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
Funded by the Department of Health

EVIDENCE SUMMARY

RESEARCH QUESTION: Among adults with previous infection, what is the clinical and immunologic efficacy and effectiveness and safety of a booster?

Review by: Carolina Linda Tapia, MD, Gloriosa Galindez, 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
Among adult individuals with previous COVID-19 infection who received standard doses of COVID-19 vaccine primary series, we suggest the use of a **homologous** first booster dose of monovalent mRNA vaccines.	Very low	Weak
Among adult individuals with previous COVID-19 infection who received standard doses of COVID-19 primary vaccine series, there is no recommendation for the use of a **heterologous** first booster dose of monovalent mRNA vaccines due to insufficient evidence.	Very low	None

Consensus Issues

The Panel opted to withhold a recommendation for heterologous vaccination due to the evidence having very low certainty. Indirect evidence was used when considering heterologous vaccination, with no studies looking into severe COVID-19 outcomes, actual adverse events, and other safety issues arising from boosters among those with previous COVID-19 infection.

KEY FINDINGS

- There were 4 observational studies and 3 RCTs that investigated the effect of monovalent mRNA booster dose among individuals with previous infection compared to those with 2 doses (primary series) and had not received a booster dose.
- A homologous booster dose of mRNA vaccine showed significant reduction in the odds of BA.1, BA.2 and any Omicron infection, regardless of variant. The odds of severe, critical or fatal BA.1, BA.2 and any Omicron infection, were not significantly reduced.
- A heterologous booster of mRNA vaccine, demonstrated significant harm for BA.1, BA.2 and any Omicron infection, regardless of variant.
- A booster dose of an mRNA vaccine with unspecified primary series combinations, did not show a significant difference in the odds of having Omicron BA.2 COVID-19 infection. One study showed that the odds of hospitalization due to Omicron infection were four-fold higher.
- Indirect evidence for the safety of a booster dose of an mRNA vaccine was evaluated from two RCTs on healthy individuals and one that included a few individuals with evidence of current or previous COVID-19 infection. A homologous booster dose of BNT162b2 did not show a significant reduction in the risk of all adverse events, serious adverse events and mortality. A heterologous booster dose of either BNT162b2 or mRNA-1273, showed no significant difference in the risk of serious adverse events but significantly increased risk of all adverse events which were mostly mild (Grade 1).

- All studies had serious risk of bias due to selection, misclassification, unblinding and attrition. The risk of bias contributed to further downgrading of evidence to very low certainty due to inconsistency, indirectness and imprecision.

INTRODUCTION

It has been shown that vaccination, regardless of previous infection, elicits increased humoral memory and that SARS-CoV-2 infection prior to vaccination elicits a robust cellular immunity. SARS-CoV-2 infection and vaccination or hybrid immunity (i.e. a combination of vaccination and prior infection) is also shown to be more immunogenic. However, the addition of a third vaccine dose may not provide additional protection [1]. There has been little data revealing the dynamics of the antibody response after booster vaccination in comparison to the initial primary series among those who have previous COVID-19 infection.

In the background of vaccine supply shortage, the administration of booster doses must be based on sound evidence of its efficacy, effectiveness and safety.

REVIEW METHODS

A systematic search was done from October 17 to December 28, 2022 using Medline, Cochrane, ClinicalTrials.gov, Chinese Clinical Trial Registry, EU Clinical Trials Register medRxiv.org bioRxiv.org and COVID-NMA L.OVE Platform with adults previously infected with COVID-19 as the population, booster or third dose of COVID-19 vaccine as exposure, primary series without a booster dose as comparator, clinical and immunologic safety and effectiveness as outcomes. Combined free text and MeSH search terms were “covid-19”, “sars cov 2”, “ncov”, “covid-recovered adult”, “prior infection”, “post Covid 19”,”previous infection”, “covid-19 vaccines”, “first booster”,” third dose”; control as “primary series”, “first and second dose vaccine”, “efficacy”, “effectiveness”, “safety”, “clinical efficacy” and “immunologic efficacy.” The references of identified studies were examined to find any further potential studies for inclusion. Update search was done on March 6, 2023 which added the terms to the list: “covid 19 nucleic acid testing”, “covid 19 serological testing” and “covid 19 testing”, which yielded no new additional studies. (Appendix 2)

Included were observational studies comparing a booster dose with those who received only a primary series with no booster or a placebo among previously infected. Outcomes of interest were risk of infection, severe, critical or fatal COVID-19 infection, immunogenicity and safety. No language restriction was applied. Excluded were duplicates, studies with ineligible population, case report and correspondence/letters. (Appendix 3)

In the absence of data on the safety of a monovalent mRNA booster dose among individuals with previous infection in the included studies, articles and their references were screened for studies in the general population on the safety of a booster dose of mRNA vaccines.

The observational studies were appraised using Newcastle–Ottawa scale, while RoB II was used for the RCT.

Subgroup analysis by variant-dependent risk of infection (Omicron BA.1 and BA.2) and severity was done. Outcomes related to Delta infection were not included in the analysis because it is no longer considered a variant of concern [2]. Pooling of studies was done using RevMan 5.4.

RESULTS

Characteristics of included studies

This review identified four published observational studies that evaluated the effectiveness of a monovalent mRNA vaccine booster dose on previously infected individuals. A pre-print article was reviewed but was not included among the studies since preliminary analysis showed that excluding it from the pooled analyses did not affect the results. For evaluation of safety, two published articles that assessed the safety of a booster dose of mRNA vaccines in healthy individuals and one that included a few individuals with evidence of current or previous infection were reviewed.

Populations included the general population and healthcare workers who had previous SARS-CoV-2 infection and received a COVID-19 booster or third dose compared with those without booster. Although two studies included young and elderly individuals [3,4], sub-group analysis was not done because of the lack of stratification of data by age.

Only two studies specified the type of vaccination - homologous booster dose [4] or heterologous booster [5] of mRNA vaccine, while it was not stated in two other studies [3,6].

Outcomes measured during the follow-up period that ranged from 7 to 322 days after booster, were BA.1 COVID-19 infection, [4-5], BA.2 infection [4-6], any Omicron infection [4], severe, fatal or critical BA.1 COVID-19 infection and BA.2 COVID-19 infection [4] and hospitalization due to Omicron infection [3]. (Appendix 4)

Of the three RCT that evaluated safety, two were done among adults, including the elderly [7-8] while one included adolescents as participants [9]. Although one RCT had 5.4% of the study population with evidence of current or previous infection, the data for this group were not analyzed separately. Safety of a homologous or heterologous booster dose of BNT162b2 and mRNA-1273 were studied with outcomes on all adverse events [7], serious adverse events (SAE) [7,9], local and systemic adverse reactions [8] and mortality [9]. Follow-up periods in the three studies ranged from within seven days up to 2.7 months post-booster. Two studies were ongoing trials at the time of publication and provided only interim analysis of results [8,9]. (Appendix 4)

Effectiveness outcomes

Homologous Booster *mRNA vaccines [either BNT162b2 (Pfizer-BioNTech) or mRNA-1273 (Moderna)]*
Overall results of a study (n=6,031) showed that previously infected individuals with a booster dose were 42% significantly less likely to have any Omicron infection (OR 0.58, 95% CI 0.52-0.66; I^2=0%). Subgroup analysis by variant showed the same beneficial effect. Including the result of a pre-print article [10] also showed beneficial effect. There was no significant difference in the odds of severe, critical or fatal overall Omicron infection regardless of variant (OR 0.35, 95% CI 0.06-2.16; I^2 0%; n=210) compared with those without booster [4].

Heterologous Booster *mRNA vaccines [either BNT162b2 (Pfizer-BioNTech) or mRNA-1273 (Moderna)]*
A heterologous booster dose of mRNA vaccine demonstrated a significantly higher odds of any Omicron infection among individuals with previous infection (OR 1.33, 1.12-1.59; I^2 83%; n=37,364) [5]. Subgroup analysis by variant showed the same harmful effect.

Not Stated if Homologous or Heterologous Booster *mRNA vaccines [either BNT162b2 (Pfizer-BioNTech) or mRNA-1273 (Moderna)]*
A booster dose of an mRNA vaccine with unspecified primary series combinations, did not show a significant difference in the odds of having Omicron BA.2 COVID-19 infection compared with those who received a primary series without booster (OR 0.85, 95% CI 0.53-1.350) [6].

One study showed a significant four-fold higher odds of hospitalization due to Omicron infection compared with individuals without booster (OR 3.96, 95% CI 2.33-6.71) [3].

Safety outcomes

Homologous Booster *BNT162b2 (Pfizer-BioNTech)*
Pooling results of two studies (n=10,293) showed a lower risk of SAEs which was however, not significant (RR 0.71, 95% CI 0.38-1.31) [7,9]. The risk of all adverse events was also shown not to be significant (RR 1.29, 95% CI 0.95-1.760) [7]. One study showed a lower risk of mortality that was not significant (RR 0.33, 95% CI 0.01-8.12) [9].

Heterologous Booster *BNT162b2 (Pfizer-BioNTech)*
One study showed no significant difference in risk of SAEs (RR 0.33, 95% CI 0.01-8.09) but significantly increased the risk of mild (Grade 1) AEs (RR 1.53, 95% CI 1.12-2.090) among healthy individuals who received a heterologous first booster of BNT162b2 [7].

Homologous Booster *mRNA-1273 (Moderna)*
Interim analysis of an ongoing clinical trial (n=80) showed that within seven days after the booster, most solicited local and systemic adverse reactions were mild (40 to 68%) or moderate (11 to 40%) with no Grade 4 adverse reactions. The most common local adverse reaction was injection site pain. Systemic adverse reactions were mostly fatigue, headache, arthralgia and myalgia. There were no serious adverse reactions reported [8].

Heterologous Booster *mRNA-1273 (Moderna)*
One study demonstrated no significant risk for SAE (RR 3.05, 95% CI 0.13-74.16). A slight increase in risk of all AEs (RR 1.31, 95% CI 1.03-1.65; I^2 0%) with a heterologous first booster of mRNA-1273 was seen in the same study (n=649) [7].

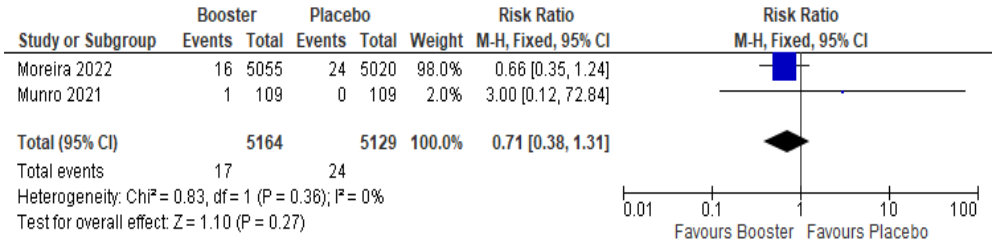

Figure 1. Comparison of Homologous BNT1262b Booster vs placebo or control in having severe, adverse events, using Fixed Effect Model

Certainty of Evidence

Of the 4 studies on effectiveness, 2 studies were judged to have poor quality [3,5]. The study by Andeweg, 2022 [10] had serious risk of bias due to misclassification of previous exposure and vaccination status. The study by Martin, 2022 [3] also had serious risk of bias due to misclassification bias. (Appendix 4) All 3 RCT on safety had concerns of indirectness since two were conducted on healthy individuals and the one that included individuals with evidence of current or previous infection did not analyze the data separately. Two

studies had a high risk of bias. The study by Moreira [9] did early blinding while the study by Choi [8] was non-randomized and there was no concealment of allocation. The study by Munro, 2021 [7] had small sample sizes for events measured. Overall certainty of evidence was downgraded to very low because of the serious risk bias, inconsistency, imprecision and indirectness.

RECOMMENDATIONS FROM OTHER GROUPS

Table 1. Summary of Recommendations from Other Groups

Group / Agency	Recommendation	Strength of Recommendation
DOH/HTAC as of Jan. 18, 2022	Individuals who just had a bout with COVID-19 may get boosted if it has already been three months since their second dose of AstraZeneca, Moderna, Pfizer, Sinovac or Sputnik; or two months from a single dose of Janssen, has finished prescribed isolation period, had no fever for the last 24 hours and respiratory symptoms have improved [11].	Not available
CDC as of Dec. 9, 2022	For booster vaccination, bivalent mRNA vaccines, homologous or heterologous, are recommended. People who recently had SARS-CoV-2 infection may consider delaying their primary or booster COVID-19 vaccine dose by 3 months from symptom onset or positive test (if infection was asymptomatic) [12].	Not available

ONGOING STUDIES AND RESEARCH GAPS

As of March 6, 2023, no ongoing trial was found on the clinical and immunologic efficacy and effectiveness and safety of a booster dose among individuals with previous COVID-19 infection.

More studies with higher certainty of evidence are needed to demonstrate the effectiveness of a booster dose among individuals with previous infection, in the following areas:

1. optimum interval of time between primary series and booster dose among individuals with previous COVID-19 infection
2. duration of protection of hybrid immunity (previous infection and vaccination)
3. long-term clinical efficacy and effectiveness and safety of booster doses in individuals with previous COVID-19 infection
4. clinical efficacy and effectiveness and safety of a booster dose for mRNA versus non-MRNA vaccines, in individuals with previous COVID-19 infection
5. clinical efficacy and effectiveness and safety of a booster dose in individuals with previous COVID-19 infection against new variants of concern

ADDITIONAL CONSIDERATIONS FOR EVIDENCE TO DECISION (ETD) PHASE

COST

The cost of BNT162b2 as a booster dose to achieve vaccination targets is as follows [13]:

2021 Primary Series	2022 Booster Dose	Total Cost of Implementation
Pfizer-BioNTech	Pfizer-BioNTech	Php 8.42B
CoronaVac		Php 8.35B
Moderna*		Php 4.81B
AstraZeneca*		Php 4.49B

The cost of mRNA-1273 as a booster dose is as follows [13]:

2021 Primary Series	2022 Booster Dose	Total Cost of Implementation
CoronaVac	Moderna (1 full dose)	Php 23.45B
Moderna (2 full doses)	Moderna (half of 1 dose)	Php 6.94B

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

No study on the acceptance or non-acceptance of a booster dose among previously infected individuals was found.

An online survey among 1,692 18 to 24 year old university students found that 57.03% did not intend to complete their vaccination. Respondents who rated their health as very good to excellent had lower odds of vaccination intention while those who reported low life satisfaction had greater odds of vaccination intention [14].

In the DOH COVID-19 vaccine survey done on May 16 to 31, 2021, 97% of the respondents (n=6,176) said "yes, highly likely" when asked about the likelihood of getting a second dose of COVID-19 vaccine, while 2.36% were not sure and 0.57% were not likely [15]. No studies were found on acceptance of COVID-19 boosters.

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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 (5)	Varies (1)	Uncertain			COVID-19 has been the most important public health concern worldwide since 2020. As of November 24, 2022, there were 4,029,201 COVID-19 cases reported in the Philippines, with 64,524 deaths [19]. As of December 13, 2022, around 73.7 million people have been fully vaccinated from the COVID-19 virus, including those who received single-dose vaccines. However, about 71 million people have yet to receive their second dose of vaccine. Only about 21.06 million (28.06%) have received a booster shot [20]. Prior infection in patients with COVID-19 is shown to be highly protective against reinfection and symptomatic disease. If infection provides substantial long-lasting immunity, it may be appropriate to reconsider vaccination distribution [21].
Benefits	Large	Moderate (6)	Small	Trivial	Varies	Uncertain	A homologous booster dose of mRNA vaccine in individuals with previous COVID-19 infection reduced the odds of Omicron BA.1, BA.2 infection but not severe, critical or fatal infection. A heterologous mRNA booster demonstrated significantly higher odds of Omicron BA.1 and BA.2 infection among individuals with previous infection.

							A booster dose of an mRNA vaccine with unspecified primary series combinations did not show a significant difference in the odds of having Omicron BA.2 COVID-19 infection. Indirect evidence from three clinical trials on the safety of a booster dose of an mRNA vaccine among healthy individuals showed that either homologous or heterologous booster doses of BNT162b2 lowered the risk of serious adverse events (SAEs). With mRNA1273, a homologous booster dose demonstrated mild to moderate solicited local or systemic adverse reactions, with no serious adverse reactions reported.
Harm	Large	Moderate (3)	Small (1)	Trivial	Varies (2)	Uncertain	The odds of hospitalization due to Omicron infection were four-fold higher among previously infected individuals who received a booster dose of an mRNA vaccine with unspecified primary series combination. Indirect evidence from three clinical trials on the safety of a booster dose of an mRNA vaccine among healthy individuals showed that the risk of all adverse reactions (AEs) was higher in those who received a homologous BNT1262b booster. A heterologous mRNA1273 booster dose demonstrated increased risk of all AEs, including SAEs.
Certainty of Evidence	High	Moderate	Low (3)	Very low (3)			Low to very low certainty of evidence for effectiveness from observational studies. It was downgraded due to serious risk of bias, inconsistency and imprecision.

							Moderate to very low certainty of evidence for safety from clinical trials due to serious risk of bias, indirectness and imprecision.
Balance of effects	Favors vaccination	Probably favors vaccination (3)	Does not favor vaccination	Probably favors no vaccination (1)	Favors no intervention	Varies (2)	Indirect evidence from three clinical trials on the safety of a booster dose of an mRNA vaccine among healthy individuals showed that although either homologous or heterologous booster doses of BNT162b2 lowered the risk of serious adverse events (SAEs), a homologous booster dose increased the risk of all adverse events. With mRNA1273, a homologous booster dose demonstrated mild to moderate solicited local or systemic adverse reactions, with no serious adverse reactions reported. A heterologous mRNA1273 booster dose demonstrated increased risk of all AEs, including SAEs.
Values	Important uncertainty or variability (2)	Possibly important uncertainty or variability (3)	Possibly NO important uncertainty or variability (1)	No important uncertainty or variability			No study was found on the acceptance or non-acceptance of a booster dose among previously infected individuals. An online survey among 1,692 18-24 year old university students found that 57.03% did not intend to complete their vaccination. Respondents who rated their health as very good to excellent had lower odds of vaccination intention while those who reported low life satisfaction had greater odds of vaccination intention [22]. In the DOH COVID-19 vaccine survey done on May 16 to 31,2021, 97% of the respondents (n=6,176) said “yes, highly likely” when asked about the likelihood of getting a second dose of COVID-19 vaccine, while 2.36% were

								not sure and 0.57% were not likely [23].
Resources Required	Don't know	Varies	Large cost (5)	Moderate cost (1)	Negligible cost or savings	Moderate savings	Large savings	The cost of BNT162b2 as a booster dose is as follows [24]: 2021 Primary Series / 2022 Booster Dose / Total Cost of Implementation Pfizer- BioNTech / Pfizer-BioNTech / Php 8.42 B CoronaVac / Php 8.35 B Moderna* / Php 4.81 B AstraZeneca* / Php 4.49 B The cost of mRNA-1273 as a booster dose is as follows [24]: 2021 Primary Series / 2022 Booster Dose / Total Cost of Implementation CoronaVac* / Moderna (1 full dose) / Php 23.45 B Moderna (2 full doses) / Moderna (half of 1 dose) / Php 6.94 B
Certainty of evidence of required resources	No included studies (2)		Very low (1)	Low (1)	Moderate (2)	High		
Cost effectiveness	No included studies (5)	Varies	Favors the comparison	Probably favors the comparison (1)	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	As of Nov. 15, 2021, there have been no studies done on cost-effectiveness of booster vaccination [24].
Equity	Uncertain (5)	Varies	Reduced	Probably reduced	Probably no impact	Probably increased	Increased (1)	
Acceptability	Don't know (2)		Varies	No (1)	Probably no	Probably yes (2)	Yes (1)	
Feasibility	Don't know (1)		Varies	No (1)	Probably no	Probably yes (4)	Yes	

Appendix 2: Search Strategy

Table 3. Database search strategy

Database	Search Strategy/Search Terms	Date/Time	Results	
			Yield	Eligible
PubMed	((("COVID-19 Vaccin*"[Mesh] AND "booster"[All Fields] OR "third dose"[All Fields] AND "COVID-19" [Supplementary Concept] OR "severe acute respiratory syndrome coronavirus 2" [Supplementary Concept] OR "2019-nCoV" OR "2019nCoV" OR "cov 2" OR "Covid-19" OR "sars coronavirus 2" OR "sars cov 2" OR "SARS-CoV-2" OR "severe acute respiratory syndrome coronavirus 2" OR "coronavirus 2" OR "COVID 19" OR "COVID-19" OR "2019 ncov" OR "2019nCoV" OR "corona virus disease 2019" OR "cov2" OR "COVID-19" OR "COVID19" OR "nCov 2019" OR "nCoV" OR "new corona virus" OR "new coronaviruses" OR "novel corona virus" OR "novel coronaviruses" OR "SARS Coronavirus 2" OR "SARS2" OR "SARS-COV-2" AND "hospitalized"[MeSH Terms] OR "recovered"[All Fields] OR "previous infection" [All Fields] OR "prior infection" [All Fields] OR "positive"[All Fields] Filter: January 1, 2022 to October 17, 2022	Oct 17, 2022, 22:02:21	215	15
Cochrane	COVID-19 vaccines AND booster OR third dose AND recovered OR infected OR positive OR "previous infect*" OR "prior Infect*"	Oct 17, 2022, 17:24:48	79	0
ClinicalTrials.Gov	Condition or disease: "Covid19" Intervention/treatment: "booster dose" OR "third dose" Others: recovered OR infected OR "previous infection" OR "prior infection"	Dec 28, 2022 10:07:00	29	0
Chinese Clinical Trial Registry	Target Disease: "covid-19" Intervention: "covid-19 booster vaccine" (multiple words not allowed)	Dec 28, 2022, 10:23:00	0	0
EU Clinical Trials Register	"COVID 19 vaccine" AND booster OR "third dose" AND recovered OR infected OR "previous infect*" OR "prior infect*"	Dec 28, 2022, 10:26:00	0	0
medRxiv.org bioRxiv.org	"COVID 19, booster, positive, recovered" Filter: January 1, 2022 to September 10, 2021	Oct 17, 2022, 10:00:00 Oct 18, 2022 10:00:00	131 93	6 1
COVID-NMA	Vaccines > Living Mapping > Infected	Oct 17, 2022 09:45:00	0	0
LOVE Platform for COVID-19 Evidence	covid-19 AND vaccine AND (3rd dose OR booster OR 3-dose) AND infected	Oct 16, 2022 16:00:00	228	14
Cross-referencing		Oct 31, 2022, 11:34:00	4	4
			798	40

DATABASE	SEARCH STRATEGY / SEARCH TERMS	DATE AND TIME OF SEARCH	RESULTS	
			Yield	Eligible
Medline https://pubmed.ncbi.nlm.nih.gov/	""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 third dose"[Supplementary Concept] OR "covid 19 nucleic acid testing"[All Fields] OR "covid 19 nucleic acid testing"[MeSH Terms] OR "covid 19 serological testing"[All Fields] OR "covid 19 serological testing"[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 “bivalent” (("coronavirus"[MeSH Terms] OR "coronavirus"[All Fields] OR "cov"[All Fields]) AND ("hospitalized"[MeSH Terms] OR "hospital"[All Fields] OR "infection"[All Fields] OR "recovered"[All Fields] OR "positive"[All Fields])	Mar. 6, 2023, 21:04:00GMT +8	543	1
CENTRAL https://www.cochranelibrary.com/advanced-search	COVID-19 vaccine, booster vaccination, recovered, infected, positive, bivalent	March 6, 2023 21:05:00GMT +8	92	0
ClinicalTrials.gov https://clinicaltrials.gov/	Condition or disease: “Covid19” Intervention/treatment: “booster dose” Others: positive, recovered, infected	March 6, 2023; 21:07:21 GMT +8	33	0
Chinese Clinical Trial Registry http://www.chictr.org.cn/searchprojen.aspx	Target Disease: “covid-19” Intervention: “booster”, “recovered”, “positive”	March 6, 2023, 21:08:21 GMT +8	2	0
EU Clinical Trials Register https://www.clinicaltrialsregister.eu/	“COVID-19 vaccine AND booster AND positive”	March 6, 2023, 21:09:00 GMT +8	45	0
medRxiv.org bioRxiv.org	“COVID 19, booster, positive, recovered”	March 6, 2023, 21:10:21 GMT +8	457	9
https://covid-nma.com/ https://covid-nma.com/vaccines/mapping/	Vaccines > Living Mapping > Infected	March 6, 2023, 21:11:59 GMT +8	3	0
LOVE Platform for COVID-19 Evidence (https://app.iloveevidence.com/loves/5e6fdb9669c00e4ac072701d?utm=ile)	covid-19 AND vaccine AND (3rd dose OR booster OR 3-dose) AND infected	March 6, 2023, 21:12:01 GMT +8	17	2

Appendix 3: PRISMA flow diagram

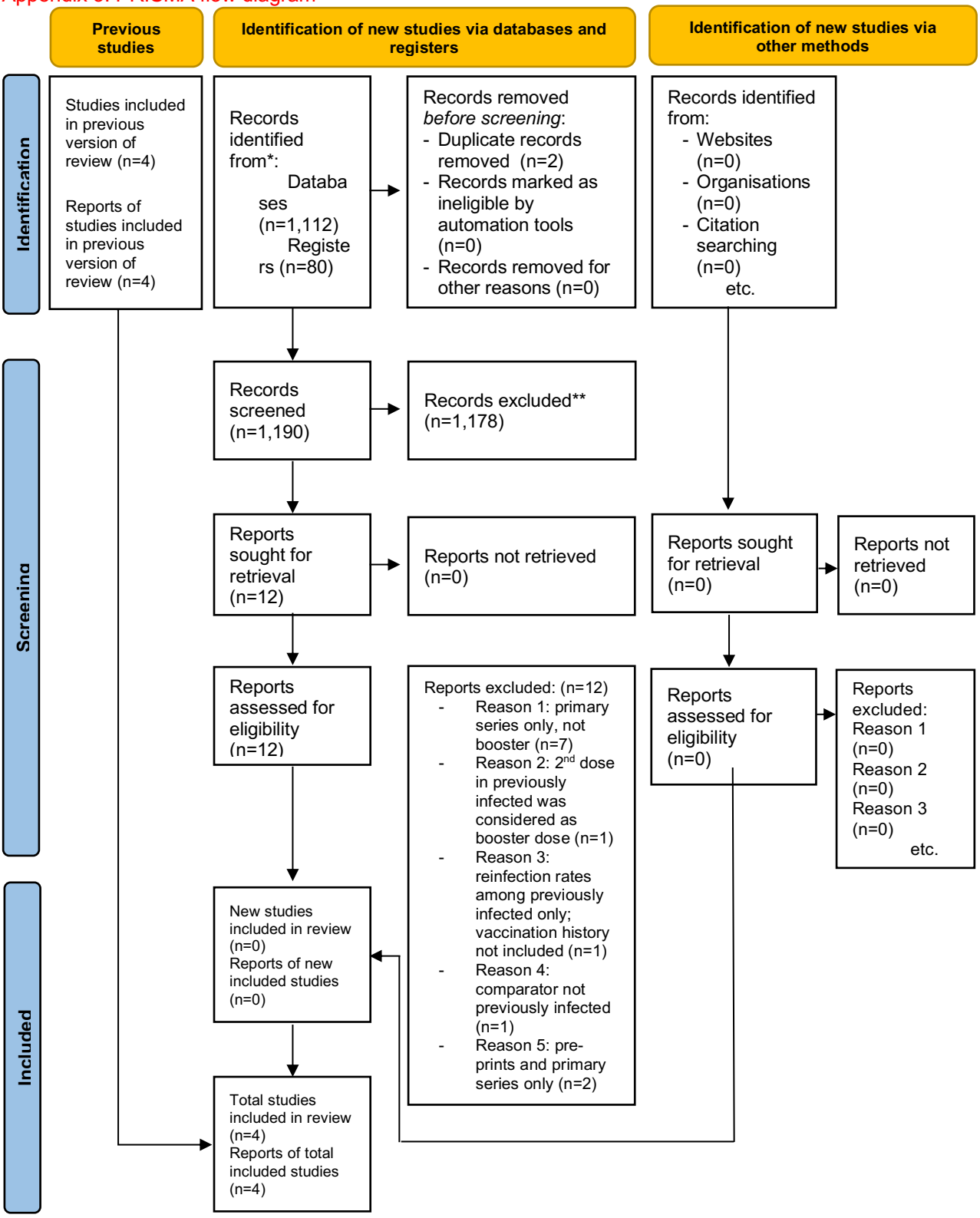

Figure 2. PRISMA flow diagram.

Appendix 4: Characteristics of Included Studies

Table 4a. Characteristics of included studies on Effectiveness

Title/ Author	Study design	Country	Number of patients	Population	Intervention Group(s)	Control	Outcomes
HOMOLOGOUS BOOSTER DOSE, mRNA vaccines [either BNT162b2, (Pfizer-BioNTech) or Moderna (mRNA1273)]							
Altarawneh et al. 2022	Matched test negative case control	Qatar	Cases (n=52,245) Controls (n=52,245)	General population Median age = 32 years (IQ range =20-43)	Previous infection, with booster (n=818)	Previous infection, no booster (2 doses) (n=4,359)	Follow-up: median of 42 days (7 to 322 days) post-booster Symptomatic BA.1, BA.2 and any Omicron infection Severe, critical or fatal BA.1, BA.2 or any Omicron infection
Lind, et.al 2022 **(pre-print)**	Test-negative case control	USA	Cases (n=10,676) Control (n=119,397)	Vaccine-eligible (≥ 5 years of age) with at least 1 SARS-CoV-2 RT-PCR test or mRNA273 or BNT162b2 vaccine dose Median age =35 years (p25-p75 = 21, 50)	Previous infection and booster, (n=669)	Previous infection, no booster, (n=3,181)	Follow-up: 14-59 days post-booster Omicron BA.1
HETEROLOGOUS BOOSTER DOSE, mRNA vaccines [either BNT162b2, (Pfizer-BioNTech) or Moderna (mRNA1273)]							
Andeweg ,et.al 2022	Test negative case control	Nether-lands	Cases (n=109,557; BA.1 n=67,887; BA.2 n=41,670) Control (n=207,553)	General population 18 to 60+ years old	Previous infection, booster, (n=22,094)	Primary vaccination, then infection (n=15,270)	Follow-up: up to 7 months post booster: BA.1, BA.2 Omicron infection
NOT STATED IF HOMOLOGOUS or HETEROLOGOUS BOOSTER DOSE, mRNA vaccines [either BNT162b2, (Pfizer) or Moderna (mRNA1273)]							
Martin, et.al 2022	Cross-sectional	Czech Republic	N=10,701,777	All individuals who tested positive for SARS-CoV-2 0 to 80+years	Previous infection with booster, (n=88,230)	Previous infection, no booster, (n=918,836)	Events from Dec. 7, 2021 to Feb 13, 2022, follow-up: calendar time in 61-day periods after vaccination and 121-day periods after previous infection: Hospitalization due to Omicron infection

Carazo. et.al 2022	Test negative case control	Canada	Cases (n=37,732) Controls (n=73,507)	All health care workers aged 18 years and older in Quebec	Previous Omicron BA.1 infection and 3 doses, (n=498)	Previous Omicron BA.1 infection and 3 doses, (n=498)	Follow-up period = 7 to 89 days post booster BA.2 infection

Table 4b. Characteristics of included studies on Safety

Title/ Author	Study design	Country	Number of patients	Population	Intervention Group(s)	Control	Outcomes
HOMOLOGOUS BOOSTER DOSE BNT162b2, (Pfizer-BioNTech)							
Moreira, et al. 2022 Interim analysis	RCT	Multi-country: Brazil, Canada, Germany, Israel, South Africa, USA	N=10,125	Individuals, 16-65 y/o who completed a 2-dose primary (5.4% with evidence of current or previous infection)	BNT162b2 booster dose 30 µg, at least 6 months after 2nd dose, (n=5,055)	Placebo, at least 6 months after 2nd dose, (n=5,020)	Follow-up: up to 2 .5 months after booster dose Serious Adverse events Mortality
Munro, et al. 2021	RCT	UK (multi-center)	N=2,883	Healthy adults 30 years and older, who received a complete homologous 2 dose primary course	BNT162b2 booster dose 30 µg, at least 84 days after 2nd dose (n=110)	Quadrivalent meningococcal conjugate vaccine (Pfizer-BioNTech) (n=109)	Follow-up: 2.7 months after booster Adverse events Serious adverse events
HETEROLOGOUS BOOSTER DOSE BNT162b2, (Pfizer-BioNTech)							
Munro, 2021	RCT	UK (multi-center)	N=2,883	Healthy adults 30 years and older, who received a complete homologous 2 dose primary course	BNT162b2 booster dose 30 µg, at least 84 days after 2nd dose (n=107)	Quadrivalent meningococcal conjugate vaccine (Pfizer-BioNTech) (n=106)	Follow-up: 2.7 months after booster Adverse events Serious adverse events
HOMOLOGOUS BOOSTER DOSE mRNA1273							
Choi, et al. 2021 Interim analysis	RCT	USA		Healthy adults, who completed primary series of 100 µg mRNA1273 and proceeded to mRNA1273 booster phase (n=558) and mRNA1273 variant booster phase (n=60)	mRNA-1273 50 µg booster (n=20); mean age = 63.8 y (38-76 y) Variant boosters (n=60)	Data not provided	Follow-up: within 7 days after booster Local and systemic adverse reaction

HETEROLOGOUS BOOSTER DOSE mRNA1273							
Munro, 2021	RCT	UK (multi-center)	N=2,883	Healthy adults 30 years and older, who received a complete homologous 2 dose primary course (N=2,883) Primary series: BNT162b2	mRNA1273, at least 84 days after 2nd dose (n=111)	Quadrivalent meningococcal conjugate vaccine (Pfizer-BioNTech) (n=112)	Follow-up: 2.7 months after booster Adverse events Serious adverse events
				Primary Series: ChadOx1	mRNA1273, at least 84 days after 2nd dose (n=112)	Quadrivalent meningococcal conjugate vaccine (Pfizer-BioNTech) (n=114)	

Appendix 5: Study Appraisal

Table 5a. Risk of bias assessment for Case Control Studies – Newcastle Ottawa Scale

Study	Selection				Comparabil-ity of cohorts based on design and analysis	Exposure			Quality
	Case Definition	Representative-ness of cases	Selection of Controls	Definition of controls		Ascertain-ment	Method of ascertain-ment for cases and controls	Non-response rate	
Altarawneh, et al 2022	*	*	*	*	*	*	*	*	good
Andeweg, et al 2022	*		*		*			*	poor
Carazo, et al 2022	*		*	*	*	*	*	*	good
Lind, et al 2022 **(pre-print)**	*		*	*	**		*	*	fair

Table 5b. Risk of bias assessment for Cross-sectional Studies – Newcastle Ottawa Scale

Study	Selection				Comparabi-lity based on design and analysis; control of confounders	Outcome		Quality
	Representa-tiveness of sample	Sample size	Non-respondents	Ascertain-ment of exposure		Assess-ment	Statisti-cal test	
Martin	*			*	*		*	poor

Risk of bias assessment randomized control trials – RoB II

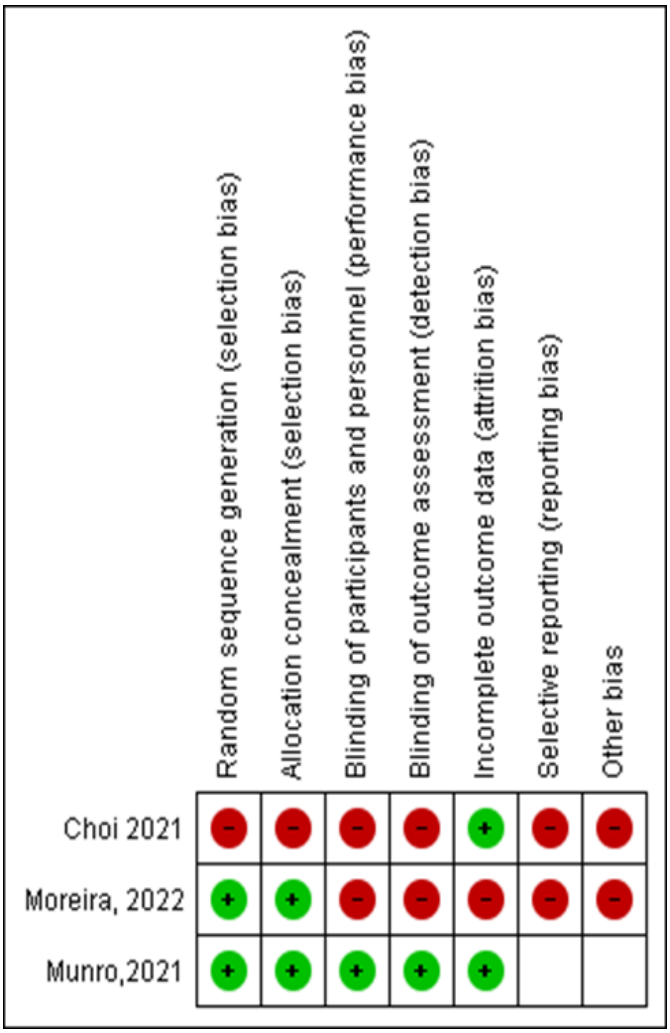

Figure 3. Risk of bias summary

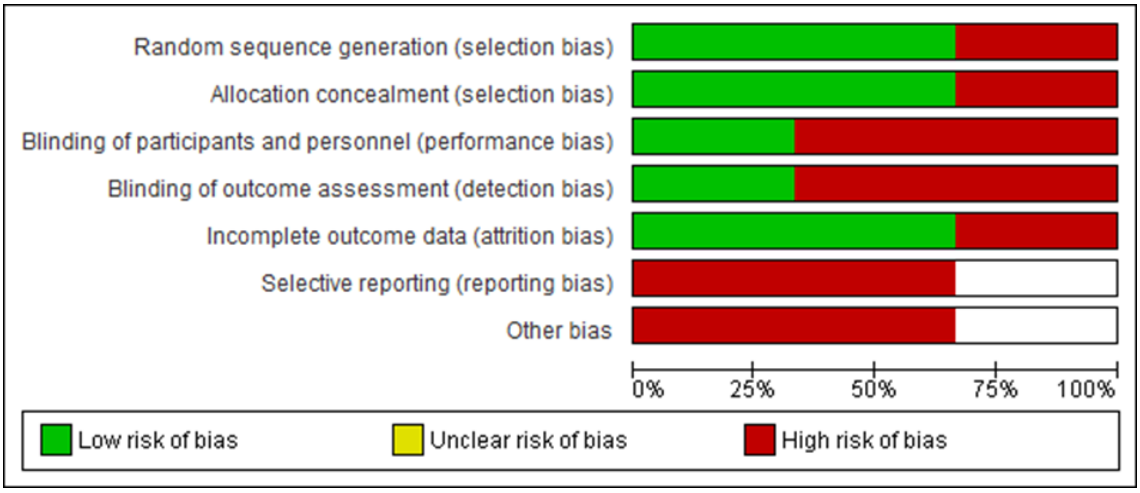

Figure 4. Risk of bias summary

Appendix 6: Grade Evidence Profile

Table 6. GRADE Evidence Profile for Effectiveness and Safety of Homologous mRNA Booster Among Adults with Previous SARS-CoV-2 Infection

Author(s): Carolina Linda Tapia, MD, Gloriosa Galindez, MD and Ma. Lucila M. Perez, MD
Question: mRNA homologous COVID-19 booster dose compared to no booster for adults with previous SARS-CoV-2 infection
Bibliography: [1]Altarawneh 2022, [2]Moreira 2022, [3]Munro 2021

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	COVID-19 booster dose	no booster	Relative (95% CI)	Absolute (95% CI)		
m-RNA Homologous 1st Booster, Omicron BA.1 Infection												
1[1]	observational studies	not serious	not serious	not serious	not serious	none	47/178 (26.4%)	402/1090 (36.9%)	**OR 0.61** (0.43 to 0.88)	**106 fewer per 1,000** (from 168 fewer to 29 fewer)	⨁⨁◯◯ Low	Critical
m-RNA Homologous 1st Booster, Omicron BA.2 Infection												
1[1]	observational studies	not serious	not serious	not serious	not serious	none	153/642 (23.8%)	1160/3268 (35.5%)	**OR 0.57** (0.47 to 0.69)	**116 fewer per 1,000** (from 149 fewer to 80 fewer)	⨁⨁◯◯ Low	Critical
m-RNA Homologous 1st Booster, all Omicron, regardless of variant												
1[1]	observational studies	not serious	not serious	not serious	not serious	none	387/1591 (24.3%)	2922/8219 (35.6%)	**OR 0.58** (0.52 to 0.66)	**113 fewer per 1,000** (from 133 fewer to 89 fewer)	⨁⨁◯◯ Low	Critical
mRNA Homologous 1st Booster, Severe, critical or fatal Omicron BA.1 Infection												
1[1]	observational studies	not serious	not serious	not serious	serious[a]	none	0/7 (0.0%)	1/9 (11.1%)	**OR 0.38** (0.01 to 10.75)	**66 fewer per 1,000** (from 110 fewer to 462 more)	⨁◯◯◯ Very low	Critical
mRNA Homologous 1st Booster, Severe, critical or fatal Omicron BA.2 Infection												
1[1]	observational studies	not serious	not serious	not serious	serious[a]	none	0/23 (0.0%)	1/42 (2.4%)	**OR 0.59** (0.02 to 15.04)	**10 fewer per 1,000** (from 23 fewer to 245 more)	⨁◯◯◯ Very low	Critical
mRNA Homologous booster, Severe, critical or fatal all Omicron , regardless of variant												
1[1]	observational studies	not serious	not serious	not serious	serious[a]	none	0/77 (0.0%)	0.0%	**OR 0.35** (0.06 to 2.16)	**0 fewer per 1,000** (from 0 fewer to 0 fewer)	⨁◯◯◯ Very low	Critical
BNT162b2 Homologous booster, Serious Adverse Events												
2[2,3]	randomised trials	serious[b]	not serious	serious[c]	serious[a]	none	17/5164 (0.3%)	24/5129 (0.5%)	**RR 0.71** (0.38 to 1.31)	**1 fewer per 1,000** (from 3 fewer to 1 more)	⨁◯◯◯ Very low	Critical
BNT162b2 Homologous booster, mortality												
1[2]	randomised trials	serious[b]	not serious	serious[c]	serious[a]	none	0/5055 (0.0%)	1/5019 (0.0%)	**RR 0.33** (0.01 to 8.12)	**0 fewer per 1,000** (from 0 fewer to 1 more)	⨁◯◯◯ Very low	Critical
BNT162b2 Homologous booster, all adverse events												
1[3]	randomised trials	not serious	not serious	serious[c]	serious[a]	none	53/109 (48.6%)	41/109 (37.6%)	**RR 1.29** (0.95 to 1.76)	**109 more per 1,000** (from 19 fewer to 286 more)	⨁⨁◯◯ Low	Critical

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

Explanations

a. wide confidence interval
b. failure to analyze participants according to their randomized assignment due to early unblinding and large number of exclusions (withdrawal and not completing follow-up) in placebo group. (Moreira, 2022)
c. different population - healthy individuals (Moreira, 2022; Munro 2021)

Table 7. GRADE Evidence Profile for Effectiveness and Safety of Heterologous mRNA Booster Among Adults with Previous SARS-CoV-2 Infection

Author(s): Carolina Linda Tapia, MD, Gloriosa Galindez, MD and Ma. Lucila M. Perez, MD
Question: mRNA Heterologous COVID-19 booster compared to no booster in previously infected individuals
Bibliography: [1]Andeweg 2022, [2]Munro 2021

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	heterologous COVID-19 booster	no booster	Relative (95% CI)	Absolute (95% CI)		
mRNA Heterologous booster, Omicron BA.1 infection												
1[1]	observational studies	very serious[a]	not serious	not serious	not serious	none	1189/11086 (10.7%)	691/7711 (9.0%)	**OR 1.22** (1.11 to 1.35)	**18 more per 1,000** (from 9 more to 28 more)	⨁◯◯◯ Very low	Critical
mRNA Heterologous booster, Omicron BA.2 infection												
1[1]	observational studies	very serious[a]	not serious	not serious	not serious	none	1111/11008 (10.1%)	539/7559 (7.1%)	**OR 1.46** (1.31 to 1.63)	**29 more per 1,000** (from 20 more to 40 more)	⨁◯◯◯ Very low	Critical
mRNA Heterologous booster, Omicron Infection regardless of variant												
1[1]	observational studies	very serious[a]	serious[b]	not serious	not serious	none	2300/22094 (10.4%)	1230/15270 (8.1%)	**OR 1.33** (1.12 to 1.59)	**24 more per 1,000** (from 9 more to 42 more)	⨁◯◯◯ Very low	Critical
BNT162b2 Heterologous booster, serious adverse events												
1[2]	randomised trials	not serious	not serious	serious[c]	serious[d]	none	0/106 (0.0%)	1/106 (0.9%)	**RR 0.33** (0.01 to 8.09)	**6 fewer per 1,000** (from 9 fewer to 67 more)	⨁⨁◯◯ Low	Critical
BNT162b2 Heterologous booster, all adverse events												
1[2]	randomised trials	not serious	not serious	serious[c]	serious[d]	none	57/106 (53.8%)	37/105 (35.2%)	**RR 1.53** (1.12 to 2.09)	**187 more per 1,000** (from 42 more to 384 more)	⨁⨁◯◯ Low	Critical
mRNA-1273 Heterologous booster, serious adverse events												
1[2]	randomised trials	not serious	not serious	serious[c]	serious[d]	none	1/222 (0.5%)	0/226 (0.0%)	**RR 3.05** (0.13 to 74.16)	**0 fewer per 1,000** (from 0 fewer to 0 fewer)	⨁⨁◯◯ Low	Critical
mRNA-1273 Heterologous booster, all adverse events												
1[2]	randomised trials	not serious	not serious	serious[c]	not serious	none	119/341 (34.9%)	82/308 (26.6%)	**RR 1.31** (1.03 to 1.65)	**83 more per 1,000** (from 8 more to 173 more)	⨁⨁⨁◯ Moderate	Critical

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

Explanations

a. misclassification of vaccination status due to self-reporting and those with previous infection were given the choice to have 2nd dose or not (2nd dose misclassified as booster to 1st dose of primary series); misclassification of previous infection due to restrictive testing policy during peak of pandemic (many children may not have been tested) (Andeweg, 2022)
b. substantial heterogeneity
c. different population - healthy individuals (Munro, 2021)
d. wide confidence interval

Table 8. GRADE Evidence Profile for Effectiveness and Safety of mRNA Booster, Not Stated if Homologous or Heterologous, Among Adults with Previous SARS-CoV-2 Infection

Author(s): Carolina Linda Tapia, MD, Gloriosa Galindez, MD and Ma. Lucila M. Perez, MD

Question: Not stated if homo or hetero COVID-19 booster dose compared to no booster in previously infected individuals

Bibliography: [1]Carazo 2022, [2]Martin 2022

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Not stated if homo or hetero COVID-19 booster dose	no booster	Relative (95% CI)	Absolute (95% CI)		
mRNA Not stated if Homologous or Heterologous, Omicron BA.2 infection												
1[1]	observational studies	serious[a]	not serious	serious[b]	serious[c]	none	20/498 (4.0%)	262/5314 (4.9%)	**OR 0.85** (0.53 to 1.35)	**7 fewer per 1,000** (from 23 fewer to 16 more)	⨁◯◯◯ Very low	Critical
mRNA Not stated if Homologous or Heterologous, Hospitalization												
1[2]	observational studies	serious[d]	not serious	not serious	not serious[c]	none	19/88230 (0.0%)	50/918836 (0.0%)	**OR 3.96** (2.33 to 6.71)	**0 fewer per 1,000** (from 0 fewer to 0 fewer)	⨁◯◯◯ Very low	Critical

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

Explanations

a. asymptomatic infections undetected; sublineages BA.1 and BA.2 were identified based on calendar time (Carazo, 2022)

b. study population consisted of healthcare workers (Carazo, 2022)

c. wide confidence interval

d. Bec. of very high prevalence (high reproduction number) of COVID-19 infection at the peak of the epidemic, a much higher proportion of patients were hospitalized with COVID-19 as a concomitant finding rather than the COVID-19 being the reason for hospitalization (Martin, 2022)