in Thailand observed the incidence of severe COVID-19 infection during the Omicron-dominant period among COVID-19 patients who received heterologous vaccines [10]. Subjects were given a second booster of either Pfizer-BioNTech (47.9%), Moderna (44.4%), or ChAdOx1 (7.5%). Vaccination with these vaccines as second booster did not significantly prevent the progression to severe COVID-19 (OR 0.20, 95%CI 0.01-3.22) compared to those without a second booster. The median time of follow-up was 92 days.

Immunogenicity outcomes

The study by Munro evaluated IgG titers and cellular response among those who received heterologous vaccination schedules with either half-dose (50ug) monovalent mRNA-1273 or BNT162b2 as second booster. The combinations were: (1) 2 primary doses of ChAdOx1 with BNT162b2 as first and second booster doses (n=35), (2) 2 primary doses of ChAdOx1 with BNT162b2 as first booster and mRNA-1273 as second booster (n=34), and (3) 2 primary doses of BNT162b2 with BNT162b2 as first booster and mRNA-1273 as second booster (n=33) [7].

Subgroup analysis for those <70 years old was done in the study. Large fold increases in IgG were noted in all vaccine combinations from day 0 to day 14 of second booster ranging from 13.15-fold to 19.73-fold with those given two doses of ChAdOx1 plus one BNT162b2 and one mRNA-1273 combination with the highest fold increase at 19.73-fold (17.59–22.13). All heterologous combinations with second boosters also showed large increases (six to eleven-fold change) in cellular response against the different sub-variants (wild-type, beta, and delta) [7].

Safety outcomes

In the study by Munro et al., the most solicited local and systemic adverse events for those who received heterologous second booster dose were pain, fatigue, headache, malaise, and muscle ache. Four unspecified adverse events of special interest were reported in the group that received three doses of the heterologous mRNA-1273 booster combination but was unrelated to the vaccination. No serious adverse events related to vaccination were reported [7].

Certainty of evidence

The certainty of evidence for effectiveness of a heterologous second booster vaccination of either ChAdOx1 (AstraZeneca), BNT162b2 (Pfizer-BioNTech), or mRNA-1273 (Moderna) against COVID-19 infection is Very Low due to serious risk of bias and imprecision. Immunogenicity outcomes have very low certainty of evidence due to serious risk of bias, indirectness, and imprecision. The certainty of evidence of safety outcome was downgraded to Very Low due to imprecision in an observational study. The overall certainty of evidence is Very Low.

Bivalent Vaccines

Bivalent mRNA Vaccines Second Booster VS No Second Booster

Effectiveness Outcomes

Two test-negative case-control studies [14-15] investigated the effectiveness of the two mRNA vaccines as a homologous second booster compared to having no second booster. Link-Gelles et al. (n=3,446) looked at effectiveness in preventing COVID-19 infection during the Omicron-dominant period. After an interval period of 2 to 3 months, receipt of a bivalent second booster vaccine among those 18 to 49 years of age decreased the risk for COVID-19 infection (OR 0.76, 95% CI 0.67-0.86) but not for the elderly 50 to 64 years old (OR 0.85, 95% CI 0.69-1.04). Among those who had a longer time interval since receiving their monovalent booster dose (>4 months interval period), the administration of a bivalent booster dose was consistently associated with a significantly lower risk of COVID-19 infection among both age groups: 18 to 49 years (OR 0.59, 95% CI 0.53-0.65) and 50 to 64 years (OR 0.69, 95% CI 0.58-0.88) [14].

In Tenforde et al.'s study, receiving a second bivalent booster dose after 2, 3, or 4 monovalent doses (n=15,526, median age=73) was associated with a significant decrease in COVID-19 hospitalization compared to having no second booster (OR 0.55, 95% CI 0.40-0.75) [15].

Safety outcomes

One retrospective descriptive study [16] looked at the real-world safety data and received 211,959 reports from patients who were boosted with either BNT162b2 Bivalent (Pfizer-BioNTech) (58%) or mRNA-1273.214 (Moderna) (42%) vaccine. Sixty percent of the participants were between 18 to 64 years of age. Only 45% percent (96,241) reported using a bivalent dose as their fourth COVID-19 vaccine, with the rest as their fifth. Of the reports received, 95.5% were nonserious events. Five reports of myocarditis and four reports of pericarditis were described after bivalent booster vaccination (n=211,959) following the administration of 22.6 million doses in the United States. Fifty-five recipients reported hospitalization following booster vaccination, with 29 indicating that this was unrelated to the vaccination [16].

Certainty of evidence

The certainty of evidence for effectiveness against COVID-19 infection of a bivalent mRNA second booster vaccination compared to a no second booster vaccination is Very Low due to serious risk of bias in an observational study. Certainty of evidence against COVID-19 hospitalization is Very Low due to indirectness as data is pooled from those who received 2, 3 and 4 doses of monovalent mRNA vaccine in the observational study. Safety outcome has Very Low certainty of evidence due to serious risk of bias in an observational study. Overall certainty of evidence is Very Low.

Bivalent mRNA Vaccines Second Booster VS Monovalent mRNA Vaccines Second Booster

Homologous Bivalent mRNA-1273.214 (Moderna) Vaccination

Effectiveness Outcomes

Chalkias et al. studied 50µg mRNA-1273.214 bivalent and 50µg mRNA-1273 monovalent vaccines when administered as homologous second booster doses (n=594) [12]. As an exploratory outcome, the risk for COVID-19 infection was not significantly different (OR 1.06, 95% CI 0.43-2.58).

Chalkias et al. also studied the immunogenicity and safety of bivalent and monovalent mRNA-1273 vaccines. The geometric mean titer (GMT) of neutralizing antibodies against Omicron B.1.1.529 at 28 days after giving the second booster was compared to baseline (prior to the booster). Results show that regardless of prior history of SARS-CoV-2 infection, bivalent booster induced a higher immunogenicity. This was consistent among the different variants. Against the ancestral SARS-CoV-2 D614G, the bivalent group showed a 4.1-fold change (95% CI 3.8-4.4) and was non-inferior to the monovalent group with a 3.1-fold change (95% CI 2.9-3.4). The observed neutralizing antibody response against omicron BA.4/5 subvariants at 28 days was 68% higher after the bivalent booster (5.4 fold change increase, 95% CI 5.0-5.9) compared to the monovalent booster (3.1 fold change increase, 95% CI 2.8-3.3) [12].

Immunogenicity outcomes

Seroresponse after administering both bivalent and monovalent vaccines against ancestral SARS-CoV-2 D614G or Omicron BA.1 variant was comparable at 99.4% to 100%. The analysis showed a trend wherein GMFRs were higher in the bivalent booster group than in the monovalent booster group against the omicron, beta, delta, gamma, and alpha variants [12].

Safety outcomes

Adverse reaction rates within 7 days from mRNA-1273.214 (bivalent Moderna) vaccination were similar in both groups (OR 1.11, 95% CI 0.74-1.67). Injection site pain was the most frequent local adverse reaction for both boosters. Fatigue, headache, myalgia, and arthralgia were the most frequent systemic reactions reported [12].

Adverse events occurring within 28 days after receiving mRNA-1273.214 (bivalent Moderna) vaccination were similar for both groups (OR 0.98, 95% CI 0.54-1.77). Medically attended adverse events occurred in two participants in the bivalent group (grade 2 fatigue and grade 1 dermatitis) and two in the monovalent group (hypertension and urticaria, both grade 1). No serious adverse events considered related to vaccination were observed in both vaccine. No deaths, myocarditis, or pericarditis were reported [12].

Homologous BNT162b2 Bivalent (Pfizer-BioNTech) Vaccination

Immunogenicity outcomes

Zou et al. observed the immunogenicity of bivalent and monovalent BNT162b2 as a homologous second booster dose among adults aged 55 and above (n=78). Regardless of COVID-19 infection status, a second booster of bivalent vaccine consistently induced a large geometric mean neutralizing titer fold rise in antibody response across the following COVID-19 strains: BA.4/5, 13 fold change (95% CI 8.0-21.1); BA.4.6,11.1 fold change (95% CI 7.1-17.3); BA.2.75.2, 6.7 fold change (95% CI 4.4-10.2); and XBB.1, 4.8 fold change (95% CI 3.3-6.9). Compared to the newer bivalent vaccines, monovalent booster dose only elicited a minimal to moderate increase in neutralizing titers for the same strains as above (range of 1.5-2.9 fold change). Comparing geometric mean fold rise ratios, bivalent vaccines showed constant superiority for all strains (4.5x higher titers for BA.4/5; 4.8x higher titers for BA.4.6; 3.2x higher titers for BA.2.75.2; 3.2x higher titers for XBB.1). No safety data was reported [13].

Certainty of evidence

The certainty of evidence for effectiveness against COVID-19 infection of a bivalent mRNA-1273.214 (Moderna) second booster vaccination compared to a monovalent mRNA-1273 (Moderna) second booster vaccination is Very Low due to issues in risk of bias, indirectness, and imprecision. Immunogenicity outcomes of bivalent mRNA-1273.214 (Moderna) and BNT162b2 Bivalent (Pfizer-BioNTech) is Very Low due to issues on the risk of bias and indirectness. Imprecision and risk of bias led to a Very Low certainty of evidence for the safety outcome of bivalent mRNA-1273.214 (Moderna). Overall, the certainty of evidence is Very Low.

RECOMMENDATIONS FROM OTHER GROUPS

WHO-SAGE and ECDC-EMA recommends a second COVID-19 booster to high-risk groups (elderly, immunocompromised, healthcare workers) only [1,17]. CDC-ACIP does not have recommendations for a second booster dose. However, as of their December 12, 2022 interim clinical considerations, monovalent mRNA vaccines are not recommended as booster doses [18-19]. In the Philippines, those that are eligible to receive a second booster dose are the following: Workers in Essential Health Services (A1), Senior Citizens (A2), individuals 18 to 49 years old with comorbidities, and individuals more than 50 years old [20-21].

Table 1. Summary of Recommendations from Other Groups

Group / Agency	Recommendation	Strength of Recommendation
World Health Organization/ Strategic Advisory Group of Experts (SAGE) recommendations [1] As of August 18, 2022	WHO recommends that countries consider a second booster dose for the following population groups: 1. All older persons (age specific cut-off should be defined by countries based on local COVID-19 epidemiology) 2. All persons with moderately and severely immunocompromising conditions 3. Adults with comorbidities that put them at higher risk of severe disease 4. Pregnant women and Health workers	Not reported
Center for Disease Control & Prevention (CDC) Advisory Committee on Immunization Practice (ACIP) [18,19] As of December 12, 2022	No recommendations for second booster dose Recommendations available are for the first booster dose: Booster vaccination People ages 6 months and older are recommended to receive 1 bivalent mRNA booster dose after completion of any FDA-approved or FDA-authorized primary series or previously received monovalent booster dose(s) with the following exception: children ages 6 months to 4 years who receive 2 primary series doses of a monovalent Pfizer-BioNTech vaccine and 1 bivalent Pfizer-BioNTech vaccine for the third primary series dose are not authorized to receive a booster dose at this time. Monovalent mRNA vaccines are not authorized as a booster dose. A monovalent Novavax booster dose (instead of a bivalent mRNA booster dose) may be used in limited situations in people ages 18 years and older who completed any FDA-approved or FDA-authorized monovalent primary series, have not received any previous booster dose(s), and are unable (i.e., contraindicated or not available) or unwilling to receive an mRNA vaccine and would otherwise not receive a booster dose	Not reported
European Centre For Disease Prevention and Control (ECDC) &	Second booster dose of mRNA vaccines for people aged 60 years and above and vulnerable persons.	Not reported

European Medicines Agency (EMA) [17] As of July 11, 2022		
Department of Health Advisory No. 154 dated 19 May 2022 [20] Advisory No. 3 dated 27 July 2022 [21]	DOH Advisory (19 May 2022) 1. Individuals 18 years old and above belonging to Priority Groups A1: Workers in Essential Health Services (including all its sub-groups) and A2: Senior Citizens are eligible to be given a second COVID-19 booster dose, either homologous or heterologous; 2. Previously categorized individuals under Priority Group A1: Workers in Frontline Health Services are still qualified to be given the second COVID-19 booster doses. 3. Based on the recommendations of HTAC and World Health Organization, the following COVID-19 vaccines with approved EUAs issued by the Philippine FDA shall be use for the administration of second booster doses to Priority Groups mentioned above: a. Tozinameran/Comirnaty [Pfizer] COVID-19 vaccine b. Spikevax [Moderna] COVID-19 vaccine 4. The 2nd booster dose shall be administered at least four (4) months after the third (3rd) dose or first (1st) booster dose. DOH Advisory (27 July 2022) Second booster to individuals 50 years old and above & adults 18 to 49 years old with comorbidities	Not reported

ONGOING STUDIES AND RESEARCH GAPS

As of February 16, 2023, there are 12 ongoing trials on clinicaltrials.gov and 2 ongoing trials in EU Clinical Trials Register. Among those that have an “active, not recruiting” status, the earliest completion date is June 2023. (Appendix 7)

The following are identified research gaps regarding COVID-19 second booster vaccination in the general healthy adult population.

1. Effectiveness, efficacy, and safety of other COVID-19 vaccine types (monovalent/bivalent) as second booster for the general adult population.
2. Duration of protection of second booster vaccination in the general adult population
3. Optimum interval of the second booster vaccination from the first booster vaccination.

ADDITIONAL CONSIDERATIONS FOR EVIDENCE TO DECISION (ETD) PHASE

COST

As per DOH statement dated March 18, 2021, the Philippine government estimates an average composite cost of around PHP 1,300.00 per person for the vaccination program (inclusive of a two-dose requirement and ancillary) [22].

A study on cost-effectiveness of COVID-19 vaccination in 91 low- and middle-income countries was done. Philippines is one of the countries that were included. In the data that the study provided, as of May 2022, the Philippines has a vaccine coverage of 58%. From the study, increasing the vaccination coverage of our country to 60% during an Omicron-like setting can prevent around 415,000 new infections and 3,100 COVID-related deaths. This would cost around US$27 million. An incremental cost-effectiveness ratio of US$101 per infection prevented [23]. As of this writing, there were no available economic evaluation specifically on second COVID-19 booster dose done in the Philippines. As per Department of Health (DOH)

statement dated March 18, 2021, a full-blown cost-effectiveness analysis is not done under a pandemic situation. Cost-effectiveness is not a priority during this time [24].

The potential cost-effectiveness of a booster will reduce when the population incidence rate falls. A booster strategy will no longer be cost-effective if the population incidence in older adults reduces below 8.1/100,000 person-day. In a setting with already high 2-dose vaccination coverage, the booster may further reduce the population incidence to below the threshold value in the elderly population and render it not cost-effective [25].

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

There were no studies found on patient's preference, equity, acceptability and feasibility of second booster vaccination in the general adult population.

Values

A cross-sectional study among 18 to 24 year old Filipinos (n=1,692) showed that 57.03% of the respondents do not intend to complete their COVID-19 vaccinations. Young adults who rate their health as "very good" or "excellent" report higher life satisfaction and higher pandemic fatigue and have no exposure to persons with COVID-19 are less likely to complete their COVID-19 vaccination [26].

REFERENCES

[1] World Health Organization. Good Practice Statement on the Use of Second Booster Doses for COVID-19 Vaccines [Internet]. 2022 Aug. Available from: https://apps.who.int/iris/bitstream/handle/10665/361714/WHO-2019-nCoV-Vaccines-SAGE-Boosters-2022.1-eng.pdf

[2] Intawong K, Chariyalertsak S, Chalom K, Wonghirundecha T, Kowatcharakul W, Thongprachum A, et al. Effectiveness of heterologous third and fourth dose COVID-19 vaccine schedules for SARS-CoV-2 infection during delta and omicron predominance in Thailand: A test-negative, case-control study. Lancet Reg Health Southeast Asia [Internet]. 2022;100121. Available from: http://dx.doi.org/10.1016/j.lansea.2022.100121

[3] Higgins JPT, Altman DG, Gøtzsche PC, Jüni P, Moher D, Oxman AD, et al. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. BMJ [Internet]. 2011;343(oct18 2):d5928. Available from: http://dx.doi.org/10.1136/bmj.d5928

[4] Wells GA, Shea B, O'Connell D, Peterson J, Welch V, Losos M, et al. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses [Internet]. Ohri.ca. [cited 2023 Mar 18]. Available from: https://www.ohri.ca/programs/clinical_epidemiology/oxford.asp

[5] Tufanaru C, Munn Z, Aromataris E, Campbell J, Hopp L. Chapter 3: Systematic reviews of effectiveness. In: JBI Manual for Evidence Synthesis. JBI; 2020.

[6] Melo-González F, Méndez C, Peñaloza HF, Schultz BM, Piña-Iturbe A, Ríos M, et al. Humoral and cellular response induced by a second booster of an inactivated SARS-CoV-2 vaccine in adults [Internet]. bioRxiv. 2022. Available from: http://dx.doi.org/10.1101/2022.08.22.22279080

[7] Munro APS, Feng S, Janani L, Cornelius V, Aley PK, Babbage G, et al. Safety, immunogenicity, and reactogenicity of BNT162b2 and mRNA-1273 COVID-19 vaccines given as fourth-dose boosters following two doses of ChAdOx1 nCoV-19 or BNT162b2 and a third dose of BNT162b2 (COV-BOOST): a multicentre, blinded, phase 2, randomised trial. Lancet Infect Dis [Internet]. 2022;22(8):1131–41. Available from: http://dx.doi.org/10.1016/S1473-3099(22)00271-7

[8] Surie D, Bonnell L, Adams K, Gaglani M, Ginde AA, Douin DJ, et al. Effectiveness of monovalent mRNA vaccines against COVID-19-associated hospitalization among immunocompetent adults during BA.1/BA.2 and BA.4/BA.5 predominant periods of SARS-CoV-2 Omicron variant in the United States - IVY Network, 18 states, December 26, 2021-August 31, 2022. MMWR Morb Mortal Wkly Rep [Internet]. 2022;71(42):1327–34. Available from: http://dx.doi.org/10.15585/mmwr.mm7142a3

[9] Tseng HF, Ackerson BK, Bruxvoort KJ, Sy LS, Tubert JE, Lee GS, et al. Effectiveness of mRNA-1273 vaccination against SARS-CoV-2 omicron subvariants BA.1, BA.2, BA.2.12.1, BA.4, and BA.5. Nat Commun [Internet]. 2023;14(1):189. Available from: http://dx.doi.org/10.1038/s41467-023-35815-7

[10] Intawong K, Chariyalertsak S, Chalom K, Wonghirundecha T, Kowatcharakul W, Ayood P, et al. Reduction in severity and mortality in COVID-19 patients owing to heterologous third and fourth-dose vaccines during the periods of delta and omicron predominance in Thailand. Int J Infect Dis [Internet]. 2023;126:31–8. Available from: http://dx.doi.org/10.1016/j.ijid.2022.11.006

[11] Alves K, Plested JS, Galbiati S, Chau G, Cloney-Clark S, Zhu M, et al. Immunogenicity and safety of a 4thhomologous booster dose of a SARS-CoV-2 recombinant spike protein vaccine (NVX-CoV2373): a phase 2, randomized, placebo-controlled trial [Internet]. bioRxiv. 2022 [cited 2023 Mar

8]. p. 2022.11.18.22282414. Available from: https://www.medrxiv.org/content/10.1101/2022.11.18.22282414v1

[12] Chalkias S, Harper C, Vrbicky K, Walsh SR, Essink B, Brosz A, et al. A bivalent omicron-containing booster vaccine against covid-19. N Engl J Med [Internet]. 2022;387(14):1279–91. Available from: http://dx.doi.org/10.1056/NEJMoa2208343

[13] Zou J, Kurhade C, Patel S, Kitchin N, Tompkins K, Cutler M, et al. Improved neutralization of Omicron BA.4/5, BA.4.6, BA.2.75.2, BQ.1.1, and XBB.1 with bivalent BA.4/5 vaccine [Internet]. bioRxiv. 2022. Available from: http://dx.doi.org/10.1101/2022.11.17.516898

[14] Link-Gelles R, Ciesla AA, Fleming-Dutra KE, Smith ZR, Britton A, Wiegand RE, et al. Effectiveness of bivalent mRNA vaccines in preventing symptomatic SARS-CoV-2 infection - Increasing Community Access to testing program, United States, September-November 2022. MMWR Morb Mortal Wkly Rep [Internet]. 2022;71(48):1526–30. Available from: http://dx.doi.org/10.15585/mmwr.mm7148e1

[15] Tenforde MW, Weber ZA, Natarajan K, Klein NP, Kharbanda AB, Stenehjem E, et al. Early estimates of Bivalent mRNA vaccine effectiveness in preventing COVID-19-associated emergency department or urgent care encounters and hospitalizations among immunocompetent adults - VISION Network, nine states, September-November 2022. MMWR Morb Mortal Wkly Rep [Internet]. 2022;71(5152):1616–24. Available from: http://dx.doi.org/10.15585/mmwr.mm715152e1

[16] Hause AM, Marquez P, Zhang B, Myers TR, Gee J, Su JR, et al. Safety monitoring of bivalent COVID-19 mRNA vaccine booster doses among persons aged ≥12 years - United States, August 31-October 23, 2022. MMWR Morb Mortal Wkly Rep [Internet]. 2022;71(44):1401–6. Available from: http://dx.doi.org/10.15585/mmwr.mm7144a3

[17] European Centre for Disease Prevention and Control, European Medicines Agency. Updated joint statement from ECDC and EMA on additional booster doses of COVID-19 vaccines [Internet]. 2022 Jul. Available from: https://www.ema.europa.eu/en/documents/public-statement/updated-joint-statement-ecdc-ema-additional-booster-doses-covid-19-vaccines_en.pdf

[18] Centers for Disease Control and Prevention. Clinical guidance for COVID-19 vaccination [Internet]. Cdc.gov. 2023 [cited 2023 Mar 18]. Available from: https://www.cdc.gov/vaccines/covid-19/clinical-considerations/interim-considerations-us.html

[19] Rosenblum HG, Wallace M, Godfrey M, Roper LE, Hall E, Fleming-Dutra KE, et al. Interim recommendations from the Advisory Committee on Immunization Practices for the use of bivalent booster doses of COVID-19 vaccines - United States, October 2022. MMWR Morb Mortal Wkly Rep [Internet]. 2022;71(45):1436–41. Available from: http://dx.doi.org/10.15585/mmwr.mm7145a2

[20] Department of Health. DOH Advisory No. 154: Guidance on the Vaccination Rollout for Second Booster Doses to Priority Groups A1: Workers in Essential Health Services and A2: Senior Citizens [Internet]. 2022 May. Available from: https://doh.gov.ph/sites/default/files/health-update/Advisory%20No.%20154.pdf

[21] Department of Health. DOH Advisory No. 3: Implementation Of Covid-19 Second Booster Strategy To Individuals 50 Years Old And Above And Adults 18-49 Years Old With Comorbidities [Internet]. 2022 Jul. Available from: https://doh.gov.ph/sites/default/files/health-update/Advisory%20No.%203%20%282%29.pdf

[22] Department of Health. How much is the cost or what is the price range for each available vaccine? (FAQs-Procurement of COVID-19 Vaccines) [Internet]. Gov.ph. 2021 [cited 2022 Dec 6]. Available from: https://doh.gov.ph/node/28134

[23] Siedner MJ, Alba C, Fitzmaurice KP, Gilbert RF, Scott JA, Shebl FM, et al. Cost-effectiveness of Coronavirus disease 2019 vaccination in low- and middle-income countries. J Infect Dis [Internet]. 2022;226(11):1887–96. Available from: http://dx.doi.org/10.1093/infdis/jiac243

[24] Department of Health. How cost efficient are the vaccines being procured? (FAQs-Procurement of COVID-19 Vaccines) [Internet]. Gov.ph. 2021 [cited 2022 Dec 6]. Available from: https://doh.gov.ph/node/28135

[25] Li R, Liu H, Fairley CK, Zou Z, Xie L, Li X, et al. Cost-effectiveness analysis of BNT162b2 COVID-19 booster vaccination in the United States. Int J Infect Dis [Internet]. 2022;119:87–94. Available from: http://dx.doi.org/10.1016/j.ijid.2022.03.029

[26] Cleofas JV, Oducado RMF. Demographic, health and pandemic-related determinants of COVID-19 vaccination intention among Filipino emerging adults. Emerg Adulthood [Internet]. 2022;10(3):815–20. Available from: http://dx.doi.org/10.1177/21676968221084876

[27] Adjei S, Hong K, Molinari N-AM, et al. Morbidity and Mortality Weekly Report Mortality Risk Among Patients Hospitalized Primarily for COVID-19 During the Omicron and Delta Variant Pandemic Periods-United States. Published Online First: 2020.https://www. (accessed 21 Jan 2023).

[28] Külper-Schiek W, Piechotta V, Pilic A. Facing the Omicron variant-how well do vaccines protect against mild and severe COVID-19? Third interim analysis of a living systematic review. Front Immunol [Internet]. 2022;13. Available from: http://dx.doi.org/10.3389/FIMMU.2022.940562/BIBTEX

Appendix 1: Preliminary Evidence to Decision

Table 2. Summary of initial judgements prior to the panel discussion (N=6/10)

FACTORS	JUDGEMENT						RESEARCH EVIDENCE/ADDITIONAL CONSIDERATIONS
Problem	No	Yes (6)	Varies	Uncertain			
Benefits	Large (3)	Moderate (2)	Small	Trivial	Varies	Uncertain (1)	**Homologous Vaccines** • Coronavac (Sinovac) - moderate 2.5 fold increase in neutralization response 4 to 9 weeks post vaccination. 67% seroconversion against Delta; 18.4% seroconversion against Omicron [1]. • BNT162b2 (Pfizer-BioNTech) - large 8.45-fold increase in anti-spike protein IgG response while moderate to large cellular response against wild type 4.4-fold increase, beta 3.46-fold increase, delta 5.6-fold increase [2]. • mRNA1273 (Moderna) – 1) significantly reduced COVID-19 infection for BA.2; BA.2.12.1; BA.4, and BA.5, 2) significantly reduced hospitalization for BA.2 var but not for BA.4/BA.5 [3]. • Bivalent mRNA1273.214 vs Monovalent mRNA1273 – similar risk for COVID-19 infection. 24% more effective in increasing neutralization antibody against ancestral variant and 78% more effective for omicron [4]. **Heterologous Vaccination** • Vaccination with second booster was associated with a significant reduction in risk for COVID-19 infection compared to no second

							booster. (OR 0.48, 95% 0.40-0.57) [5]. • Progression to severe COVID-19 was similar between among those who received 2nd booster and those who did not [6]. • ChAdOx1/ChAdOx1; Pfizer, Pfizer – large 13.15-fold increase in antispike-protein IgG antibody titers and large 11.07-fold increase in cellular response against wild type [2]. • ChAdOx1/ ChAdOx1; Pfizer, Moderna – large 19.73-fold increase in antispike-protein IgG antibody titers and large 6.34 fold increase in cellular response against wild type [2]. • Pfizer/ Pfizer; Pfizer, Moderna – large 14.38-fold increase in antispikeprotein IgG antibody titers and large 6.08-fold increase in cellular response against wild type.
Harm	Large		Moderate (1)	Small (2)	Trivial (2)	Varies	Uncertain (1)	No serious adverse events related to vaccination was reported in the 6 studies [1-6].
Certainty of Evidence	High		Moderate (1)	Low (1)	Very low (4)			Very low due to serious risk of bias, inconsistency and imprecision in several critical outcomes.
Balance of effects	Favors vaccination (4)		Probably favors vaccination (1)	Does not favor vaccination	Probably favors no vaccination (1)	Favors no intervention	Varies	
Values	Important uncertainty or variability (1)		Possibly important uncertainty or variability (5)	Possibly NO important uncertainty or variability	No important uncertainty or variability			
Resources Required	Don't know	Varies	Large cost (3)	Moderate cost (3)	Negligible cost or savings	Moderate savings	Large savings	
Certainty of evidence of	No included studies (4)		Very low	Low (1)	Moderate (1)	High		

required resources								
Cost effectiveness	No included studies	Varies (3)	Favors the comparison	Probably favors the comparison (1)	Does not favor either the intervention or the comparison (1)	Probably favors the intervention	Favors the intervention (1)	The potential cost-effectiveness of a booster will reduce when the population incidence rate falls. A booster strategy will no longer be cost-effective if the population incidence in older adults reduces below 8.1/100,000 person-day. In a setting with an already high 2-dose vaccination coverage, the booster may further reduce the population incidence to below the threshold value in the elderly population and render it not cost-effective [21].
Equity	Uncertain (1)	Varies (3)	Reduced	Probably reduced	Probably no impact	Probably increased (2)	Increased	
Acceptability	Don't know		Varies (2)	No	Probably no	Probably yes (4)	Yes	
Feasibility	Don't know		Varies (2)	No	Probably no (1)	Probably yes (3)	Yes	

Appendix 2: Search Strategy

Table 3a. Initial Search

Information Source	Search Strategy (as of 10 September 2022)	Yield: 2,961	Eligible
MEDLINE (PubMed)	"prophyla*"[All Fields] OR "prevent*"[All Fields]) AND ("covid 19"[All Fields] OR "covid 19"[MeSH Terms] OR "covid 19 vaccines"[All Fields] OR "covid 19 vaccines"[MeSH Terms] OR "covid 19 booster"[All Fields] OR "covid 19 second booster"[Supplementary Concept] OR "covid 19 fourth dose"[All Fields] OR "covid 19 additional dose"[MeSH Terms] OR "covid 19 third dose"[All Fields] OR "covid 19 second booster"[MeSH Terms] OR "covid 19 testing"[All Fields] OR "covid 19 testing"[MeSH Terms] OR "sars cov 2"[All Fields] OR "sars cov 2"[MeSH Terms] OR "severe acute respiratory syndrome coronavirus 2"[All Fields] OR "ncov"[All Fields] OR "2019 ncov"[All Fields] OR (("coronavirus"[MeSH Terms] OR "coronavirus"[All Fields] OR "cov"[All Fields]) AND ("adults"[MeSH Terms] OR "healthy"[All Fields] OR "older"[All Fields] OR "50"[All Fields] OR "general"[All Fields]) Filter	318	1
ClinicalTrials.gov	Condition or disease: “Covid19” Intervention/treatment: “booster dose” Others: adults	181	0
Chinese Clinical Trial Registry	Target Disease: “covid-19” Intervention: “booster”, “4th dose”, “second booster”	2	0
EU Clinical Trials Register	“COVID-19 vaccine AND booster”	50	0
medRxiv.org and bioRxiv.org	“COVID 19 second booster” Filter: January 1, 2022 to September 9, 2021	794	0
COVID-NMA	Vaccines > Living Mapping > 2nd booster	957	0
LOVE Platform for COVID-19 Evidence	For the COVID-19 L·OVE platform, the search was by PICO with the following filters in order: "prevention or treatment", “public health”, "vaccination", and “SARS-CoV-2 vaccines”, “COVID-19”. The search filters were the following: “fourth”, “4th”, “second”, and “2nd”,	653	3
metaevidence.org	Second booster dose vs first booster dose.	6	0

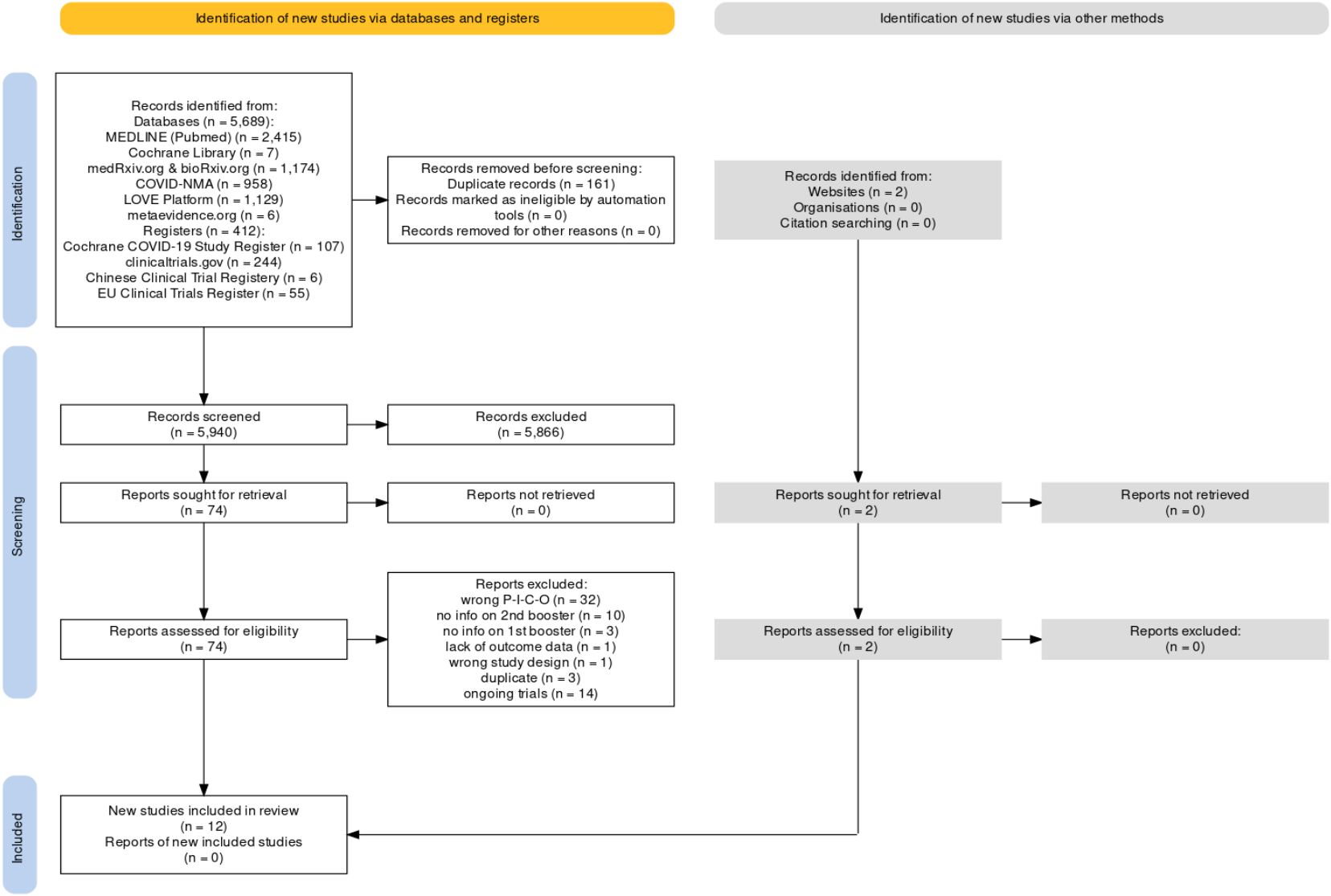
Table 3b. Bivalent Update **(December 30, 2023)**

Information Source	Bivalent Search Strategy (as of 30 December 2022)	Yield: 231	Eligible
MEDLINE (PubMed)	("covid 19"[Supplementary Concept] OR "Severe Acute Respiratory Syndrome Coronavirus 2"[Supplementary Concept] OR "2019-nCoV"[All Fields] OR "2019nCoV"[All Fields] OR "cov 2"[All Fields] OR "covid 19"[All Fields] OR "SARS Coronavirus 2"[All Fields] OR "sars cov 2"[All Fields] OR "sars cov 2"[All Fields] OR "Severe Acute Respiratory Syndrome Coronavirus 2"[All Fields] OR "coronavirus 2"[All Fields] OR "covid 19"[All Fields] OR "covid 19"[All Fields] OR "2019-nCoV"[All Fields] OR "2019nCoV"[All Fields] OR "corona virus disease 2019"[All Fields] OR "cov2"[All Fields] OR "covid 19"[All Fields] OR "COVID19"[All Fields] OR "nCov 2019"[All Fields] OR "nCoV"[All Fields] OR "new corona virus"[All Fields] OR "new coronaviruses"[All Fields] OR "novel corona virus"[All Fields] OR "novel coronaviruses"[All Fields] OR "SARS Coronavirus 2"[All Fields] OR "SARS2"[All Fields] OR "sars cov 2"[All Fields] OR "Severe Acute Respiratory Syndrome Coronavirus 2"[All Fields] OR (("19"[Title/Abstract] OR "2019"[Title/Abstract] OR "2019-nCoV"[All Fields] OR "Beijing"[All Fields] OR "China"[All Fields] OR "covid 19"[All Fields] OR "epidem*"[Title/Abstract] OR "epidemic*"[All Fields] OR ("epidemies"[All Fields] OR "epidemy"[All Fields]) OR "new"[Title/Abstract] OR "novel"[Title/Abstract] OR "outbreak"[All Fields] OR "pandem*"[All Fields] OR "sars cov 2"[All Fields] OR "Shanghai"[All Fields] OR "Wuhan"[All Fields]) AND ("Coronavirus Infections"[MeSH Terms] OR "coronavirus"[MeSH Terms] OR "coronavirus*"[All Fields] OR "corona virus*"[All Fields] OR "cov"[Title/Abstract] OR "pneumonia virus*"[Title/Abstract])))) AND 2019/12/01:3000/12/31[Date - Publication] AND ("vaccin"[Supplementary Concept] OR "vaccin"[All Fields] OR "vaccination"[MeSH Terms] OR "vaccination"[All Fields] OR "vaccinable"[All Fields] OR "vaccinal"[All Fields] OR "vaccinate"[All Fields] OR "vaccinated"[All Fields] OR "vaccinates"[All Fields] OR "vaccinating"[All Fields] OR "vaccinations"[All Fields] OR "vaccination s"[All Fields] OR "vaccinator"[All Fields] OR "vaccinators"[All Fields] OR "vaccine s"[All Fields] OR "vaccined"[All Fields] OR "vaccines"[MeSH Terms] OR "vaccines"[All Fields] OR "vaccine"[All Fields] OR "vaccins"[All Fields]) AND ("bivalence"[All Fields] OR "bivalency"[All Fields] OR "bivalent"[All Fields] OR "bivalently"[All Fields] OR "bivalents"[All Fields])	104	2
Cochrane COVID study registry	“bivalent” and “vaccine”	42	0
ClinicalTrials.gov	Condition or disease: “Covid19” Intervention/treatment: “bivalent” Others: adults	45	0
Chinese Clinical Trial Registry	Target Disease: “covid-19” Intervention: “bivalent”	4	0
EU Clinical Trials Register	“COVID-19 AND Bivalent”	4	0
LOVE Platform for COVID-19 Evidence	For the COVID-19 L·OVE platform, the search was by PICO with the following filters in order: "prevention or treatment", “public health”, "vaccination", and “SARS-CoV-2 vaccines”, “COVID-19”. The search filters were the following: “bivalent”	32	2

Table 3c. Monovalent Update **(February 16, 2023)**

Information Source	Monovalent Update Search Strategy (as of 16 February 2023)	Yield: 2909	Eligible
MEDLINE (PubMed)	Search: (((prophyla*) OR (prevent*)) AND ((((((((((covid 19 vaccine) OR (covid 19 vaccine[MeSH Terms])) OR (sars-cov-2 vaccine)) OR (sars-cov-2 vaccine[MeSH Terms])) OR (covid 19 vaccine booster)) OR (covid 19 vaccine booster[MeSH Terms])) OR (covid 19 monovalent vaccine)) OR (covid 19 monovalent vaccine[MeSH Terms])) OR (covid 19 monovalent booster vaccine)) OR (covid 19 vaccine second booster)) OR (covid 19 vaccine second booster[MeSH Terms])) OR (covid 19 vaccine fourth dose))) AND ((((adult[MeSH Terms]) OR (healthy)) OR (general)) OR (older)) Filters: from 2022/9/11 - 2023/2/16	1993	0
Cochrane Library	#1: MesH descriptor:[COVID-19 Vaccines] explode all trees #2: MesH descriptor:[Immunization, Secondary] explode all trees #3: #1 AND #2 #4: COVID-19 vaccine second booster #5: COVID-19 vaccine fourth dose #6: #3 OR #4 OR #5 #7: MesH descriptor:[Adult] explode all trees #8: healthy adults #9: #7 OR #8 #10: #6 AND #9 Date Range – Sept 11, 2022 – Feb. 16, 2023	7	0
Cochrane COVID-19 Study Register	"second booster dose" or "fourth dose"	65	0
ClinicalTrials.gov	Condition or disease: "Covid19" Intervention/treatment: "booster dose" Others: adults Filters: Adult (18-64), Accepts Healthy Volunteers Date: Sept 11, 2022 – Feb 16, 2023	18	9
Chinese Clinical Trial Registry	Target Disease: "covid-19" Intervention: "booster", "4th dose", "second booster"	0	0
EU Clinical Trials Register	"COVID-19 vaccine AND booster" Date: Sept 11, 2022 – Feb 16, 2023	1	1
medRxiv.org and bioRxiv.org	"COVID 19 second booster" Filter: January 1, 2022 to September 9, 2021	380	1
COVID-NMA	Vaccines > Living Mapping > 2nd booster	1	0
LOVE Platform for COVID-19 Evidence	For the COVID-19 L·OVE platform, the search was by PICO with the following filters in order: "prevention or treatment", "public health", "vaccination", and "SARS-CoV-2 vaccines", "COVID-19 vaccine booster', "COVID-19". The search filters were the following: "fourth", "4th", "second", and "2nd",	444	2

Appendix 3: PRISMA flow diagram



Appendix 4: Characteristics of Included Studies

Table 4. Characteristics of included studies

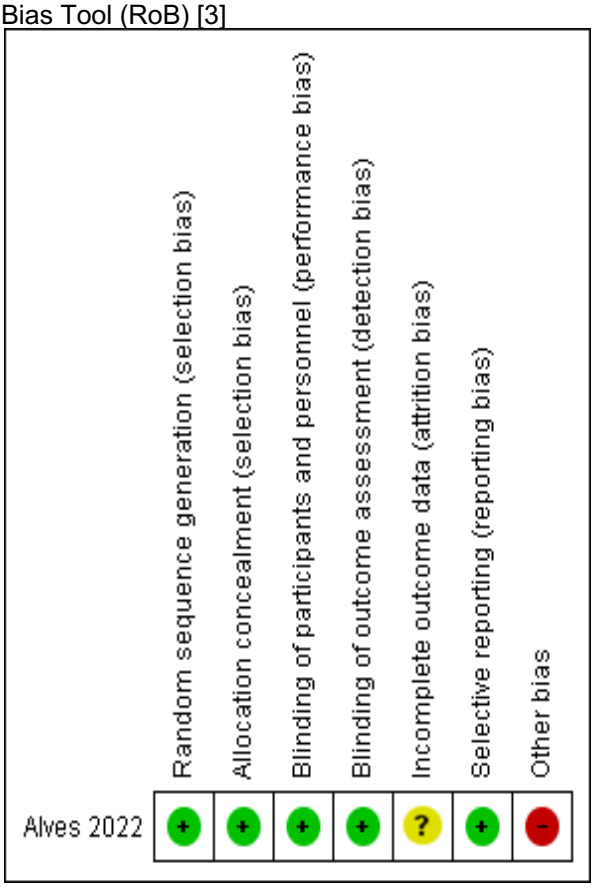
Study ID	Study Design	Country	Population	Intervention	Comparator	Outcomes
MONOVALENT VACCINE						
Alves et al., 2022 [11] *Preprint*	Part of an Ongoing Phase 2, randomized, observer-blinded, placebo-controlled trial	USA & Australia	Healthy Adults 18 to 84 years old N=257 Primary Series: NVX-CoV2373 (Novavax) SARS-CoV-2 recombinant protein vaccine (0.5 mL containing 5 µg SARS-CoV-2 rS with 50 µg Matrix-M adjuvant) Placebo (sterile sodium chloride injection)	2nd Booster NVX-CoV2373 (Novavax) SARS-CoV-2 recombinant protein vaccine (0.5 mL containing 5 µg SARS-CoV-2 rS with 50 µg Matrix-M adjuvant) Homologous n=45 - 18 to 59 years old (n=20): 44%	1st Booster NVX-CoV2373 (Novavax) SARS-CoV-2 recombinant protein vaccine (0.5 mL containing 5 µg SARS-CoV-2 rS with 50 µg Matrix-M adjuvant) Homologous n=105 - 18 to 59 years old (n=57): 54%	Safety - Local/Systemic Reactogenicity - Unsolicited Adverse Events Immunogenicity - Anti-spike neutralization assays against ancestral strain and Omicron sublineage Follow-Up period: 28 days after each vaccination
Intawong et al., 2022A [2] *Published*	Test-negative Case-Control	Thailand	Thai Individuals, aged 18 years or above and tested for SARS-CoV02 Age Range 16 to ≥85 yrs old Total N = 63,471 Omicron Wave (N= 36,170) 18 to 59 yrs old (n=33,094): - 91% of Omicron population - Case: Positive SARS-Cov-2 infection (n=13,535) - Control: Negative SARS-Cov-2 (n=19,559) Primary Series: CoronaVac/ Sinopharm/ ChAdOx1/ BNT162b2/ mRNA-1273 Predominant Variant: Delta & Omicron (2nd booster done during Omicron wave only)	2nd Booster ChAdOx1 (6%)/ BNT162b2 (50%)/ mRNA-1273 (43%) Heterologous Total n = 823 Case: Positive SARS-Cov-2 infection from PCR or medically administered antigen testing (n=172) Control: Negative SARS-Cov-2 infection from PCR or medically administered antigen testing (n=651) Interval from 1st Booster: not specified	1st Booster ChAdOx1/ BNT162b2/ mRNA-1273/ CoronaVac/ Sinopharm Total n = 12,366 Case: Positive SARS-Cov-2 infection from PCR or medically administered antigen testing (n=4,416) Control: Negative SARS-Cov-2 infection from PCR or medically administered antigen testing (n=7,950)	Real World Effectiveness - vs COVID infection Median time between test and last vaccination: 1st booster – 53 days 2nd booster – 40 days
Intawong et al., 2022B [10] *Published*	Retrospective Cohort	Thailand	Thai residents aged 18 years or older, with laboratory-confirmed SARS-CoV-2 infection Age Range 16 to ≥70 yrs old Total N = 205,090 Omicron Wave (n= 188,043) - 18 to 59 years old (n=156,350): 83% of Omicron wave population	2nd Booster ChAdOx1 (8%)/ BNT162b2 (48%)/ mRNA-1273 (44%) Heterologous n = 6829 Interval from 1st Booster: not specified	1st Booster ChAdOx1/ BNT162b2/ mRNA-1273 n = 65492	Real World Effectiveness - vs Severe COVID infection (invasive mechanical ventilation & death) Follow-up period: Median of 53 days after 2nd booster

			Primary Series: CoronaVac/ Sinopharm/ ChAdOx1/ BNT162b2/ mRNA-1273 Predominant Variant: Delta & Omicron (2nd booster done during Omicron wave only)			
Melo-González, et al., 2022 [6] *Pre-print*	Quasi-experimental study	Chile	Healthy adults (18 and above) Primary series: CoronaVac (n=138)	2nd booster: CoronaVac (Monovalent) n=138 Interval from 1st Booster: 6 months	1st booster: CoronaVac (Monovalent)	Humoral vs Cellular Immunity (Neutralizing Ab) against omicron or ancestral SARS-CoV-2 (WT SARS-CoV-2); ffup 4-9 wks Seroconversion; ffup 4-9 wks
Munro et al., 2022 [7] *Published*	Quasi-experimental study	UK	Healthy Adults (30 and above) Primary series: BNT162b2 (n=78)	2nd booster: 1) BNT162b2 (30 µg in 0·30 mL; full dose) (n=44) Interval from 1st Booster: 7 months	1st booster: BNT162b2 (7 months prior) (n=78)	Immunogenicity; ffup 14 days Safety; ffup median 3 mos
Surie et al., 2022 [8] *Published*	Test-negative Case-Control	USA	immunocompetent adults aged ≥ 18 years admitted for COVID-19-like illness Total N = 4730 Age range: 18 to ≥85 yrs old median age 65 yrs (52-76yrs IQR) ~30% with underlying condition (non-immunocompromising) 18 to 64 years old (n=2357): 50% of total population Primary Series: not specified Predominant Variant: Omicron - BA.1/BA.2 lineage & BA.4/BA.5 lineage	2nd Booster Monovalent mRNA Not specified if homologous/ heterologous Total n = 236 Case: Positive NAAT or antigen for SARS-Cov-2 infection (n=93) Control: Negative NAAT for SARS-Cov-2 infection (n=143) Interval from 1st Booster: 120 days	1st Booster Monovalent mRNA Not specified if homologous/ heterologous Total n = 1636 Case: Positive NAAT or antigen for SARS-Cov-2 infection (n=709) Control: Negative NAAT for SARS-Cov-2 infection (n=927)	Real World Effectiveness - vs COVID-19-associated hospitalization Follow-up time: 7-120 days after vaccination of 1st and 2nd booster
Tseng et al., 2023 [9] *Published*	Test-negative Case-Control	USA (California)	Adults more than 18 yrs old Total N = 123,236 Age Range 18 to ≥75 yrs old Median age: 46 yrs Case: Positive SARS-Cov-2 RT PCR (n=30,809) Control: Negative SARS-Cov-2 RT PCR (n=92,427) 18 to 64 years old (n=100,976): 82% of population 79% with chronic condition	2nd Booster mRNA-1273 (monovalent mRNA) Homologous Total n = 5050 Case: Positive SARS-Cov-2 RT PCR (n=966) Control: Negative SARS-Cov-2 RT PCR (n=4084)	1st Booster mRNA-1273 (monovalent mRNA) Homologous Total n = 56719 Case: Positive SARS-Cov-2 RT PCR (n=12724) Control: Negative SARS-Cov-2 RT PCR (n=43995)	Real World Effectiveness - vs COVID infection BA.2, BA.2.12.1, BA.4, BA.5 - vs COVID-19 hospitalization (hospitalized for severe COVID) Time since vaccination 1st booster – up to >150 days 2nd booster – up to >90 days

			4% immunocompromised Primary Series: mRNA-1273 Predominant Variant: Omicron	Interval from 1st Booster: not specified		
BIVALENT VACCINE						
Chalkias et al., 2022 [12] *Published*	Quasi-experimental study	US	Adults (18 and above) Primary series and 1st booster: mRNA-1273 (n=814)	2nd booster (bivalent): mRNA-1273.214 bivalent vaccine (50-µg dose) (1:1 ratio, 25 µg each encoding the prefusion-stabilized spike glycoproteins of ancestral SARS-CoV-2 (Wuhan-Hu-1) and the omicron variant (BA.1). n= 334 Interval from 1st booster: at least 90 days	2nd booster (monovalent): mRNA-1273 monovalent vaccine (50-µg dose) n= 260 Interval from 1st booster: at least 90 days	Immunogenicity: ffup 28 days Safety; ffup 43-57 days Exploratory objectives: incidence of SARS-CoV 2 Infection (asymptomatic and symptomatic), but no vaccine effectiveness
Hause et al., 2022 [16] *Published*	Descriptive study	US	Patients (12 and above) n=211,959 12-17yrs n=1,464 18-49 yrs n=41,022 50-64 yrs n=34,947 >65 yrs n=45,520	Any bivalent booster	No comparator	Non-serious adverse event Serious adverse event
Link-Gelles et al., 2022 [14] *Published*	Case-Control study	US	Healthy adults (18 and above) n=360,626	2nd booster: Bivalent mRNA vaccine, Pfizer or Moderna	1st booster only Monovalent mRNA vaccine, Pfizer or Moderna	Infection rate
Tenforde et al., 2022 [15] *Published*	Case-Control study	US	Healthy adults (18 and above) N=15,526 Ffup 2 months	Bivalent booster after 2nd, 3rd, or 4th, monovalent mRNA vaccine (Pfizer or Moderna) Interval from last booster (25 days median) Case: COVID positive Control: COVID negative	No bivalent booster after 2nd, 3rd, or 4th, monovalent mRNA vaccine (Pfizer or Moderna) Interval from last booster (25 days median) Case: COVID positive Control: COVID negative	Hospitalization
Zou et al., 2022 [13] *Pre-print*	Quasi-experimental study	US	Healthy adults (18 and above) n=360,626	2nd booster: Bivalent mRNA vaccine, Pfizer or Moderna	1st booster only Monovalent mRNA vaccine, Pfizer or Moderna	Infection rate

Appendix 5: Methodological Quality Assessment

Using Cochrane Risk of Bias Tool (RoB) [3]



Using Newcastle-Ottawa Scale for Case-Control/Cohort [4]

Newcastle-Ottawa Scale for Case-Control/Cohort				
Study ID	**SELECTION**	**COMPARIBILITY**	**EXPOSURE**	**QUALITY**
MONOVALENT VACCINES				
Intawong 2022A	****	**	**	*Good*
Intawong 2022B#	****	**	**	*Good*
Surie 2022	***	**	**	*Good*
Tseng 2023	****	**	**	*Good*
BIVALENT VACCINES				
Link-Gelles 2022	***		**	*High Risk*
Tenforde 2022	***	*	**	*Good*

- cohort study

Using JBI Critical Appraisal Checklist for Quasi-Experimental Studies [5]

JBI Critical Appraisal Checklist for Quasi-Experimental Studies	Chalkias 2022	Melo-Gonzalez 2022	Munro 2022	Zou 2022
1. Is it clear in the study what is the 'cause' and what is the 'effect' (i.e. there is no confusion about which variable comes first)?	Yes	Yes	Yes	Yes
2. Were the participants included in any comparisons similar?	Yes	Yes	Yes	Yes
3. Were the participants included in any comparisons receiving similar treatment/care, other than the exposure or intervention of interest?	No	Yes	Yes	Yes
4. Was there a control group?	No	No	No	No
5. Were there multiple measurements of the outcome both pre and post the intervention/exposure?	No	No	No	No
6. Was follow up complete and if not, were differences between groups in terms of their follow up adequately described and analyzed?	Yes	No	No	Unclear
7. Were the outcomes of participants included in any comparisons measured in the same way?	Yes	Yes	Yes	Yes
8. Were outcomes measured in a reliable way?	Yes	Yes	Yes	Yes
9. Was appropriate statistical analysis used?	Yes	No	Yes	Yes
Total and Quality Rating	66%	55%	66%	66%
	Moderate	Moderate	Moderate	Moderate
Good at least 80%; Moderate 50-80%; poor less than 50%				

Appendix 6: Grade Evidence Profile

Monovalent mRNA [BNT162b2 (Pfizer) or mRNA-1273 (Moderna)] Homologous &/or Heterologous Vaccination

Author(s): Adajar, Perez
Question: Monovalent mRNA 2nd booster compared to no 2nd booster (1st booster) for general healthy adult population
Setting: hospital
Bibliography: Surie 2022

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Monovalent mRNA 2nd booster	no 2nd booster	Relative (95% CI)	Absolute (95% CI)		
COVID-19 associated Hospitalization												
1 (n=1872)	observational studies	not serious	not serious	not serious	serious[a]	none	93/236 (39.4%)	709/1636 (43.3%)	**OR 0.85** (0.64 to 1.12)	**39 fewer per 1,000** (from 105 fewer to 28 more)	⨁◯◯◯ Very low	CRITICAL

CI: confidence interval; **OR:** odds ratio

Explanations

a. crosses 1.0 threshold

Monovalent BNT162b2 (Pfizer) Homologous Vaccination

Author(s): Joson, Perez, Saroca
Question: A 2nd booster dose of Pfizer BNT162b2 compared to no 2nd booster dose for the general healthy adult population
Setting: community
Bibliography: Munro 2022

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Baseline	Day 14 after the fourth dose	Relative (95% CI)	Absolute (95% CI)		
Immunogenicity (follow-up: median 14 days; assessed with: SARS-CoV-2 anti-spike protein IgG titers, ELU/mL)												
1 (n=12)[a]	observational studies	not serious	not serious	serious[b]	not serious	none	Baseline titers anti-spike IgG titers: 3895 (3486–4351)	Day 14 after the fourth dose: 35,116 (31,868–38,696)	-	mean **8.45 fold change (ELU) higher** (7.83 higher to 9.11 higher)	⨁◯◯◯ Very low	Not critical
Cellular response (wild-type) (follow-up: median 14 days; assessed with: spot forming cells per 10^6 PBMCs)												
1 (n=8)[a]	observational studies	serious[c]	not serious	serious[b]	serious	none	Baseline cellular response: 19.93 (9.14–43,48)	Day 14 after the fourth dose: 84.87 (51.94–138.66)	-	mean **4.14 fold change (PBMCs) higher** (1.04 higher to 16.54 higher)	⨁◯◯◯ Very low	Not critical
Cellular response (Beta variant) (follow-up: median 14 days; assessed with: spot forming cells per 10^6 PBMCs)												
1 (n=8)[a]	observational studies	serious[c]	not serious	serious[b]	serious[d]	none	Baseline cellular response: 21.07 (9.64–46.06)	Day 14 after the fourth dose: 74.08 (33.34–164.60)	-	mean **3.46 fold change (PBMCs) higher** (0.85 higher to 14.08 higher)	⨁◯◯◯ Very low	Not critical
Cellular response (Delta variant) (follow-up: median 14 days; assessed with: spot forming cells per 10^6 PBMCs)												
1 (n=8)[a]	observational studies	serious[c]	not serious	serious[b]	serious	none	Baseline cellular response: 14.22 (6.02–33.58)	Day 14 after the fourth dose: 79.49 (46.55–135.72)	-	mean **5.64 fold change (PBMCs) higher** (1.27 higher to 25.06 higher)	⨁◯◯◯ Very low	Not critical
Adverse events (follow-up: median 3 months)												
1[a] (n=39)	observational studies	not serious	not serious	not serious	serious[d]	none	No serious adverse event related to the 2nd booster of a monovalent BNT162b2 vaccine was reported in the study. But, they documented four unspecified non-serious adverse events.				⨁◯◯◯ Very low	Critical

CI: confidence interval; **MD:** mean difference

Explanations

a. Munro 2022
b. Neutralizing antibody titers are surrogate markers of COVID-19 protection.
c. only 50% of the study sites collected cellular immunology samples due to logistic reasons (n=8/16)
d. wide confidence interval or small number of events

Monovalent mRNA-1273 (Moderna) Homologous Vaccination

Author(s): Joson, Perez, Saroca
Question: A 2nd booster dose of mRNA-1273 compared to no 2nd booster dose for the general healthy adult population
Setting: community
Bibliography: Tseng 2022

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	2nd booster dose of mRNA-1273	no 2nd booster dose	Relative (95% CI)	Absolute (95% CI)		
COVID-19 Infection, Omicron BA.2;BA.2.12.1; BA.4; BA.5 (follow-up: range 31 days to 90 days; assessed with: PCR result)												
1 (n= 21,234)	observational studies	serious[a]	not serious	not serious	not serious	none	328/1653 (19.8%)	5279/19581 (27.0%)	**OR 0.67** (0.59 to 0.76)	**71 fewer per 1,000** (from 91 fewer to 51 fewer)	⊕◯◯◯ Very low	CRITICAL
Hospitalization, Omicron BA.2; BA.4; BA.5 (assessed with: PCR result)												
1 (n=385)	observational studies	serious[a]	not serious	not serious	not serious	none	9/100 (9.0%)	50/285 (17.5%)	**OR 0.46** (0.22 to 0.97)	**86 fewer per 1,000** (from 131 fewer to 4 fewer)	⊕◯◯◯ Very low	CRITICAL

CI: confidence interval; **OR:** odds ratio

Explanations

a. possible selection bias from laboratory data sampling

Monovalent CoronaVac (Sinovac) Homologous Vaccination

Author(s): Joson, Perez, Saroca
Question: A 2nd booster dose of Coronavac compared to no 2nd booster dose for the general healthy adult population
Setting: community
Bibliography: Melo-Gonzalez 2022

Certainty assessment							Impact	Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations			
Neutralization response (Wild-Type) (follow-up: range 4 weeks to 9 weeks; assessed with: titer, geometric mean)									
1 (n=87)[a]	observational studies	serious[b]	not serious	serious[c]	serious[d]	none	Inoculation of a second booster led to a 2.5 fold-increase in neutralization response observed 4 to 9 weeks post-vaccination (549.2 vs 220.4 geometric mean units; p<0.001)	⊕◯◯◯ Very low	Not critical
Seroconversion (Delta Var) (follow-up: range 4 weeks to 9 weeks; assessed with: titer, geometric mean)									
1 (n=87)	observational studies	serious[b,e]	not serious	serious[c]	serious[d]	none	Inoculation of a second booster led to a 67.8% seroconversion (n=59/87) against Delta variant	⊕◯◯◯ Very low	Not critical
Seroconversion (Omicron Var) (follow-up: range 4 weeks to 9 weeks; assessed with: titer, geometric mean)									
1 (n=87)	observational studies	serious[b,f]	not serious	serious[c]	serious[d]	none	Inoculation of a second booster led to an 18.4% seroconversion (n=16/87) against Omicron variant	⊕◯◯◯ Very low	Not critical

CI: confidence interval

Explanations

a. not enough data reported to compute for 95% CI in terms of fold changes.
b. Significant dropout rate 37% n=51/138 due to lost to follow-up or breakthrough COVID-19 infections.
c. Neutralizing antibody titers and seroconversion are surrogate markers of COVID-19 protection.
d. confidence intervals were not reported.
e. Fold change cannot be computed; no baseline titer levels were reported for Delta variant
f. Fold change cannot be computed; no baseline titer levels were reported for Omicron variant

Monovalent NVX-CoV2373 (Novavax) Homologous Vaccination

Author(s): Adajar, Perez
Question: Homologous 2nd booster NVX-CoV2373 (Novavax) compared to no 2nd booster for general healthy adult population
Setting: community
Bibliography: Alves 2022

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Homologous 2nd booster NVX-CoV2373 (Novavax)	no 2nd booster	Relative (95% CI)	Absolute (95% CI)		
Safety: Any Local Adverse Reaction												
1 (n=150)	randomised trials	serious[a]	not serious	not serious	serious[b,c]	none	30/45 (66.7%)	80/105 (76.2%)	**OR 0.63** (0.29 to 1.34)	**93 fewer per 1,000** (from 281 fewer to 49 more)	⊕⊕◯◯ Low	CRITICAL
Safety: Grade 3 Local Adverse Reaction												
1 (n=150)	randomised trials	serious[a]	not serious	not serious	serious[b,c]	none	8/45 (17.8%)	13/105 (12.4%)	**OR 1.53** (0.59 to 4.00)	**54 more per 1,000** (from 47 fewer to 237 more)	⊕⊕◯◯ Low	CRITICAL
Safety: Any Systemic Adverse Reaction												
1 (n=150)	randomised trials	serious[a]	not serious	not serious	serious[b,c]	none	28/45 (62.2%)	77/105 (73.3%)	**OR 0.60** (0.29 to 1.26)	**111 fewer per 1,000** (from 290 fewer to 43 more)	⊕⊕◯◯ Low	CRITICAL
Safety: Grade 3 Systemic Adverse Reaction												
1 (n=150)	randomised trials	serious[a]	not serious	not serious	serious[b,c]	none	7/45 (15.6%)	15/105 (14.3%)	**OR 1.11** (0.42 to 2.93)	**13 more per 1,000** (from 77 fewer to 185 more)	⊕⊕◯◯ Low	CRITICAL
Safety: Unsolicited Adverse Reaction												
1 (n=150)	randomised trials	serious[a]	not serious	not serious	serious[b,c]	none	4/45 (8.9%)	4/105 (3.8%)	**OR 2.46** (0.59 to 10.32)	**51 more per 1,000** (from 15 fewer to 252 more)	⊕⊕◯◯ Low	CRITICAL

CI: confidence interval; **OR:** odds ratio

Explanations

a. pre-print, short duration of follow-up, small number of participants received the treatment
b. crosses 1.0 threshold
c. wide confidence interval

Heterologous Monovalent Vaccination [ChAdOx1 (Astra-Zeneca), BNT162b2 (Pfizer), mRNA-1273 (Moderna)]

Author(s): Joson, Perez, Saroca, Adajar
Question: A 2nd heterologous booster dose compared to no 2nd booster dose for the general healthy adult population
Setting: community
Bibliography: Intawong 2022A, Intawong 2022B, Munro 2022

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	2nd heterologous booster dose	no 2nd booster dose	Relative (95% CI)	Absolute (95% CI)		
COVID-19 Infection Risk with either BNT162b2, mRNA-1273 or ChAdOx1 as 2nd booster (assessed with: PCR result)												
1[a] (n=13193)	observational studies	serious[b]	not serious	not serious	not serious	none	173/824 (21.0%)	4419/12369 (35.7%)	**OR 0.48** (0.40 to 0.57)	**147 fewer per 1,000** (from 175 fewer to 117 fewer)[c]	⊕◯◯◯ Very low	Critical
Progression to severe COVID-19 with either BNT162b2, mRNA-1273 or ChAdOx1 as 2nd booster												
1[d] (n=72,231)	observational studies	serious[e]	not serious	not serious	serious[f]	none	0/6829 (0.0%)	24/65492 (0.0%)	**OR 0.20** (0.01 to 3.22)	**0 fewer per 1,000** (from 0 fewer to 1 more)[g]	⊕◯◯◯ Very low	Critical
Immunogenicity IgG titers, (ChAdOx1/ChAdOx1, BNT162b2, BNT162b2 combination) (follow-up: median 14 days; assessed with: neutralizing antibody titers)												
1 (n=16)[h]	observational studies	serious[h]	not serious	serious[i]	not serious	none	Baseline: 2630 (2,415–2,865)	Day 14 after fourth dose 34,582 (32,335–36,985)	-	mean **13.15 fold change (ELU) higher** (12.09 higher to 14.29 higher)	⊕◯◯◯ Very low	Not critical
Immunogenicity Cellular response, against wild type (ChAdOx1/ChAdOx1, BNT162b2, BNT162b2 combination) (follow-up: median 14 days; assessed with: spot forming cells per 10^6 PBMCs*)												
1 (n=11)[h]	observational studies	serious[h]	not serious	serious[i]	serious[j]	none	Baseline: 18.85 (8.31–42.77)	Day 14 after fourth dose 141.99 (92.57–217.80)	-	mean **11.07 fold change (PBMCs) higher** (4.21 higher to 29.12 higher)	⊕◯◯◯ Very low	Not critical
Immunogenicity IgG titers, (ChAdOx1/ChAdOx1, BNT162b2, mRNA-1273 combination) (follow-up: median 14 days; assessed with: neutralizing antibody titers)												
1 (n=15)[h]	observational studies	serious[h]	not serious	serious[i]	not serious	none	Baseline: 2,391 (2,130–2,683)	Day 14 after fourth dose 47,167 (43,536–51,102)	-	mean **19.73 fold change (ELU) higher** (17.59 higher to 22.1 higher)	⊕◯◯◯ Very low	Not critical
Immunogenicity Cellular response, against wild type (ChAdOx1/ChAdOx1, BNT162b2, mRNA-1273 combination) (follow-up: median 14 days; assessed with: spot forming cells per 10^6 PBMCs*)												
1 (n=11)[h]	observational studies	serious[h]	not serious	serious[i]	serious[j]	none	Baseline: 42.13 (18.58–95.51)	Day 14 after fourth dose 232.98 (116.70–465.12)	-	mean **6.34 fold change (PBMCs) higher** (2.89 higher to 13.92 higher)	⊕◯◯◯ Very low	Not critical

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	2nd heterologous booster dose	no 2nd booster dose	Relative (95% CI)	Absolute (95% CI)		
Immunogenicity IgG titers, (BNT162b2/BNT162b2, BNT162b2, mRNA-1273 combination) (follow-up: median 14 days; assessed with: neutralizing antibody titers)												
1 (n=15)[h]	observational studies	serious[h]	not serious	serious[i]	not serious	none	Baseline: 3,203 (2,971–3,452)	Day 14 after fourth dose 46,053 (42,311–50,126)	-	mean **14.38 fold change (ELU) higher** (13 higher to 15.91 higher)	⨁◯◯◯ Very low	Not critical
Immunogenicity Cellular response, against wild type (BNT162b2/BNT162b2, BNT162b2, mRNA-1273) (follow-up: median 14 days; assessed with: spot forming cells per 10^6 PBMCs*)												
1 (n=9)[h]	observational studies	serious[h]	not serious	serious[i]	not serious	none	Baseline: 30.20 (14.71–62.02)	Day 14 after fourth dose 241.91 (118.79–492.64)	-	mean **6.08 fold change (PBMCs) higher** (3.86 higher to 9.56 higher)	⨁◯◯◯ Very low	Not critical
Adverse Events												
1 (n=39)[h]	observational studies	not serious	not serious	not serious	serious[j]	none	The most common solicited local and systemic adverse events for those who received heterologous 2nd booster dose were pain, fatigue, headache, malaise, and muscle ache. Four unspecified adverse events of special interest were reported in the group who received heterologous mRNA-1273 booster but was unrelated to the vaccination. No serious adverse events related to vaccination were reported				⨁◯◯◯ Very low	Critical

CI: confidence interval; **OR:** odds ratio

Explanations

a. Intawong 2022A
b. Non-randomized control trials (test-negative case control). Risk downgraded due to the possibility that not enough time (3 months) has elapsed to observe any considerable decrease in vaccine effectiveness. Samples from the 2nd booster population received their vaccines in Jan 2022 with an end collection date for the study at April 2022.
c. 2nd booster in the Omicron-dominant period, most received Pfizer-BioNTech (50%), Moderna (44%), or ChAdOx1 (6)
d. Intawong 2022B
e. Retrospective Cohort. Insufficient follow up for those given 2nd homologous booster.
f. wide confidence interval, small event rate
g. 2nd booster in the Omicron-dominant period, most received either Pfizer-BioNTech (47.9%), Moderna (44.4%) vaccine, or ChAdOx1 (7.5%).
h. Munro 2022, selective reporting
i. Neutralizing antibody titers or spot forming cells per 10^6 PBMCs* as surrogate outcomes
j. small sample size

Bivalent mRNA Vaccines Second Booster VS No Second Booster

Author(s): Joson, Perez, Saroca
Question: A 2nd booster dose of bivalent compared to no 2nd booster dose for the general healthy adult population (new)
Setting: community
Bibliography: Tenforde 2022, Link-Gelles 2022, Hause 2022

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	2nd booster dose of bivalent	no 2nd booster dose	Relative (95% CI)	Absolute (95% CI)		
Real-world Covid-19 Infection - Bivalent Moderna or Pfizer (timing of exposure: median 3 months)												
1[a] (n=3,446)	observational studies	serious[b]	not serious	not serious	not serious	none	18-49 years old: OR 0.76 (95% CI 0.67 - 0.86) 50–64 years old: OR 0.85 (95% CI 0.69, 1.04) Time interval period of 2-3 months between 1st and 2nd booster				⊕◯◯◯ Very low	CRITICAL
Real-world Covid-19 Infection - Bivalent Moderna or Pfizer (timing of exposure: range 4 months to 5 months)												
1[a] (n=3,446)	observational studies	serious[b]	not serious	not serious	not serious	none	18-49 years old: OR 0.59 (95% CI 0.53-0.65) 50-64 years old: OR 0.69 (95% CI 0.58-0.88) Time interval of >4 months between 1st and 2nd booster doses				⊕◯◯◯ Very low	CRITICAL
Real-world Hospitalization - Bivalent Moderna or Pfizer (timing of exposure: median 23 days)												
1[c] (n=15,526)	observational studies	not serious	not serious	serious[d]	not serious	none	OR 0.55, 95% CI 0.40 - 0.75 Having received a bivalent booster dose after 2, 3, or 4 monovalent doses (n=15,526, median age=73) was associated with a significant decrease in COVID-19 hospitalization compared to having no bivalent booster .				⊕◯◯◯ Very low	CRITICAL
Real-world safety data - Bivalent Moderna or Pfizer (follow-up: median 2 months)												
1[e] (n=211,959)	observational studies	serious[f]	not serious	not serious	not serious	none	Among the reports received, most were classified as nonserious events (95.5%, 5,291). Five reports of myocarditis and four reports of pericarditis were described after bivalent booster vaccination following the administration of 22.6 million doses in the United States. Fifty-five recipients reported hospitalization following booster vaccination, with 29 indicating that this was unrelated to vaccination				⊕◯◯◯ Very low	CRITICAL

CI: confidence interval

Explanations

a. Link-Gelles 2022
b. Vaccination history, patient co-morbidities are unverified patient reported outcomes; data used for statistical analysis are not documented
c. Tenforde 2022
d. Data is pooled with those who received 2, 3, or 4 monovalent vaccines. For those who did not receive a bivalent dose, 3,355 (22%), 4,766 (31%), and 2,531 (16%) had received 2, 3, and 4 doses of monovalent mRNA vaccine, respectively. Of those who received a bivalent booster, 49 (6%) had received 2 monovalent doses, 252 (32%) had received 3 monovalent doses, and 482 (62%) had received 4 monovalent doses.
e. Hause 2022
f. serious due to possible reporting bias due to real world data. some subjects may not have reported their side effects.

Bivalent mRNA Vaccines Second Booster VS Monovalent mRNA Vaccines Second Booster

Author(s): Joson, Perez, Saroca
Question: A 2nd booster dose of bivalent compared to monovalent vaccine for the general healthy adult population (final)
Setting: community
Bibliography: Chalkias 2022, Zou 2022

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	2nd booster dose of bivalent	monovalent vaccine	Relative (95% CI)	Absolute (95% CI)		
Covid-19 Infection, regardless of symptoms - Bivalent Moderna (follow-up: median 28 days; assessed with: PCR positivity)												
1[a] (n=814)	randomised trials	very serious[b]	not serious	serious[c]	serious[d]	none	11/437 (2.5%)	9/377 (2.4%)	**OR 1.06** (0.43 to 2.58)	**1 more per 1,000** (from 13 fewer to 35 more)	⊕◯◯◯ Very low	CRITICAL
Immunogenicity (Omicron B.1.1.529) - Bivalent Moderna (follow-up: median 28 days; assessed with: Geometric Mean Neutralizing Antibody Titers)												
1[a] (n=795)	randomised trials	very serious[b]	not serious	serious[e]	not serious	none	428	367	-	Geometric mean titer ratio **1.78 higher** (1.56 to 2.04)	⊕◯◯◯ Very low	NOT IMPORTANT
Immunogenicity (Omicron BA.4/BA.5) - Bivalent Moderna (follow-up: median 28 days; assessed with: Neutralization antibody titers)												
1[a] (n=795)	randomised trials	very serious[b]	not serious	serious[e]	not serious	none	428	367	-	mean **1.68 Geometric mean titer ratio higher** (1.52 to 1.84)	⊕◯◯◯ Very low	NOT IMPORTANT
Immunogenicity (Omicron) - Bivalent Pfizer (follow-up: median 28 days; assessed with: Neutralization antibody titers)												
1[f] (n=78)	randomised trials	very serious[g]	not serious	serious[e]	not serious	none	Regardless of COVID-19 infection status, a 2nd booster of bivalent vaccine consistently induced geometric mean neutralizing titer fold rise in antibody response across the COVID-19 strains: BA.4/5, 13 fold (95% CI 8.0 – 21.1); BA.4.6,11.1 fold (95% CI 7.1 – 17.3); BA.2.75.2, 6.7 fold (95% CI 4.4 – 10.2); and XBB.1, 4.8 fold (95% CI 3.3 – 6.9). Geometric mean fold rise ratios of bivalent vaccines showed constant superiority for all strains (higher titers of 4.5x for BA.4/5; 4.8x for BA.4.6; 3.2xfor BA.2.75.2; 3.2x higher titers for XBB.1)				⊕◯◯◯ Very low	NOT IMPORTANT
Adverse events, unsolicited - Moderna (follow-up: range 43 days to 57 days)												
1[a] (n=814)	randomised trials	very serious[b]	not serious	not serious	serious[h]	none	25/437 (5.7%)	22/377 (5.8%)	**OR 0.98** (0.54 to 1.77)	**1 fewer per 1,000** (from 26 fewer to 40 more)	⊕◯◯◯ Very low	CRITICAL
Medically Attended Adverse events - Moderna (follow-up: range 43 days to 57 days)												
1[a] (n=47)	randomised trials	very serious[b]	not serious	not serious	serious[h]	none	2/25 (8.0%)	2/22 (9.1%)	**OR 0.87** (0.11 to 6.75)	**11 fewer per 1,000** (from 80 fewer to 312 more)	⊕◯◯◯ Very low	CRITICAL

CI: confidence interval; **OR:** odds ratio

Explanations

a. Chalkias 2022;
b. non-randomized controlled trials, sequential allocation sequence, open-label trial;
c. compared bivalent vs monovalent vaccine. Ideally 2nd booster vs no 2nd booster;
d. wide confidence interval, OIS too small, exploratory outcome;
e. immunogenicity is a surrogate outcome;
f. Zou 2022;
g. non-randomized controlled trials;
h. small event rate, wide confidence interva

Appendix 7: Ongoing Studies

1	Immunogenicity Evaluation of Omicron Variant-based Vaccine and a Trivalent Vaccine in Adults Against COVID-19 in Chile (CoronaVarCL) Status: Recruiting Expected completion – September, 2023; NCT05593042
2	COVID-19 Booster Study in Healthy Adults in Australia Status: Recruiting Expected completion – August 2024; NCT05658523
3	A Preliminary Exploratory Study to Evaluate the Safety and Immunogenicity of Omicron Variant Bivalent Vaccine V-01-B5 (COVID-19) Status: Active, not recruiting Expected completion - September 2023; NCT05585567
4	Trial of 2nd Booster Dose of COVID-19 Vaccine Status: Not yet recruiting Expected completion - June 2023; NCT05539703
5	Exploratory Clinical Study to Evaluation of the Safety and Immunogenicity of Bivalent Vaccine V-01D-351 (COVID-19) Status: Active, not recruiting Expected completion – August 2023; NCT05583357
6	A Phase 1, Randomised, Double-blinded, Placebo-controlled, Dose-escalation Study to Evaluate the Safety and Immunogenicity of RH109 as Booster Status: Not yet recruiting Expected completion – March 2023; NCT05609045
7	Immunogenicity and Safety of COVID-19 Vaccine as a Booster Vaccination in Population Aged 18 Years and Above Status: Active, not recruiting Expected completion – December 2023; NCT05664932
8	Efficacy and Safety of LYB001 as Booster Vaccination in Adults 18 Years of Age or Older Status: Active, not recruiting Expected completion – January 2024; NCT05683600
9	Immunogenicity and Safety of ChulaCov19 BNA159 Vaccine as a Booster Dose in Adults Status: Not yet recruiting Expected completion – November, 2023; NCT05605470
10	A parallel group, prevention, phase iv, unblinded 2-arm study to investigate hospital admission and deaths due to COVID-19, after receiving an invitation to take a second booster COVID-19 vaccine compared with not receiving an invitation in participants 45 to 64 years of age without any COVID-19 risk factors, who have received 3 doses of a COVID-19 vaccine and with the last dose administered at least 4 months ago. Status: Ongoing EUDRACT: 2022-001590-31

11	Immunogenicity and Safety of a Booster Vaccination With a Recombinant Protein RBD Candidate Vaccine Against SARS-CoV-2 in Healthy Adults Volunteers Fully Vaccinated Followed by an Extension Period to Study a Fourth Dose Administration. Status: Active, not recruiting Expected completion - June 1, 2023; NCT05142553
12	Immunogenicity, Efficacy and Safety of Inhaled (IH) Viral Vectored Vaccine (Convidecia, CanSino) as Second Booster Dose Against Emerging Variants of Concern (VOC) Status: Active, not recruiting Expected completion - July 2023; NCT05517642
13	Heterologous Boost Immunization With Ad5-nCoV After Three-dose Priming With an Inactivated SARS-CoV-2 Vaccine Status: Active, not recruiting Expected completion - March 2023 but Last Update Posted on this is on August 16, 2022; NCT05303584
14	An International Multicentre, Phase 2, Randomised, Adaptive Protocol to determine the need for, optimal timing of and immunogenicity of administering a 4th homologous mRNA vaccination dose against SARS-CoV-2 in the general population (18+ years) already vaccinated against SARS-CoV-2 (EU-COVAT-2 BOOSTAVAC) Status: Ongoing 2021-004889-35