Evidence Summary on *Second Booster of COVID-19 vaccines* for the prevention of COVID-19 among individuals aged 50 years old and older and individuals with comorbidities aged 18 to 49 years old

Service Line	Evidence Summary
Publication Date	23 August 2022
Summary Length	45 Pages
Prepared by	Health Technology Assessment Council Health Technology Assessment Division
Contact details	hta@doh.gov.ph

Section 1. Background

In October 2021, the HTAC released its recommendation on the use of *Pfizer-BioNTech, Moderna, AstraZeneca, Janssen and CoronaVac COVID-19* vaccines as booster for priority groups A2 (60 years of age and older) and A1 (healthcare workers) at least 6 months after the primary series, and as an additional dose for immunocompromised individuals, at least 28 days after the completion of the initial COVID-19 vaccine series. In the same recommendation, the HTAC also recommended the same booster vaccination strategy for other priority groups (i.e. A3-A5) once acceptable primary series coverage is reached.

In November 2021, the Philippines started implementing booster vaccination of COVID-19 vaccines for health workers (A1). This was followed by additional dose for the immunocompromised population (ICP) and booster vaccination among the elderly (A2), individuals with comorbidities (A3). Lastly, all individuals ages 18 years old and above became eligible to receive booster doses in December 2021.

The WHO statement on booster vaccination (Oct 4, 2021), emphasized that implementing booster doses should be guided by evidence on waning vaccine effectiveness, in particular a decline in protection against severe disease in the general population and in high-risk populations, or due to a circulating VoC. On 22 December 2021, the World Health Organization (WHO) released a statement recommending the introduction of the first booster dose in targeted population groups at highest risk of serious disease, as well as those necessary to protect the health system. In consideration of the potential waning protection and especially the rise of new COVID-19 variants, the WHO recommended the administration of a fourth dose among ICPs for the following brands: *Pfizer-BioNTech* (21 January 2022), *Moderna* (23 February 2022), *CoronaVac* (15 March 2022), *Sinopharm* (7 May 2022), and *AstraZeneca* (15 March 2022). In terms of a second booster for the immunocompetent population, the WHO did not have an explicit recommendation. However, in an electronic email addressed to the HTAD dated 04 July 2022, the WHO advised that countries may also refer to the decisions from advanced levels of public health authorities and regulatory authorities.

In a letter addressed to the Secretary of Health dated 13 April 2022, the Philippine Food and Drug Administration (FDA) issued an emergency use authorization (EUA) for the administration of COVID-19 vaccine additional booster doses to senior citizens, frontline healthcare workers (HCWs), and ICPs. The target population of 2nd booster doses was then extended to individuals 50 years old and above and adults 18 to 49 years old with comorbidities through an FDA letter to the Department of Health dated 25 July 2022. The FDA specified that the additional booster doses should be limited to *Pfizer-BioNTech, Moderna, CoronaVac, AstraZeneca, Sputnik, and Janssen* as requested by the DOH, with a dosing interval of at least 4 months after the 3rd dose or 1st booster.

Pursuant to the role of the Health Technology Assessment Council (HTAC) to develop coverage recommendations particularly in the selection and financing of COVID-19 vaccines using the Evaluation Framework set by the HTAC for the COVID-19 Vaccine Implementation for 2022, this review looked at the currently available evidence on the use of six vaccines as part of second booster vaccination strategies for individuals aged 50 years and older, and 18 to 49 years old with comorbidities:

1. *Pfizer-BioNTech*
2. *Moderna*
3. *AstraZeneca*
4. *CoronaVac*
5. *Janssen*
6. *Sputnik*

This assessment followed the HTAC evaluation framework to evaluate COVID-19 vaccines using the following criteria: **(1) responsiveness to magnitude and severity; (2) clinical efficacy and safety; (3) affordability, viability and feasibility; (4) household financial impact; (5) social impact; and (6) responsiveness to equity.**

Policy Question

Should the DOH finance ***Pfizer-BioNTech, Moderna, AstraZeneca, CoronaVac, Janssen, and Sputnik*** as **second booster dose for individuals aged 50 years and older and 18 to 49 years old with comorbidities** as part of the 2022 COVID-19 vaccination strategies, to reduce COVID-19 cases, severe infection, and deaths?

Section 2. HTAC Recommendation

Second Booster Vaccination for Individuals aged 50 years and older *(as of 26 July 2022)*

The HTAC recommends the DOH financing of the use of *Pfizer-BioNTech* (Comirnaty) and *Moderna* (Spikevax) 50 ug as second booster of COVID-19 vaccines for the prevention of COVID-19 among individuals 50 years and older at least 4 months after the first booster dose and its inclusion in the Philippine National Deployment and Vaccination Plan for COVID-19 (NDVP).

Second Booster Vaccination for Individuals aged 18 to 49 years old with comorbidities *(as of 26 July 2022)*

The HTAC recommends the DOH financing of the use of *Pfizer-BioNTech* (Comirnaty) and *Moderna* (Spikevax) 50 ug, as second booster of COVID-19 vaccines for the prevention of COVID-19 among individuals 18 to 49 years old with comorbidities at least 4 months after the first booster dose and its inclusion in the Philippine National Deployment and Vaccination Plan for COVID-19 (NDVP).

The HTAC based its recommendations on a review of the evidence on effectiveness and safety as well as the social, ethical, financial and implementation issues of the first booster vaccination. Although there is no direct clinical evidence specifically for the population with comorbidities, protecting them is highly necessary to protect the most vulnerable groups as inferred evidence from the immunocompetent population aged 18 years and older shows that there is pronounced waning against symptomatic disease, thus the need for a second booster.

The HTAC reiterates the need to enhance the coverage of primary and booster vaccination among our higher priority groups A1 to A3 across the country.
To address the challenges of low uptake of booster vaccination as currently seen among adults, the HTAC highly recommends the DOH conduct acceptability studies to inform strategies for demand generation for booster vaccination of eligible populations.

The HTAC recommendations are interim and HTAC is actively on the watch for evidence as it is rapidly evolving.

Section 3. Presentation of the Evidence Considered on the assessment of Second Booster Vaccination

Criteria 1: Responsiveness to Disease Magnitude and Severity

RQ1: What is the rate of breakthrough infection or hospitalization among the general population? Is COVID-19 a priority?

HTAC Specifications: The vaccine can potentially reduce the COVID-19 disease burden (health, social and economic impact).

I. Local burden (cases and weekly positivity rate)

Data from the DOH Epidemiological Bureau (EB) show that after the Omicron surge period in December 2021 to January 2022, decline in cases was observed from February to May 2022. However, there has been an increase in COVID-19 cases observed starting June 2022 across all age groups. Consistently, the 18-59 years age group had the highest rates of infections followed by the elderly population aged 60 years and older.

Table 1.1 Philippine data on number of SARS-CoV-2 infections, by age group from December 2021 to July 2022 (as of 30 July 2022)

Age Group	Total PSA Population	Cases per 100,000 at risk (Number of SARS-CoV-2 infection)							
		December 2021 (1st booster roll out - A2, A3, ROAP	January 2022	February 2022	March 2022	April 2022	May 2022	June 2022	July 2022
<6 years	**13,385,060**	4.48 (599)	159.60 (21,362)	32.87 (4,400)	4.74 (635)	1.75 (234)	1.69 (226)	3.32 (445)	17.29 (2,314)
6-11	**13,203,138**	3.86 (510)	143.40 (18,933)	20.13 (2,658)	2.54 (335)	1.05 (139)	0.86 (113)	2.04 (270)	12.69 (1,675)
12-17	**12,729,206**	4.40 (560)	143.73 (18,296)	23.88 (3,040)	3.34 (425)	1.67 (212)	1.16 (148)	3.15 (401)	16.67 (2,122)
18-59	**61,994,737**	19.37 (12,010)	951.52 (589,891)	123.87 (76,795)	20.09 (12,456)	9.03 (5,601)	6.31 (3,911)	17.95 (11,131)	91.89 (56,964)
60 and older	**10,260,113**	24.19 (2,482)	665.03 (68,233)	152.86 (15,684)	29.78 (3,055)	12.40 (1,272)	9.03 (927)	14.65 (1,503)	80.44 (8,253)

Similarly, weekly data from June to July 2022 showed the increasing trend in the number of cases and reported positivity rates.

Table 1.2 Philippine data on number of weekly SARS-CoV-2 infections and positivity rate, May 26 to July 27 2022

Week	SARS-CoV-2 infections	Positivity Rate
May 26 - June 1, 2022	1,334	1.2%
June 2 - 8, 2022	1,673	1.9%
June 9 - 15, 2022	2,862	3.2%

June 16 - 22, 2022	4,490	5.0%
June 23 -29, 2022	7,152	7.0%
June 30 - July 6, 2022	9,848	9.7%
July 7 - 13, 2022	14,072	11.9%
July 14 -20, 2022	18,600	14.3%
July 21-27, 2022	22,722	14.8%

II. Local data on Variants of Concern (VoCs)

Predominant VoC

Cumulatively, as of 31 March 2022, 18,217 samples taken through convenience and purposive sampling by the Philippine Genome Center were detected with VoCs across all ages (total number of samples tested was not available). In June 2021, Alpha and Beta variants were the dominant variants in our country. The Delta variant became the dominant variant in our setting from the 3rd to 4th quarter of 2021. The Omicron variant was first detected in the 4th quarter of 2021, with it becoming the dominant variant in our country from the 1st quarter of 2022 onwards.

Table 1.3 Philippine Data on COVID-19 Cases Detected with Variant of Concern per quarter, from June 2021 to March 2022. (DOH EB, as of 1 Aug 2022).

COVID-19 Variant	Time Period					
	June 2021	Q3 2021	Q4 2021	Q1 2022	Q2 2022	1 July to 1 August 2022
Alpha	649	661	4	1	1	Not reported
Beta	778	709	1	Not reported	1	Not reported
Gamma	1	Not reported	Not reported	Not reported	No data available	Not reported
Delta	86	4,952	3,626	22	14	1
Omicron	None detected	None detected	763	6,589	1,546	2,159
Total	**1,514**	**6,322**	**4,394**	**6,612**	**1,562**	**2,160**

Omicron sub variants

Data from DOH EB from April 1 to 1 August 2022 showed that there are a total of 3,705 Omicron variant samples detected (total number of samples not available). Of these, BA.5 is the most dominant Omicron subvariant among all sequenced samples (81.30%, n= 3,012 samples).

Table 1.4 Philippine data on COVID-19 Cases Detected with Omicron sub variants by Outcome (DOH EB, as of 1 July to 1 August 2022)

Variant	Total Number of cases who tested positive for indicated variant	Outcome	
		Death	Being Verified

BA.5	3,012	0	142
B.1.1.529 and other BA sublineages	422	2	28
BA.2.12.1	172	0	2
BA.4	97	0	4
BA.2.75	2	0	0
Total Omicron	**3,705**	**2**	**176**

HTAC Judgment on the Responsiveness to Disease Magnitude and Severity:

There is an overall observed increase in COVID-19 cases and weekly positivity rates from May 2022 to July 2022.

The emergence of new COVID-19 variants poses a potential threat of reduced protection and more rapid waning of immunity, thus the need to evaluate the potential impact of introducing a second booster of vaccines. Apart from the risk of COVID-19 disease, the burden of COVID-19 also includes non-clinical impact such as the disruption of livelihood and the additional burden to the healthcare system.

A second booster vaccination can reduce the disease burden by averting a significant number of infections including any SARS-CoV-2 infection, symptomatic COVID-19, hospitalization due to COVID-19, severe COVID-19 and death due to COVID-19.

Criteria 2: Clinical Efficacy, Effectiveness, and Safety

Part 1. BOOSTER VACCINATION FOR INDIVIDUALS AGED 18-49 YEARS OLD WITH COMORBIDITIES AND 50 YEARS AND OLDER

RQ.2.1: What is the effectiveness over time of 1st booster vaccinations using COVID-19 vaccines against the original strain and variants of concern individuals aged ≥ 50 years old and 18 to 49 years old with comorbidities in terms of symptomatic COVID-19, severe COVID-19, hospitalization and death due to COVID-19?

***HTAC Specifications (Absolute vaccine efficacy/effectiveness)*:**
Symptomatic COVID-19
- Preferred: At least 70% (point estimate), lower 95% confidence interval ≥50%
- Minimum/Critical: At least 50% (point estimate) and lower 95% confidence interval ≥30%.

Severe COVID-19 and Hospitalization due to COVID-19
- Preferred: At least 90% (point estimate) and 70% lower bound
- Minimum/Critical: At least 70-80% (point estimate) and 50% lower bound

Death due to COVID-19
- Preferred: None
- Minimum/Critical: None

The evidence on the efficacy and effectiveness of different COVID-19 vaccines as first booster dose is based on the review of the International Vaccine Access Center (IVAC) of the Johns Hopkins Bloomberg School of Public Health and World Health Organization as of 15 July 2022. Evidence cited by national regulatory authorities and ministries of health of other countries with 2nd booster recommendation for the general population aged 50 years and older and individuals ages 18 to 49 years old with comorbidities were also reviewed.

Evidence on Waning of First Booster among 18 TO 49 YEARS OLD WITH COMORBIDITIES

There were no studies identified which evaluated the VE over time of COVID-19 vaccine first booster dose specifically for population aged 18 to 49 years old with comorbidities. However, duration of protection in this population can be inferred from evidence in the general population. Since the last HTAC review on waning of protection of the first booster (27 April 2022), evidence has shown that the first booster of COVID-19 vaccines offer sustained protection for severe infection due to Omicron while there is more pronounced waning of protection against symptomatic COVID-19 at 3 to 6 months.

Since then, there were two new studies (Link-Gelles et al., 2022 and Kirsebom et al., 2022) which evaluated the effectiveness over time of the first booster of COVID-19 vaccines in the general population aged 18 years and older. Both studies assessed first booster vaccinations during the Omicron BA.1-dominant and Omicron BA.2-dominant periods. Link-Gelles et al. provided VE specifically for the 18 to 49 year age group while Kirsebom et al. did not disaggregate VEs by specific age groups. Previous and new evidence on waning of protection of first booster in the general population (inferred evidence for individuals aged 18 to 49 years old with comorbidities) is available for *Pfizer-BioNTech*, *Moderna*, *CoronaVac*, *Astrazeneca* and *Janssen*.

VE of First Booster Relative to the Unvaccinated Individuals

Both Link-Gelles et al., 2022 and Kirsebom et al., 2022 compared the first booster with the unvaccinated. Link-Gelles et al., 2022 reported VE against emergency department/ urgent care encounters and hospitalization due to COVID-19 while Kirsebom et al., 2022 reported VE against symptomatic COVID-19 and hospitalization due to COVID-19.

Outcome 1: Hospitalization

In the general population aged 18 years and older, there appears to be sustained protection against hospitalization due to the Omicron BA.1 subvariant after the first booster relative to the unvaccinated population. However, there is a pronounced waning of protection against hospitalization due to the Omicron BA.2 subvariant. Compared to the VE against symptomatic infection, VEs for hospitalization are relatively more sustained. Detailed findings from the included studies are in Table 2.1.

Table 2.1. Summary of Findings on Waning Protection of First Booster against Hospitalization due to Omicron BA.1 and BA.2 subvariants relative to the Unvaccinated among the General Population aged 18 years and older

#	Author, Year	Intervention Arm		Time point of last passing VE	%VE at 14 days to < 3 months	%VE at 3 to < 6 months
		Primary Series	Booster			
Omicron BA.1						
1	Link-Gelles et al., 2022 [published]	mRNA vaccines	mRNA vaccines	≥4 months	91% (87 to 94)	94% (62 to 99)
2	Kirsebom et al., 2022 [published]	*AstraZeneca, Pfizer-BioNTech or Moderna*	*Pfizer-BioNTech or Moderna*	≥3.75 months	90.8% (85.1 to 94.3)	80.4% (75.6 to 84.3)
Omicron BA.2						
1	Kirsebom et al., 2022 [published]	*AstraZeneca, Pfizer-BioNTech or Moderna*	*Pfizer-BioNTech or Moderna*	≤1 month	82.8% (41.9 to 94.9)	56.5% (38.4 to 69.3)

Outcome 2: Symptomatic COVID-19

In the general population aged 18 years and older, there appears to be evidence of pronounced waning of protection against symptomatic COVID-19 due to the Omicron BA.1 and BA.2 subvariants after the first booster relative to the unvaccinated population. Detailed findings from the study are in Table 2.2.

Table 2.2. Summary of Findings on Waning Protection of First Booster against Symptomatic Infection due to Omicron BA.1 and BA.2 subvariants relative to the Unvaccinated among the General Population aged 50 years and older

#	Author, Year	Intervention Arm		Time point of last passing VE	%VE at 14 days to < 3 months	%VE at 3 to < 6 months
		Primary Series	Booster			
Omicron BA.1						
1	Kirsebom et al., 2022 [published]	*AstraZeneca, Pfizer-BioNTech or Moderna*	*Pfizer-BioNTech or Moderna*	≤1 month	68.7% (68.0 to 69.5)	37.4% (35.8 to 39.0)
Omicron BA.2						
1	Kirsebom et al., 2022 [published]	*AstraZeneca, Pfizer-BioNTech or Moderna*	*Pfizer-BioNTech or Moderna*	≤1 month	74.1% (72.9 to 75.3)	43.7% (42.3 to 45.1)

Outcome 3: Emergency Department/ Urgent Care Encounters

In the general population aged 18 to 49 years, there appears to be evidence of pronounced waning of protection against emergency department/ urgent care (EC/UC) encounters due to the Omicron BA.1 and BA.2 subvariant after the first booster relative to the unvaccinated population. It is noted that for this outcome, there is no set HTAC specification. Detailed findings from the study are in Table 2.3.

Table 2.3. Summary of Findings on Waning Protection of First Booster against Emergency Department/ Urgent Care Encounters due to Omicron BA.1 and BA.2 subvariants relative to the Unvaccinated among the General Population aged 50 years and older

#	Author, Year	Intervention Arm	Omicron BA.1		Omicron BA.2	
			%VE at 14 days to	%VE at 3 to	%VE at 14 days to < 3	%VE at 3 to

		Primary Series	Booster	< 3 months	< 6 months	months	< 6 months
1	Link-Gelles et al., 2022 [published]	mRNA vaccines	mRNA vaccines	76% (75 to 78)	29% (−1 to 50)	55% (47 to 62)	17% (10 to 25)

HTAC Judgment Waning of First Booster among 18 TO 49 YEARS OLD WITH COMORBIDITIES: Evidence inferred from the general population suggests that, among individuals aged 18 to 49 years old with comorbidities, waning due to Omicron variant is likely (assuming immune response is similar among among the health population, with or without comorbidities) especially for symptomatic COVID-19 at 3 to 6 months after the first booster. In terms of emergency department/ urgent care encounters, there is pronounced waning of protection against both Omicron BA.1 and BA.2 subvariants.

Evidence on Waning of First Booster among INDIVIDUALS AGED 50 YEARS AND OLDER

Overall, there was one study (Link-Gelles et al., 2022) which evaluated the effectiveness over time of the first booster of COVID-19 vaccines specifically in individuals aged 50 years and older during the Omicron BA.1-dominant and Omicron BA.2-dominant periods. Evidence on vaccine effectiveness over time for the general population as detailed in the previous section were also considered.

VE of First Booster Relative to the Unvaccinated Individuals

Link-Gelles et al., 2022 reported VE against hospitalization and emergency department/ urgent care encounters due to COVID-19 after the first booster compared to the unvaccinated population. Evidence on waning of protection of the first booster specific to individuals aged 50 years old and older is available for *Pfizer-BioNTech* and *Moderna*.

Outcome 1: Hospitalization

In the 50 years and older population, there appears to be sustained protection against hospitalization due to the Omicron BA.1 subvariant after the first booster relative to the unvaccinated population. However, there is a pronounced waning of protection against hospitalization due to the Omicron BA.2 subvariant after the first booster relative to unvaccinated population. Detailed findings from the included studies are in Table 2.4.

Table 2.4. Summary of Findings on Waning Protection of First Booster against Hospitalization due to Omicron BA.1 and BA.2 subvariants relative to the Unvaccinated among the 50 years and older population

Omicron Subvariant	Intervention Arm		Time point of last passing VE	%VE at 14 days to < 3 months	%VE at 3 to < 6 months
	Primary Series	Booster			
Omicron BA.1	mRNA vaccines	mRNA vaccines	≥4 months	92% (91 to 93)	86% (82 to 89)
Omicron BA.2			< 4 months	73% (63 to 81)	55% (46 to 62)

Outcome 2: Emergency Department/ Urgent Care Encounters

In the general population aged 50 years and older, there appears to be sustained protection against emergency department/ urgent care (EC/UC) encounters due to the Omicron BA.1 subvariant after the first booster relative to the unvaccinated population. However, there is a pronounced waning of protection against EC/UC encounters due to the Omicron BA.2 subvariant after the first booster. It is noted that for this outcome, there is no set HTAC specification. Detailed findings from the study are in Table 2.5.

Table 2.5. Summary of Findings on Waning Protection of First Booster against Emergency Department/ Urgent Care Encounters due to Omicron BA.1 and BA.2 subvariants relative to the Unvaccinated among 50 years and older population

Omicron Subvariant	Intervention Arm		%VE at 14 days to < 3 months	%VE at 3 to < 6 months
	Primary Series	Booster		
Omicron BA.1	mRNA vaccines	mRNA vaccines	87% (86 to 88)	81% (77 to 84)
Omicron BA.2			58% (51 to 64)	32% (26 to 38)

HTAC Judgment Waning of First Booster among INDIVIDUALS AGED 50 YEARS OLD AND OLDER: Data from US (Link-Gelles et al. 2022) and UK (Kirsebom et al. 2022) showed a more pronounced waning of protection from mRNA vaccines against hospitalization due to the BA.2 variant at approximately 4 months after the first booster (VE from approximately 73 to 89.1% to only 55 to 56.5%). In terms of emergency department/ urgent care encounters (ED/UC encounters), there is sustained protection against Omicron BA.1 (VE from 87% to 81%). However, there is a pronounced waning of protection against ED/UC encounters due to Omicron BA.2 (VE from 58% to 32%).

RQ.2.2: What are the indications for 2nd booster vaccination?

***HTAC Specifications*: N/A**

Evidence considered:

A total of 16 COVID-19 recommendation/guidelines on second booster of COVID-19 vaccines from the World Health Organization (WHO), the European Medicines Agency (EMA), the European Center for Disease Control (ECDC) and national regulatory authorities/ministries of health (referred to as NRAs) of different countries (US FDA, US CDC, UK JCVI, Canada NACI, Ontario Health, Australia ATAGI, Israel MOH, Chile MOH, Singapore MOH, Bahrain MOH, WHO-Thailand, Hong Kong DOH and Abu Dhabi Media Office) were reviewed to look at the current indications of this vaccination policy.

Summary of Findings:

50 years and older population

Out of the 16 recommendations/guidelines reviewed, 8 recommended that a second booster should be given to individuals 50 years old and older (UK JCVI, US FDA, US CDC, ATAGI, Chile MOH, Bahrain MOH, Thailand MOH, and Abu Dhabi Media Office). Meanwhile, 3 of the 16 recommendations/guidelines stated that a second booster may be offered to the same age group (Singapore MOH, Canada NACI, Ontario Health) depending on the individual's discretion. Meanwhile, the remaining 5 of the 16 NRAs recommended second boosters only for the elderly, ages 60 years old and older (WHO, European CDC, EMA, Israel MOH, HongKong DOH).

18 to 49 years old with comorbidities

Eight out of the 16 NRAs recommended a second booster of individuals with comorbidities ages 18 to 49 years old (European CDC, EMA, UK JCVI, ATAGI, Chile MOH, Singapore MOH, HongKong DOH, and Canada NACI). Additionally, 3 out of these 8 NRAs also recommended second boosters for younger individuals (UK JCVI - ≥5 y.o.; Canada NACI - ≥12 y.o.; ATAGI - ≥16 y.o.) with comorbidities.

Most of the reviewed guidelines (14 out of 16) recommended mRNA vaccines (*Pfizer-BioNTech* and *Moderna)* to be used as second boosters while two guidelines did not specify vaccine brands (Canada NACI, Ontario Health). Seven (7) of these guidelines exclusively recommended mRNA vaccines (European CDC, EMA, UK JCVI, US FDA, US CDC, Singapore MOH, and Chile MOH), 2 stated preference for mRNA vaccines (ATAGI and Israel MOH) while 5 also recommended other vaccine platforms (WHO, Bahrain MOH, Thailand MOH, HongKong DOH, and Abu Dhabi Media Office).

For the timing of administration of the 2nd booster, the recommended dosing intervals among the scoped NRAs ranges from 3 to 9 months after the first booster. For other details of the guidelines and recommendations such as recommendation for other population groups, other conditions, refer to Annex 1.

RQ.2.3: Is a second booster of COVID-19 vaccine efficacious/effective in individuals aged 18 to 49 years old with comorbidities and 50 years and older?

HTAC Specifications (Absolute vaccine efficacy/effectiveness):

Symptomatic COVID-19

- Preferred: At least 70% (point estimate), lower 95% confidence interval ≥50%
- Minimum/Critical: At least 50% (point estimate) and lower 95% confidence interval ≥30%.

Severe COVID-19 and Hospitalization due to COVID-19

- Preferred: At least 90% (point estimate) and 70% lower bound
- Minimum/Critical: At least 70-80% (point estimate) and 50% lower bound

Death due to COVID-19

- Preferred: None
- Minimum/Critical: None

The evidence on the efficacy and effectiveness of different COVID-19 vaccines as second booster dose is based on the review of the International Vaccine Access Center (IVAC) of the Johns Hopkins Bloomberg School of Public Health and World Health Organization as of 15 July 2022. Evidence cited by national regulatory authorities and ministries of health of other countries with 2nd booster recommendation for the general population aged 50 years and older and individuals ages 18 to 49 years old with comorbidities were also reviewed.

Efficacy or Effectiveness of Second Booster among 18 TO 49 YEARS OLD WITH COMORBIDITIES

There were no studies identified which evaluated the second booster of COVID-19 vaccine specifically for population aged 18 to 49 years old with comorbidities. However, efficacy and effectiveness in this population can be inferred from evidence in the general population. One study (Kiss et al., 2022) assessed effectiveness of the second booster of COVID-19 vaccines relative to the first booster among the general population aged 16 to 54 years old while one study (Munro et al. 2022) evaluated immunogenicity of second booster in the general population aged 30 years and older.

Evidence from trials: Efficacy outcomes

The reference review did not detect any trials which evaluated the efficacy of a second booster of any COVID-19 vaccine for 18 to 49 years old with comorbidities.

Evidence from trials: Immunogenicity outcomes

Description of Evidence

There is one published Phase II RCT in the UK (Munro et al. 2022) which evaluated the immunogenicity of a second booster compared to the first booster of mRNA vaccines in the general population with a subgroup analysis for general population ages 30 years and older. The study was conducted during a period of Omicron variant dominance.The detailed characteristics of the study are presented below.

	Munro et al. (2022) [Published] UK Omicron variant
Study design	Phase II RCT (COV-BOOST Trial) 11 January 2022 to 25 January 2022
Population	Adults aged 30 years or older who had received third dose of *Pfizer-BioNTech* N=133 *(No disaggregation for elderly ages 50 years old and above)*
Intervention	**INTERVENTION 1:** Primary series: *Pfizer-BioNTech* 1st booster: *Pfizer-BioNTech* 2nd booster: *Pfizer-BioNTech* n=31
	INTERVENTION 2: Primary series: *Pfizer-BioNTech* 1st booster: *Pfizer-BioNTech* 2nd booster: *Moderna* n=33
	INTERVENTION 3: Primary series: *AstraZeneca* 1st booster: *Pfizer-BioNTech* 2nd booster: *Pfizer-BioNTech* n=35
	INTERVENTION 4: Primary series: *AstraZeneca* 1st booster: *Pfizer-BioNTech* 2nd booster: *Moderna* n=34
Comparator	First booster titers, 28 days after

Outcome	• Anti-spike protein IgG • T-cell responses
Follow-up	14 days after second booster

Key findings

Munro et al. 2022 reported immunogenicity outcomes in the general population, specifically aged 30 years and older, in terms of SARS-CoV-2 anti-spike IgG concentration and T-cell response. Across intervention arms (i.e. second booster of *Pfizer-BioNTech* or *Moderna*), the study showed that SARS-CoV-2 anti-spike protein IgG decreases from 28 days after the first booster to before the second booster. Then, at 14 days after the second booster there is an observed increase in titers, even going higher than titers achieved after the first booster. The same trend is observed for T-cell response.

Table 2.6. Anti-spike protein IgG concentration and T-cell response of second booster dose of *Pfizer-BioNTech* and *Moderna* at different time points

Time Point	Second booster: *Pfizer-BioNTech*	Second booster: *Moderna*
Anti-spike protein IgG concentration, ELU/mL		
Day 28 after the first booster	23,325 (20,030–27,162) n=66	25,317 (20,996–30,528) n=66
Day 0 of second booster	3,049 (2,550–3,646) n=66	3,469 (2,730–4,407) n=66
Day 14 after the second booster	37,460 (31,996–43,857) n=65	54,936 (46,826–64,452) n=67
Fold change *(Day 14 after the second booster vs Day 28 after the first booster)*	1.59 (1.41–1.78) n=65	2.19 (1.90–2.52) n=66
Cellular response *(vs wild-type) spot forming cells per 10^6 PBMCs*		
Day 28 after the third dose	96.03 (65.68–140.42) n=35	111.19 (75.87–162.95) n=33
Day 0 of second booster	19.32 (10.99–33.97) n=36	35.32 (20.66–60.40) n=34
Day 14 after the second booster	112.64 (80.61–157.38) n=20	236.95 (146.04–384.48) n=20
Fold change *(Day 14 after the second booster vs Day 28 after the first booster)*	1.10 (0.72- 1.70) n = 18	1.69 (1.22 - 2.34) N = 19

Evidence from real world studies: *Effectiveness outcomes*

Description of Evidence

The only study identified (Kiss et al., 2022) on second booster effectiveness among 18 to 49 years old was conducted during a period of Omicron variant dominance. In terms of the intervention, Kiss et al. evaluated *Pfizer-BioNTech*, *Moderna*, *AstraZeneca*, *Sputnik V*, *Sinopharm* and *Janssen* with no brand disaggregation in the analysis. Despite the lack of VE disaggregation by brand, it was noted that 98.45% of the 2nd booster doses administered in Hungary were mRNA vaccines. In terms of the comparator, Kiss et al. compared the second booster to the first booster. Detailed characteristics of the study are presented below.

	Kiss et al. (2022) [Published] Hungary Omicron
Study design	Retrospective observational study
Population	16 to 54 years old, who were received 1st booster or 2nd booster of vaccine N = 1,431,091
Intervention	Primary series, first booster and second booster: *Pfizer-BioNTech, Moderna, AstraZeneca, Sputnik-V, Sinopharm, Janssen* (3 doses) 2nd Booster: n = 2,490 *(98.45% of 2nd booster administered in Hungary were mRNA vaccines)*
Comparator	1st Booster: n = 1,428,601
Outcome	VE against SARS-CoV-2 infection vs 1st booster group (HTAD computation)
Follow up	25.08 days after 2nd booster

Key findings

Risk of bias

The HTAC rated the RoB of Kiss et al. (2022) as very serious due to lack of random sequence generation, allocation concealment, and blinding. The study adjusted for age; however, factors such as exposure risk and comorbidities were not considered as confounding factors. Details on the RoB assessment of the study is reflected in Appendix 2.

Results of real world effectiveness studies

Kiss et al (2022) reported VE of the second booster against any SARS-CoV-2 infection relative to the first booster group per age group (16 to 24 yo, 25 to 34 yo, 35 to 44 yo, 45 to 54 yo). VEs and event rates are presented in the table below. Details of the GRADE assessment is presented in Appendix 3.

Table 2.7. Effectiveness against any COVID-19 of second booster dose compared to first booster in general population aged 16 to 54 years old reported by Kiss et al. (2022)

Outcomes	**Age Group**	**Intervention (n/N) (%)** *2nd booster*	**Comparator (n/N) (%)** *1st Booster*	**VE (95% CI)** *(HTAD computation)*	**Certainty of Evidence**
VE against any SARS-CoV-2 infection relative to the 1st booster group	16 to 24 years old	1/81 (1.2%)	7,473/141,768 (5.3%)	76.58% (-66.20 to 96.70)	**VERY LOW**

	25 to 34 years old	14/285 (4.9%)	18,240/271,260 (6.7%)	26.94% (-23.40 to 56.74)	**VERY LOW**
	35 to 44 years old	27/727 (3.7%)	31,210/435,770 (7.2%)	31.41% (0.00 to 52.97)	**VERY LOW**
	45 to 54 years old	50/1,397 (3.6%)	34,595/579,803 (6.0%)	40.01% (20.84 to 54.54)	**VERY LOW**

HTAC Judgment on the Efficacy or Effectiveness of a Second Booster among 18 TO 49 YEARS OLD WITH COMORBIDITIES:

Pfizer-BioNTech	Moderna	AstraZeneca	CoronaVac	Janssen	Sputnik Light
Current evidence on the effectiveness of a second booster against any SARS-CoV-2 infection for younger immunocompetent population showed mostly inconclusive results [16-24 y.o.: 76.58% (95% CI: -66.2 to 96.70); 25-34 y.o.: 26.94% (95% CI: -23.4 to 56.74); 35-44 y.o.: 31.41% (0 to 52.97)], or low vaccine effectiveness [45 to 54 yo: 40.01% (95% C: 20.84 to 54.54), based on very low certainty of evidence. Meanwhile, one immunogenicity study showed an increase in both humoral and cell-mediated response from a 2nd booster or mRNA vaccine (Munro et al.).	*Cannot be assessed due to current lack of evidence*				

Efficacy or Effectiveness of Second Booster among INDIVIDUALS AGED 50 YEARS AND OLDER

Two studies assessed the effectiveness of the second booster of COVID-19 vaccines among the general population aged 50 years and older (Link-Gelles et al., 2022; and Kiss et al., 2022). Link-Gelles et al., 2022 reported VE relative to the unvaccinated while Kiss et al., 2022 reported VE relative to the first booster. Meanwhile, one trial reported immunogenicity outcomes of a second booster compared to the first booster (Munro et al., 2022).

Evidence from trials: Efficacy outcomes

The reference review did not detect any trials which evaluated the efficacy of a second booster of any COVID-19 vaccine for the general population aged 50 years and older.

Evidence from trials: Immunogenicity outcomes

Details and key findings of Munro et al. are presented in the previous section.

Evidence from real world studies: *Effectiveness outcomes*

Description of Evidence

Overall, the reference review detected two real world studies (Link-Gelles et al. and Kiss et al.) on second booster effectiveness among the general population aged 50 years and older which were all conducted during a period of Omicron variant dominance. In terms of intervention, Link-Gelles et al. evaluated mRNA vaccines while Kiss et al. evaluated *Pfizer-BioNTech, Moderna, AstraZeneca, Sputnik-V, Sinopharm and Janssen*. Both studies did not provide analysis disaggregated by vaccine brand although it was noted in Kiss et al.that 98.45% of the 2nd booster doses administered in Hungary were mRNA vaccines.

In terms of the comparator, Link-Gelles et al. compared the second booster to the unvaccinated population while Kiss et al. compared the second booster to the first booster. Detailed characteristics of the study are presented below.

	Link-Gelles et al. (2022) [Published] US Omicron BA.2/BA.2.12.1	Kiss et al. (2022) [Published] Hungary Omicron
Study design	Test-negative study	Retrospective observational study
Population	≥ 50 years old, adults without immunocompromising conditions who were unvaccinated or received at least 4 doses of vaccine who had emergency department (ED)/urgent care (UC) encounter or were hospitalized ED/UC: N= 13,572 Hospitalization: N= 5,799	≥ 45 years old, who received 1st booster or 2nd booster of vaccine N = 2,478,660
Intervention	4 doses of mRNA vaccine ED/UC: n= 4,094 Hospitalization: n= 1,204	Primary series, first booster and second booster: *Pfizer-BioNTech, Moderna, AstraZeneca, Sputnik-V, Sinopharm, Janssen* (3 doses) 2nd booster: n= 30,434 *(98.45% of 2nd booster were mRNA vaccines)*
Comparator	Unvaccinated ED/UC: n=9,478 Hospitalization: n=4,595	1st Booster: n= 2,448,226
Outcome	• VE against Emergency Department/ Urgent Care Encounters after the 2nd booster (relative to unvaccinated) ≥7 days after 2nd booster • VE against Hospitalization after the 2nd booster (relative to unvaccinated) ≥7 days after 2nd booster	VE against SARS-CoV-2 infection vs 1st booster group (HTAD computation) VE against COVID-19 related death (HTAD computation)
Follow up period	ED/UC: median interval = 28 days (17–42) Hospitalization: median interval = 27 days (17–41)	25.08 days after 2nd booster

Key findings

Risk of bias

The HTAC rated the RoB of Link-Gelles et al. (2022) as serious due to lack of random sequence generation, allocation concealment, and blinding. However, it was noted that the study had low risk of bias due to control of confounders since the analysis adjusted for the age and exposure risk of the study population. The ROB of Kiss et al. (2022) was presented in the previous section. Details on the RoB assessment of the studies are reflected in Appendix 2.

Results of real world effectiveness studies

Second Booster Versus the Unvaccinated population

Link-Gelles et al. (2022) reported VE against hospitalization due to the Omicron BA.2/BA.2.12.1 subvariant of 80% (95% CI: 71 to 85) 7 days after the second booster dose relative to the unvaccinated population. This passed HTAC specification for severe outcomes [VE of at least 70-80%]. Meanwhile, VE against emergency department/ urgent care encounters, 7 days after the second booster dose was at 66% (95% CI: 60 to 71) (No HTAC specification for this outcome). Details of the GRADE assessment are presented in Appendix 3.

Table 2.8. Effectiveness outcomes of a second booster dose in general population aged ≥50 years old compared to the unvaccinated population reported by Link-Gelles et al. (2022)

Outcomes	Intervention (n/N)	Comparator (n/N)	VE (95% CI)	Certainty of Evidence

	(%) *2nd booster*	(%) *Unvaccinated*		
VE against Hospitalization due to COVID-19, ≥7 days after second booster dose	74/1,204 (6.1%)	393/4,595 (8.6%)	80% (71–85)	**HIGH**
VE against Emergency Department/ Urgent Care Encounters, ≥7 days after second booster dose	355/4,094 (8.7%)	1,232/9,478 (13.0%)	66% (60–71)	**HIGH**

Kiss et al. (2022) reported VE against any SARS-CoV-2 infection relative to the first booster group per age group (45 to 54 yo, 55 to 64 yo, 65 to 74 yo, 75 to 84 yo, and ≥ 85 years old) and VE against COVID-19 related death for 75 to 84 age group only as this is the only age group which had events for both the intervention and comparator arms. VE against any SARS-CoV-2 infection relative to the first booster group of the age groups ranges from 40.01% (20.84 to 54.54) to 63.72% (43.06 to 76.89). VE against COVID-19 related death in the 75 to 84 years old age group was at 86.75% (5.71 to 98.14) with one reported death in the second booster group. It is noted that there is no HTAC specification for both outcomes. VEs and event rates for each age group are presented in the table below. Details of the GRADE assessment are presented in Appendix 3.

Table 2.9. Effectiveness against any COVID-19 of second booster dose compared to first booster in general population aged ≥45 years old reported by Kiss et al. (2022)

Outcomes	Age Group	Intervention (n/N) (%) *2nd booster*	Comparator (n/N) (%) *Unvaccinated*	VE (95% CI)	Certainty of Evidence
VE against any SARS-CoV-2 infection relative to the 1st booster group *(HTAD computation)*	45 to 54 years old	50/1,397 (3.6%)	34,595/579,803 (6.0%)	40.01% (20.84 to 54.54)	**VERY LOW**
	55 to 64 years old	81/3,939 (2.1%)	23,854/574,551 (4.2%)	50.47% (38.39 to 60.18)	**LOW**
	65 to 74 years old	179/14,242 (1.3%)	18,298/770,164 (2.4%)	47.11% (38.73 to 54.35)	**LOW**
	75 to 84 years old	81/9,333 (0.9%)	9,664/417,796 (2.3%)	62.49% (53.32 to 69.86)	**LOW**
	≥ 85 years old	19/1,523 (1.2%)	3,642/105,912 (3.4%)	63.72% (43.06 to 76.89)	**VERY LOW**
VE against COVID-19 related death *(HTAD computation)*	75 to 84 years old (Note: Only this age group had events for both arms)	1/9,333 (0.01%)	341/417,796 (0.08%)	86.75% (5.71 to 98.14)	**LOW**

HTAC Judgment on the Efficacy or Effectiveness of a Second Booster among INDIVIDUALS AGED 50 YEARS AND OLDER:

Pfizer-BioNTech	Moderna	AstraZeneca	CoronaVac	Janssen	Sputnik Light
Based on a short follow up period, there is data to support some protection from mRNA vaccines against any SARS-CoV-2 infection (Kiss, et al.) and against hospitalization due to COVID-19 (Link-Gelles, et al.).		*Cannot be assessed due to current lack of evidence*			

RQ.2.4: What is the duration of protection of a 2nd booster dose in individuals aged 18 to 49 years old with comorbidities and 50 years and older in terms of reducing the incidence of symptomatic and severe COVID-19, hospitalization due to COVID-19 and death due to COVID-19 ?

HTAC Specifications:
Minimum acceptable duration of protection: confers at least 6 months protective immunity

Preferred: ≥1-year protective immunity

Duration of Protection of Second Booster among the 18 TO 49 YEARS OLD WITH COMORBIDITIES

One study (Kiss et al. 2022) assessed the efficacy and effectiveness of COVID-19 vaccines among the general population aged 18 to 49 years old. The study had a follow up period of 25.08 days only.

HTAC Judgment on the Duration of Protection of Second Booster among 18 TO 49 YEARS OLD WITH COMORBIDITIES: Among individuals aged 18 to 49 years old with comorbidities, the duration of protection of 2nd booster cannot be assessed due to the short follow up period of currently available evidence.

Duration of Protection of Second Booster among INDIVIDUALS AGED 50 YEARS AND OLDER

Two studies assessed the efficacy and effectiveness of COVID-19 vaccines among the general population aged 50 years and older. Of these, 1 study (Kiss et al., 2022) reported VE relative to the first booster, and 1 study (Link-Gelles et al., 2022) reported VE relative to the unvaccinated population. The follow up period of both studies ranged from 25.08 to 28.00 days only.

HTAC Judgment for all brands on the Duration of Protection of Second Booster among the INDIVIDUALS AGED 50 YEARS AND OLDER:
Among individuals aged 50 years and older, the duration of protection of 2nd booster cannot be assessed due to the short follow up period of currently available evidence.

RQ.2.5: Is a 2nd booster of COVID-19 vaccine safe in individuals aged 18 to 49 years old with comorbidities and 50 years and older?

HTAC Specifications:
- Local and systemic reactions are tolerable, self-limiting and do not require hospitalization. No serious adverse events were caused by the vaccine.
- Short term outcomes (e.g., reactogenicity and allergic reactions, SAEI): at least 2 months
- Long term outcomes (e.g., serious AEs, all-cause mortality, SAEI, Vaccine-associated enhanced disease): at least 1 year

Safety of Second Booster among 18 TO 49 YEARS OLD WITH COMORBIDITIES

There were no studies identified which evaluated the second booster of COVID-19 vaccine specifically for population aged 18 to 49 years old with comorbidities. However, safety in this population can be inferred from evidence in the general population. Two studies, including one Phase II RCT (Munro et al. 2022) and one real world safety report (Pharmacovigilance Subdepartment of the Chilean Institute of Public Health) in the general population were identified.

Evidence from trials

Description of Evidence

Overall, the reference review detected one trial safety study, Munro et al. (2022), which assessed the safety of a second booster among the general population aged 30 and older. The study was conducted during the Omicron variant dominance, and in terms of intervention, it evaluated mRNA vaccines (both *Pfizer-BioNTech* and *Moderna*). Detailed characteristics of the study are presented below.

	Munro et al. (2022) [Published] UK Omicron variant
Study design	Phase II RCT (COV-BOOST Trial) 11 January 2022 to 25 January 2022
Population	Adults aged 30 years or older who had received third dose of *Pfizer-BioNTech* (*No disaggregation for elderly ages 50 years old and above*) N = 166
Intervention	**INTERVENTION ARM 1:** Primary series: *Pfizer-BioNTech* 1st booster: *Pfizer-BioNTech* 2nd booster: *Pfizer-BioNTech* n=39
	INTERVENTION ARM 2: Primary series: *Pfizer-BioNTech* 1st booster: *Pfizer-BioNTech* 2nd booster: *Moderna* n=39
	INTERVENTION ARM 3: Primary series: *AstraZeneca* 1st booster: *Pfizer-BioNTech* 2nd booster: *Pfizer-BioNTech* n=44
	INTERVENTION ARM 4: Primary series: *AstraZeneca* 1st booster: *Pfizer-BioNTech* 2nd booster: *Moderna* n=44
Comparator	Not applicable
Outcomes and	• Solicited local and systemic adverse events (within 7 days)

follow up periods	• Unsolicited adverse events (within 28 days) • Adverse Events of Special Interest (AESI) (until cut-off date: 02 March 2022) • Serious adverse events (until cut-off date: 02 March 2022)

Key Findings

Results of the trial on safety

Munro et al. reported results were for the general population aged 30 years and older. It was noted that there were 16 adverse events reported among 15 unique individuals (18.07% of 83 participants) after a second booster of *Pfizer-BioNTech*, and 18 adverse events reported among 16 unique individuals (19.28% of 83 participants) after a second booster of *Moderna*. Three serious adverse events, all in recipients of *Pfizer-BioNTech* as second booster (3.61% of 83 participants) were reported. Meanwhile, four adverse events of special interest (i.e. COVID-19) were reported, all in participants who received a second booster of *Moderna* (4.81% of 83 participants). It was noted that none of these serious adverse events and adverse events of special interest were considered related to the vaccine. Moreover, the study did not report any deaths.

Evidence from real world studies

Description of Evidence

One real world safety study was identified from the Pharmacovigilance Subdepartment of the Chilean Institute of Public Health which assessed the safety of a second booster of *Pfizer-BioNtech* among the general population aged 18 and older. Detailed characteristics of the study are presented below.

	Pharmacovigilance Subdepartment of the Chilean Institute of Public Health Chile Omicron variant
Population	General population 18 and above N = 1,174,384 2nd booster doses of *Pfizer-BioNTech* have been administered as of February 2022
Intervention	2nd booster of *Pfizer-BioNTech* *(16- 24 weeks post 1st booster)* N = 1,174,384
Comparator	N/A
Outcome	**Serious** and **Non-serious** Events Supposedly Attributed to Vaccination or Immunization (ESAVI)
Reporting system	Electronic reporting systems ESAVI-EPRO, RED-RAM and NOTI-RAM-ESAVI, and email
Period of observation	24 December 2020 to 26 February 2022

Key Findings

Results of the real world evidence on safety

Overall, 41,682,302 doses of SARS-CoV-2 vaccines were administered to people over 18 years of age in Chile from 24 December 2020 to 26 February 2022. The report did not provide disaggregation of doses administered and safety reports by age groups or vaccination received (i.e. primary series, first booster, or second booster).

The safety surveillance observed a total 15,004 cases (0.04% of 41,682,302 doses administered) of Events Supposedly Attributed to Vaccination or Immunization (ESAVI) which corresponds to 36.00 notifications per 100,000 doses administered. Among the total cases, 94.41% (33.98 notifications per 100,000 doses administered) were considered non-serious ESAVIs while only 5.59% (2.01 notifications per 100,000 doses

administered) of all reported cases were considered serious events. Furthermore, no cases of events of special interest (e.g., myocarditis, pericarditis, and Guillain-Barre syndrome) were reported.

HTAC Judgment for all brands on the Safety of Second Booster among 18 to 49 YEARS WITH COMORBIDITIES:

Pfizer-BioNTech	Moderna	AstraZeneca	CoronaVac	Janssen	Sputnik Light
Short-term safety of 2nd booster *Pfizer BioNTech* is acceptable based on limited trial data (Munro et al., 2022; 30 years old and above) and real world post-marketing safety surveillance (Instituto de Salud Publico Chile; 18 years old and above). However, further follow-up data is needed to establish longer-term safety.	Short-term safety of 2nd booster *Moderna* is acceptable based on limited trial data (Munro et al., 2022; 30 years old and above). However, further follow-up data is needed to establish longer-term safety.	*Cannot be assessed due to current lack of evidence*			

Safety of Second Booster among INDIVIDUALS AGED 50 YEARS AND OLDER

There were no studies identified which evaluated the second booster of COVID-19 vaccine specifically for the population aged 50 years and older. However, safety in this population can be inferred from evidence in the general population. Two studies, including one Phase II RCT (Munro et al. 2022) and one real world safety report (Pharmacovigilance Subdepartment of the Chilean Institute of Public Health) in the general population were identified. Details and key findings of these were presented in the previous section.

HTAC Judgment for all brands on the Safety of Second Booster among the INDIVIDUALS AGED 50 YEARS AND OLDER:

Pfizer-BioNTech	Moderna	AstraZeneca	CoronaVac	Janssen	Sputnik Light
Short-term safety of 2nd booster *Pfizer-BioNTech* is acceptable based on limited trial data (Munro et al., 2022; 30 years old and above) and real world post-marketing safety surveillance (Instituto de Salud Publico Chile; 18 years old and above). However, further follow-up data is needed to establish longer-term safety.	Short-term safety of 2nd booster *Moderna* is acceptable based on limited trial data (Munro et al., 2022; 30 years old and above). However, further follow-up data is needed to establish longer-term safety.	*Cannot be assessed due to current lack of evidence*			

RQ.2.6: Does the COVID-19 vaccine provide a highly favorable risk-benefit profile in the context of observed vaccine efficacy as a 2nd booster dose?

HTAC specifications: Favorable benefit/risk profile

Risk-Benefit Profile of Second Booster among 18 TO 49 YEARS OLD WITH COMORBIDITIES

The following table summarizes the evidence on efficacy, effectiveness, and safety of a second booster in individuals aged 18 to 49 years old with comorbidities. Given the limited available data on efficacy/effectiveness and safety of second boosters of mRNA COVID-19 vaccines, the second booster of mRNA COVID-19 vaccines has an acceptable risk-benefit profile.

Outcomes		mRNA vaccine outcomes
Efficacy		No trial data reporting clinical efficacy outcomes
Effectiveness	Duration of Protection	Evidence inferred from the general population suggests that, among individuals aged 18 to 49 years old with comorbidities, waning due to Omicron variant is likely especially for symptomatic COVID-19 at 3 to 6 months after the first booster.
	2nd booster	Current evidence on the effectiveness of a second booster against any SARS-CoV-2 infection for the younger immunocompetent population showed inconclusive results, based on very low certainty of evidence.
Immunogenicity		One immunogenicity study showed an increase in both humoral and cell-mediated response from a 2nd booster or mRNA vaccine (Munro et al.).
Safety		Short term safety of 2nd booster of mRNA vaccine is acceptable (Munro et al., & Instituto de Salud Publico Chile). However, further follow-up data is needed to establish longer-term safety.

HTAC Judgment on the risk-benefit profile of second booster among the 18 to 49 YEARS OLD WITH COMORBIDITIES:

Pfizer-BioNTech	Moderna	AstraZeneca	CoronaVac	Janssen	Sputnik Light
Among individuals aged 18 to 49 years old with comorbidities, a second booster of *Pfizer-BioNTech* or *Moderna* has an acceptable benefit-risk profile based on limited evidence on effectiveness and short term safety data.		*Risk benefit profile cannot be assessed due to current lack of evidence on efficacy, effectiveness, and safety.*			

Risk-Benefit Profile of Second Booster among the INDIVIDUALS AGED 50 YEARS AND OLDER

The following table summarizes the evidence on efficacy, effectiveness, and safety of a second booster in the general population aged 50 years and older. Given the limited available data on efficacy/effectiveness and safety of second boosters of mRNA COVID-19 vaccines, the second booster of mRNA COVID-19 vaccines has an acceptable risk-benefit profile.

Outcomes		mRNA vaccine outcomes
Efficacy		No trial data reporting clinical efficacy outcomes
Effectiveness	Duration of Protection	Data from US (Link-Gelles et at. 2022) and UK (Kirsebom et al. 2022) showed a more

	of 1st booster	pronounced waning of protection from mRNA vaccines against hospitalization due to the BA.2 variant at approximately 4 months after the first booster.
	2nd booster	Based on a short follow up period, there is data to support some protection from mRNA vaccines against any SARS-CoV-2 infection (Kiss, et al) and against hospitalization due to COVID-19 (Link-Gelles, et al).
Immunogenicity		One immunogenicity study showed an increase in both humoral and cell-mediated response from a 2nd booster or mRNA vaccine (Munro et al.).
Safety		Short term safety of 2nd booster of mRNA vaccine is acceptable (Munro et al., & Instituto de Salud Publico Chile). However, further follow-up data is needed to establish longer-term safety.

HTAC Judgment on the risk-benefit profile of second booster among INDIVIDUALS AGED 50 YEARS AND OLDER:

Pfizer-BioNTech	Moderna	AstraZeneca	CoronaVac	Janssen	Sputnik Light
Among individuals aged 18 to 49 years old with comorbidities, a second booster of *Pfizer-BioNTech* or *Moderna* has an acceptable benefit-risk profile based on limited evidence on effectiveness and short term safety data.		*Risk benefit profile cannot be assessed due to current lack of evidence on efficacy, effectiveness, and safety.*			

Criteria 3: Affordability and Viability

RQ 3.1: What are the current implementation experiences, challenges and strengths related to the use of COVID-19 Vaccines as 3rd dose/1st booster dose?

- ***Challenges***
- ***Best Practices and Control Measures***

HTAC Specifications
There are no significant barriers and if there are, the plans to address the barriers are clearly reflected in the vaccine roadmap and other relevant documents.

During the implementation of COVID-19 booster vaccination, the NVOC noted several strategies to increase access and ramp up vaccination coverage.These strategies include the use of additional vaccination sites such as primary care clinics, occupational health clinics, private physician's clinics, private sector facilities and workplaces. Apart from setting up more accessible vaccination sites, house-to-house vaccinations were also continuously implemented.

Meanwhile, the NVOC cited the following general challenges encountered in the implementation of the COVID-19 booster vaccination:

- **Poor demand generation:** There is difficulty in promoting booster vaccination because of the public's perception that booster doses are not as important as primary series. Moreover, the opening up of the economy and loosening of restrictions compounded the demand generation problem.
- **Brand preferences:** There is a general preference for *Pfizer-BioNTech*. Given this brand preference, it is difficult to push booster vaccination of other vaccines. They also noted that *Moderna* is less preferred due to perceived higher risk for adverse events.

In terms of brand-specific challenges, the NVOC highlighted that at the beginning of their booster implementation, there was a difficulty in reporting the utilization of *Moderna* due to the change in dosage from full to half dose.

Despite these challenges, the NVOC, DOH regional offices, and LGUs are implementing measures to improve vaccination roll-out.

HTAC Judgment on the current implementation experiences in the COVID-19 Booster Vaccination Program: The best practices and lessons learned from the previous implementations in the rollout of a second booster should be applied for the current target population. The rollout of second boosters among the general population aged 50 years old and above and for individuals with comorbidities aged 18 to 49 years old is viable and feasible.

RQ 3.2: Is a 2nd booster of COVID-19 vaccine affordable?

HTAC Specifications
The vaccine unit cost is comparable with those in other ASEAN countries. The vaccine implementation cost is a reasonable and acceptable allocation of resources.

Pfizer-BioNTech and Moderna

According to the UNICEF vaccine market dashboard, the price at which the Philippine government procures *Pfizer-BioNTech* is lower compared to the prices in other low-middle income countries while *Moderna* is slightly higher. The prices of both *Pfizer-BioNTech* and *Moderna* are within the price range at which these vaccines are available in the international market.

HTAC Judgment on affordability for Pfizer-BioNTech and Moderna: mRNA vaccines *(Pfizer-BioNTech* and *Moderna) are* considered affordable and within the range of price at which it is available in other countries.

AstraZeneca
Affordability was not further assessed due to lack of clinical evidence as a second booster.
CoronaVac
Affordability was not further assessed due to lack of clinical evidence as a second booster.
Janssen
Affordability was not further assessed due to lack of clinical evidence as a second booster.
Sputnik Light
Affordability was not further assessed due to lack of clinical evidence as a second booster.
RQ 3.3: What are the budget implications of using COVID-19 Vaccines as a second booster? ***HTAC Specifications*** The share of the cost to implement the COVID-19 vaccine within the total vaccination budget is not too disproportionate to the share of the population to be vaccinated using the said vaccine in the total population to be vaccinated.
Pfizer-BioNTech and Moderna
The DOH has no plans to procure COVID-19 vaccines (including *Pfizer-BioNTech* and *Moderna*) and will use existing supplies for the second booster vaccination in the general population aged 50 years old and older and individuals with comorbidities aged 18 to 49 years old, thus the use of *Pfizer-BioNTech and Moderna* as second booster for this target population will not incur additional budget impact. **HTAC Judgment in the budget implications for Pfizer-BioNTech and Moderna:** The implementation of a second booster of *Pfizer-BioNTech* and *Moderna* for the general population aged 50 years and older and individuals aged 18 to 49 years old with comorbidities will not incur additional budget impact.
AstraZeneca
Budget implication was not further assessed due to lack of clinical evidence as a second booster.
CoronaVac
Budget implication was not further assessed due to lack of clinical evidence as a second booster.
Janssen

Budget implication was not further assessed due to lack of clinical evidence as a second booster.

Sputnik Light

Budget implication was not further assessed due to lack of clinical evidence as a second booster.

RQ 3.4: Do second boosters of COVID-19 vaccine represent good value for money in terms of preventing COVID-19 morbidity and mortality?

HTAC Specifications
The HTAC deems that the health, economic, and social benefits of the vaccination program outweigh the costs.
The vaccine is a cost-effective/ efficient allocation of resources.

Pfizer-BioNTech and Moderna

For the general population aged 50 years old and older, mRNA vaccines (*Pfizer-BioNTech* and *Moderna)* as second booster represents good value for money in terms of providing some protection against any SARS-CoV-2 infection (Kiss, et al.) and against hospitalization due to COVID-19 (Link-Gelles, et al.). While for the individuals with comorbidities aged 18 to 49 years old, immunogenicity study showed increase in both humoral and cell-mediated response from a second booster of mRNA vaccines (Munro et al.).

HTAC Judgment on Value for Money for Pfizer-BioNTech and Moderna: A second booster of mRNA vaccines (*Pfizer-BioNTech* and *Moderna)* may represent good value for money as it is likely to be effective/efficacious based on limited evidence.

AstraZeneca

Value for money was not further assessed due to lack of clinical evidence as a second booster.

CoronaVac

Value for money was not further assessed due to lack of clinical evidence as a second booster.

Janssen

Value for money was not further assessed due to lack of clinical evidence as a second booster.

Sputnik Light

Value for money was not further assessed due to lack of clinical evidence as a second booster.

Criteria 4: Household Financial Impact

RQ4. Will COVID-19 Vaccines reduce or not add further to the out-of-pocket expenses of Filipino households?

HTAC Specifications
The adoption of the vaccine can reduce out-of-pocket spending of individuals and families due to averted COVID-19 disease and/or hospitalization.

As mandated by PhilHealth Circular 2020-0009; PhilHealth Circular 2020-0012; and PhilHealth Circular 2021-0014, the following benefit packages with corresponding case rates related to COVID-19 are available for the general population. For healthcare workers and their beneficiaries, a Full Financial Risk Protection benefit package is available as mandated by PhilHealth Circular 2020-0011**.**

1. Home Isolation Package for asymptomatic and mild cases (C19HI) = Php 5,917.00
2. Community Isolation Package for symptomatic and confirmed cases (C19CI): Case rate= Php 22,499.00
3. Admissions that were referred to the Community Isolation Units (CIU) from higher level facilities for step-down care (C19IS) = Php 22,499.00
4. Mild COVID-19 pneumonia for elderly and with comorbidities (C19IP1): Case rate= Php 43,997.00
5. Moderate COVID-19 pneumonia (C19IP2): Case rate= Php 143,267.00
6. Severe COVID-19 pneumonia (C19IP3): Case rate= Php 333,519.00
7. Critical COVID-19 pneumonia (C19IP4): Case rate= Php 786,384.00

Based on PhilHealth data, there were a total of 123,120 hospitalization claims from May 2020 to June 2022 for the general population ages 18 years old and above (35,133 claims for 18 to 49 years old and 87,987 claims for 50 years old and older). Table 3.1 below summarizes the cost of COVID-19 illness (inferred from total hospital bill) and out-of-pocket expenses incurred by patients belonging to the general population ages 18 years old and above at different levels of severity. The mean percentage of financial coverage for hospitalization ranged from 59.34% to 81.86% for claims from individuals aged 18-49 years old and 53.11% to 78.41% for claims from individuals aged 50 years and older. Financial coverage was seen to increase with severity of the COVID-19 disease.

Table 3.1. PhilHealth data on COVID-19 Hospitalization Costs and Claims in the general population ages 18 years old and above

Severity *[Benefit package]*	**Case Rate**	**Total Number of Paid Claims**	**Total Hospital Cost**		**Out-of-Pocket Payment**		**Average % of Financial Coverage** *[proportion of financial coverage out of the total bill]*
			Range of Hospitalization Cost *[PHP]*	**Median Hospitalization Cost** *[PHP]*	**Range of Out-of-Pocket Payment** *[PHP]*	**Median Out-of-Pocket Payment** *[PHP]*	
18-49 years old							
Mild COVID-19 *[C19IP1]*	₱ 43,997.00	6,731	₱0.00 to ₱2,149,790.82	₱78,513.66	₱0.00 to ₱2,105,793.82	₱34,611.38	59.34%
Moderate COVID-19 *[C19IP2]*	₱143,267.00	20,165	₱0.00 to ₱6,283,902.40	₱194,154.68	₱0.00 to ₱6,140,635.40	₱53,306.50	70.90%
Severe COVID-19 *[C19IP3]*	₱ 333,519.00	6,105	₱0.00 to ₱8,231,810.95	₱372,236.53	₱0.00 to ₱7,898,291.95	₱52,593.01	76.82%
Critical COVID-19 *[C19IP4]*	₱ 786,384.00	2,132	₱0.00 to ₱8,748,710.27	₱786,384.00	₱0.00 to ₱7,962,326.27	₱19,652.58	81.86%

50 years old and above							
Mild COVID-19 *[C19IP1]*	₱ 43,997.00	13,597	₱0.00 to ₱5,523,611.00	₱94,702.00	₱0.00 to ₱5,479,614.00	₱50,742.68	53.11%
Moderate COVID-19 *[C19IP2]*	₱143,267.00	43,321	₱0.00 to ₱8,374,451.42	₱217,225.00	₱0.00 to ₱8,231,184.42	₱75,470.21	66.00%
Severe COVID-19 *[C19IP3]*	₱ 333,519.00	20,024	₱0.00 to ₱7,306,540.85	₱409,977.81	₱0.00 to ₱6,973,021.85	₱88,215.23	72.78%
Critical COVID-19 *[C19IP4]*	₱ 786,384.00	11,045	₱0.00 to ₱9,581,106.30	₱805,992.62	₱0.00 to ₱8,794,722.30	₱92,473.79	78.41%

Meanwhile, there were a total of 64,311 community isolation claims recorded by PhilHealth from February 2021 to June 2022 for asymptomatic and mild cases for the general population ages 18 and above (54,046 claims for 18 to 49 years old and 10,265 claims for 50 years and older). The median cost of community isolation based on bills recorded and median claims cost for individuals 18 to 49 years old, and 50 years old and older were both at Php 22,449.00. The median out-of-pocket expenses for community isolation is at Php 0.00 (₱0.00 to ₱8,352,778.00 for 18-49 years old; ₱0.00 to ₱366,033.15 for 50 years old and above). The median financial coverage is at 96.00% (18 to 49 years old) and 94% (50 years old and above).

The out-of-pocket expenses reflected above only represents medical costs shouldered by patients and their families. Other non-medical costs such as transportation, food, and productivity loss of the patients and their caregivers were not incorporated due to lack of data. In addition, the above costing of household costs did not include the treatment/management cost of other family members within the household who had likely contracted COVID-19.

Considering these other incurred costs shouldered by households further increases the potential of the vaccine to reduce out-of-pocket expenses of households due to COVID-19.

HTAC Judgment on Household Financial Impact:

Pfizer-BioNTech	Moderna	AstraZeneca	CoronaVac	Janssen	Sputnik Light
Based on current evidence, mRNA vaccines have the potential to reduce out-of-pocket expenses due to averted costs of isolation and treatment of mild, moderate, and severe COVID-19 in individuals 18-49 years old with comorbidities and individuals aged 50 years old and above.		*Potential to reduce out-of-pocket expenses was not further assessed due to lack of clinical evidence as a second booster.*			*Potential to reduce out-of-pocket expenses was not further assessed due to lack of clinical evidence as second booster and its non-inclusion in the WHO EUL listing*

Criteria 5: Social Impact

RQ5.1: Do the vaccines possess the characteristics desired by key stakeholders (i.e., policy- and decision makers, health workers, program managers and/or implementers, patient groups, CSOs, communities, general public)?

- *Safety*
- *Efficacy*
- *Transparency in the regulatory/approval process and information on the vaccines*
- *Availability*
- *Potential for high and equitable coverage*
- *Ease in logistical and implementation requirements*
- *Cost-efficiency to the government*
- *Public acceptability*
- *Availability of mechanisms to compensate vaccine recipients for any untoward event following vaccination*
- *Appropriateness of the vaccine to special at-risk groups and patients with comorbidities*

HTAC Specifications: The vaccine possesses all or most of the characteristics desired by key stakeholders. Qualitative responses will contextualize the Filipino experience and may impact on implementation strategy

Pfizer-BioNTech and Moderna

Based on the results of the focus group discussions conducted in the context of vaccinating the adult population by the HTAC among *healthcare workers, patient groups, civil society organizations and community leaders* from low- and high-prevalence areas, the results from the deliberations in congressional inquiries on the COVID-19 vaccination roadmap, public hearings, and consultations with government decision-makers and implementers, the following are the important and desirable attributes of COVID-19 vaccines and the corresponding evidence for second booster vaccination.

1) **Safe and efficacious** - *please refer to Criteria 2: Clinical Efficacy, Effectiveness, and Safety*

2) Underwent a **transparent regulatory process** of being evaluated and approved by health authorities
   - Evidence: The Philippine FDA has issued an Emergency Use Authorization (EUA) for the use of *Pfizer-BioNTech* and *Moderna* as second booster dose vaccination for immunocompromised patients, HCWs, individuals 50 years old and above and adults 18 to 49 years old with comorbidities.

3) **Potential for high and equitable coverage across the population**

Pfizer-BioNTech	- Once thawed, it can be stored at temperatures of 2°C to 8°C for 10 weeks which can be catered by most RHUs. - Storage for a longer period of time requires more stringent logistical requirements such as ultra-cold freezers (-90°C to -60°C for 12 months) which are only available in tertiary hospitals.
Moderna	- Once thawed, it can be stored at 2°C to 8°C for a maximum of 30 days. After removal from refrigeration, it can be stored at 8°C to 25°C for up to 24 hours. These temperatures can be catered by most RHUs - Storage for a longer period of time requires more stringent logistical requirements such as ultra-cold freezer (-25°C to -15°C for 9 months) which are only available in tertiary hospitals.

4) **Ease in logistics and administration**
   - NVOC and regional offices also plan to **adopt best practices observed during the previous roll-outs** and utilize existing distribution, logistics, waste management and monitoring systems in place (previously mentioned in Criteria 3: Affordability, Viability and Feasibility section).
   - NVOC has expressed **concern regarding poor demand generation for booster vaccination** due to the perception of the population that booster doses are not as important as compared to the administration of primary doses. Aside from this, the opening up of the economy and loosening of the restriction compounded the demand generation problem.
   - In terms of administration, it requires intricate vaccine preparation (formulation for dilution).

5) **Cost-effective** - *please refer to Criteria 3: Affordability, Viability, and Feasibility*

6) **Public acceptability**

- Evidence: A nationwide online survey with 2,599 survey responses conducted by the DOH Health Promotion Bureau last May 2022 aimed to identify the determinants of vaccination uptakes and reasons for getting vaccinated or not. Among the 2,599 survey respondents, 96.7% (n=2,513) completed primary series vaccination. A total of 1,783 (68.6%) respondents received one booster dose. Of the 1,783 respondents who received their first booster, 26.2% (n=468) already received their second booster, 63.0% (n=1,123) had not received but is willing to receive a second booster dose, and 10.8% (n=192) is not willing to receive a second booster dose. However, it was noted from NVOC that poor demand generation is observed for booster doses due to the public perception that booster doses are not as important compared to the primary series. Further, loosening of restrictions and opening up of the economy during COVID-19 vaccination implementation compounded the problem of demand generation.

7) Availability of mechanisms to manage any untoward serious adverse reactions following vaccination

- Evidence: Republic Act 11525 or the COVID-19 Vaccination Program Act of 2021 establishes the COVID-19 National Vaccine Indemnity Fund to provide funds and authorize PhilHealth to pay compensation to any person inoculated through the vaccination program, in the case of death and permanent disability. In response to RA 11525, PhilHealth released PhilHealth Circular No. 2021-0007 (The COVID-19 Vaccine Injury Compensation Package) last 17 June 2021 to provide coverage for cases of hospital confinement, permanent disability, or death due to SAEs from the use of COVID-19 vaccines administered through the COVID-19 vaccination program. Under this benefit package, the benefit for hospitalization claims and the lump sum compensation for death or permanent disability are both capped at Php 100,000.00 each.
- As of 18 July 2022, PhilHealth has received 65 claims linked to the Vaccine Injury Compensation Package. To determine whether PhilHealth should pay for these claims, the causality of the injury to the vaccine shall be validated by the National Adverse Events Following Immunization Committee (NAEFIC).

8) Appropriateness of the vaccine as booster and additional dose to special at-risk groups and patients with comorbidities

- Evidence: Currently, there are studies on the use of *Pfizer-BioNTech* and *Moderna* for second booster for individuals aged 50 and older and 18 to 49 years old with comorbidities. Thus, these vaccines are appropriate for use in this population.

HTAC Judgment on Social Impact for *Pfizer-BioNTech* and *Moderna*:

Given the available clinical evidence, ease in logistics and ability to allow for equitable coverage, and availability of WHO recommendation and FDA EUA, *Pfizer-BioNTech* and *Moderna* possess most of the characteristics desired by key stakeholders for its use as booster dose for the elderly. However, local acceptability in this population showed a general hesitancy towards getting a second booster.This stems from the belief that individuals will not be infected again by the COVID-19 since after the primary series of the vaccine.

AstraZeneca
Social impact was not further assessed due to lack of clinical evidence as a second booster.
CoronaVac
Social impact was not further assessed due to lack of clinical evidence as a second booster.
Janssen
Social impact was not further assessed due to lack of clinical evidence as a second booster.
Sputnik Light
Social impact was not further assessed due to lack of clinical evidence as a second booster and its non-inclusion in the WHO EUL listing.

Criteria 6: Responsiveness to Equity

RQ6: How will the COVID-19 Vaccine and its use impact pre-COVID-19 and COVID-generated health and socioeconomic inequities? Which groups might be unfairly disadvantaged in relation to the COVID-19 disease burden and delivery of the COVID-19 Vaccine?

HTAC Specifications: Health interventions can be fairly adopted and distributed/ implemented for eligible populations without aggravating existing health inequities especially for vulnerable sectors of our society.

Out of the 78,100,578 target population for 2022, a total of 71,439,854 individuals have already received the full primary series regimen of COVID-19 vaccines, which translates as 91.47% full vaccination coverage among the eligible populations (as of 20 July 2022). For booster doses, 15,797,385 individuals (or 22.11%% of the primary vaccinated individuals) have received their first booster dose of COVID-19 vaccine and 1,146,735 individuals (7.26% of boosted individuals) have received their second dose of COVID-19 vaccine.

Vaccination coverage by priority group

Primary series vaccine coverages among the priority groups were high to very high (according to WHO classification with high coverage at 40-70% and very high coverage at >70%). Meanwhile, the 1st booster coverages per priority group were moderate to high (according to WHO classification with moderate at 10-40% and high coverage at 40-70%). Lastly, the 2nd booster coverage of the eligible age groups (HCW and senior citizens aged 60 years and older only) are still low to moderate coverage (according to WHO classification with low a <10% and moderate at 10-40%). Details of the vaccination coverage per priority group, by vaccination policy is presented in the table below.

Table 6.1. Full primary series and booster vaccination coverages by priority group in the Philippines

DOH Prioritization groups	Philippine COVID-19 Vaccination Coverage *(EB-CSQAU, 20 July 2022)*		
	Primary Series	1st Booster Dose	2nd Booster Dose
Workers in Frontline Health Services (A1)	96.55%	56.13%	13.73%
Senior Citizens (A2)	77.84%	26.38%	4.37%
Persons with Comorbidities (A3)	94.40%	27.06%	Not yet eligible
Frontline personnel in essential sectors, including uniformed personnel (A4)	69.64%	19.67%	Not yet eligible
Indigent population (A5)	72.62%	11.28%	Not yet eligible
Pediatric population (5-11 years old)	36.40%	Not yet eligible	Not yet eligible
Pediatric population (12-17 years old)	108.54%	1.74%	Not yet eligible

Vaccination coverage by region

There is an observed disparity in the vaccination coverage across all regions, both for the vaccination coverage of the full primary series and the first booster dose. As of July 20, 2022, NCR reported the highest vaccination coverage (full primary series: 124.19%; first booster dose: 44.30%) while the Bangsamoro Autonomous Region in Muslim Mindanao (BARMM) recorded the lowest vaccination coverage (full primary series: 51.05%; first booster dose: 5.26%). According to the NVOC, the observed disparity among the regions is greatly impacted by logistical problems in BARMM. Meanwhile, in terms of second booster dose, although a similar trend is observed wherein the NCR has the highest coverage (4.59%) and BARMM had the lowest coverage (0.11%), disparity is apparent compared to the previous vaccination strategies as this is a newly rolled out strategy.

HTAC Judgment per vaccine brand on the responsiveness to equity:

<table>
<tr><th colspan="2">Pfizer-BioNTech</th><th colspan="2">Moderna</th><th colspan="2">AstraZeneca</th><th colspan="2">CoronaVac</th><th colspan="2">Janssen</th><th colspan="2">Sputnik</th></tr>
<tr><td colspan="2">The HTAC reiterates the importance of the following measures in the success of the implementation of COVID-19 second booster vaccination :
emphasis on strategies to increase primary series and first booster vaccination coverage among priority groups
ensure that IEC and other vaccination-related documents are accessible and comprehensible (i.e., translated into the local language of the target population)
Second booster vaccination shall be rolled out following the country's prioritization criteria, cognizant of the following:
burden of COVID-19 in the priority groups, especially those with comorbidities;
sufficient supply to cover the all other vaccination strategies in the pipeline along with second booster (remaining primary for adult and pediatric population, remaining first booster/3rd dose for adults and adolescent population)
high first booster vaccination coverage (40-70%, per WHO criteria) for the general population aged 18 years and above
We note that the National Vaccination Operations Center (NVOC) has started implementing alternative vaccination sites to increase access to vaccines.</td><td colspan="6">The appropriateness of the use of AstraZeneca, CoronaVac, and Janssen as second booster was not further assessed due to lack of clinical evidence.</td><td colspan="2">The appropriateness of the use of Sputnik Light as second booster was not further assessed due to lack of clinical evidence as second booster and its non-inclusion in the WHO EUL.</td></tr>
</table>

Section 4. References

1. Abu Dhabi Media Office [@admediaoffice]. (February 8, 2022). *Tweets* [Twitter profile]. Retrieved from https://twitter.com/admediaoffice/status/1490991420593012737
2. Australian Technical Advisory Group on Immunization. (July 2022). COVID-19 booster vaccine advice. Retrieved from https://www.health.gov.au/initiatives-and-programs/covid-19-vaccines/getting-your-vaccination/booster-doses#fourth-dose
3. Bahrain Ministry of Health. (May 19, 2022). COVID-19 Protocols. Retrieved from https://healthalert.gov.bh/en/article/vaccination-and-booster-dose-criteria
4. Cerqueira-Silva,T., Oliveira, V., . Paixão, E.S., Florentino, P.T., Penna, G.O., Pearce, N.,...Barral-Netto,M [preprint]. (April 13, 2022). Protection conferred by vaccine plus previous infection (hybrid immunity) with vaccines of three different platforms during the Omicron variant period in Brazil. Retrieved from https://doi.org/10.1101/2022.04.12.22273752.
5. Chilean Institute of Public Health Pharmacovigilance Subdepartment. (February 2022). ESAVI associated with the administration of SARS-CoV-2 vaccines in Chile in persons 18 years old and above (*translated).* Retrieved from https://drive.google.com/file/d/19ZICUDOVGa0TIVvJeh1UmzBYtglaup0G/view
6. Chile Ministry of Health. (June 6, 2022). Guidelines on Fourth Dose of Vaccine Against SARS-CoV-2: General Population ages 18 years old and above (*translated)*.Retrieved from https://www.minsal.cl/wp-content/uploads/2022/06/Cuarta-dosis-de-vacuna-contra-SARS-CoV-2-en-población-general-desde-los-18-años-ACTUALIZACIÓN.pdf
7. Chile Ministry of Health. (January 2022). Guidelines on Fourth Dose of Vaccine Against SARS-CoV-2: Immunocompromised People (*translated).* Retrieved from https://www.minsal.cl/wp-content/uploads/2022/01/Cuarta-dosis-de-vacuna-contra-SARS-CoV-2-Personas-Inmunocomprometidas.pdf
8. Chile Ministry of Health. (January 2022). Guidelines on Fourth Dose of Vaccine Against SARS-CoV-2: Healthcare Workers (*translated).* Retrieved from https://www.minsal.cl/wp-content/uploads/2022/01/Cuarta-dosis-de-vacunas-contra-SARS-CoV-2-para-Personal-de-Salud.pdf
9. Chile Ministry of Health. (June 6, 2022). Guidelines on Fourth Dose of Vaccine Against SARS-CoV-2:General Population ages 3 to 17 years old (*translated).* Retrieved from https://www.minsal.cl/wp-content/uploads/2022/06/Cuarta-dosis-Poblacio%CC%81n-general-de-3-a-17-an%CC%83os.pdf
10. DOH Epidemiology Bureau. (2022). COVID-19 Tracker. Retrieved from https://doh.gov.ph/covid19tracker
11. DOH Epidemiology Bureau. Data on Local Variants of Concern. *Personal communication*
12. DOH Health Promotion Bureau (May 2022). COVID-19 vaccination hesitancy among adult Filipinos: results of a nationwide survey. https://drive.google.com/file/d/1rNJToKz65XSazpayHl0VoAiGCh_4y64g/view
13. European Center for Disease Prevention and Control. (July 11, 2022). Updated joint statement from ECDC and EMA on additional booster doses of COVID-19 vaccines . Retrieved from https://www.ema.europa.eu/en/documents/public-statement/updated-joint-statement-ecdc-ema-additional-booster-doses-covid-19-vaccines_en.pdf
14. European Center for Disease Prevention and Control. (28 April 2022). Public health considerations and evidence to support decisions on the implementation of a second mRNA COVID-19 vaccine booster dose. Retrieved from: https://www.ecdc.europa.eu/sites/default/files/documents/Public-health-considerations-to-support-decisions-on-implementing-a-second-mRNA-COVID-19-vaccine-booster-dose.pdf
15. Hansen, C., Schelde, A., Moustsen-Helm, I., Hanne-Dorthe , E., Eriksen, R., Stegger, M., Krause,T., Molbak. K., Valentiner-Branth, P. [preprint].(March 30, 2022). Vaccine effectiveness against infection and COVID-19-associated hospitalisation with the Omicron (B.1.1.529) variant after vaccination with the BNT162b2 or mRNA-1273 vaccine: A nationwide Danish cohort study. Retrieved from https://doi.org/10.21203/rs.3.rs-1486018/v1
16. Hong Kong Department of Health- Center for Health Protection. (May 20, 2022).Scientific Committees under CHP update consensus interim recommendations on use of COVID-19 vaccines in Hong Kong. Retrieved from https://www.info.gov.hk/gia/general/202205/20/P2022052000284.htm
17. Israel Ministry of Health.(2022). COVID-19 Vaccine. Retrieved from https://corona.health.gov.il/en/vaccine-for-covid/over-12/
18. Kirsebom, F., Andrews, N., Sachdeva, R., Stowe, J., Ramsay, M., Bernal, J.L.[preprint].(May 1, 2022). Effectiveness of ChAdOx1-S COVID-19 Booster Vaccination against the Omicron and Delta variants in England. Retrieved from https://doi.org/10.1101/2022.04.29.22274483.
19. Kirsebom, F. C. M., Andrews, N., Stowe, J., Toffa, S., Sachdeva, R., Gallagher, E., Groves, N., O'Connell, A.-M., Chand, M., Ramsay, M., & Bernal, J. L. (May 24 2022). COVID-19 vaccine effectiveness against the omicron (BA.2) variant in England. The Lancet Infectious Diseases, 22(7), 931–933. https://doi.org/10.1016/S1473-3099(22)00309-7
20. Kiss, Z., Wittmann, I., Polivka, L., Surján, G., Surján, O., Barcza, Z., Molnár, G. A., Nagy, D., Müller, V., Bogos, K., Nagy, P., Kenessey, I., Wéber, A., Pálosi, M., Szlávik, J., Schaff, Z., Szekanecz, Z., Müller, C., Kásler, M., & Vokó, Z. (2022). Nationwide Effectiveness of First and Second SARS-CoV2 Booster Vaccines During the Delta and Omicron Pandemic Waves in Hungary (HUN-VE 2 Study). Frontiers in Immunology, 13. https://doi.org/10.3389/fimmu.2022.905585
21. Link-Gelles R, Levy ME, Gaglani M, et al.(July 22,2022). Effectiveness of 2, 3, and 4 COVID-19 mRNA Vaccine Doses Among Immunocompetent Adults During Periods when SARS-CoV-2 Omicron BA.1 and BA.2/BA.2.12.1 Sublineages Predominated — VISION Network, 10 States, December 2021–June 2022. MMWR Morb Mortal Wkly Rep 2022;71:931–939. DOI: http://dx.doi.org/10.15585/mmwr.mm7129e1
22. Munro, A.P., Feng, S., Janani, L., Cornelius, V., Aley, P.K., Babbage, G. Baxter, D., Bula, M., Cathie, K., Catterjee, K., Dodd, K., Enever, Y.,Qureshi, E., Goodman, A.L., Green, C.A., Harndahl, L., Haughney, J., Hicks, A., van der Klaaw, A., Kanji, N.,...Faust, S. Safety, immunogenicity, and reactogenicity of BNT162b2 and mRNA-1273 COVID-19 vaccines given as fourth-dose boosters following two doses of ChAdOx1 nCoV-19 or BNT162b2 and a third dose of BNT162b2 (COV-BOOST): a multicentre, blinded, phase 2, randomised trial. Retrieved from: https://www.thelancet.com/action/showPdf?pii=S1473-3099%2822%2900271-7
23. National Advisory Committee on Immunization - Canada (June 29, 2022). Interim guidance on planning considerations for a fall 2022 COVID-19 vaccine booster program in Canada. Retrieved from https://www.canada.ca/en/public-health/services/immunization/national-advisory-committee-on-immunization-naci/guidance-planning-fall-2022-covid-19-vaccine-booster.html
24. Ontario Health. (July 28, 2022). Getting the COVID-19 vaccine. Retrieved from https://covid-19.ontario.ca/getting-covid-19-vaccine#three-dose-primary-series-and-boosters-for-individuals-who-are-immunocompromised

25. Philippine Health Insurance Corporation (2020). PhilHealth Circular 2020-0009: Benefit packages for inpatient care of probable and confirmed COVID-19 developing severe illness/outcomes. Retrieved 12 January 2022 from:https://www.philhealth.gov.ph/circulars/2020/circ2020-0009.pdf
26. Philippine Health Insurance Corporation (2020). PhilHealth Circular 2020-0011: Full financial risk protection for Filipino health workers and patients against coronavirus disease (COVID-19). Retrieved 12 January 2022 from: https://www.philhealth.gov.ph/circulars/2020/circ2020-0011.pdf
27. Philippine Health Insurance Corporation (2020). PhilHealth Circular 2020-0012: Guidelines on the COVID-19 Community Isolation Benefit Package (CCIBP). Retrieved 12 January 2022 from: https://www.philhealth.gov.ph/circulars/2020/circ2020-0012.pdf
28. Philippine Health Insurance Corporation (2021). PhilHealth Circular 2021-0007: Implementing Guidelines on the Coverage of COVID-19 Vaccine Injury due to Serious Adverse Effects (SAEs) Following Immunization Resulting in Hospitalization, Permanent Disability, or Death under the COVID-19 National Vaccine Indemnity Fund (The COVID-19 Vaccine Injury Compensation Package). Retrieved from: https://www.philhealth.gov.ph/circulars/2021/circ2021-0007.pdf
29. Philippine Health Insurance Corporation (2021). PhilHealth Circular 2021-0014: COVID-19 Home Isolation Benefit Package (CHIBP). Retrieved 12 January 2022 from: https://www.philhealth.gov.ph/circulars/2021/circ2021-0014.pdf
30. Philippine Health Insurance Corporation. (2022). PhilHealth Data on COVID-19 Case Claims. *Personal Communication.*
31. Philippine Food and Drug Administration (FDA). Fourth dose/ second booster EUA (ICP and HCW). Retrieved from https://drive.google.com/file/d/1LzbtpQ0NQgURf1WS777ViudZfdSDGYyT/view.
32. Philippine Food and Drug Administration (FDA). Fourth dose/ second booster EUA (Individuals 50 years old and above and adults 18-49 years old with comorbidities).Retrieved from https://drive.google.com/file/d/1aC3K95beT3rltrP8QZbqPR2fAoC7k37Q/view .
33. Ranzani, O.T., Hitchings, M.D.T., de Melo, R.L., de França, G.V.A., Fernandes, C.F.R., Lind, M.L.,... Croda, J [preprint]. (April 1, 2022). Effectiveness of an Inactivated Covid-19 Vaccine with Homologous and Heterologous Boosters against the Omicron (B.1.1.529) Variant. Retrieved from https://doi.org/10.1101/2022.03.30.22273193
34. Singapore Ministry of Health. (July 8, 2022). FAQS - BOOSTER DOSES. Retrieved from https://www.moh.gov.sg/covid-19/vaccination/faqs---booster-doses#secondbooster
35. Šmíd,M., Berec,L., Přibylová,L., Májek, O., Pavlík, T., Jarkovský, J., Weiner, J., Barusová, T., Trnka, J.(April 28, 2022). Protection by vaccines and previous infection against the Omicron variant of SARS-CoV-2. *The Journal of Infectious Diseases*, 2022; jiac161.https://doi.org/10.1093/infdis/jiac161
36. Social Weather Station. (January 27, 2022). Fourth Quarter 2021 Social Weather Survey: 4 out of 5 vaccinated adult Filipinos are willing to get a booster dose of the COVID-19 vaccine. Retrieved from https://drive.google.com/file/d/1DUKjU56S_Mr-sPmBcFKLvuGUpb6VwUpZ/view
37. Stowe, J. Andrews, N., Kirsebom, F., Ramsay, M., Bernal, J.L.(April 1, 2022). Effectiveness of COVID-19 vaccines against Omicron and Delta hospitalisation: test negative case-control study. Retrieved from https://www.medrxiv.org/content/10.1101/2022.04.01.22273281v1
38. Tartof, S.Y., Slezak, J.M., Puzniak, L., Hong, V., Xie, F., Ackerson, B.K., Jodar, L., McLaughlin, J.M. (January 18, 2022). BNT162b2 (Pfizer–Biontech) mRNA COVID-19 Vaccine Against Omicron-Related Hospital and Emergency Department Admission in a Large US Health System: A Test-Negative Design. *SSRN.* Retrieved from http://dx.doi.org/10.2139/ssrn.4011905
39. Unicef (2022). COVID-19 Vaccine Market Dashboard. Retrieved from https://www.unicef.org/supply/covid-19-vaccine-market-dashboard
40. UK Health Security Agency. (January 27, 2022). COVID-19 vaccine surveillance report: Week 4. Retrieved from https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/1050721/Vaccine-surveillance-report-week-4.pdf
41. UK Health Security Agency. (February 21, 2022). JCVI advises a spring COVID-19 vaccine dose for the most vulnerable. Retrieved from https://www.gov.uk/government/news/jcvi-advises-a-spring-covid-19-vaccine-dose-for-the-most-vulnerable
42. UK Joint Committee on Vaccination and Immunization.(July 15, 2022). Joint Committee on Vaccination and Immunization (JCVI) updated statement on the COVID-19 vaccination programme for autumn 2022. Retrieved from https://www.gov.uk/government/publications/jcvi-updated-statement-on-the-covid-19-vaccination-programme-for-autumn-2022/joint-committee-on-vaccination-and-immunisation-jcvi-updated-statement-on-the-covid-19-vaccination-programme-for-autumn-2022
43. US CDC. (July 20, 2022). COVID-19 Vaccine Booster Shots.Retrieved from https://www.cdc.gov/coronavirus/2019-ncov/vaccines/booster-shot.html
44. US FDA. (March 29, 2022). Coronavirus (COVID-19) Update: FDA Authorizes Second Booster Dose of Two COVID-19 Vaccines for Older and Immunocompromised Individuals. Retrieved from https://www.fda.gov/news-events/press-announcements/coronavirus-covid-19-update-fda-authorizes-second-booster-dose-two-covid-19-vaccines-older-and
45. World Health Organization. (December 22, 2021). Interim statement on booster doses for COVID-19 vaccination. Retrieved from https://www.who.int/news/item/22-12-2021-interim-statement-on-booster-doses-for-covid-19-vaccination---update-22-december-2021
46. World Health Organization. (January 21, 2022). Interim recommendations for use of the Pfizer–BioNTech COVID-19 vaccine, BNT162b2, under Emergency Use Listing. Retrieved from https://www.who.int/publications/i/item/WHO-2019-nCoV-vaccines-SAGE_recommendation-BNT162b2-2021.1
47. World Health Organization. (February 23, 2022). Interim recommendations for use of the Moderna mRNA-1273 vaccine against COVID-19. Retrieved from https://www.who.int/publications/i/item/WHO-2019-nCoV-vaccines-SAGE-recommendation-mRNA-1273-2021.3
48. World Health Organization. (March 15, 2022). Interim recommendations for use of the inactivated COVID-19 vaccine, CoronaVac, developed by Sinovac. Retrieved from https://www.who.int/publications/i/item/WHO-2019-nCoV-vaccines-SAGE_recommendation-Sinovac-CoronaVac-2021.1

49. World Health Organization. (May 7, 2022). Interim recommendations for use of the inactivated COVID-19 vaccine BIBP developed by China National Biotec Group (CNBG), Sinopharm. Retrieved from https://www.who.int/publications/i/item/WHO-2019-nCoV-vaccines-SAGE-recommendation-BIBP
50. World Health Organization. (March 15, 2022). Interim recommendations for use of the ChAdOx1-S [recombinant] vaccine against COVID-19 (AstraZeneca COVID-19 vaccine AZD1222 Vaxzevria™, SII COVISHIELD™). Retrieved from https://www.who.int/publications/i/item/WHO-2019-nCoV-vaccines-SAGE_recommendation-AZD1222-2021.1
51. World Health Organization. (May 17, 2022). Interim statement on the use of additional booster doses of Emergency Use Listed mRNA vaccines against COVID-19. Retrieved from https://www.who.int/news/item/17-05-2022-interim-statement-on-the-use-of-additional-booster-doses-of-emergency-use-listed-mrna-vaccines-against-covid-19
52. World Health Organization - Thailand. (June 15, 2022). WHO Thailand Weekly Situation Update No. 240 COVID-19Situation, Thailand 15 June 2022. Retrieved from https://cdn.who.int/media/docs/default-source/searo/thailand/2022_06_15_tha-sitrep-240-covid-19.pdf?sfvrsn=6ee80816_1

Section 5. Acknowledgments

- DOH-Bureau of International Health Cooperation (BIHC)
- DOH-Disease Prevention and Control Bureau (DPCB)
- DOH-Epidemiology Bureau (EB)
- DOH-Health Promotion Bureau (HPB)
- Department of Foreign Affairs (DFA)
- Department of Finance (DOF)
- National Center for Vaccines Operation (NVOC)
- Philippine Living Clinical Practice Guidelines Group (LCPG Group)
- Philippine Insurance Corporation (PhilHealth)

Section 6. Appendix

Appendix 1. Scoping Review of Indications of Second Booster Vaccination (as of 23 July 2022)

Agency	Recommendation Brand Dosing interval	General Population	With Comorbidities	ICP	Elderly (≥ 60 yo)	HCW	Other populations
		✔ - *recommended;* ╳- *no recommendation;* ★- discretionary Age group eligible (if applicable)					
WHO *(statement as of 17 May 2022)*	**Homologous and Heterologous vaccines** **(PH :*CoronaVac, Sinopharm, Moderna, Pfizer, AZ*)**	╳	╳	✔	✔	✔	╳
European CDC & EMA *(joint statement as of 11 July 2022)*	***Pfizer, Moderna*** 4 months after previous booster* **priority are those who received their booster >6 mos ago*	╳	✔ People with underlying health conditions (e.g. high blood pressure, overweight /obese, diabetes etc.) that could make them more likely to develop severe disease if infected.	✔	✔	╳	╳
UK JCVI *(report as of 15 July 2022)*	***mRNA*** **No explicitly mentioned brand, but cited evidence on 4th dose mRNA vaccines*	✔ ≥ 50 yo	✔ *Persons aged 5 to 49 years in a clinical risk group*	✔ ≥ 5 yo	✔	✔	✔ • Frontline social care workers • residents in a care home for older adults and staff working in care homes for older adults • persons aged 5 to 49 years who are household contacts of people with immunosuppression • Persons who are the sole or primary carer of an elderly or disabled person
US FDA and US CDC *(FDA :press release as of 29 March 2022)* *(CDC guideline as of 24 June 2022)*	***Pfizer, Moderna*** 4 months after previous booster	✔ ≥ 50 yo	╳	✔ ≥ 12 yo	✔	╳	╳

AUS ATAGI *(guideline as of 8 July 2022)*	***Pfizer, Moderna (preferred), AZ*** 3 months after previous booster	✔ ≥ 50 yo ★ 30 to 49 yo	✔ ≥ 16 yo with a medical condition that increases the risk of severe COVID-19 illness with disability with significant or complex health needs or multiple comorbidities which increase risk of poor outcome	✔ ≥ 16 yo	✔	✗	✔ • a resident of an aged care or disability care facility • Aboriginal or Torres Strait Islander and aged 50 years and older
Chile MOH *GP Guidelines as of June 2022* *ICP Guidelines as of June 2022* *HCP Guidelines as of 18 Jan 2022* *Pedia Guidelines as of 06 June 2022*	**Pediatric, Gen pop & Elderly** 20 weeks after 3rd dose **ICP** 16 weeks after 3rd dose	✔ ≥ 18 yo ***Pfizer, Moderna***	✔	✔ ≥ 12 yo ***Pfizer***	✔ ***Pfizer, Moderna***	✔ ***Pfizer***	✔ ***Pediatric*** • 3-4 yo - ***CoronaVac*** • 5-11 yo - ***Pfizer pediatric*** • 12- 17 yo - ***Pfizer adult***
Israel MOH	***Pfizer (preferred) , Half-dose Moderna (preferred), AZ*** 4 months after previous booster	✗	✗	✔	✔	✔	✔ • Caregivers of individuals who belong to high risk groups • Those who are at high risk of exposure to COVID-19 in their line of work
Singapore MOH *Guidelines as of 8 July 2022*	***Pfizer, Moderna*** 5 months after previous booster; 28 days - 3 months after post 1st booster infection	★ 50 to 59 yo	✔ *Medically vulnerable persons at higher risk of severe disease*	✗	★ 60 to 79 yo ✔ ≥ 80 yo	✗	✔ • Persons living in aged care facilities, such as nursing homes
Bahrain MOH *Guidelines as of 19 May 2022*	***Pfizer, Valneva or Sinopharm*** 3 months after 3rd dose Gen pop who received 3 doses of Sinopharm ***Pfizer, Valneva or same brand as 3rd booster*** 9 months after 3rd dose Gen pop vaccinated with other brands:	✔ ≥ 18 yo	✗	✗	✔ **Any vaccine** **Currently available vaccines in Bahrain* • *Pfizer* • *Sputnik Light* • *Sputnik V* • *Janssen* • *AZ* • *Covaxin* • *Sinopharm* • *Valneva* 3 months after 3rd dose	✔ **Any vaccine**	✔ 12-17 yo ***Pfizer*, or same brand as 3rd booster** 9 months after 3rd dose

Thailand *WHO Report as of 15 June 2022*	**Gen Pop and Elderly:** ***Pfizer*, Moderna, AZ*** ≥ 4 months after first booster *half-dose *Pfizer* may be administered, depending on on the clinician's discretion and the vaccine recipient's choice **ICP and HCW:** **No brand specified** ≥ 3 months after first booster	✔ ≥ 18 yo	╳	✔ ≥ 18 yo	✔	✔	╳
Hong Kong MOH *Press Release as of 20 May 2022*	***CoronaVac, Pfizer***	╳	✔ 18-59 yo *at higher risk of COVID-19 exposure* ** at least 6 months after first booster*	✔ ≥ 12 yo	✔ 3 months after 3rd dose	✔ 6 months after 3rd dose	╳
Abu Dhabi Media Office *Press release as of 8 February 2022*	***Pfizer, Sinopharm***	✔ ≥ 18 yo ≥ 6 months after previous booster	╳	✔ ≥ 18 yo ≥ 3 months after previous booster	✔	╳	╳
Canada *NACI guidelines, as of 29 June 2022*	**no brand yet** Waiting on evidence on multivalent vaccines	★ 12 to 59 yo	✔ ≥ 12 yo *with an underlying medical condition that places them at high risk of severe COVID-19*	✔ ≥ 12 yo	✔ ≥ 65 yo ★ 60 to 64 yo	╳	✔ • *Adults in First Nations, Métis, or Inuit communities;* • *racialized communities and/or marginalized communities* • *residents of other congregate living settings who are 12 years of age and older*
Ontario, Canada *Gov't of Ontario guidelines as of 14 July 2022*	**No brand explicitly mentioned** Waiting on evidence on multivalent vaccines 3-5 months after 3rd booster	★ 18 to 59 yo	╳	✔	✔	╳	✔ • *First Nation, Inuit and Métis individuals or a non-Indigenous household member aged 18 and over* • *a resident of a long-term care home, retirement home, or Elder Care Lodge or an older adult living in other congregate settings that provide assisted-living and health services*

Appendix 2. Risk of bias of included studies

		Link Gelles et al. 2022		Kiss et al. 2022	
DOMAINS		**REVIEWER JUDGMENT (HIGH / UNCLEAR / LOW / NA)**	**SUPPORT FOR JUDGMENT**	**REVIEWER JUDGMENT (HIGH / UNCLEAR / LOW / NA)**	**SUPPORT FOR JUDGMENT**
STUDY DESIGN		test negative control		Retrospective observational study	
RANDOMIZATION		HIGH	Study design entails no randomization, allocation concealment and blinding done.	HIGH	Study design entails no randomization, allocation concealment and blinding done.
ALLOCATION CONCEALMENT		HIGH		HIGH	
BLINDING OF PARTICIPANTS		HIGH		HIGH	
BLINDING OF INVESTIGATORS		HIGH		HIGH	
BLINDING OF ASSESSORS		HIGH		HIGH	
MISSING OUTCOMES / FOLLOW-UP		HIGH	No missing outcomes. Short follow-up period, (≥ 7 days, median of 28 days)	HIGH	Short follow-up period (25.08 days). Second booster status in the supplementary table does not match the number of 2nd booster recipients investigated for vaccine effectiveness.
SELECTIVE REPORTING		LOW	Outcomes reported matches declared outcomes of interest in the protocol	UNCLEAR	Protocol is not available.
Overall ROB		HIGH		**HIGH**	
ASSESSMENT OF CONFOUNDING FACTORS					
AGE	A	YES	"VE was estimated using a test-negative case-control design, ... using multivariable logistic regression, weighted for inverse propensity to be vaccinated, and adjusted for age, calendar time of index date (days since January 1, 2021),*** study site, and local virus circulation."	YES	Age was considered a confounder. We studied the effect of vaccination by age, and adjusted for age when studying total populations.
	B	NO		NO	Age not balanced between intervention and comparator group.
	C	YES	"VE was estimated using a test-negative case-control design, ... using multivariable logistic regression, weighted for inverse propensity to be vaccinated, and adjusted for age, calendar time of index date (days since January 1, 2021),*** study site, and local virus circulation."	YES	We studied the effect of vaccination by age, and adjusted for age when studying total populations. Haenszel mortality rate ratios were estimated for the total populations to adjust for age.
EXPOSURE RISK	A	YES	"VE was estimated using a test-negative case-control design, ... using multivariable logistic regression, weighted for inverse propensity to be vaccinated, and adjusted for age, calendar time of index date (days since January 1, 2021),*** study site, and local virus circulation."	NO	Exposure risk not considered as confounder and not balanced between arms.

	B	UNCLEAR	exposure risk data not explicitly reported	N/A	
	C	YES	"VE was estimated using a test-negative case-control design, ... using multivariable logistic regression, weighted for inverse propensity to be vaccinated, and adjusted for age, calendar time of index date (days since January 1, 2021),*** study site, and local virus circulation."	N/A	
COMORBIDITIES	A	NO	No mention of considering comorbidities as a confounder	NO	We studied the effect of vaccination by age, and adjusted for age when studying total populations, but an i**mportant limitation of our study is that we could not adjust for other potential confounders, most importantly for chronic diseases.**
	B	N/A		N/A	
	C	N/A		N/A	
OVERALL FOR CONTROL OF CONFOUNDERS		LOW		**HIGH**	
OVERALL APPRAISAL		**SERIOUS**		**VERY SERIOUS**	

Appendix 3. GRADE Table

Efficacy Outcome		Quality Assessment					Summary of Findings			Certainty	IMPORTANCE
		Risk of Bias	Inconsistency	Indirectness	Imprecision	Other considerations	Vaccine n/N (%)	Control n/N (%)	Vaccine Efficacy (CI)		
EFFICACY OUTCOMES											
Link Gelles et al. 2022											
Emergency department/Urgent Care Encounter >7 days after 2nd booster (50 yo)	1 Observational Study	Serious study design entails no randomization, allocation concealment and blinding done	Cannot be assessed	Not Serious	Not Serious	Published Report Strong Association Large magnitude of Effect Dose Response Gradient: N/A Plausible Confounding: None	355/4,094 (8.7%)	1,232/9,478 (13.%0)	**VE:** 66% (60 to 71)	⊕⊕⊕⊕ **HIGH**	CRITICAL
Hospitalization >7 days after 2nd booster (50 yo)	1 Observational Study	Serious study design entails no	Cannot be assessed	Not Serious	Not Serious	Published Report Strong	74/1,204 (6.1%)	393/4,595	**VE:** 80% (71 to 85)	⊕⊕⊕⊕ **HIGH**	CRITICAL

		randomization, allocation concealment and blinding done				Association Large magnitude of Effect Dose Response Gradient: N/A Plausible Confounding: None					
Kiss et al. 2022											
Any SARS-CoV-2 infection after 2nd booster 16 to 24 yo	1 Observational Study	Very Serious (Short follow up period, missing outcome data)	Cannot be assessed	Not Serious	Very Serious (Wide CI, crosses null)	Published Report No Strong Association Magnitude of Effect Not Large Dose Response Gradient: N/A Plausible Confounding: None	1/81 (1.2%)	7,473/141,768 (5.3%)	**VE:**76.58 (-66.20 to 96.70)	⊕◯◯◯ **VERY LOW**	IMPORTANT
Any SARS-CoV-2 infection after 2nd booster 25 to 34 yo	1 Observational Study	Very Serious (Short follow up period, missing outcome data)	Cannot be assessed	Not Serious	Very Serious (Wide CI, crosses null)	Published Report No Strong Association Magnitude of Effect Not Large Dose Response Gradient: N/A Plausible Confounding: None	14/285 (4.9%)	18,240/271,260 (6.7%)	**VE:** 26.94% (-23.40 to 56.74)	⊕◯◯◯ **VERY LOW**	IMPORTANT
Any SARS-CoV-2 infection after 2nd booster 35 to 44 yo	1 Observational Study	Very Serious (Short follow up period, missing outcome data)	Cannot be assessed	Not Serious	Very Serious (Wide CI, lower CI < 30%)	Published Report No Strong Association Magnitude of Effect Not Large Dose Response Gradient: N/A	27/727 (3.7%)	31,210/435,770 (7.2%)	**VE:** 31.41% (0.00 to 52.97)	⊕◯◯◯ **VERY LOW**	IMPORTANT

						Plausible Confounding: None					
Any SARS-CoV-2 infection after 2nd booster 45 to 54 yo	1 Observational Study	Very Serious (Short follow up period, missing outcome data)	Cannot be assessed	Not Serious	Serious (Wide CI)	Published Report No Strong Association Magnitude of Effect Not Large Dose Response Gradient: N/A Plausible Confounding: None	50/1,397 (3.6%)	34,595/579,803 (6.0%)	**VE:** 40.01% (20.84 to 54.54)	⊕◯◯◯ **VERY LOW**	IMPORTANT
Any SARS-CoV-2 infection after 2nd booster 55 to 64 yo	1 Observational Study	Very Serious (Short follow up period, missing outcome data)	Cannot be assessed	Not Serious	Not Serious	Published Report No Strong Association Magnitude of Effect Not Large Dose Response Gradient: N/A Plausible Confounding: None	81/3,939 (2.1%)	23,854/574,551 (4.2%)	**VE:** 50.47% (38.39 to 60.18)	⊕⊕◯◯ **LOW**	IMPORTANT
Any SARS-CoV-2 infection after 2nd booster 65 to 74 yo	1 Observational Study	Very Serious (Short follow up period, missing outcome data)	Cannot be assessed	Not Serious	Not Serious	Published Report No Strong Association Magnitude of Effect Not Large Dose Response Gradient: N/A Plausible Confounding: None	179/14,242 (1.3%)	18,298/770,164 (2.4%)	**VE:** 47.11% (38.73 to 54.35)	⊕⊕◯◯ **LOW**	IMPORTANT
Any SARS-CoV-2 infection after 2nd booster 75 to 84 yo	1 Observational Study	Very Serious (Short follow up period, missing outcome data)	Cannot be assessed	Not Serious	Not Serious	Published Report No Strong Association	81/9,333 (0.9%)	9,664/417,796 (2.3%)	**VE:**62.49 (53.32 to 69.86)	⊕⊕◯◯ **LOW**	IMPORTANT

						Magnitude of Effect Not Large Dose Response Gradient: N/A Plausible Confounding: None					
Any SARS-CoV-2 infection after 2nd booster ≥ 85 yo	1 Observational Study	Very Serious (Short follow up period, missing outcome data)	Cannot be assessed	Not Serious	Serious (Wide CI)	Published Report No Strong Association Magnitude of Effect Not Large Dose Response Gradient: N/A Plausible Confounding: None	19/1,523 (1.2%)	3,642/105,912 (3.4%)	**VE:**63.72 (43.06 to 76.89)	⊕◯◯◯ **VERY LOW**	IMPORTANT
COVID-19 related deaths 75 to 84 yo	1 Observational Study	Very Serious (Short follow up period, missing outcome data)	Cannot be assessed	Not Serious	Very Serious (Wide CI, lower CI < 30%)	Published Report No Strong Association Magnitude of Effect Not Large Dose Response Gradient: N/A Plausible Confounding: None	1/9,333 (0.01%)	341/417,796 (0.08%)	**VE:** 86.75 (5.71 to 98.14)	⊕⊕◯◯ **LOW**	IMPORTANT