Evidence Summary on *Booster and Additional Dose Vaccination* for the prevention of COVID-19

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Section 1. Background

In March 2021, the Philippines started implementing COVID-19 vaccination for priority groups A1 to A5 (workers in frontline health services, senior citizens, persons with comorbidities, frontline personnel in essential sectors, including uniformed personnel, and indigent population) as part of the global and national exit strategies against COVID-19. From the roll out of these vaccines across the globe, several countries worldwide have started implementing booster doses, in consideration of the waning protection of the current vaccine portfolio, especially with the rise of the new variants. In relation to this, prioritizing additional doses for special populations are also being implemented already in some settings to ensure attainment of sufficient protection to those who did not mount sufficient immune response. For context, booster vaccine is defined as a dose needed to address waning immunity over time in healthy individuals with sufficient immune response after the primary series while additional dose vaccination applies to immunocompromised individuals whose immune response may be insufficient. Sharing these similar issues, the Philippines has also started exploring the possibility of implementing booster and additional dose vaccination, and for which specific groups.

In the latest WHO statement on booster vaccination (Oct 4, 2021), it emphasizes the following points:

- The rationale for 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.
- The evidence remains limited and still inconclusive on any widespread need for booster doses following a primary vaccination series.
- In the context of ongoing global vaccine supply constraints, broad-based administration of booster doses risks exacerbating inequities in vaccine access by driving up demand and diverting supply while priority populations in some countries, or in subnational settings, have not yet received a primary vaccination series.
- The focus remains on urgently increasing global vaccination coverage with the primary series driven by the objective to protect against severe disease

As for additional doses for the immunocompromised sub-populations, based on the WHO statement dated 31 Aug 2021, third doses should be prioritized for the vulnerable: those most at-risk populations when there is evidence of waning immunity against severe disease and death. Emerging data shows that immunocompromised people should receive a third dose if they did not respond sufficiently to their initial doses or if they are no longer producing antibodies. They added that the number of immunocompromised individuals globally who would potentially benefit from a third dose is very small, especially when compared to the health workers, older populations at risk who have not had their first or second vaccinations globally. However, they noted that when global supplies are so limited, when the world is in a place where billions of people have not yet received any doses, focus must be on administering first and second doses.

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 updated review looks at the currently available evidence on the use of five presently being used vaccines in the Philippines, as part of *booster dose* and *additional dose* vaccination strategies:

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

This review is part of an overarching evidence appraisal process that is currently being undertaken to assess the vaccination strategies being explored for the 2022 rollout: pediatric vaccination and heterologous primary vaccination, based on best available evidence.

This assessment follows 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 and viability; (4) household financial impact; (5) social impact; and (6) responsiveness to equity.**

Policy Question

Should the DOH use ***Pfizer-BioNTech, Moderna, AstraZeneca, Janssen*** *and* ***CoronaVac*** for **booster dose** and **additional dose vaccination** as part of the 2022 COVID-19 vaccination strategies, to reduce COVID-19 cases, severe infection, and deaths?

Section 2. HTAC Recommendation (as of 11 October 2021)

Booster Vaccination

The HTAC recommends booster vaccination for priority groups **A2 (60 years of age and older) and A1 (healthcare workers)** to commence during the **4th quarter of 2021** and administered **at least 6 months after the primary series**. This is guided by evidence of waning vaccine protection, in particular, against severe disease in the elderly and by the need to maintain the nation's health workforce and health care capacity. This recommendation is predicated on **government confirmation of sufficient vaccine supply in 2021** to also provide the primary series for the unvaccinated population, including adolescents, and an additional dose for immunocompromised individuals. HTAC notes that the requests for assessment received from the DOH DPCB were for 2022 COVID-19 vaccine implementation. However, in consideration of the evidence demonstrating the urgency for booster vaccination for elderly and healthcare workers, HTAC recommended booster vaccination for these eligible populations in the last quarter of 2021.

The HTAC also recommends the implementation of booster vaccination in **2022** implementation following the same prioritization among eligible groups (i.e., A1-A5) **only if acceptable vaccination coverage with the primary series** [i.e., 50% for all priority groups including A1 (Workers in Frontline Health Services), A2 (Senior Citizens), A3 (Individuals with Comorbidities), A4 (Frontline Personnel in Essential Sector) and A5 (Poor population); and at least 70% of the total target population in the hotspot regions (Manila, Cebu, Davao, Iloilo, Calabarzon and Region 3)] **is achieved among the originally identified priority groups (i.e., A1 to A5)**.

The rationale for the set threshold prior to implementation of booster includes ensuring maximum coverage for the primary series as the premature roll-out of booster vaccination without attaining acceptable coverage would exacerbate existing inequities. Considering the current vaccination rate and coverage, these set thresholds are deemed attainable and thus will not delay the booster program.

In addition, HTAC recommends the following booster vaccination strategies for both 2021 and 2022 implementations.

Primary Series	Recommended Booster	Booster Vaccination Strategy
Pfizer-BioNTech	Pfizer-BioNTech	Homologous
AstraZeneca	*Preferred:* Pfizer-BioNTech (based on JCVI)	Heterologous
	AstraZeneca	Homologous
Janssen	Janssen	Homologous
CoronaVac	*Preferred*: Pfizer-BioNTech, AstraZeneca	Heterologous
	CoronaVac	Homologous (if mRNA/AstraZeneca contraindicated)
Moderna	*Preferred*: Pfizer-BioNTech (based on JCVI)	Heterologous (preferred due to cost)
	Moderna [half-dose, 50µg]	Homologous

Additional Dose Vaccination

For the 2021 and 2022 implementation, the HTAC recommends an **additional homologous dose to be given at least 28 days after the completion of the initial COVID-19 vaccine series for the following immunocompromised individuals** considering studies demonstrating improved immune response after an additional dose/third dose

- Been receiving active cancer treatment for tumors or cancers of the blood
- Received an organ transplant and are taking medicine to suppress the immune system
- Received a stem cell transplant within the last 2 years or are taking medicine to suppress the immune system
- Moderate or severe primary immunodeficiency (such as DiGeorge syndrome, Wiskott-Aldrich syndrome)
- Advanced or untreated HIV infection
- Active treatment with high-dose corticosteroids or other drugs that may suppress immune response
- Dialysis patients
- People living with autoimmune disease and on treatment with specific immunosuppressive medications
- Diagnosed with conditions that are considered to have an equivalent level of immunocompromise as advised by the physician (e.g., severe malnutrition)
- People with rare diseases (e.g., amino acid disorders, organic acidurias, urea cycle defects, galactosemia, mitochondrial respiratory chain disorders, lysosomal storage disorders, and other conditions based on data of the UP Manila National Institutes of Health - Institute of Human Genetics)

Currently, there is no available evidence for a homologous additional dose for Janssen and CoronaVac. However, if data from available booster studies will be extrapolated, HTAC recommends a heterologous additional dose using Pfizer-BioNTech for immunocompromised individuals who received Janssen and CoronaVac as primary series.

With this, the HTAC recommends the following additional dose vaccination strategies for both 2021 and 2022 implementations.

Primary Series	Recommended Additional Dose	Additional Dose Strategy
Pfizer-BioNTech	Pfizer-BioNTech	Homologous
Moderna	Moderna	Homologous
AstraZeneca	AstraZeneca	Homologous
Janssen	Pfizer-BioNTech	Heterologous
CoronaVac	Pfizer-BioNTech	Heterologous

Based on the WHO statement on 04 October 2021, immunocompromised individuals with an insufficient immune response to primary series must be prioritized for an additional dose particularly when there is evidence of waning immunity, severe disease, and death. Data on breakthrough infections have also shown a high proportion in immunocompromised individuals at risk of severe COVID-19 complications and death. Further, several studies have also demonstrated improved immunogenicity and considerable safety after giving homologous additional mRNA vaccine to an mRNA primary series. HTAC notes that the requests for assessment received from the DOH DPCB were for 2022 COVID-19 vaccine implementation. However, in consideration of the evidence demonstrating the urgency for additional dose for immunocompromised individuals, HTAC recommended additional dose for these eligible population in the last quarter of 2021

Prior to the implementation of boosters and additional doses, the HTAC recommends that an Emergency Use Authorization (EUA) by the Philippine Food and Drug Administration (FDA) be issued for the aforementioned vaccination strategies. In addition, HTAC recommends exploring mechanisms to allow flexibility in the procurement plans to accommodate next-generation vaccines that may be effective against future variants of concerns (e.g., delta, gamma, beta).

Furthermore, we emphasize that these recommendations are interim and HTAC is actively on the watch for evidence as it is rapidly evolving. The HTAC shall consider in its recommendations the WHO SAGE guidance which is anticipated to be released by 15 November 2021. The HTAC shall update its recommendation when new information becomes available, if necessary.

Overview of Evidence Considered and HTAC Judgments on Booster and Additional Dose Vaccination

Pfizer-BioNTech	Moderna	AstraZeneca	Janssen	CoronaVac
mRNA	mRNA	Vector vaccine (chimpanzee adenovirus)	Vector vaccine (Ad26 adenovirus)	Inactivated virus
BOOSTER DOSE VACCINATION				
Can it significantly reduce the magnitude and severity of COVID-19?				
Booster vaccination has the potential to 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 assuming sufficient vaccine coverage.				
Do current vaccines work for the general population? How long does protection from primary vaccination of COVID-19 vaccines last for the general population?				
Pfizer-BioNTech	**Moderna**	**AstraZeneca**	**Janssen**	**CoronaVac**
Pfizer-BioNTech passed the HTAC vaccine effectiveness threshold of 60% against any SARS-CoV-2 infection and symptomatic COVID-19; and the 80% threshold against hospitalization due to COVID-19. However, other available studies reviewed have shown a decrease in vaccine effectiveness against these outcomes over time. *Pfizer-BioNTech* passed the HTAC vaccine effectiveness threshold of 80% against severe COVID-19 and COVID-19 deaths. Current available studies reviewed have shown that protection against these outcomes has remained sufficient over time.	*Moderna,* for the general population, passed the HTAC vaccine effectiveness threshold of 60% against any SARS-CoV-2 infection and symptomatic COVID-19; and the 80% threshold against severe COVID-19, hospitalization and death due to COVID-19. Current available studies reviewed have shown that protection against these outcomes has remained sufficient over time.	*AstraZeneca,* for the general population, passed the HTAC vaccine effectiveness threshold of 60% against any SARS-CoV-2 infection and symptomatic COVID-19; and the 80% threshold against hospitalization due to COVID-19 and death due to COVID-19. However, other available studies reviewed have shown a decrease in vaccine effectiveness against these outcomes over time. *AstraZeneca,* for the general population, passed the HTAC vaccine effectiveness threshold of 80% against severe COVID-19. Current available studies reviewed have shown that protection against these outcomes has remained sufficient over time.	*Janssen,* for the general population, passed the HTAC vaccine effectiveness threshold of 60% against symptomatic COVID-19 caused by the Alpha and original strain; and the 80% threshold for severe COVID-19 and death due to COVID-19. However, other studies have shown conflicting evidence and reported VEs that did not pass the HTAC threshold for the outcomes any SARS-CoV-2 infection, symptomatic COVID-19 caused by other VOCs including Delta variant, and hospitalization due to COVID-19 at follow-up periods that ranged from 1 month to 5 months after vaccination.	Based on a single study, *CoronaVac* passed the HTAC vaccine effectiveness threshold of 60% against symptomatic COVID-19; and the 80% threshold against hospitalization due to COVID-19 and death due to COVID-19. However, another study reviewed has shown that *CoronaVac* did not pass the HTAC vaccine effectiveness threshold for these outcomes.

Do current vaccines work among healthcare workers and the elderly? How long does primary vaccination of COVID-19 vaccines last for healthcare workers and the elderly?				
Pfizer-BioNTech	**Moderna**	**AstraZeneca**	**Janssen**	**CoronaVac**
Based on the best available evidence so far, VE against symptomatic infection among healthcare workers has decreased over time but still remained above the HTAC threshold at 5 months (Alpha/Delta). Meanwhile, there is decreased duration of protection against any SARS-CoV-2 infection and symptomatic COVID-19 compared to the general population. For the elderly, VE against any SARS-CoV-2 infection and symptomatic COVID-19 decreased over time reaching below the HTAC threshold at 5 to 7 months (Alpha/Delta). VE against severe COVID-19, COVID-19 hospitalization and death slightly decreased over time but still generally remained above the HTAC threshold at 3 months (Alpha) to 6 months (Delta). Meanwhile, compared to the general population, there is decreased duration of protection against any SARS-CoV-2 infection, symptomatic COVID-19 and COVID-19 hospitalization. Duration of protection against severe COVID-19 and COVID-19 death for the elderly is comparable to the general population.	Based on the best available evidence so far, VE against symptomatic infection among healthcare workers has decreased over time but still remained above the HTAC threshold (i.e., at least 60% VE) at 5 months (Alpha/Delta). Meanwhile, there is decreased duration of protection against symptomatic COVID-19 compared to the general population. For the elderly population, VE against hospitalization due to COVID-19 decreased over time reaching below the HTAC threshold (i.e, at least 60% VE) at 3.7 months (Alpha) to 4 months (Delta). VE against COVID-19 death decreased over time reaching below the HTAC threshold (i.e. at least 80%) at 3.2 months. Compared to the general population, there is decreased duration of protection against hospitalization and death due to COVID-19.	Based on the best available evidence so far, the general trend of vaccine effectiveness over time for all outcomes among healthcare workers cannot be concluded due to limited evidence of VE over time. In terms of duration of protection, duration of protection against any SARS-CoV-2 infection, symptomatic COVID-19 and hospitalization due to COVID-19 cannot be inferred based on available studies, and therefore cannot be compared to the general population. For the elderly population, duration of protection against any SARS-CoV-2 infection cannot be inferred based on available studies, and therefore cannot be compared to the general population. VE against symptomatic COVID-19, hospitalization due to COVID-19, and death due to COVID-19 decreased over time reaching below the HTAC threshold (i.e., at least 60% for symptomatic COVID-19 and at least 80% for hospitalization and death due to COVID-19) at 5 months (Delta).	Based on the best available evidence so far, the general trend of vaccine effectiveness over time for all outcomes among healthcare workers cannot be concluded due to limited evidence of VE over time. Meanwhile, there is decreased duration of protection against symptomatic COVID-19 among HCWs. For the elderly population, the general trend of vaccine effectiveness over time for all outcomes among the elderly population cannot be concluded due to limited evidence of VE over time. Meanwhile, duration of protection against symptomatic COVID-19 and hospitalization due to COVID-19 cannot be inferred based on available studies, and therefore cannot be compared to the general population.	Based on the best available evidence so far, VE of *CoronaVac* against symptomatic COVID-19 passed the HTAC VE threshold for this outcome (i.e., at least 60%) up to 1.25 months after dose 2 (Gamma). There is decreased duration of protection against symptomatic COVID-19 compared to the general population. Meanwhile, VE of *CoronaVac* against any SARS-CoV-2 infection passed the HTAC VE threshold for this outcome (i.e., at least 60%); however, duration of protection for this outcome cannot be inferred based on available evidence. There is insufficient evidence to determine the effectiveness and duration of protection of *CoronaVac* against symptomatic COVID-19, hospitalization due to COVID-19, and death due to COVID-19 among the elderly population.
Is booster vaccination efficacious?				
Pfizer-BioNTech	**Moderna**	**AstraZeneca**	**Janssen**	**CoronaVac**
Homologous booster Yes, *Pfizer-BioNTech* is likely to be effective/ efficacious as a homologous booster dose based on limited evidence. Currently, evidence on effectiveness of *Pfizer-BioNTech* as a homologous booster dose is limited to 2 studies, (	**Homologous booster dose** Yes, a 50 µg *Moderna booster dose* (i.e. equivalent to half of one dose in the 2-dose primary series used in the rollout which is at 100 µg) is potentially efficacious as a homologous booster dose based on very limited evidence.	**Homologous booster dose** Yes, it is potentially efficacious as a homologous booster dose based on very limited evidence. Currently, there is no available evidence on the efficacy or effectiveness of *AstraZeneca* as a homologous booster	**Homologous booster dose** Yes, it is potentially efficacious as a homologous booster dose based on very limited evidence. Currently, there is no available evidence on the efficacy of *Janssen* as a homologous booster dose.	**Homologous booster dose** Yes, it is potentially efficacious as a homologous booster dose based on limited evidence. Currently, there is no available evidence on the efficacy of *CoronaVac* as a homologous booster dose.

Bar-on et, 2021, Patalon et al, 2021; all with serious risk of bias based on LCPG and HTAU-jSC appraisal) from the same setting (Israel). ACIP analysis from these studies showed that a booster dose of Pfizer-BioNTech results in at least 70% increase in vaccine effectiveness against symptomatic COVID-19 and 95% increase in vaccine effectiveness against hospitalization compared to a two-dose regimen. In terms of immunogenicity, interim results of one trial (Study C4591001 or the Pfizer US booster trial; with very low certainty based on US ACIP appraisal) measuring immunogenicity with short follow-up period (1 month) showed that Pfizer-BioNTech booster dose induced immune responses (GMR, seroresponse) noninferior to those following dose 2. **Heterologous booster** Yes, it is potentially effective/ efficacious as a heterologous booster dose based on limited evidence. Currently, there is no available evidence on the efficacy of *Pfizer BioNTech* as a heterologous booster dose. Evidence on effectiveness of *Pfizer BioNTech* as a heterologous booster dose with *CoronaVac* as primary series is limited to the Chilean MOH report which notes a substantial increase in vaccine effectiveness against confirmed COVID-19 infection (56% to 90%) and comparable effectiveness against hospitalization (84% to 87%) after booster dose compared to dose 2. In addition, there is available evidence which is limited to immunogenicity studies. Preprint versions of 2 immunogenicity studies (Patamatamkul et al., 2021; Keskin et al., 2021 both with very serious risk of bias due to study	Currently, there is no available evidence on the efficacy or effectiveness of *Moderna* as a homologous booster dose. However, there is currently available evidence limited to 1 immunogenicity trial using 50 µg homologous booster dose of *Moderna* (i.e. equivalent to half of one dose in the 2-dose primary series which is at 100 µg) in combination with either 100 µg or 50 µg of Moderna as primary dose . (Chu et al., 2021; follow up period = 1 month; dosing interval of 7.2 months after dose 2; with very serious risk of bias with the following findings: - Increase in neutralizing antibodies against wild-type and Delta variant pseudoviruses at day 28 post boost, as compared to day 28 levels following dose 2 of primary vaccination - High percentage of booster recipients (92.2%; 95% CI, 88.5-95.0%; n=293) met the definition of a seroresponse to the Delta variant i.e.,a four-fold increase from pre-booster baseline. **Heterologous booster dose** Cannot assess the efficacy as a heterologous booster dose due to current lack of evidence.	dose. One challenge in the implementation of homologous booster vaccination using viral-vector vaccines is the theoretical possibility of anti-vector immunity wherein pre-existing immunity to a viral-vector will raise an immune response against the viral vector that will be delivered in the subsequent doses, resulting in the inhibition of potential vaccine efficacy or effectiveness (Mendonca et al., 2021; GAVI, 2021). While there are knowledge gaps on the effect of anti-vector immunity in the real world implementation of booster vaccination, there is one study on the immunogenicity of a homologous booster dose using AstraZeneca. The study is a case series measuring immunogenicity with a short follow up period (Flaxman et al., 2021; dosing interval of 28 - 38 weeks after dose 2; follow up period = 28 days with very serious risk of bias based on LCPG appraisal). The study showed increased neutralizing antibody titers and spike-specific cellular immune responses after receiving a booster dose of *AstraZeneca* compared to the immune response after receiving the second dose of the primary vaccine series. **Heterologous booster dose** Yes, it is potentially effective/ efficacious as a heterologous booster dose based on **very** limited evidence. Currently, there is no available evidence on the efficacy of AstraZeneca as a heterologous booster dose. Evidence on effectiveness of *AstraZeneca* as a heterologous booster dose with CoronaVac as primary series is limited to the Chilean MOH report which notes a substantial increase in vaccine effectiveness against confirmed	Available immunogenicity evidence on *Janssen* as homologous booster is a report on interim results of on-going trials. i.e. COV1001, COV1002, COV 2001). The studies assessed the immunogenicity of Janssen as a booster dose to people aged 18 years and above. Three dosing levels were used in the RCTs - 2-month, 3-month, and 6-month.Results show that In general, there was a 1.5-fold to 4.5-fold increase in immune response after booster vaccination with 5x1010 vp Janssen compared to pre-booster baseline levels, based on the three RCTs. **Heterologous booster dose** Cannot assess the efficacy as a heterologous booster dose due to current lack of evidence.	Evidence on effectiveness of *CoronaVac* as a homologous booster dose is limited to the Chilean MOH report which notes a substantial increase in vaccine effectiveness against confirmed COVID-19 infection (56% to 93%) and against hospitalization (84% to 96%) after booster dose compared to dose 2 However, there is currently available evidence limited to 5 immunogenicity studies: - 4 Phase I/II trials (Li, J et al., 2021; Li, M et al., 2021; Pan et al., 2021- with not serious risk of bias based on LCPG appraisal ; Wang, K. et al., 2021; with very serious risk of bias based on LCPG appraisal) - 1 real world study (Keskin et al., 2021 with a very serious risk of bias due to study design, non-randomization, unblinding and failure to control for confounding factors). Evidence from these showed an increase in neutralizing antibody and spike-specific cellular immune responses after receiving a booster dose of *CoronaVac* compared to the immune response after receiving dose 2 of the primary vaccine series, with a follow up period ranging from 4 to 26 weeks. **Heterologous *booster dose*** Cannot assess the effectiveness or efficacy as a heterologous booster dose due to current lack of evidence.

design, non-randomization, unblinding and failure to control for confounding factors) on the use of *Pfizer-BioNTech* as a booster dose in combination with *CoronaVac* as primary series, among health care workers. Results showed an increase in neutralizing antibody and spike-specific cellular immune responses after receiving a booster dose of *Pfizer-BioNTech* compared to the immune response after receiving the second dose of the primary vaccine series. However, in the study by Keskin et al. 2021, IgG-N protein antibody titers decreased after a booster dose of *Pfizer-BioNTech* compared to after the second dose of *CoronaVac*.		COVID-19 infection (56% to 93%) and against hospitalization (84% to 96%) after booster dose compared to dose 2. However, there is available evidence limited to a preprint version of 1 immunogenicity study (Patamatamkul et al., 2021 with very serious risk of bias due to study design, non-randomization, unblinding and failure to control for confounding factors) with a follow up period of 2 to 3 weeks on the use of *AstraZeneca* as a booster dose in combination with *CoronaVac* as primary series, among health care workers. Results showed an increase in neutralizing antibody and spike-specific cellular immune responses after receiving a booster dose of *AstraZeneca* compared to the immune response after receiving the second dose of the primary vaccine series.		

Is booster vaccination safe?				
Pfizer-BioNTech	**Moderna**	**AstraZeneca**	**Janssen**	**CoronaVac**
Homologous booster Yes, *Pfizer-BioNTech* is considered safe as a homologous booster dose based on limited evidence. Current safety evidence limited to 1 booster trial (US Study C4591001; with very low certainty based on US ACIP appraisal) and 2 preliminary safety monitoring reports from 2 NRAs (Israeli MOH; Hause et al, 2021 [US CDC]). Evidence from the US trial showed: - Acceptable short term safety (Follow up period: 1 month). Evidence from NRA reports (Israel and US CDC) showed:	**Homologous booster dose** Yes, a full-dose (100ug) or half-dose (50 ug) *Moderna* is considered safe as a homologous booster dose based on limited evidence. Current safety evidence limited to 1 booster trial (Chu et al. 2021, with very serious risk of bias) and 1 preliminary safety monitoring reports from US CDC (Hause et al., 2021). The booster schedule are as follows: - Chu et al., 2021: 7.2 months after dose 2 - Hause et. al., 2021: 6 months after dose 2	**Homologous *booster dose*** Yes, *AstraZeneca* is considered safe as a homologous booster dose based on very limited evidence. Current safety evidence limited to a case series study (Flaxman et al., 2021; dosing interval of 28-38 weeks after dose 2; with very serious risk of bias based on LCPG appraisal) with a follow up period of 28 days. Evidence from the case series showed more local reactogenicity with booster dose of *AstraZeneca* compared to those after the second dose of the primary series. Meanwhile, the study also showed comparable systemic	**Homologous *booster dose*** Yes, *Janssen* is considered safe as a homologous booster dose based on limited evidence. Current safety evidence is limited to 1 trial (Sadoff et al., 2021) and 1 NRA report from the US with limited sample size (n=48, less than 1% of the whole sample size). The booster schedule are as follows: - Sadoff et al., 2021: 6- 9 months after dose - Hause et. al., 2021: ~3 months after dose 2 Evidence from the trial showed:	**Homologous *booster dose*** Yes, *CoronaVac* is considered safe as a homologous booster dose based on limited evidence. Current safety evidence limited to 3 trial safety studies (Li, J et al., 2021; Li, M et al., 2021; Pan et al., 2021- all rated as not serious risk of bias based on LCPG appraisal). Evidence from trials showed similar to less local and systemic adverse reactions after a booster dose of *CoronaVac* compared to those after the second dose of the primary series. However, these trials (Li, J et al., 2021; Li, M et al., 2021; Pan et al., 2021) had a

- similar to less local and systemic reactogenicity profile of a booster dose of *Pfizer-BioNTech* compared to dose 2 of *Pfizer-BioNTech*. - There were 44 serious adverse events out of 3.7M administered doses reported after receiving the booster dose as per the Israeli MOH report. Out of the 44 reports, 17 of these were myocarditis and perimyocarditis cases which all have probable causalities and are currently reviewed. For the other adverse events, Two (2) cases were found to have causality with the booster dose, 2 were found to have possible causality and 14 were found to have none. The remaining 9 cases including 1 death are currently under investigation. However, the short follow up period (0 to 45 days after booster dose) of the study (Study C4591001) and the Israel and US reports do not meet the HTAC - preferred median follow up period of at least 2 months. **<u>Heterologous booster</u>** Yes, it is potentially safe as a heterologous booster vaccine, based on very limited evidence. Currently, evidence on the safety of *Pfizer-BioNTech* as a heterologous booster dose (Moderna+Pfizer-BioNTech, 12 weeks to 6 months apart; Janssen +Pfizer-BioNTech,12 weeks to 5 months apart) is limited to 1 preliminary safety monitoring report from the US CDC (Hause et al. 2021) which showed: - acceptable short-term reactogenicity of a booster dose of *Pfizer-BioNTech* after a primary series of either *Moderna* or *Janssen, after 0-7 days after vaccination.* - no unexpected patterns of	Evidence from trial showed: - Acceptable short term safety outcomes of a booster dose of *Moderna* is, based on a follow up period of 6 months. - Comparable local and systemic reactogenicity after the booster dose compared to after the second dose of the primary series were. - Low incidence of any Grade 3 solicited local or systemic adverse reaction (4.8%-12.9%). - No Grade 4 solicited local or systemic adverse events CDC real world safety report showed: - Booster dose of *Moderna is associated* with more frequent local (84.7% vs 83.5%) and systemic reactogenicity compared to dose 2 of *Moderna* (79.0% vs 81.3%). - No unexpected patterns of adverse reactions; - Transient and mild to moderate adverse reactions However, the short follow up period (0 to 7 days after each dose) of the US CDC report does not meet the HTAC - preferred median follow up period of at least 2 months. **<u>Heterologous booster</u>** Yes, it is potentially safe as a heterologous booster vaccine, based on very limited evidence. Currently, evidence on the safety of *Moderna* as a heterologous booster dose (Pfizer-BioNTech +Moderna, 12 weeks to 6 months apart; Janssen + Moderna, 12 weeks to 5 months apart) is limited to 1 preliminary safety monitoring report from the US CDC (Hause et al. 2021) which showed: - acceptable short-term safety of a booster dose of *Moderna* after a primary series of either	reactogenicity of a booster dose of AstraZeneca compared to those after the second dose of the primary series. However, the short follow up period (7 days after booster dose) of this study does not meet the HTAC - preferred follow up period of at least 2 months. **<u>Heterologous *booster dose*</u>** Cannot assess the overall safety as a heterologous booster dose due to current lack of evidence	- Acceptable short term safety outcomes, with a follow up period of 6 to 9 months - Decreased systemic reactogenicity after the second dose is compared to the first and only dose of the primary series CDC real world safety report: - No unexpected patterns of adverse reaction; - Transient and mild to moderate adverse reactions - Small number of individuals who reported adverse events in the vsafe application limits any conclusion. The short follow up period (0 to 7 days after each dose) of the US CDC report does not meet the HTAC - preferred median follow up period of at least 2 months. **<u>Heterologous booster dose</u>** Yes, it is potentially safe as a heterologous booster vaccine, based on very limited evidence. Currently, evidence on the safety of *Janssen* as a heterologous booster dose (Pfizer-BioNTech + Janssen, 12 weeks to 4 months apart; Moderna + Janssen, 12 weeks to 5.6 months apart) is limited to 1 preliminary safety monitoring report from the US CDC (Hause et al. 2021) which showed: - acceptable short-term safety of a booster dose of *Janssen* after a primary series of either *Pfizer-BioNTech* or *Moderna, after 0-7 days after vaccination.* - no unexpected patterns of adverse reactions However, data for *Janssen* as a heterologous booster dose in the NRA report (Hause et al., 2021) is small, (0.5% of the sample size) limiting further	short follow up period (28 days after booster dose) which did not meet the HTAC - preferred follow up period of at least 2 months. **<u>Heterologous booster dose</u>** Cannot assess the overall safety as a heterologous booster dose due to current lack of evidence

adverse reactions - transient and mild to moderate adverse reactions However, the short follow up period (0 to 7 days after each dose) of the US CDC report does not meet the HTAC - preferred median follow up period of at least 2 months	*Pfizer-BioNTech* or *Janssen after 0-7 days after vaccination.* - no unexpected patterns of adverse reactions However, the short follow up period (0 to 7 days after each dose) of the US CDC report does not meet the HTAC - preferred median follow up period of at least 2 months.		conclusions. In addition, the short follow up period (0 to 7 days after each dose) of the US CDC report does not meet the HTAC - preferred median follow up period of at least 2 months.	
Is it affordable and feasible to use in a national immunization program?				
Pfizer-BioNTech	**Moderna**	**AstraZeneca**	**Janssen**	**CoronaVac**
Yes, it is affordable. The share of the cost of the booster vaccination *Pfizer-BioNTech* to the total 2022 vaccine budget is considered ***commensurate*** to the share of the population to be vaccinated using the said vaccine. **Yes, it is feasible.** Although the implementation was generally challenging due to the intricacies in the storage, handling, and preparation of *Pfizer-BioNTech*, the NVOC implements measures and ensures proper training and preparation prior to the rollout of *Pfizer-BioNTech* to mitigate these challenges.	**Yes, it is affordable since the total implementation cost is within the 2022 budget.** The share of the cost of a homologous (half-dose, 50µg) booster of *Moderna* to the total 2022 vaccine budget is considered commensurate to the share of the target population to be vaccinated with a booster dose using the said vaccine. However, the share of the cost of a heterologous booster of full-dose *Moderna* to the *CoronaVac* primary series is disproportionate to the share of the target population to be vaccinated with this booster strategy. **Yes, it is feasible.** Although the implementation was generally challenging due to the intricacies in the storage, handling, and preparation of *Moderna*, the NVOC implements measures and ensures proper training and preparation prior to the rollout of *Moderna* to mitigate these challenges.	**Yes, it is affordable.** The share of the cost of the booster vaccination *AstraZeneca* to the total 2022 vaccine budget is considered ***commensurate*** to the share of the population to be vaccinated using the said vaccine. **Yes, it is feasible.** Based on the current experience in the COVID-19 Vaccination Program, the implementation of *AstraZeneca* in the Philippine COVID-19 Vaccination Program was generally manageable to roll out. However, despite its manageable cold chain requirement, the longer dosing interval and the lack of a centralized database for the vaccination program as a mechanism to track vaccinees have made the vaccine less viable to implement compared to other vaccines with the same storage temperature requirement.	**Yes, it is affordable.** The share of the cost of the booster vaccination *Janssen* to the total 2022 vaccine budget is considered ***commensurate*** to the share of the population to be vaccinated using the said vaccine. **Yes, it is feasible.** The implementation of Janssen was generally manageable to roll out due to its single-dose regimen and storage temperature requirement. A longer waiting time for vaccinees as a result of it being a multi-dose vial preparation was noted.	**Yes, it is affordable.** The share of the cost of the booster vaccination *CoronaVac* to the total 2022 vaccine budget is considered ***commensurate*** to the share of the population to be vaccinated using the said vaccine. **Yes, it is feasible.** Based on the current experience in the COVID-19 Vaccination Program, the implementation of *CoronaVac* in the Philippine COVID-19 Vaccination Program was generally manageable to roll out due to its temperature requirement and single-dose vial presentation.
Does it reduce out-of-pocket (OOP) expenses of households due to COVID-19?				
Yes, based on current evidence booster vaccination has the potential to reduce out-of-pocket expenses of Filipino households due to averted costs of isolation and treatment of mild, moderate, and severe COVID-19. Based on available claims data from PhilHealth for the period 2020 to August 2021: ● Among health careworks, the median out-of-pocket payment for COVID-19 is relatively lower and the financial coverage is relatively higher, compared to those for the general population. ● Among the elderly population, the costs of COVID-19 illness is higher across all severity as compared to the general population. This constitutes a higher out-of-pocket expense and relatively lower coverage in				

the elderly.Yes, based on current evidence it has the potential to reduce out-of-pocket expenses of Filipino households due to averted costs of isolation and treatment of mild, moderate, and severe COVID-19.
Does it possess characteristics desired by key stakeholders?
The assessed COVID-19 Vaccines in this review possess most of the characteristics desired by key stakeholders for the use as a booster dose for the general population 18 years and above. Further, based on a survey conducted among the general population and HCWs in the Philippines, there is high willingness to receive booster shots. The respondents noted their current knowledge on the vaccine effectiveness and safety as basis for their willingness to receive a booster dose. Specifically for the HCWs, their confidence that booster doses can strengthen their protection against severe COVID-19 infection and against VOCs augments this willingness to receive booster doses of the vaccine. However, there are currently no COVID-19 vaccines authorized by the Philippine FDA for emergency use as booster doses.
Does it reduce or not further add to existing inequities in the health system?
Yes, **booster vaccination will reduce inequities in the health system**, as its implementation provides **sustained protection against COVID-19 among high risk populations i.e. healthcare workers and elderly.** Further, booster vaccination in healthcare workers shall strengthen the current existing interventions to maintain the resilience of the health system. This is assuming that the decision to provide booster vaccination is made in consultation with stakeholders, and shall be rolled out following the country's prioritization criteria, cognizant of the following**:** ● Breakthrough COVID-19 infections in healthcare workers and eldery; ● Sufficient supply to ensure that booster vaccination will not hinder primary vaccination of unvaccinated population.
ADDITIONAL DOSE VACCINATION
Can it significantly reduce the magnitude and severity of COVID-19 among immunocompromised patients?
Cannot be assessed since there is no available data of breakthrough infections among immunocompromised patients.
Do current vaccines work for immunocompromised patients? How long does protection from primary vaccination of COVID-19 vaccines last for immunocompromised patients?

Pfizer-BioNTech	Moderna	AstraZeneca	Janssen	CoronaVac
Based on the best available evidence so far, VE against hospitalization among the immunocompromised population decreased over time reaching below the HTAC threshold at 5 to 6 months (Alpha/Delta). Meanwhile, there is decreased duration of protection against COVID-19 hospitalization for this population compared to the duration of protection for the general population.	Based on the best available evidence so far, the general trend of vaccine effectiveness over time for all outcomes cannot be concluded due to limited evidence of VE over time. Additionally, duration of protection against hospitalization due to COVID-19 cannot be inferred based on available studies, and therefore cannot be compared to the general population.	Based on the best available evidence so far, VE against hospitalization among the immunocompromised population decreased over time reaching below the HTAC threshold at 5 months (Delta). Meanwhile, the duration of protection against hospitalization due to COVID-19 for this population is comparable to that of the general population.	Based on the best available evidence so far, VE against symptomatic COVID-19 of *Janssen* remained over the HTAC threshold (i.e., at least 60% VE) at 2.5 months (Alpha/Delta). However, the general trend of vaccine effectiveness over time for all outcomes cannot be concluded due to limited evidence of VE over time. Meanwhile, there is decreased duration of protection against symptomatic COVID-19 compared to that of the general population. Duration of protection against COVID-19 hospitalization cannot be inferred based on available studies, and therefore cannot be compared to the general population.	Cannot assess the effectiveness or duration of protection of *CoronaVac* primary series among the immunocompromised due to lack of evidence

Is additional dose vaccination efficacious for immunocompromised population?				
Pfizer-BioNTech	**Moderna**	**AstraZeneca**	**Janssen**	**CoronaVac**
Homologous additional dose Yes, it is potentially efficacious as a homologous additional dose based on limited evidence. Currently, there is no available evidence on the efficacy or effectiveness of the use of *Pfizer-BioNTech* as a homologous additional dose. However, there is available evidence limited to 7 real world immunogenicity studies on the use of *Pfizer-BioNTech* as third dose among hemodialysis and peritoneal dialysis patients, immunocompromised organ transplant patients and adults with chronic-inflammatory rheumatic or neurologic diseases under current rituximab therapy (Ducloux et al., 2021; Kamar et al., 2021; Masset et al., 2021; Chavarot et al., 2021; Bonelli et al., 2021; Bensouna et al., 2021, Werbel et al. 2021). The additional dose schedule of these studies ranged from 28 to 91 days after dose 2. Results showed a comparable to increased immune response after receiving an additional dose of *Pfizer-BioNTech* compared to a second dose of the primary vaccine series. **Heterologous additional dose** Yes, *Pfizer-BioNTech* is potentially efficacious as a heterologous additional dose based on limited evidence. There is limited evidence on the safety of *Pfizer-BioNTech* as a heterologous additional dose.	**Homologous additional dose** Yes, it is potentially efficacious as a homologous additional dose based on limited evidence. Currently, there is no available evidence on the efficacy or effectiveness of Moderna as a homologous additional dose. However, there is available evidence limited to 3 immunogenicity studies on the use of Moderna as the third dose among immunocompromised patients who are transplants patients and who have chronic-inflammatory rheumatic or neurologic diseases receiving rituximab therapy (Hall et al., 2021; Bonelli et al., 2021; and Benotmane et al., 2021, Werbel et al. 2021). The additional dose schedule are as follows: - Hall et al., 2021: 60 days after dose 2 - Benotmane et al., 2021: 51 days after dose 2. Results showed an increase in immune response after receiving an additional dose of Moderna compared to a second dose of the primary series. **Heterologous additional dose** Yes, *Moderna* is potentially efficacious as a heterologous additional dose based on limited evidence. Currently, there is no available evidence on the efficacy or effectiveness of Moderna as a heterologous additional dose.	**Homologous additional dose** Cannot assess the clinical efficacy or effectiveness of *AstraZeneca* as a homologous additional dose due to lack of evidence. **Heterologous additional dose** Yes, *AstraZeneca* is potentially efficacious as a heterologous additional dose based on limited evidence. Currently, there is no available evidence on the efficacy or effectiveness of *AstraZeneca* as a heterologous additional dose. However, there is limited available evidence from an immunogenicity study on the use of *AstraZeneca* as a third dose in combination with an *mRNA* primary series for immunocompromised patients with chronic-inflammatory diseases undergoing rituximab therapy. The additional dose schedule is 85 days after dose 2 (Bonelli et al, 2021). Results showed that an additional dose of vector vaccines (*AstraZeneca)* has comparable seroconversion rates with additional dose of mRNA vaccines for these subpopulations after 4 weeks follow up (Bonelli et al., 2021).	**Homologous additional dose** Cannot assess the clinical efficacy or effectiveness of *Janssen* as a homologous additional dose based on current lack of evidence **Heterologous additional dose** Yes, *Janssen* is potentially efficacious as a heterologous additional dose based on limited evidence. Currently, there is no available evidence on the efficacy or effectiveness of Janssen as a heterologous additional dose. However, there is available evidence limited to immunogenicity studies on the use of Janssen as a third dose in combination with an mRNA primary series as primary series, among immunocompromised organ transplant patients. The additional dose schedule is 67 days after dose 2 (Werbel et al. 2021). Results showed comparable to increased immune response after a third dose compared to after the second dose for these subpopulations (Werbel et al. 2021).	Cannot assess the clinical efficacy or effectiveness of *CoronaVac* as a homologous and a heterologous additional dose due to lack of evidence

Current evidence adults with chronic-inflammatory rheumatic or neurologic diseases under current rituximab therapy showed: - acceptable short term safety outcomes of a third dose of *Pfizer-BioNTech* after 30-day follow-up (Bensouna et al., 2021, with very serious risk of bias based on LCPG appraisal). - no serious adverse events recorded in recipients of an additional dose of Pfizer-BioNTech (Werbel et al., 2021, with very serious risk of bias based on LCPG appraisal). However, the studies had a short follow up period (2 weeks to 1 month after booster dose) which does not meet the HTAC - preferred follow up period of at least 2 months. The additional dose schedule are as follows: - Bonelli et al. 2021: 74 days after dose 2 - Bensouna et al 2021; 28 days after dose 2 - Werbel et al. 2021: 67 days after dose 2 More studies with longer follow up are needed to strongly conclude on the overall safety of this vaccine as a homologous third dose.	However, there is limited available evidence from an immunogenicity study on the use of *Moderna* as a third dose in combination with *Pfizer-BioNTech* as primary series, among immunocompromised organ transplant patients. The additional dose schedule is 67 days after dose 2 (Werbel et al, 2021). Results showed improvement in humoral immunity (increase in neutralizing antibody) for these subpopulations after 14 days follow up (Werbel et al., 2021).			

Is additional dose vaccination safe for immunocompromised population?

Pfizer-BioNTech	Moderna	AstraZeneca	Janssen	CoronaVac
Homologous additional dose Yes, *Pfizer-BioNTech* is considered safe as a homologous additional dose based on limited evidence. Currently, there is no available evidence on the efficacy or effectiveness of the use of Pfizer-BioNTech as a heterologous	**Homologous additional dose** Yes, *Moderna* is considered safe as a homologous additional dose based on limited evidence. There is limited evidence on the safety of *Moderna* as a homologous additional dose.	**Homologous additional dose** Cannot assess the overall safety of *AstraZeneca* as a homologous additional dose due to lack of evidence. **Heterologous additional dose** Safety of *AstraZeneca* cannot be assessed at this time due to currently	**Homologous additional dose** Cannot assess the overall safety of *Janssen* as a homologous additional dose based on current lack of evidence **Heterologous additional dose** Safety of *Janssen* cannot be assessed at this time due to currently limited	Cannot assess the overall safety of *CoronaVac* as a homologous and a heterologous additional dose based on current lack of evidence

additional dose. However, there is available evidence limited to immunogenicity studies on the use of *Pfizer-BioNTech* as a third dose in combination with *Moderna* as primary series among immunocompromised organ transplant patients. The additional dose schedule is 67 days after dose 2 (Werbel et al, 2021). Results showed improvement in humoral immunity (increase in neutralizing antibody) for these subpopulations after 14 days follow up (Werbel et al., 2021). **<u>Heterologous additional dose</u>** Safety of *Pfizer-BioNTech* cannot be assessed at this time due to currently limited evidence on heterologous additional doses. There is limited evidence on the safety of *Pfizer-BioNTech* as the additional dose in a heterologous vaccination. The currently existing evidence which is specific to its use as a third dose in combination with *Moderna* as primary series for the limited number of transplant patients (Werbel et al., 2021, with very serious risk of bias based on LCPG appraisal) showed: - acceptable short-term safety outcomes after 14 days - No serious adverse events were also recorded. However, the varying antibody responses of additional dose vaccinations pose potential risks, such as organ rejection and should be evaluated on an individual basis. Moreover, the long-term safety profile of heterologous vaccination strategies using *Pfizer-BioNTech* cannot be assessed since a longer follow-up period	Current available evidence among immunocompromised patients showed: - slightly higher systemic adverse reactions after a booster dose of *Moderna* compared to after the second dose of the primary series or a placebo booster dose after 30-day follow-up (Hall et al, 2021, with not serious risk of bias based on LCPG appraisal). - no serious adverse events were recorded in recipients of an additional dose of Pfizer-BioNTech (Werbel et al., 2021, with very serious risk of bias based on LCPG appraisal). However, the studies had a short follow up period (1 month after booster dose) which does not meet the HTAC - preferred follow up period of at least 2 months. The additional dose schedule are as follows: - Hall et al., 2021: 60 days after dose 2 - Werbel et al. 2021: 67 days after dose 2 More studies with longer follow up are needed to strongly conclude on the overall safety of this vaccine as a homologous third dose. **<u>Heterologous additional dose</u>** Safety of *Moderna* cannot be assessed at this time due to currently limited evidence on heterologous additional doses. There is limited evidence on the safety of *Moderna* as the additional dose in a heterologous vaccination. The currently existing evidence which is specific to its use as a third dose in combination with *Pfizer-BioNTech* as	limited evidence on heterologous additional doses. There is limited evidence on the safety of *AstraZeneca* as the additional dose in a heterologous vaccination. The currently existing evidence which is specific to its use as a third dose in combination with *Pfizer-BioNTech or Moderna* as primary series for immunocompromised patients with chronic-inflammatory diseases undergoing rituximab therapy.(Bonelli et al, 2021, with serious risk of bias based on LCPG appraisal). showed: - acceptable short-term safety outcomes after 14 days - No serious adverse events were also recorded. However, the varying antibody responses of additional dose vaccinations pose potential risks, such as organ rejection and should be evaluated on an individual basis. Moreover, the long-term safety profile of heterologous vaccination strategies using *AstraZeneca* cannot be assessed since a longer follow-up period from clinical trials and real world evidence is needed.	evidence on heterologous additional doses. There is limited evidence on the safety of *Janssen Ad26.COV2.S (COVID-19)* as the additional dose in a heterologous vaccination. The currently existing evidence which is specific to its use as a third dose in combination with an mRNA primary series for the limited number of transplant patients (Werbel et al., 2021, with very serious risk of bias based on LCPG appraisal) showed: - acceptable short-term safety outcomes after 14 days - No serious adverse events were also recorded. However, the varying antibody responses of additional dose vaccinations pose potential risks, such as organ rejection and should be evaluated on an individual basis. Moreover, long-term safety profile of heterologous vaccination strategies using *Janssen* cannot be assessed since a longer follow-up period from clinical trials and real world evidence is needed.	

from clinical trials and real world evidence is needed.	primary series for the limited number of transplant patients (Werbel et al., 2021, with very serious risk of bias based on LCPG appraisal) showed: - acceptable short-term safety outcomes after 14 days - No serious adverse events were also recorded. However, the varying antibody responses of additional dose vaccinations pose potential risks, such as organ rejection and should be evaluated on an individual basis. Moreover, the long-term safety profile of heterologous vaccination strategies using *Moderna* cannot be assessed since a longer follow-up period from clinical trials and real world evidence is needed.			
Is it affordable and feasible to use in a national immunization program?				
Pfizer-BioNTech	**Moderna**	**AstraZeneca**	**Janssen**	**CoronaVac**
Yes, it is affordable. The share of the cost of the additional dose vaccination with *Pfizer-BioNTech* to the total 2022 vaccine budget is considered commensurate to the share of the immunocompromised population to be vaccinated using the said vaccine. **Yes, it is feasible.** Although the implementation was generally challenging due to the intricacies in the storage, handling, and preparation of Pfizer-BioNTech, the NVOC implements measures and ensures proper training and preparation prior to the rollout of Pfizer-BioNTech to mitigate these challenges.	**Yes, it is affordable since the total implementation cost is within the 2022 budget.** However, the share of the cost of the additional dose vaccination using *Moderna* to the total 2022 vaccine budget is not commensurate to the share of the population to be vaccinated using the said vaccine. **Yes, it is feasible.** Although the implementation was generally challenging due to the intricacies in the storage, handling, and preparation of *Moderna*, the NVOC implements measures and ensures proper training and preparation prior to the rollout of Moderna to mitigate these challenges.	**Yes, it is affordable.** The share of the cost of the additional dose vaccination with *AstraZeneca* to the total 2022 vaccine budget is considered commensurate to the share of the immunocompromised population to be vaccinated using the said vaccine. **Yes, it is feasible.** Based on the current experience in the COVID-19 Vaccination Program, the implementation of AZ in the Philippine COVID-19 Vaccination Program was generally manageable to roll out. However, despite its manageable cold chain requirement, this longer dosing interval and the lack of a centralized database for the vaccination program as a mechanism to track vaccinees have made the vaccine less viable to implement compared to other vaccines with the same storage temperature requirement.	**Yes, it is affordable.** The share of the cost of the additional dose vaccination with *Janssen* to the total 2022 vaccine budget is considered commensurate to the share of the immunocompromised population to be vaccinated using the said vaccine. **Yes, it is feasible.** The implementation of Janssen was generally manageable to roll out due to its single-dose regimen and storage temperature requirement. A longer waiting time for vaccinees as a result of it being a multi-dose vial preparation was noted.	Affordability was not assessed for this brand due to limited clinical evidence for additional dose vaccination. **Yes it is feasible.** Based on the current experience in the COVID-19 Vaccination Program, the implementation of CoronaVac in the Philippine COVID-19 Vaccination Program was generally manageable to roll out due to its temperature requirement and single-dose vial presentation.

Does it reduce OOP expenses of households due to COVID-19?
Yes, based on current evidence it has the potential to reduce out-of-pocket expenses of Filipino households due to averted costs of isolation and treatment of mild, moderate, and severe COVID-19. Based on available claims data from PhilHealth for the period of 2020 to August 2021: ● Among health careworks, the median out-of-pocket payment for COVID-19 is relatively lower and the financial coverage is relatively higher, compared to those for the general population. ● Among the elderly population, the costs of COVID-19 illness is higher across all severity as compared to the general population. This constitutes a higher out-of-pocket expense and relatively lower coverage in the elderly.
Does it possess characteristics desired by key stakeholders?
Cannot be assessed due to lack of evidence. There are currently no available surveys on the acceptability of implementing an additional dose for immunocompromised populations. While the consultation with program implementers were made in the context of booster doses, the identified main challenges *(i.e., heterologous booster vaccination resulting in supplemental training of human resources and extensive adverse events monitoring)* are expected to be similar should the implementation of additional doses using heterologous vaccines take place. In addition, should this additional dose vaccination among immunocompromised patients take place, it will be in parallel with the primary series vaccination of the remaining target vaccinees from priority groups A1 to A5. As such, it will require additional human and supply chain management-related resources.
Does it reduce or not further add to existing inequities in the health system?
Yes, additional dose vaccination will reduce inequities in the health system, as its implementation ensures that the immunocompromised population attain sufficient protection against COVID-19. This is assuming that the decision to provide additional dose to the immunocompromised population is made in consultation with stakeholders; and, shall be rolled out following the country's prioritization criteria, cognizant that supplies are sufficient to ensure that provision of additional doses will not hinder primary vaccination of unvaccinated population.

Section 3. Presentation of Evidence on Booster and Additional Dose Vaccination

Criteria 1: Responsiveness to Disease Magnitude and Severity

RQ1: Can the COVID-19 Vaccine significantly reduce the magnitude and severity of COVID-19?

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

Magnitude and severity of COVID-19 breakthrough infections

Breakthrough infections, as defined by the Philippine FDA are SARS-CoV-2 infections that happened more than 14 days after the last dose. Data on breakthrough infections were taken from the Philippine FDA (2021) report as of 26 September 2021. Meanwhile, there is currently no data on breakthrough infections in immunocompromised patients. However, among breakthrough infections recorded, the following are their comorbidities: arthritis, cancer, cholesterolemia, diabetes, gout, heart disease, HIV, hypertension, kidney disease, lung disease, obesity, prostate disease , sleep disorder, stroke, thyroid disease and vascular disease. Further, the following are the comorbidities of the 14 fatal cases of breakthrough infections, diabetes (2), hypertension (2), diabetes and hypertension (2), kidney disease (1), diabetes and kidney disease (1), and 8 cases had no comorbidities or were not indicated.

Pfizer-BioNTech	Moderna	AstraZeneca	Janssen	CoronaVac
The total number of *Pfizer-BioNTech* doses administered is 4,505,757 doses. Out of the total 2,562,227 fully and partially vaccinated individuals, 0.001% (n=28) were reported to have had breakthrough infections. Two (0.0004%) of these cases were individuals 60 years and older. Lastly, zero (0) deaths were reported.	The total number of Moderna doses administered is 3,336,741 doses. Out of the total 1,986,307 fully and partially vaccinated individuals, no breakthrough infections were reported.	The total number of *AstraZeneca* doses administered is 6,942,940 doses. Out of the total 4,379,090 fully and partially vaccinated individuals, 0.003% (n=125) were reported to have had breakthrough infections. Nine (0.0002%) of these cases were individuals 60 years and older. Lastly, one (1) (0.00002%) death was reported.	The total number of *Janssen* doses administered is 3,585,355 doses. Out of the total 3,585,355 fully and partially vaccinated individuals, 0.001% (n=35) were reported to have had breakthrough infections. Twelve (12) (0.0003%) of these cases were individuals 60 years and older. Lastly, five (5) (0.0001%) deaths were reported.	The total number of *CoronaVac* doses administered is 24,813,589 doses. Out of the total 24,813,589 fully and partially vaccinated individuals, 0.002% (n=327) were reported to have had breakthrough infections. 51 (0.0004%) of these cases were individuals 60 years and older. Lastly, eight (8) (0.00006%) deaths were reported.

HTAC Judgment: Booster vaccination has the potential to 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 assuming sufficient vaccine coverage for primary series.

Criteria 2: Clinical Efficacy, Effectiveness, and Safety

BOOSTER VACCINATION

RQ.2.1: What is the effectiveness over time of primary vaccinations using COVID-19 vaccines against the original strain and variants of concern in the general population in terms of symptomatic COVID-19, severe COVID-19, hospitalization and death due to COVID-19? How long does protection from primary vaccination last in the general population?

HTAC Specifications:
Preferred VE: ≥70% reduction in the risk of symptomatic infection with vaccination versus no vaccination
Minimum acceptable VE (point estimate) : at least 60% reduction of any SARS-CoV-2 infection, symptomatic COVID-19; **at least 80% reduction** of severe COVID-19, hospitalization due to COVID-19; **at least 80% reduction** of death due to COVID-19

Evidence considered
For the evidence on the effectiveness of COVID-19 vaccines over time against the original strain and variants of concern for the general population, reviews from the following organizations were synthesized: 1) the International Vaccine Access Center (IVAC) of the Johns Hopkins Bloomberg School of Public Health and World Health Organization as of 01 Oct 2021; 2) COVID-NMA as of 07 Oct 2021; 3) LCPG review on effectiveness of vaccines against the Delta as of 31 Aug 2021; 4) LCPG Review on Janssen as of 06 Sep 2021 and CoronaVac as of 16 Sep 2021 5) the US CDC Advisory Committee on Immunization Practices (ACIP) as of 23 Sept 2021. Due to limited data for CoronaVac, real world surveillance data from the Ministry of Health (MOH) of Chile as of 03 Aug 2021 for *CoronaVac* were included in the review.

Pfizer-BioNTech

Quality of the studies
Overall, there were 22 studies included in the reviews that reported vaccine effectiveness over time of *Pfizer-BioNTech* in the general population. Risk of Bias (RoB) appraisals were extracted from the reviews of the NCPG group and COVID-NMA. RoB ratings ranged from 'some concerns of bias' to 'serious risk of bias'. One study (Thomas et al., 2021) had some concerns of bias, 6 studies (Pouwels et al., 2021; Lopez-Bernal et al., 2021; Bajema et al., 2021; Grannis et al., 2021; Nasreen et al., 2021; and Stowe et al., 2021) had moderate RoB, 9 studies (Puranik et al., 2021; Goldberg et al., 2021; Israeli MOH; Tenforde et al., 2021; Rosenberg et al., 2021; Tang et al., 2021; Tartof et al., 2021; Seppala et al., 2021; and McKeigue et al., 2021) had serious RoB, while 6 (ICATT; Andrews et al., 2021; VISION Network study; Self et al., 2021; Eyre et al., 2021; and Chemaitelly et al., 2021) studies included in the reviews were not appraised by the NCPG or COVID-NMA since they were detected from other sources of data (i.e., the IVAC review or data from the US CDC presentation) which do not perform appraisal. The most common source of bias was the lack of control for confounding variables. Results of the risk of bias appraisals of each study are summarized in Appendix **5**.

Results
Based on real world effectiveness studies over time, *Pfizer-BioNTech* remains effective for 3.2 to 7.7 months after the second dose for the following outcomes in the general population:

- **VE against any SARS-CoV-2 infection:** Overall, there were 10 studies (Tartof et al., 2021; Puranik et al., 2021; Rosenberg et al., 2021; Pouwels et al., 2021; Eyre et al., 2021; Seppala et al., 2021; Israeli MOH; Goldberg et al., 2021; Tang et al., 2021; and Chemaitelly et al., 2021) from the relevant reviews which evaluated this outcome caused by the Alpha and Delta variant.
  - ***Against the Alpha variant:*** Five studies were found - one (Eyre et al., 2021) reported VE specifically against the Alpha variant while the other 4 (Tartof et al., 2021; Puranik et al., 2021; Pouwels et al., 2021; and Chemaitelly et al., 2021) reported overall VE at the time when the Alpha was one of the variants circulating in the setting. Specifically, against the Alpha variant, Eyre et al., (2021) had the longest follow-up period (i.e., 3.2 months) with a VE that passed the HTAC threshold for this outcome (i.e., at least 60% VE). Thus, it can be inferred that *Pfizer-BioNTech* is effective against any Alpha SARS-CoV-2 infection for at least **3.2** months. Meanwhile, of the 4 studies that reported the overall VE in the setting where Alpha was one of the dominant circulating variants (other VOCs included Delta and Beta), three studies (Tartof et al., 2021; Puranik et al., 2021; and Chemaitelly et al., 2021) reported VEs that did not pass the HTAC threshold for this outcome during the longest time point of measurement of the respective studies (i.e., Tartof et al., 2021: ≥5 months; Puranik et al., 2021: 4 months; Chemaitelly et al., 2021: ≥7 months).
  - ***Against the Delta variant:*** Seven studies (Tartof et al., 2021; Rosenberg et al., 2021; Eyre et al., 2021; Seppala et al., 2021; Israeli MOH; Goldberg et al., 2021; and Tang et al., 2021) were found that reported VEs specifically against the Delta variant while another 4 studies reported overall VE at the time when Delta was one of the variants circulating in the setting, as discussed in the section above. Of these, Seppala et al., (2021) reported the longest follow-up period (i.e., 7.7 months after dose 2) with a VE that passed the HTAC threshold for any SARS-CoV-2 infection. Thus, it can be inferred that *Pfizer-BioNTech* is effective against any Delta SARS-CoV-2 infection for at least **7.7** months. However, 4 other studies (Tartof et al., 2021; Israel MOH; Goldberg et al., 2021; Tang et al., 2021) reported VEs that did not pass the HTAC threshold for this outcome during the longest time point of measurement of the respective studies (i.e., Tartof et al., 2021: ≥5 months; Israel MOH: 6.93 months; Goldberg et al., 2020: 6 months; Tang et al., 2021: 6.25 months)

- **VE against symptomatic COVID-19**: Overall, there were 10 studies (Thomas et al., 2021; Puranik et al., 2021; ICATT; Pouwels et al., 2021; Andrews et al., 2021; Lopez-Bernal et al., 2021; Israeli MOH; Tang et al., 2021; Nasreen et al., 2021; and Chemaitelly et al., 2021) from the relevant reviews which evaluated this outcome caused by the Alpha or Delta variants.
  - ***Against the Alpha variant:*** Six studies were found - 3 (Thomas et al., 2021; ICATT; and Andrews et al., 2021) reported the VE specifically against the Alpha variant, while the other 3 (Puranik et al., 2021; Pouwels et al., 2021; and Chemaitelly et al., 2021) reported the overall VE during the time when Alpha was one of the dominant variants circulating in the study setting (other VOCs included Delta and Beta). Of the studies, Thomas et al. (2021) had the longest follow-up period (i.e., 6 months after dose 2) with a VE that passed the HTAC threshold for symptomatic COVID-19 (i.e., at least 60% VE). Thus, it can be inferred that *Pfizer-BioNTech* is effective against symptomatic COVID-19 caused by the Alpha variant for at least **6** months. One study, Chemaitelly et al. (2021), a study in Qatar, reported a VE that did not pass the HTAC threshold (i.e., at least 60% VE) at the longest time point of measurement of study which is at ≥7 months. However, this study did not report the VE specifically for the Alpha variant but the VE over time when the Alpha, Beta and Delta variants circulated in Qatar.
  - ***Against the Delta variant:*** Nine studies reported VEs against Delta symptomatic COVID-19. Six of these studies (ICATT; Andrews et al., 2021; Lopez-Bernal et al., 2021; Israeli MOH; Tang et al., 2021; and Nasreen et al., 2021) reported the VE specifically against the Delta variant, while the other 3 (Pouwels et al., 2021; Puranik et al., 2021; and Chemaitelly et al., 2021) reported the overall VE during the time when Delta was one of the dominant variants circulating in the study setting as discussed in the section above. Of the included studies that reported specifically against the Delta variant, 2 studies (Israel MOH and Tang et al., 2021), reported VEs that did not pass the HTAC threshold at the longest time point of measurement after dose 2 in these studies (i.e., Israel MOH: 6.93 months; Tang et al., 2021: 25 weeks). The same is true for Chemaitelly et al., 2021, which reported the overall VE over time for the Alpha, Beta, and Delta variants which failed the HTAC threshold (i.e., at least 60% VE) at ≥ 7 months after dose 2. Meanwhile, Nasreen et al. (2021) had the longest follow-up period of 6.1 months after dose 2 that reported a VE that passed the HTAC threshold for this outcome. Thus, it can be inferred that *Pfizer-BioNTech* is effective against symptomatic COVID-19 caused by the Delta variant for at least **6.1** months.
- **VE against severe COVID-19**: Overall, there were 4 studies (Tang et al., 2021; Goldberg et al., 2021; McKeigue et al., 2021; and Israeli MOH) from the relevant reviews which evaluated this outcome caused by the Delta variant. None of the studies reported this outcome against the Alpha variant.
  - ***Against the Delta variant:*** All 4 studies reported VEs that passed the HTAC VE threshold for severe COVID-19 (i.e., at least 80% VE). Of these, the surveillance data from the Israel Ministry of Health had the longest follow-up period (i.e., 6.93 months after dose 2). Thus, it can be inferred that *Pfizer-BioNTech* is effective against severe COVID-19 caused by the Delta variant for at least **6.93** months.
  - **VE against hospitalization due to COVID-19**: Overall, there were 12 studies (Thomas et al., 2021; Tartof et al., 2021; VISION Network study; Tenforde et al., 2021; Bajema et al., 2021; Self et al., 2021; Puranik et al., 2021; Grannis et al., 2021; Rosenberg et al., 2021; Andrews et al., 2021; Stowe et al., 2021; and Chemaitelly et al., 2021) from the relevant reviews which evaluated this outcome against the Alpha and Delta variants.
  - ***Against the Alpha variant:*** Four studies (Thomas et al., 2021; VISION Network study; Andrews et al., 2021; Stowe et al., 2021) included in the reviews reported VE against Alpha hospitalization while another six studies (Tartof et al., 2021; Tenforde et al., 2021; Puranik et al., 2021; Bajema et al., 2021; Self et al., 2021; and Chemaitelly et al., 2021) were conducted during the dominance of the Alpha, followed by the Delta variant. Of the studies, Thomas et al. (2021) had the longest follow-up period (i.e., 6 months after dose 2) with a VE that passed the HTAC threshold for hospitalization due to COVID-19 (i.e., at least 80% VE). Thus, it can be inferred that *Pfizer-BioNTech* is effective against hospitalization due to COVID-19 caused by the Alpha variant for at least **6** months.
  - ***Against the Delta variant:*** Six studies (Stowe et al., 2021; Tartof et al., 2021; Andrews et al., 2021; Grannis et al., 2021; Rosenberg et al., 2021; and VISION Network study) included in the reviews reported VE against Delta hospitalization while six studies were conducted during the dominance of the Alpha, followed by the Delta variant as mentioned in the previous section. Of the studies, Tartof et al. (2021) had the longest follow-up period (i.e., 7.25 months after dose 2) that reported a VE that passed the HTAC threshold for hospitalization due to COVID-19 (i.e., at least 80% VE). Thus, it can be inferred that *Pfizer-BioNTech* is effective against hospitalization due to COVID-19 caused by the Delta variant for at least **7.25** months.
- **VE against death due to COVID-19***:* Only one study (Andrews et al., 2021) reported the VE of *Pfizer-BionTech* against death due to COVID-19 caused by the Delta variant over time. No study was detected against the Alpha variant.
  - ***Against the Delta variant:*** Andrews et al. (2021) reported that *Pfizer-BioNTech* still passed the HTAC VE threshold for death (i.e., at least 80%) due to COVID-19 caused by the Delta variant even beyond 20 weeks after dose 2. Thus, it can be inferred that *Pfizer-BioNTech* is effective against death due to COVID-19 caused by the Delta variant for at least **5** months.

HTAC Judgment: *Pfizer-BioNTech,* for the general population, passed the HTAC vaccine effectiveness threshold of 60% against any SARS-CoV-2 infection and symptomatic COVID-19; and the 80% threshold against hospitalization due to COVID-19. However, other available studies reviewed have shown a decrease in vaccine effectiveness against these outcomes over time.

Pfizer-BioNTech, for the general population, passed the HTAC vaccine effectiveness threshold of 80% against severe COVID-19 and death due to COVID-19. Current available studies reviewed have shown that protection against these outcomes has remained sufficient over time.

Moderna

Quality of the studies

Overall, there were 16 studies included in the reviews that reported vaccine effectiveness over time of *Moderna* in the general population. RoB appraisals were extracted from the reviews of the LCPG group and COVID-NMA. RoB ratings ranged from 'moderate RoB' to 'serious RoB'. Two studies (Grannis et al., 2021 and Bajema et al.) has moderate RoB based on COVID-NMA appraisal, 9 studies (Puranik et al., 2021; Rosenberg et al., 2021; Bruxvoort et al, 2021; Tang et al, 2021; Barlow R., 2021; Seppala E., 2021; Nasreen et al., 2021; Tenforde et al 2021 ; and McKeigue et al., 2021) had serious RoB based on COVID-NMA appraisal, 1 study

(Nasreen et al., 2021) has high RoB based on LCPG appraisal, while 5 studies (El Sahly et al., 2021; ICATT study; Andrews et al., 2021; VISION Network; and Self et al., 2021) included in the reviews were not appraised by the LCPG or COVID-NMA since they were detected from other sources of data (i.e.. the IVAC review or data from the US CDC presentation) which do not perform appraisal. The most common source of bias was the lack of control for confounding variables. Results of the risk of bias appraisals of each study are summarized in Appendix **5**.

Results

Based on real world effectiveness studies over time, *Moderna* remains effective for 1 to 7.7 months after the second dose for the following outcomes in the general population.

- **VE against any SARS-CoV-2 infection**: Overall, there were 6 studies (Puranik et al., 2021; Rosenberg et al., 2021; Bruxvoort et al, 2021; Tang et al, 2021; Barlow R., 2021; and Seppala E., 2021) from the relevant reviews which evaluated this outcome caused by the Alpha and Delta variant. All studies reported passing VEs across a range of follow up periods.
  - ***Against the Alpha variant:*** Three studies were found - 2 studies (Puranik et al., 2021 and Rosenberg et al., 2021) were found that reported VE specifically against the Alpha variant while the other study by Bruxvoort et al, 2021 reported an overall VE during the time when Alpha was one of the dominant variants circulating in the study setting (other VOC being Delta). Of the studies, the study by Bruxvoort et al, 2021 reported a VE that passed the HTAC threshold for this outcome (i.e., at least 60% VE) at the longest follow up period (i.e. 6.1 months). Thus, it can be inferred that *Moderna* is effective against symptomatic COVID-19 caused by the Alpha variant for at least **6.1** months.
  - ***Against the Delta variant:*** Five studies (Puranik et al., 2021; Rosenberg et al., 2021; Tang et al, 2021; Barlow R., 2021; and Seppala E., 2021) were found that reported VE specifically against the Delta variant. Of the studies, Seppala E., 2021 reported a VE that passed the HTAC threshold for this outcome (i.e., at least 60% VE) with the longest followup period (i.e. 7.7 months). Thus, it can be inferred that *Moderna* is effective against symptomatic COVID-19 caused by the Delta variant for at least **7.7** months
- **VE against symptomatic COVID-19**: Overall, there were 6 studies (El Sahly et al., 2021; ICATT study; Nasreen et al., 2021; Bruxvoort et al, 2021; Andrews et al., 2021; and Tang et al, 2021) from the relevant reviews which evaluated this outcome caused by the original, Alpha, and Delta variant. All studies reported passing VEs across a range of follow up periods.
  - ***Against the original strain:*** Only one study reported VE specifically against the original variant. The study by El Sahly et al reported the longest follow up period (i.e. 5.3 months) with a VE that passed the HTAC threshold for this outcome (i.e., at least 60% VE). Thus, it can be inferred that *Moderna* is effective against symptomatic COVID-19 caused by the original variant for at least **5.3** months.
  - ***Against the Alpha variant:*** Three studies were found - 2 studies (ICATT study and Nasreen et al., 2021) reported VE specifically against the Alpha variant while the other study by Bruxvoort et al, 2021 reported an overall VE during the time when Alpha was one of the dominant variants circulating in the study setting (other VOC being Delta). Of the studies, the study by Nasreen et al. (2021) reported the longest follow up period (i.e. 6.1 months) with a VE that passed the HTAC threshold for this outcome at the longest follow up period (i.e., at least 60% VE). Thus, it can be inferred that *Moderna* is effective against symptomatic COVID-19 caused by the Alpha variant for at least **6.1** months.
  - ***Against the Delta variant:***, Three studies (ICATT study; Andrews et al., 2021; and Tang et al, 2021) were found that reported VE specifically against the Delta variant. Of the studies, Tang et al. reported a VE that passed the HTAC threshold for this outcome (i.e., at least 60% VE) with the longest follow up period (i.e. 6 months). Thus, it can be inferred that *Moderna* is effective against symptomatic COVID-19 caused by the Delta variant for at least **6** months
- **VE against hospitalization due to COVID-19**: Overall there were 9 studies (Nasreen et al., 2021; Bruxvoort et al, 2021; Tenforde et al 2021; Puranik et al, 2021; Bajema et al., 2021; Self et al., 2021; VISION Network; Grannis et al., 2021; and Andrews et al., 2021) from the relevant reviews which evaluated this outcome caused by the Alpha and Delta variant.
  - ***Against the Alpha variant***: Seven studies were found - 2 studies (Nasreen et al., 2021 and VISION Network) reported VE specifically against the Alpha variant while the other 5 studies (Bruxvoort et al, 2021; Tenforde et al 2021; Puranik et al, 2021; Bajema et al., 2021; Self et al., 2021) reported an overall VE during the time when Alpha was one of the dominant variants circulating in the study setting (other VOC being Delta). Of the studies, Nasreen, et al. reported a VE that passed the HTAC threshold for this outcome (i.e., at least 80% VE) at the longest follow up period (i.e. 6.1 months). Thus, it can be inferred that *Moderna* is effective against hospitalization due to COVID-19 caused by the Alpha variant for at least **6.1** months. However, one real world study from the VISION Network surveillance data reported a VE that did not pass the HTAC threshold (i.e., at least 80% VE) at the longest time point of measurement of study which is at >5 months.
  - ***Against the Delta Variant***: Three studies (VISION Network; Grannis et al.; and Andrews et al.) reported VE specifically against the Delta variant. Of the studies, the VISION Network reported a VE that passed the HTAC threshold for this outcome (i.e., at least 80% VE) surveillance data with the longest follow up period (i.e. <5 months). However, the same study reported a VE that failed the HTAC threshold at its longest follow up, which is at >5 months. Thus, it can be inferred that *Moderna* is effective against hospitalization due to COVID-19 caused by the Delta variant at 5 months.
- **VE against severe COVID-19**: Overall there were 3 studies (El Sahly et al., 2021; McKeigue et al., 2021; and Tang et al, 2021) from the relevant reviews which evaluated this outcome caused by the Alpha and Delta variant. All studies reported passing VEs across a range of follow up periods.
  - ***Against the original strain***: Only one study (El Sahly et al., 2021) reported VE specifically against the original COVID-19 variant. The study by El Sahly et al. (2021) reported that *Moderna* still passed the HTAC VE threshold against severe COVID-19 (i.e. 80% VE) caused by the original variant with a follow up period of 5.3 months. Thus, it can be inferred that *Moderna* is effective against severe COVID-19 caused by the original variant for at least 5.3 months.
  - ***Against the Delta variant***: Two studies (McKeigue et al., 2021 and Tang et al, 2021) reported VE specifically against the Delta variant. Of the studies, the study by Tang et al. reported a VE that passed the HTAC threshold for this outcome (i.e., at least 80% VE) with the longest follow up period (i.e. 6 months). Thus, it can be inferred that *Moderna* is effective against severe COVID-19 caused by the Delta variant for at least 6 months.
- **VE against COVID-19 death**: Overall there were two 2 studies (El Sahly et al., 2021 and Bruxvoort et al, 2021) from the relevant reviews which evaluated this outcome caused by the Alpha and Delta variant. All studies reported passing VEs across a range of follow up periods.
  - ***Against the original strain***: Only one study (El Sahly et al., 2021) reported VE specifically against the original COVID-19 variant. The study by El Sahly et al. (2021) reported that *Moderna* passed the HTAC VE

threshold against death due to COVID-19 (i.e. 80% VE) caused by the original variant with a follow up period of 5.3 months. Thus, it can be inferred that *Moderna* is effective against death due to COVID-19 caused by the original variant for at least 5.3 months.

- ***Against the Delta variant***: Only one study by Bruxvoort et al, 2021 reported an overall VE during the time when Delta was one of the dominant variants circulating in the study setting (other VOC being Alpha). Bruxvoort et al, 2021 reported a VE that passed the HTAC threshold for this outcome (i.e., at least 80% VE) at a follow up period of 5 months. Thus, it can be inferred that *Moderna* is effective against death due to COVID-19 caused by the Delta variant for at least 5 months.

HTAC Judgment: *Moderna,* for the general population, passed the HTAC vaccine effectiveness threshold of 60% against any SARS-CoV-2 infection and symptomatic COVID-19; and the 80% threshold against hospitalization due to COVID-19. Current available studies reviewed have shown that protection against these outcomes has remained sufficient over time.

Moderna, for the general population, passed the HTAC vaccine effectiveness threshold of 80% against severe COVID-19 and death due to COVID-19. Current available studies reviewed have shown that protection against these outcomes has remained sufficient over time.

AstraZeneca

Quality of studies

Overall, there were 10 studies included in the reviews that reported vaccine effectiveness over time of *AstraZeneca* in the general population. RoB appraisals were extracted from the reviews of the LCPG group and COVID-NMA. RoB ratings ranged from 'low RoB' to 'serious RoB'. One study (Lopez-Bernal et al., 2021) had low RoB based on LCPG appraisal, two studies (Pouwels et al., 2021 and Stowe et al., 2021) had moderate RoB based on COVID-NMA appraisal, 3 studies (Thiruvengadam et al., 2021; Sheikh et al., 2021; and McKeigue et al., 2021) had serious RoB based on COVID-NMA appraisal, while 4 studies (Andrews et al., 2021; Whitaker et al., 2021; Cerqueria-Silva et al., 2021; and Eyre et al., 2021) included in the reviews were not appraised by the LCPG or COVID-NMA since they were detected from other sources of data (i.e., the IVAC review or data from the US CDC presentation) which do not perform appraisal. The most common source of bias was the lack of control for confounding variables. Results of the RoB appraisals of each study are summarized in Appendix 5.

Results

Based on real world effectiveness studies over time, *AstraZeneca* remains effective for 2 to 6.4 months after the second dose for the following outcomes in the general population:

- **VE against any SARS-CoV-2 infection:** Overall, there were four studies (Eyre et al., 2021; Sheikh et al., 2021; Pouwels et al., 2021; and Thiruvengadam et al., 2021) from the relevant reviews which evaluated this outcome caused by the Alpha and Delta variant.
  - ***Against the Alpha variant*:** Three studies (Eyre et al., 2021; Sheikh et al., 2021; and Pouwels et al., 2021) were found that reported VE specifically against the Alpha variant. Of these, Pouwels et al. (2021) had the longest follow-up period (i.e., 6.4 months) with a VE that passed the HTAC threshold for this outcome (i.e., at least 60% VE). Thus, it can be inferred that *AstraZeneca* is effective against any Alpha SARS-CoV-2 infection for at least **6.4** months.
  - ***Against the Delta variant*:** Four studies (Eyre et al., 2021; Sheikh et al., 2021; Pouwels et al., 2021; and Thiruvengadam et al., 2021) were found that reported VE specifically against the Delta variant. Of these, Pouwels et al. (2021) reported the longest follow-up period (i.e., 6.4 months) with a VE that passed the HTAC threshold for any SARS-CoV-2 infection. Thus, it can be inferred that *AstraZeneca* is effective against any Delta SARS-CoV-2 infection for at least **6.4** months.
- **VE against symptomatic COVID-19**: Overall, there were five studies (Andrews et al., 2021; Whitaker et al., 2021; Cerqueria-Silva et al., 2021; Pouwels et al., 2021; and Lopez-Bernal et al., 2021) from the relevant reviews which evaluated this outcome caused by the Alpha, Delta, and Gamma variant.
  - ***Against the Alpha variant***: Four studies (Andrews et al., 2021; Whitaker et al., 2021; Pouwels et al., 2021; and Lopez-Bernal et al., 2021) were found that reported VE specifically against the Alpha variant. Of these, Lopez-Bernal et al., (2021) reported the longest follow-up period (i.e., 4.25 months) that passed the HTAC threshold for symptomatic COVID-19 (i.e., at least 60% VE). Thus, it can be inferred that *AstraZeneca* is effective against symptomatic COVID-19 caused by the Alpha variant for at least **4.25** months.
  - ***Against the Delta variant*:** Three studies (Andrews et al., 2021; Pouwels et al., 2021; and Lopez-Bernal et al., 2021) were found that reported VE against the Delta variant. Of the included studies, one study (Andrews et al., 2021) reported a VE that did not pass the HTAC threshold (i.e., at least 60% VE) starting 2.5 to 3.5 months into the study. Meanwhile, Lopez-Bernal et al. (2021) reported the longest follow-up period (i.e., 4.25 months) that passed the HTAC threshold for this outcome (i.e., at least 60% VE). Thus, it can be inferred that *AstraZeneca* is effective against symptomatic COVID-19 caused by the Delta variant for at least **4.25** months.
  - ***Against the Gamma variant:*** One study (Cerqueria-Silva et al., 2021) reported a VE that passed HTAC threshold for this outcome (i.e., at least 60% VE) at 1 to 2 months after the second dose. Thus, it can be inferred that *AstraZeneca* is effective against symptomatic COVID-19 caused by the Gamma variant for at least 2 months.
- **VE against severe COVID-19:** There was only one study (McKeigue et al., 2021) from the relevant reviews which evaluated this outcome caused by the Delta variant. None of the studies reported this outcome against the Alpha and Gamma variant.
  - ***Against the Delta variant***: McKeigue et al. (2021) reported a VE that passed the HTAC threshold for this outcome (i.e., at least 80% VE) at 4 months after the second dose. Thus, it can be inferred that *AstraZeneca* is effective against severe COVID-19 caused by the Delta variant for at least **4** months.

- **VE against hospitalization due to COVID-19**: Overall, there were four studies (Andrews et al., 2021; Stowe et al., 2021; Thiruvengadam et al., 2021; and Cerqueria-Silva et al., 2021) from the relevant reviews which evaluated this outcome caused by the Alpha, Delta, and Gamma variant.
  - ***Against the Alpha variant*:** Two studies (Andrews et al., 2021 and Stowe et al., 2021) were found that reported VE against the Alpha variant. Andrews et al. (2021) reported the longest follow-up period (i.e., ≥ 2.5 months) with a VE that passed the HTAC threshold for this outcome (i.e., at least 80% VE). Thus, it was noted that *AstraZeneca* is effective against hospitalization due to COVID-19 caused by the Alpha variant for at least **2.5** months. However, among the population aged 40 to 64 years, the same study reported a VE that did not pass the HTAC threshold (i.e., at least 80% VE) at a longer time point of measurement (i.e., 0.5 to 2.25 months).
  - ***Against the Delta variant*:** Three studies (Andrews et al., 2021; Stowe et al., 2021; and Thiruvengadam et al., 2021) were found that reported VE against the Delta variant. One study (Andrews et al., 2021) reported a VE that passed the HTAC threshold (i.e., at least 80% VE) at 4.4 months. Thus, it was noted that *AstraZeneca* is effective against hospitalization due to COVID-19 caused by the Delta variant for at least **4.4** months. However, the same study reported a VE that failed the HTAC threshold (i.e., at least 80% VE) at 5 months.
  - ***Against the Gamma variant*:** One study (Cerqueria-Silva et al., 2021) reported a VE that passed the HTAC threshold for this outcome (i.e., at least 80% VE) at 1 to 2 months after the second dose. Thus, it can be inferred that *AstraZeneca* is effective against hospitalization due to COVID-19 caused by the Gamma variant for at least **2** months.
- **VE against death due to COVID-19:** Overall, there were two studies (Andrews et al., 2021 and Cerqueria-Silva et al., 2021) from the relevant reviews which evaluated this outcome caused by the Delta and Gamma variant. None of the studies reported this outcome against the Alpha variant.
  - ***Against the Delta variant*:** One study (Andrews et al., 2021) reported a VE that passed the HTAC threshold (i.e., at least 80% VE) at 4.4 months. Thus, it can be inferred that *AstraZeneca* is effective against death due to COVID-19 caused by the Delta variant for at least **4.4** months.However, the same study reported a VE that failed the HTAC threshold (i.e., at least 80% VE) at 5 months.
  - ***Against the Gamma variant*:** One study (Cerqueria-Silva et al., 2021) reported a VE that passed the HTAC threshold for this outcome (i.e., at least 80% VE) at 1 to 2 months after the second dose. Thus, it can be inferred that *AstraZeneca* is effective against death due to COVID-19 caused by the Gamma variant for at least **2** months.

HTAC Judgment: *AstraZeneca,* for the general population, passed the HTAC vaccine effectiveness threshold of 60% against any SARS-CoV-2 infection and symptomatic COVID-19; and the 80% threshold against hospitalization due to COVID-19 and death due to COVID-19. However, other available studies reviewed have shown a decrease in vaccine effectiveness against these outcomes over time.

*AstraZeneca, for the general population, pass*ed the HTAC vaccine effectiveness threshold of 80% against severe COVID-19. Current available studies reviewed have shown that protection against these outcomes has remained sufficient over time.

Janssen

Quality of the studies

Overall, there were 8 studies included in the reviews that reported vaccine efficacy or effectiveness over time of *Janssen* in the general population. RoB appraisals were extracted from the reviews of the LCPG group and COVID-NMA. RoB ratings ranged from 'moderate RoB' to ' serious RoB'. Two studies (Thompson et al., 2021 and Grannis et al., 2021) has moderate RoB based on COVID-NMA appraisal, 2 studies (Barlow et al., 2021 and Corchado-Garcia et al., 2021) had serious RoB based on COVID-NMA appraisal, 1 study (Polinski et al., 2021**)** has pending appraisal from COVID-NMA, 2 studies (ICATT study, Self et al., 2021, and the) included in the reviews were not appraised by the LCPG or COVID-NMA since they were detected from other sources of data (i.e., the IVAC review or data from the US CDC) which do not perform appraisal, while 1 study from the US FDA report is unpublished (VRBPAC presentation) and not available for appraisal. The most common source of bias was the lack of control for confounding variables. Results of the risk of bias appraisals of each study are summarized in Appendix 5.

Results

Based on real world effectiveness studies over time, *Janssen* remains effective for at least 5 months after the second dose for the following outcomes in the general population.

- **VE against any SARS-CoV-2 infection:** Overall, there were 2 studies (Corchado-Garcia et al., 2021 and Barlow et al., 2021) that reported VE for this outcome caused by the original strain, Alpha and Delta variant.
  - ***Against the Alpha variant or Original strain:*** Only one study (Corchado-Garcia et al., 2021) reported VE for this outcome specifically against the Alpha variant. Corchado-Garcia et al. (2021) reported a VE that passed the HTAC threshold for any SARS-CoV-2 infection (i.e. at least 60%) but the longest follow up period was not indicated in the study. Therefore, the duration of protection of *Janssen* against any Alpha SARS-CoV-2 infection in the general population cannot be determined.
  - ***Against the Delta Variant:*** Only one study (Barlow et al., 2021) reported VE for this outcome specifically against the Delta variant. The study by Barlow et al., 2021 measured a VE that did not pass the HTAC threshold for this outcome (i.e. at least 60%) at one month after a single dose of *Janssen.* Therefore, the duration of protection of *Janssen* against any Delta SARS-CoV-2 infection in the general population cannot be determined.
- **VE against symptomatic COVID-19:** Overall, there were 3 studies (COV3001; Polinski et al., 2020 and ICATT study) from the relevant reviews which evaluated this outcome against the Alpha and Delta variants.
  - ***Against the original strain:*** Only one study (COV3001) reported a VE specifically against the original variant. COV3001 reported a VE that passed the HTAC VE threshold against symptomatic COVID-19 (i.e. at least 60%) at its median follow up period (i.e., 4 months). Thus, it can be inferred that *Janssen* is effective against symptomatic COVID-19 caused by the original variant for at least 4 months.
  - ***Against the Alpha variant:*** Three studies (COV3001, Polinski et al., 2020 and ICATT study) reported VEs against the Alpha variant. COV3001 reported VE for this outcome specifically against the Alpha variant

while Polinski et al., 2020 and ICATT study reported overall VEs for this outcome when Alpha variant was the dominant variant circulating in the study setting (other VOC being Delta). All studies reported VEs that passed the HTAC threshold for symptomatic COVID-19 (i.e., at least 60% VE). Of the studies, Polinski et al. (2021) measured a passing VE against symptomatic COVID-19 caused by the Alpha variant with the longest follow up of approximately 5 months after vaccination with a single dose of *Janssen*. Thus, it can be inferred that *Janssen* is effective against symptomatic COVID-19 caused by the Alpha variant for at least 5 months.

- ***Against the Delta Variant:*** Three studies (COV3001; Polinski et al., 2020 and ICATT study) reported VEs for this outcome specifically against the Delta variant. Of the studies, the study by Polinski et al. reported a VE that passed the HTAC threshold for symptomatic COVID-19 (i.e., at least 60% VE) with the longest follow up of approximately 5 months after vaccination with a single dose of *Janssen*. Meanwhile, of the three studies that reported VE against the Delta variant, 2 studies (COV3001 and ICATT study) reported VEs that did not pass the HTAC threshold (i.e., at least 60% VE) for this outcome during the longest or median time point measurement of the respective studies (COV3001: 4 months; ICATT study: 1-2 months). Therefore, the duration of protection of *Janssen* against the symptomatic COVID-19 caused by the Delta variant cannot be determined.
- ***Against the Beta Variant:*** Only one study (COV3001) reported a VE specifically against the Beta variant. COV3001 reported a VE that did not pass the HTAC VE threshold against symptomatic COVID-19 (i.e. at least 60%) at its median follow up period (i.e., 4 months). Therefore, the duration of protection of *Janssen* against symptomatic COVID-19 caused by the Beta variant cannot be determined
- ***Against the Gamma Variant:*** Only one study (COV3001) reported a VE specifically against the Gamma variant. COV3001 reported a VE that did pass the HTAC VE threshold against symptomatic COVID-19 (i.e. at least 60%) at its median follow up period (i.e., 4 months). Therefore, the duration of protection of *Janssen* against symptomatic COVID-19 caused by the Gamma variant cannot be determined

- **VE against severe COVID-19:** Only one study (COV3001) reported VE for this outcome. COV3001 is the Phase III RCT for the Janssen primary series with a median follow-up period of up to 4 months.
  - ***Against the original strain:*** COV3001 reported a VE that did not pass the HTAC VE threshold against severe COVID-19 (i.e., at least 80%) at its median follow-up period (i.e., 4 months). Thus, the duration of protection of *Janssen* against severe COVID-19 caused by the original strain cannot be determined.
- **VE against hospitalization due to COVID-19:** Overall, there were 5 studies (Polinski et al., Thompson et al., Self et al., and Grannis et al., and COV3001) that reported VE for this outcome caused by the original strain, Alpha and Delta variant.
  - ***Against the original strain:*** Only one study (COV3001) reported VE against hospitalization (reported in the VRBPAC document as COVID-19 requiring medical intervention) when the original was the dominant variant circulating in the study setting (other VOCs being Alpha, Delta, Beta and Gamma). COV3001 reported a VE that did not pass the HTAC VE threshold against hospitalization due to COVID-19 (i.e., at least 80%) at its median follow-up period (i.e., 4 months). Therefore, the duration of protection of *Janssen* against hospitalization due to COVID-19 caused by the original variant cannot be determined.
  - ***Against the Alpha variant***: Only one study (Thompson et al.) reported VE specifically against the Alpha variant while 2 other studies (Polinski et al. and Self et al.) reported VEs at a time when the Alpha variant was the dominant variant circulating in the study setting (other VOC being Delta). The study by Polinski et al. reported a VE against COVID-19 hospitalization caused by the Alpha variant that passed the HTAC threshold (i.e. at least 80% VE) at its longest follow up of 5 months after vaccination with a single dose of *Janssen*. Thus, it can be inferred that *Janssen* is effective against COVID-19 hospitalization caused by the Alpha variant for at least 5 months. Meanwhile, 2 studies (Thompson et al. and Self et al.) reported VE against hospitalization due to COVID-19 caused by the Alpha variant that did not pass the HTAC threshold for this outcome (i.e. at least 80% VE) during the longest time point of measurement of the respective studies (i.e., Thompson et al.: 3 months; Self et al.: ≥1 month)
  - ***Against the Delta variant:*** Only one study (Grannis et al.) reported VE specifically against the Delta variant while the other study (Polinski et al.) reported its VE at a time when the Delta variant was the dominant variant circulating in the study setting (other VOC being Alpha). The study by Polinski et al. measured a VE against hospitalization due to COVID-19 caused by the Delta variant passed the HTAC threshold (i.e. at least 80%) at its longest follow-up of 5 months after vaccination with a single dose of *Janssen*. Thus, it can be inferred that *Janssen* is effective against hospitalization due to COVID-19 caused by the Delta variant for at least 5 months. Meanwhile, the study by Grannis et al., reported a VE that did not pass the HTAC threshold for this outcome (i.e. 80% VE) during the longest time point of measurement of the study (i.e., 3.1 months).
- **VE against death due to COVID-19:** Only one study (COV3001) reported VE for this outcome when the original was the dominant variant circulating in the study setting (other VOCs being Alpha, Delta, Beta and Gamma). COV3001 is the Phase III RCT for the Janssen primary series with a median follow-up period of up to 4 months.
  - ***Against the original strain:*** COV3001 reported a VE that passed the HTAC VE threshold against death due to COVID-19 (i.e., at least 80%) at its median follow-up period (i.e., 4 months). Thus, it can be inferred that *Janssen* is effective against death due to COVID-19 for at least 4 months.

HTAC Judgment: *Janssen*, for the general population, passed the HTAC vaccine effectiveness threshold of 60% against symptomatic COVID-19 caused by the Alpha and original strain; and the 80% threshold for severe COVID-19 and death due to COVID-19. However, other studies have shown conflicting evidence and reported VEs that did not pass the HTAC threshold for the outcomes any SARS-CoV-2 infection, symptomatic COVID-19 caused by other VOCs including Delta variant, and hospitalization due to COVID-19 at follow-up periods that ranged from 1 month to 5 months after vaccination.

CoronaVac

As there is limited evidence on the effectiveness over time of CoronaVac, studies on immunogenicity over time were also included.

Vaccine effectiveness

Quality of the studies

Overall there were 2 studies (Cerqueria-Silva et al., 2021 and the surveillance data from the Chile MOH) included in the reviews that reported vaccine effectiveness over time of *CoronaVac* for the general population. RoB

appraisal of Cerqueria-Silva et al. was extracted from the review of LCPG group since the COVID-NMA did not include the two reports in their review while the data from the Chile MOH was not included in both reviews. Based on the RoB assessment of the LCPG group, Cerqueria-Silva et al. had a very serious RoB due to its observational study design. However, it was noted that the study of Cerqueria-Silva et al. adjusted for the following confounders: age, sex, region of residence, socioeconomic status, month of first dose.

Results

Based on real world effectiveness studies over time, *CoronaVac* remains effective for 4 to 6 months after the second dose for the following outcomes in the general population:

- **VE against symptomatic COVID-19:** There were two studies (Cerqueria-Silva et al., 2021 and the vaccine effectiveness surveillance data from the Chile MOH for the months of April, May, June, and August 2021) from the relevant reviews which evaluated this outcome caused by the Gamma variant. There are currently no available studies on the effectiveness of *CoronaVac* against symptomatic COVID-19 caused by the Alpha or Delta variant.
  - ***Against the Gamma variant:*** Of the two studies, only the surveillance data from the Chile MOH reported VE for this outcome over time. Based on their data, *CoronaVac* passed the HTAC VE threshold for this outcome (i.e., at least 60% VE) at the 4th month of the follow-up period but did not pass at the longest time point of measurement (i.e., at 6 months). Thus, it can be inferred that *CoronaVac* is effective against symptomatic COVID-19 caused by the Gamma variant for **4** months. Meanwhile, Cerqueria-Silva et al., 2021 reported a VE for this outcome that did not pass the HTAC VE threshold for this outcome (i.e. at least 60% VE) at one time point of measurement with a follow-up period of 3 to 4 months after the second dose.
- **VE against hospitalization due to COVID-19:** There were two studies (Cerqueria-Silva et al., 2021 and the vaccine effectiveness surveillance data from the Chile MOH for the months of April, May, June, and August 2021) from the relevant reviews which evaluated this outcome caused by the Gamma variant. There are currently no available studies on the effectiveness of *CoronaVac* against hospitalization due to COVID-19 caused by the Alpha or Delta variant.
  - ***Against the Gamma variant:*** Of the two studies, only the surveillance data from the Chile MOH reported VE for this outcome over time. Based on their data, *CoronaVac* passed the HTAC VE threshold for this outcome (i.e., at least 80% VE) at the longest time point of measurement (i.e., at 6 months). Thus, it can be inferred that *CoronaVac* is effective against hospitalization due to COVID-19 caused by the Gamma variant for at least **6** months. Meanwhile, Cerqueria-Silva et al., 2021 reported a VE that did not pass the HTAC VE threshold for this outcome (i.e. at least 80% VE) at one time point of measurement with a follow-up period of 3 to 4 months after the second dose.
- **VE against death due to COVID-19:** There were two studies (Cerqueria-Silva et al., 2021 and the vaccine effectiveness surveillance data from the Chile MOH for the months of April, May, June, and August 2021) from the relevant reviews which evaluated this outcome caused by the Gamma variant. There are currently no available studies on the effectiveness of *CoronaVac* against death due to COVID-19 caused by the Alpha or Delta variant.
  - ***Against the Gamma variant:*** Of the two studies, only the surveillance data from the Chile MOH reported VE for this outcome over time. Based on their data, *CoronaVac* passed the HTAC VE threshold for this outcome (i.e., at least 80%) at the longest time point of measurement (i.e., at 6 months). Thus, it can be inferred that *CoronaVac* is effective against death due to COVID-19 caused by the Gamma variant for at least **6** months. Meanwhile, Cerqueria-Silva et al., 2021 reported a VE that did not pass the HTAC VE threshold for this outcome (i.e. at least 80% VE) at one time point of measurement with a follow-up period of 3 to 4 months after the second dose.

Immunogenicity

Only real world studies reporting the VE of *CoronaVac* against clinical outcomes caused by the Gamma variant were found. No real world studies were detected for the other VOCs (i.e. Alpha and Delta variants). Due to limited evidence on the real world effectiveness over time of *CoronaVac*, an added search for immunogenicity studies over time was conducted to supplement data.

Quality of the studies

Risk of bias was not appraised by the LCPG group or COVID-NMA for studies that report immunogenicity outcomes.

Results

The search detected one Phase II RCT (Pan et al., 2021) that reported immune response of the *CoronaVac* primary series at 6 months after the second dose among the general population. The trial was conducted in two parts: the evaluation of the immune persistence of the *CoronaVac* primary series and the evaluation of the immunogenicity and safety of a booster dose of *CoronaVac.* Only the results on immune persistence will be discussed in this section while the booster dose will be discussed in the sections below as evidence for the appropriate research question. There were no real world studies that reported immunogenicity over time of *CoronaVac* among the general population. The study characteristics and key findings from the study are detailed below.

	Pan et al., 2021 **China, Phase II RCT** **[pre-print]**
Population	Adults aged 18-59 years old; N= 544
Intervention	Primary vaccination: two doses of either a 3ug or 6ug vaccine, 14 or 28 days apart.
Comparator	Placebo, 14 or 28 day interval
Outcomes	Geometric mean titers of neutralizing antibodies to live SARS CoV 2 Seropositivity or seroconversion Time points of measurement: Day 0, 28 days after dose 2 and 6 months after dose 2

At baseline, none of the participants had detectable neutralizing antibodies against live SARS-CoV-2. At 28 days after the two doses, GMT of neutralizing antibodies was 49.1 (95% CI: 40.1 to 60.2). However, after 6 months, neutralizing antibody titers declined to 6.7 (95% CI: 5.2 to 8.6) which was at a level that was below the seropositive cutoff (i.e. antibody titer of at least 8). As for seropositivity, at 28 days after dose 2, seropositivity was high at 100% (95% CI: 93.8 to 100.0) which meant that all participants in this cohort had a neutralizing antibody titers of at least 8. At 6 months after dose 2, seropositivity among this cohort declined to 95.92% (95% CI: 86.0 to 99.5).

HTAC Judgment: Based on a single study, *CoronaVac* passed the HTAC vaccine effectiveness threshold of 60% against symptomatic COVID-19; and the 80% threshold against hospitalization due to COVID-19 and death due to COVID-19. However, another study reviewed has shown that *CoronaVac* did not pass the HTAC vaccine effectiveness threshold for these outcomes.

RQ.2.2: What is the effectiveness over time of primary vaccination using COVID-19 vaccines against the original strain and variants of concern in special populations, specifically, healthcare workers and the elderly population in terms of symptomatic COVID-19, severe COVID-19, hospitalization and death due to COVID-19? How long does protection from primary vaccination last in these special populations?

***HTAC Specifications*:**
Preferred VE: ≥70% reduction in the risk of symptomatic infection with vaccination versus no vaccination
Minimum acceptable VE (point estimate) : at least 60% reduction of symptomatic COVID-19; **at least 80% reduction** of severe COVID-19, hospitalization due to COVID-19; **at least 80% reduction** of death due to COVID-19

Evidence considered
For the evidence on the effectiveness of *COVID-19 vaccines* over time against the original strain and variants of concern among special populations, reviews from the following organizations were synthesized: 1) the International Vaccine Access Center (IVAC) of the Johns Hopkins Bloomberg School of Public Health and World Health Organization as of 01 Oct 2021; 2) COVID-NMA as of 07 Oct 2021; 3) LCPG review on effectiveness of vaccines against the Delta as of 31 Aug 2021; 4) LCPG Review on Janssen as of 06 Sep 2021 and CoronaVac as of 16 Sep 2021 5) the US CDC Advisory Committee on Immunization Practices (ACIP) as of 23 Sept 2021.

Pfizer-BioNTech

Quality of studies
Overall, there were 16 studies included in the reviews that reported vaccine effectiveness over time of *Pfizer-BioNTech* for the special populations. RoB appraisals were extracted from the review of COVID-NMA. RoB ratings ranged from 'moderate RoB' to 'serious RoB'. Three studies (Fowlkes et al., 2021; Bajema et al., 2021; and Thompson et al., 2021) had moderate RoB, 6 studies (Goldberg et al., 2021; Rosenberg et al., 2021;

Tenforde et al., 2021; Nunes et al., 2021; Nanduri et al., 2021; and Tartof et al., 2021) had serious RoB, while 7 studies (Rovida et al., 2021; Iliaki et al., 2021; Keehner et al., 2021; Pilishvili et al., 2021; Andrews et al., 2021; VISION Network; and Chemaitelly et al., 2021) included in the reviews were not appraised by the NCPG or COVID-NMA since they were detected from other sources of data (i.e. IVAC review or data from the US CDC) which do not perform appraisal. The most common source of bias was the lack of control for confounding variables. Results of the risk of bias appraisals of each study are summarized in Appendix 5.

Results

FOR HEALTHCARE WORKERS (HCWs)

Based on real world effectiveness studies over time, *Pfizer-BioNTech* remains effective for 3 to 5 months after the second dose for the following outcomes in HCWs:

- **VE against any SARS-CoV-2 infection:** Only one study (Rovida et al., 2021) from the relevant reviews evaluated this outcome caused by the Alpha variant among HCWs. No study was detected against the Delta variant.
  - ***Against the Alpha variant***: The study by Rovida et al. (2021) reported that *Pfizer-BioNTech* still passed the HTAC VE threshold against any SARS-CoV-2 infection (i.e, at least 60% VE) caused by the Alpha variant at its 3 months follow-up. Thus, it can be inferred that *Pfizer-BioNTech* is effective against any Alpha SARS-CoV-2 infection for at least **3** months.
- **VE against symptomatic COVID-19**: Overall, there were 4 studies (Iliaki et al., 2021; Pilishvili et al., 2021; Keehner et al. 2021; and Fowlkes et al., 2021) from the relevant reviews which evaluated this outcome for mRNA vaccines (i.e., *Pfizer-BioNTech* or *Moderna*). All studies reported passing VEs across a range of follow-up periods.
  - ***Against the Alpha variant***: Two studies (Iliaki et al., 2021and Pilishvili et al., 2021) reported VE specifically against the Alpha variant. The study by Pilishvili et al. (2021) reported a VE against the Alpha variant symptomatic infection that passed the HTAC threshold for this outcome (i.e,. at least 60% VE) with the longest follow-up period (i.e., 3.2 months). Thus, it can be inferred that *Pfizer-BioNTech* is effective against symptomatic COVID-19 caused by the Alpha variant for at least **3.2** months among HCWs.
  - ***Against the Delta variant***: Two studies (Keehner et al. 2021; and Fowlkes et al., 2021) reported an overall VE during the time when Delta was one of the dominant variants circulating in the study setting (other VOC being Alpha) The study by Fowlkes et al., (2021) among HCWs reported a VE against symptomatic infection that passed the HTAC threshold for this outcome (i.e., at least 60% VE) with the longest follow-up period (i.e., 5 months). Thus, it can be inferred that the mRNA vaccines (i.e. *Pfizer-BioNTech* or *Moderna*) are effective against symptomatic COVID-19 caused by the Delta variant for at least **5** months among HCWs. However, it is important to note that this study did not report the VE specifically for the Delta variant but the VE over time when the Alpha followed by the Delta variants circulated in the US.

There were no studies included in the reviews that reported VE against COVID-19 hospitalization, severe COVID-19, or death due to COVID-19 for HCWs.

FOR ELDERLY POPULATION

Based on real world effectiveness studies over time, *Pfizer-BioNTech* remains effective for 3 to 5 months after the second dose for the following outcomes in the elderly population:

- **VE against any SARS-CoV-2 infection:** Overall, there were 4 studies (Tartof et al, 2021; Nanduri et al., 2021; Goldberg et al., 2021; and Cheimatelly et al., 2021) from the relevant reviews which evaluated this outcome caused by the Alpha and Delta variant among the elderly population.
  - ***Against the Alpha variant:*** Three studies (Tartof et al, 2021; Nanduri et al., 2021; and Cheimatelly et al., 2021) were found that reported the VE of *Pfizer-BioNTech* for this outcome during the period when the Alpha variant was the dominant strain, followed by the Delta variant. All studies reported a VE that did not pass the HTAC threshold for this outcome (i.e, at least 60% VE) at the longest time point of measurement of the respective studies (i.e., Tartof et al., 2021: ≥5 months; Nanduri et al., 2021: 4 to 5 months; Chemaitelly et al., 2021: ≥7 months). Of the 3 studies, Chemaitelly et al. (2021) had the longest follow-up period (i.e., 3 months after dose 2) with a VE that passed the HTAC threshold for this outcome (i.e., at least 60% VE). Thus, it can be inferred that *Pfizer-BioNTech* is effective against any Alpha SARS-CoV-2 infection for at least **3** months among the elderly population.
  - ***Against the Delta variant:*** Only one study (Goldberg et al. 2021) reported the VE specifically against the Delta variant. The study by Goldberg et al., (2021) reported that *Pfizer-BioNTech* still had a VE that passed the HTAC threshold (i.e., at least 60% VE) at 5 months. However, the same study noted that the VE of *Pfizer-BioNTech* failed the HTAC VE threshold at the longest time point of measurement in the study which is at 6 months. Thus, it can be inferred that *Pfizer-BioNTech* is effective against any Delta SARS-CoV-2 infection for 5 months among the elderly population.
- **VE against symptomatic COVID-19**: Only one study by Andrews et al., (2021) was detected that reported the VE over time against symptomatic COVID-19 for both the Alpha and Delta variants among the elderly population.
  - ***Against the Alpha variant:*** Vaccine effectiveness reported by Andrews et al., (2021) among the elderly against symptomatic COVID-19 caused the Alpha variant passed the HTAC threshold (i.e., at least 60% VE) during the longest follow-up period of this study (i.e., 0.5 to 2.25 months). Thus, it can be inferred that *Pfizer-BioNTech* is effective against symptomatic COVID-19 caused by the Alpha variant for at least **0.5** to **2.25** months among the elderly population.
  - ***Against the Delta variant:*** Andrews et al., (2021) reported a passing VE for the elderly population against symptomatic COVID-19 caused by the Delta variant at the time point of 3.75 to 4.75 months. However, the reported VE went below the threshold (i.e., at least 60% VE) at the longest follow-up period of the study (i.e., beyond 5 months). Thus, it can be inferred that *Pfizer-BioNTech* is effective against symptomatic COVID-19 caused by the Delta variant for **3.75** to **4.4** months among the elderly population.
- **VE against severe COVID-19:** Only one study (Goldberg et al., 2021) was found that reported VE over time against severe COVID-19 caused by the Delta variant among the elderly population. No study was detected against the Alpha variant.
  - ***Against the Delta variant:*** The study reported a VE that passed the HTAC threshold against severe COVID-19 (i.e., at least 80% VE) at its longest follow-up period (i.e, 6 months). Thus, it can be inferred that *Pfizer-BioNTech* is effective against severe COVID-19 caused by the Delta variant for **6** months among the elderly population.
- **VE against hospitalization due to COVID-19:** Overall, there were 9 studies (Bajema et al., 2021; Thompson et al., 2021; Rosenberg et al., 2021; VISION Network; Tenforde et al., 2021; Tartof et al, 2021; Andrews et al.,

2021; Nunes et al., 2021; and Cheimatelly et al., 2021) from the relevant reviews which evaluated this outcome caused by the Alpha and Delta variant for the elderly population. Among the nine studies found, 2 (Thompson et al., 2021 and Andrews et al., 2021) reported VE specifically against the Alpha variant while 6 (Bajema et al., 2021; VISION Network; Tenforde et al., 2021; Tartof et al, 2021; and Cheimatelly et al., 2021) reported overall VE at the time when the Alpha was one of the variants circulating in the setting, and 1 study (Rosenberg et al., 2021) reported VE specifically against the Delta variant.

- ***Against the Alpha variant:*** Thompson et al. (2021) had the longest follow-up period (i.e., 112 days or 3.7 months) with a VE that passed the HTAC threshold (i.e., at least 80% VE) for this outcome among the elderly population 50 years and above. Thus, it can be inferred that *Pfizer -BioNTech* is effective against hospitalization due to COVID-19 caused by the Alpha variant for **3.7** months among the elderly population. Meanwhile, of the 6 studies that reported the overall VE in the setting where Alpha was one of the dominant circulating variants (other VOCs included Delta and Beta), three studies (Bajema et al., 2021; the VISION Network; and Chemaitelly et al., 2021) reported VEs that did not pass the HTAC threshold for this outcome during the longest time point of measurement of the respective studies (i.e. Bajema et al., 2021: 2.7 months; VISION Network: not indicated; Chemaitelly et al., 2021: ≥7 months).
- ***Against the Delta variant:*** Two studies (Rosenberg et al., 2021 and Andrews et al., 2021) were found that reported VEs specifically against the Delta variant while another 6 studies reported overall VE at the time when Delta was one of the variants circulating in the setting, as discussed in the section above. Of the studies, Andrews et al., (2021) had the longest follow-up period (i.,e., beyond 20 weeks after dose 2) with a VE that passed the HTAC threshold for this outcome among the elderly 65 years and above (i.e., at least 80% VE). Thus, it can be inferred that *Pfizer -BioNTech* is effective against hospitalization due to COVID-19 caused by the Delta variant for **5** months among the elderly population.

- **VE against death due to COVID-19:** There were 2 (Andrews et al., 2021 and Nunes et al., 2021) studies that reported the VE over time of *Pfizer-BioNTech* against death due to COVID-19 among the elderly population.
  - ***Against the Alpha variant:*** One study (Nunes et al., 2021) reported overall VE at the time when the Alpha variant was the dominant circulating variant in the setting (other VOC being the Delta variant). Among the population 80 years and above, *Pfizer-BioNTech* passed the HTAC VE threshold for this outcome up to 97 days after the second dose (i.e., at least 80% VE) then failed at a follow-up period of 98 days and beyond. Thus, it can be inferred that *Pfizer-BioNtech* is effective against death due to COVID-19 caused by the Alpha variant for up to **3** months among the elderly population.
  - ***Against the Delta variant:*** One study (Andrews et al., 2021) reported a VE that passed the HTAC threshold against death due to COVID-19 caused by the Delta variant at its longest follow-up period (i.e, beyond 20 weeks). Thus, it can be inferred that *Pfizer-BioNtech* is effective against death due to COVID-19 caused by the Delta variant for **5** months.

HTAC Judgment: Generally, there is limited evidence on the VE over time of *Pfizer-BioNTech* among special subgroups of interest compared to the available evidence on VE over time among the general population.

For HCWs: Based on the available evidence so far, VE of *Pfizer-BioNTech* against symptomatic infection among healthcare workers has decreased over time but still remained above the HTAC threshold (i.e., at least 60% VE) at 5 months (Alpha/Delta). Meanwhile, there is decreased duration of protection of *Pfizer-BioNTech* against any SARS-CoV-2 infection and symptomatic COVID-19 compared to the general population. There were no studies included in the reviews that reported VE against COVID-19 hospitalization, severe COVID-19, or death due to COVID-19 for HCWs.

For the elderly population: VE of *Pfizer-BioNTech* against any SARS-CoV-2 infection and symptomatic COVID-19 decreased over time reaching below the HTAC threshold (i.e, at least 60% VE) at 5 to 7 months (Alpha/Delta). VE of *Pfizer-BioNTech* against severe COVID-19, COVID-19 hospitalization and death slightly decreased over time but still generally remained above the HTAC threshold (i.e, at least 80% VE) at 3 months (Alpha) to 6 months (Delta). Meanwhile, compared to the general population, there is decreased duration of protection of *Pfizer-BioNTech* against any SARS-CoV-2 infection, symptomatic COVID-19 and COVID-19 hospitalization. Duration of protection of *Pfizer-BioNTech* against severe COVID-19 and COVID-19 death for the elderly is comparable to the general population.

Moderna

Quality of studies

Overall, there were 11 studies included in the reviews that reported vaccine effectiveness over time of *Moderna* for the special populations. RoB appraisals were extracted from the review of COVID-NMA. RoB ratings ranged from 'moderate RoB' to 'serious RoB'. Three studies (Fowlkes et al., 2021; Bajema et al., 2021; and Thompson et al., 2021) had moderate RoB based on COVID-NMA appraisal, 4 studies (Rosenberg et al., 2021; Tenforde et al., 2021; Nunes et al., 2021; and Nanduri et al., 2021) had serious RoB based on COVID-NMA appraisal, while 4 studies (Iliaki et al., 2021; Keehner et al., 2021; Pilishvili et al., 2021; and VISION Network study) included in the reviews were not appraised by the NCPG or COVID-NMA since they were detected from other sources of data (i.e. IVAC review or data from the US CDC) which do not perform appraisal. The most common source of bias was the lack of control for confounding variables. Results of the risk of bias appraisals of each study are summarized in Appendix 5.

Results

FOR HEALTHCARE WORKERS (HCWs)

Based on real world effectiveness studies over time, *Moderna* remains effective for 2.5 to 5 months after the second dose for the following outcome in HCWs:

- **VE against symptomatic COVID-19**: Overall, there were 4 studies (Iliaki et al., 2021; Pilishvili et al., 2021; Keehner et al. 2021; and Fowlkes et al., 2021) from the relevant reviews which evaluated this outcome for mRNA vaccines (i.e., *Pfizer-BioNTech* or *Moderna*) among HCWs. All studies reported passing VEs across a range of follow-up periods.
  - ***Against the Alpha variant***: Two studies (Iliaki et al., 2021; Pilishvili et al., 2021) reported VE specifically against the Alpha variant. The study by Pilishvili et al. (2021) reported a VE against the Alpha variant symptomatic OVID-19 that passed the HTAC threshold for this outcome (i.e, at least 60% VE) with the longest follow-up period (i.e., 3.2 months). Thus, it can be inferred that mRNA vaccines (i.e. *Pfizer-BioNTech* or *Moderna*) is effective against symptomatic COVID-19 caused by the Alpha variant for at least 3.2 months among HCWs.

- ***Against the Delta variant***: Two studies (Keehner et al., 2021 and Fowlkes et al., 2021) reported an overall VE during the time when Delta was one of the dominant variants circulating in the study setting (other VOC being Alpha). The study by Fowlkes et al. (2021) among HCWs reported a VE against symptomatic infection that passed the HTAC threshold for this outcome (i.e, at least 60% VE) with the longest follow-up period (i.e., 5 months). Thus, it can be inferred that the mRNA vaccines (i.e. *Pfizer-BioNTech* or *Moderna*) are effective against symptomatic COVID-19 caused by the Delta variant for at least 5 months among HCWs. However, it is important to note that this study did not report the VE specifically for the Delta variant but the VE over time when the Alpha followed by the Delta variants circulated in the US.

There were no studies included in the reviews that reported VE against any SARS-CoV-2 infection, hospitalization due to COVID-19, severe COVID-19, or death due to COVID-19 for HCWs.

FOR ELDERLY POPULATION

Based on real world effectiveness studies over time, *Moderna* remains effective for 3 to 4 months after the second dose for the following outcomes in the elderly population:

- **VE against Any SARS-CoV-2 infection:** Only one study (Nanduri S., 2021) from the relevant reviews evaluated this outcome caused by the Delta variant among the elderly population. None of the studies reported this outcome against the Alpha variant for this population.
  - ***Against the Delta Variant***: The study by Nanduri S., 2021 reported a VE that failed the HTAC threshold (i.e. at least 60%) against any SARS-CoV-2 infection caused by the Delta variant at a single time point of measurement, with a follow-up period of 1.33 months. Thus, the duration of protection of *Moderna* against any Delta SARS-CoV-2 infection among the elderly population cannot be determined.
- **VE against hospitalization due to COVID-19**: Overall there were six 6 studies (Thompson et al., 2021; Bajema et al., 2021; VISION Network; Rosenberg et al., 2021; Nunes et al., 2021;and Tenforde et al., 2021) from the relevant reviews which evaluated this outcome caused by the Alpha and Delta variant.
  - ***Against the Alpha variant:*** Only one study (Thompson et al., 2021) reported VE specifically against the Alpha variant. Thompson et al. (2021) reported a VE against hospitalization due to COVID-19 caused by the Alpha variant that passed the HTAC threshold for this outcome (i.e, 80% VE) with the longest follow-up period (i.e., 3.7 months). Thus, it can be inferred that *Moderna* is effective against symptomatic COVID-19 caused by the Alpha variant for at least 3.7 months among the elderly population.
  - ***Against the Delta Variant***: Five studies were found - Only one study (Rosenberg et al., 2021) reported a VE specifically against the Delta variant while the other 4 studies (Bajema et al., 2021; VISION Network; Tenforde et al., 2021; Nunes et al., 2021) reported an overall VE during the time when Delta was one of the dominant variants circulating in the study setting (other VOC included was Alpha). Tenforde et al. (2021) reported a VE against hospitalization due to COVID-19 caused by the Alpha variant that passed the HTAC threshold for this outcome (i.e, at least 80% VE) with the longest follow-up period (i.e., 4 months).Thus, it can be inferred that *Moderna* is effective against symptomatic COVID-19 caused by the Delta variant for at least 4 months among the elderly population. However, one study (Bajema et al., 2021) reported a VE that did not pass the HTAC threshold for this outcome during the longest time point of measurement (i.e., 2.7 months).
- **VE Against COVID-19 death:** Only one study (Nunes et al., 2021) was found from the relevant reviews which evaluated this outcome caused by the Alpha and Delta variant.
  - ***Against the Alpha variant or Delta variant:*** The study by Nunes et al. (2021) reported a VE against death due to COVID-19 caused by the Alpha variant that passed the HTAC threshold for this outcome (i.e, at least 80% VE) at up to 3.2 months follow up. However, the same study reported a VE that failed the HTAC threshold (i.e., at least 80% VE) against COVID-19 deaths at >3.2 months days follow up. Thus, it can be inferred that *Moderna* is effective against death due to COVID-19 caused by the Alpha or Delta variant for up to 3.2 months.

There were no studies that reported VE against symptomatic COVID-19, or severe COVID-19 among the elderly population included in the reviews.

HTAC Judgment: Generally, there is limited evidence on the VE over time of *Moderna* among special subgroups of interest compared to the available evidence on VE over time among the general population.

For HCWs: Based on the available evidence so far, VE of *Moderna* against symptomatic infection among healthcare workers has decreased over time but still remained above the HTAC threshold (i.e., at least 60% VE) at 5 months (Alpha/Delta). Meanwhile, there is decreased duration of protection of *Moderna* against any SARS-CoV-2 infection and symptomatic COVID-19 compared to the general population. There were no studies included in the reviews that reported VE against hospitalization due to COVID-19, severe COVID-19, or death due to COVID-19 for HCWs.

For the elderly population: VE of *Moderna* against hospitalization due to COVID-19 decreased over time reaching below the HTAC threshold (i.e, at least 60% VE) at 3.7 months (Alpha) to 4 months (Delta). VE against COVID-19 death decreased over time reaching below the HTAC threshold (i.e. at least 80%) at 3.2 months. Meanwhile, compared to the general population, there is decreased duration of protection of *Moderna* against hospitalization due to COVID-19 and COVID-19 death for the elderly. There were no studies that reported VE against symptomatic COVID-19, or severe COVID-19 among the elderly population included in the reviews.

AstraZeneca

Quality of studies

Overall, there were 5 studies included in the reviews that reported vaccine effectiveness over time of *AstraZeneca* for the special populations. RoB appraisals were extracted from the reviews of the LCPG group and COVID-NMA. RoB ratings ranged from 'high RoB' to 'serious RoB'. One study (Alencar et al., 2021) had high RoB based on LCPG appraisal, one study (Pramod et al., 2021) had serious RoB based on COVID-NMA appraisal, while 3 studies (Andrews et al., 2021; Hitchings et al., 2021; and Amirthalingam et al., 2021) included in the reviews were not appraised by the LCPG or COVID-NMA since they were detected from other sources of data (i.e., the IVAC review or data from the US CDC presentation) which do not perform appraisal. The most common source of bias was the lack of control for confounding variables. Results of the RoB appraisals of each study are summarized in Appendix 5.

Results

FOR HEALTHCARE WORKERS (HCWs)

Based on real world effectiveness studies over time, duration of protection of *AstraZeneca* cannot be inferred due to the limited on the VE over time in HCWs:

- **VE against any SARS-CoV-2 infection:** Only one study (Pramod et al., 2021) from relevant reviews evaluated this outcome caused by the Delta variant among HCWs. None of the studies reported this outcome against the Alpha and Gamma variant.
  - ***Against the Delta variant*:** Pramod et al., (2021) reported a VE that failed the HTAC threshold (i.e., at least 60%) for this outcome. The study did not indicate the follow-up period of the VE in the study. Therefore, the duration of protection of *AstraZeneca* against any SARS-CoV-2 Delta infection among HCWs cannot be determined.
- **VE against symptomatic COVID-19:** Only one study (Pramod et al., 2021) from relevant reviews evaluated this outcome caused by the Delta variant among HCWs. None of the studies reported this outcome against the Alpha and Gamma variant.
  - ***Against the Delta variant***: Pramod et al., (2021) reported a VE that passed the HTAC threshold (i.e., at least 60%) for this outcome. However, the study did not indicate the follow-up period of the VE in the study. Therefore, the duration of protection of *AstraZeneca* against any symptomatic COVID-19 caused by the Delta variant among HCWs cannot be determined.
- **VE against hospitalization due to COVID-19:** Only one study (Pramod et al., 2021) from relevant reviews evaluated this outcome caused by the Delta variant among HCWs. None of the studies reported this outcome against the Alpha and Gamma variant.
  - ***Against the Delta variant***: Pramod et al., (2021) reported a VE that passed the HTAC threshold (i.e., at least 80%) for this outcome. However, the study did not indicate the follow-up period of the VE in the study. Therefore, the duration of protection of *AstraZeneca* against any hospitalization due to COVID-19 caused by the Delta variant among HCWs cannot be determined.

There were no studies that reported VE against severe COVID-19 and death due to COVID-19 among the healthcare workers that were included in this review.

FOR ELDERLY POPULATION

Based on real world effectiveness studies over time, *AstraZeneca* remains effective for 1 week to 5 months after the second dose for the following outcomes in the elderly population:

- **VE against any SARS-CoV-2 infection:** Only one study (Amirthalingam et al., 2021) from relevant reviews evaluated this outcome caused by the Alpha variant among the elderly population. None of the studies reported this outcome against the Delta and Gamma variant.
  - ***Against the Alpha variant*:** Amirthalingam et al. (2021) reported a VE that passed the HTAC threshold (i.e., at least 60%) for this outcome. However, the study did not indicate the follow-up period of the VE in the study. Therefore, the duration of protection of *AstraZeneca* against any SARS-CoV-2 Alpha infection among the elderly population cannot be determined.
- **VE against symptomatic COVID-19:** Overall, there were two studies (Andrews et al., 2021 and Hitchings et al., 2021) from the relevant reviews which evaluated this outcome caused by the Alpha, Delta, and Gamma variant among the elderly population.
  - ***Against the Alpha variant*:** Andrews et al. (2021) reported a VE that passed the HTAC threshold for this outcome (i.e., at least 60% VE) at 2.5 months after the second dose. Thus, it can be inferred that *AstraZeneca* is effective against symptomatic COVID-19 caused by the Alpha variant for at least **2.5** months.
  - ***Against the Delta variant*:** Andrews et al. (2021) reported a VE that did not pass the HTAC threshold for this outcome (i.e., at least 60% VE) at 2 weeks after the second dose. Thus, it can be inferred that *AstraZeneca* is effective against symptomatic COVID-19 caused by the Delta variant for at least **1** week.
  - ***Against the Gamma variant*:** Hitchings et al. (2021) reported a VE that passed the HTAC threshold for this outcome (i.e., at least 60% VE) at 2.2 months after the second dose. Thus, it can be inferred that *AstraZeneca* is effective against symptomatic COVID-19 caused by the Gamma variant for at least **2.2** months.
- **VE against hospitalization due to COVID-19:** Overall, there were two studies (Andrews et al., 2021 and Hitchings et al., 2021) from the relevant reviews which evaluated this outcome caused by the Alpha, Delta, and Gamma variant among the elderly population.
  - ***Against the Alpha variant*:** Andrews et al. (2021) reported a VE that passed the HTAC threshold for this outcome (i.e., at least 80% VE) at 2.25 months after the second dose. Thus, it can be inferred that *AstraZeneca* is effective against hospitalization due to COVID-19 caused by the Alpha variant for at least **2.25** months.
  - ***Against the Delta variant*:** Andrews et al. (2021) reported a VE that did not pass the HTAC threshold for this outcome (i.e., at least 80% VE) at 4.4 months after the second dose. Thus, it can be inferred that *AstraZeneca* is effective against hospitalization due to COVID-19 caused by the Delta variant for at least **4.4** months.
  - ***Against the Gamma variant*:** Hitchings et al. (2021) reported a VE that passed the HTAC threshold for this outcome (i.e., at least 80% VE) at 2.2 months after the second dose. Thus, it can be inferred that *AstraZeneca* is effective against hospitalization due to COVID-19 caused by the Gamma variant for at least **2.2** months.
- **VE against death due to COVID-19:** Overall, there were three studies (Andrews et al., 2021; Hitchings et al., 2021; and Alencar et al., 2021) from the relevant reviews which evaluated this outcome caused by the Delta and Gamma variant among the elderly population. None of the studies reported this outcome against the Alpha variant.
  - ***Against the Delta variant*:** Andrews et al. (2021) reported a VE that passed the HTAC threshold for this outcome (i.e., at least 80% VE) at 4.4 months after the second dose. Thus, it can be inferred that *AstraZeneca* is effective against death due to COVID-19 caused by the Delta variant for at least **4.4** months. However, the same study reported a VE that failed the HTAC threshold (i.e., at least 80% VE) at 5 months.
  - ***Against the Gamma variant*:** Two studies (Hitchings et al., 2021 and Alencar et al., 2021) reported VE specifically against the Gamma variant. Hitchings et al. (2021) reported a VE that passed the HTAC threshold for this outcome (i.e., at least 80% VE) at 2.2 months after the second dose. Thus, it can be inferred that *AstraZeneca* is effective against death due to COVID-19 caused by the Gamma variant for at least **2.2** months.

There were no studies that reported VE against severe COVID-19 among the elderly population that were included in this review.

HTAC Judgment: Generally, there is limited evidence on the VE over time of *AstraZeneca* among special subgroups of interest compared to the available evidence on VE over time among the general population.

For HCWs: Based on the available evidence so far, the general trend of vaccine effectiveness of *AstraZeneca* over time for all outcomes cannot be concluded due to limited evidence of VE over time. In terms of duration of protection, duration of protection of *AstraZeneca* against any SARS-CoV-2 infection, symptomatic COVID-19 and hospitalization due to COVID-19 cannot be inferred based on available studies, and therefore cannot be compared to the general population. There were no studies included in the reviews that reported VE of *AstraZeneca* against any severe COVID-19 infection, or death due to COVID-19 for the elderly population.

For the elderly population: Duration of protection of *AstraZeneca* against any SARS-CoV-2 infection cannot be inferred based on available studies, and therefore cannot be compared to the general population. VE against symptomatic COVID-19, hospitalization due to COVID-19, and death due to COVID-19 decreased over time reaching below the HTAC threshold (i.e., at least 60% for symptomatic COVID-19 and at least 80% for hospitalization and death due to COVID-19) at 5 months (Delta). Meanwhile, compared to the general population, there is increased duration of protection of *AstraZeneca* against symptomatic COVID-19 (Gamma), hospitalization due to COVID-19 (Alpha/Gamma) and death due to COVID-19 (Gamma).

Janssen

Quality of the studies
Overall, there were 2 studies (Polinski et al., 2021 and Iliaki et al., 2021) included in the reviews that reported vaccine effectiveness over time of *Janssen* among special populations. The study by Polinski et al., (2021) has pending appraisal from COVID-NMA, while Iliaki et al., 2021 was not appraised by the LCPG or COVID-NMA since it was detected from other sources of data (i.e.. the IVAC review) which does not perform appraisal. Results of the risk of bias appraisals of each study are summarized in Appendix 5.

Results
FOR HEALTHCARE WORKERS (HCWs)
Based on real world effectiveness studies over time, *COVID-19 Vaccine Janssen* remains effective for 2.5 months after the second dose for the following outcomes in HCWs:
- **VE against symptomatic COVID-19:** Only one study (Iliaki et al., 2021) from the relevant reviews evaluated this outcome caused by the Alpha variant among HCWs. There were no studies that reported VE against SARS-CoV-2 infection caused by the Delta and Beta variant among healthcare workers.
  - ***Against the Alpha variant:*** Iliaki et al. (2021) measured a VE that passed the HTAC threshold against symptomatic COVID-19 caused by the Alpha variant (i.e. 60% VE) with a follow-up period of 2.5 months. Thus, it can be inferred that *Janssen* is effective against symptomatic COVID-19 infection caused by the Alpha variant for at least 2.5 months.

There were no studies included in the reviews that reported VE against any SARS-CoV-2 infection, COVID-19 hospitalization, severe COVID-19 infection, or death due to COVID-19 for HCWs.

FOR ELDERLY POPULATION
Based on real world effectiveness studies over time, the effectiveness of primary vaccination of *Janssen* over time for all outcomes cannot be determined due to limited evidence of VE over time.
- **VE against symptomatic COVID-19:** Only one study (Polinski et al., 2021) from the relevant reviews evaluated this outcome caused by the Alpha and Delta variant among the elderly population.
  - ***Against the Alpha variant or Delta variant:*** Polinski et al. (2021) reported a VE that passed the HTAC threshold (i.e, at least 60%) against symptomatic COVID-19 at the time when Alpha and Delta variant was among the variants circulating in the setting. However, the study did not indicate its follow up period for the VE in the study. Therefore, the duration of protection of *Janssen* against symptomatic COVID-19 infection caused by the Alpha and Delta variant among the elderly population cannot be determined.
- **VE against hospitalization due to COVID-19:** Only one study (Polinski et al., 2021) from the relevant reviews evaluated this outcome caused by the Alpha and Delta variant among the elderly population.
  - ***Against the Alpha variant or Delta variant:*** Polinski et al. (2021) reported a VE that failed the HTAC threshold (i.e. at least 80%) against hospitalization due to COVID-19 caused by the Alpha or Delta variant. Therefore, the duration of protection of *Janssen* against COVID-19 hospitalization caused by the Alpha and Delta variant among the elderly population cannot be determined.

There were no studies included in the reviews that reported VE against any SARS-CoV-2 infection, severe COVID-19, or death due to COVID-19 for the elderly population.

HTAC Judgment: Generally, there is limited evidence on the VE over time among special subgroups of interest compared to the available evidence on VE over time among the general population.

For HCWs: Based on the available evidence so far, VE against symptomatic COVID-19 infection for *Janssen* remained over the HTAC threshold (i.e., at least 60% VE) at 2.5 months (Alpha/Delta). However, the general trend of vaccine effectiveness over time for all outcomes cannot be concluded due to limited evidence of VE over time. Meanwhile, there is decreased duration of protection against symptomatic COVID-19 among HCWs. There were no studies included in the reviews that reported VE against any SARS-CoV-2 infection, COVID-19 hospitalization, severe COVID-19 infection, or death due to COVID-19 for HCWs.

For the elderly population: Based on the available evidence so far, the general trend of vaccine effectiveness over time for all outcomes cannot be concluded due to limited evidence of VE over time. Duration of protection against symptomatic COVID-19 and COVID-19 hospitalization cannot be inferred based on available studies, and therefore cannot be compared to the general population. There were no studies included in the reviews that reported VE against any SARS-CoV-2 infection, severe COVID-19, or death due to COVID-19 for the elderly population.

CoronaVac

Quality of studies

Overall there were 5 studies included in the reviews that reported vaccine effectiveness over time of *CoronaVac* for the special populations. Risk of bias (RoB) appraisals were extracted from the review of COVID-NMA and the LCPG group. Based on the RoB assessment of the LCPG group, the 5 real world studies (Hitchings et al., 2021; De Faria et al., 2021; Ranzani et al., 2021; Cerqueria-Silva et al., 2021; and Alencar et al., 2021) had 'very serious RoB' due to the observational study design. However, it was noted by the LCPG group that the study by Cerqueria-Silva et al., 2021 adjusted for the following confounders: age, sex, region of residence, socioeconomic status, month of first dose; Ranzani et al., 2021 performed matching by the date of testing, age, sex, race, residence, previous COVID-19 status; and Hitchings et al., 2021 performed matching by sample collection date, age, neighborhood residence, and had the following covariates in the logistic regression: sex, occupation category, race, number of health interactions, COVID infection since start of pandemic. Meanwhile, Alencar et al., 2021 was deemed 'high risk' due to poorly defined unexposed groups and limited control of confounders. On the other hand, the RoB assessment of COVID-NMA saw 'moderate RoB' for Hitchings et al., 2021 and 'serious RoB' for Ranzani et al., 2021 due to uncontrolled confounding and selection of participants in the study.
Meanwhile, studies that reported immunogenicity outcomes were not appraised for risk of bias by the LCPG group or COVID-NMA.

Results

FOR HEALTHCARE WORKERS (HCWs)

Effectiveness

Based on real world effectiveness studies over time, *CoronaVac* remains effective for at least 1.25 months after the second dose for the following outcomes in HCWs:

- **VE against any SARS-CoV-2 infection:** There was one study (Hitchings et al., 2021) from the relevant reviews that evaluated this outcome for *CoronaVac* caused by the Gamma variant among HCWs. There are currently no available studies on the effectiveness of CoronaVac against any SARS-CoV-2 infection caused by the Alpha or Delta variant.
  - ***Against the Gamma variant:*** Hitchings et al., 2021 reported a VE that did not pass the HTAC VE threshold for this outcome (i.e., at least 60% VE) among HCWs. However, the follow-up period of the study was not indicated.
- **VE against symptomatic COVID-19:** There was one study (De Faria et al., 2021) from the relevant reviews that evaluated this outcome for *CoronaVac* caused by the Gamma variant among HCWs. There are currently no available studies on the effectiveness of *CoronaVac* against symptomatic COVID-19 caused by the Alpha or Delta variant.
  - ***Against the Gamma variant:*** De Faria et al., 2021) reported a VE that passed the HTAC VE threshold for this outcome (i.e., at least 60%) at 5 weeks. Thus it can be inferred that *CoronaVac* is effective against symptomatic COVID-19 caused by the Gamma variant for **1.25** months among HCWs.

There were no studies included in the reviews that reported VE against hospitalization due to COVID-19, severe COVID-19, or death due to COVID-19 for HCWs.

Immunogenicity

Only real world studies reporting the VE of *CoronaVac* against clinical outcomes caused by the Gamma variant were found. No real world studies were detected for the other VOCs (i.e. Alpha and Delta variants). Due to limited evidence on the real world effectiveness over time of *CoronaVac* among special populations, an added search for immunogenicity studies over time was conducted to supplement data.
The search detected three prospective cohort studies (Jantarabenjakul et al., 2021; Kara et al., 2021; and Patamatamkul et al., 2021) that evaluated the immunogenicity of *CoronaVac* among HCWs. All three studies compared the immune response from two doses of *CoronaVac* at 1 month and 3 months after the second dose. Study characteristics and key findings from these studies are detailed in the table below.

	Jantarabenjakul et al., 2021 Thailand (Preprint)	**Kara, et al., 2021 Turkey (Preprint)**	**Patamatamkul et al., 2021 Thailand (Preprint)**
Population	Healthcare workers ≥18 years with no history of COVID-19 (N=94)	Adult healthcare workers (N=272)	Healthcare personnel (N=41)
Intervention	*CoronaVac*, 2 doses, 21-28 days	*CoronaVac*, 2 doses, 28 days apart	*CoronaVac*, 2 doses, (dosing interval

	interval		not indicated)
Comparator	N/A	N/A	N/A
Outcomes	Neutralizing antibody response and SARS-COV-2 total antibodies Time point of measurement: 4 and 12 weeks after dose 2	Anti-SARS-CoV-2 S-RBD IgG, total anti-spike, and anti-nucleocapsid IgG antibody, seroconversion Time point of measurement: 1 months and 3 months after dose	Anti-S-RBD antibodies measured Time point of measurement: 1 months and 3 months after dose
Test used	Surrogate viral neutralization test	Chemiluminescence immunoassay reaction	Surrogate viral neutralization test

All three studies observed declines in immune response for the following outcomes from 1 month after dose 2 to 3 months after dose 2:

Total Anti-spike and anti- nucleocapsid IgG
- Kara et al., 2021: decreased from 19.80 AU/mL in the first month after the second dose to 6.16 AU/mL at 3rd month after the second dose.

Anti-SARS-CoV-2 S-RBD IgG
- Kara et al., 2021: decreased from 29.14 AU/mL in the first month after the second dose to 10.46 AU/mL at 3rd month after the second dose.
- Patamatamkul et al., 2021: Did not differ significantly in recipients of *CoronaVac* at 64.72 U/mL (IQR: 22.23 to 188.86) compared to recipients of *AstraZeneca* at 106.8 U/mL (IQR: 49.89 to 151.7). No substantial decline was also observed between recipients of *CoronaVac* at 37.78 U/mL (IQR: 16.79 to 73.8) to recipients of *Pfizer-BioNTech* at 37.46 U/mL (IQR: 23.39 to 51.60).

Neutralizing antibody (% inhibition)
- Jantarabenjakul et al., 2021: decreased from 77.0% (95% CI: 58.5 to 87.9) at 4 weeks after the second dose to 38.7% (95% CI: 22.1 to 55.7) at 12 weeks after the second dose.
- Patamatamkul et al., 2021: decreased from 37.67% (IQR: 25.58 to 61.54) after the second dose to 18.71% (IQR: 9.66 to 20.98) before the booster dose

Seroconversion rates
- Jantarabenjakul et al., 2021: decreased from 60.6% (95%CI: 50.0 to 70.6) at 4 weeks after the second dose to 12.2% (95%CI: 6.3 to 20.8) at 12 weeks after the second dose using surrogate viral neutralization test (sVNT) (i.e., ≥68%inhibition)
- Kara et al., 2021: decreased anti-spike/anti- nucleocapsid IgG seropositivity from 93.0% at 1 month after the second dose to 87.5% at 3 months after the second dose.
- Kara et al., 2021: decreased anti-SARS-CoV-2 S-RBD IgG from 98.2% at 1st month after the second dose to 97.8% at third month after the second dose.
- Patamatamkul et al., 2021: decreased from 65.7% (95% CI: 49.1 to 79.2) after the second dose to 12.9% (95% CI: 4.5 to 29.5) before the booster dose.

FOR THE ELDERLY POPULATION

Effectiveness

Based on real world effectiveness studies over time, there is insufficient evidence to determine the effectiveness and duration of protection of *CoronaVac* for the following outcomes among the elderly population:
- **VE against symptomatic COVID-19:** There were two studies (Ranzani et al., 2021 and Cerqueria-Silva et al., 2021) from the relevant reviews which evaluated this outcome caused by the Gamma variant among the elderly. There are currently no available studies on the effectiveness of *CoronaVac* against symptomatic COVID-19 caused by the Alpha or Delta variant.
  - ***Against the Gamma variant:*** Both studies (Ranzani et al., 2021 and Cerqueria-Silva et al., 2021) reported VEs for this outcome among the elderly population that did not pass the HTAC VE threshold for this outcome (i.e. at least 60%) at a single time point of measurement, with a follow-up period of 2.75 months for Ranzani et al. and 3 months for Cerqueria-Silva et al., after the second dose. Subgroup analysis of Cerqueria-Silva et al. by age (i.e., 60-69 years, 70 to 79 years, 80 to 89 years, and ≥90 years) showed that VEs for this outcome did not pass the HTAC VE threshold for any age group in the elderly population. Therefore, the duration of protection of CoronaVac against any symptomatic COVID-19 in the elderly population cannot be determined.
- **VE against hospitalization due to COVID-19:** There were two studies (Ranzani et al., 2021 and Cerqueria-Silva et al., 2021) from the relevant reviews which evaluated this outcome caused by the Gamma variant among the elderly. There are currently no available studies on the effectiveness of *CoronaVac* against hospitalization due to COVID-19 caused by the Alpha or Delta variant.
  - ***Against the Gamma variant:*** Both studies (Ranzani et al., 2021 and Cerqueria-Silva et al., 2021) reported VEs for this outcome among the elderly population that did not pass the HTAC VE threshold for this outcome (i.e. at least 80%) at a single time point of measurement, with a follow-up period of 2.75 months for Ranzani et al. and 3 months for Cerqueria-Silva et al., 2021 after the second dose. Subgroup analysis of Cerqueria-Silva et al. by age (i.e., 60-69 years, 70 to 79 years, 80 to 89 years, and ≥90 years) show that VEs for this outcome did not pass the HTAC VE threshold for any age group in the elderly population.

Therefore, the duration of protection of CoronaVac against any hospitalization due to COVID-19 in the elderly population cannot be determined.

- **VE against death due to COVID-19:** There were three studies (Ranzani et al., 2021; Cerqueria-Silva et al., 2021; and Alencar et al., 2021) from the relevant reviews which evaluated this outcome caused by the Gamma variant among the elderly. There are currently no available studies on the effectiveness of *CoronaVac* against death due to COVID-19 caused by the Alpha or Delta variant.
  - ***Against the Gamma variant:*** One study (Alencar et al., 2021) reported a VE that passed the HTAC VE threshold for this outcome (i.e., at least 80%); however, the follow-up period of the study was not indicated. Thus, the duration of protection against death due to COVID-19 among the elderly population cannot be inferred. Meanwhile**,** Ranzani et al., 2021 and Cerqueria-Silva et al., 2021 reported VEs for this outcome among the elderly population that did not pass the HTAC VE threshold for this outcome (i.e. at least 80%) at a single time point of measurement, with a follow-up period of 2.75 months for Ranzani et al. and 3 months for Cerqueria-Silva et al., 2021 after the second dose. Subgroup analysis of Cerqueria-Silva et al. by age (i.e., 60-69 years, 70 to 79 years, 80 to 89 years, and ≥90 years) show that VEs for this outcome did not pass the HTAC VE threshold for any age group in the elderly population.

There were no studies included in the reviews that reported VE against any SARS-CoV-2 infection and severe COVID-19 for the elderly population.

Immunogenicity

The search detected 3 studies - one Phase I/II RCT (Li et al., 2021) and two prospective cohort studies (Medeiros et al., 2021 and Karamese and Tutuncu, 2021) that evaluated the immunogenicity of *CoronaVac* among the elderly population. Li et al. (2021) was conducted in two parts: the evaluation of the immune persistence of the *CoronaVac* primary series among the elderly and the evaluation of the immunogenicity and safety of a booster dose of *CoronaVac.* Only the results on immune persistence will be discussed in this section while the booster dose will be discussed in the sections below as evidence for the appropriate research question. Meanwhile, both prospective cohort studies did not report immunogenicity over time; instead, immune response in the elderly was measured 1 month after dose 2. Study characteristics and key findings from these studies are detailed below.

	Li, et al., 2021 China (Preprint)	**Medeiros et al., 2021** Brazil (Preprint)	**Karamese and Tutuncu, 2021** Turkey (Published)
Study design	Phase I/II RCT	Prospective cohort study	Prospective cohort study
Population	Older adults ≥60 years; N=68	Adults aged 23-90 *Vaccinated* (N=101); *Convalescent* (N=72); *Seronegative controls* (N=36)	≥65 years old; 51.1% with at least one comorbidity; N=235
Intervention	CoronaVac, 2 doses 28 days apart	CoronaVac, 3 weeks apart	CoronaVac, 2 doses, 28 days interval
Comparator	Placebo	N/A	N/A
Outcomes	GMT and seropositivity rates of neutralizing antibodies to live SARS-CoV-2 measured at day 0, 28, 56, and 208 after the first dose	Antigen-induced cellular cytokine and/or antibody responses cellular and humoral responses measured 28 days after 2nd dose	Level of anti-SARS-CoV-2 IgG antibodies measured at 4 weeks after dose 1 and 4 weeks after dose 2
Test used	Micro cytopathogenic effect assay	Enzyme-linked immunosorbent assay (ELISA)	ELISA (IgG) test using recombinant protein of the S1 subunit of S protein

The three studies reported low immune response for the following outcomes among older adults:

Neutralizing antibodies

- Li et al., 2021: Decreased from 42.7 (95% CI: 35.0 to 52.0) at 28 days after dose 2 to 3.4 (95% CI: 2.8 to 4.1) at 6 months after dose 2
- Medeiros et al., 2021: GMT of neutralization titers for participants ≥55 years were 6 times lower among vaccinated elderly (GMT=13.9) as compared to the elderly convalescent patients (GMT=85.8). Compared to the younger age group, the study observed 3.6-fold lower GMT neutralization titers for participants >55 years.

Anti-SARS-CoV-2 IgG

- Karamese and Tutuncu, 2021: Mean level of anti-SARS-CoV-2 IgG antibody 4 weeks after dose 2 was 194.61 ± 174.88 IU/mL among participants ≥65 years

Seroconversion
- Li et al., 2021: Decreased from 97.78% (95% CI: 92.20 to 99.73) at 28 days after dose 2 to 17.78% (95%CI: 10.52 to 27.26) at 6 months after dose 2
- Karamese and Tutuncu, 2021: 11.48% of older participants had antibody levels under 25.6 IU/mL and were evaluated as seronegative 4 weeks after dose 2
- Medeiros et al., 2021: Only 83% of male subjects ≥55 years displayed any detectable antibody or T-cell responses. Meanwhile, 94% of female subjects ≥55 years had detectable antibody or T-cell responses.

HTAC Judgment: Generally, there is limited evidence on the VE of *CoronaVac* over time among special subgroups of interest compared to the available evidence on VE over time among the general population.

For HCWs: Based on available evidence so far, VE of *CoronaVac* against symptomatic COVID-19 passed the HTAC VE threshold for this outcome (i.e., at least 60%) up to 1.25 months after dose 2 (Gamma). There is decreased duration of protection of *CoronaVac* against symptomatic COVID-19 compared to the general population. Meanwhile, VE of *CoronaVac* against any SARS-CoV-2 infection passed the HTAC VE threshold for this outcome (i.e., at least 60%); however, duration of protection for this outcome cannot be inferred based on available evidence. There were no studies included in the reviews that reported VE against hospitalization due to COVID-19, severe COVID-19, or death due to COVID-19 for HCWs.

For the elderly: There is insufficient evidence to determine the effectiveness and duration of protection of *CoronaVac* against symptomatic COVID-19, hospitalization due to COVID-19, and death due to COVID-19 among the elderly population.

RQ.2.3: What are the indications of booster vaccination?

HTAC Specifications: N/A

Evidence considered:
A total of 34 COVID-19 vaccination guidelines from different countries (US, UK, Canada, Australia, Switzerland, Japan, Italy, Germany, France, Thailand, Vietnam, South Korea, Indonesia, Russia, India, Mexico, Nepal, Bahrain, Mauritius, Israel, Chile, Singapore, Cambodia, Greece, Austria, Czech Republic, Hungary, Uruguay, Ireland, Turkey, Finland, and Philippines) and from the World Health Organization (WHO) and the European Medicines Agency (EMA) /European Center for Disease Control (ECDC) were reviewed to determine recommendations on the implementation of booster of COVID-19 vaccines.

Of the 34 countries and institutions reviewed:
- 22 countries (Bahrain, Russia, Thailand, Germany, Canada, Singapore, Cambodia, Greece, Austria, Indonesia, UK, Ireland, Italy, Japan, South Korea, Turkey, Finland, France , Australia, Mexico, India, Philippines) have guidelines and/or press releases on booster dose vaccination. Of these:
  - 12 countries (Bahrain, Russia, Thailand, Germany, Canada, Singapore, Cambodia, Greece, Austria, Indonesia, UK, Ireland) are currently **recommending** booster dose vaccination.
  - 4 countries (Australia, Mexico, India, and Philippines) are currently **not recommending** booster dose vaccination
  - 6 countries (Italy, Japan, South Korea, Turkey, Finland, France) are **planning to implement** booster vaccination.
- There were no guidelines on booster dose vaccination for the following 3 countries: Mauritius, Nepal, and Vietnam.

Pfizer-BioNTech

Booster Vaccination using Pfizer-BioNTech
Of the 12 countries currently recommending booster dose vaccination:
- No country is recommending the use of *Pfizer-BioNTech* for homologous booster dose strategy only.
- 2 countries (Bahrain, Thailand) are recommending the use of *Pfizer-BioNTech* for heterologous booster dose strategy only.
- 4 countries (Austria, Cambodia, Ireland, UK) are recommending the use of *Pfizer-BioNTech* for both homologous and heterologous boosters strategies
- 2 countries (Singapore, Greece) are recommending the use of *Pfizer-BioNTech* as a booster but did not mention the brand of the primary series.

Of the countries/guidelines recommending and implementing the use of *Pfizer-BioNTech* as part of their booster vaccination, below are the noted target vaccine recipients, dosing combinations, and dosing interval:

Country	Target Vaccine Recipients	Dosing Combination	Dosing Interval from second dose of the primary series
Bahrain	General population	Sinopharm-Sinopharm-Pfizer	1 month
Thailand	Health and social care frontline workers	Sinovac-Sinovac-Pfizer	1 month
Austria	Health and social personnel	Pfizer-Pfizer-Pfizer	9-12 months
		Moderna-Moderna-Pfizer	
		AZ-AZ-Pfizer	
		Janssen-Pfizer	
Cambodia	General population	Sinopharm-Sinopharm-Pfizer	6-8 months
		Sinovac-Sinovac-Pfizer	
		AZ-AZ-Pfizer	
		Janssen-Pfizer	
	Frontline officers, elderly, over the age of 60	Sinopharm-Sinopharm-Pfizer	4-6 months
		Sinovac-Sinovac-Pfizer	
		AZ-AZ-Pfizer	
		Janssen-Pfizer	
Ireland	Residents aged 65 years and older living in long term residential care facilities and aged 80 years and older living in the community	Pfizer-Pfizer-Pfizer	At least 6 months
		Moderna-Moderna-Pfizer	
		Janssen-Pfizer	
		AZ-AZ-Pfizer	
UK	Health and social care frontline workers	Pfizer-Pfizer-Pfizer	No earlier than 6 months
		AZ-AZ-Pfizer	
		Moderna-Moderna-Pfizer	
		Janssen-Pfizer	
Singapore	Individuals who are residents of long-term care homes, high-risk retirement homes and elder care lodges	mRNA (did not mention brand of primary series)	At least 6 months
Greece	Individuals over the age of 60	mRNA (did not mention brand of primary series)	6-8 months

Moderna

Booster Vaccination using Moderna

Of the 12 countries currently recommending booster dose vaccination:

- No country is recommending the use of *Moderna* homologous booster dose strategy only.
- 3 countries (Thailand, Cambodia, Indonesia) are recommending the use of *Moderna* heterologous booster dose strategy only.
- 3 countries (Austria, Ireland, UK) are recommending the use of *Moderna* for both homologous and heterologous boosters strategies.
- 2 countries (Singapore, Greece) are recommending the use of *Moderna* as a booster but did not mention the brand of the primary series.

Of the countries/guidelines recommending and implementing the use of *Moderna* as part of their booster vaccination, below are the noted target vaccine recipients, dosing combinations, and dosing interval:

Country	Target Vaccine Recipients	Dosing Combination	Dosing Interval from second dose of the primary series
Thailand	Health and social care frontline workers	Sinovac-Sinovac-Moderna	1 month
Indonesia	Health and social care frontline workers	Sinovac-Sinovac-Moderna	Not specified
Austria	Health and social personnel	Pfizer-Pfizer-Moderna	9-12 months
		Moderna-Moderna-Moderna	
		AZ-AZ-Moderna	
		Janssen-Moderna	
Cambodia	General population	Sinopharm-Sinopharm-Moderna	6-8 months
		Sinovac-Sinovac-Moderna	
		AZ-AZ-Moderna	
		Janssen-Moderna	
	Frontline officers, elderly, over the age of 60	Sinopharm-Sinopharm-Moderna	4-6 months
		Sinovac-Sinovac-Moderna	
		AZ-AZ-Moderna	
		Janssen-Moderna	
Ireland	Residents aged 65 years and older living in long term residential care facilities and aged 80 years and older living in the community	Pfizer-Pfizer-Moderna	At least 6 months
		Moderna-Moderna-Moderna	
		Janssen-Moderna	
		AZ-AZ-Moderna	

UK	Health and social care frontline workers	Pfizer-Pfizer-Moderna (half-dose)	No earlier than 6 months
		AZ-AZ-Moderna (half-dose)	
		Moderna-Moderna-Moderna (half-dose)	
		Janssen-Moderna (half-dose)	
Singapore	Individuals who are residents of long-term care homes, high-risk retirement homes and elder care lodges	mRNA (did not mention brand of primary series)	At least 6 months
Greece	Individuals over the age of 60	mRNA (did not mention brand of primary series)	6-8 months

AstraZeneca

Booster Vaccination using AstraZeneca

Of the 12 countries currently recommending booster dose vaccination:

- No country is recommending the use of *AstraZeneca* COVID-19 homologous booster dose strategy only.
- 3 countries (Thailand, Chile, Cambodia) are recommending the use of *AstraZeneca* heterologous booster dose strategy only.
- The UK is recommending the use of *AstraZeneca* for both homologous and heterologous boosters strategies.

Of the countries/guidelines recommending and implementing the use of *Astrazeneca* as part of their additional dose vaccination, below are the noted target vaccine recipients, dosing combinations, and dosing interval:

Country/ Institution	Target Vaccine Recipients	Dosing Combination	Dosing Interval from second dose of the primary series
Thailand	Health and social care frontline workers who have received complete primary vaccination SARS-CoV-2 Vaccine (Vero cell), Inactivated [CoronaVac]	Sinovac-Sinovac-AZ	3 to 4 weeks
UK	Health and Social workers	Pfizer-Pfizer-AZ	2 months For special cases delayed until 2 weeks after the period of immunosuppression
		Moderna-Moderna-AZ	
		AZ-AZ-AZ	
		Janssen-AZ	
Chile	For individuals who have received a complete series of vaccinations of SARS-CoV-2 Vaccine (Vero cell), Inactivated [CoronaVac]	Sinovac-Sinovac-AZ	4 months
Cambodia	General population	Sinovac-Sinovac-AZ	4 months
		Sinopharm-Sinopharm-AZ	
	For individuals who are residents of long-term care homes, high-risk retirement homes and elder care lodges	Sinovac-Sinovac-AZ	4 months
		Sinopharm-Sinopharm-AZ	

Janssen

Booster Vaccination using Janssen
Among the 12 countries currently recommending booster dose vaccination, **none of the countries/guidelines reviewed recommended the use of *Janssen* as a booster dose**, while 2 countries (Germany, Canada) are recommending COVID-19 booster dose vaccination but did not mention the brand used.

CoronaVac

Booster Vaccination using Sinovac
Of the 12 countries currently recommending booster dose vaccination, **2 countries** (Turkey, Cambodia) are using *Sinovac* homologous booster dose strategy only.

Of the countries/guidelines recommending and implementing the use of *Sinovac* as part of their additional dose vaccination, below are the noted target vaccine recipients, dosing combinations, and dosing interval:

Country/ Institution	Target Vaccine Recipients	Dosing Combination	Dosing Interval from second dose of the primary series
Turkey	General population	Sinovac-Sinovac-Sinovac	3 months
Cambodia	General population	Sinovac-Sinovac-Sinovac	4 months
	For individuals who are residents of long-term care homes, high-risk retirement homes and elder care lodges	Sinovac-Sinovac-Sinovac	4 months

RQ.2.4: Is homologous booster vaccination efficacious?

HTAC Specifications:
Preferred VE: ≥70% reduction in the risk of symptomatic infection with vaccination versus no vaccination
Minimum acceptable VE (point estimate) : at least 60% reduction of symptomatic COVID-19; **at least 80% reduction** of severe COVID-19, hospitalization due to COVID-19; **at least 80% reduction** of death due to COVID-19

Evidence considered:
The evidence on the efficacy, effectiveness and immunogenicity of *COVID-19 Vaccines* as a homologous booster dose were searched from reviews of the following 1) Philippine Living Clinical Practice Guidelines Group (LCPG Group), updated 24 September (Appendix 2, Part 5); 2) the International Vaccine Access Center (IVAC) of the Johns Hopkins Bloomberg School of Public Health and World Health Organization as of 01 Oct 2021; 3) COVID-NMA as of 07 October 2021; and 4) the US CDC Advisory Committee on Immunization Practices (ACIP) as of 23 Sept 2021.

Pfizer-BioNTech

Evidence from Clinical trials

Efficacy outcomes

The reference reviews did not detect any clinical trial evidence examining the clinical efficacy of *Pfizer-BioNTech* as a homologous booster dose. This shall be updated once new clinical evidence has been reviewed.

Immunogenicity outcomes

Description of Evidence

The reference reviews detected a report on the interim results of an ongoing Phase 1/2/3 (Study C4591001) trial examining the immunogenicity of *Pfizer-BioNTech* as a homologous booster dose with dosing interval of 6-8 months after dose 2. The characteristics of the detected study are presented are as follows:

	Study C4591001 (ongoing Phase 1/2/3 study, US)
Population	Participants aged 18-85 years old who received a primary series of 30 µg *Pfizer-BioNTech (N=329)*
Intervention	Phase 1 cohort: Booster dose of 30 µg *Pfizer-BioNTech,* approximately 8 months after dose 2 of BNT162b2 (started early 2021)- 18-55 (n= 11); 65-85 (n= 12) Phase 2/3 cohort: Booster dose of 30 µg*Pfizer-BioNTech* approximately 6 months after dose 2 of BNT162b2 (started March 2021) - 18-55 years of age (N= 306)
Comparator	2 doses (primary series) of 30 µg *Pfizer-BioNTech*
Outcomes	Noninferiority of neutralizing antibody geometric mean titers (GMTs) Immunogenicity vs Wild type Immunogenicity vs Beta and Delta Reactogenicity Adverse Events
Follow up	1 month after booster dose

Key Findings

Study C4591001 or the Pfizer US booster trial with short follow-up period (1 month) showed that *Pfizer-BioNTech* booster dose induced immune responses: [geometric mean ratio (GMR), seroresponse] noninferior to those following dose 2.

- **Neutralizing antibodies**
  - In trial participants aged 18 to 55 years, the GMR of neutralizing antibodies at 1 month after booster dose vs at 1 month after dose 2 was 3.29 (95% CI 2.76-3.91). Noninferiority was declared because the lower bound of the 2-sided 97.5% CI for the GMR is > 0.67 and the point estimate of the GMR is ≥0.8.
  - For trial participants aged 65 to 85 years, the GMT of neutralizing antibodies at 1 month after booster dose (1612.7 (95% CI: 875.5 to 2,970) was higher than the GMT detected at 1 month after dose 2 (195.8 [95% CI 114.7, 334.4]) the GMR was 8.2 (95% CI for the point estimates do not overlap).
- **Plaque-reduction neutralization test (PRNT) titers against variants of concern**
  - ***Delta variant vs wild-type neutralization*** - Post booster dose geometric mean titers indicate a substantial boost to the delta variants similar to wild type.

	Wild type neutralization (post booster titers vs after dose 2 titers)	Delta variant neutralization (post booster titers vs after dose 2 titers)
participants 18 to 55 years old	**~5-fold increase** in PRNT titers	**5.4-fold increase** in PRNT titers
participants 65 to 85 years old	**8.2-fold increase** in PRNT titers	**12-fold increase** in PRNT titers

  - ***Beta variant vs wild-type neutralization -*** Post booster dose titers indicate a substantial boost and reduced gap between wild type and beta neutralization.

	Wild type neutralization (post booster titers vs after dose 2 titers)	Beta variant neutralization (post booster titers vs after dose 2 titers)
participants 18 to 55 years old	**5.4 -fold increase** in PRNT titers	**15 -fold increase** in PRNT titers
participants 65 to 85 years old	**7.8 -fold increase** in PRNT titers	**20 -fold increase** in PRNT titers

- **Seroresponse**
  - For seroresponse, 197/198 participants (99.5%) in the booster trial had a seroresponse at 1 month after booster dose, and 194/198 (98%) had a seroresponse at 1 month after dose 1, for a 1.5% difference (95% CI -0.7–3.7%). Noninferiority was declared because the lower bound of the 2-sided CI for the % difference is greater than -10.

Evidence from Real World Studies

Effectiveness outcomes

Description of evidence

The reference reviews detected three real-world observational studies from Israel (i.e. Bar-on et, 2021, , Patalon et al, 2021) examining the effectiveness of *Pfizer-BioNTech* as a homologous booster dose with dosing interval of at least 5 months after dose 2 .Further, data from Bar-on et, 2021 and Patalon et al, 2021 were reviewed and analyzed by US ACIP, The characteristics of the detected study are presented are as follows:

	Bar-on et al., 2021 (Retrospective observational study; Israel)	**Patalon et al., 2021** (Retrospective matched case-control study; Israel)
Population	Individuals aged 60 years and older who were fully vaccinated for at least 5 months (N=1,137,804)	Maccabi Health Services (MHS) members, aged 40 and above, who received either two or three doses of the *Pfizer-BioNTech vaccine* (N=153,753)
Intervention	booster dose of *Pfizer-BioNTech at least 5 months after primary series*	booster dose of *Pfizer-BioNTech at least 5 months after primary series (n=32,697)*
Comparator	second dose of *Pfizer-BioNTech vaccine*	second dose of *Pfizer-BioNTech vaccine (n=149,379)*
Outcomes	effectiveness vs confirmed infection and vs severe illness	effectiveness against confirmed infection
Follow up	16-21 days	up to 20 days

Key Findings

Quality of Studies

The LCPG rated both the studies of Bar-on et al, 2021 and Patalon et al., 2021 with serious RoB due to non randomization, failure to conceal allocation, and non-blinding of both participants and investigators. In addition, ACIP rated the evidence using GRADE with very low certainty due to very serious indirectness (due to use of any COVID-19 infection outcome which is an indirect measure of symptomatic COVID-19; short follow up. Summary of the ACIP GRADE and LCPG RoB assessments for these studies are presented in Appendix 5.

Effectiveness Results

Confirmed COVID-19

- Available data from Bar-on et al, 2021 with a short follow-up period (minimum of 16- days to 21 days) show *11.4-fold decrease* in relative risk against confirmed COVID -19 infection compared to dose 2.
- Available data from Patalon et al., 2021 with a short follow-up period (up to 21 days) show 70-84% reduction in odds against confirmed COVID -19 infection compared to dose 2.

Symptomatic COVID-19

- *ACIP analysis of* real world data from Bar-on et al, 2021areported the following VE against symptomatic COVID-19:
  - *≥60 years old* - 91.2% [95% CI: 90.4 to 91.9%]

- *ACIP analysis of* real world data from Patalon et al., 2021 reported the following VE against symptomatic COVID-19:
  - *≥40 years old (Test negative design)* - 79% [95% CI: 72 to 84%]
  - *≥40 years old (Matched case control)* - 70% [95% CI: 62 to 76%]

Hospitalization due to COVID-19

- Available data from Bar-on et al, 2021 with a short follow-up period (minimum of 16- days to 21 days) show >10- fold reduction in relative risk against hospitalization due to COVID-19 compared to dose 2.
- *ACIP analysis of* real world data from Bar-on et al, 2021 reported VE of 95% [95% CI: 92%-97%] against severe COVID-19

Immunogenicity outcomes

Description of evidence

No real-world studies examining the immunogenicity of *Pfizer-BioNTech* as a homologous booster dose were detected from the reference reviews. This shall be updated once new clinical evidence has been reviewed.

HTAC Judgement: Yes, it is likely to be effective/ efficacious as a homologous booster dose based on limited evidence.

Moderna

Evidence from Clinical trials

Efficacy outcomes

The reference reviews did not detect any clinical trial evidence examining the clinical efficacy of *Moderna* as a homologous booster dose. This shall be updated once new clinical evidence has been reviewed.

Immunogenicity outcomes

Description of Evidence

The reference reviews detected an open-label interventional phase of a Phase 2 trial (Chu, et al., 2021 [preprint]) examining the immunogenicity of a 50 µg homologous booster dose of *Moderna* (i.e. equivalent to half of one dose in the 2-dose primary series which is at 100 µg) in combination with either 100 µg or 50 µg of Moderna as primary dose . The dosing interval was 7.2 months after dose 2 of either 100-µg or 50-µg primary series. The characteristics of the detected study are presented are as follows:

	Chu, et al., 2021 (preprint) Open-label interventional study; US
Population	Participants 18 years and older who had initially received 2 injections of 50 µg or 100 µg of *Moderna (N=344)*
Intervention	*Intervention arm 1: Moderna* 50µg primary (2 doses) + *Moderna* 50µg booster* (1 dose), n=173 *Intervention arm 2: Moderna* 100µg primary (2 doses) + *Moderna* 50µg booster* (1 dose), n=171 [per protocol set = 149] Dosing interval 7.2 months after primary series **equivalent to a half of a dose in the 2-dose* primary *series*
Comparator	*Moderna* 50µg primary series (2 doses) *Moderna* 100µg primary series (2 doses) Historical comparator: Primary Series of Two Injections of 100 µg of *Moderna* [Phase 3 COVE random sub-cohort] n=1080 [per protocol set = 1,055]
Outcomes	(i) Geometric mean titers (GMT) of serum nAb and (ii) Seroresponse rates for nAb based on the pseudovirus neutralizing antibody assay Solicited and unsolicited adverse events

	Serious adverse events Adverse events of special interest Medically attended adverse events Immunobridging analysis against D614G strain
Follow up	1 month

Key Findings

With a short follow-up period of 1 month after the booster dose, the Chu, et al., 2021 study noted that a *Moderna* booster dose induced higher immune response against the wild type and delta variant:

- **Neutralizing antibodies**
  - A 50µg *Moderna* booster dose induced a 2.1-fold increase (95% CI: 1.9 to 2.3) in GMT 28 days after booster compared to 28 days after 2nd dose of either 50µg and 100µg primary series.

  - *Neutralizing antibody titers against wild-type pseudovirus*
    - A 50µg *Moderna* booster dose induced a 1.7 -fold (95% CI: 1.5 to 1.9) increase in GMT vs wild-type pseudovirus 28 days after booster compared to 28 days after 100µg 2nd dose of the primary series
  - *Neutralizing antibody titers against Delta variant*
    - A 50µg *Moderna* booster dose induced a 2.1-fold (95% CI: 1.8 to 2.4) increase in GMT vs Delta pseudovirus 28 days after booster compared to 28 days after 100µg 2nd dose of the primary series
- **Seroresponse**
  - In the pooled 50 and 100µg primary group, 92.2% of booster recipients [(95% CI, 88.5 to 95.0%) n=293] met the definition of a seroresponse to the Delta variant i.e., a four-fold increase from pre-booster baseline.

Evidence from Real world studies

Effectiveness outcomes

The reference reviews did not detect any real world evidence examining the effectiveness of *Moderna* as a homologous booster dose. This shall be updated once new clinical evidence has been reviewed.

Immunogenicity outcomes

The reference reviews did not detect any real world evidence examining the immunogenicity of *Moderna* as a homologous booster dose. This shall be updated once new clinical evidence has been reviewed.

HTAC Judgement: Yes, a 50 µg *Moderna booster dose* (i.e. equivalent half of a one dose in the 2-dose primary series used in the rollout which is at 100 µg) is potentially efficacious as a homologous booster dose based on very limited evidence.

AstraZeneca

Evidence from Clinical trials

Efficacy outcomes

The reference reviews did not detect any clinical trial examining the clinical efficacy of *AstraZeneca* as a homologous booster dose. This shall be updated once new clinical evidence has been reviewed.

Evidence from Real world studies

Effectiveness outcomes

The reference reviews did not detect any real-world evidence examining the effectiveness of *AstraZeneca* as a homologous booster dose. This shall be updated once new clinical evidence has been reviewed.

Immunogenicity outcomes

Description of Evidence

The reference reviews detected one real-world observational study from UK (i.e. Flaxman et al., 2021) examining the immunogenicity of *AstraZeneca* as a homologous booster dose, with dosing interval of 28-38 weeks after dose 2. The characteristics of the detected study are presented as follows:

	Flaxman et al., 2021 (Single cohort)
Population	Volunteers aged 18-55 years who were enrolled in the Phase 1/2 or Phase 2/3 clinical trial of *AstraZeneca* and had received either one or two doses of the standard dose *AstraZeneca* invited to receive a delayed second dose or a third dose (N=130)
Intervention	Received the booster dose 28-38 weeks after the second dose (n= 90) ● Dosing interval for 15 participants tested for cellular immune response (subgroup): 263 to 266 days between dose 2 and booster dose
Comparator	Second dose of *AstraZeneca (n=40)*
Outcomes	● Comparison of titers at day 28 after dose 2 and titers after dose 3 ● NAb antibody levels to SARS-Cov2 Victoria spike, measured by single dilutional total IgG ELISA, compared to 28 days after dose 2 ● T-cell response (IFN-γ by ELISpot) 14 and 28 days after dose 3, compared to 28 days after dose 2
Follow-up	28 days

Key Findings

Immunogenicity Results

Flaxman et al. with 1 year follow-up period showed that *AstraZeneca* booster dose induced immune responses: [geometric mean titers (GMT), seroresponse] noninferior to those following dose 2.

- **Outcome 1: Neutralizing antibodies (total IgG)**
  - In this study, antibody titers [measured in 73 participant (81%)] were significantly higher 28 days after a third dose (median total IgG titre: 3746 EUs [IQR 2047–6420]) than 28 days after a second dose (median 1792 EUs [IQR 899–4634]; Wilcoxon signed rank test p=0·0043).
  - *AstraZeneca* homologous booster showed the following fold increases in GMT against variants of concern compared to dose 2:
    - 1.95-fold increase against Alpha variant
    - 2.7-fold increase against Beta variant
    - 2.6-fold increase against Delta variant
- **Outcome 2: Interferon-gamma (IFN-y) titers**
  - Spike-specific cellular immune responses of 15 participants increased by 1.8-fold 28 days after a booster dose of *AstraZeneca compared to to dose 2*
- **Outcome 3: Focus reduction neutralization test (FRNT) titers**
  - FRNT50 titers also showed the following measures against variants of concern after being given *AstraZeneca* booster dose:
    - Alpha: higher [545 (95% CI: 426 to 698)] compared to after the second dose [279 (95% CI: 200, 389)]
    - Beta: higher [118 (CI: 78, 179)]compared to after the second dose [43 (95% CI: 30, 61)]
    - Delta: higher [206 (95% CI: 149, 284]) compared to after the second dose [78 (CI: 55, 110)]

HTAC Judgement: Yes, it is potentially efficacious as a homologous booster dose based on very limited evidence.

Janssen

Evidence from Clinical trials

Effectiveness outcomes

The reference reviews did not detect any clinical trial examining the effectiveness of *Janssen* as a booster dose. This shall be updated once new clinical evidence has been reviewed.

Immunogenicity outcomes

Description of evidence

The reference reviews detected 1 preprint version of a Phase 1/2 trial (Sadoff et al., 2021) examining the immunogenicity of *Janssen* as a homologous booster dose. Study characteristics of Sadoff et al., 2021 is presented as follows:

	Sadoff et al., 2021(preprint) Phase 1/2 , US & Belgium
Population	Phase I/II and Phase II clinical trial participants aged 18 to 55 years and >65 years old: Phase I/II ● Cohort 1a: 18 to 55 years old (N = 25) ● Cohort 2a: 18 to 55 years old (N = 17) ● Cohort 3: >65 years old (N = 22) Phase II ● 18 to 55 years old and >65 years old (N = 73)
Intervention	$5x10^{10}$ vp booster dose of *Janssen* Or $1.25x10^{10}$ booster dose of *Janssen*
Comparator	Primary vaccination (single dose) of *Janssen*
Outcomes	Reactogenicity Adverse events
Dosing interval	6-9 months
Follow-up	1 month

Key Findings

- **Neutralizing antibodies**
  - Sadoff et al., 2021 reported an increase in the titer after the second dose of *Janssen*.
    - a $5x10^{10}$ vp booster dose at 6 months post prime vaccination in 18–55-year-old adults elicited a steep and robust 9-fold increase at Day 7 post boost compared to Day 29 levels following the initial immunization.
    - A lower booster dose of 1.25x1010 vp at 6 months in adults 18–55 and ≥65 years of age also elicited a rapid and high increase of 6–7.7 fold at Day 28 post boost compared to Day 29 levels following the initial immunization, with similar magnitude of post-boost responses in both age groups.

Evidence from Real World Studies

Effectiveness outcomes

The LCPG Group did not detect any real-world evidence examining the effectiveness of *Janssen* as a booster dose. This shall be updated once new clinical evidence has been reviewed.

Immunogenicity outcomes

The LCPG Group did not detect any real-world evidence examining the immunogenicity of *Janssen* as a booster dose. This shall be updated once new clinical evidence has been reviewed.

HTAC Judgement: Yes, it is potentially efficacious as a homologous booster dose based on **very** limited evidence.

CoronaVac

Evidence from Clinical trials

Efficacy outcomes

The reference reviews did not detect any clinical trial evidence examining the clinical efficacy of *CoronaVac* as a homologous booster dose. This shall be updated once new clinical evidence has been reviewed.

Immunogenicity outcomes

Description of Evidence

The reference reviews detected 1 randomized controlled observer blinded trial (Li, J. et al., 2021), 3 Phase I/II trials (Li, M. et al., 2021, Pan et al., 2021 and Wang et al., 2021) examining the immunogenicity of *CoronaVac* as a homologous booster dose with dosing interval of 28 days to 6 months after dose 2. The characteristics of the detected study are presented are as follows:

	Li, J. et al., 2021 (preprint) China Randomized, controlled, observer-blinded trial	**Li, M. et al., 2021 [preprint] China Phase I/II**	**Pan et al., 2021 [preprint] China Phase I/II**	**Wang et al., 2021 [preprint] China Phase I/II**
Population	Adults 18-59 years old N=540	Healthy adults >=60 years old, participants in the Ph2 trial; N= 303	Adults 18-59 years old; N= 544	Adults 16 to 69 years old
Intervention	**Schedule 1:** Primary doses of CoronaVac (3µg, 6µg) (at 14 day interval) + CoronaVac booster (given at 28 days after d2) [n=55;58] **Schedule 2:** Primary doses of CoronaVac (3µg, 6µg) (at 14 day interval) + CoronaVac booster (given at 6 mos after d2) [n=54;50] **Schedule 3:** Primary doses of CoronaVac (3µg, 6µg) (at 28 day interval) + CoronaVac booster (given at 28 days after d2) [n=55;56] **Schedule 4:** Primary doses of CoronaVac (3µg, 6µg) (at 28 day interval) + CoronaVac booster (given at 6 mos after d2) [n=52;50]	d3 at 8 months or more after d2 1.5ug n = 85 | 3ug n = 90 | 6ug n = 81	Primary vaccination: two doses of either a 3ug or 6ug vaccine, 14 or 28 days apart. Booster vaccination: to be discussed separately	Adults vaccinated with 3 doses of *CoronaVac* at months 0, 1, 7 (n=38)
Comparator	Placebo, 14 or 28 day interval, Placebo d3 at 6mos after d2 [n=110]	Placebo = 47	Placebo, 14 or 28 day interval	COVID- 19 convalescents (n=22) Healthy, SARS-CoV-2 RT-PCR negative adults (n=6) Adults vaccinated with 2 doses of *CoronaVac* (n=38)
Outcomes	• GMT of NAbs to live SARS CoV 2 • Seropositivity / seroconversion At 6 months after d2, 14 days, 28 days and 6 months after d3 • Reactogenicity • Serious adverse event	• GMT of NAb to live SARS-CoV-2 on day 180 after d2 and 7, 14, 28 days after d3 • Seropositivity rate (cut off at 1/8) • Safety : local and systemic adverse event rates(days 0-7), spontaneous recording of adverse event rate till day 28 • Serious adverse events till 6 months after d2	• GMT of NAbs to live SARS CoV 2 • Seropositivity / seroconversion At 6 months after d2, 14 days after d3 and 6 months after d3 • Reactogenicity • Serious adverse event	Immunogenicity: • Neutralizing antibody levels • Anti-RBD, anti-NTD, anti-S and anti-N titers for SARS-CoV-2 variants
Follow up	Planned 1 year for safety Actual follow up 6 mos	28 days	Planned 1 year for safety Actual follow up 6 mos	1.3 months after infection and vaccination

Key Findings

- **Neutralizing antibodies**
  - Li J, et al: The study reported a 15.2 fold increase in GMT 28 days after the booster dose vaccination compared to before booster vaccination in homologous booster recipients (dosing interval 3 to 6 months after the second dose)
  - Li M., et al: The study reported a 7.0-fold increase in GMT compared with after the second dose (dosing interval 8 months after after dose 2)
- **Neutralizing antibodies against delta variant [**Geometric mean half-maximal neutralizing titers (Plasma dilution)]
  - Wang et al: The study reported a 2.5-fold increase in the neutralizing potency of *CoronaVac* against delta variant than the convalescents and 2-dose vaccinees
- **Seropositivity / seroconversion**

- Pan, et al: There was 1.05 fold increase in the proportion of seropositive patients from 93.2% to 98.1% after booster dose compared with after dose 2 (dosing interval 6 months of receiving the second dose)

Evidence from Real world studies

Effectiveness outcomes

Description of Evidence

The reference reviews detected evidence on effectiveness of *CoronaVac* as a homologous booster dose to *CoronaVac* primary series from 1 NRA report (Chile Ministerio de Salud). This report was published 07 October 2021 following Chile's booster vaccination implementation last August 2021. It analyzed a cohort of individuals aged 16 years and older, with no history of SARS-CoV-2 infection and have already received *CoronaVac* as primary vaccination. This included 140,132 individuals boosted with *CoronaVac* out of 4,785,749 individuals previously immunized with *CoronaVac* as primary series. It is to note however that data from this report are only from a presentation from the official MOH website, but not supplemented by a full published paper.

Key Findings

Quality of Studies

RoB assessment was not done for the Chilean report since it is a government report without a published study.

Results

Effectiveness against COVID-19 Infection

- The study showed that the vaccine effectiveness of *CoronaVac* against COVID-19 infection substantially increased from 56% after the second dose to 80%, 14 days after the booster dose.

Effectiveness against hospitalization due to COVID-19

- The study showed that the vaccine effectiveness of *CoronaVac* against hospitalization due to COVID-19 increased from 84% after the second dose to 88%, 14 days after the booster dose.

Immunogenicity outcomes

Description of Evidence

The reference reviews detected one real world evidence (Keskin et al, 2021) from Turkey on the immunogenicity of *CoronaVac* as a booster dose on health care workers (n=113). The summary of the study characteristics is provided on the table below:

	Keskin et al., 2021 Turkey (preprint) Observational study
Population	Healthcare workers N= 113
Intervention	Homologous booster of *CoronaVac* (dosing interval of 6 mos after dose 2) N=18
Comparator	Non-vaccinated and non-infected n=23 2-dose CoronaVac (dosing interval of 28 days) n=45
Outcome	IgG - S ; IgG- N
Follow up	1 month

Key Findings

IgG- S titers

- The Keskin et al, 2021 study reported that the third dose of *CoronaVac* yielded a 1.7 times increase in the median values of IgG-S titer

IgG- N titers

- The Keskin et al, 2021 study reported that the third dose of *CoronaVac* yielded a 1.8 increase in the median values of the IgG-N titer.

HTAC Judgement: Yes, it is potentially efficacious as a homologous booster dose based on limited evidence.

RQ.2.5: Is homologous booster vaccination safe?

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

Evidence considered:
The evidence on the safety of *COVID-19 Vaccines* as a homologous booster dose were searched from reviews of the following 1) Philippine Living Clinical Practice Guidelines Group (LCPG Group), updated 24 September (Appendix 2, Part 5); 2) the International Vaccine Access Center (IVAC) of the Johns Hopkins Bloomberg School of Public Health and World Health Organization as of 01 Oct 2021; 3) COVID-NMA as of 07 October 2021; and 4) the US CDC Advisory Committee on Immunization Practices (ACIP) as of 23 Sept 2021.

Pfizer-BioNTech

Evidence on Safety from Clinical Trials

Description of evidence
Interim results from an ongoing Phase 1/2/3 clinical trial was detected (Study C4591001) which is examining the safety of *Pfizer-BioNTech* as a homologous booster dose with dosing interval of 6- 8 months after dose 2. The characteristics of the detected study are previously presented in the effectiveness part.

Key Findings

Quality of Studies
The LCPG rated Study C4591001 with very serious RoB due to non randomization; failure to conceal allocation; non-blinding of both participants and investigators; and failure to control for confounding factors. In addition, in their review, ACIP rated the safety evidence using GRADE. Evidence on reactogenicity was rated as having very low certainty due to very serious RoB, serious indirectness and serious imprecision. Meanwhile, ACIP rated evidence on serious adverse events with very low certainty due to very serious RoB, serious indirectness and very serious imprecision. Summary of the ACIP GRADE and LCPG ROB assessments for these studies are presented in Appendix 5.

Safety results
Evidence from the trial showed acceptable short term safety (follow-up period: 1-2 months after booster dose):

- **Local Reactogenicity -** Local reactions by maximum severity within 7 days of a homologous booster dose were similar to post-dose 2 in both Phase 1 and Phase 2/3 trial participants.
- **Systemic Reactogenicity -** Systemic events by maximum severity within 7 days of a homologous booster dose dose were similar to post-dose 2 in both Phase 1 and Phase 2/3 trial participants.
- **Adverse Events -** One severe event of lymphadenopathy reported but resolved within 5 days. No participants withdrew due to AEs. No cases of anaphylaxis, Bell's palsy, or myocarditis.

ACIP analysis from this trial showed that a homologous booster dose of *Pfizer-BioNTech* showed decreased risk of reactogenicity after booster dose vs after dose 2 (RR 0.62 [95% CI: 0.40 to 0.97]). Risk of adverse events are also lower after the booster dose vs after dose 2 (RR 0.82 [95% CI:0.11 to 5.96]). No Serious AEs were attributed to booster dose.

Safety data from Real World Evidence

Description of evidence
Two safety reports (Israeli Ministry of Health and US CDC: Hause et al., 2021) on the use of *Pfizer-BioNTech* as a booster dose were found. The Israeli MOH report consisted of safety surveillance from July 30, to September 2021 Meanwhile, the report of Hause et al., 2021 (US CDC) consisted of safety reports from booster vaccines (median dosing interval of 183 days after dose 2) from V-safe - a voluntary, smartphone-based safety surveillance system, from August 12 to September 19, 2021 (N= 22,191).

Key Findings

Quality of Studies
RoB assessments for the Israeli MOH report and Hause et al.,2021 were not performed as these are surveillance studies. These surveillance reports rely on passive adverse event reporting, thus are expected to be underestimated.

Safety results
Evidence from NRA reports (Israel and US CDC) showed the following:

- ***Local reactogenicity***
  - Israeli MOH reported that a homologous booster dose of *Pfizer-BioNTech* is associated with less local adverse reaction rates within 30 days of the booster dose compared to within 30 days after the 2nd dose.
  - Hause et al., 2021 (US CDC) reported more frequent local reactions after a homologous booster dose of *Pfizer-BioNTech* than post-dose 2 of (4,674; 74.1% and 4,523;71.7%; p-value <0.001).
- **Systemic *reactogenicity***
  - Israeli MOH reported that a homologous booster dose of *Pfizer-BioNTech* is associated with less systemic reaction rates within 30 days of the booster dose compared to within 30 days after the 2nd dose.
  - Hause et al., 2021 (US CDC) reported less frequent systemic reactions after a homologous booster dose of *Pfizer-BioNTech compared to* reactions post- dose 2 (4,363; 69.2% and 4,524; 71.7%; p-value <0.001).

Altogether, both NRA reports found an acceptable safety profile for *Pfizer-BioNTech* as a homologous booster dose.The Israeli report found that the booster dose so far had similar safety profile to the primary series. However, the short follow up period of the Israel (12 to 45 days after booster dose) and US reports (0 to 7 days after booster dose) do not meet the HTAC - preferred median follow up period of at least 2 months.

HTAC Judgment: Yes, *Pfizer* is considered safe as a homologous booster dose based on limited evidence.

Moderna

Evidence on Safety from Clinical Trials

Description of Evidence

The reference reviews detected an open-label interventional phase of a Phase 2 trial (Chu, et al., 2021 [preprint]) examining the immunogenicity of a 50 µg-homologous booster dose of *Moderna* (i.e. equivalent to half of one dose in the 2-dose primary series used in the COVID-19 vaccination rollout which is at 100 µg) in combination with two doses of either 100µg or 50µg of Moderna as primary dose. The dosing interval was7.2 months after dose 2 of either 100-µg or 50-µg primary series. The characteristics of the detected study are previously presented in the trial immunogenicity part.

Key Findings

Quality of the Study
Chu et al., 2021 had 'very serious RoB' based on the HTAC RoB assessment due to non randomization; failure to conceal allocation; non-blinding of both participants and investigators; and low control for confounding factors. Summary of the RoB assessment for the study is presented in Appendix 5.

Safety results
Evidence from the trial showed acceptable short term safety profile:

- **Local Reactogenicity**
  - A 50 µg booster dose of *Moderna* showed similar local adverse reaction rates compared with that of the second dose
- **Systemic Reactogenicity**
  - A 50 µg booster dose of *Moderna* showed similar systemic adverse reaction rates compared with that of the second dose.
- **Adverse Events**
  - Lymphadenopathy was reported higher in the group which received a 50 µg booster dose of *Moderna*: compared to participants in the Phase III trial by Baden et al. (2021) after receiving the second dose of *Moderna*.
  - The incidence of any Grade 3 solicited local or systemic adverse reaction after the 50 µg booster injection were low (4.8% and 7.2% respectively) and;
  - There were no Grade 4 solicited local or systemic adverse events after the booster injection
- **Adverse event of special interest**
  - An event of Bell's palsy was reported 5 hours after the 50 µg booster dose. However, it was considered to be unlikely related to the vaccine based on temporal implausibility. The primary series received (treatment group) by this patient is not indicated in the study.

However, the short follow up period (1 month) of the study does not meet the HTAC - preferred median follow up period of at least 2 months.

Safety data from Real world studies

Description of Evidence

One safety report (US CDC: Hause et al., 2021) on the use of *Moderna* as a booster dose was found. The report of Hause et al., 2021 (US CDC) consisted of safety reports from booster vaccines (median dosing interval of 182 days after dose 2) from V-safe - a voluntary, smartphone-based safety surveillance system, from August 12 to September 19, 2021 (N= 22,191). The study did not indicate whether the dosage strength *Moderna* used was a 100 µg or 50 µg booster dose. However, since the dosage strength in the US FDA EUA at the time of this evidence review is at 100 ug (full-dose) it is assumed that included surveillance reports were from patients who received an additional or booster full-dose (100 ug) of *Moderna*.

Key Findings

Quality of Studies

RoB assessment for Hause et al.,2021 was not performed as this is a surveillance study.

Safety results

Evidence from Hause et al.,2021 (US CDC) showed the following:

- ***Local reactogenicity***
  - More frequent local reactions were reported more frequently after dose 3 than dose 2 (5,323; 84.7% and 5,249; 83.5%; p-value =0.03)
- **Systemic reactogenicity**
  - Systemic reactions were reported less frequently after dose 3 than dose 2 (4,963; 79.0% and 5,105; 81.3%; p-value < 0.001).

However, the short follow up period (0 to 7 days after booster dose) of the US report does not meet the HTAC - preferred median follow up period of at least 2 months.

HTAC Judgement: Yes, a full-dose (100ug) or half-dose (50 ug) *Moderna* is considered safe as a homologous booster dose based on limited evidence.

AstraZeneca

Evidence from Clinical trials

Safety outcomes

The reference reviews did not detect any clinical trial evidence examining the safety of *AstraZeneca* as a homologous booster dose. This shall be updated once new clinical evidence has been reviewed.

Evidence from Real World Evidence

Description of evidence

One cohort study (Flaxman et al, 2021) detected by the LCPG evaluated the safety of a late second dose or a booster dose of *AstraZeneca* in volunteers who participated in the Phase I/II or Phase II/III trial of *AstraZeneca*. The study characteristics are summarized in the table in the previous section above.

Key Findings

Quality of Studies

The LCPG rated Flaxman et al. with very serious RoB due to non randomization and failure to conceal allocation. The assessment indicated that it is unclear if the study blinded participants, investigators, and assessors; had any missing outcomes/follow-up, or had selective reporting.

Safety results

Flaxman et al, 2021 showed that the booster/third dose of *AstraZeneca* was associated with more local adverse reactions but comparable systemic events compared to the second dose. The booster dose was also less reactogenic in terms of moderate and severe systemic symptoms than the first dose. The table below summarizes the safety outcomes reported by the study.

Safety Outcome	After booster dose *AstraZeneca*	After 2nd dose *AstraZeneca*	After 1st dose *AstraZeneca*

Local Adverse reaction (within 7 days after vaccination)	65/80 (81%)	8-12 week group: 201/267 (75%) 15-25 week group: 15/24 (62%) 44-45 week group: 23/30 (70%)	*Not reported*
Moderate to severe systemic reactions (within 7 days after vaccination)	4/80 (5%)	*Not reported*	27/80 (34%)

HTAC Judgment: Yes, *Astrazeneca* is considered safe as a homologous booster dose based on very limited evidence.

Janssen

Evidence from Clinical trials

Description of evidence

The reference reviews detected 1 preprint version of a Phase 1/2 trial (Sadoff et al., 2021) examining the safety of *Janssen* as a homologous booster dose. Study characteristics of Sadoff et al., 2021 is presented as follows:

	Sadoff et al., 2021(preprint) Phase 1/2 , US & Belgium
Population	Phase I/II and Phase II clinical trial participants aged 18 to 55 years and >65 years old: Phase I/II ● Cohort 1a: 18 to 55 years old (N = 25) ● Cohort 2a: 18 to 55 years old (N = 17) ● Cohort 3: >65 years old (N = 22) Phase II ● 18 to 55 years old and >65 years old (N = 73)
Intervention	$5x10^{10}$ vp booster dose of *Janssen* Or $1.25x10^{10}$ booster dose of *Janssen*
Comparator	Primary vaccination (single dose) of *Janssen*
Outcomes	Reactogenicity Adverse events
Follow-up	6 months

Key Findings

Quality of the Study

The HTAC/ joint SC reviewers rated Sadoff, et al., 2021 with 'very serious' RoB based on the HTAC RoB assessment due to non randomization; failure to conceal allocation; non-blinding of both participants and investigators; and failure to control for confounding factors. Summary of the RoB assessment for the study is presented in Appendix 5.

Results

- ***Local Reactogenicity***
  - *Sadoff et al., 2021* reports that the reactogenicity of a homologous *Janssen* booster dose was found to be less or similar to that of post-primary series reactogenicity.
- **Systemic Reactogenicity**
  - *Sadoff et al., 2021* and *Study COV 3009* report that the reactogenicity of a homologous *Janssen* booster dose was found to be less or similar to that of post-primary series reactogenicity.
- **Adverse Events**
  - *Sadoff et al., 2021* reports that there were less AEs after the booster dose than the post-primary regimen.

Safety data from Real World Evidence

Description of evidence

One safety report [Hause et al., 2021 (US CDC)] on the use of *Janssen* as a homologous booster was found. The report of Hause et al., 2021 (US CDC) consisted of safety reports from booster vaccines (median dosing interval of 84 days after dose 2) from V-safe - a voluntary, smartphone-based safety surveillance system, from August 12 to September 19, 2021 (N= 22,191).

Key Findings

Quality of Study

An RoB assessment for Hause et al.,2021 was not performed as it is a surveillance study.

Results

Evidence from Hause et al.,2021 (US CDC) showed the following:

- **Local reactogenicity**
  - 25% (12/48) of booster recipients experienced any injection site reaction within 0-7 days after the booster vaccine. Most common was pain in the injection site [20.8%].
- **Systemic reactogenicity**
  - 31.3% (15/48) of booster recipients experienced any systemic reaction within 0-7 days after the booster vaccine. Myalgia was the most common [20.8%].
- **Any health impact**
  - 16.7% (8/48) vaccinees were unable to perform normal daily activities within 0-7 days after booster vaccine

HTAC Judgment: Yes, *Janssen* is considered safe as a homologous booster dose based on limited evidence.

CoronaVac

Evidence on Safety from Clinical Trials

The reference reviews did not detect any clinical trial evidence examining the clinical efficacy of *CoronaVac* as a homologous booster dose. This shall be updated once new clinical evidence has been reviewed.

Safety data from Real world studies

Description of Evidence

The reference reviews detected 1 randomized controlled observer blinded trial (Li, J. et al., 2021), 1 Phase I/II trial (Li, M. et al., 2021) and 1 pre-print study (Pan et al., 2021) examining the safety of *CoronaVac* as a homologous booster dose with dosing interval of 28 days to 6 months after dose 2. The characteristics of the detected study are presented in the efficacy part of this report.

Key Findings

Quality of studies

The LCPG rated the RoB of the studies (Li J, et al, Li M, et al and Pan et al) as "Not serious". Summary of the LCPG RoB assessments for these studies are presented in Appendix 2.

Results

- **Local and Systemic Reactogenicity**
  - Li M., et al: Participants who received the third dose with a *CoronaVac* following a homologous prime-boost immunization had significantly less solicited injection-site reactions and solicited systemic reactions than those who received a heterologous dose of Convidecia 8 months after the second dose
  - Pan, et al: The *CoronaVac* booster dose showed similar local and systemic adverse reaction rates compared with that of the second dose.
- **Serious adverse event**

- Li J, et al: There was no reported thromboses or vaccine-related anaphylaxis, or serious adverse event was seen in any cohort of the participants
- Li M., et al: There was no significant differences in the serious adverse events between the intervention and comparator arm
- Pan, et al: Only singular cases of serious adverse events were reported in the included trials, but were considered to be not related to vaccination.

HTAC Judgement: Yes, *CoronaVac* is considered safe as a homologous booster dose based on limited evidence.

RQ.2.6: Is heterologous booster vaccination efficacious?

HTAC Specifications:
Preferred VE: ≥70% reduction in the risk of symptomatic infection with vaccination versus no vaccination
Minimum acceptable VE (point estimate) : at least 60% reduction of symptomatic COVID-19; **at least 80% reduction** of severe COVID-19, hospitalization due to COVID-19; **at least 80% reduction** of death due to COVID-19

Evidence considered:
The evidence on the efficacy, effectiveness and immunogenicity of *COVID-19 Vaccines* as a heterologous booster dose were searched from reviews of the following 1) Philippine Living Clinical Practice Guidelines Group (LCPG Group), updated 24 September (Appendix 2, Part 5); 2) the International Vaccine Access Center (IVAC) of the Johns Hopkins Bloomberg School of Public Health and World Health Organization as of 01 Oct 2021; 3) COVID-NMA as of 07 October 2021; 4) the US CDC Advisory Committee on Immunization Practices (ACIP) as of 23 Sept 2021 and 5) the Chile Ministerio de Salud report on the Early estimates of the effectiveness of booster shots in Chile.

Pfizer-BioNTech

Evidence from Clinical trials

Efficacy outcomes

The reference reviews did not detect any clinical trial evidence examining the clinical efficacy of *Pfizer-BioNTech* as a heterologous booster dose. This shall be updated once new clinical evidence has been reviewed. The LCPG also noted that there will be a local multi-site, unblinded, convenience sampling trial (de Vera et al) which will evaluate the efficacy, immunogenicity, and safety of using *Pfizer-BioNTech* as a booster to *CoronaVac.* Results will be available by December 2021.

Immunogenicity outcomes

The reference reviews did not detect any clinical trial evidence examining the immunogenicity of *Pfizer-BioNTech* as a heterologous booster dose. This shall be updated once new clinical evidence has been reviewed.

Evidence from Real world studies

Effectiveness outcomes

Description of Evidence

The reference reviews detected evidence on effectiveness of *Pfizer-BioNTech* as a heterologous booster dose to *CoronaVac* primary series from 1 NRA report (Chile Ministerio de Salud). This report was published 07 October 2021 following Chile's booster vaccination implementation last August 2021. It analyzed a cohort of individuals aged 16 years and older, with no history of SARS-CoV-2 infection and have already received *CoronaVac* as primary vaccination. This included 371,592 individuals boosted with *Pfizer-BioNTech* out of 2,017,878 individuals previously immunized with *CoronaVac* as primary series. It is to note however that data from this report are only from a presentation from the official MOH website, but not supplemented by a full published paper.

Key Findings

- **Vaccine effectiveness against COVID-19 infection -** The Chilean MOH report showed that the *Pfizer-BioNTech* heterologous booster induced a substantial increase in vaccine effectiveness against COVID -19 infection of 90% from 56% vaccine effectiveness of the *CoronaVac* primary series.
- **Vaccine effectiveness against hospitalization due to COVID-19 -** The Chilean MOH report showed that the *Pfizer-BioNTech* heterologous booster induced a comparable vaccine effectiveness against hospitalization due to COVID-19 of 87% compared to 84% vaccine effectiveness of the CoronaVac primary series.

However, the short follow up period (14 days after booster dose) of the Chilean report does not meet the HTAC - preferred median follow up period of at least 2 months.

Immunogenicity outcomes

Description of Evidence

The reference reviews detected two real-world observational studies from Thailand [Patamatamkul et al., 2021 (preprint)] and Turkey [Keskin, et al., 2021 (preprint)] examining the effectiveness of *Pfizer-BioNTech* as a heterologous booster dose to *CoronaVac* primary series The characteristics of the detected study are presented are as follows:

	Patamatamkul et al., 2021 (preprint) (Prospective observational study; Thailand)	**Keskin, et al., 2021** (preprint) (observational study; Turkey)
Population	Healthcare workers who received *CoronaVac* as primary vaccination series (N=41)	Healthcare workers who received *CoronaVac* as primary vaccination series (N=113)
Intervention	Booster dose of the *Pfizer- BioNTech* vaccine (n=23) Booster dose of the *AstraZencea* vaccine (n=18) *dosing interval not indicated	Homologous booster of *CoronVac* (dosing interval of 6 mos after dose 2; n=18) Heterologous booster of *Pfizer-BioNTech* (dosing interval of 6 mos after dose 2; n=27)
Comparator	Second dose of *CoronaVac* primary series	Non-vaccinated and non-infected (n=23) 2-dose *CoronaVac* (n=45)
Outcomes	Viral neutralization	anti- IgG-S; IgG-N
Follow up	2-3 weeks	1 month

Key Findings

- **Surrogate neutralizing antibody titers**
  - Patamatamkul et al., 2021 reported that *Pfizer-BioNTech* heterologous booster to *CoronaVac* primary series induced a 2.5 fold increase in median neutralizing antibody titers against the delta variant 2 weeks post-booster against 11 weeks post dose 2.
- **Anti-S RBD antibody titers**
  - Patamatamkul et al., 2021 reported that *Pfizer-BioNTech* heterologous booster to *CoronaVac* primary series induced a substantial ~600- fold increase in anti-S antibody titers 2 weeks post-booster against 11 weeks post dose 2.
- **IgG - S antibody titers**
  - Keskin, et al., 2021 reported that *Pfizer-BioNTech* heterologous booster to *CoronaVac* primary series induced a substantial 46.6- fold increase in IgG - S median titers compared to after dose 2
- **IgG - N antibody titers**
  - Keskin, et al., 2021 reported that *Pfizer-BioNTech* heterologous booster to *CoronaVac* primary series induced a 46.6- fold decrease in IgG - N median titers compared to after dose 2.

HTAC Judgment: Yes, it is potentially effective/ efficacious as a heterologous booster dose based on limited evidence.

Moderna

Evidence from Clinical trials

Efficacy outcomes

The reference reviews did not detect any clinical trial evidence examining the clinical efficacy of *Moderna* as a heterologous booster dose. This shall be updated once new clinical evidence has been reviewed.

Immunogenicity outcomes

The reference reviews did not detect any clinical trial evidence examining the immunogenicity of *Moderna* as a heterologous booster dose. This shall be updated once new clinical evidence has been reviewed.

Evidence from Real world studies

Effectiveness outcomes

The reference reviews did not detect any real world evidence examining the effectiveness of *Moderna* as a heterologous booster dose. This shall be updated once new clinical evidence has been reviewed.

Immunogenicity outcomes

The reference reviews did not detect any real world evidence examining the immunogenicity of *Moderna* as a heterologous booster dose. This shall be updated once new clinical evidence has been reviewed.

HTAC Judgment: Yes, it is potentially efficacious as a heterologous booster dose based on very limited evidence.

AstraZeneca

Evidence from Clinical trials

Efficacy outcomes

The reference reviews did not detect any clinical trial examining the clinical efficacy of *Astrazeneca* as a heterologous booster dose. This shall be updated once new clinical evidence has been reviewed.

Immunogenicity outcomes

The reference reviews did not detect any clinical trial examining the immunogenicity of *Astrazeneca* as a heterologous booster dose. This shall be updated once new clinical evidence has been reviewed.

Evidence from Real world studies

Effectiveness outcomes

Description of Evidence

The reference reviews detected evidence on effectiveness of *AstraZeneca* as a heterologous booster dose to *CoronaVac* primary series was from 1 NRA report (Chile Ministerio de Salud). This report was published 07 October 2021 following Chile's booster vaccination implementation last August 2021(dosing interval of at least 5 months after dose 2). It analyzed a cohort of individuals aged 16 years and older, with no history of SARS-CoV-2 infection and have already received *CoronaVac* as primary vaccination. This included 1,506,154 individuals boosted with *Pfizer-BioNTech* out of 2,017,878 individuals previously immunized with *CoronaVac* as primary series. It is to note however that data from this report are only from a presentation from the official MOH website, but not supplemented by a full published paper.

Key Findings

- **Vaccine effectiveness against COVID-19 infection -** The Chilean MOH report showed that the *AstraZeneca* heterologous booster induced a substantial increase in vaccine effectiveness against COVID -19 infection of 93% from 56% vaccine effectiveness of the *CoronaVac* primary series.
- **Vaccine effectiveness against hospitalization due to COVID-19 -** The Chilean MOH report showed that the *AstraZeneca* heterologous booster induced a comparable vaccine effectiveness against hospitalization due to COVID-19 of 96% compared to 84% vaccine effectiveness of the *CoronaVac* primary series.

However, the short follow up period (14 days after booster dose) of the Chilean report does not meet the HTAC - preferred median follow up period of at least 2 months.

Immunogenicity outcomes

Description of Evidence

The reference reviews detected one real-world observational study from Thailand [Patamatamkul et al., 2021 (preprint)] examining the effectiveness of *AstraZeneca* as a heterologous booster dose to *CoronaVac* primary series. The characteristics of the detected study are presented are as follows:

	Patamatamkul et al., 2021 (preprint) (Prospective observational study; Thailand)
Population	Healthcare workers who received *CoronaVac* as primary vaccination series (N=41)
Intervention	Booster dose of the *Pfizer- BioNTech* vaccine (n=23)

	Booster dose of the *AstraZeneca* vaccine (n=18) *dosing interval not indicated
Comparator	Second dose of *CoronaVac* primary series
Outcomes	Viral neutralization
Follow up	2-3 weeks

Key Findings

- **Surrogate neutralizing antibody titers**
  - Patamatamkul et al., 2021 reported that *AstraZeneca* heterologous booster to *CoronaVac* primary series induced a 2.5-fold increase in median neutralizing antibody titers against the delta variant 2 weeks post-booster versus 4 weeks post 2nd dose (no dose interval indicated).

- **Anti-S RBD antibody titers**
  - Patamatamkul et al., 2021 reported that *AstraZeneca* heterologous booster to *CoronaVac* primary series induced a substantial ~80-fold increase in anti-S antibody titers 2 weeks post-booster versus 4 weeks post 2nd dose (no dose interval indicated).

HTAC Judgment: Yes, it is potentially effective/ efficacious as a heterologous booster dose based on very limited evidence.

Janssen

The reference reviews did not detect any clinical trial and real world evidence examining the clinical efficacy, effectiveness and safety of *Janssen* as a heterologous booster dose. This shall be updated once new clinical evidence has been reviewed.

HTAC Judgment: Cannot assess the effectiveness or efficacy of *Janssen* as a heterologous booster dose due to current lack of evidence

CoronaVac

The reference reviews did not detect any clinical trial and real world evidence examining the clinical efficacy, effectiveness and safety of *CoronaVac* as a heterologous booster dose. This shall be updated once new clinical evidence has been reviewed.

HTAC Judgment: Cannot assess the effectiveness or efficacy of *CoronaVac* as a heterologous booster dose due to current lack of evidence

RQ.2.7: Is heterologous booster vaccination safe?

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

Evidence considered:
The evidence on the safety of *COVID-19 Vaccines* as a heterologous booster dose were searched from reviews of the following 1) Philippine Living Clinical Practice Guidelines Group (LCPG Group), updated 24 September (Appendix 2, Part 5); 2) the International Vaccine Access Center (IVAC) of the Johns Hopkins Bloomberg School of Public Health and World Health Organization as of 01 Oct 2021; 3) COVID-NMA as of 07 October 2021; and 4) the US CDC Advisory Committee on Immunization Practices (ACIP) as of 23 Sept 2021.

Pfizer-BioNTech

Evidence from Clinical trials

The reference reviews did not detect any clinical trial evidence examining the safety of *Pfizer-BioNTech* as a heterologous booster dose. This shall be updated once new clinical evidence has been reviewed.

Safety data from Real World Evidence

Description of evidence

One safety report [Hause et al., 2021 (US CDC)] on the use of *Pfizer-BioNTech* as a heterologous booster dose to *Moderna* and *Janssen* primary series was found. The report of Hause et al., 2021 (US CDC) consisted of safety reports from booster vaccines (median dosing interval of 183 days after dose 2) from V-safe - a voluntary, smartphone-based safety surveillance system, from August 12 to September 19, 2021 (N= 22,191).

Key Findings

Quality of Study

An RoB assessment for Hause et al.,2021 was not performed as it is a surveillance study.

Safety results

Evidence from the NRA report (US CDC) showed acceptable safety profile of the *Pfizer-BioNTech* booster strategy:

- ***Local reactogenicity***
  - **With Moderna (Primary series):** 64.6% experienced any injection site reaction. Most common was pain in the injection site.
  - **With Janssen (Primary series)**: 80.3% experienced any injection site reaction. Most common was pain in the injection site
- **Systemic *reactogenicity***
  - **With Moderna (Primary series):** 59.7% experienced any systemic reaction. Fatigue was the most common [61.8%].
  - **With Janssen (Primary series):** 63.6% experienced any systemic reaction. Fatigue was the most common [50.0%].

However, the short follow up period (0 to 7 days after booster dose) of the US report does not meet the HTAC - preferred median follow up period of at least 2 months.

HTAC Judgement: Yes, it is potentially safe as heterologous booster vaccine, based on very limited evidence.

Moderna

Evidence on Safety from Clinical Trials

The reference reviews did not detect any clinical trial evidence examining the safety of *Moderna* as a heterologous booster dose. This shall be updated once new clinical evidence has been reviewed.

Safety data from Real world studies

Description of evidence

One safety report [Hause et al., 2021 (US CDC)] on the use of *Moderna* as a heterologous booster dose to *Pfizer-BioNTech* and *Janssen* primary series was found. The report of Hause et al., 2021 (US CDC) consisted of safety reports from booster vaccines (median dosing interval of 182 days after dose 2) from V-safe - a voluntary, smartphone-based safety surveillance system, from August 12 to September 19, 2021 (N= 22,191).

Key Findings

Quality of Study

An RoB assessment for Hause et al.,2021 was not performed as it is a surveillance study.

Safety results

Evidence from the NRA report (US CDC) showed acceptable safety profile of the *Pfizer-BioNTech* booster strategy:

- ***Local reactogenicity***
  - **With *Pfizer-BioNTech* (Primary series):** 81.7% experienced any injection site reaction. Most common was pain in the injection site
  - **With *Janssen* (Primary series)**: 70% experienced any injection site reaction. Most common was pain in the injection site.
- **Systemic *reactogenicity***

- **With *Pfizer-BioNTech* (Primary series):** 76.1% experienced any systemic reaction. Fatigue was the most common [61.8%].
- **With *Janssen* (Primary series):** 68.8% experienced any systemic reaction. Fatigue was the most common [48.8%].

However, the short follow up period (0 to 7 days after booster dose) of the US report does not meet the HTAC - preferred median follow up period of at least 2 months.

HTAC Judgement: Yes, it is potentially safe as heterologous booster vaccine, based on very limited evidence

AstraZeneca

The reference reviews did not detect any clinical trial and real world evidence examining the clinical safety of *AstraZeneca* as a heterologous booster dose. This shall be updated once new clinical evidence has been reviewed.

HTAC Judgment: Cannot assess the overall safety as a heterologous booster dose due to current lack of evidence

Janssen

Evidence on Safety from Clinical Trials

The reference reviews did not detect any clinical trial evidence examining the safety of *Janssen* as a heterologous booster dose. This shall be updated once new clinical evidence has been reviewed.

Safety data from Real World Evidence

Description of evidence

One safety report [Hause et al., 2021 (US CDC)] on the use of *Janssen* as a heterologous booster dose to *Pfizer-BioNTech* and *Moderna* primary series was found.The report of Hause et al., 2021 (US CDC) consisted of safety reports from booster vaccines (median dosing interval of 84 days after dose 2) from V-safe - a voluntary, smartphone-based safety surveillance system, from August 12 to September 19, 2021 (N= 22,191; n=48).

Key Findings

Quality of Study

An RoB assessment for Hause et al.,2021 was not performed as it is a surveillance study.

Results

Evidence from Hause et al.,2021 (US CDC) showed the following:

- **Local reactogenicity**
  - ***With Moderna*** (Primary series)***:*** 75% experienced any injection site reaction.
  - ***With Pfizer*** (Primary series) **:** 83% experienced any injection site reaction.
- **Systemic reactogenicity**
  - ***With Moderna*** (Primary series)***:*** 50% experienced any systemic reaction.
  - ***With Pfizer***(Primary series): 100% experienced any systemic reaction.
- **Any health impact**
  - ***With Moderna*** (Primary series)***:*** None were unable to perform normal daily activities
  - ***With Pfizer***(Primary series): 33.3% were unable to perform normal daily activities

HTAC Judgement: Yes, it is potentially safe as heterologous booster vaccine, based on very limited evidence

CoronaVac

The reference reviews did not detect any clinical trial and real world evidence examining the clinical safety of *CoronaVac* as a heterologous booster dose. This shall be updated once new clinical evidence has been reviewed.

HTAC Judgment: Cannot assess the safety of *CoronaVac* as a heterologous booster dose due to current lack of evidence

RQ.2.8: Does the COVID-19 vaccine provide a highly favorable benefit/risk profile in the context of observed vaccine efficacy as a booster?

Pfizer-BioNTech	Moderna	AstraZeneca	Janssen	CoronaVac

As there is currently insufficient evidence on the efficacy and safety of *COVID-19 Vaccines* as a homologous and heterologous booster dose, assessing benefit/risk profile is not feasible at the moment.

HTAC Judgment: Cannot be assessed based on current lack of evidence

ADDITIONAL DOSE VACCINATION

RQ.2.9: What is the effectiveness over time of primary vaccination using COVID-19 vaccines against the original strain and variants of concern in special populations, specifically, immunocompromised patients in terms of symptomatic COVID-19, severe COVID-19, hospitalization and death due to COVID-19? How long does protection from primary vaccination last in this special population?

HTAC Specifications:
Preferred VE: ≥70% reduction in the risk of symptomatic infection with vaccination versus no vaccination
Minimum acceptable VE (point estimate) : at least 60% reduction of symptomatic COVID-19; **at least 80% reduction** of severe COVID-19, hospitalization due to COVID-19; **at least 80% reduction** of death due to COVID-19

Evidence considered
For the evidence on the effectiveness of *COVID-19 Vaccines* over time against variants of concern for the immunocompromised populations, reviews from the following organizations were synthesized: 1) the International Vaccine Access Center (IVAC) of the Johns Hopkins Bloomberg School of Public Health and World Health Organization as of 01 Oct 2021; 2) COVID-NMA as of 07 Oct 2021; 3) LCPG review on effectiveness of vaccines against the Delta as of 31 Aug 2021; and 4) the US CDC Advisory Committee on Immunization Practices (ACIP) as of 23 Sept 2021.

Pfizer-BioNTech

Key findings

Quality of studies
Overall, there were 2 studies (Tenforde et al., 2021 and Andrews et al., 2021) included in the reviews that reported vaccine effectiveness over time of *Pfizer-BioNTech* for the immunocompromised population. However, only 1 study (Tenforde et al., 2021) had a RoB appraisal which was from the review of COVID-NMA. The study had serious RoB due to uncontrolled confounding, classification of interventions, measurement of outcome, and selection of reported results. Results of the risk of bias appraisals of each study are summarized in Appendix 5.

Results
Based on real world effectiveness studies over time, *Pfizer-BioNTech* remains effective for 4.4 months after the second dose for the following outcome in immunocompromised patients:

- **VE against hospitalization due to COVID-19:** Overall, there were 2 studies (Tenforde et al., 2021 and Andrews et al., 2021) from relevant reviews which evaluated the effectiveness over time of mRNA vaccines (i.e., *Pfizer-BioNTech* or *Moderna*) for this outcome among the immunocompromised population.
  - ***Against the Alpha variant:*** One study was found measuring the VE against hospitalization due to COVID-19 that was conducted during the period when Alpha variant was the dominant variant circulating in the study setting (other VOC being the Delta variant). During the follow-up period of 6 months, Tenforde et al. (2021) measured a VE that did not pass the HTAC threshold (i.e., at least 80% VE) for this outcome. Therefore, the duration of protection of *mRNA vaccines* (i.e., *PfizerBioNTech* or *Moderna*) for this outcome among the immunocompromised cannot be determined.
  - ***Against the Delta variant:*** Two studies were found - one study (Andrews et al., 2021) measured the VE specifically against the Delta variant while the other (Tenforde et al., 2021) was conducted during which both Alpha and Delta variants were circulating in the study setting. Of the 2 studies, the study by Andrews et al. (2021), had reported a VE that passed the HTAC threshold (i.e. at least 80% VE) with the longest follow up period (i.e., at least 4.4 months). However, the same study noted a VE that failed the HTAC threshold beyond 20 weeks for individuals ≥65 years who are clinically extremely vulnerable. Thus, it can be inferred that *Pfizer-BioNTech* is effective against hospitalization due to COVID-19 caused by the Delta variant for up to 4.4 months among immunocompromised patients.

There were no studies included in the reviews that reported VE against any SARS-CoV-2 infection, symptomatic COVID-19, severe COVID-19, hospitalization or death due to COVID-19 for the immunocompromised population.

HTAC Judgment: Generally, there is limited evidence on the VE over time among immunocompromised patients compared to the available evidence on VE over time among the general population.

Based on the available evidence so far, VE against hospitalization among the immunocompromised population decreased over time reaching below the HTAC threshold at 5 to 6 months (Alpha/Delta). Meanwhile, there is decreased duration of protection against COVID-19 hospitalization for this population compared to the duration of protection for the general population.
There were no studies included in the reviews that reported VE against any SARS-CoV-2 infection, symptomatic COVID-19, severe COVID-19 or death due to COVID-19 for immunocompromised population.

Moderna

Key findings

Quality of studies

Overall, there was 1 study (Tenforde et al., 2021) included in the reviews that reported vaccine effectiveness over time of *Moderna* for the immunocompromised population. The study had a 'serious RoB' based on COVID-NMA appraisal due to uncontrolled confounding, classification of interventions, measurement of outcome, and selection of reported results. Results of the risk of bias appraisals of each study are summarized in Appendix 5.

Results

Based on real world effectiveness studies over time, the effectiveness of primary vaccination of *Moderna* over time for all outcomes cannot be determined due to limited evidence of VE over time.

- **VE against hospitalization due to COVID-19:** Only one study (Tenforde et al., 2021) from relevant reviews which evaluated the effectiveness over time of mRNA vaccines (i.e., *Pfizer-BioNTech* or *Moderna*) for this outcome among the immunocompromised population.
    - ***Against the Alpha variant:*** Tenforde et al. (2021) reported the VE against hospitalization due to COVID-19 at a single time point during the period when Alpha and Delta variant was the dominant variant circulating in the study setting (other VOC being the Delta variant). Tenforde et al. (2021) reported a VE that did not pass the HTAC threshold (i.e., at least 80% VE) for this outcome at a follow-up period of 6 months. Therefore, the duration of protection of *mRNA vaccines* (i.e., *PfizerBioNTech* or *Moderna*) for this outcome among the immunocompromised cannot be determined.

There were no studies included in the reviews that reported VE against any SARS-CoV-2 infection, symptomatic COVID-19, severe COVID-19, or death due to COVID-19 for the immunocompromised population.

HTAC Judgment: Generally, there is limited evidence on the VE over time among immunocompromised patients compared to the available evidence on VE over time among the general population.

Based on the available evidence so far, the general trend of vaccine effectiveness over time for all outcomes cannot be concluded due to limited evidence of VE over time. Additionally, duration of protection against hospitalization due to COVID-19 cannot be inferred based on available studies, and therefore cannot be compared to the general population.

There were no studies included in the reviews that reported VE against any SARS-CoV-2 infection, symptomatic COVID-19, severe COVID-19, or death due to COVID-19 for the immunocompromised population

AstraZeneca

Key findings

Quality of studies

One study (Andrews et al., 2021) included in the reviews reported vaccine effectiveness over time of *AstraZeneca* for the immunocompromised population. However, this study was not appraised by the LCPG Group or COVID-NMA since this was detected from other sources of data (i.e., the IVAC review) which does not perform appraisal. Results of the risk of bias appraisals for this study are summarized in Appendix 5.

Results

Based on real world effectiveness studies over time, *AstraZeneca* remains effective for 4.4 months after the second dose for the following outcome in immunocompromised patients:

- **VE against hospitalization due to COVID-19:** There was one study (Andrews et al., 2021) from relevant reviews which evaluated the effectiveness over time of *AstraZeneca* for this outcome among the immunocompromised population. None of the studies reported this outcome against the Alpha variant.
    - ***Against the Delta variant*:** Andrews et al. (2021) reported a VE that passed the HTAC threshold (i.e., at least 80% VE) for this outcome at 4.4 months for immunocompromised patients aged 40 to 64 years

old. Therefore, it can be inferred that *AstraZeneca* is effective against hospitalization due to COVID-19 caused by the Delta variant for at least **4.4** months for this age group. Thus, it was noted that *AstraZeneca* is effective against hospitalization due to COVID-19 caused by the Delta variant for at least **4.4** months. However, the same study reported a VE that failed the HTAC threshold (i.e., at least 80% VE) at 5 months.

There were no studies included in the reviews that reported VE against any SARS-CoV-2 infection, symptomatic COVID-19, severe COVID-19, hospitalization or death due to COVID-19 for the immunocompromised population.

HTAC Judgment: Generally, there is limited evidence on the VE over time among immunocompromised patients compared to the available evidence on VE over time among the general population.

Based on the available evidence so far, VE against hospitalization among the immunocompromised population decreased over time reaching below the HTAC threshold at 5 months (Delta). Meanwhile, the duration of protection against COVID-19 hospitalization for this population is comparable to that of the general population.

There were no studies included in the reviews that reported VE against any SARS-CoV-2 infection, symptomatic COVID-19, severe COVID-19 or death due to COVID-19 for immunocompromised population.

Janssen

Key findings

Quality of the studies

Overall, there was 1 study (Polinski et al., 202) included in the reviews that reported vaccine effectiveness over time of *Janssen* in the immunocompromised population. The study by Polinski et al., (2021) has a pending appraisal from COVID-NMA.

Results

Based on real world effectiveness studies over time, *COVID-19 Vaccine Janssen* remains effective for 2.5 months after the second dose for the following outcomes in the immunocompromised population.

- **VE against symptomatic COVID-19:** Only one study (Polinski et al., 2021) from the relevant reviews evaluated this outcome caused by the Alpha and Delta variant among the immunocompromised population.
  - ***Against the Alpha variant or Delta variant:*** Polinski et al. (2021) reported a VE that passed the HTAC threshold (i.e, at least 60% VE) against symptomatic COVID-19 at the time when Alpha and Delta variant was among the variant circulating in the setting at its longest follow-up period of 2.5 months. Thus, it can be inferred that *Janssen* is effective against symptomatic COVID-19 in the immunocompromised population for at least 2.5 months.
- **VE against hospitalization due to COVID-19:** Only one study (Polinski et al., 2021) from the relevant reviews evaluated this outcome caused by the Alpha and Delta variant among the immunocompromised population.
  - ***Against the Alpha variant or Delta variant:*** Polinski et al. (2021) reported a VE that failed the HTAC threshold (i.e. at least 80%) against COVID-19 hospitalization caused by the Alpha or Delta variant at a single time point of measurement, with a follow-up period of 5 months. Therefore, the duration of protection of *Janssen* against hospitalization caused by the Alpha or Delta variant among the immunocompromised population cannot be determined.

There were no studies included in the reviews that reported VE against any SARS-CoV-2 infection, severe COVID-19, or death due to COVID-19 for the immunocompromised population.

HTAC Judgment: Generally, there is limited evidence on the VE over time among immunocompromised patients compared to the available evidence on VE over time among the general population.

Based on the available evidence so far, VE against symptomatic COVID-19 of *Janssen* remained over the HTAC threshold (i.e., at least 60% VE) at 2.5 months (Alpha/Delta). However, the general trend of vaccine effectiveness over time for all outcomes cannot be concluded due to limited evidence of VE over time. Meanwhile, there is decreased duration of protection against symptomatic COVID-19 compared to that of the general population. Duration of protection against COVID-19 hospitalization cannot be inferred based on available studies, and therefore cannot be compared to the general population.

There were no studies included in the reviews that reported VE against any SARS-CoV-2 infection, severe COVID-19 infection, or death due to COVID-19 for the immunocompromised population.

CoronaVac

There is currently **no evidence on the duration of protection or effectiveness of *CoronaVac* for immunocompromised patients.** For the evidence on the use of *CoronaVac* in immunocompromised patients, which is limited to immunogenicity studies, studies from the review of the LCPG group on *CoronaVac* as of 16 Sep 2021 and a separate search conducted by the HTAU were synthesized.

Immunogenicity outcomes

Quality of the studies

Overall, there were 4 studies identified that evaluated the immunogenicity of *CoronaVac* in immunocompromised patients.

Risk of bias (RoB) appraisals for Karacin et al., 2021, Seyahi et al., 2021; and Medeiros-Ribeiro et al., 2021 were extracted from the review of the LCPG group. Meanwhile, Bruminhent et al., 2021 was not appraised by the LCPG group since it was detected from a separate search by the HTAU. Based on the RoB appraisal of the LCPG group, all three studies had 'serious risk of bias' due to indirectness and their observational study design. However, it was noted that Medeiros-Ribeiro et al., 2021 controlled for age and sex while Karacin et al., 2021 controlled for age, sex, and systemic treatment regimen.

Results

There were 4 studies – one Phase 4 controlled clinical trial (Medeiros-Ribeiro et al., 2021) and 3 real world cohort studies (Karacin et al., 2021; Seyahi et al., 2021; and Bruminhent et al., 2021) that evaluated the immunogenicity of CoronaVac in immunocompromised patients. Study characteristics and key findings are detailed below.

	Bruminhent, et al., 2021 Bangkok (preprint)	**Seyahi et al., 2021 Turkey (Published)**	**Karacin et al, 2021 Turkey (Published)**	**Medeiros-Ribeiro et al., 2021 Brazil (Published)**
Population	Kidney transplant (KT) patients and non-transplant controls, aged 42-54 (N=75)	Hospital workers and elderly with immune mediated disease (N=104)	Cancer patients (N=47)	Patients ≥18 years with autoimmune rheumatic disease (N=910)
Intervention	2 doses of CoronaVac, 4 weeks apart	Coronavac, 2 doses, 4 weeks interval	CoronaVac, 2 doses, 3µg each dose, 28 days apart	CoronaVac, 2 doses, 3µg each dose, 28 days apart
Comparator	Healthy non-transplant patients (N=38)	Healthy controls (hospital workers and the elderly) (N=347)	N/A	Healthy controls (N=182)
Outcomes	Humoral- and cell-mediated immunity measured 2 weeks after the 2nd dose	Level of anti-spike SARS-CoV-2 IgG antibodies measured median of 30.7 ± 9.0 days after dose 2	SARS-CoV2 antibody level (Immunogenic if: >1IU/mL) Measured 4 weeks after last dose	Measured 6 weeks after dose 2: Anti-S1/S2 SARS-CoV-2 IgG and neutralizing antibody

The four studies reported low immune response for the following outcomes in immunocompromised patients:

Anti-RBD IgG titers

- Brumenthent et al., 2021: Compared to non-transplant controls, mean anti-RBD IgG titers were significantly lower in the kidney transplant group at 2 weeks after dose 2 [2691 (95% CI: 1581 to 3802) vs. 7.8 (95% CI: 0.2 to 15.5), p<0.001]. Further, there was no significant increase in anti-RBD IgG titers among kidney transplant patients at 2 weeks after dose 2 compared to baseline [7.8 (95% CI: 0.2 to 15.5) vs 1.8 (95%CI: 1.3 to 2.3), p=0.07].

Anti-spike SARS-CoV-2 IgG

- Seyahi et al., 2021: Patients with immune-mediated were less likely to have detectable antibodies than hospital worker controls (92.7% vs 99.7%, p < 0.001). The same is true for patients with IMD in the elderly population compared to elderly controls (77.3% vs 97.9%, p = 0.011). Further, being diagnosed with immune-mediated disease [OR 17.31; 95% CI (3.57–85.95), p<0.001] and being ≥60 years [OR 4.32; 95% CI (1.20–15.50), p = 0.025] were found to be independently associated with being seronegative for anti-spike SARS-CoV-2 IgG antibodies.
- Medeiros-Ribeiro et al., 2021: Compared to healthy controls, GMTs were significantly lower among adults with autoimmune rheumatic diseases at 6 weeks after dose 2 [67.0 (95% CI: 59.8 to 54.9) vs 27.0 (95% CI: 24.7 to 29.5), p=0.0010]

Neutralization antibodies (% inhibition)

- Brumenthent et al., 2021: Compared to non-transplant controls, mean percentages of surrogate virus neutralization antibody inhibition was significantly lower in the kidney transplant patients at 2 weeks post-second dose [71% (95%CI: 61 to 81) vs 2% (95% CI: -1 to 6), p<0.001].

- Medeiros-Ribeiro et al., 2021: Compared to healthy controls, neutralizing activity in adults with autoimmune rheumatic diseases was significantly lower at 6 weeks after dose 2 [64.5 (95% CI: 48.4 to 81.4) vs 58.7 (95% CI: 43.1 to 77.2), p=0.0130]

SARS-CoV-2-specific T-cell responses

- Brumenthent et al., 2021: At 2 weeks after dose 2, there was no significant difference between kidney transplant recipients and non-transplant controls in SARS-CoV-2-specific IFN-γ-producing T-cell responses to the S1 protein [62 (95%CI: 26 to 97) vs 42 (95%CI: 21 to 62), p=0.355], S2N protein [33 (95%CI: 19 to 46) vs 18 (95%CI: 8 to 28), p=0.132] and the SMNO protein [69 (95%CI: 41 to 97) vs 66 (95%CI: 36 to 99), p=0.713].

Seroconversion/seropositivity

- Medeiros-Ribeiro et al., 2021: Lower seroconversion rates for anti-SARS-CoV-2 IgG (70.4 vs 95.5% p<0.001) and neutralizing antibody positivity (56.3 vs 79.3%, p<0.001) at 6 weeks after dose 2 among adults with autoimmune rheumatic diseases compared to healthy controls.
- Karacin et al., 2021: Among cancer patients, only 63.8% seroconverted (i.e., SARS-COV-2 antibody level of ≥1 IU) for SARS-CoV-2 total antibodies. Further, 59.5% of patients receiving at least one cytotoxic drug demonstrated seroconversion. Lastly, seroconversion rate was 100% among those receiving monoclonal antibody or immunotherapy alone.

HTAC Judgment: Cannot be assessed for efficacy or effectiveness in immunocompromised patients due to current lack of evidence

RQ.2.10: What are the indications for additional dose vaccination?

HTAC Specifications: N/A

A total of 34 COVID-19 vaccination guidelines from different countries (US, UK, Canada, Australia, Switzerland, Japan, Italy, Germany, France, Thailand, Vietnam, South Korea, Indonesia, Russia, India, Mexico, Nepal, Bahrain, Mauritius, Israel, Chile, Singapore, Cambodia, Greece, Austria, Czech Republic, Hungary, Uruguay, Ireland, Turkey, Finland, and Philippines) and from the WHO and the EMA /European Center for Disease Control (ECDC) were reviewed to determine recommendations on the implementation of booster of COVID-19 vaccines. Of these:

- 19 countries (US, Chile, Israel, Czech Republic, Hungary, Uruguay, UK, Ireland, France, Bahrain, Austria, Cambodia, Singapore, Greece, Switzerland, Australia, Mexico, India, and Philippines) and 2 institutions (WHO, EMA) have guidelines and/or press releases on additional dose vaccination.
- 14 countries (US, Chile, Israel, Czech Republic, Hungary, Uruguay, UK, Ireland, Bahrain, Austria, Cambodia, Singapore, Greece, Hungary) and 2 institutions (EMA, WHO) are currently **recommending** additional dose vaccination.
- 2 institutions (WHO and the EMA) are **recommending** the use of additional dose but did not mention the recommended brand to be used.
- 4 countries (Australia, Mexico, India, and Philippines) are currently **not recommending** additional dose vaccination.
- There were no guidelines on additional vaccination for the following 3 countries: Mauritius, Nepal, and Vietnam.

Pfizer-BioNTech

Additional Dose Vaccination using Pfizer-BioNTech

Of the 13 countries currently using *Pfizer-BioNTech* as part of their additional dose vaccination strategy:

- 2 countries (US, Israel) are recommending the use of *Pfizer-BioNTech* for homologous additional dose strategy only.
- 3 countries (Chile, Bahrain, Cambodia) are recommending the use of *Pfizer-BioNTech* for heterologous additional dose strategy only.
- 6 countries (Czech Republic, Uruguay, UK, Ireland, Austria, Hungary) are recommending the use of *Pfizer-BioNTech* for both homologous and heterologous additional dose strategies.
- 2 countries (Singapore, Greece) are recommending the use of *Pfizer-BioNTech* as an additional dose but did not mention the brand of the primary series.

Of the countries/guidelines recommending and implementing the use of *Pfizer-BioNTech* as part of their additional dose vaccination, below are the noted target vaccine recipients, dosing combinations, and dosing interval:

Country/ Institution	Target Vaccine Recipients	Dosing Combination	Dosing Interval from second dose of the primary series
WHO	Immunocompromised	No specific brand	No information

EMA	Immunocompromised	No specific brand	No information
US	Moderately to severely immunocompromised	Pfizer-Pfizer-Pfizer	2 weeks
Chile	Immunocompromised	Sinovac-Sinovac-Pfizer	Not specified
Israel	People living with organ or stem cell transplants, blood cancer, autoimmune disease, and treatment with specific immunosuppressive medications	Pfizer-Pfizer-Pfizer	5 months
	General Population (>60 years old) vaccinated with two doses and if at least four months after the second dose	Pfizer-Pfizer-Pfizer	5 months
Czech Republic	People living with organ or stem cell transplants, blood cancer, autoimmune disease, and treatment with specific immunosuppressive medications	Pfizer-Pfizer-Pfizer	8 months
		Moderna-Moderna-Pfizer	
		AZ-AZ-Pfizer	
		Janssen-Pfizer	
Hungary	18 years and older, elderly, those with chronic illness, and individuals with a weakened immune system	Pfizer-Pfizer-Pfizer	4 months
		AZ-AZ-Pfizer	
		Janssen-Pfizer	
Uruguay	Moderately to severely immunocompromised	Pfizer-Pfizer-Pfizer	3 months
		AZ-AZ-Pfizer	
		Sinovac-Sinovac-Pfizer	
UK	Severely immunosuppressed, preferred for 12-17 years old	Pfizer-Pfizer-Pfizer	2 months For special cases delayed until 2 weeks after the period of immunosuppression
		Moderna-Moderna-Pfizer	
		AZ-AZ-Pfizer	
		Janssen-Pfizer	
Ireland	Immunocompromised individuals aged 12 years and older	Pfizer-Pfizer-Pfizer	2 months
		Moderna-Moderna-Pfizer	
		Janssen-Pfizer	
		AZ-AZ-Pfizer	
Bahrain	High-risk population	Sinopharm-Sinopharm-Pfizer	6 months
Austria	At-risk and immunocompromised	Pfizer-Pfizer-Pfizer	6-9 months
		Moderna-Moderna-Pfizer	

		AZ-AZ-Pfizer	
		Janssen-Pfizer	
Cambodia	Frontline officers, elderly, over the age of 60 and those with weakened immune systems	Sinopharm-Sinopharm-Pfizer	4-6 months
		Sinovac-Sinovac-Pfizer	
		AZ-AZ-Pfizer	
		Janssen-Pfizer	
Singapore	Immunocompromised, individuals who are residents of long-term care homes, high-risk retirement homes and elder care lodges	mRNA (did not mention brand of primary series)	At least 6 months
Greece	Immunocompromised and at-risk individuals	mRNA (did not mention brand of primary series)	1 month

Moderna

Additional Dose Vaccination using Moderna

Of the 9 countries currently using *Moderna* as part of their additional dose vaccination strategy:

- The US is recommending the use of *Moderna* homologous additional dose strategy only.
- Cambodia is recommending the use of *Moderna* heterologous additional dose strategy only.
- 5 countries (Czech Republic, UK, Ireland, Austria, Hungary) are recommending the use of *Moderna* for both homologous and heterologous additional dose strategies.
- 2 countries (Singapore, Greece) are recommending the use of *Moderna* COVID-19 vaccine as an additional dose but did not mention the brand of the primary series.

Of the countries/guidelines recommending and implementing the use of *Moderna* as part of their additional dose vaccination, below are the noted target vaccine recipients, dosing combinations, and dosing interval:

Country/ Institution	Target Vaccine Recipients	Dosing Combination	Dosing Interval from second dose of the primary series
WHO	Immunocompromised	No specific brand	No information
EMA	Immunocompromised	No specific brand	No information
US	Moderately to severely immunocompromised	Moderna-Moderna-Moderna	2 weeks
Czech Republic	People living with organ or stem cell transplants, blood cancer, autoimmune disease, and treatment with specific immunosuppressive medications	Pfizer-Pfizer-Moderna	8 months
		Moderna-Moderna-Moderna	
		AZ-AZ-Moderna	
		Janssen-Moderna	
Hungary	18 years and older, elderly, those with chronic illness, and individuals with a weakened immune system	Moderna-Moderna-Moderna	4 months

		AZ-AZ-Moderna	
		Janssen-Moderna	
UK	Severely immunosuppressed, preferred for 12-17 years old	Pfizer-Pfizer-Moderna (half-dose)	2 months For special cases delayed until 2 weeks after the period of immunosuppression
		Moderna-Moderna-Moderna (half-dose)	
		AZ-AZ-Moderna (half-dose)	
		Janssen-Moderna (half-dose)	
Ireland	Immunocompromised individuals aged 12 years and older	Pfizer-Pfizer-Moderna	2 months
		Moderna-Moderna-Moderna	
		Janssen-Moderna	
		AZ-AZ-Moderna	
Austria	At-risk and immunocompromised	Pfizer-Pfizer-Moderna	6-9 months
		Moderna-Moderna-Moderna	
		AZ-AZ-Moderna	
		Janssen-Moderna	
Cambodia	Frontline officers, elderly, over the age of 60 and those with weakened immune systems	Sinopharm-Sinopharm-Moderna	4-6 months
		Sinovac-Sinovac-Moderna	
		AZ-AZ-Moderna	
		Janssen-Moderna	
Singapore	Immunocompromised, individuals who are residents of long-term care homes, high-risk retirement homes and elder care lodges	mRNA (did not mention brand of primary series)	At least 6 months
Greece	Immunocompromised and at-risk individuals	mRNA (did not mention brand of primary series)	1 month

AstraZeneca

Additional Dose Vaccination using AstraZeneca

Of the 3 countries currently using *AstraZeneca* as part of their additional dose vaccination strategy:

- No country is recommending the use of *AstraZeneca* homologous additional dose strategy only.
- Cambodia is recommending the use of *AstraZeneca* heterologous additional dose strategy only.

- The UK and Hungary are recommending the use of *AstraZeneca* COVID-19 for both homologous and heterologous additional dose strategies.

Of the countries/guidelines recommending and implementing the use of *AstraZeneca* as part of their additional dose vaccination, below are the noted target vaccine recipients, dosing combinations, and dosing interval:

Country/ Institution	Target Vaccine Recipients	Dosing Combination	Dosing Interval from second dose of the primary series
WHO	Immunocompromised	No specific brand	No information
EMA	Immunocompromised	No specific brand	No information
Hungary	18 years and older, elderly, those with chronic illness, and individuals with a weakened immune system	AZ-AZ-AZ	4 months
		Pfizer-Pfizer-AZ	
		Moderna-Moderna-AZ	
UK	Severely immunosuppressed or if AZ is contraindicated or when mRNA vaccines are unavailable, preferred for 12-17 years old	Pfizer-Pfizer-AZ	2 months For special cases delayed until 2 weeks after the period of immunosuppression
		Moderna-Moderna-AZ	
		AZ-AZ-AZ	
		Janssen-AZ	
Cambodia	Immunocompromised and at-risk individuals	Sinopharm-Sinopharm-AZ	4-6 months
		Sinovac-Sinovac-AZ	

Janssen

Additional Dose Vaccination using Janssen

Of the 13 countries currently recommending additional dose vaccination, **none of the countries/guidelines reviewed recommended the use of *Janssen* as an additional dose**.

CoronaVac

Additional Dose Vaccination using Sinovac

Only Cambodia is using *Sinovac* COVID-19 vaccine for homologous additional dose strategy as part of their vaccination strategy for immunocompromised patients.

Of the countries/guidelines recommending and implementing the use of *Sinovac* as part of their additional dose vaccination, below are the noted target vaccine recipients, dosing combinations, and dosing interval:

Country/ Institution	Target Vaccine Recipients	Dosing Combination	Dosing Interval from second dose of the primary series
WHO	Immunocompromised	No specific brand	No information
EMA	Immunocompromised	No specific brand	No information

Cambodia	Immunocompromised and at-risk individuals	Sinovac-Sinovac-Sinovac	4-6 months

RQ.2.11: Is homologous additional dose vaccination efficacious?

HTAC Specifications:
Preferred VE: ≥70% reduction in the risk of symptomatic infection with vaccination versus no vaccination
Minimum acceptable VE (point estimate) : at least 60% reduction of symptomatic COVID-19; **at least 80% reduction** of severe COVID-19, hospitalization due to COVID-19; **at least 80% reduction** of death due to COVID-19

The evidence on the efficacy and effectiveness of *Pfizer-BioNTech* as a homologous additional dose is based on the following 1), Philippine Living Clinical Practice Guidelines Group (LCPG Group), updated 24 September (Appendix 2, Part 5); 2) the International Vaccine Access Center (IVAC) of the Johns Hopkins Bloomberg School of Public Health and World Health Organization as of 01 Oct 2021; 3) COVID-NMA as of 07 October 2021; and 4) the US CDC Advisory Committee on Immunization Practices (ACIP) as of 23 Sept 2021.

Pfizer-BioNTech

Evidence from Clinical trials

Efficacy outcomes

The reference reviews did not detect any clinical trials that examined the clinical efficacy of homologous additional dose vaccination using *Pfizer*. This shall be updated once new clinical evidence has been reviewed.

Immunogenicity outcomes

Description of evidence

The detected trial (i.e. Bonelli et al., 2021) has examined the immunogenicity of *Pfizer-BioNTech* as a homologous additional dose. The characteristics of the detected study are presented below.

Study	Population	Intervention	Comparator	Outcome	Follow up	Study Design
Bonelli et al., 2021	Adults w/ chronic-inflammatory rheumatic or neurologic diseases under current rituximab therapy N=60 Austria	Pfizer (third dose) Moderna or Pfizer (primary series) 10.6 weeks after 2nd dose	Pfizer, Moderna, or AZ (third dose) Moderna or Pfizer (primary series)	Difference in Ab seroconversion rates, seroconversion rate, Ab levels	10.6 weeks	Prospective RCT

Key Findings

- *Outcome 1: Seropositivity rates*
  - Bonelli et al reported a 32% seroconversion rate four weeks after the third dose of mRNA vaccine in a homologous series vs 22% seroconversion rate in the mRNA with an additional dose of AstraZeneca.
- *Outcome 2:* anti-RBD titer
  - The study of Bonelli et al reported a median anti-RBD titer of 12.4 BAU/mL [IQR: 3.8, 17.8] for the homologous mRNA arm vs 19.4 [IQR: 8.2, 114.8] for the heterologous mRNA + AZ arm.

Evidence from Real World Studies

Effectiveness outcomes

Description of evidence

Of the 6 detected real world studies, four studies (i.e. Werbel et al.,2021, Bensouna et al., 2021, Kamar et a.l, 2021, Chavarot et al.), reported cases of breakthrough infections in immunocompromised patients

after a primary series and after a homologous additional dose of *Pfizer-BioNTech*. The characteristics of the detected studies are presented below.

Study	Population	Intervention	Comparator	Outcome	Follow up	Study Design
Werbel et al. (2021)	Solid organ transplant recipients N=30 US	3rd dose of mRNA-1273 (median of 67 days after dose 2 of primary vaccine series)	Two doses of Pfizer or Moderna no third dose	Breakthrough Infections	Median 14 days after the third dose	Case series
Bensouna et al. (2021)	Patients receiving maintenance hemodialysis or peritoneal dialysis N=69 France	Pfizer (third dose) 4 weeks after 2nd dose	Pfizer (primary series), no third dose	Breakthrough Infections	30 days	Observational study
Kamar et al. (2021)	Solid-organ transplant patients N=101 France	Pfizer (third dose) 61±1 days after 2nd dose	Pfizer (primary series) no third dose	Breakthrough Infections	1 month	Retrospective Cohort
Chavarot et al. (2021)	Kidney transplant recipients treated with belatacept N=62 US	Pfizer (third dose)	Pfizer (primary series) no third dose	RT-PCR or IgG antibody confirmed infection	~44 days	Retrospective Cohort

Key Findings

Quality of Studies

The LCPG rated all four studies with a very serious RoB due to non-randomization, failure to conceal allocation, non-blinding of both participants and investigators, and failure to assess confounding factors.

Effectiveness results

Bensouna et al (2021) noted that none of the hospitalized cases reported after the third dose were breakthrough infections compared to the 4 symptomatic COVID cases after the second dose. Werbel et al (2021) and Kamar et al (2021) reported that there were no breakthrough infections in their respective cohorts. In contrast, Chavarot et al (2021) noted that 8 patients developed infection after the completion of primary series while only 1 patient developed infection 6 days after the third dose using either RT-PCR or IgG antibody confirmation.

Immunogenicity outcomes

Description of evidence

Of the 6 detected real world studies (i.e. Ducloux et al., 2021; Werbel et al., 2021; Bensouna et al., 2021; Kamar et al., 2021; Chavarot et al., 2021; Masset et al., 2021), all have examined the immunogenicity of *Pfizer-BioNTech* as a homologous additional dose. The characteristics of the detected studies are presented below.

Study	Population	Intervention	Comparator	Outcome	Follow up	Study Design
Ducloux et al, 2021	Patients on hemodialysis	Pfizer (third dose) Dosing Interval - Not	Pfizer (primary series) no third dose	GMT 1 month after 3rd dose	1 month	Case Series/ Comparative Cohort

	N=50 France	Indicated				
Werbel et al., 2021	Solid organ transplant recipients N=30 US	3rd dose of mRNA-1273 (median of 67 days after dose 2 of primary vaccine series)	Two doses of either Pfizer or Moderna	Anti-S1 IgG or anti-RBD assays	Median 14 days after the third dose	Case series
Bensouna et al., 2021	Patients receiving maintenance hemodialysis or peritoneal dialysis N=69 France	Pfizer (third dose) 4 weeks after 2nd dose	Pfizer (primary series) no third dose	Anti-spike Ab, ratio of antibody level (3rd:2nd)	30 days	Observational study
Kamar et al., 2021	Solid-organ transplant patients N=101 France	Pfizer (third dose) 61±1 days after 2nd dose	Pfizer (primary series) no third dose	Anti-spike Ab levels	1 month	Retrospective Cohort
Chavarot et al., 2021	Kidney transplant recipients treated with belatacept N=62 US	Pfizer (third dose)	Pfizer (primary series) no third dose	Anti-spike IgG titer	~44 days	Retrospective Cohort
Masset et al., 2021	Kidney transplant patients N=456 France	Pfizer (third dose) 50 days after 2nd dose	mRNA vaccine (primary series) no third dose	Anti spike (IgG) responses, serologic conversion	4 weeks	Retrospective cohort

Key Findings

- *Outcome 1: Seropositivity rates*
  - Ducloux et al. (2021) reported an increase in seropositivity rates for anti-RBD IgG titers from 89% after the second dose to 93% after the third dose
  - Masset et al. (2021) reported that 69.2% participants had serologic conversion at week 4 after the third dose.
  - Werbel et al. (2021) reported that one out of three patients (33.3%) who had homologous *Pfizer-BioNTech* turned seropositive after the third dose compared to none after the second dose.
  - Kamar et al. (2021) reported that among seronegative patients after the third dose, 44% turned seropositive at 4 weeks after the third dose resulting in 1.67-fold-increase in seropositivity rates.

- *Outcome 2: Anti-RBD titer*
  - Ducloux et al (2021) reported an increase in anti-RBD IgG titers from 5,156 AU/mL (95% CI: 1,502 to 21,569) after the second dose to 6,435 AU/mL (2,790 to 17,014) after the third dose.

- *Outcome 3: Anti-S1 antibody level*
  - Bensouna et al (2021) also reported an increase in Anti-S1 antibody titer from a median titer after the second dose of 284 AU/mL (95% CI: 83 to 1190) to 7,554 AU/mL (95% CI: 2,268 to 11,736) after the third dose.
  - Maset et al (2021) noted that nearly all patients with a positive serology after the second mRNA vaccine had a high titer of anti-spike antibody (>250UI/L).

- *Outcome 3: Anti–SARS-CoV-2 Antibody Titers*
  - Kamar et al. (2021) reported a 74-fold increase in GMT in seropositive participants from 36 GMT to 2, 676 GMT one month after the administration of the third dose.

- *Outcome 4: SARS-CoV-2 anti-Spike IgG titer*
  - Chavarot et al study concluded that there was no change from titer after dose 2 to titer after dose 3 from 0 to 0 for kidney transplant recipients treated with belatacept without prior COVID-19.

HTAC Judgment: Yes, it is potentially efficacious as a homologous additional dose based on limited evidence.

Moderna

Evidence from Clinical trials

Efficacy outcomes

The reference reviews did not detect any clinical trials that examined the clinical efficacy of homologous additional dose vaccination using *Moderna*. This shall be updated once new clinical evidence has been reviewed.

Immunogenicity outcomes

Description of evidence

The LCPG Group review detected two trials (i.e. Hall et al., 2021, Bonelli et al., 2021), examining the immunogenicity of *Moderna* as a homologous additional dose for immunocompromised patients. The characteristics of the detected study are presented below.

Study	Population	Intervention	Comparator	Outcome	Follow up	Study Design
Hall et al, 2021	Transplant patients aged 18 years and older N=120 Canada	3rd dose of *Moderna* given at 2 months after the second dose of mRNA (n=60)	Saline solution given at 2 months after the second dose of *Moderna* (n=57) Note: 1 developed COVID-19 and excluded from analysis – not indicated at which time point the patient developed COVID	Anti-RBD IgG level of at least 100U/mL at month 4 (2 months after the second dose) [Test used: Elecys Anti-SARS-CoV-2 immunoassay]; Neutralization by surrogate virus neutralization assay; Increase in polyfunctional T-cell response compared to pre-vaccination	4 weeks	Phase I/II Safety and Immunogenicity
Bonelli et al, 2021	Adults w/ chronic-inflammatory rheumatic or neurologic diseases under current rituximab therapy (non-seroconverted after 2 doses) N=60 Austria	3rd dose of *Moderna* or *Pfizer-BioNTech* 10.6 weeks after 2nd dose	ChAdOx1 nCoV-19 vector vaccine (third dose); mRNA (primary series)	Antibody seroconversion rate	4 weeks	Blinded randomized clinical trial

Key Findings

- *Outcome 1: Seropositivity rates*
  - Hall et al. (2021) noted a 2.4-fold increase of neutralizing antibodies from 25% of the placebo compared to the 60% after the third dose.
  - Bonelli et al reported a 32% seroconversion rate four weeks after the third dose of mRNA vaccine in a homologous series vs 22% seroconversion rate in the mRNA with an additional dose of *AstraZeneca.*

- *Outcome 2: Anti-RBD titer*
  - Hall et al (2021) reported a 36.5-fold increase in titers after the additional dose compared to placebo.
  - The study of Bonelli et al reported a median anti-RBD titer of 12.4 BAU/mL [IQR: 3.8, 17.8] for the homologous mRNA arm vs 19.4 [IQR: 8.2, 114.8] for the heterologous mRNA + *AstraZeneca* arm.

- *Outcome 3: CD4+ T Cell*
  - Hall et al (2021) also reported a 6.45-fold increase in cell count after the administration of the third dose compared to placebo.

Evidence from Real World Studies

Effectiveness outcomes

Description of evidence

Of the 2 detected real world studies, one study (i.e. Werbel et al.,2021), reported cases of breakthrough infections in immunocompromised patients after a primary series and after a homologous additional dose of *Pfizer-BioNTech*. The characteristics of the detected study are presented below.

Study	Population	Intervention	Comparator	Outcome	Follow up	Study Design
Werbel et al. (2021)	Solid organ transplant recipients N=30 US	3rd dose of *Moderna* (median of 67 days after dose 2 of primary vaccine series)	Two doses of either of either two doses of Pfizer or Moderna; no third dose	Breakthrough Infections	Median 14 days after the third dose	Case series

Key Findings

Quality of Studies

The LCPG rated Werbel et al.,2021 with a very serious RoB due to non-randomization, failure to conceal allocation, non-blinding of both participants and investigators, and failure to assess confounding factors.

Effectiveness results

The study of Werbel et al (2021) reported that there were no breakthrough infections in their cohort.

Immunogenicity outcomes

Description of evidence

Of the 2 detected real world studies (i.e. Werbel et al.,2021, Benotmane et al., 2021), all have examined the immunogenicity of *Moderna* as a homologous additional dose for immunocompromised patients. The characteristics of the detected studies are presented below.

Study	Population	Intervention	Comparator	Outcome	Follow up	Study Design
Benotmane et al., 2021	Kidney transplant recipients N=159 France	3rd dose of *Moderna* given at median of 51 days	Two doses *Moderna*; no third dose	Anti–receptor-binding domain IgG response	28 days	Retrospective cohort
Werbel et al, 2021	Solid organ transplant recipients N=30 US	3rd dose of *Moderna* (median of 67 days after dose 2 of primary vaccine series)	Two doses of either Pfizer or Moderna (no third dose)	Anti-S1 IgG or anti-RBD assays	Median 14 days after the third dose	Case series

Key Findings

- *Outcome: Seropositivity rates*
  - Werbel et al. (2021) reported that two out of three patients (66.7%) turned seropositive under the homologous additional dose of *Moderna* arm compared *to* one out of three patients (33.3%) under the homologous primary series of *Moderna*.
  - Benotmane et al (2021) reported a 49% seropositivity post-third dose from 0% seropositivity after the second dose in terms of anti-RBD IgG titers.

HTAC Judgment: Yes, it is potentially efficacious as a homologous additional dose based on limited evidence.

AstraZeneca

Evidence on the efficacy and effectiveness of *AstraZeneca as a homologous additional dose* for immunocompromised patients were searched from the reviews of the LCPG Group (updated as of 3 October 2021), IVAC (updated as of 23 September 2021), and COVID-NMA (updated as of 29 September 2021). Relevant studies are currently not available yet on the effectiveness, efficacy, or immunogenicity of a homologous additional dose of *AstraZeneca* for immunocompromised patients.

HTAC Judgment: Cannot assess the efficacy or effectiveness as a homologous additional dose due to current lack of evidence

Janssen

Evidence on the efficacy and effectiveness of *Janssen as a homologous additional dose* for immunocompromised patients were searched from the reviews of the LCPG Group (updated as of 3 October 2021), IVAC (updated as of 23 September 2021), and COVID-NMA (updated as of 29 September 2021). Relevant studies are currently not available yet on the effectiveness, efficacy, or immunogenicity of a homologous additional dose of *Janssen* for immunocompromised patients.

HTAC Judgment: Cannot assess the efficacy or effectiveness as a homologous additional dose due to current lack of evidence

CoronaVac

Evidence on the efficacy and effectiveness of *CoronaVac as a homologous additional dose* for immunocompromised patients were searched from the reviews of the LCPG Group (updated as of 3 October 2021), IVAC (updated as of 23 September 2021), and COVID-NMA (updated as of 29 September 2021). Relevant studies are currently not available yet on the effectiveness, efficacy, or immunogenicity of a homologous additional dose of *CoronaVac* for immunocompromised patients.

HTAC Judgment: Cannot assess the efficacy or effectiveness as a homologous additional dose due to current lack of evidence

RQ.2.12. Is homologous additional dose vaccination safe?

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

The evidence on the safety of *Pfizer-BioNTech* as a homologous additional dose is based on the following 1), Philippine Living Clinical Practice Guidelines Group (LCPG Group), updated 24 September (Appendix 2, Part 5); 2) the International Vaccine Access Center (IVAC) of the Johns Hopkins Bloomberg School of Public Health and World Health Organization as of 01 Oct 2021; 3) COVID-NMA as of 07 October 2021; and 4) the US CDC Advisory Committee on Immunization Practices (ACIP) as of 23 Sept 2021.

Pfizer-BioNTech

Safety data from Clinical Trials
Description of evidence

The reference reviews detected one trial (Bonelli, et al, 2021), examining the safety of *Pfizer-BioNTech* as a homologous additional dose, the same study presented in the previous section. The characteristics of the detected study were presented in the previous section.

Key Findings

Quality of Studies

The LCPG rated Bonelli et al. (2021) with serious RoB due to its lack of clarity on the following: randomization, concealment allocation, and blinding of both participants and investigators.

Safety results

- *Outcome 1: Local Adverse Events*
  - Bonelli et al (2021) reported that most side effects were similar between homologous mRNA arm and heterologous mRNA+*AstraZeneca* arm, with an interval of 10.6 weeks.

- *Outcome 2: Systemic Adverse Events*
  - Bonelli et al (2021) concluded that most side effects were similar between homologous mRNA arm and heterologous mRNA+*AstraZeneca* arm. Numerically, a higher prevalence of systemic reactogenicity was reported in the heterologous *Pfizer-BioNTech* + *AstraZeneca* group vs. homologous *Pfizer-BioNTech* strategy for fatigue, arthralgia and myalgias.

- *Outcome 3: Serious Adverse Events*
  - Bonelli et al (2021) also noted that no serious adverse events were recorded in both the homologous mRNA arm and heterologous mRNA+AZ arm.

Safety data from Real World Evidence

Description of evidence

The reference reviews detected two real world studies (Bensouna, et al, 2021, Werbel, et al, 2021), examining the safety of *Pfizer-BioNTech* as a homologous additional dose. The characteristics of the detected studies are presented below.

Study	Population	Intervention	Comparator	Outcome	Follow up	Study Design
Werbel et al., 2021	Solid organ transplant recipients N=30 US	3rd dose of *Moderna or Pfizer-BioNTech ; mRNA (primary series)* (median of 67 days after dose 2 of primary vaccine series)	3rd dose of Janssen; mRNA (primary series)	• Local Reactogenicity • Systemic Reactogenicity • Serious Adverse Event	Median 14 days after the third dose	Case series
Bensouna et al., 2021	Patients receiving maintenance hemodialysis or peritoneal dialysis N=69 France	*Pfizer-BioNTech* (third dose) 4 weeks after 2nd dose	Pfizer (primary series)	Self-reported AEs, hospitalizations, visits to the Emergency Department	30 days	Observational study

Key Findings

Quality of Studies

The LCPG noted that both studies (Werbel et al.,2021, Bensouna et al., 2021) had a very serious RoB due to non-randomization, failure to conceal allocation, non-blinding of both participants and investigators, and failure to assess confounding factors.

Safety results

- *Outcome 1: Local Adverse Events*
  - Werbel et al (2021) reported that there were more participants in the mRNA vaccine third dose arm who experienced local reactions than those who received *Janssen* as an additional dose.
  - Bensouna et al (2021) noted that the most frequent self-reported reaction was pain at the injection site (27%) after an additional dose with an interval of 4 weeks.

- *Outcome 2: Systemic Adverse Events*
  - Werbel et al (2021) reported that there were fewer participants in the mRNA vaccine third dose arm who experienced systemic reactions than those who received Janssen as an additional dose.
  - Bensouna et al (2021) noted that 23% of patients had at least one systemic reaction, mostly fatigue (17%) after an additional dose with an interval of 4 weeks.

- *Outcome 3: Serious Adverse Events*
  - Of the 5 patients who received *Pfizer-BioNTech* as an additional dose in the study of Werbel et al (2021), no serious adverse events were reported.

- *Outcome 4: Hospitalization*
  - The study of Bensouna et al (2021) reported 6 incidents of hospitalizations after the additional dose due to the following reasons: 3 bacterial peritonitis, 1 aseptic peritonitis, 1 pulmonary embolism, and 1 osteitis. Furthermore, it reported 2 visits to the emergency room due to chest pain and fatigue.

HTAC Judgment: Yes, it is considered safe as a homologous additional dose based on limited evidence.

Moderna

Safety data from Clinical Trials

Description of evidence

The LCPG Group review detected two trials (i.e. Hall et al., 2021; Bonelli et al., 2021), examining the safety of *Moderna* as a homologous additional dose for immunocompromised patients. The characteristics of the detected study are presented below.

Study	Population	Intervention	Comparator	Outcome	Follow up	Study Design
Hall et al, 2021	Transplant patients aged 18 years and older N=120 Canada	3rd dose of *Moderna* given at 2 months after the second dose (n=60)	Saline solution given at 2 months after the second dose of *Moderna* (n=57) Note: 1 developed COVID-19 and excluded from analysis – not indicated at which time point the patient developed COVID	*Safety:* • Local adverse events • Systemic adverse events	4 weeks	Phase I/II Safety and Immunogenicity
Bonelli et al., 2021	Adults w/ chronic-inflammatory rheumatic or neurologic diseases under current rituximab therapy N=60 Austria	Moderna/Pfizer (third dose) same primary series 10.6 weeks after 2nd dose	AZ (third dose) to mRNA primary series	Adverse events (Fever, arthralgia, local reactions, pruritus, headache, etc.)	4 weeks	Prospective RCT

Key Findings

Quality of Studies

The LCPG rated Hall et al. (2021) with not serious RoB while they rated Bonelli et al. (2021) with serious RoB due to its lack of clarity on the following: randomization, concealment allocation, and blinding of both participants and investigators.

Safety results

- *Outcome 1: Local Adverse Events*
  - Hall et al (2021) reported that the additional dose of *Moderna* was associated with slightly higher local adverse reaction rates when compared to placebo or second dose of the same vaccine.
  - Bonelli et al (2021) reported that most side effects were similar between homologous mRNA arm and heterologous mRNA+AstraZeneca arm, with an interval of 10.6 weeks.

- *Outcome 2: Systemic Adverse Events*
  - Hall et al (2021) reported that the additional dose of *Moderna* was associated with slightly higher systemic adverse reaction rates when compared to placebo or second dose of the same vaccine.
  - Bonelli et al (2021) concluded that most side effects were similar between homologous mRNA arm and heterologous mRNA + AstraZeneca arm.

- *Outcome 3: Serious Adverse Events*
  - Bonelli et al (2021) also noted that no serious adverse events were recorded in both the homologous mRNA arm and heterologous mRNA + AstraZeneca arm.

Safety data from Real World Evidence

Description of evidence

The LCPG Group review detected one study (i.e. Werbel et al., 2021), examining the safety of *Moderna* as a homologous additional dose for immunocompromised patients. The characteristics of the detected study are presented below.

Study	Population	Intervention	Comparator	Outcome	Follow up	Study Design
Werbel et al, 2021	Solid organ transplant recipients N=30 US	3rd dose of *Moderna or Pfizer; mRNA (primary series)* (median of 67 days after dose 2 of primary vaccine series)	3rd dose of Janssen; mRNA (primary series)	• Local Reactogenicity • Systemic Reactogenicity • Serious Adverse Event	Median 14 days after the third dose	Case series

Key Findings

Quality of Studies

The LCPG rated Werbel et al. (2021) with very serious RoB due to its non-randomization, failure to conceal allocation, and non-blinding of both participants and investigators.

Safety results

- *Outcome 1: Local Adverse Events*
  - Werbel et al (2021) reported that there were more participants in the homologous third dose mRNA arm who experienced local reactions than those who received heterologous *Janssen* as an additional dose to mRNA vaccine (primary series) .

- *Outcome 2: Systemic Adverse Events*
  - Werbel et al (2021) reported that there were fewer participants in the homologous third dose mRNA arm who experienced systemic reactions than those who received heterologous Janssen as an additional dose to mRNA vaccine (primary series).

- *Outcome 3: Serious Adverse Events*
  - No serious adverse events were reported among the patients in the homologous third dose mRNA arm and patients who received heterologous Janssen as an additional dose to mRNA vaccine (primary series) in the study of Werbel et al (2021)

HTAC Judgment: Yes, it is considered safe as a homologous additional dose based on limited evidence.

AstraZeneca

Evidence on the safety of *AstraZeneca as a homologous additional dose* for immunocompromised patients were searched from the reviews of the LCPG Group (updated as of 3 October 2021), IVAC (updated as of 23 September 2021), and COVID-NMA (updated as of 29 September 2021). Relevant studies are currently not available yet on the safety of a homologous additional dose of *AstraZeneca* for immunocompromised patients.

HTAC Judgment: Cannot assess the overall safety as a homologous additional dose based on current lack of evidence

Janssen

Evidence on the safety of *Janssen as a homologous additional dose* for immunocompromised patients were searched from the reviews of the LCPG Group (updated as of 3 October 2021), IVAC (updated as of 23 September 2021), and COVID-NMA (updated as of 29 September 2021). Relevant studies are currently not available yet on the safety of a homologous additional dose of *Janssen* for immunocompromised patients.

HTAC Judgment: Cannot assess the overall safety as a homologous additional dose based on current lack of evidence

CoronaVac

Evidence on the safety of *CoronaVac as a homologous additional dose* for immunocompromised patients were searched from the reviews of the LCPG Group (updated as of 3 October 2021), IVAC (updated as of 23 September 2021), and COVID-NMA (updated as of 29 September 2021). Relevant studies are currently not available yet on the safety of a homologous additional dose of *CoronaVac* for immunocompromised patients.

HTAC Judgment: Cannot assess the overall safety as a homologous additional dose based on current lack of evidence

RQ.2.13: Is heterologous additional dose vaccination efficacious?

HTAC Specifications:
Preferred VE: ≥70% reduction in the risk of symptomatic infection with vaccination versus no vaccination
Minimum acceptable VE (point estimate) : at least 60% reduction of symptomatic COVID-19; **at least 80% reduction** of severe COVID-19, hospitalization due to COVID-19; **at least 80% reduction** of death due to COVID-19

The evidence on the efficacy and effectiveness of *Pfizer-BioNTech* as a heterologous additional dose is based on the following 1), Philippine Living Clinical Practice Guidelines Group (LCPG Group), updated 24 September (Appendix 2, Part 5); 2) the International Vaccine Access Center (IVAC) of the Johns Hopkins Bloomberg School of Public Health and World Health Organization as of 01 Oct 2021; 3) COVID-NMA as of 07 October 2021; and 4) the US CDC Advisory Committee on Immunization Practices (ACIP) as of 23 Sept 2021.

Pfizer-BioNTech

Evidence from Clinical trials

The relevant reviews did not detect any clinical trial examining the clinical efficacy or immunogenicity of *Pfizer-BioNTech* as an additional dose to any heterologous booster vaccine strategy. This shall be updated once new clinical evidence has been reviewed.

Evidence from Real World Studies

Effectiveness outcomes

Description of evidence

Werbel, et al, 2021 reported cases of breakthrough infections in immunocompromised patients after a heterologous additional dose of *Pfizer-BioNTech* in combination with *Moderna* as a primary series for immunocompromised patients. The characteristics of the detected study are presented below.

Study	Population	Intervention	Comparator	Outcome	Follow up	Study Design
Werbel et al. (2021)	Solid organ transplant recipients N=30 US	3rd dose of *Pfizer-BioNTech* (median of 67 days after dose 2 of primary vaccine series)	Two doses of either Pfizer or Moderna	Breakthrough Infections	Median 14 days after the third dose	Case series

Key Findings

Quality of Study

The LCPG rated the study with a very serious RoB due to non-randomization, failure to conceal allocation, non-blinding of both participants and investigators, and failure to assess confounding factors.

Effectiveness results

The study of Werbel et al (2021) reported that there were no breakthrough infections in both arms . The third dose of the vaccine was administered after a median of 67 days dosing interval. The median follow up period of the study was 14 days after the third dose.

Immunogenicity outcomes

Description of evidence

The same real world study mentioned above (i.e. Werbel, et al, 2021), examined the immunogenicity of *Pfizer-BioNTech* as an additional dose in combination with *Moderna* as primary series. The characteristics of the detected study are presented below.

Study	Population	Intervention	Comparator	Outcome	Follow up	Study Design
Werbel et al. (2021)	Solid organ transplant recipients N=30 US	3rd dose of *Moderna* (median of 67 days after dose 2 of primary vaccine series)	Two doses of either Pfizer or Moderna	Anti-S1 IgG or anti-RBD assays	Median 14 days after the third dose	Case series

Key Findings

The study of Werbel et al, 2021 reported that there was no change (one out of two patients) in terms of the proportion of patients who turned seropositive after an additional dose of *Pfizer-BioNTech* following a *Moderna* primary series compared to the proportion after 2 does of mRNA. The median dosing interval of the study was 67 days while repeated antibody testing was done at a median of 14 days (IQR: 14 to 17 days) after the third dose of vaccine.

HTAC Judgment: Yes, it is potentially efficacious as a heterologous additional dose based on limited evidence.

Moderna

Evidence from Clinical trials

The relevant reviews did not detect any clinical trial examining the clinical efficacy or immunogenicity of *Moderna* as an additional dose to any heterologous additional dose vaccine strategy. This shall be updated once new clinical evidence has been reviewed.

Evidence from Real World Studies

Effectiveness outcomes

Description of evidence

Werbel, et al, 2021 reported cases of breakthrough infections in immunocompromised patients after a heterologous additional dose of *Moderna* in combination with *Pfizer-BioNTech* as a primary series for immunocompromised patients compared to those who had an additional dose of *Janssen*. The characteristics of the detected study were presented in the previous section.

Key Findings

Quality of Study

The LCPG rated the study with a very serious RoB due to non-randomization, failure to conceal allocation, non-blinding of both participants and investigators, and failure to assess confounding factors.

Effectiveness results

The study of Werbel et al (2021) reported that there were no breakthrough infections among those who had an additional dose of *Moderna*. The third dose of the vaccine was administered after a median of 67 days dosing interval. The median follow up period of the study was 14 days after the third dose.

Immunogenicity outcomes

Description of evidence

The same real world study mentioned above (i.e. Werbel, et al, 2021), examined the immunogenicity of *Moderna* as an additional dose to *Pfizer-BioNTech* as primary series. The characteristics of the detected study were presented in the previous section.

Key Findings

The study of Werbel et al, 2021 reported that there was an increase in terms of the proportion of patients who turned seropositive after an additional dose of *Moderna* following a *Pfizer-BioNTech* as primary series (5 out of 7 patients; 71%) compared to the proportion after the second dose of *Pfizer-BioNTech* (2 out of 7 patients; 29%). The median dosing interval of the study was 67 days while repeated antibody testing was done at a median of 14 days (IQR: 14 to 17 days) after the third dose of vaccine.

HTAC Judgment: Yes, it is potentially efficacious as a heterologous additional dose based on limited evidence.

AstraZeneca

Evidence from Clinical trials

Efficacy outcomes

The reference reviews did not detect any clinical trials that examined the clinical efficacy of heterologous additional dose vaccination using *AstraZeneca*. This shall be updated once new clinical evidence has been reviewed.

Immunogenicity outcomes

Description of evidence

The detected trial (i.e. Bonelli et al., 2021), examined the immunogenicity of *AstraZeneca* as an additional dose in combination with an mRNA vaccine (i.e. *Moderna or Pfizer-BioNTech*) as a primary series. The characteristics of the detected study are presented below.

Study	Population	Intervention	Comparator	Outcome	Follow up	Study Design
Bonelli et al., 2021	Adults w/ chronic-inflammatory rheumatic or neurologic diseases under current rituximab therapy N=60 Austria	AZ (third dose) to mRNA primary 10.6 weeks after 2nd dose	mRNA (third dose) to mRNA primary series	Antibody seroconversion rate	4 weeks	Prospective RCT

Key Findings

- *Outcome: Seropositivity rates*
  - Bonelli et al (2021) reported a lower proportion of patients who seroconverted using *AstraZeneca* as a heterologous additional dose mRNA primary series (6 out of 27; 22%) compared to those who seroconverted using a homologous additional dose of mRNA vaccine (9 out of 28; 32%).
- *Outcome 2:* anti-RBD titer
  - The study of Bonelli et al reported a median anti-RBD titer of 12.4 BAU/mL [IQR: 3.8, 17.8] for the homologous mRNA arm vs 19.4 [IQR: 8.2, 114.8] for the heterologous mRNA + AZ arm.

Evidence from Real World Studies

The relevant reviews did not detect any clinical trial examining the clinical efficacy or immunogenicity of *Pfizer-BioNTech* as an additional dose to any heterologous booster vaccine strategy. This shall be updated once new clinical evidence has been reviewed.

HTAC Judgment: Yes, it is potentially efficacious as a heterologous additional dose based on limited evidence.

Janssen

Evidence from Clinical trials

The relevant reviews did not detect any clinical trial examining the clinical efficacy or immunogenicity of as an additional dose to any heterologous additional dose vaccine strategy for immunocompromised patients. This shall be updated once new clinical evidence has been reviewed.

Evidence from Real World Studies

Effectiveness outcomes

Description of evidence

Werbel, et al, 2021 reported cases of breakthrough infections in immunocompromised patients after a heterologous additional dose of *Janssen* in combination with *Pfizer-BioNTech* or *Moderna* as a primary series for immunocompromised patients compared to mRNA primary series only (no additional dose). The characteristics of the detected study are presented below.

Study	Population	Intervention	Comparator	Outcome	Follow up	Study Design
Werbel et al. (2021)	Solid organ transplant recipients N=30 US	Additional dose of Janssen to an mRNA primary series *(median of 67 days after dose 2 of primary vaccine series)*	Two doses of either Pfizer or Moderna (no additional dose)	Breakthrough Infections	Median 14 days after the third dose	Case series

Key Findings

Quality of Study

The LCPG rated the study with a very serious RoB due to non-randomization, failure to conceal allocation, non-blinding of both participants and investigators, and failure to assess confounding factors.

Effectiveness results

The study of Werbel et al (2021) reported that there were no breakthrough infections among those who had *Janssen* as an additional dose to mRNA primary series, and among those who had mRNA primary series only. The third dose of *Janssen* was administered after a median of 67 days dosing interval. The median follow up period of the study was 14 days after the third dose.

Immunogenicity outcomes

Description of evidence

The same real world study mentioned above (i.e. Werbel, et al, 2021), examined the immunogenicity of *Janssen* as an additional dose in combination with *Pfizer-BioNTech* or *Moderna* as primary series compared to those who had the two doses of *Pfizer-BioNTech* or *Moderna (no additional dose)*. The characteristics of the detected study are presented below.

Study	Population	Intervention	Comparator	Outcome	Follow up	Study Design
Werbel et al. (2021)	Solid organ transplant recipients N=30 US	Additional dose of Janssen to an mRNA primary series *(median of 67 days after dose 2 of primary vaccine series)*	Two doses of either Pfizer or Moderna (no additional dose)	Anti-S1 IgG or anti-RBD assays	Median 14 days after the third dose	Case series

Key Findings

The study of Werbel et al, 2021 reported that there was an increase in terms of the proportion of patients who turned seropositive after an additional dose of *Janssen* (to mRNA as primary series), compared to with no additional dose. Following a *Pfizer-BioNTech* primary series, an additional dose of *Janssen* turned 4 out of 7 patients (57%) seropositive compared to the two-dose arm of the Pfizer-BioNTech (primary series), (1 out of 7 patients; 14%). Following a *Moderna* primary series, an additional dose of *Janssen* turned 1 out of 8 patients (13%) seropositive compared to none out of 8 patients in the two-dose arm of *Moderna* (primary series). The median dosing interval of the study was 67 days while repeated antibody testing was done at a median of 14 days (IQR: 14 to 17 days) after the third dose of vaccine.

HTAC Judgment: Yes, it is potentially efficacious as a heterologous additional dose based on limited evidence.

CoronaVac

Relevant studies are currently not available yet on the effectiveness, efficacy, or immunogenicity of a heterologous additional dose of *CoronaVac* in combination with any primary series vaccine for immunocompromised patients.

HTAC Judgment: Cannot assess the effectiveness as a heterologous additional dose based on current lack of evidence

RQ.2.14: Is heterologous additional dose vaccination safe?

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

The evidence on the efficacy and effectiveness of *Pfizer-BioNTech* as a heterologous additional dose is based on the following 1), Philippine Living Clinical Practice Guidelines Group (LCPG Group), updated 24 September (Appendix 2, Part 5); 2) the International Vaccine Access Center (IVAC) of the Johns Hopkins Bloomberg School of Public Health and World Health Organization as of 01 Oct 2021; 3) COVID-NMA as of 07 October 2021; and 4) the US CDC Advisory Committee on Immunization Practices (ACIP) as of 23 Sept 2021. From these reference reviews , only one relevant study (i.e. Werbel, et al, 2021) was detected which is a real world study.

Pfizer-BioNTech

Safety data from Clinical Trials
The LCPG Group did not detect any clinical trial examining the clinical safety of *Pfizer-BioNTech* as an additional dose. This shall be updated once new clinical evidence has been reviewed.

Safety data from Real World Evidence

Description of evidence
The LCPG Group review detected one real world study (Werbel, et al, 2021), examining the safety of *Pfizer-BioNTech* as a heterologous additional dose with *Moderna* as primary series for immunocompromised patients. The characteristics of the detected study are presented below.

Study	Population	Intervention	Comparator	Outcome	Follow up	Study Design
Werbel et al., 2021	Solid organ transplant recipients N=30 US	3rd dose of *Moderna or Pfizer; mRNA (primary series)* (median of 67 days after dose 2 of primary vaccine series)	3rd dose of Janssen; mRNA (primary series)	• Local Reactogenicity • Systemic Reactogenicity • Serious Adverse Event	Median 14 days after the third dose	Case series

Key Findings

Quality of Study
The LCPG noted that the study had a very serious RoB (Werbel et al., 2021) due to non-randomization, failure to conceal allocation, non-blinding of both participants and investigators, and failure to assess confounding factors.

Safety results

- *Outcome 1: Local Adverse Events*
  - Werbel et al (2021) reported that there were more participants in the mRNA vaccine third dose arm who experienced local reactions than those who received *Janssen* as an additional dose to mRNA as primary series.

- *Outcome 2: Systemic Adverse Events*

- Werbel et al (2021) reported that there were fewer participants in the mRNA vaccine third dose arm who experienced systemic reactions than those who received Janssen as an additional dose to mRNA as primary series.

- *Outcome 3: Serious Adverse Events*
  - Of the 5 patients who received *Pfizer-BioNTech* as an additional dose in the study of Werbel et al (2021), no serious adverse events were reported in both additional dose of *Pfizer-BioNTech* in combination with *mRNA* as a primary series for immunocompromised patients compared to those who had additional dose of *Janssen* primary series only (no additional dose).

Based on the detected study on heterologous additional dose vaccination of *Pfizer BioNTech* to *Moderna* (Werbel et al., 2021), the short-term vaccine safety is acceptable in organ transplant patients. However, the varying antibody responses of booster vaccinations poses potential risks, such as organ rejection and should be evaluated on an individual basis.

HTAC Judgment: Safety of *Pfizer-BioNTech* cannot be assessed at this time due to currently limited evidence on heterologous additional doses.

Moderna

Safety data from Clinical Trials

The LCPG Group did not detect any clinical trial examining the clinical safety of *Moderna* as an additional dose. This shall be updated once new clinical evidence has been reviewed.

Safety data from Real World Evidence

Description of evidence

The LCPG Group review detected one real world study (Werbel et al., 2021), examining the safety of *Moderna* as a heterologous additional dose with *Pfizer-BioNTech* as primary series for immunocompromised patients, the same study cited in the previous sections. The characteristics of the detected study were presented in the previous section.

Key Findings

Quality of Study

The LCPG noted that the study had a very serious RoB (Werbel et al., 2021) due to non-randomization, failure to conceal allocation, non-blinding of both participants and investigators, and failure to assess confounding factors.

Safety results

- *Outcome 1: Local Adverse Events*
  - Werbel et al (2021) reported that there were more participants in the mRNA vaccine third dose arm [which includes people who received *Pfizer (primary series) + Moderna (additional dose)* but did not provided disaggregated results] who experienced local reactions than those who received *Janssen* as an additional dose to mRNA.

- *Outcome 2: Systemic Adverse Events*
  - Werbel et al (2021) reported that there were fewer participants in the mRNA vaccine third dose arm [which includes people who received *Pfizer (primary series) + Moderna (additional dose)* but did not provided disaggregated results] who experienced systemic reactions than those who received Janssen as an additional dose to mRNA.

- *Outcome 3: Serious Adverse Events*
  - Of the 7 patients who received *Moderna* as an additional dose to *Pfizer-BioNTech* (primary series) in the study of Werbel et al (2021), 1 heart transplant recipient (with *Pfizer* as primary series) had biopsy-proven, antibody- mediated rejection in the transplanted organ 7 days after her third dose of vaccine (years since transplant = 6.5).

Based on the detected study on heterologous additional dose vaccination of *Moderna* to *Pfizer BioNTech* (Werbel et al., 2021), the short-term vaccine safety is acceptable in organ transplant patients. However, the varying antibody responses of booster vaccinations poses potential risks, such as organ rejection and should be evaluated on an individual basis.

HTAC Judgment: Safety of *Moderna* cannot be assessed at this time due to currently limited evidence on heterologous additional doses.

AstraZeneca

Safety Data from Clinical trials

Description of evidence

The detected trial (i.e. Bonelli et al., 2021), examined the safety of *AstraZeneca* as an additional dose in combination with an mRNA vaccine (i.e. *Moderna or Pfizer-BioNTech*) as a primary series. The characteristics of the detected study are presented below.

Study	Population	Intervention	Comparator	Outcome	Follow up	Study Design
Bonelli et al., 2021	Adults w/ chronic-inflammatory rheumatic or neurologic diseases under current rituximab therapy N=60 Austria	AZ (third dose) to mRNA primary series 10.6 weeks after 2nd dose	mRNA (third dose) to mRNA primary series	Adverse events (Fever, arthralgia, local reactions, pruritus, headache, etc.)	4 weeks	Prospective RCT

Key Findings

- *Outcome 1: Local Reactogenicity*
  - Bonelli et al (2021) noted that most side effects were similar between the heterologous *AstraZeneca* third dose arm and the mRNA third dose arm
- *Outcome 2: Systemic Reactogenicity*
  - Bonelli et al (2021) noted that most side effects were similar between the heterologous AstraZeneca third dose arm and the mRNA third dose arm. Numerically, a higher prevalence of systemic reactogenicity was reported in the heterologous *AstraZeneca* third dose arm vs. the mRNA third dose arm for fatigue, arthralgia and myalgias.
- *Outcome 3: Serious Adverse Events*
  - Bonelli et al (2021) also noted that no serious adverse events were recorded in both the homologous mRNA arm and heterologous mRNA + AstraZeneca arm.

Evidence from Real World Studies

The relevant reviews did not detect any clinical trial examining the clinical efficacy or immunogenicity of *Pfizer-BioNTech* as an additional dose to any heterologous booster vaccine strategy. This shall be updated once new clinical evidence has been reviewed.

HTAC Judgment: Safety of *AstraZeneca* cannot be assessed at this time due to currently limited evidence on heterologous additional doses.

Janssen

Evidence on Safety from Clinical Trials

The LCPG Group did not detect any clinical trial examining the clinical safety of *Janssen* as an additional dose. This shall be updated once new clinical evidence has been reviewed.

Safety data from Real World Evidence

Description of evidence

One safety report [Hause et al., 2021 (US CDC)] on the use of *Janssen* as a heterologous booster dose to *Pfizer-BioNTech* and *Moderna* primary series was found.The report of Hause et al., 2021 (US CDC) consisted of safety reports from booster vaccines (median dosing interval of 84 days after dose 2) from V-safe - a voluntary, smartphone-based safety surveillance system, from August 12 to September 19, 2021 (N= 22,191; n=48).

Key Findings

Quality of Study

An RoB assessment for Hause et al.,2021 was not performed as it is a surveillance study.

Results
Evidence from Hause et al.,2021 (US CDC) showed the following:

- **Local reactogenicity**
  - ***With Moderna*** (Primary series)***:*** 75% experienced any injection site reaction.
  - ***With Pfizer*** (Primary series) ***:*** 83% experienced any injection site reaction.
- **Systemic reactogenicity**
  - ***With Moderna*** (Primary series)***:*** 50% experienced any systemic reaction.
  - ***With Pfizer***(Primary series): 100% experienced any systemic reaction.
- **Any health impact**
  - ***With Moderna*** (Primary series)***:*** None were unable to perform normal daily activities
  - ***With Pfizer***(Primary series): 33.3% were unable to perform normal daily activities

HTAC Judgement: Safety of *Janssen* cannot be assessed at this time due to currently limited evidence on heterologous additional doses.

CoronaVac

Relevant studies are currently not available yet on the safety of a heterologous additional dose of *CoronaVac* in combination with any primary series vaccine for immunocompromised patients.

HTAC Judgment: Cannot assess the overall safety as a heterologous additional dose due to current lack of evidence

RQ.2.15: Does the COVID-19 vaccine provide a highly favorable benefit/risk profile in the context of observed vaccine efficacy as an additional dose?

Pfizer-BioNTech	Moderna	AstraZeneca	Janssen	CoronaVac

As there is currently insufficient evidence on the efficacy and safety of *COVID-19 Vaccines* as a homologous and heterologous additional dose, assessing benefit/risk profile is not feasible at the moment.

HTAC Judgment: Cannot be assessed based on current lack of evidence

Criteria 3: Affordability and Viability

BOOSTER DOSE VACCINATION

RQ 3.1: Is the vaccine affordable for booster vaccination?

HTAC Specifications
Affordability will be measured using the sufficiency of the allocated amount to achieve vaccination targets.

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

One of the possible vaccine strategies that will be implemented in 2022 is booster dose vaccination for the A1 to A5 priority groups assumed to have received primary vaccines in 2021. Hence, costing analysis was conducted for this vaccine strategy but only for combinations with available clinical evidence. The unit costs of vaccines used in the analyses were based on the latest price offer to the government as disclosed in confidence by the Department of Finance (DOF). The additional cost of consumables, logistics, and other operations cost were sourced from the DOH National Immunization Program.

Pfizer-BioNTech

2021 Primary Series	2022 Booster Dose	Total Cost of Implementation	Proportion to the 45 B Budget	Proportion of Target Vaccinees for the brand to the A1-A5 Population
Pfizer- BioNTech	*Pfizer-BioNTech*	Php 8.42 B	18.70%	28.39%
CoronaVac		Php 8.35 B	18.55%	28.15%
*Moderna**		Php 4.81 B	10.69%	16.23%
*AstraZeneca**		Php 4.49 B	9.97%	15.13%

** Note: Based on JCVI recommendations.*

Across all combinations, the share of the cost of a booster dose of *Pfizer-BioNTech* to the total 2022 vaccine budget is considered proportionate to the share of the target population to be vaccinated with a booster dose using the said vaccine.

HTAC Judgment: Homologous and heterologous booster vaccination strategies with *Pfizer-BioNTech* (in addition to *CoronaVac or Moderna* as primary series) are considered affordable.

Moderna

2021 Primary Series	2022 Booster Dose	Total Cost of Implementation	Proportion to the 45 B Budget	Proportion of Target Vaccinees for the brand to the A1-A5 Population
*CoronaVac**	*Moderna (1 full dose)*	Php 23.45 B	52.11%	28.15%
Moderna (2 full doses)	*Moderna (half of 1 dose)*	Php 6.94 B	15.44%	16.23%

** Note: The clinical evidence for Moderna as a booster for CoronaVac is an ongoing local study with no available interim results yet.*

The share of the cost of a homologous (half-dose, 50µg) booster of *Moderna* to the total 2022 vaccine budget is considered proportionate to the share of the target population to be vaccinated with a booster dose using the said vaccine. However, the share of the cost of a heterologous booster dose of *Moderna* to the *CoronaVac* primary series is disproportionate to the share of the target population to be vaccinated with this booster strategy.

HTAC Judgment: Homologous (half-dose, 50µg) and heterologous booster vaccination strategies with *Moderna* (specifically in addition to *CoronaVac* as primary series) are considered affordable since it is within the 2022 budget. However, heterologous booster vaccination with Moderna in addition to *CoronaVac* is considered disproportionate to the share of the population if A1 to A5 will be prioritized for roll-out.

AstraZeneca

2021 Primary Series	2022 Booster Dose	Total Cost of Implementation	Proportion to the 45 B Budget	Proportion of Target Vaccinees for the brand to the A1-A5 Population

AstraZeneca	*AstraZeneca*	Php 3.50 B	7.79%	15.13%
CoronaVac		Php 6.52 B	14.49%	28.15%

Across all combinations, the share of the cost of a booster dose of *AstraZeneca* to the total 2022 vaccine budget is considered proportionate to the share of the target population to be vaccinated with a booster dose using the said vaccine.

HTAC Judgment: Homologous and heterologous booster vaccination strategies with *AstraZeneca* (in addition to *CoronaVac* as primary series) are considered affordable.

Janssen

2021 Primary Series	2022 Booster Dose	Total Cost of Implementation	Proportion to the 45 B Budget	Proportion of Target Vaccinees for the brand to the A1-A5 Population
Janssen	*Janssen*	Php 4.11 B	9.14%	12.10%
CoronaVac		Php 9.57 B	21.26%	28.15%

Across all combinations, the share of the cost of a booster dose of *Janssen* to the total 2022 vaccine budget is considered proportionate to the share of the target population to be vaccinated with a booster dose using the said vaccine.

HTAC Judgment: Homologous and heterologous booster vaccination strategies with *Janssen* (in addition to *CoronaVac* as primary series) are considered affordable.

CoronaVac

2021 Primary Series	2022 Booster Dose	Total Cost of Implementation	Proportion to the 45 B Budget	Proportion of Target Vaccinees for the brand to the A1-A5 Population
CoronaVac	*CoronaVac*	Php 11.24 B	24.98%	28.15%

The share of the cost of a booster dose of *CoronaVac* to the total 2022 vaccine budget is considered proportionate to the share of the target population to be vaccinated with a booster dose using the said vaccine.

HTAC Judgment: Homologous booster vaccination strategy with *CoronaVac* is considered affordable.

RQ 3.2: What are the budget implications of using the vaccine for booster vaccination?

HTAC Specifications
Proportionality of the size of the population to be vaccinated versus the cost.

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	Moderna	AstraZeneca	Janssen	CoronaVac
The potential budget impact to the national government of the use of *Pfizer-BioNTech* as a booster dose was calculated to range from **Php 4.49 B** to **Php 8.42 B**, depending on the brand of the primary series. Between the 4 vaccination strategies explored using *Pfizer-BioNTech* as a booster dose, the highest calculated budget impact was noted for its use as a homologous booster dose for people who received *Pfizer-BioNTech* as their primary series *(***Php 8.42 B)**. It is estimated that **18.70%** of the 2022 total government budget for vaccines (**Php 8.42 B of the Php 45 B total budget)** will go to 28.39**%** of the expected vaccine recipients (A1 to A5) for booster dose in 2022.	The potential budget impact to the national government of the use of *Moderna* as a booster dose was calculated to range from **Php 6.94 B** to **Php 23.45 B**, depending on the brand of the primary series. Between the 2 vaccination strategies explored using *Moderna* as a booster dose, the highest calculated budget impact was noted for its use as a heterologous booster dose for individuals who received *CoronaVac* as their primary series *(***Php 23.45 B)**. It is estimated that **52.11%** of the 2022 total government budget for vaccines (**Php 23.45 B of the Php 45 B total budget)** will go to 28.15**%** of the expected vaccine recipients (A1 to A5) for booster dose in 2022.	The potential budget impact to the national government of the use of *AstraZeneca* as a booster dose was calculated to range from **Php 3.50 B** to **Php 6.52 B**, depending on the brand of the primary series. Between the 2 vaccination strategies explored using *AstraZeneca* as a booster dose, the highest calculated budget impact was noted for its use as a heterologous booster dose for people who received *CoronaVac* as their primary series *(***Php 6.52 B)**. It is estimated that **14.49%** of the 2022 total government budget for vaccines (**Php 6.52 B of the Php 45 B total budget)** will go to 28.15**%** of the expected vaccine recipients (A1 to A5) for booster dose in 2022.	The potential budget impact to the national government of the use of *Janssen* as a booster dose was calculated to range from **Php 4.11 B** to **Php 9.65 B**, depending on the brand of the primary series. Between the 2 vaccination strategies explored using *Janssen* as a booster dose, the highest calculated budget impact was noted for its use as a heterologous booster dose for people who received *CoronaVac* as their primary series *(***Php 9.57 B)**. It is estimated that **21.26%** of the 2022 total government budget for vaccines (**Php 9.57 B of the Php 45 B total budget)** will go to 28.15**%** of the expected vaccine recipients (A1 to A5) for booster dose in 2022.	The potential budget impact to the national government of the use of *CoronaVax* as a booster dose was estimated at **Php 11.24 B** for people who received *CoronaVac* as their primary series.It is estimated that **24.98%** of the 2022 total government budget for vaccines (**Php 11.24 B of the Php 45 B total budget)** will go to 28.15**%** of the expected vaccine recipients (A1 to A5) for booster dose in 2022.
HTAC Judgment: The share of the cost of *Pfizer, Moderna* (homologous half-dose booster, 50µg), *AstraZeneca, Janssen,* and *CoronaVac* as a booster dose to the total vaccine budget is considered **highly commensurate** to the share of the population to be vaccinated using the said vaccine. However, the share of the cost of heterologous booster using 100µg *Moderna* dose (in addition to CoronaVac) to the total vaccine budget is considered **disproportionate** to the share of the population to be vaccinated using the said vaccine.				
RQ 3.3: Does booster vaccination 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. ● Formal cost-effectiveness analysis (CEA) will be done (not under EUA). It will be performed when enough evidence is available at the time of full marketing authorization ● Societal perspective will be taken due to the observed social and economic impacts of COVID-19 ● CEA currently not done in rapid reviews under pandemic situation because of emergency nature.				
Pfizer-BioNTech	**Moderna**	**AstraZeneca**	**Janssen**	**CoronaVac**
Homologous booster vaccination Based on available evidence, homologous booster vaccination with *Pfizer-BioNTech* represents good value for money in terms of lowering symptomatic COVID-19, severe	**Homologous booster vaccination** Based on limited evidence, homologous booster vaccination with 50µg *Moderna* may potentially represent good value for money in terms of inducing immune response against the original strain ang	**Homologous booster vaccination** Based on limited evidence, homologous booster vaccination with *AstraZeneca* may represent good value for money in terms of inducing immune response against waning immunogenicity when	**Homologous booster vaccination** Based on limited evidence, homologous booster vaccination with *Janssen* may represent good value for money in terms of immunogenicity, the homologous booster dose of *Janssen* also induced an	**Homologous booster vaccination** Based on limited evidence, homologous booster vaccination with *CoronaVac* may potentially represent good value for money in terms of inducing immune response against waning

COVID-19, hospitalization, and COVID-19 deaths due to waning immunity when given at least 5 to 8 months after full vaccination (US CDC ACIP, 2021; Bar-on, et al., 2021b). In terms of immunogenicity, interim results of one trial with a short follow-up period (1 month) showed that a homologous booster dose of *Pfizer-BioNTech* induced immune responses noninferior to those following dose 2 (Study C4591001 or the Pfizer US booster trial). **HTAC Judgment:** Homologous booster vaccination with *Pfizer-BioNTech* represents good value for money as it is likely to be effective/efficacious based on limited evidence. **Heterologous booster vaccination** Based on limited evidence, heterologous booster vaccination with *Pfizer-BioNTech* represents good value for money in terms of lowering the risk of any COVID-19 infection and hospitalization due to waning immunity when given at least 6 months after 2nd dose of *CoronaVac* (Chilean MOH Report). Furthermore, it also has the potential of inducing immune response when given at around 5.5 months after full vaccination with *CoronaVac* (Patamatamkul et al., 2021; Keskin et al., 2021). **HTAC Judgment:** Heterologous booster vaccination with Pfizer-BioNTech at around 5.5 to 6 months after CoronaVac represents good value for money as it is likely to be effective/efficacious based on limited evidence.	Delta variant when given at around 7.2 months after the 2nd dose (Chu et al., 2021). However, there are currently no clinical studies found examining the effectiveness/efficacy of homologous booster vaccination with *Moderna*. **HTAC Judgment:** Homologous booster vaccination with 50µg *Moderna* represents good value for money as it is deemed potentially efficacious as a homologous booster dose based on very limited evidence **Heterologous booster vaccination** The effectiveness or efficacy as a heterologous booster dose vaccination of *Moderna* cannot be assessed due to current lack of evidence. An ongoing DOST study on the use of *Moderna* as a booster dose after *CoronaVac* was noted, however, interim results are not currently available. **HTAC Judgment:** Cannot be assessed due to limited evidence.	given at 28 to 38 weeks after full vaccination (Flaxman et al., 2021). However, there are currently no clinical studies found examining the effectiveness/efficacy of homologous booster vaccination with *AstraZeneca*. **HTAC Judgment:** Homologous booster vaccination with *AstraZeneca* may represent good value for money as it is potentially efficacious based on very limited evidence. **Heterologous booster vaccination** Based on limited evidence, heterologous booster vaccination with *AstraZeneca* may represent good value for money in terms of inducing immune response against waning immunogenicity when given after a 2nd dose of *CoronaVac* (Patamatamkul et al., 2021). However, the dosing interval for the said strategy was not indicated. Furthermore, there are currently no clinical studies found examining the effectiveness/efficacy of heterologous booster vaccination with *AstraZeneca*. **HTAC Judgment:** Heterologous booster vaccination with *AstraZeneca* after *CoronaVac* may represent good value for money as it is potentially effective/efficacious based on very limited evidence.	immune response when given at 6-9 months after vaccination. (Sadoff et al., 2021). **HTAC Judgment:** Homologous booster vaccination with *Janssen* represents good value for money as it is likely to be effective/efficacious based on limited evidence. **Heterologous booster vaccination** The effectiveness or efficacy as a heterologous booster dose vaccination of *Janssen* cannot be assessed due to current lack of evidence. An ongoing DOST study on the use of *Janssen* as a booster dose after *coronaVac* was noted, however, interim results are not currently available. **HTAC Judgment:** Cannot be assessed due to limited evidence.	immunogenicity when given at 3 to 8 months after full vaccination (Li, J et al., 2021; Li, M et al., 2021; Pan et al., 2021, Wang, K. et al., 2021, Keskin, et al, 2021). There are currently no clinical studies found examining the effectiveness/efficacy of homologous booster vaccination with *CoronaVac*. **HTAC Judgment:** Homologous booster vaccination with *CoronaVac* may represent good value for money as it is potentially efficacious based on limited evidence. **Heterologous booster vaccination** The effectiveness or efficacy as a heterologous booster dose vaccination of *CoronaVac* cannot be assessed due to current lack of evidence. **HTAC Judgment:** Cannot be assessed.
ADDITIONAL DOSE VACCINATION				
RQ 3.1: Is the vaccine affordable for additional dose vaccination? ***HTAC Specifications***				

Affordability will be measured using the sufficiency of the allocated amount to achieve vaccination targets.

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

One of the possible vaccine strategies that will be implemented in 2022 is additional dose vaccination for the immunocompromised population. Hence, costing analysis was conducted for this vaccine strategy but only for combinations with available clinical evidence (i.e., Heterologous additional dose of *Janssen to Pfizer-BioNTeach* or *Moderna)*.

Since there is no available data of the proportion of immunocompromised (IC) population in the NVOC target for vaccination, the target population was based on the local prevalence data of diseases covered by the US CDC standard definition on immunocompromised conditions. Conditions without local prevalence data (e.g. *systemic lupus erythematosus, idiopathic pulmonary fibrosis, scleroderma*) were excluded from the analysis. The unit costs of vaccines used in the analyses were based on the latest price offer to the government as disclosed in confidence by DOF. The additional cost of consumables, logistics, and other operations cost were sourced from the DOH National Immunization Program. The table below shows the total cost of implementation if *the vaccine brand* will be administered as an additional dose in 2022 for the different primary series administered in 2022. Details on the prevalence data, costing assumptions, and matrix for vaccine combinations are provided in Appendix 6.

Pfizer-BioNTech

2021 Primary Series	2022 Additional Dose	Total Cost of Implementation	Proportion to the 45 B Budget	Proportion of IC Vaccinees for the brand to the A1-A5 Population
Pfizer-BioNTech	*Pfizer-BioNTech*	Php 206.93 M	0.46%	0.70%
Moderna		Php 118.33 M	0.26%	0.40%

Across all combinations, the share of the cost of an additional dose of *Pfizer-BioNTech* to the total 2022 vaccine budget is considered proportionate to the share of the target IC population to be vaccinated with additional dose using the said vaccine.

HTAC Judgment: Homologous and heterologous additional dose vaccination strategies with *Pfizer-BioNTech* (in addition to *Moderna* as primary series) are considered affordable.

Moderna

2021 Primary Series	2022 Additional Dose	Total Cost of Implementation	Proportion to the 45 B Budget	Proportion of IC Vaccinees for the brand to the A1-A5 Population
Moderna	*Moderna*	Php 332.49 M	0.74%	0.40%
Pfizer-BioNTech		Php 581.45 M	1.29%	0.70%

Across all combinations, the share of the cost of an additional dose of *Moderna* to the total 2022 vaccine budget is considered disproportionate to the share of the target IC population to be vaccinated with additional dose using the said vaccine.

HTAC Judgment: Homologous and heterologous additional dose vaccination strategies with *Moderna* (in addition to *Pfizer* as primary series) are considered affordable since it is within the 2022 budget. However, it is considered **disproportionate** to the share of the population if A1 to A5 will be prioritized for roll-out.

AstraZeneca

2021 Primary Series	2022 Additional Dose	Total Target Number of IC Vaccinees	Total Cost of Implementation	Proportion to the 45 B Budget	Proportion of IC Vaccinees for the brand to the A1-A5 Population
Moderna	*Moderna*	304,843	Php 332.49 M	0.74%	0.40%
Pfizer-BioNTech		533,104	Php 581.45 M	1.29%	0.70%

Across all combinations, the share of the cost of an additional dose of *AstraZeneca* to the total 2022 vaccine budget is considered proportionate to the share of the target IC population to be vaccinated with additional dose using the said vaccine.

HTAC Judgment: Homologous and heterologous additional dose vaccination strategies with *AstraZeneca* (in addition to *Pfizer or Moderna* as primary series) are considered affordable. The share in the 2022 budget is also considered **proportionate** to the share of the population if A1 to A5 will be prioritized for roll-out.

Janssen

Across all combinations, the share of the cost of an additional dose of *Janssen* to the total 2022 vaccine budget is considered proportionate to the share of the target IC population to be vaccinated with an additional dose using the said vaccine.

HTAC Judgment: Heterologous additional dose vaccination strategies with *Janssen* (in addition to *Pfizer-BioNTech* or *Moderna* as primary series) are considered affordable.

CoronaVac

Affordability was not assessed for this brand due to limited clinical evidence for additional dose vaccination.

RQ 3.2: What are the budget implications of using the vaccine for additional dose vaccination?

HTAC Specifications
Proportionality of the size of the population to be vaccinated versus the cost.

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	Moderna	AstraZeneca	Janssen	CoronaVac
The potential budget impact to the national government of the use of *Pfizer-BioNTech* as an additional dose was calculated to range from **Php 118.33 M** to **Php 206.93 M**, depending on the brand of the primary series.	The potential budget impact to the national government of the use of *Moderna* as an additional dose was calculated to range from **Php 332.49 M** to **Php 581.45 M**, depending on the brand of the primary series.	The potential budget impact to the national government of the use of *AstraZeneca* as an additional dose was calculated to range from **Php 92.43 M** to **Php 161.64 M**, depending on the brand of the primary series.	The potential budget impact to the national government of the use of *Janssen* as a booster dose was calculated to range from **Php 135.65 M** to **Php 237.22 M**, depending on the brand of the primary series.	*Budget implications were not assessed for this brand due to limited clinical evidence for additional dose vaccination.*

Between the 2 vaccination strategies explored using *Pfizer-BioNTech* as an additional dose, the highest calculated budget impact was noted for its use as an additional dose for IC vaccinees who received *Pfizer-BioNTech* as their primary series *(***Php 206.93 M)**. It is estimated that **0.46%** of the 2022 total government budget for vaccines (**Php 206.91 M of the Php 45 B total budget)** will go to **0.70%** of the 76.3M expected vaccine recipients (A1 to A5) that will use the 2022 budget.	Between the 2 vaccination strategies explored using *Moderna* as an additional dose, the highest calculated budget impact was noted for its use as an additional dose for IC vaccinees who received *Pfizer-BioNTech* as their primary series *(***Php 581.45 M)**. It is estimated that **1.29%** of the 2022 total government budget for vaccines (**Php 581.45M of the Php 45 B total budget)** will go to **0.70%** of the 76.3M expected vaccine recipients (A1 to A5) that will use the 2022 budget.	Between the 2 vaccination strategies explored using *AstraZeneca* as an additional dose, the highest calculated budget impact was noted for its use as an additional dose for IC vaccinees who received *Pfizer-BioNTech* as their primary series *(***Php 161.64 M)**. It is estimated that **0.36%** of the 2022 total government budget for vaccines (**Php 161.64 M of the Php 45 B total budget)** will go to **0.70%** of the 76.3M expected vaccine recipients (A1 to A5) that will use the 2022 budget.	Between the 2 vaccination strategies explored using *Janssen* as an additional dose, the highest calculated budget impact was noted for its use as an additional dose for IC vaccinees who received *Pfizer-BioNTech* as their primary series *(***Php 237.22 M)**. It is estimated that **0.53%** of the 2022 total government budget for vaccines (**Php 237.22 M of the Php 45 B total budget)** will go to **0.70%** of the 76.3M expected vaccine recipients (A1 to A5) that will use the 2022 budget.	
HTAC Judgment: The share of the cost of *Pfizer-BioNTech, AstraZeneca, and Janssen* as an additional dose to the total vaccine budget is considered **highly commensurate** to the share of the population to be vaccinated using the said vaccine. However, the share of the cost of *Moderna* as an additional dose to the total vaccine budget is considered **disproportionate** to the share of the population to be vaccinated using the said vaccine.				
RQ 3.3: Does additional dose vaccination 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. ● Formal cost-effectiveness analysis (CEA) will be done (not under EUA). It will be performed when enough evidence is available at the time of full marketing authorization ● Societal perspective will be taken due to the observed social and economic impacts of COVID-19 ● CEA currently not done in rapid reviews under pandemic situation because of emergency nature.				
Pfizer-BioNTech	**Moderna**	**AstraZeneca**	**Janssen**	**CoronaVac**
<u>Homologous additional dose vaccination</u> Based on limited evidence, homologous additional dose vaccination with *Pfizer-BioNTech* may potentially represent good value for money in terms of inducing immune response when given at around 3 months after the 2nd dose of *Pfizer-BioNTech* for hemodialysis and peritoneal dialysis patients, immunocompromised organ transplant patients and adults with chronic-inflammatory rheumatic or neurologic diseases under current	**<u>Homologous additional dose vaccination</u>** Based on limited evidence, homologous additional dose vaccination with *Moderna* may potentially represent good value for money in terms of inducing immune response when given at around 2 months after the 2nd dose of *Moderna* for transplants patients and patients with chronic-inflammatory rheumatic or neurologic diseases receiving rituximab therapy (Hall et al., 2021; Bonelli et al., 2021; and Benotmane et al., 2021, Werbel et al. 2021). However, there are currently	**<u>Homologous additional dose vaccination</u>** The effectiveness or efficacy as a homologous additional dose vaccination of *AstraZeneca* in the immunocompromised population cannot be assessed due to current lack of evidence. **HTAC Judgment:** Cannot be assessed. **<u>Heterologous additional dose vaccination</u>** Based on limited evidence, heterologous	**<u>Homologous additional dose vaccination</u>** The effectiveness/efficacy of *Janssen* as a homologous additional dose in immunocompromised patients cannot be assessed due to lack of evidence. **HTAC Judgment:** Cannot be assessed. **<u>Heterologous additional dose vaccination</u>** Based on limited evidence, heterologous additional dose vaccination of *Janssen* may potentially represent good value for	*Value for money was not assessed for this brand due to limited clinical evidence for additional dose vaccination.*

rituximab therapy (Ducloux et al., 2021; Kamar et al., 2021; Masset et al., 2021; Chavarot et al., 2021; Bonelli et al., 2021; Bensouna et al., 2021, Werbel et al. 2021). However, there are currently no clinical studies found examining the effectiveness/efficacy of *Pfizer-BioNTech* as an additional dose in the immunocompromised population. **HTAC Judgment:** Homologous additional dose vaccination with *Pfizer-BioNTech* represents good value for money as it is potentially efficacious based on limited evidence. **Heterologous additional dose vaccination** Based on limited evidence, heterologous additional dose vaccination with *Pfizer-BioNTech* may potentially represent good value for money in terms of inducing immune response at around 67 days after full vaccination with *Moderna* in immunocompromised organ transplant patients (Werbel et al., 2021). However, there were no clinical studies found examining effectiveness/efficacy of heterologous additional dose vaccination with *Pfizer-BioNTech* in the immunocompromised population. **HTAC Judgment:** Heterologous additional dose vaccination with Pfizer-BioNTech at 2 months after 2nd dose of Moderna represents good value for money as it is potentially efficacious based on limited evidence.	no clinical studies found examining the effectiveness/efficacy of *Moderna* as an additional dose in the immunocompromised population. **HTAC Judgment:** Homologous additional dose vaccination with *Moderna* represents good value for money as it is potentially efficacious based on limited evidence. **Heterologous additional dose vaccination** Based on limited evidence, heterologous additional dose vaccination with *Moderna* may potentially represent good value for money in terms of inducing immune response when given at around 67 days after full vaccination with *Pfizer-BioNTech* in the immunocompromised organ transplant patients (Werbel et al., 2021). However, there were no clinical studies found examining effectiveness/efficacy of heterologous additional dose vaccination with *Pfizer-BioNTech* in the immunocompromised population. **HTAC Judgment:** Heterologous additional dose vaccination with *Moderna* at 2 months after 2nd dose of *Pfizer-BioNTech* represents good value for money as it is potentially efficacious based on limited evidence.	additional dose vaccination with *AstraZeneca* may potentially represent good value for money in terms of inducing immune response when given at around 3 months (85 days) after full vaccination with mRNA vaccine - *Pfizer-BioNTech or Moderna* in the immunocompromised patients with chronic-inflammatory diseases undergoing rituximab therapy (Bonelli et al., 2021). However, there were no clinical studies found examining effectiveness/efficacy of heterologous additional dose vaccination with *AstraZeneca* in the immunocompromised population. **HTAC Judgment:** Heterologous additional dose vaccination with *AstraZeneca* after a 2nd dose of *Pfizer-BioNTech* or *Moderna* represents good value for money as it is potentially efficacious based on limited evidence.	money in terms of inducing immune response when given at around 67 days after full vaccination with mRNA vaccines (i.e. *Pfizer-BioNTech, Moderna*) in immunocompromised organ transplant patients (Werbel et al., 2021). However, there were no clinical studies found examining effectiveness/efficacy of heterologous additional dose vaccination with *Janssen* in the immunocompromised population. **HTAC Judgment:** Heterologous additional dose vaccination with *Janssen* at 2 months after 2nd dose of mRNA vaccine represents good value for money as it is potentially efficacious based on limited evidence.	

Criteria 4: Household Financial Impact

RQ4.1a: Will COVID-19 Vaccines reduce or not add further to the out-of-pocket expenses of Filipino households? [General Population]

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 2021-0014 and Philhealth Circular 2020-0009, the following benefit packages with corresponding case rates related to COVID-19 are available for the general population:

1. Isolation Package for asymptomatic and mild cases (C19CI): Case rate = Php 22,499.00
2. Mild COVID-19 pneumonia for elderly and with comorbidities (C19IP1): Case rate= Php 43,997.00
3. Moderate COVID-19 pneumonia (C19IP2): Case rate= Php 143, 267.00
4. Severe COVID-19 pneumonia (C19IP3): Case rate= Php 333,519.00
5. Critical COVID-19 pneumonia (C19IP4): Case rate= Php 786,384.00

Based on Philhealth data, there were a total of 12,164 hospitalization claims from April 15, 2020 to August 10, 2021 for the general population aged 15-59 years old. The table 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 at different levels of severity. The mean financial coverage ranged from 61.90% to 80.12%. Financial coverage was seen to increase with severity of the COVID-19 disease.

Severity *[Benefit package]*	**Total Number of Paid Claims**	**Total Hospital Bill**		**Out-of-Pocket Payment (Median)** *[PHP]*	**Average % Coverage** *[proportion of financial coverage out of the total bill]*
		Range of Hospitalization Cost *[PHP]*	**Median Hospitalization Cost** *[PHP]*		
Mild COVID-19 *[C19IP1]*	1,688	₱0 to ₱1,751,629.51	₱74,988.62	₱30,991.62	61.90%
Moderate COVID-19 *[C19IP2]*	7,488	₱0 to ₱326,482,781.10	₱206,294.29	₱63,027.29	70.16%
Severe COVID-19 *[C19IP3]*	2,226	₱0 to ₱5,404,430.74	₱399,404.39	₱65,885.39	76.31%
Critical COVID-19 *[C19IP4]*	762	₱0 to ₱6,574,031.60	₱850,472.44	₱64,088.44	80.12%

Meanwhile, there were a total of 15,119 community isolation claims recorded by PhilHealth from 2020 to August 2021 for asymptomatic and mild cases, however, there was no data on age indicated in the Philhealth data. The median cost of COVID-19 isolation recorded was Php 22,449.00, while the median claims cost was also at PHP 22,449.00. Therefore, the median out-of-pocket-expenses for community isolation is at Php 0.00 and the median financial coverage is at 100%.

HTAC Judgment: Based on current evidence, booster vaccination has the potential to reduce out-of-pocket expenses in the general population due to averted costs of isolation and treatment of mild, moderate, and severe COVID-19.

RQ4.1b: Will COVID-19 Vaccines reduce or not add further to the out-of-pocket expenses of Filipino households? [Healthcare Workers]

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 2020-0011, full financial risk protection (i.e. no cap in terms of case rate) for hospitalization due to COVID-19 is being granted to healthcare workers (Benefit package: C19FRP).

Based on Philhealth data, there were a total of 3,286 hospitalization claims from 2020 to September 15, 2021 for healthcare workers. The median cost of COVID-19 illness (inferred from total hospital bill) was at **₱ 136,818.84** (range of hospital bill: **₱0 to ₱ 279,130,579.00**), while the median out-of-pocket-expenses incurred for the healthcare workers was at **₱ 4,352.50**. The cost was not disaggregated per severity level. However, it can be noted that the mean financial coverage for healthcare workers is higher (**86.27%)** than the financial coverage for the general population and the elderly population. This is expected since there is a separate COVID-19 benefit package for HCWs with no cap for the case rate.

HTAC Judgment: Based on current evidence, booster vaccination has the potential to reduce out-of-pocket expenses in the healthcare workers due to averted costs of isolation and treatment of mild, moderate, and severe COVID-19.

RQ4.1c: Will COVID-19 Vaccines reduce or not add further to the out-of-pocket expenses of Filipino households? [Elderly Population]

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.

PhilHealth issues the same benefit packages and case rates for the elderly and general population. Based on Philhealth data, there were a total of 11,402 hospitalization claims from April 15, 2020 to August 10, 2021 for the elderly population aged 60 years old and above. The table below summarizes the cost of COVID-19 illness (inferred from total hospital bill), and out-of-pocket-expenses incurred by patients belonging to the elderly population at different levels of severity.

Severity *[Benefit package]*	**Total Number of Paid Claims**	**Total Hospital Bill**		**Out-of-Pocket Payment (Median)** *[PHP]*	**Average % Coverage** *[proportion of financial coverage out of the total bill]*
		Range of Hospitalization Cost *[PHP]*	**Median Hospitalization Cost** *[PHP]*		
Mild COVID-19 *[C19IP1]*	1,216	₱ 0 to ₱16.34 M	₱102,654.66	₱58,657.66	53.08%
Moderate COVID-19 *[C19IP2]*	5,844	₱ 0 to ₱150.39 M	₱223,596.60	₱80,400.77	66.17%
Severe COVID-19 *[C19IP3]*	2,810	₱ 0 to ₱12.48 M	₱424,069.35	₱90,550.35	73.55%
Critical COVID-19 *[C19IP4]*	1,532	₱0 to ₱402.70 B	₱864,290.03	₱79,201.95	78.55%

The cost of COVID-19 illness (based on hospital bills) is generally higher in the elderly than in the general population across all severity. Despite this, the mean financial coverage ranged from 53.08% to 78.55% which is slightly lower than the coverage for the general population. Meanwhile, financial coverage was also seen to follow the same trend as the general population where financial coverage increases with severity of the COVID-19 disease.

HTAC Judgment: Based on current evidence, booster vaccination has the potential to reduce out-of-pocket expenses in the elderly population due to averted costs of isolation and treatment of mild, moderate, and severe COVID-19.

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

Based on the results of the focus group discussions conducted 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 evidences for the *Pfizer-BioNTech*:

1) **Safe and efficacious**

<u>*Clinical evidence for booster vaccination*</u>

Currently, there is limited available evidence on the efficacy or effectiveness of *Pfizer-BioNTech* both as a homologous and heterologous booster dose. Current evidence on effectiveness is limited to 3 observational studies and 2 NRA reports from Israel and and Chile - all with short follow-up periods (12 days - 1 month). For the effectiveness of *Pfizer-BioNTech* as a homologous booster, the ACIP analysis of real world data from Israel showed substantial increase in vaccine effectiveness against symptomatic COVID-19 and against hospitalization due to COVID-19 after the administration of booster compared to dose 2, with a follow-up period of 14 days after booster dose For the effectiveness of *Pfizer-BioNTech* as a heterologous booster, the only available data is with its use as a booster to *CoronaVac* as primary series. The Chilean report on early effectiveness showed substantial increase in vaccine effectiveness vs COVID-19 infections post booster compared to after dose 2; and, similar vaccine effectiveness vs hospitalization due to COVID-19.

In terms of safety, current evidence is limited to 1 trial and 2 NRA reports from Israel and US CDC (follow up of 1 month for the trial; 0-7 days after vaccination for the NRA report). Overall, as a homologous booster, *Pfizer-BioNTech* showed an acceptable short term safety profile. NRA reports showed similar to less systemic reactogenicity of the booster vs dose 2 of the primary series. There were 44 serious adverse events out of 3.7M administered doses reported after receiving the booster dose as per the Israeli MOH report. Out of the 44 reports, 17 of these were myocarditis and perimyocarditis cases which all have probable causalities and are currently reviewed. For the other adverse events, two (2) cases were found to have causality with the booster dose, 2 were found to have possible causality and 14 were found to have none. The remaining 9 cases including 1 death are currently under investigation. As for safety of *Pfizer-BioNTech* as heterologous booster, the only available evidence is its use as a booster to *Moderna and Janssen* as primary series. The surveillance reports showed acceptable short-term safety 0-7 days after vaccination. However, the long-term safety profile of both strategies using *Pfizer BioNTech* cannot be assessed since a longer follow-up period from clinical trials and real world evidence is needed.

<u>*Clinical evidence for additional dose vaccination*</u>

Currently, there is no available evidence on the efficacy or effectiveness of the use of *Pfizer-BioNTech* either as a homologous and a heterologous additional dose for immunocompromised patients. However, there is available evidence limited to 7 real world immunogenicity studies on the use of *Pfizer-BioNTech* as third dose among hemodialysis and peritoneal dialysis patients, immunocompromised organ transplant patients, and adults with chronic-inflammatory rheumatic or neurologic diseases under current rituximab therapy. Results showed a comparable to increased immune response after receiving an additional dose of *Pfizer-BioNTech* compared to a second dose of the same primary vaccine series (7 studies) or a second dose of the *Moderna* primary series (1 study).

There is limited evidence on the safety of Pfizer both as a homologous and a heterologous additional dose. In addition, the varying antibody responses of additional dose vaccinations pose potential risks, such as organ rejection and should be evaluated on an individual basis. Moreover, the long-term safety profile of heterologous vaccination strategies using Pfizer-BioNTech cannot be assessed since a longer follow-up period from clinical trials and real world evidence is needed.

2) Underwent a **transparent regulatory process** of being evaluated and approved by health authorities
- Evidence: The Philippine FDA has not yet issued the amended Emergency Use Authorization of *Pfizer-BioNTech* to include its use for booster vaccination or additional dose vaccination for immunocompromised patients.

3) **Potential for high and equitable coverage across the population**
- Evidence: Due to stringent logistical requirements, the *Pfizer-BioNTech* can only be deployed in tertiary hospitals where special freezers are available. The *Pfizer-BioNTech* has low potential to be distributed to isolated geographic locations.
- Further, the WHO emphasized the following points in its statement on booster vaccination dated 04 October 2021:
  - The rationale for 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.
  - The evidence remains limited and still inconclusive on any widespread need for booster doses following a primary vaccination series.
  - In the context of ongoing global vaccine supply constraints, broad-based administration of booster doses risks exacerbating inequities in vaccine access by driving up demand and diverting supply while priority populations in some countries, or in subnational settings, have not yet received a primary vaccination series.
  - The focus remains on urgently increasing global vaccination coverage with the primary series driven by the objective to protect against severe disease.
- As for additional dose vaccination for immunocompromised patients, the WHO statement on 31 August 2021 emphasized that third doses should be prioritized for the vulnerable: those most at-risk populations when there is evidence of waning immunity against severe disease and death. They added that the number of immunocompromised individuals globally who would potentially benefit from a third dose is very small, especially when compared to the health workers, older populations at risk who have not had their first or second vaccinations globally. However, they noted that when global supplies are so limited, when the world is in a place where billions of people have not yet received any doses, focus must be on administering first and second doses.

4) **Ease in logistics and administration**
- Evidence: The *Pfizer-BioNTech* may only be stored in ultra-cold freezers with a storage requirement of -60 to -80 degrees Celsius. More intensive training on the special storage, handling, and administration of the *Pfizer-BioNTech* is required to ensure product integrity across an uninterrupted cold chain.Based on current experience, the implementation of *Pfizer-BioNTech (BNT162b2)* in the Philippine COVID-19 Vaccination Program was generally challenging due to the intricate vaccine preparation which is prone to error and temperature requirement for storage and handling.
- Further, the NVOC and the DOH-Epidemiology Bureau were consulted for their insights on the implications of implementing booster dose to the current COVID-19 Vaccination program. Generally, homologous booster vaccination is perceived to be more acceptable to the program implementers compared to heterologous booster vaccination.
  - Based on the feedback of the consulted groups, administering a booster dose of the same vaccine brand will require less training, accounting for similar experience on the brands used in the primary vaccine series. However, this will still entail additional resources particularly vaccination sites, human resources (such as vaccinators), and supply of vaccines, if booster vaccination will run simultaneously with the primary vaccination.
  - Meanwhile, adopting a booster of a different brand on top of the vaccine used in the primary series will need supplemental training of human resources, and extensive monitoring and surveillance of adverse events. Furthermore, similar to introducing new vaccines or vaccination strategies, they highlighted the difficulty in monitoring late-onset adverse events. To address this, retrospective studies or other pharmacovigilance methods such as active safety surveillance, involving cohort-event monitoring or hospital sentinel surveillance should be conducted.

5) **Cost-effective**
- Evidence: The health, economic, and social benefits of implementing homologous or heterologous booster vaccination with *Pfizer-BioNTech* mitigate the negative impact of COVID-19 such as deaths due to COVID-19, medical costs, loss of productivity, social disruption, and unprecedented challenges in the health system. As for additional dose vaccination, based on evidence that is limited to immunogenicity outcomes, the potential health, economic, and social benefits of implementing homologous or heterologous additional dose vaccination with *Pfizer-BioNTech* outweigh the negative impact of COVID-19 in immunocompromised patients.

6) **Public acceptability**
- Evidence:

  General Public's Acceptability of Booster Vaccination

  With regard to the general public 's acceptability of booster vaccination strategies, an online survey by the DOH Health Promotion Bureau was conducted from August 20 to September 21, 2021 (N= 15,439). In this survey, of the 7,307 fully vaccinated respondents, 87.90% were willing to receive a booster dose. Among the 4,267 partially vaccinated respondents, 77.08% were willing to receive a booster dose.

Healthcare Workers' Acceptability of Booster Vaccination

With regard to the healthcare worker's acceptability of booster vaccination strategies, a survey by the DOH Health Promotion Bureau was conducted from September 15 to 21, 2021 (N=10,525) . In this survey, of the 10,323 fully vaccinated respondents, 97.30% were willing to receive a booster dose. Among the 158 partially vaccinated respondents, 85.44% were willing to receive a booster dose. Regard for evidence of additional protection and expert opinion can be seen among the participants as the percentage of those highly likely to receive the booster increased to 98.58% (fully vaccinated) and 91.77% (partially vaccinated) if the evidence of additional protection are available and boosters are recommended by experts. Additionally, participants also shared reasons for their willingness to get the booster dose.

- Among those likely to get boosters, the top three reasons are: (1) confidence in booster effectiveness in preventing serious and severe COVID-19. (22.83%); (2) perception of high risk of getting infected with COVID-19 if one will not get a booster dose. (16.34%); and (3) confidence in booster effectiveness against COVID-19 variants (15.59%).
- Among those not likely to get boosters, the top three reasons are: (1) Lack of confidence in booster effectiveness against COVID-19 variants (18.18%); (2) lack of confidence in the safety of the booster and is likely to cause severe adverse reactions (15.15%); and (3) they would want to wait and see until more people they know get the booster dose (14.14%).
- Among those who are unsure to get boosters, the top three reasons are: (1) they would want to wait and see until more people they know get the booster dose (24.43%); (2) lack of confidence in the safety of COVID-19 booster vaccine and is likely to cause severe adverse reactions (14.98%); and (3) lack of confidence in the booster effectiveness against COVID-19 variants (14.33%).

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 last 17 June 2021. The circular, otherwise known as the "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)", aims 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.
  Note to jSC: This is the same evidence used in V2 of the ES.

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

- Evidence: Currently, there is limited data from studies on the use of *Pfizer-BioNTech* for booster dose and additional dose vaccination. However, the current available studies for these vaccination strategies included the following populations:
  - **Booster vaccinations:** Among the studies reviewed, the elderly and those with controlled comorbidities were included as participants. Meanwhile, persons living with HIV, children, adolescents, pregnant and lactating women and the immunocompromised were not included, thus the appropriateness of a booster dose of *Pfizer-BioNTech* to these special populations cannot be determined.

  - **Additional dose vaccination:** Among the studies reviewed, the immunocompromised including: adults with chronic-inflammatory rheumatic or neurologic disease under therapy; solid organ transplant recipients; and kidney transplant patients were included. Meanwhile, immunocompromised patients with past SARS-CoV-2 infections were not included, thus the appropriateness of an additional dose of *Pfizer-BioNTech* to these special populations cannot be determined.

HTAC Judgment: *Pfizer-BioNTech* possesses most of the characteristics desired by key stakeholders for its use as booster dose for the general population 18 years and above. Further, based on a survey conducted among the general population and HCWs in the Philippines, there is high willingness to receive booster shots. The respondents noted their current knowledge on the vaccine effectiveness and safety as basis for their willingness to receive a booster dose. Specifically for the HCWs, their confidence that booster doses can strengthen their protection against severe COVID-19 infection and against VOCs augments this willingness to receive booster doses of the vaccine. However, there are currently no COVID-19 vaccines approved by the Philippine FDA for emergency use as booster dose or additional dose. Meanwhile, evidence for the desired characteristics for its use as an additional dose is yet to be established.

Moderna

Based on the results of the focus group discussions conducted 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 evidences for the *Moderna*:

1) **Safe and efficacious** for the general population (aged 18 years and older) and for some vulnerable groups like the older population and individuals with comorbidities.

- Evidence:

  <u>*Clinical evidence for booster vaccination*</u>

Currently, there is no available evidence on the efficacy or effectiveness of the use of *Moderna* either as a homologous or a heterologous booster dose. Current evidence is limited to 1 trial (Chu et al., 2021) on the immunogenicity of homologous (half-dose, 50µg) *Moderna* booster strategy which showed an increase in neutralizing antibody titers post-booster compared to after dose 2; and, a high percentage of participants that exhibited seroresponse.

In terms of safety, current evidence is limited to 1 trial (follow-up of 1 month) and 1 NRA (follow-up of 0-7 days after booster dose) report from US CDC. Overall, as a homologous booster, *Moderna* showed an acceptable short term safety profile. Further, reported unsolicited adverse events did not reflect any new safety concerns and no deaths or SAEs considered causally related to the booster dose. For the safety of *Moderna* as heterologous booster, evidence is limited to its use as a booster to *Pfizer-BioNTech and Janssen as primary series.* The surveillance and trial reports showed acceptable short-term safety. However, the short-follow up period of the trials (0 to 30 days after booster dose) of the report and trials does not meet the HTAC - preferred median follow up period of at least 2 months. In addition, the long-term safety profile of both strategies using *Moderna* cannot be assessed since a longer follow-up period from clinical trials and real world evidence is needed.

Clinical evidence for additional dose vaccination
Currently, there is no available evidence on the efficacy or effectiveness of the use of *Moderna* either as a homologous and a heterologous additional dose for immunocompromised patients. However, there is available evidence limited to 2 real world immunogenicity studies and 2 trials on the use of *Moderna* as third dose among immunocompromised organ transplant patients, and adults with chronic-inflammatory rheumatic or neurologic diseases under current rituximab therapy. Results showed a comparable to increased immune response after receiving an additional dose of *Moderna* compared to a second dose of the same primary vaccine series (4 studies) or a second dose of the *Pfizer-BioNTech* primary series (1 study).

There is limited evidence on the safety of *Moderna* both as a homologous and a heterologous additional dose. In addition, the varying antibody responses of additional dose vaccinations pose potential risks, such as organ rejection and should be evaluated on an individual basis. Moreover, the long-term safety profile of heterologous vaccination strategies using *Moderna* cannot be assessed since a longer follow-up period from clinical trials and real world evidence is needed.

2) Underwent a **transparent regulatory process** of being evaluated and approved by health authorities
- Evidence: The Philippine FDA has not yet issued the amended Emergency Use Authorization of *Moderna* to include its use for booster vaccination or additional dose vaccination for immunocompromised patients.

3) **Potential for high and equitable coverage across the population**
- Evidence: *Moderna* has a lower storage temperature requirement which makes it harder to roll out since limited areas and RHUs have the required equipment for storage and handling.
- Further, the WHO emphasized the following points in its statement on booster vaccination dated 04 October 2021:
  - The rationale for 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.
  - The evidence remains limited and still inconclusive on any widespread need for booster doses following a primary vaccination series.
  - In the context of ongoing global vaccine supply constraints, broad-based administration of booster doses risks exacerbating inequities in vaccine access by driving up demand and diverting supply while priority populations in some countries, or in subnational settings, have not yet received a primary vaccination series.
  - The focus remains on urgently increasing global vaccination coverage with the primary series driven by the objective to protect against severe disease.
- As for additional dose vaccination for immunocompromised patients, the WHO statement on 31 August 2021 emphasized that third doses should be prioritized for the vulnerable: those most at-risk populations when there is evidence of waning immunity against severe disease and death. They added that the number of immunocompromised individuals globally who would potentially benefit from a third dose is very small, especially when compared to the health workers, older populations at risk who have not had their first or second vaccinations globally. However, they noted that when global supplies are so limited, when the world is in a place where billions of people have not yet received any doses, focus must be on administering first and second doses.

4) **Ease in logistics and administration**
- Evidence: *Moderna* can be stored for 7 months at -25 to -15 degrees Celsius in freezers that are present in most RHUs. According to the EUA fact sheet, the vaccine may also be stored at 2 to 8 degrees Celsius, protected from light for 30 days prior to first use. The vaccine also does not require dilution at the vaccination site which may simplify implementation of the vaccine especially in community settings. Based on current experience, the implementation of *Moderna* in the Philippine COVID-19 Vaccination Program was generally challenging due to the intricate vaccine preparation which is prone to error and a stringent temperature requirement for storage and handling.
- Further, the NVOC and the DOH-Epidemiology Bureau were consulted for their insights on the implications of implementing booster dose to the current COVID-19 Vaccination program. Generally, homologous booster vaccination is perceived to be more acceptable to the program implementers compared to heterologous booster vaccination.
  - Based on the feedback of the consulted groups, administering a booster dose of the same vaccine brand will require less training, accounting for similar experience on the brands used in the primary vaccine series. However, this will still entail additional resources particularly vaccination sites, human resources (such as vaccinators), and supply of vaccines, if booster vaccination will run

simultaneously with the primary vaccination.
- Meanwhile, adopting a booster of a different brand on top of the vaccine used in the primary series will need supplemental training of human resources, and extensive monitoring and surveillance of adverse events. Furthermore, similar to introducing new vaccines or vaccination strategies, they highlighted the difficulty in monitoring late-onset adverse events. To address this, retrospective studies or other pharmacovigilance methods such as active safety surveillance, involving cohort-event monitoring or hospital sentinel surveillance should be conducted.

5) **Cost-effective**
- Evidence: Based on evidence that is limited to immunogenicity outcomes, the potential health, economic, and social benefits of implementing homologous or heterologous booster vaccination with *Moderna* mitigate the negative impact of COVID-19 such as deaths due to COVID-19, medical costs, loss of productivity, social disruption, and unprecedented challenges in the health system. Similarly, based on evidence that is limited to immunogenicity outcomes, the potential health, economic, and social benefits of implementing homologous or heterologous additional dose vaccination with *Moderna* mitigate the negative impact of COVID-19 in immunocompromised patients.

6) **Public acceptability**
- Evidence:

General Public's Acceptability of Booster Vaccination

With regard to the general public 's acceptability of booster vaccination strategies, an online survey by the DOH Health Promotion Bureau was conducted from August 20 to September 21, 2021 (N= 15,439). In this survey, of the 7,307 fully vaccinated respondents, 87.90% were willing to receive a booster dose. Among the 4,267 partially vaccinated respondents, 77.08% were willing to receive a booster dose.

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- Among those likely to get boosters, the top three reasons are: (1) confidence in booster effectiveness in preventing serious and severe COVID-19. (22.83%); (2) perception of high risk of getting infected with COVID-19 if one will not get a booster dose. (16.34%); and (3) confidence in booster effectiveness against COVID-19 variants (15.59%).
- Among those not likely to get boosters, the top three reasons are: (1) Lack of confidence in booster effectiveness against COVID-19 variants (18.18%); (2) lack of confidence in the safety of the booster and is likely to cause severe adverse reactions (15.15%); and (3) they would want to wait and see until more people they know get the booster dose (14.14%).
- Among those who are unsure to get boosters, the top three reasons are: (1) they would want to wait and see until more people they know get the booster dose (24.43%); (2) lack of confidence in the safety of COVID-19 booster vaccine and is likely to cause severe adverse reactions (14.98%); and (3) lack of confidence in the booster effectiveness against COVID-19 variants (14.33%).

7) Availability of mechanisms to manage any untoward serious adverse reactions following vaccination
- Evidence: 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 last 17 June 2021. The circular, otherwise known as the "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), aims 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.

8) Appropriateness of the vaccine as booster and additional dose to special at-risk groups and patients with comorbidities
- Evidence: Currently, there is limited data from studies on the use of *Moderna* for booster dose and additional dose vaccination. However, the current available studies for these vaccination strategies included the following populations:
  - **Booster vaccinations:** Among the studies reviewed, the elderly and those with controlled comorbidities were included as participants. Meanwhile, persons living with HIV, children, adolescents, pregnant and lactating women and the immunocompromised were not included, thus the appropriateness of a booster dose of *Moderna* to these special populations cannot be determined.

  - **Additional dose vaccination:** Among the studies reviewed, the immunocompromised including: adults with chronic-inflammatory rheumatic or neurologic disease under therapy; solid organ transplant recipients; hemodialysis and peritoneal dialysis patients; and kidney transplant patients were included. Meanwhile, immunocompromised patients with past SARS-CoV-2 infections were not included, thus the appropriateness of an additional dose of *Moderna* to these special populations cannot be determined.

HTAC Judgment: *Moderna* possesses most of the characteristics desired by key stakeholders for its use as a booster for the general population 18 years and above. Further, based on a survey conducted among the general population and HCWs in the Philippines, there is high willingness to receive booster shots. The respondents noted their current knowledge on the vaccine effectiveness and safety as basis for their willingness to receive a booster dose. Specifically for the HCWs, their confidence that booster doses can strengthen their protection against severe COVID-19 infection and against VOCs augments this willingness to receive booster doses of the vaccine. However, there are currently no COVID-19 vaccines approved by the Philippine FDA for emergency use as booster dose or additional dose. Meanwhile, evidence for the desired characteristics for its use as an additional dose is yet to be established.

AstraZeneca

Based on the results of the focus group discussions conducted 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 evidences for the *AstraZeneca*:

1) **Safe and efficacious**
- Evidence
- *Clinical evidence for booster vaccination*
  The efficacy and effectiveness of *AstraZeneca* as a booster dose is yet to be established. Based on one cohort study, the immune response after the third dose of *AstraZeneca* is much higher compared to the levels following the second dose of the primary vaccine series.

  Currently, there is limited available evidence on the efficacy or effectiveness of *AstraZeneca* both as a homologous and heterologous booster dose. No studies were found measuring efficacy and effectiveness of *AstraZeneca* as a homologous booster dose. However, there is currently available evidence limited to 1 case series (Flaxman et al., 2021) measuring immunogenicity with a short follow up period (28 days). The study showed comparable to increased neutralizing antibody titers and spike-specific cellular immune responses after receiving a booster dose of *AstraZeneca* compared to receiving the second dose of the primary vaccine series. Current safety evidence on homologous booster vaccination is limited to 1 case series study (Flaxman et al., 2021) with a short follow-up period. Evidence from the case series showed more local reactogenicity and comparable systemic reactogenicity compared to the second dose of the primary series.

  In terms of heterologous booster vaccination, no studies on efficacy are currently available. However, an NRA Report (Chile MOH) with a short follow-up period (14 days after booster vaccination) on the use of *CoronaVac (primary series) + AstraZeneca (booster)* reported an increase in vaccine effectiveness against COVID-19 infection (from 56% to 93%) and hospitalization due to COVID-19 (84% to 96%). Further, there is available evidence (Patamatamkul et al., 2021) on the immunogenicity of the same heterologous booster combination among health care workers, with a follow up period of 2 to 3 weeks,. Results showed an increase in neutralizing antibody and spike-specific cellular immune responses after receiving a booster dose of *AstraZeneca* compared to the immune response after receiving the second dose of the primary vaccine series.

  Clinical evidence for additional dose vaccination
  Currently, there is no available evidence on the efficacy or effectiveness of the use of *AstraZeneca* either as a homologous and a heterologous additional dose for immunocompromised patients. However, there is available evidence limited to 1 trial (Bonelli et al., 2021; follow up of 4 weeks) on the use of *AstraZeneca* as third dose to mRNA among immunocompromised adults with chronic-inflammatory rheumatic or neurologic diseases under current rituximab therapy. Results showed a comparable to increased immune response after receiving an additional dose of *AstraZeneca* compared to a second dose of an *mRNA* primary series (1 study).

  There is limited evidence on the safety of *AstraZeneca* both as a homologous and a heterologous additional dose. In addition, the varying antibody responses of additional dose vaccinations pose potential risks, such as organ rejection and should be evaluated on an individual basis. Moreover, the long-term safety profile of heterologous vaccination strategies using *AstraZeneca* cannot be assessed since a longer follow-up period from clinical trials and real world evidence is needed.

2) Underwent a **transparent regulatory process** of being evaluated and approved by health authorities
- Evidence: The Philippine FDA has not yet issued the amended Emergency Use Authorization of *AstraZeneca* to include its use for booster vaccination or additional dose vaccination for immunocompromised patients.

3) **Potential for high and equitable coverage across the population**
- Evidence: *AstraZeneca* can be made more available since vaccine handling and storage are within the capacity of the RHUs.
- Further, the WHO emphasized the following points in its statement on booster vaccination dated 04 October 2021:

- The rationale for 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.
- The evidence remains limited and still inconclusive on any widespread need for booster doses following a primary vaccination series.
- In the context of ongoing global vaccine supply constraints, broad-based administration of booster doses risks exacerbating inequities in vaccine access by driving up demand and diverting supply while priority populations in some countries, or in subnational settings, have not yet received a primary vaccination series.
- The focus remains on urgently increasing global vaccination coverage with the primary series driven by the objective to protect against severe disease.

- As for additional dose vaccination for immunocompromised patients, the WHO statement on 31 August 2021 emphasized that third doses should be prioritized for the vulnerable: those most at-risk populations when there is evidence of waning immunity against severe disease and death. They added that the number of immunocompromised individuals globally who would potentially benefit from a third dose is very small, especially when compared to the health workers, older populations at risk who have not had their first or second vaccinations globally. However, they noted that when global supplies are so limited, when the world is in a place where billions of people have not yet received any doses, focus must be on administering first and second doses.

4) **Ease in logistics and administration**

- Evidence: *AstraZeneca* can be stored at 2-8 degrees Celsius which is present in most RHUs. However, according to the NVOC, despite its manageable cold chain requirement, the lack of a centralized database for the vaccination program as mechanism to track vaccine recipients and the longer dosing interval of *AstraZeneca* have made the vaccine less viable to implement compared to other vaccines with the same storage temperature requirement.
- Further, the NVOC and the DOH-Epidemiology Bureau were consulted for their insights on the implications of implementing booster dose to the current COVID-19 Vaccination program. Generally, homologous booster vaccination is perceived to be more acceptable to the program implementers compared to heterologous booster vaccination.
  - Based on the feedback of the consulted groups, administering a booster dose of the same vaccine brand will require less training, accounting for similar experience on the brands used in the primary vaccine series. However, this will still entail additional resources particularly vaccination sites, human resources (such as vaccinators), and supply of vaccines, if booster vaccination will run simultaneously with the primary vaccination.
  - Meanwhile, adopting a booster of a different brand on top of the vaccine used in the primary series will need supplemental training of human resources, and extensive monitoring and surveillance of adverse events. Furthermore, similar to introducing new vaccines or vaccination strategies, they highlighted the difficulty in monitoring late-onset adverse events. To address this, retrospective studies or other pharmacovigilance methods such as active safety surveillance, involving cohort-event monitoring or hospital sentinel surveillance should be conducted.

5) **Cost-effective**

- Evidence: Based on evidence that is limited to immunogenicity outcomes, the potential health, economic, and social benefits of implementing homologous or heterologous booster vaccination with *AstraZeneca* mitigate the negative impact of COVID-19 such as deaths due to COVID-19, medical costs, loss of productivity, social disruption, and unprecedented challenges in the health system. As for additional dose vaccination, based on evidence that is limited to immunogenicity outcomes, the potential health, economic, and social benefits of implementing heterologous additional dose vaccination with *AstraZeneca* mitigate the negative impact of COVID-19 in immunocompromised patients. Currently, there is no evidence on the efficacy, effectiveness, or immunogenicity of homologous additional dose vaccination with *AstraZeneca* in immunocompromised patients.

6) **Public acceptability**

- Evidence:

  General Public's Acceptability of Booster Vaccination

  With regard to the general public 's acceptability of booster vaccination strategies, an online survey by the DOH Health Promotion Bureau was conducted from August 20 to September 21, 2021 (N= 15,439). In this survey, of the 7,307 fully vaccinated respondents, 87.90% were willing to receive a booster dose. Among the 4,267 partially vaccinated respondents, 77.08% were willing to receive a booster dose.

  Healthcare Workers' Acceptability of Booster Vaccination

  With regard to the healthcare worker's acceptability of booster vaccination strategies, a survey by the DOH Health Promotion Bureau was conducted from September 15 to 21, 2021 (N=10,525) . In this survey, of the 10,323 fully vaccinated respondents, 97.30% were willing to receive a booster dose. Among the 158 partially vaccinated respondents, 85.44% were willing to receive a booster dose. Regard for evidence of additional protection and expert opinion can be seen among the participants as the percentage of those highly likely to receive the booster increased to 98.58% (fully vaccinated) and 91.77% (partially vaccinated) if the evidence of additional protection are available and boosters are recommended by experts. Additionally, participants also shared reasons for their willingness to get the booster dose.
    - Among those likely to get boosters, the top three reasons are: (1) confidence in booster effectiveness in preventing serious and severe COVID-19. (22.83%); (2) perception of high risk of getting infected with COVID-19 if one will not get a booster dose. (16.34%); and (3) confidence in booster effectiveness against COVID-19 variants (15.59%).
    - Among those not likely to get boosters, the top three reasons are: (1) Lack of confidence in booster effectiveness against COVID-19 variants (18.18%); (2) lack of confidence in the safety of the booster and is likely to cause severe adverse reactions (15.15%); and (3) they would want to wait and see until more people they know get the booster dose (14.14%).
    - Among those who are unsure to get boosters, the top three reasons are: (1) they would want to wait and see until more people they know get the booster dose (24.43%); (2) lack of confidence in the

safety of COVID-19 booster vaccine and is likely to cause severe adverse reactions (14.98%); and (3) lack of confidence in the booster effectiveness against COVID-19 variants (14.33%).

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 last 17 June 2021. The circular, otherwise known as the "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), aims 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. The updated WHO recommendation is consistent with the updated DOH guidelines (Department Memorandum 2021-0175) which states that individuals who have previously had COVID-19 infection may be vaccinated after recovery or after completion of treatment, whether for first or second dose, without restarting the vaccine dose schedule.

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

- Evidence: Currently, there is limited data from studies on the use of *AstraZeneca* for booster dose and additional dose vaccination. However, the current available studies for these vaccination strategies included the following populations:
  - **Booster vaccinations:** Among the studies reviewed, the elderly and those with controlled comorbidities were included as participants. Meanwhile, persons living with HIV, children, adolescents, pregnant and lactating women and the immunocompromised were not included, thus the appropriateness of a booster dose of *AstraZeneca* to these special populations cannot be determined.

  - **Additional dose vaccination:** Among the studies reviewed, the immunocompromised including : adults with chronic-inflammatory rheumatic or neurologic disease under therapy were included. Meanwhile, immunocompromised patients with past SARS-CoV-2 infections were not included, thus the appropriateness of an additional dose of *AstraZeneca* to these special populations cannot be determined.

HTAC Judgment: *AstraZeneca* possesses most of the characteristics desired by key stakeholders for its use as a booster for the general population 18 years and above. Further, based on a survey conducted among the general population and HCWs in the Philippines, there is high willingness to receive booster shots. The respondents noted their current knowledge on the vaccine effectiveness and safety as basis for their willingness to receive a booster dose. Specifically for the HCWs, their confidence that booster doses can strengthen their protection against severe COVID-19 infection and against VOCs augments this willingness to receive booster doses of the vaccine. However, there are currently no COVID-19 vaccines approved by the Philippine FDA for emergency use as booster dose or additional dose. Meanwhile, evidence for the desired characteristics for its use as an additional dose is yet to be established.

Janssen

Based on the results of the focus group discussions conducted 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 evidences for the *Moderna*:

1) **Safe and efficacious**

- Evidence:
  Clinical evidence for booster vaccination
  Currently, there is no available evidence on the efficacy or effectiveness of the use of *Janssen* as a homologous booster. Currently, evidence is limited to one preprint version of a Phase 1/2 trial (Sadoff et al., 2021) examining the immunogenicity of *Janssen* as a homologous booster. Results show an increase in the titer after the second dose of *Janssen*. RMeanwhile,the efficacy and effectiveness of *Janssen* as a heterologous booster dose is yet to be established.

  In terms of safety, current evidence is limited to 1 trial (Sadoff et al., 2021) and 1 NRA report from US CDC. Overall, as a homologous booster, *Janssen* showed an acceptable short term safety profile. Further, reported unsolicited adverse events did not reflect any new safety concerns and no deaths or SAEs considered causally related to the booster dose. For safety of heterologous booster, evidence is limited to its use as a booster to *Pfizer-BioNTech and Moderna* as primary series. The surveillance and trial reports showed acceptable short-term safety. However, the short-follow up period of the trials (0 to 30 days after booster dose) of the report and trials does not meet the HTAC - preferred median follow up period of at least 2 months. In addition, the long-term safety profile of both strategies using *Janssen* cannot be assessed since a longer follow-up period from clinical trials and real world evidence is needed.

  Clinical evidence for additional dose vaccination

Currently, there is no available evidence on the efficacy or effectiveness of the use of *Janssen* either as a homologous and a heterologous additional dose for immunocompromised patients. However, there is available evidence limited to 1 real world study on the use of *Janssen* as third dose to mRNA among immunocompromised patients who are transplant patients. Results showed a comparable to increased immune response after receiving an additional dose of *Janssen* compared to a second dose of an *mRNA* primary series (Werbel, et al, 2021; follow up of median 14 days after booster dose).

There is limited evidence on the safety of *Janssen* both as a homologous and a heterologous additional dose. In addition, the varying antibody responses of additional dose vaccinations pose potential risks, such as organ rejection and should be evaluated on an individual basis. Moreover, the long-term safety profile of heterologous vaccination strategies using *Janssen* cannot be assessed since a longer follow-up period from clinical trials and real world evidence is needed.

2) Underwent a **transparent regulatory process** of being evaluated and approved by health authorities
- Evidence: The Philippine FDA has not yet issued the amended Emergency Use Authorization of *Janssen* to include its use for booster vaccination or additional dose vaccination for immunocompromised patients.

3) **Potential for high and equitable coverage across the population**
- Evidence: The one-dose vaccination requirement with *Janssen* can facilitate utility in a wider setting especially for those experiencing difficulty with completing their second dose required in other vaccines, thereby improving compliance. In addition, this can be made more available since vaccine handling and storage are within the capacity of the RHUs.
- Further, the WHO emphasized the following points in its statement on booster vaccination dated 04 October 2021:
  - The rationale for 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.
  - The evidence remains limited and still inconclusive on any widespread need for booster doses following a primary vaccination series.
  - In the context of ongoing global vaccine supply constraints, broad-based administration of booster doses risks exacerbating inequities in vaccine access by driving up demand and diverting supply while priority populations in some countries, or in subnational settings, have not yet received a primary vaccination series.
  - The focus remains on urgently increasing global vaccination coverage with the primary series driven by the objective to protect against severe disease.
- As for additional dose vaccination for immunocompromised patients, the WHO statement on 31 August 2021 emphasized that third doses should be prioritized for the vulnerable: those most at-risk populations when there is evidence of waning immunity against severe disease and death. They added that the number of immunocompromised individuals globally who would potentially benefit from a third dose is very small, especially when compared to the health workers, older populations at risk who have not had their first or second vaccinations globally. However, they noted that when global supplies are so limited, when the world is in a place where billions of people have not yet received any doses, focus must be on administering first and second doses.

4) **Ease in logistics and administration**
- Evidence: *Janssen* can be stored for 3 months at 2-8 degrees Celsius in a refrigerator which is present in most RHUs. The vaccine also does not require dilution at the vaccination site which may simplify implementation of the vaccine especially in community settings.
- Further, the NVOC and the DOH-Epidemiology Bureau were consulted for their insights on the implications of implementing booster dose to the current COVID-19 Vaccination program. Generally, homologous booster vaccination is perceived to be more acceptable to the program implementers compared to heterologous booster vaccination.
  - Based on the feedback of the consulted groups, administering a booster dose of the same vaccine brand will require less training, accounting for similar experience on the brands used in the primary vaccine series. However, this will still entail additional resources particularly vaccination sites, human resources (such as vaccinators), and supply of vaccines, if booster vaccination will run simultaneously with the primary vaccination.
  - Meanwhile, adopting a booster of a different brand on top of the vaccine used in the primary series will need supplemental training of human resources, and extensive monitoring and surveillance of adverse events. Furthermore, similar to introducing new vaccines or vaccination strategies, they highlighted the difficulty in monitoring late-onset adverse events. To address this, retrospective studies or other pharmacovigilance methods such as active safety surveillance, involving cohort-event monitoring or hospital sentinel surveillance should be conducted.

5) **Cost-effective**
- Evidence: Based on evidence that is limited to immunogenicity outcomes, the potential health, economic, and social benefits of implementing homologous or heterologous booster vaccination with *Janssen* mitigate the negative impact of COVID-19 such as deaths due to COVID-19, medical costs, loss of productivity, social disruption, and unprecedented challenges in the health system. Similarly, based on evidence that is limited to immunogenicity outcomes, the potential health, economic, and social benefits of implementing heterologous additional dose vaccination with *Janssen* mitigate the negative impact of COVID-19 in immunocompromised patients. Currently, there is no evidence on the efficacy, effectiveness, or immunogenicity of homologous additional dose vaccination with *Janssen* in immunocompromised patients.

6) **Public acceptability**

- Evidence:

General Public's Acceptability of Booster Vaccination

With regard to the general public 's acceptability of booster vaccination strategies, an online survey by the DOH Health Promotion Bureau was conducted from August 20 to September 21, 2021 (N= 15,439). In this survey, of the 7,307 fully vaccinated respondents, 87.90% were willing to receive a booster dose. Among the 4,267 partially vaccinated respondents, 77.08% were willing to receive a booster dose.

Healthcare Workers' Acceptability of Booster Vaccination

With regard to the healthcare worker's acceptability of booster vaccination strategies, a survey by the DOH Health Promotion Bureau was conducted from September 15 to 21, 2021 (N=10,525) . In this survey, of the 10,323 fully vaccinated respondents, 97.30% were willing to receive a booster dose. Among the 158 partially vaccinated respondents, 85.44% were willing to receive a booster dose. Regard for evidence of additional protection and expert opinion can be seen among the participants as the percentage of those highly likely to receive the booster increased to 98.58% (fully vaccinated) and 91.77% (partially vaccinated) if the evidence of additional protection are available and boosters are recommended by experts. Additionally, participants also shared reasons for their willingness to get the booster dose.

- Among those likely to get boosters, the top three reasons are: (1) confidence in booster effectiveness in preventing serious and severe COVID-19. (22.83%); (2) perception of high risk of getting infected with COVID-19 if one will not get a booster dose. (16.34%); and (3) confidence in booster effectiveness against COVID-19 variants (15.59%).
- Among those not likely to get boosters, the top three reasons are: (1) Lack of confidence in booster effectiveness against COVID-19 variants (18.18%); (2) lack of confidence in the safety of the booster and is likely to cause severe adverse reactions (15.15%); and (3) they would want to wait and see until more people they know get the booster dose (14.14%).
- Among those who are unsure to get boosters, the top three reasons are: (1) they would want to wait and see until more people they know get the booster dose (24.43%); (2) lack of confidence in the safety of COVID-19 booster vaccine and is likely to cause severe adverse reactions (14.98%); and (3) lack of confidence in the booster effectiveness against COVID-19 variants (14.33%).

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 last 17 June 2021. The circular, otherwise known as the "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), aims 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.

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

- Evidence: Currently, there is limited data from studies on the use of *Janssen* for booster dose and additional dose vaccination. However, the current available studies for these vaccination strategies included the following populations:
  - **Booster vaccinations:** Among the studies reviewed, the elderly and those with controlled comorbidities were included as participants. Meanwhile, persons living with HIV, children, adolescents, pregnant and lactating women and the immunocompromised were not included,thus the appropriateness of a booster dose of *Janssen* to these special populations cannot be determined

  - **Additional dose vaccination:** Among the studies reviewed, the immunocompromised including: solid organ transplant recipients were included. Meanwhile, immunocompromised patients with past SARS-CoV-2 infections were not included, thus the appropriateness of a booster dose of *Janssen* to these special populations cannot be determined.

HTAC Judgment: *Janssen* possesses most of the characteristics desired by key stakeholders for its use among the general population as booster dose for the general population 18 years and above. Further, based on a survey conducted among the general population and HCWs in the Philippines, there is high willingness to receive booster shots. The respondents noted their current knowledge on the vaccine effectiveness and safety as basis for their willingness to receive a booster dose. Specifically for the HCWs, their confidence that booster doses can strengthen their protection against severe COVID-19 infection and against VOCs augments this willingness to receive booster doses of the vaccine. However, there are currently no COVID-19 vaccines approved by the Philippine FDA for emergency use as booster dose or additional dose. Meanwhile, evidence for the desired characteristics for its use as an additional dose is yet to be established.

CoronaVac

Based on the results of the focus group discussions conducted 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 evidences for the *CoronaVac*:

1) **Safe and efficacious** for the general population (aged 18 years and older) and for some vulnerable groups like the older population and individuals with comorbidities.

- Evidence:

Clinical evidence for booster vaccination
Currently, there is limited available evidence on the clinical efficacy or effectiveness of *CoronaVac* as a homologous booster dose. There was one reference on vaccine effectiveness of *CoronaVac* from 1 NRA report from Chile (Chile Ministerio de Salud; follow up period of 14 days after booster dose). The report noted that *CoronaVac,* as a homologous booster dose, induced substantial increase in effectiveness against COVID-19 infection and similar vaccine effectiveness against hospitalization compared to after dose 2. However, the data from this NRA report was not supplemented with a full published paper. Remaining evidence were limited to immunogenicity studies showing that there is an increase in neutralizing antibody and spike-specific cellular immune responses after receiving a booster dose of *CoronaVac* compared to the immune response after receiving dose 2 of the primary vaccine series, with a follow up period ranging from 4 to 26 weeks.

Meanwhile, in terms of safety of *CoronaVac* as a homologous booster dose, 2 clinical trials from China reported that both the local and systemic adverse events as well as the serious adverse events were deemed acceptable. Lastly, the efficacy, effectiveness and safety of *CoronaVac* as a heterologous booster dose is yet to be established due to lack of evidence.

Clinical evidence for additional dose vaccination
Currently, there is no available evidence on the efficacy and safety of *CoronaVac* as a homologous and heterologous additional dose for immunocompromised population.

2) Underwent a **transparent regulatory process** of being evaluated and approved by health authorities
- Evidence: The Philippine FDA has not yet issued the amended Emergency Use Authorization of *CoronaVac* to include its use for booster vaccination or additional dose vaccination for immunocompromised patients.

3) **Potential for high and equitable coverage across the population**
- Evidence: *CoronaVac* can be made more available since vaccine handling and storage are within the capacity of the RHUs.
- Further, the WHO emphasized the following points in its statement on booster vaccination dated 04 October 2021:
  - The rationale for 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.
  - The evidence remains limited and still inconclusive on any widespread need for booster doses following a primary vaccination series.
  - In the context of ongoing global vaccine supply constraints, broad-based administration of booster doses risks exacerbating inequities in vaccine access by driving up demand and diverting supply while priority populations in some countries, or in subnational settings, have not yet received a primary vaccination series.
  - The focus remains on urgently increasing global vaccination coverage with the primary series driven by the objective to protect against severe disease.
- As for additional dose vaccination for immunocompromised patients, the WHO statement on 31 August 2021 emphasized that third doses should be prioritized for the vulnerable: those most at-risk populations when there is evidence of waning immunity against severe disease and death. They added that the number of immunocompromised individuals globally who would potentially benefit from a third dose is very small, especially when compared to the health workers, older populations at risk who have not had their first or second vaccinations globally. However, they noted that when global supplies are so limited, when the world is in a place where billions of people have not yet received any doses, focus must be on administering first and second doses.

4) **Ease in logistics and administration**
- Evidence: *CoronaVac* can be stored at 2 to 8 degrees Celsius which is present in most RHUs.
- Further, the NVOC and the DOH-Epidemiology Bureau were consulted for their insights on the implications of implementing booster dose to the current COVID-19 Vaccination program. Generally, homologous booster vaccination is perceived to be more acceptable to the program implementers compared to heterologous booster vaccination.
  - Based on the feedback of the consulted groups, administering a booster dose of the same vaccine brand will require less training, accounting for similar experience on the brands used in the primary vaccine series. However, this will still entail additional resources particularly vaccination sites, human resources (such as vaccinators), and supply of vaccines, if booster vaccination will run simultaneously with the primary vaccination.
  - Meanwhile, adopting a booster of a different brand on top of the vaccine used in the primary series will need supplemental training of human resources, and extensive monitoring and surveillance of adverse events. Furthermore, similar to introducing new vaccines or vaccination strategies, they highlighted the difficulty in monitoring late-onset adverse events. To address this, retrospective studies or other pharmacovigilance methods such as active safety surveillance, involving cohort-event monitoring or hospital sentinel surveillance should be conducted.

5) **Cost-effective**
- Evidence: Based on evidence that is limited to immunogenicity outcomes, the potential health, economic, and social benefits of implementing homologous booster vaccination with *CoronaVac* mitigate the negative impact of COVID-19 such as deaths due to COVID-19, medical costs, loss of productivity, social disruption, and unprecedented challenges in the health system. Currently, there is no evidence on the efficacy, effectiveness, or immunogenicity of heterologous booster vaccination, and homologous or heterologous additional dose vaccination in immunocompromised patients with *CoronaVac*.

6) **Public acceptability**

- Evidence:

  General Public's Acceptability of Booster Vaccination

  With regard to the general public 's acceptability of booster vaccination strategies, an online survey by the DOH Health Promotion Bureau was conducted from August 20 to September 21, 2021 (N= 15,439). In this survey, of the 7,307 fully vaccinated respondents, 87.90% were willing to receive a booster dose. Among the 4,267 partially vaccinated respondents, 77.08% were willing to receive a booster dose.

  Healthcare Workers' Acceptability of Booster Vaccination

  With regard to the healthcare worker's acceptability of booster vaccination strategies, a survey by the DOH Health Promotion Bureau was conducted from September 15 to 21, 2021 (N=10,525) . In this survey, of the 10,323 fully vaccinated respondents, 97.30% were willing to receive a booster dose. Among the 158 partially vaccinated respondents, 85.44% were willing to receive a booster dose. Regard for evidence of additional protection and expert opinion can be seen among the participants as the percentage of those highly likely to receive the booster increased to 98.58% (fully vaccinated) and 91.77% (partially vaccinated) if the evidence of additional protection are available and boosters are recommended by experts. Additionally, participants also shared reasons for their willingness to get the booster dose.

  - Among those likely to get boosters, the top three reasons are: (1) confidence in booster effectiveness in preventing serious and severe COVID-19. (22.83%); (2) perception of high risk of getting infected with COVID-19 if one will not get a booster dose. (16.34%); and (3) confidence in booster effectiveness against COVID-19 variants (15.59%).
  - Among those not likely to get boosters, the top three reasons are: (1) Lack of confidence in booster effectiveness against COVID-19 variants (18.18%); (2) lack of confidence in the safety of the booster and is likely to cause severe adverse reactions (15.15%); and (3) they would want to wait and see until more people they know get the booster dose (14.14%).
  - Among those who are unsure to get boosters, the top three reasons are: (1) they would want to wait and see until more people they know get the booster dose (24.43%); (2) lack of confidence in the safety of COVID-19 booster vaccine and is likely to cause severe adverse reactions (14.98%); and (3) lack of confidence in the booster effectiveness against COVID-19 variants (14.33%).

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 last 17 June 2021. The circular, otherwise known as the "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), aims 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.

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

- Evidence: Currently, there is limited data from studies on the use of *CoronaVac* for booster dose and no evidence on the use of *CoronaVac* for additional dose vaccination. However, the current available studies for booster vaccination included the following populations:
  - **Booster vaccinations:** Among the studies reviewed, the elderly and those with controlled comorbidities were included as participants. Meanwhile, persons living with HIV, children, adolescents, pregnant and lactating women and the immunocompromised were not included, thus the appropriateness of a booster dose of *CoronaVac* to these special populations cannot be determined.

HTAC Judgment: *CoronaVac* possesses most of the characteristics desired by key stakeholders for its use among the general population as a booster for the general population 18 years and above. Further, based on a survey conducted among the general population and HCWs in the Philippines, there is high willingness to receive booster shots. The respondents noted their current knowledge on the vaccine effectiveness and safety as basis for their willingness to receive a booster dose. Specifically for the HCWs, their confidence that booster doses can strengthen their protection against severe COVID-19 infection and against VOCs augments this willingness to receive booster doses of the vaccine. However, there are currently no COVID-19 vaccines approved by the Philippine FDA for emergency use as booster and additional dose. Meanwhile, evidence for the desired characteristics for its use as an additional dose is yet to be established.

Criteria 6: Responsiveness to Equity

RQ6.1: 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 77,139,058 target population for 2021 (i.e. 70% of the total population), a total of 14,650,065 individuals have already received the full regimen of COVID-19 vaccines, which translates as 18.99% full vaccination coverage among the eligible populations. Meanwhile, 9,388,338 individuals (or 12.17%) are yet to receive their second dose COVID-19 vaccine as of 03 September 2021.

Vaccination coverage by priority group

Among the priority groups A1, A2, and A3 included in the roll-out in March 2021, complete vaccine coverage for senior citizens (A2) lags at 48.29% (n=3,993,308/8,269,178) compared to A1 at 98.49% (n=1,614,141/1,638,917), and A3 at 60.29% (n=5,239,911/8,691,541); despite the senior citizens having the highest number of cases at 233,171 cases (as of 11 August 2021) and highest CFR among the priority groups at 8.08% (as of 11 August 2021).

Full vaccination coverage in other priority groups which started to roll-out in June 2021 were also noted: frontline personnel in essential sectors, including uniformed personnel (A4) (10.07%); and, indigent population (A5) (4.40%).

The vaccination coverage per priority group are as follows:

- Workers in Frontline Health Services (A1):
  - Of the 1,638,917 eligible A1 population, 98.49% (1,614,141) have received a full dose of COVID-19 vaccines. This group has the highest coverage across all priority groups, to date.
- Senior Citizen (A2):
  - Of the 8,269,178 eligible A2 population, 48.29% (3,993,308) have received a full dose of COVID-19 vaccines.
- Persons with Comorbidities (A3):
  - Of the 8,691,541 eligible A3 population, 60.29% (5,239,911) have received a full dose of COVID-19 vaccines.
- Frontline personnel in essential sectors, including uniformed personnel (A4):
  - Of the 28,300,410 eligible A4 population, 10.07% (2,850,281) have received a full dose of COVID-19 vaccines.
- Indigent Population (A5):
  - Of the 12,911,193 eligible A5 population, 4.40% (568,297) have received a full dose of COVID-19 vaccines.

Vaccination coverage by region

There is an observed disparity in the vaccination coverage across all regions, both for the vaccination coverage of at least one dose and the full regimen. As of September 3, 2021, NCR reported the highest vaccination coverage (full regimen: 48.81%; at least one dose: 84.14% of the total target population i.e. 70% of the population) while the Bangsamoro Autonomous Region in Muslim Mindanao (BARMM) recorded the lowest vaccination coverage (full regimen: 7.07%; at least one dose: 9.30% of the total target population i.e. 70% of the population). According to the NVOC, the observed disparity between regions is greatly impacted by the allocation-based (regional prioritization) strategy of the government. Currently, NCR is given higher priority due to the relatively higher incidence of COVID-19 in the region. The NVOC also acknowledges that there are logistical problems in BARMM that might also have led to its low coverage.

Pfizer-BioNTech	Moderna	AstraZeneca	Janssen	CoronaVac
Pfizer-BioNTech demonstrated efficacy in preventing symptomatic COVID-19 of 91.7% (95% CI: 44.2 to 99.8) in older adults aged 65 years and above and 95.3% (95% CI: 87.7 to 98.8) in individuals with comorbidities in the published trial Additionally, real world effectiveness studies demonstrate that *Pfizer-BioNTech* provides protection against symptomatic COVID-19 and reduces risk of severe COVID-19, COVID-19 hospitalization, and deaths in the general population and protection against symptomatic COVID-19, severe COVID-19, and hospitalization in older adults (≥65 years old). Meanwhile, efficacy and real world effectiveness of	*Moderna* demonstrated an efficacy against symptomatic COVID-19 of 86.4% (95% CI: 61.4 to 95.2) in older adults ≥ 65 years and 90.9% (95% CI: 74.7 to 96.7) in individuals with comorbidities in the published trial. Additionally, based on real world evidence *Moderna* has demonstrated protection against hospitalization due to COVID-19 and severe COVID-19 in the older population ≥65 years. Meanwhile, efficacy and real world effectiveness of the vaccine as a booster vaccine or additional dose is yet to be established. Based on current experience in the Philippine COVID-19 Vaccination	*AstraZeneca* has been shown to have an efficacy of 63.1% (95%CI: 51.8 to 71.7) in preventing symptomatic COVID-19, in the general population, including those with well-controlled comorbidities in the published trial. Additionally, real world effectiveness studies demonstrate that *AstraZeneca* provides protection against COVID-19 in the older population. Meanwhile, efficacy and real world effectiveness of the vaccine as a booster vaccine or additional dose is yet to be established. There may be issues/gaps in access for special and vulnerable populations such as those with allergy to one of the	*Janssen* demonstrated effectiveness in preventing COVID-19 in the older population Meanwhile, efficacy and real world effectiveness of the vaccine as a booster vaccine or additional dose is yet to be established. *Janssen* can be stored at normal cold storage conditions (2 to 8 degrees Celsius) for 3 months and protected from light. This made vaccine distribution in geographically isolated and disadvantaged areas possible. Compared to other new vaccines, *Janssen* only has a one-dose vaccination requirement. The US Advisory	*CoronaVac* has been shown to have an efficacy against symptomatic COVID-19 at 50.65% (95%CI: 35.94 to 61.98) in healthcare workers who have direct contact with suspected or confirmed cases of COVID-19, based on the interim results of the Phase III trial in Brazil (Palacios et al. 2021). Meanwhile, *CoronaVac* has been shown to have an efficacy against symptomatic COVID-19 at 83.5% (95% CI: 65.4 to 92.1) in population including both healthcare workers and the general population, based on the results of the Phase III trial in Turkey. Meanwhile, efficacy and real world effectiveness of the vaccine as a booster vaccine or additional dose is yet

the vaccine as a booster vaccine or additional dose is yet to be established. As *Pfizer-BioNTech* requires ultra-low temperatures of -90 °C to -60 °C, the existing cold chain infrastructure of the Department of Health can only allow the distribution to areas with the required logistical facility (i.e., NCR, Region VII, and Region XI) resulting in inequities for rural areas with no specialized freezers and capacity to handle the vaccine. In hospitals where refrigeration units are commonly available, the vaccine can be stored for five days in such refrigerators at 2–8 °C. With this, vaccination sites must ensure efficient roll out of the vaccines to avoid wastage. The requirement for two doses may also make compliance problematic for individuals who may have difficulty going to tertiary facilities such as indigents because of transportation costs and the elderly who may be unable to reach the tertiary facilities.. Of the 59,811,239 individuals eligible in the A1 to A5 priority group, 1,300,688 individuals (2.17%) received a full regimen of *Pfizer-BioNTech.* The relatively lower utilization of the *Pfizer-BioNTech* compared to the *CoronaVac* and *Janssen* which were the two most utilized vaccines in the Philippines can be attributed to supply issues. The vaccination coverage per priority group are as follows: ● Workers in Frontline Health Services (A1): ○ Of those individuals eligible under A1, 3.10% or 50,866 individuals received a full dose of *Pfizer-BioNTech.* Further, there are 15,567 individuals under A1 who are about to receive their second dose of the vaccine.	Program, due to the lower temperature requirement of *Moderna,* the vaccine is harder to roll out since limited areas have the required equipment for storage and handling. Of the 59,811,239 individuals eligible in the A1 to A5 priority group, 65,507 individuals (0.11%) received a full regimen of *Moderna.* The relatively lower utilization of the *Pfizer-BioNTech* compared to the *CoronaVac* and *Janssen* which were the two most utilized vaccines in the Philippines can be attributed to supply issues. The vaccination coverage per priority group are as follows: ● Workers in Frontline Health Services (A1): ○ Of those individuals eligible under A1, 0.28% or 4,594 individuals received a full dose of *Moderna.* Further, there are 20,653 individuals under A1 who are about to receive their second dose of the vaccine. ● Senior Citizen (A2): ○ Of those individuals eligible under A2, 0.11% or 9,171 individuals received a full dose of *Moderna.* Further, there are 109,095 individuals under A2 who are about to receive their second dose of the vaccine. ● Persons with Comorbidities (A3): ○ Of those individuals eligible under A3, 0.15% or 12,700 individuals received a full dose of *Moderna.* Further, there are 460,254 individuals under A3 who are about to receive their second dose of the vaccine. ● Frontline personnel in essential sectors, including uniformed personnel (A4):	components of the vaccine and individuals with known history of thrombosis with thrombocytopenia syndrome following any COVID-19 vaccine or capillary leak syndrome. *AstraZeneca* can be stored at normal cold storage conditions (2 to 8 degrees Celsius). This made vaccine distribution in geographically isolated and disadvantaged areas possible. Compared to other new vaccines, the price per dose and the logistical and operational cost of *AstraZeneca* allow it to be utilized widely. Of the 59,811,239 individuals eligible in the A1 to A5 priority group, 2,006,587 individuals (3.35%) received a full regimen of *AstraZeneca.* The relatively lower utilization of the *AstraZeneca* compared to the *CoronaVac* and *Janssen* which were the two most utilized vaccines in the Philippines can be attributed to longer dosing interval. The vaccination coverage per priority group are as follows: ● Workers in Frontline Health Services (A1): ○ Of those individuals eligible under A1, 31.63% or 518,321 individuals received a full dose of *AstraZeneca.* Further, there are 105,718 individuals under A1 who are about to receive their second dose of the vaccine. ● Senior Citizen (A2): ○ Of those individuals eligible under A2, 9.78% or 808,328 individuals received a full dose of *AstraZeneca.* Further, there are 203,588 individuals under A2 who are about to receive their second dose of the vaccine.	Community on Immunization Practices (ACIP) noted that the single-dose regimen of *Janssen* can facilitate completion of the vaccination series especially for those experiencing difficulty in returning for a second dose thereby improving compliance. In addition, the price per dose and the logistical and operational costs of *Janssen* allow it to be utilized widely which can provide an opportunity to improve equitable access to safe and effective COVID-19 vaccines. Of the 59,811,239 individuals eligible in the A1 to A5 priority group, 3,479,899 individuals (5.82%) received a full regimen of *Janssen.* The vaccination coverage per priority group are as follows: The vaccination coverage per priority group are as follows: ● Workers in Frontline Health Services (A1): ○ Of those individuals eligible under A1, 5.92% or 97,061 individuals received a full dose of *Janssen.* ● Senior Citizen (A2): ○ Of those individuals eligible under A2, 15.95% or 1,318,607 individuals received a full dose of *Janssen.* ● Persons with Comorbidities (A3): ○ Of those individuals eligible under A3, 21.14% or 1,837,174 individuals received a full dose of *Janssen.* ● Frontline personnel in essential sectors, including uniformed personnel (A4): ○ Of those individuals eligible under A4, 0.56% or 158,894 individuals received a full dose of *Janssen.*	to be established. There may be issues/gaps in access for special and vulnerable populations such as those with allergy to one of the components of the vaccine. *CoronaVac* can be stored at normal cold storage conditions (2 to 8 degrees Celsius). This made vaccine distribution in geographically isolated and disadvantaged areas possible. Compared to other new vaccines, the price per dose and the logistical and operational cost of *CoronaVac* allow it to be utilized widely. Of the 59,811,239 individuals eligible in the A1 to A5 priority group, 7,353,005 individuals (12.29%) received a full regimen of *CoronaVac.* The vaccination coverage per priority group are as follows: The vaccination coverage per priority group are as follows: ● Workers in Frontline Health Services (A1): ○ Of those individuals eligible under A1, 57.44% or 941,475 individuals received a full dose of *CoronaVac.* Further, there are 105,929 individuals under A1 who are about to receive their second dose of the vaccine. ● Senior Citizen (A2): ○ Of those individuals eligible under A2, 19.07% or 1,577,152 individuals received a full dose of *CoronaVac.* Further, there are 360,708 individuals under A2 who are about to receive their second dose of the vaccine. ● Persons with Comorbidities (A3): ○ Of those individuals eligible under A3, 24.79% or 2,154,718

• Senior Citizen (A2): ○ Of the 8,269,178 eligible A2 population, 48.29% (3,993,308) have received a full dose of COVID-19 vaccines. • Persons with Comorbidities (A3): ○ Of those individuals eligible under A3, 7.12% or 618,677 individuals received a full dose of *Pfizer-BioNTech*. Further, there are 139,529 individuals under A3 who are about to receive their second dose of the vaccine. • Frontline personnel in essential sectors, including uniformed personnel (A4): ○ Of those individuals eligible under A4, 0.32% or 91,039 individuals received a full dose of *Pfizer-BioNTech*. Further, there are 303,469 individuals under A4 who are about to receive their second dose of the vaccine. • Indigent Population (A5): ○ Of those individuals eligible under A5, 2.11% or 272,188 individuals received a full dose of *Pfizer-BioNTech*. Further, there are 140,525 individuals under A5 who are about to receive their second dose of the vaccine.	○ Of those individuals eligible under A4, 0.11% or 31,564 individuals received a full dose of *Moderna*. Further, there are 208,402 individuals under A4 who are about to receive their second dose of the vaccine. • Indigent Population (A5): ○ Of those individuals eligible under A5, 0.08% or 10,478 individuals received a full dose of *Moderna*. Further, there are 767,701 individuals under A5 who are about to receive their second dose of the vaccine.	• Persons with Comorbidities (A3): ○ Of those individuals eligible under A3, 6.75% or 586,828 individuals received a full dose of *AstraZeneca*. Further, there are 442,654 individuals under A3 who are about to receive their second dose of the vaccine. • Frontline personnel in essential sectors, including uniformed personnel (A4): ○ Of those individuals eligible under A4, 0.31% or 87,895 individuals received a full dose of *AstraZeneca*. Further, there are 940,289 individuals under A4 who are about to receive their second dose of the vaccine. • Indigent Population (A5): ○ Of those individuals eligible under A5, 0.04% or 5,215 individuals received a full dose of *AstraZeneca*. Further, there are 200,966 individuals under A5 who are about to receive their second dose of the vaccine.	• Indigent Population (A5): ○ Of those individuals eligible under A5, 0.53% or 68,163 individuals received a full dose of *Janssen*	individuals received a full dose of *CoronaVac*. Further, there are 1,064,915 individuals under A3 who are about to receive their second dose of the vaccine. • Frontline personnel in essential sectors, including uniformed personnel (A4): ○ Of those individuals eligible under A4, 8.72% or 2,467,469 individuals received a full dose of *CoronaVac*. Further, there are 2,689,476 individuals under A4 who are about to receive their second dose of the vaccine. • Indigent Population (A5): ○ Of those individuals eligible under A5, 1.64% or 212,191 individuals received a full dose of *CoronaVac*. Further, there are 450,397 individuals under A5 who are about to receive their second dose of the vaccine.
HTAC Judgment: Vaccination coverage showed that there is a disparity in distribution of vaccines across priority groups and regions. The stringent logistic requirements (i.e., -90 °C to -60 °C) and intricate vaccine storage, handling and preparation of *Pfizer-BioNTech* have made the distribution more challenging. This is supported by the observed relatively lower vaccination coverage compared to other vaccines across priority groups and regions, although this may be a result of	**HTAC Judgment:** Vaccination coverage showed that there is a disparity in distribution of vaccines across priority groups and regions. The stringent logistic requirements (i.e., -25 to -15 degrees Celsius) and intricate vaccine storage, handling and preparation of *Moderna* have made the distribution more challenging. This is supported by the relatively lower vaccination coverage compared to other vaccines across priority groups and regions, although this may be a result of	**HTAC Judgment:** Because of non-stringent logistic requirements, *AstraZeneca* does not aggravate health inequities related to inoculation of recipients residing in isolated and disadvantaged locations. Despite this, the full vaccination coverage of this vaccine is low due to a longer dosing interval required. Evidence based on real world studies demonstrate the clinical benefits of *AstraZeneca* in terms of safety and effectiveness against symptomatic	**HTAC Judgment:** The non-stringent logistic requirements (i.e., 2 to 8 degrees Celsius) allows it to be utilized widely. However, in spite of its non-stringent logistic requirements and its advantage as a one-dose vaccine, the vaccination coverage of *Janssen* has been low due to supply issues. Further, we recommend that the DOH devise an efficient supply chain management that would take into account the three-month shelf life of the vaccine especially in ensuring the	**HTAC Judgment:** Because of non-stringent logistic requirements, *CoronaVac* does not aggravate health inequities related to inoculation of recipients residing in isolated and disadvantaged locations. There is insufficient evidence based on real world studies to determine the effectiveness and duration of protection of *CoronaVac* against symptomatic COVID-19, hospitalization due to COVID-19, and death due to COVID-19 among the elderly population.

its later rollout compared to other brands. Evidence based on real world studies demonstrate the clinical benefits of *Pfizer-BioNTech* in terms of safety and effectiveness against any SARS-CoV-2 infection, symptomatic COVID-19, severe COVID-19, hospitalization and death due to COVID-19 in the elderly population. However, duration of protection against any SARS-CoV-2 infection, symptomatic COVID-19 and hospitalization is decreased in the elderly compared to the general population.	its later rollout compared to other brands. Evidence based on real world studies demonstrate the clinical benefits of *Moderna* in terms of safety and effectiveness against symptomatic COVID-1, severe COVID-19, hospitalization and death due to COVID-19 in the elderly population. However, duration of protection against hospitalization and death is decreased in the elderly compared to the general population.	COVID-19, hospitalization and death due to COVID-19 in the elderly population. However, VE decreased over time and duration of protection for these outcomes is decreased in the elderly compared to the general population.	stability of the vaccines, from distribution up to the administration to all target areas especially geographically isolated and disadvantaged areas (GIDA). Evidence based on real world studies demonstrate the clinical benefits of *Janssen* in terms of safety and effectiveness against symptomatic COVID-19in the elderly population. However, duration of protection cannot be inferred from the available evidence.	
HTAC Judgment for all vaccines: Booster vaccination will reduce inequities in the health system, as its implementation provides sustained protection against COVID-19 among high risk populations i.e. healthcare workers and elderly. Further, booster vaccination in healthcare workers shall strengthen the current existing interventions to maintain the resilience of the health system. This is assuming that the decision to provide booster vaccination is made in consultation with stakeholders, and shall be rolled out following the country's prioritization criteria, cognizant of the following: • Breakthrough COVID-19 infections in healthcare workers and eldery; • Sufficient supply to ensure that booster vaccination will not hinder primary vaccination of unvaccinated population. Additional dose vaccination will also reduce inequities in the health system, as its implementation ensures that the immunocompromised population attain sufficient protection against COVID-19. This is assuming that the decision to provide additional dose to the immunocompromised population is made in consultation with stakeholders; and, shall be rolled out following the country's prioritization criteria, cognizant that supplies are sufficient to ensure that provision of additional doses will not hinder primary vaccination of unvaccinated population.				

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Section 5. Acknowledgments

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- 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. HTAC Evidence Summaries

Pfizer-BioNTech

Version 1 dated 02 February 2021: http://bit.ly/ESbiontechC19Pfizer

Version 2 dated 25 June 2021**:** https://bit.ly/HTAC-PfizerC19_JuneReassessment

Moderna

Version 1 dated 28 May 2021: *http://bit.ly/ES-ModernaC19*

AstraZeneca

Version 1 dated 08 February 2021: http://bit.ly/2YZwIqo

Version 2 dated 25 June 2021: https://bit.ly/HTAC-AstraZenecaC19_JuneReassessment

Janssen

Version 1 dated 30 April 2021: https://drive.google.com/file/d/1nRFx0I2ReUFmWjuiIGAFdyiIcbikjjLU/view

Version 2 dated 25 June 2021: https://drive.google.com/file/d/1PDNXU7x8Ror4jxc7HTthdje7LxsidSJ5/view

CoronaVac

Version 1 dated 09 April 2021: http://bit.ly/ES-SinovacC19

Version 2 dated 30 July 2021: https://bit.ly/HTAC-SinovacC19_JulyReassessment

Appendix 2. LCPG Reviews

Efficacy, effectiveness and safety of booster (3rd dose) COVID-19 vaccination: Update v. August 31, 2021

Link: https://docs.google.com/document/d/191eZkq8U5EnWS892K3r3XTRSXO4JTVv1/edit

Are COVID-19 Vaccines efficacious in preventing COVID-19 infections caused by the B.1.617.2 (Delta) variant? v. August 31, 2021

Link: https://docs.google.com/document/d/14692ru8gvR2zU1_Kv0bhBux1wULsJnn7/edit

Updated review on Janssen v. September 6, 2021

Link: https://docs.google.com/document/d/1oI4KAkzRcUaHZ4Xv5bTzOz4TCSFFK1oC/edit

Updated review on CoronaVac v. September 16, 2021

Link: https://docs.google.com/document/d/1GUF_tTP0fbI8bUnz6GSJ0zROrm_RJ0yh/edit?rtpof=true

Rapid review on the efficacy, effectiveness and safety of booster (additional dose) COVID-19 vaccination: Update v. September 23, 2021

Link: https://docs.google.com/document/d/1NlXBoytfhDkitTCltgfSkZrIs4G1nq6S/edit

Appendix 3. Scoping Review of Indications of Heterologous and Booster Vaccination for *Pfizer, Moderna, AstraZeneca, Janssen, Coronavac (as of 31 Aug 2021)*

Link: https://docs.google.com/document/d/1N_8DIbEd3X_ZRe6XTVTvSsLnMtLVAMpvZVxf8praCBk/edit#heading=h.ajd48sg4b0b2

Appendix 4. Effectiveness over time and duration of protection of COVID-19 Vaccines among the general population and special populations

Link: https://docs.google.com/document/d/1N5yD_DyKlDI1wTbJ6qj_cFikCE0GgXJ2sN6o7NamVP0/edit#heading=h.yr3jjc7r3a31

Appendix 5. Risk of bias of included studies

Link: https://docs.google.com/document/d/1WUBPorPVz_FIMpmdCnac_2B4b5lT311ijTKVzKbKGA0/edit#heading=h.eodw75sqwd8a

Appendix 6. Costing analysis

Link: https://docs.google.com/document/d/1d3k_aXBoU0sMuW4LQC7R-MrcWJgRukvsuG8OrPnVJ_g/edit