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 healthcare workers, what is the efficacy and safety of a second COVID-19 vaccine booster dose in preventing COVID-19 infection?

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RECOMMENDATIONS

Recommendations	Certainty of Evidence	Strength of Recommendation
We recommend the use of the homologous monovalent BNT162b2 (Pfizer-BioNTech) as second booster dose to prevent symptomatic COVID-19 infection in healthcare workers.	Very low	Strong
We recommend the use of the heterologous mRNA-1273 (Moderna) as a second booster dose to prevent COVID-19 infection in healthcare workers.	Very low	Strong

Consensus Issues

The Panel voted on these recommendations considering the significant benefits for this population which commonly encounters individual COVID-19 infection. In particular, evidence leans towards favoring a second booster dose to provide protection against waning immunity and increased protection against breakthrough infection. Additionally, they have positive economic implications, allowing for preservation of work productivity, due to decreased absences and availability of healthcare workers to render COVID-related and other medical services.

KEY FINDINGS

- Evidence as of November 2022 coming from one open-labeled, non-randomized clinical trial and two multicenter prospective cohort studies (two published and one preprint) on the efficacy and safety of the COVID-19 vaccine second booster dose in healthcare workers (HCW) suggest that the monovalent BNT162b2 (Pfizer-BioNTech) homologous second booster significantly decreased the risk of symptomatic COVID-19 breakthrough infection but not for any breakthrough infection. Significant increases in anti-SARS-CoV-2 and neutralizing antibody titers were noted after administration of the second BNT162b2 booster dose.
- Very low-quality evidence from one study suggests that the heterologous monovalent mRNA-1273 (Moderna) second booster has no effect on the risk for any breakthrough infection or symptomatic breakthrough infection. Significant increases in anti-SARS-CoV-2 and neutralizing antibody titers were noted after administration of the mRNA-1273 booster dose compared to the control group. Most reported second booster adverse events were mild.
- There were no reported serious adverse events for both monovalent BNT162b2 (Pfizer-BioNTech) and monovalent mRNA-1273 (Moderna) as second boosters.
- There is no available evidence on the use of CoronaVac, ChAdOx1, BBV152, Ad26.CoV2.S and other vaccines as a second booster in health care workers.

INTRODUCTION

Interest in a second booster dose of the COVID-19 vaccine, defined as a second vaccine dose after completion of a primary series, is increasing amid concerns over waning vaccine immunogenicity and effectiveness as well as protection against new disease variants. Initial evidence collected by the World Health Organization (WHO) suggests that the administration of a second mRNA vaccine booster dose is correlated with increased neutralizing antibody titers and vaccine effectiveness relative to the first booster dose [1]. Healthcare workers (HCWs) in particular are more likely to be exposed to the SARS-CoV-2 virus and may stand to benefit from the renewed protection afforded by an additional booster dose.

This review aims to compare the COVID-19 vaccine second booster dose versus no second booster dose in terms of efficacy, effectiveness, immunogenicity, and safety against COVID-19 among HCWs.

REVIEW METHODS

A search of MEDLINE, the Cochrane COVID-19 Study Register, the COVID-NMA living database, and the COVID L·OVE Platform was done with a combination of free-text and MeSH terms including "COVID-19" and “second booster” for systematic reviews, meta-analyses, randomized controlled trials (RCTs), and cohort studies that report the effect of a second booster dose compared to no second booster dose or placebo in the development of COVID-19 morbidity, mortality, immunogenicity, duration of protection, and adverse events in adult healthcare workers. Preprints were obtained by searching the medRxiv, and bioRxiv databases. Ongoing clinical trials were searched in ClinicalTrials.gov, the WHO International Clinical Trials Registry Platform, and the Chinese Clinical Trials Registry. The final database search date was October 18, 2022, while the final clinical trial database search date was November 5, 2022.

No restrictions on country or language were applied. Studies that were not original research and studies performed *in vitro* were excluded.

Included studies were appraised for risk of bias using the Newcastle-Ottawa Scale (NOS) for cohort studies and Risk of Bias (RoB) Scale for clinical trials [6]. Data extracted included country, study design, patient profile, sample size (second booster and first booster groups), type of vaccine, patient age and sex ratio, primary outcome, and reported measures of risk. Pooled meta-analyses, whenever applicable, were done for unadjusted data using the Mantel-Haenszel test for dichotomous data. Adjusted data was also reported to minimize the risk of bias due to confounders [7]. Meta-analyses and related forest plots were generated using Review Manager 5.4 (Cochrane Collaboration).

RESULTS

Characteristics of included studies

Three studies [8-10] were obtained following the database search as of November 2022 with a total sample size of 30,919. (Appendix 2, 3) One was an open-labeled, non-randomized clinical trial [10] and two were multicenter prospective cohort studies from Israel. Two studies were published at the time of the database search [8,10], while one was a preprint [9]. A total of 6,036 patients were enrolled in the second-booster group, and 25,071 were enrolled in the first-booster group without a second booster.

All studies enrolled patients with a complete primary series and first booster dose of the BNT162b2 (Pfizer-BioNTech) vaccine at least three months prior and with no history of COVID-19 infection. All studies used a homologous BNT162b2 second booster dose. One of the studies [10] also had a heterologous intervention arm of a dose of monovalent mRNA-1273 (Moderna) vaccine as second booster to three doses of BNT162B2. A study [8] matched each patient in the intervention group 1:1 with the control group based on age, sex, profession, hospital, and date of first booster dose. All three studies used breakthrough infection as an outcome; breakthrough infections of COVID-19 in the studies were defined as occurring at

least eight days after the second booster. Clinical outcomes were observed for 30 days in two studies [8,10] and 90 days in one study [9]. Additionally, one study [10] presented immunogenicity results and vaccine adverse events for both the first booster and second-booster groups. (Appendix 4)

Methodological quality

The two cohort studies [8,9] were of low risk of methodological bias according to the Newcastle-Ottawa Scale. The clinical trial [10] had a high risk of bias according to the Risk of Bias 2 tool. (Appendix 5)

Study Outcomes

Homologous Booster
BNT162b2 (Pfizer-BioNTech)

Real World Effectiveness: Breakthrough infections
Three studies [8-10] reported results on breakthrough infections after homologous vaccination with the BNT162b2 second booster. Pooled analysis of the three studies (n=9,688) suggests that the BNT162b2 homologous second booster does not significantly protect from any breakthrough COVID-19 infection after 30 or 90 days (RR 0.64, 95% CI 0.33-1.25, I^2=96%). However, when risk for symptomatic COVID-19 breakthrough infection after a second booster was determined, there was a reduced risk based on pooled analysis of two studies (RR 0.74, 95% CI 0.60-0.90, I^2=63%) [9,10]. Observation period for the two pooled studies varied from 30 to 90 days.

Immunogenicity
One study [10] recorded anti-SARS-CoV-2 IgG and neutralizing antibody levels before and after the second BNT162b2 booster dose. A significant increase in IgG titers were recorded for the second booster group three weeks after the second booster immunization date (baseline: Geometric Mean Titer (GMT) of 326.3, 95% CI 293-363; after three weeks: GMT 2684, 95% CI 2372-3038). A significant increase in neutralizing antibody titers was also recorded (baseline: GMT 429.6, 95% CI 360-512; after three weeks: GMT 3501, 95% CI 2976-4119).

In comparison, the control group had a significant decrease in IgG titers and no significant change in neutralizing antibodies. By the end of the three weeks, IgG titers in those given second BNT162b2 booster dose were eight times higher than those in the control group [GMT 2684 (SD 2108.4) vs GMT 340 (SD 410.7)]. Neutralizing antibody titers were also higher by 9.6 times in those given a second booster than those in the control group [GMT 3501 (SD 3618.4) vs GMT 363 (SD 1885.0)].

Adverse events
One study [10] reported local adverse events in 78.6% of patients. Majority were mild (46.7%) with few severe symptoms (3.9%). Most common were pain and/or tenderness (76.6%) and induration or swelling (10.4%). The mean duration of local symptoms was around 1.5 days.

Systemic adverse events were reported by 42.8% of patients and were more common in those under 60 years old and with longer duration [1.6 days (95% CI 1.0-2.1)] compared to those over 60 [1.0 days (95% CI 0.6-1.4)]. Most systemic adverse events were mild, commonly fatigue, headache, and myalgia.

There were no reported serious adverse events (SAEs) for the BNT162b2 second booster.

Heterologous Booster
mRNA-1273 (Moderna)

Real-world effectiveness: breakthrough infections
A published study with a heterologous arm consisting of 120 patients who received three BNT162b2 doses and an mRNA-1273 second booster compared with 239 matched controls with three BNT162b2 doses [10] reported no effect on the risk for developing any breakthrough COVID-19 infections (RR 1.33, 95% CI 0.83-2.12) or symptomatic infection (RR 1.03, 95% CI 0.60-1.77).

Immunogenicity
One study [10] recorded anti-SARS-CoV-2 IgG and neutralizing antibody levels before and after the second mRNA-1273 booster dose. A significant increase in IgG titers were recorded for the second booster group three weeks after the second booster immunization date (baseline: GMT 335.2, 95% CI 285.5-393.5; after three weeks: GMT 3729, 95% CI 3132-4440). A significant increase in neutralizing antibody titers was also recorded (baseline: GMT 336.6, 95% CI 277-409; after three weeks: GMT 3510, 95% CI 2884-4272).

In comparison, the control group had a significant decrease in IgG titers and no significant change in neutralizing antibodies. By the end of the three weeks, IgG titers in those given a second BNT162b2 booster dose were 11 times higher than those in the control group [GMT 3729 (SD 3655.2) vs. GMT 340 (SD 410.7)]. Neutralizing antibody titers were also higher by 9.6 times in those given second booster than those in the control group [GMT 3510 (SD 3878.8) vs GMT 363 (SD 1885.0)].

Adverse events
One study [10] showed that following the mRNA-1273 second booster dose, local adverse events were reported by 82.5% of patients, the majority of which were mild. The most common local symptoms were pain and/or tenderness (81.7%) and induration or swelling (14.2%). Mean duration of local symptoms was longer among those under 60 years than those over 60 (2.2 days, 95% CI 1.3-3.0 vs. 1.6 days, 95% CI 1.6-3.4).

Systemic adverse events were reported by 55.8% of patients, commonly mild (25.0%) with only 4.2% reporting severe symptoms. The most common systemic symptom noted was fatigue, followed by myalgia and headache. The mean duration of systemic symptoms was short at less than 1.5 days. There were no reported SAEs for the mRNA-1273 second booster.

Certainty of evidence

For BNT162B2 (Pfizer-BioNTech), there was noted heterogeneity and imprecision of the pooled estimates of the clinical outcomes. The RCT which was included in the meta-analysis also had serious risk of bias due to problems observed in randomization, allocation concealment and blinding. These resulted in very low certainty of evidence. (Appendix 7, 8)

For mRNA-1273 (Moderna) immunogenicity outcomes were considered as indirect evidence for efficacy and evidence was downgraded because of indirectness. The RCT had serious risk of bias and this resulted in low certainty of evidence. (Appendix 7, 8)

RECOMMENDATIONS FROM OTHER GROUPS

Table 1. Summary of Recommendations from Other Groups

Group / Agency	Recommendation
WHO As of August 2022 [1]	Second booster dose recommended for: ● Older patients (age cut-off defined by country) ● Patients with moderately and severely immunocompromising conditions (e.g. active cancer with chemotherapy, transplant recipients, HIV, use of immunosuppressive drugs) ● Adults with comorbidities (e.g. diabetes, hypertension, chronic kidney disease) ● Pregnant women ● Healthcare workers
Philippine DOH As of June 2022 [11]	Second booster dose of the Pfizer-BioNTech and Moderna vaccines recommended for healthcare workers at least four months after the first booster dose

ONGOING STUDIES AND RESEARCH GAPS

As of November 5, 2022, there is one ongoing RCT and one ongoing prospective cohort study on a second booster dose in healthcare workers. (Appendix 9)

Additional research is needed to determine the vaccine efficacy of the second booster dose, especially for populations with primary series and booster vaccines other than BNT162b2.

ADDITIONAL CONSIDERATIONS FOR EVIDENCE TO DECISION (ETD) PHASE

COST

In March 18, 2021, the government estimated that it would spend an average cost of around PHP 1,300.00 per person for the country's vaccination program, to include the 2-dose vaccine cost and ancillaries [13].

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

In one included study [10], only 274 of 1050 eligible healthcare workers (26.1%) volunteered to be vaccinated with a second booster. In this same study, there was a significant number of Moderna control patients lost to follow-up, suggesting that those who do not take the second booster dose may be less compliant in reporting relevant outcomes.

No studies were obtained on Equity and Feasibility.

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Appendix 1: Preliminary Evidence to Decision

Table 1. Summary of initial judgements prior to the panel discussion (N=5/10)

FACTORS	JUDGEMENT						RESEARCH EVIDENCE/ADDITIONAL CONSIDERATIONS
Problem	No	Yes (5)	Varies	Uncertain			• In a 2022 study covering nine European countries, healthcare workers were at a significantly higher risk than non-healthcare workers to contract COVID-19 infection and to require hospitalization/ICU admission due to COVID-19 infection [12].
Benefits	Large	Moderate (5)	Small	Trivial	Varies	Uncertain	• **Pfizer vaccine** - pooled results show moderate benefit in preventing symptomatic breakthrough infection. Also good immunogenicity. • **Moderna vaccine** - one study showed it does not prevent breakthrough infection with good immunogenicity.
Harm	Large	Moderate (1)	Small (4)	Trivial	Varies	Uncertain	• Most adverse effects were local and with mild severity for both vaccine brands studied.
Certainty of Evidence	High	Moderate	Low	Very low (4)			• Certainty of evidence is very low for the homologous BNT162b2 second booster and low for the heterologous mRNA1273 second booster.
Balance of effects	Favors vaccination (2)	Probably favors vaccination (3)	Does not favor vaccination	Probably favors no vaccination	Favors no intervention	Varies	

Values	Important uncertainty or variability (1)		Possibly important uncertainty or variability (3)	Possibly NO important uncertainty or variability (1)	No important uncertainty or variability			• In one included study [10], only 274 of 1,050 eligible healthcare workers (26.1%) volunteered to be vaccinated with a second booster. In this same study, there was a significant number of Moderna control patients lost to follow-up, suggesting that those who do not take the second booster dose may be less compliant in reporting relevant outcomes.
Resources Required	Don't know	Varies	Large cost (4)	Moderate cost (1)	Negligible cost	Moderate savings	Large savings	• On March 18, 2021, the government estimated that it would spend an average cost of around ₱1,300.00 per person for the country's vaccination program, to include the 2-dose vaccine cost and ancillaries [13].
Certainty of evidence of required resources	No included studies (1)		Very low	Low (2)	Moderate	High (1)		
Cost effectiveness	No included studies	Varies	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention (5)	Favors the intervention	
Equity	Uncertain	Varies	Reduced (1)	Probably reduced	Probably no impact (1)	Probably increased	Increased (2)	
Acceptability	Don't know		Varies (2)	No	Probably no	Probably yes (3)	Yes	
Feasibility	Don't know (1)		Varies (1)	No	Probably no	Probably yes (2)	Yes (1)	

Appendix 2: Search Strategy

Table 2. Database search strategy

Database	Keywords	Last Search Date	Yield	Studies meeting inclusion criteria
COVID-19 L-OVE Platform	PICO search with following filters in order: "prevention or treatment", “public health”, "vaccination", and “SARS-CoV-2 vaccines” Search within text: “fourth”, “4th”, “second”, and “2nd” Systematic reviews and primary studies only	October 18, 2022	746	1
COVID-19 NMA	Vaccines - Living Mapping Recruitment/publication/registry status: All Vaccine targeted SARS-CoV-2 variants: All Booster shot: Booster shot, 2nd booster shot Age groups: Adults, Elderly, Older people NOT INCLUDED: Pan sarbecoronavirus vaccine, Pregnant women, Immunosuppressed	October 18, 2022	157	0
Cochrane COVID-19 Study Register	Filters: 1) worker or workers or provider or providers or employee or employees 2) vaccine or vaccines or dose or doses 3) four or 4 or fourth or 4th or two or 2 or 2nd or second	October 18, 2022	1164	3
Pubmed	((((((((("COVID-19" [Supplementary Concept] OR "COVID-19 drug treatment" [Supplementary Concept] OR "COVID-19 serotherapy" [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" OR "Severe Acute Respiratory Syndrome Coronavirus 2") OR ((19[tiab] OR 2019[tiab] OR "2019-nCoV" OR "Beijing" OR "China" OR "Covid-19" OR epidem*[tiab] OR epidemic* OR epidemy OR new[tiab] OR "novel"[tiab] OR "outbreak" OR pandem* OR "SARS-CoV-2" OR "Shanghai" OR "Wuhan") AND ("Coronavirus Infections"[Mesh] OR "coronavirus"[MeSH Terms] OR coronavirus*[all] OR corona-virus*[all] OR cov[tiab] OR pneumonia-virus*[tiab])))) AND 2019/12/1:3000/12/31[PDAT])))))) AND ((booster or dose or doses) and (second or 2nd or fourth or 4th or added or additional))) AND (worker or workers or provider or providers or employee or employees) Filters: from 2022/1/1 - 3000/12/12	October 18, 2022	22	0

Appendix 3: PRISMA flow diagram

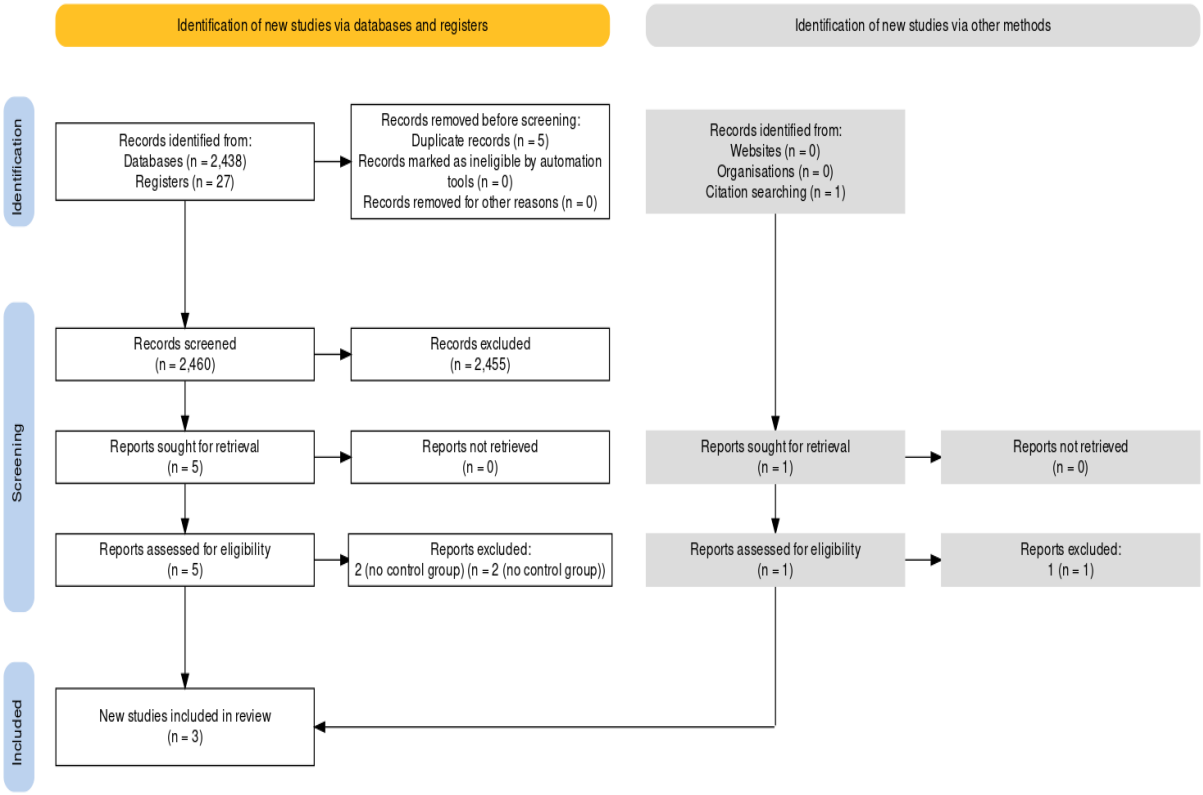

Figure 1. PRISMA flow diagram.

Appendix 4: Characteristics of Included Studies

Table 3. Characteristics of included studies for studies involving BNT162b2 and mRNA 1273 (Moderna) as second booster.

STUDY ID	COUNTRY	STUDY DESIGN	PATIENT PROFILE	SAMPLE SIZE		PATIENT AGE AND SEX RATIO	EXPOSURE	OUTCOME	FOLLOW-UP DURATION
				FIRST BOOSTER (control)	SECOND BOOSTER (intervention)				
Cohen 2022	Israel	Prospective cohort	Adult healthcare workers with completed primary series and first booster dose of the BNT162b2 (Pfizer) vaccine and with no prior COVID-19 diagnosis	24280	5331	Mean age 44 (SD 12) 65% female, 35% male	Second booster dose of BNT162b2 vaccine 3-4 months after first booster dose	COVID-19 breakthrough infection rate	30 days
Hertz 2022	Israel	Prospective cohort	Adult healthcare workers with completed primary series and first booster dose of the BNT162b2 (Pfizer) vaccine and with no prior COVID-19 diagnosis	365	243	Not stated	Second booster dose of BNT162b2 vaccine at least 3 months after first booster dose	Incidence of COVID-19 breakthrough symptomatic infection	90 days
Regev-Yochay 2022	Israel	Open label non-randomized Clinical Trial	Adult healthcare workers with completed primary series and first booster dose of the BNT162b2 (Pfizer) vaccine and with no prior COVID-19 diagnosis	239	120	Mean age: Control: 56.0 (range 29-89) Intervention: 55.1 (range 29-87) Sex: Males: 100 (27.9%) Females: 259 (72.1%)	Second booster dose of mRNA1273 vaccine at least 3 months after first booster dose	COVID-19 breakthrough infection Adverse events (local, systemic) Immunogenicity (Anti-SARS-CoV-2 IgG and neutralizing antibody levels)	30 days

Appendix 5: Study Appraisal

Table 4. Risk of bias appraisal of included studies according to the Newcastle-Ottawa Scale for cohort studies.

	Cohen 2022	Hertz 2022
I. SELECTION		
1) Representativeness of the exposed cohort	*	*
2) Selection of the non-exposed cohort	*	*
3) Ascertainment of exposure	*	*
4) Demonstration that outcome of interest was not present at the start of the study	*	*
II. COMPARABILITY		
1) Comparability of cohorts on the basis of the design or analysis	**	**
III. OUTCOME		
1) Assessment of outcome	*	*
2) Was follow-up long enough for outcomes to occur		*
3) Adequacy of follow-up of cohorts	*	*
TOTAL	**8* Low risk**	**9* Low risk**

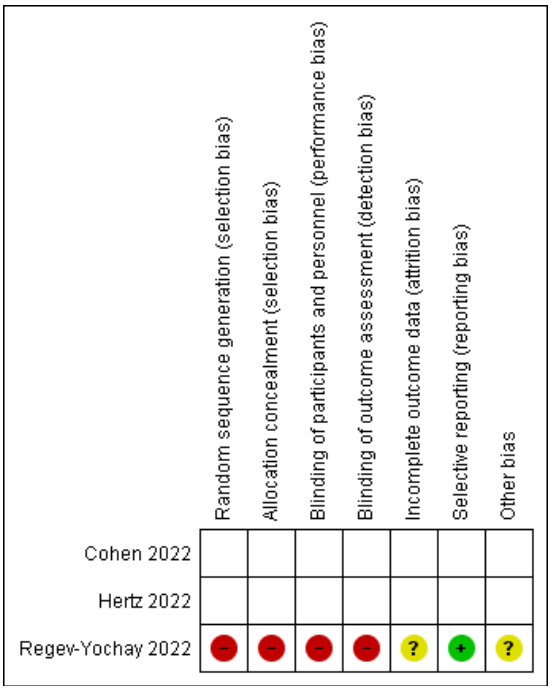

Figure 2. Risk of bias assessment for the included clinical trial according to the Risk of Bias 2 tool.

Appendix 6: Forest Plots

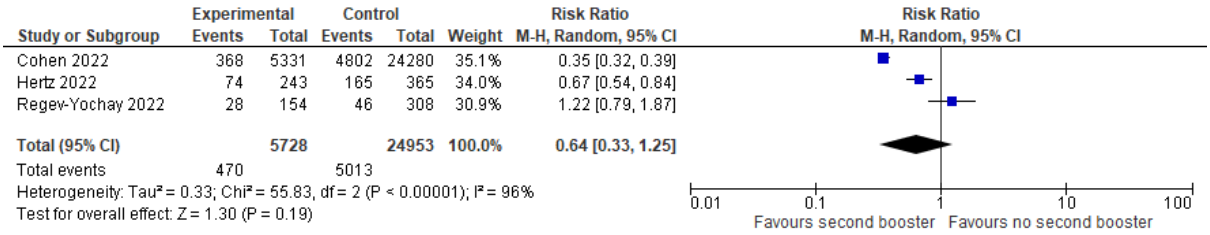

Figure 3. Forest plot for homologous monovalent BNT162b2 vaccine as second booster in health care workers and any breakthrough infection.

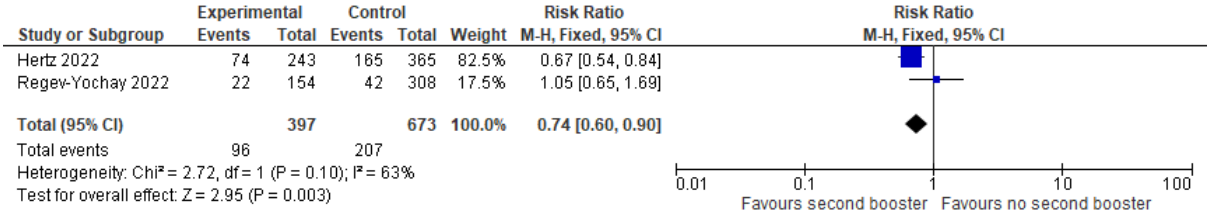

Figure 4. Forest plot for homologous monovalent BNT162b2 vaccine as second booster in health care workers and symptomatic breakthrough infection.

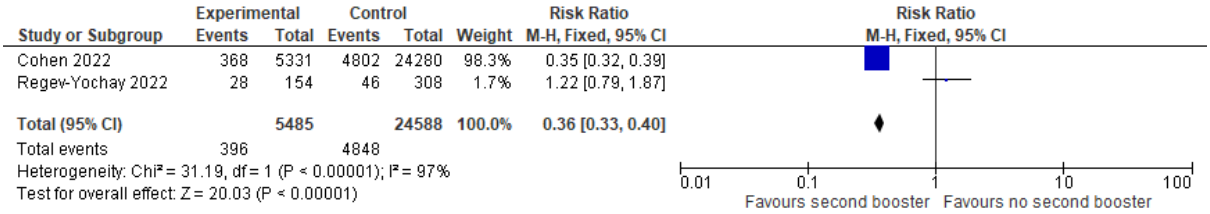

Figure 5. Forest plot of sensitivity analysis for homologous BNT162b2 vaccine as second booster in health care workers and any breakthrough infection after removing preprint studies.

Appendix 7: Grade Evidence Profile

Table 5. GRADE evidence profile for the homologous BNT162b2 (Pfizer) second booster dose.

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	homologous BNT162b2 (Pfizer) second booster dose	no second booster dose	Relative (95% CI)	Absolute (95% CI)		
All breakthrough infections (follow-up: range 30 to 90 days)												
3	observational studies	serious[a]	serious[b]	not serious	serious[c,d]	none	470/5728 (8.2%)	5013/24953 (20.1%)	**RR 0.64** (0.33 to 1.25)	**72 fewer per 1,000** (from 135 fewer to 50 more)	⨁◯◯◯ Very low	CRITICAL
Symptomatic breakthrough infection (follow-up: range 30 to 90 days)												
2	observational studies	serious[a]	serious[b]	not serious	not serious	none	96/397 (24.2%)	207/673 (30.8%)	**RR 0.74** (0.60 to 0.90)	**80 fewer per 1,000** (from 123 fewer to 31 fewer)	⨁◯◯◯ Very low	CRITICAL
Immunogenicity (anti-SARS-CoV-2 IgG) (assessed with: Geometric mean titer)												
1	randomised trials	serious[a]	not serious	serious[e]	not serious	none	154	426	-	MD **2344 GMT higher** (2032 higher to 2698 higher)	⨁⨁◯◯ Low	IMPORTANT
Immunogenicity (anti-SARS-CoV-2 neutralizing antibody) (assessed with: Geometric mean titer)												
1	randomised trials	serious[a]	not serious	serious[e]	not serious	none	154	426	-	MD **3137.1 GMT higher** (2612.1 higher to 3755.1 higher)	⨁⨁◯◯ Low	IMPORTANT
Adverse events												
1	observational studies	serious[f]	not serious	not serious	not serious	none	Local adverse effects: 78.6% of patients. Majority mild: pain/tenderness, mean duration 1.5 days. Systemic adverse events: 42.8% of patients - more common and longer duration in HCWs under 60. Mostly mild (fatigue, headache, myalgia). No SAEs.				⨁◯◯◯ Very low	CRITICAL

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

Explanations

a. Regev-Yochay et al. (2022) was determined to have risk of bias based on the Risk of Bias 2 tool
b. Significant heterogeneity
c. Confidence interval crosses decision threshold RR = 1
d. Wide confidence interval
e. Immunogenicity is a surrogate outcome for measuring protection against COVID-19 infection
f. Descriptive data with no comparator

Table 6. GRADE evidence profile for the heterologous mRNA1273 (Moderna) second booster dose.

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	heterologous mRNA1273 (Moderna) second booster dose	no second booster dose	Relative (95% CI)	Absolute (95% CI)		
All breakthrough COVID-19 infections (follow-up: 30 days)												
1	randomised trials	serious[a]	not serious	not serious	serious[b,c]	none	24/120 (20.0%)	36/239 (15.1%)	**RR 1.33** (0.83 to 2.12)	**50 more per 1,000** (from 26 fewer to 169 more)	⊕⊕◯◯ Low	CRITICAL
Symptomatic breakthrough COVID-19 infection (follow-up: 30 days)												
1	randomised trials	serious[a]	not serious	not serious	serious[b,c]	none	17/120 (14.2%)	33/239 (13.8%)	**RR 1.03** (0.60 to 1.77)	**4 more per 1,000** (from 55 fewer to 106 more)	⊕⊕◯◯ Low	CRITICAL
Immunogenicity (anti-SARS-CoV-2 IgG) (assessed with: Geometric mean titer)												
1	randomised trials	serious[a]	not serious	serious[d]	not serious	none	120	426	-	MD **3389 GMT higher** (2792 higher to 4100 higher)	⊕⊕◯◯ Low	IMPORTANT
Immunogenicity (anti-SARS-CoV-2 neutralizing antibody) (assessed with: Geometric mean titer)												
1	randomised trials	serious[a]	not serious	serious[d]	not serious	none	120	426	-	MD **3146.1 GMT higher** (2520.1 higher to 3908.1 higher)	⊕⊕◯◯ Low	IMPORTANT
Adverse effects												
1	observational studies	serious[e]	not serious	not serious	not serious	none	Local adverse events were reported by 82.5% of patients, the majority of which were mild. The most common local symptoms were pain and/or tenderness (81.7%) and induration or swelling (14.2%). Mean duration of local symptoms was longer among those under 60 years than those over 60 (2.2 days (95% CI 1.3-3.0) vs 1.6 days (95% CI 1.6-3.4) for those over 60).			⊕◯◯◯ Very low	CRITICAL

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

Explanations

a. Regev-Yochay et al. (2022) was determined to have a high risk of bias based on the Risk of Bias 2 tool

b. Wide confidence interval

c. Confidence interval crosses decision threshold RR = 1

d. Immunogenicity is a surrogate outcome for measuring protection against COVID-19 infection

e. Descriptive data with no comparator

Appendix 8: Summary of Findings Evidence Table

Table 7. GRADE summary of findings table for the homologous BNT162b2 (Pfizer) second booster dose.

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with no second booster dose	Risk difference with homologous BNT162b2 (Pfizer) second booster dose
All breakthrough infections follow-up: range 30 to 90 days	30681 (3 observational studies)	⊕◯◯◯ Very low[a,b,c,d]	**RR 0.64** (0.33 to 1.25)	201 per 1,000	**72 fewer per 1,000** (135 fewer to 50 more)
Symptomatic breakthrough infection follow-up: range 30 to 90 days	1070 (2 observational studies)	⊕◯◯◯ Very low[a,b]	**RR 0.74** (0.60 to 0.90)	308 per 1,000	**80 fewer per 1,000** (123 fewer to 31 fewer)
Immunogenicity (anti-SARS-CoV-2 IgG) assessed with: Geometric mean titer	580 (1 RCT)	⊕⊕◯◯ Low[a,e]	-		MD **2344 GMT higher** (2032 higher to 2698 higher)
Immunogenicity (anti-SARS-CoV-2 neutralizing antibody) assessed with: Geometric mean titer	580 (1 RCT)	⊕⊕◯◯ Low[a,e]	-		MD **3137.1 GMT higher** (2612.1 higher to 3755.1 higher)
Adverse events	(1 observational study)	⊕◯◯◯ Very low[f]	Local adverse effects: 78.6% of patients. Majority mild: pain/tenderness, mean duration 1.5 days. Systemic adverse events: 42.8% of patients - more common and longer duration in HCWs under 60. Mostly mild (fatigue, headache, myalgia). No SAEs.		

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

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

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

Explanations
a. Regev-Yochay et al. (2022) was determined to have risk of bias based on the Risk of Bias 2 tool
b. Significant heterogeneity
c. Confidence interval crosses decision threshold RR = 1
d. Wide confidence interval
e. Immunogenicity is a surrogate outcome for measuring protection against COVID-19 infection
f. Descriptive data with no comparator

Table 8. GRADE summary of findings table for the heterologous mRNA1273 (Moderna) second booster dose.

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with no second booster dose	Risk difference with heterologous mRNA1273 (Moderna) second booster dose
All breakthrough COVID-19 infections follow-up: 30 days	359 (1 RCT)	⊕⊕◯◯ Low[a,b,c]	**RR 1.33** (0.83 to 2.12)	151 per 1,000	**50 more per 1,000** (26 fewer to 169 more)
Symptomatic breakthrough COVID-19 infection follow-up: 30 days	359 (1 RCT)	⊕⊕◯◯ Low[a,b,c]	**RR 1.03** (0.60 to 1.77)	138 per 1,000	**4 more per 1,000** (55 fewer to 106 more)
Immunogenicity (anti-SARS-CoV-2 IgG) assessed with: Geometric mean titer	546 (1 RCT)	⊕⊕◯◯ Low[a,d]	-	The mean immunogenicity (anti-SARS-CoV-2 IgG) was **0** GMT	MD **3389 GMT higher** (2792 higher to 4100 higher)
Immunogenicity (anti-SARS-CoV-2 neutralizing antibody) assessed with: Geometric mean titer	546 (1 RCT)	⊕⊕◯◯ Low[a,d]	-	The mean immunogenicity (anti-SARS-CoV-2 neutralizing antibody) was **0** GMT	MD **3146.1 GMT higher** (2520.1 higher to 3908.1 higher)
Adverse effects	(1 observational study)	⊕◯◯◯ Very low[e]	Local adverse events were reported by 82.5% of patients, the majority of which were mild. The most common local symptoms were pain and/or tenderness (81.7%) and induration or swelling (14.2%). Mean duration of local symptoms was longer among those under 60 years than those over 60 (2.2 days (95% CI 1.3-3.0) vs 1.6 days (95% CI 1.6-3.4) for those over 60).		

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

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

GRADE Working Group grades of evidence

High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.

Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.

Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.

Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

Explanations

a. Regev-Yochay et al. (2022) was determined to have a high risk of bias based on the Risk of Bias 2 tool
b. Wide confidence interval
c. Confidence interval crosses decision threshold RR = 1
d. Immunogenicity is a surrogate outcome for measuring protection against COVID-19 infection
e. Descriptive data with no comparator

Appendix 9: Ongoing Studies

Table 9. Characteristics of ongoing studies involving the COVID-19 second booster vaccine in healthcare workers.

Clinical Trial Identifier (Location)	Official Title	Methodology	Outcome Measures	Population	Estimated Date of Completion
NCT05471440 The Netherlands	SWITCH ON: Analysing the Immunogenicity of Additional Booster Vaccinations in HCW	Parallel open-label randomized clinical trial	**Primary outcome:** Level and fold change of IgG antibodies; Level and fold change of IgG antibodies and T-cell IFN-gamma responses **Secondary outcomes:** Level of antibodies and T-cell responses 7 and 28 days post-booster dose in direct booster versus postponed booster group; PRNT against relevant variants; Correlation between antibodies and T-cell responses on day 7 and 28 post-booster dose; Adverse events within the first 7 days of booster dose; Breakthrough infections within 1 year of booster dose	400 healthcare workers between 18 and 65 years with Janssen, Moderna, or Pfizer vaccines	August 2023
NCT05516459 Israel	Prospective Monitoring of BNT162b2 Second Vaccination Booster Effects in Health Care Workers (HCW)	Observational prospective cohort study	**Primary outcomes:** Proportion of positive PCR tests for SARS-CoV-2 (by 30, 60, 90, 120, 150 days) **Secondary outcomes:** Proportion of symptomatic COVID-19 infection (by 30, 90, 182 days); Proportion of COVID-19 infection requiring hospitalization (by 30, 90, 182 days); Levels of binding and neutralizing activity and avidity of the antibodies (by 30, 60, 90, 120, 150, 180 days); Composite endpoint of serious adverse events 14 days after booster dose	635 healthcare workers 18 years and older with three doses of the Pfizer vaccine (last dose at least 4 months before recruitment)	December 2023