EVIDENCE SUMMARY

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

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RECOMMENDATIONS

Recommendations	Certainty of Evidence	Strength of Recommendation
No recommendation can be made on the use of a third booster dose of COVID-19 vaccine (to complete 5 vaccine doses) for the high-risk population because there is no available evidence.	No Evidence	None

KEY FINDINGS

- The current evidence base, as of March 6, 2023, found no published studies on third booster doses in high-risk population as there are no completed studies with its full results including indirect evidence in the healthy population and health care workers.

INTRODUCTION

The need for additional doses of a COVID-19 vaccine after completion of the standard approved dosing regimen has been raised in the light of findings of declining antibody titers over time, and the emergence of SARS-CoV-2 variants of concern that reduces vaccine effectiveness.

Most countries offering second boosters prioritize people who are at high risk (i.e., people who are more than 60 years old or with health conditions like lung or heart disease, diabetes or conditions that affect their immune system) [1]. The rationale for these policies is supported by a range of evidence, including from the UK-based Octave (Observational Cohort Trial T Cells Antibodies and Vaccine Efficacy in SARS-CoV-2) study, which found that four in ten people who were clinically vulnerable generated lower concentrations of antibodies than healthy recipients after two doses of a covid-19 vaccine [2]. In light of these interim guidance surrounding the COVID-19 vaccine, a third booster dose is being suggested for the high-risk population. However, in the background of vaccine supply shortage, the administration of the number of booster doses especially to high-risk groups must be based on sound evidence of its efficacy, effectiveness, and safety.

REVIEW METHODS

Search Strategy

A comprehensive systematic search of related literature was performed from September 10 to December 2, 2022. Medical databases included Pubmed, Clinical Trials.gov, Chinese Clinical Trials Registry, EU Clinical Trials Register, COVID-NMA and L.OVE Platform. Freehand search using Google Scholar was also done. Preprints were searched in medRxiv.org. bioRxiv.org. Retrieved studies were hand searched, if applicable. There was no limit as to date, language, and country of publication.

The search was on the following: Population of healthcare workers; Intervention of third COVID-19 booster dose or a fifth COVID-19 vaccine dose with Comparator of second COVID-19 booster dose or a fourth COVID-19 vaccine dose and Outcome of efficacy or effectiveness against symptomatic COVID-19, hospitalization due to COVID-19, severe COVID-19, COVID-19-related death, duration of protection, safety, immunogenicity. Variants were also checked. MeSH and free text search were conducted. The search done included the population of healthcare workers and, in the absence of studies, was expanded to include high-risk subjects and further to include the general population as indirect evidence.

We searched for clinical trials, observational studies, systematic reviews, and meta-analyses to answer the question on efficacy and effectiveness. Excluded were author's reviews and editorials.

Risk of bias assessment
Two authors were assigned to independently evaluate the risk of bias of included studies. The Cochrane Risk of Bias tool for RCTs and Newcastle Ottawa Scales (NOS) for Observational studies were to be used, as applicable.

Statistical Analysis
RevMan 5.4 statistical software was to be used to pool the effectiveness, efficacy, and safety outcomes, with the relative risks (RR) or odds ratio (OR) and its 95% confidence interval as the effect measures. Overall effectiveness was to be determined and stratified by variants, if applicable. Immunologic responses in antibody titers or T-cell counts after the booster dose are to be noted and compared to placebo or a second booster. Safety outcomes are to be summarized using descriptive statistics, if applicable.

RESULTS

No articles that matched the criteria for direct and indirect evidence of a third COVID-19 booster dose was found. (Appendix 2 and 3)

RECOMMENDATIONS FROM OTHER GROUPS

Group / Agency	Recommendation
DOH As of 02 December 2022.	In terms of giving the third COVID-19 booster dose, study is underway on the incoming bivalent or second generational vaccines for the immunocompromised and the healthcare workers. [3]
US FDA As of 30 March 2022	The US Food and Drug Administration has approved a fifth COVID-19 shot of Pfizer-BioNTech or Moderna for people aged over 50 and some immunocompromised individuals. The third booster or the fifth dose can be administered at least four months after receipt of a fourth dose of any authorized or approved COVID-19 vaccine. The FDA stated that emerging evidence suggests that a fifth dose of an mRNA COVID-19 vaccine improves protection against severe COVID-19 and is not associated with new safety concerns. [4]

ONGOING STUDIES AND RESEARCH GAPS

There are two ongoing studies listed in Clinical Trials.gov on the effectiveness of a third booster of COVID-19 both among the high risk and healthy population. (Appendix 4)

The first study, which is on COVID-19 Vaccine Booster in Immunocompromised Rheumatic Heart Diseases [5], is in its recruitment phase. Its outcome is on the safety and reactogenicity of the second and third booster dose using a mix and match strategy. The estimated study completion date is on December 2023.

The second study, which is on Safety and Immunogenicity of Omicron Variant-Matched Vaccine Booster in Adults [6], is also in its recruitment phase. Its outcomes are on the safety, reactogenicity and immune response of the second and third booster. Estimated study completion date is on July 2023.

WHO emphasizes the need for key gaps in the evidence to be addressed, including:

- Immunogenicity and effectiveness of COVID-19 vaccines in ICPs (immunocompromised person), especially for vectored and inactivated vaccines;
- Immunogenicity and effectiveness of COVID-19 vaccines in subpopulations with different immunocompromising conditions;
- Immunogenicity and effectiveness of COVID-19 vaccines in people living with HIV with a current CD4 cell count of count of <200 cells/µl, evidence of an opportunistic infection, not on HIV treatment, and/or with a detectable viral load (i.e. advanced HIV disease); safety, effectiveness, and duration of protection provided by additional doses in an extended primary series in ICPs;
- Optimal timing of additional doses in an extended primary series in ICPs;
- Relative benefits of heterologous versus homologous additional doses in ICPs; and
- Program considerations on how best to integrate COVID-19 vaccination within broader health care delivery to ICPs [7].

ADDITIONAL CONSIDERATIONS FOR EVIDENCE TO DECISION (ETD) PHASE

COST

As of March 18, 2021, the government estimated that it would be spending an average cost PHP 1,300.00 (primary series only) per person for the country's vaccination program [3].

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

No studies done on acceptability of boosters among Filipino population but based on the National COVID-19 Vaccination Dashboard on January 2, 2023, only 21,169,736 received a booster dose from the 73,778,354 with completed 2 doses.

REFERENCES

[1] WHO Western Pacific website Information for the Public COVID-19 advice - High risk groups | WHO Western Pacific Available from: https://www.who.int/westernpacific/emergencies/ covid-19/information/high-risk-groups

[2] Gareth Iacobucci, Covid-19: Fourth vaccine doses—who needs them and why? The BMJ BMJ 2022;376:o30 http://dx.doi.org/10.1136/bmj.o30 Published: 7 January 2022

[3] Ma. Teresa Montemayor, DOH studies benefits of 3rd booster, bivalent jabs as add'l dose | Philippine News Agency (pna.gov.ph) November 25, 2022, 4:18 pm Available from: https://www.pna.gov.ph/articles /1189462

[4] Business Standard website, Topics US FDA approves fifth Covid vaccine booster shots for 50 and older | Business Standard News (business-standard.com) Last Updated at March 30, 2022 14:15 IST Available from: https://www.business-standard.com/article/international/us-fda-approves-fifth-covid-vaccine-booster-shots-for-50-and-older-122033000525_1.html

[5] Paul R Fortin, COvid-19 Vaccine Booster in Immunocompromised Rheumatic Diseases - Full Text View - ClinicalTrials.gov Available from: https://clinicaltrials.gov/ct2/show/NCT05236491?term=booster%2C+immunocompromised&cond=covid-19&intr=5th+booster&draw=2&rank=1

[6] Gili Regev-Yochay MD Safety and Immunogenicity of Omicron Variant-Matched Vaccine Booster in Adults - Full Text View - ClinicalTrials.gov Available from: https://clinicaltrials.gov/ct2/show/NCT05383560

[7] WHO Interim Guidance: WHO-2019-nCoV-Vaccination-SAGE-recommendation-Immunocompromised-persons-2021.1-eng.pdf Available from: https://apps.who.int/iris/bitstream/handle/10665/347079/WHO-2019-nCoV-Vaccination-SAGE-recommendation-Immunocompromised-persons-2021.1-eng.pdf?sequence=2

[8] DOH website, How much is the cost or what is the price range for each available vaccine? COVID-19 Vaccine Q and A [Internet] 2021 March 18 [cited 2022 Nov 12]. Available from https://doh.gov.ph/node/28134

Appendix 1: Preliminary Evidence to Decision

Table 1. Summary of initial judgements prior to the panel discussion (N=7/10)

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

								affected feasibility of vaccination even to those who believed that the vaccine protects them from severe illness, hospitalization, and death, and that vaccines only have minimal risk. In another survey of unvaccinated individuals conducted from April to May 2021, mostly involving 18 to 25 years of age (n=565, 70.3%), the majority were willing to accept COVID-19 vaccine. For those who refused, safety was their main concern. Majority (n=384, 68%) were willing to pay PHP up to 2,000 if there is such provision. (Pagador)
Certainty of evidence of required resources	No included studies (5)		Very low	Low (1)	Moderate (1)	High		
Cost effectiveness	No included studies (3)	Varies	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention (4)	Favors the intervention	• The government estimated that it would spend an average cost of around PHP 1,300.00 per person for the country's vaccination program, to include the 2-dose vaccine cost and ancillaries. • There is no cost-effectiveness analysis on implementation of a vaccination program in the Philippines.
Equity	Uncertain (1)	Varies (2)	Reduced	Probably reduced (1)	Probably no impact	Probably increased (3)	Increased	
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	SEARCH STRATEGY / SEARCH TERMS	DATE 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 second booster"[Supplementary Concept] OR "covid 19 fourth dose"[All Fields] OR "covid 19 additional dose"[MeSH Terms] OR "covid 19 fifth dose"[All Fields] OR "covid 19 third booster"[MeSH Terms] "bivalent"[All Fields] 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 ("immunocompromised"[MeSH Terms] OR "cancer"[All Fields] OR "chemo"[All Fields] OR "HIV"[All Fields] OR "immunodeficient"[All Fields]) "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 fifth dose"[All Fields] OR "covid 19 third 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 ("health care workers"[MeSH Terms] OR "medical staff"[All Fields] OR "nursing staff"[All Fields] OR "general population"[All Fields] OR "healthy"[All Fields])	Mar. 7, 2023, 11:38:21GMT +8	111	0

CENTRAL https://www.cochranelibrary.com/advanced-search	COVID-19 vaccine, booster vaccination, 4th dose, 5th dose, high-risk, immunocompromised elderly, diabetes, heart disease, comorbidities, bivalent COVID-19 vaccine, booster vaccination, 4th dose, 5th dose, healthy population,general population, health workers	March 7, 2023 20:37:00GMT +8	146	1 ENSEMBLE 2 https://www.thelancet.com/journals/laninf/article/PIIS1473-3099(22)00506-0/fulltext?utm_source=PLSP&utm_medium=Link&utm_campaign=ENSEMBLE2+PLSP
ClinicalTrials.gov https://clinicaltrials.gov/	Condition or disease: "Covid19" Intervention/treatment: "booster dose" Others: immunocompromised, high risk, bivalent Condition or disease: "Covid19" Intervention/treatment: "booster dose" Others: health workers, general population, healthy population	March 6, 2023, 20:40:21 GMT +8	34	2 Safety and Immunogenicity of Omicron Variant-Matched Vaccine Booster in Adults (SH-MO-214) Bringing Optimised COVID-19 Vaccine Schedules To ImmunoCompromised Populations (BOOST-IC): an Adaptive Randomised Controlled Clinical Trial https://clinicaltrials.gov/ct2/show/NCT05556720?term=booster%2C+high-risk%2C+bivalent&cond=COVID-19&draw=2&rank=2
Chinese Clinical Trial Registry http://www.chictr.org.cn/searchprojen.aspx	Target Disease: "covid-19" Intervention: "booster", "4th dose", "second booster", 5th dose, high-risk, "immunocompromised" bivalent Target Disease: "covid-19" Intervention: "booster", "4th dose", "second booster", 5th dose, health workers, "general population"	Mar. 6, 2023, 20:45:21 GMT +8	2	0
EU Clinical Trials Register https://www.clinicaltrialsregister.eu/	"COVID-19 vaccine AND booster, 4th shot, 5th shot, bivalent,high-risk, AND immunocompromised" Target Disease: "covid-19" Intervention: "booster", "4th dose", "second booster", 5th dose, health workers, "general population	Mar. 6, 2023, 22:46:00 GMT +8	2	0

medRxiv.org bioRxiv.org	"COVID 19 third booster, 4th shot, 5th shot, bivalent, high-risk, immunocompromised" "COVID 19 third booster, 4th shot, 5th shot, health workers, "general population	Mar. 6, 2023, 22:46:21 GMT +8	839	1 Stirrup (2022): Clinical effectiveness of SARS-CoV-2 booster vaccine against Omicron infection in residents and staff of Long-Term Care Facilities: a prospective cohort study (VIVALDI): https://www.medrxiv.org/content/10.1101/2022.08.08.22278532v1
Covid-NMA. https://covid-nma.com/ https://covid-nma.com/vaccines/mapping/	Vaccines > Living Mapping > 3nd booster	Mar. 6, 2023, 20:57:59 GMT +8	9	0
LOVE Platform for COVID-19 Evidence (https://app.iloveevidence.com/loves/5e6fdb9669c00e4ac072701d?utm=ile)	covid-19 AND vaccine AND (5th dose OR third booster OR 5-dose) AND high-risk, immunocompromised covid-19 AND vaccine AND (5th dose OR third booster OR 5-dose) AND health workers, "general population	Mar. 6, 2023, 20:58:01	6	0

Appendix 3: PRISMA flow diagram

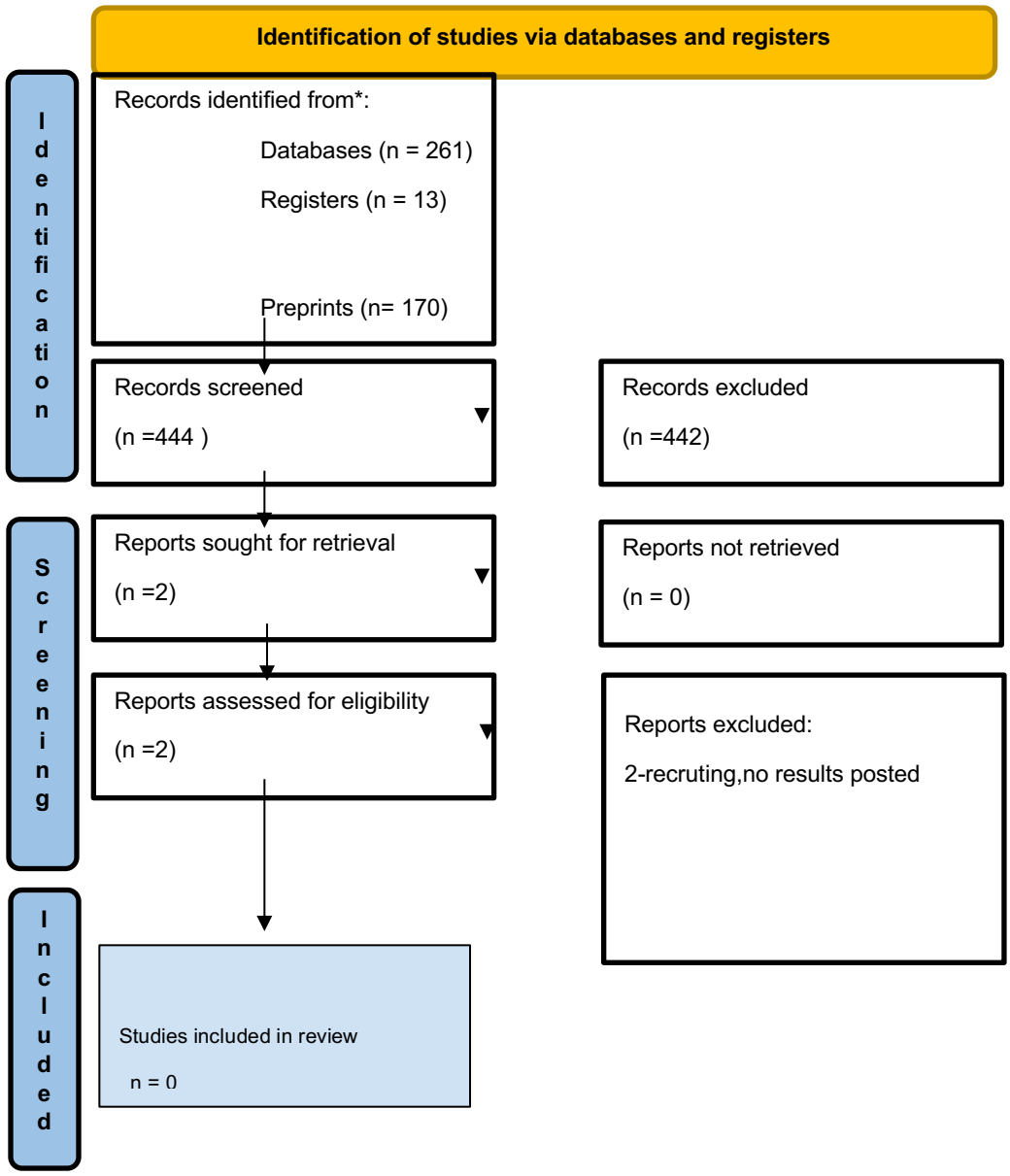

Figure 1. PRISMA flow diagram.

Appendix 4: Ongoing Studies

Table 3. Characteristics of Ongoing Studies

Clinical Trial Identifier/Title	Population	Intervention	Comparator	Outcome
ClinicalTrials.gov Identifier: NCT05236491 Recruitment Status : Recruiting First Posted : February 11, 2022 Last Update Posted : December 1, 2022 COvid-19 Vaccine Booster in Immunocompromised Rheumatic Diseases: (8) PI: Paul R Fortin, MD https://clinicaltrials.gov/ct2/show/NCT05236491?term=booster%2C+immunocompromised&cond=covid-19&intr=5th+booster&draw=2&rank=1	287 adults w/ Rheumatoid ArthritisAutoimmune Rheumatologic DiseaseSystemic Lupus ErythematosusSystemic VasculitisSystemic SclerosisScleroderma Undifferentiated Connective Tissue DiseasesOverlap Connective Tissue DiseaseImmunosuppression Country: Canada, Quebec	fourth dose of an mRNA vaccine and a dose of a protein subunit vaccine (PSV) a dose of a protein subunit vaccine (PSV) as a fifth dose.	have received 3 doses of an mRNA vaccine,	safety and reactogenicity of a booster dose of COVID-19 vaccine using a mix-and-match strategy Actual Study Start Date March 9, 2022 Estimated Study Completion Date December 2023
ClinicalTrials.gov Identifier: NCT05383560 Recruitment Status : Recruiting First Posted : May 20, 2022 Last Update Posted : October 28, 2022 Safety and Immunogenicity of Omicron Variant-Matched Vaccine Booster in Adults (SH-MO-214): (9) PI:Gili Regev-Yochay, MD https://clinicaltrials.gov/ct2/show/NCT05383560	healthy Country: Israel	Fourth and fifth dose	received mRNA primary series	Safety of the study vaccines Reactogenicity of the study vaccines Immune response given as a fourth and fifth dose Actual Study Start Date Sept 5, 2022 Estimated Study Completion Date July 2023