Evidence Summary on *SARS-CoV-2 Vaccine (Vero Cell), Inactivated [CoronaVac]* for the prevention of COVID-19

Service Line	Evidence Summary
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Prepared by	Health Technology Assessment Council Health Technology Assessment Unit
Contact details	hta@doh.gov.ph

Version history

Version	Release Date	What's new in this document
2.0	30 July 2021	**ES Parts for revision/ replacement** ● **Responsiveness to magnitude and severity (C1):** Updating of epidemiologic data ● **Affordability and viability (C3):** Updating of costing analysis for affordability and viability based on updates from DPCB **ES Parts for additional information** ● **Clinical efficacy and safety (C2):** Additional trial and real world data on efficacy, effectiveness and safety ● **Social Impact (C5):** Additional national survey results on vaccine preference, PhilHealth Circular 2021-0007. ● **Responsiveness to Equity (C6)** Contents of V1 ES that are not mentioned here remain valid.
1.0	09 April 2021	Initial release of HTAC recommendation

Rationale on updating the HTAC recommendation on *SARS-CoV-2 Vaccine (Vero Cell), Inactivated [CoronaVac]*

Considering the evolving evidence on COVID-19 vaccines, the HTAC releases its updated recommendations on the emergency use of *SARS-CoV-2 Vaccine (Vero Cell), Inactivated [CoronaVac]*. Further, there was a necessity to revisit the HTAC recommendation dated 08 April 20121 which recommends the vaccine to the healthy population with low risk of exposure aged 18 to 59 years old due to the following reasons:.

- On 24 May 2021, the World Health Organization Strategic Advisory Group of Experts (WHO SAGE) released their interim recommendation for the use of *SARS-CoV-2 Vaccine (Vero Cell), Inactivated [CoronaVac]* wherein they recommended the use of the said vaccine in persons aged 18 years and above.
- In a letter dated 07 April 2021 to the Department of Health, the Philippine FDA expressed that they have no objections to using the aforementioned vaccine on individuals aged 60 and above.
- Use of vaccines in senior citizens was allowed as stated in Department Memorandum released by DOH on 08 April 2021 (DM 2021-0175) and an advisory from the National COVID-19 Vaccination Operations Center (NVOC Advisory No. 27).

AMENDMENTS

The following sections compare versions 1 and 2 of the HTAC recommendations:

HTAC Recommendation:

Version 1 *(as of 08 April 2021)*	Version 2 *(as of 30 July 2021)*
The HTAC maintains its **recommendation for the emergency use of *SARS-CoV-2 Vaccine (Vero cell), Inactivated [CoronaVac]*** to reduce the burden of COVID-19 in a healthy population, 18-59 years of age, with low risk of exposure to COVID-19 infection.	The HTAC updates its **recommendation for the emergency use of *SARS-CoV-2 Vaccine (Vero cell), Inactivated [CoronaVac]*** to reduce the burden of COVID-19 in the general population aged 18 years and older.

Summary of HTAC judgement and considerations in formulating its recommendation for the vaccine:

Criterion	HTAC Judgment	
	Version 1 ***(as of 08 April 2021)***	**Version 2** ***(as of 30 July 2021)***
Can *SARS-CoV-2 Vaccine (Vero cell), Inactivated [CoronaVac]* significantly reduce the magnitude and severity of COVID-19?	**Yes**. *SARS-CoV-2 Vaccine (Vero cell), Inactivated [CoronaVac]* has the potential to reduce the disease burden by averting a significant number of symptomatic infections assuming sufficient vaccine coverage.	No revisions.
Is *SARS-CoV-2 Vaccine (Vero cell), Inactivated [CoronaVac]* efficacious and safe?	Based on a report of interim results of an unpublished Phase III trial on *SARS-CoV-2 Vaccine (Vero cell), Inactivated [CoronaVac] in Brazil* [Palacios, 2021) *(cut-off analysis: date: 16 December 2020)]*.	Based on the preprint of a Phase III trial on *SARS-CoV-2 Vaccine (Vero cell), Inactivated [CoronaVac]* in Brazil [Palacios, 2021 *(cut-off analysis date: 16 December 2020)]* and Turkey [Tanriover et al. 2021 *(cut-off analysis:*

	Yes, it is efficacious for preventing symptomatic COVID-19 based on moderate certainty of evidence. It may reduce the risk of severe cases and hospitalization due to COVID-19, based on very low certainty of evidence. The duration of protection cannot be assessed given the current data. **Yes**, it is safe in the known short-term safety outcomes, based on moderate certainty of evidence. Meanwhile, its long term safety outcomes cannot be determined given the short duration of observation at the time of the reports.	*16 March 2021)*]**.** **Yes**, it is efficacious for preventing symptomatic COVID-19 based on moderate to high certainty of evidence. Additionally, based on real-world effectiveness data, the vaccine has also demonstrated clinical benefits in reducing the risk of symptomatic COVID-19, hospitalization due to COVID-19, and death due to COVID-19 in the general population including older adults (≥60 years old). WHO noted that current evidence from observational studies together with immunogenicity results suggest that *SARS-CoV-2 Vaccine (Vero cell), Inactivated [CoronaVac]* is likely to have a protective effect in older persons, although whether at an equivalent level as in younger adults remains to be shown in further studies. Current evidence on immunogenicity against variants of concern is inadequate. More studies of better quality are anticipated to establish more conclusive evidence on SARS-CoV-2 Vaccine (Vero cell), Inactivated [CoronaVac]'s effectiveness against variants of concern. The duration of protection cannot be assessed given the current data. **Yes**, it is safe in the known short-term safety outcomes, based on moderate certainty of evidence. Meanwhile, its long term safety outcomes cannot be determined given

		the short duration of observation at the time of the reports. In terms of safety in older adults (≥60 years old), trials showed that adverse event rates are lower in older adults compared to the 18-59 year-old population. While Bell's Palsy is considered a rare adverse event following immunization with *SARS-CoV-2 Vaccine (Vero cell), Inactivated [CoronaVac]* based on the analysis of the HK Department of Health, the HTAC deems that the benefits of vaccination outweigh the the risks as all reported cases of Bell's Palsy were deemed not serious. It should not be given to individuals below 18 years old pending results of ongoing clinical trial results in children and adolescents and to those with a known history of severe allergic reaction to any component of the vaccine, and to a patient who is febrile, in an acute illness period, or has an acute attack of a chronic illness. The product insert also highlights precaution among the following special populations: immunocompromised patients, people with neurological conditions and people with bleeding disorders.
Is *SARS-CoV-2 Vaccine (Vero cell), Inactivated [CoronaVac]* affordable and feasible to use in a national immunization	**Yes.** It is affordable but the total budget allocation is not proportionate to the target vaccinees. The share of the cost to implement vaccination using *SARS-CoV-2 Vaccine (Vero cell), Inactivated [CoronaVac]* will constitute 47.83% of the total allocated budget for vaccination and will cover 36%	**Yes.** It is affordable but the total budget allocation is not proportionate to the target vaccinees. The share of the cost to implement vaccination using *SARS-CoV-2 Vaccine (Vero cell), Inactivated [CoronaVac]* will constitute 23.52% of the total allocated budget for vaccination and will cover 17.86% of the 70 million target

program (viability)?	of the 70 million target vaccinees for 2021. According to the Department of Finance, the price of *SARS-CoV-2* Vaccine *(Vero cell), Inactivated [CoronaVac*] offered to the Philippine government is equal to or better than the price offered in other Southeast Asian countries. **Yes**, it is feasible as there are no significant barriers in vaccine implementation using *SARS-CoV-2 Vaccine (Vero cell), Inactivated [CoronaVac]* in terms of storage, transport, and handling. However, there is still a need for training of vaccinators to ensure product integrity across the entire supply chain and close monitoring of adverse events.	vaccinees for 2021. According to the Department of Finance, the price of *SARS-CoV-2* Vaccine *(Vero cell), Inactivated [CoronaVac*] offered to the Philippine government is equal to or better than the price offered in other Southeast Asian countries. **Yes**, it is feasible as there are no significant challenges in vaccine implementation using *SARS-CoV-2 Vaccine (Vero cell), Inactivated [CoronaVac]* in terms of storage, transport, and handling. However, there is still a need for training of vaccinators to ensure product integrity across the entire supply chain and close monitoring of adverse events.
Does *SARS-CoV-2 Vaccine (Vero cell), Inactivated [CoronaVac]* (OOP) expenses of households due to COVID-19?	**Yes**. Based on interim results of the Brazil trial, *SARS-CoV-2 Vaccine (Vero cell), Inactivated [CoronaVac]* may reduce the risk of hospitalization due to COVID-19. Thus, *SARS-CoV-2 Vaccine (Vero cell), Inactivated [CoronaVac]* has the potential to reduce out-of-pocket expenses of Filipino households due to averted costs of isolation, treatment and hospitalization costs.	**Yes.** Noting its efficacy and effectiveness against symptomatic COVID-19 including hospitalization due COVID-19, based on current evidence, *SARS-CoV-2 Vaccine (Vero cell), Inactivated [CoronaVac]* has the potential to reduce out-of-pocket expenses of Filipino households due to averted treatment and isolation costs for mild, moderate and severe COVID-19.
Does *SARS-CoV-2 Vaccine (Vero cell), Inactivated [CoronaVac]* possess the characteristics desired by key stakeholders? (Social Impact)	**Yes.** Based on short term outcomes, *SARS-CoV-2 Vaccine (Vero cell), Inactivated [CoronaVac]* possesses most of the characteristics desired by key stakeholders.	No revision.

Does *SARS-CoV-2 Vaccine (Vero cell), Inactivated [CoronaVac]* reduce or not further add to existing inequities in the health system?	**Yes.** Because of non-stringent logistic requirements, *SARS-CoV-2 Vaccine (Vero cell), Inactivated [CoronaVac]* does not aggravate health inequities related to inoculation of recipients residing in isolated and disadvantaged locations. The trial population did not include important vulnerable groups such as individuals with impaired immune systems, and pregnant and lactating women. Further, the vaccine is contraindicated to those with a known history of severe allergic reaction to any component of the vaccine, and who is febrile, patient in acute illness period and acute attack of chronic disease.	Because of non-stringent logistic requirements, *SARS-CoV-2 Vaccine (Vero cell), Inactivated [CoronaVac]* does not aggravate health inequities related to inoculation of recipients residing in isolated and disadvantaged locations. New evidence based on real-world effectiveness data demonstrated clinical benefits in reducing risk of symptomatic COVID-19, hospitalization due to COVID-19, death due to COVID-19, and in older adults (≥60 years old). In terms of safety, trials which included both 18 to 59 and ≥60 age groups generally showed that adverse event rates are lower in older adults compared to the young adult population.

AMENDMENTS

The following sections in the previous HTAC ES on *SARS-CoV-2 Vaccine (Vero cell), Inactivated [CoronaVac]* are amended as follows:

Criterion 1: Responsiveness to magnitude and severity

1.1 Can the SARS-CoV-2 Vaccine (Vero cell), Inactivated [CoronaVac] significantly reduce the magnitude and severity of COVID-19?

CURRENT EVIDENCE:

As of 01 August 2021, the total number of cases has exceeded more than 196.5 million cases and breached the 4.2 million mark in terms of the total number of deaths globally.

In the Philippines, the cumulative number of laboratory-confirmed COVID-19 cases has already exceeded 1,597,689 cases with total deaths reported at 28,016 as of 01 August 2021. Based on the latest DOH-Epidemiology Bureau data (as of 01 July 2021), the young and productive age groups (20-49 years old) have the most exposure and highest prevalence of the disease. However, the most vulnerable are the senior citizens (>60 years old) who have the highest case fatality rate (CFR) of 8.23% and comprise around 64% of COVID-19 deaths. In addition, individuals with existing comorbidities such as chronic kidney disease (CKD), chronic obstructive pulmonary disease (COPD), other pulmonary, cardiovascular and hematologic diseases are also vulnerable with CFR reported at around 19.84 to 85.15%.

The DOH Philippines has also reported the detection of four variants of concern (i.e. Alpha, Beta, Gamma, and Delta) and one variant on alert for further monitoring (i.e. Theta) in the country. As of 28 July 2021, there were a total of 2,146 Beta (B.1.351) variant cases, 1,856 Alpha (B.1.1.7) variant cases, 216 Delta (B.1.617.2) variant cases, 2 Gamma (P.1) variant cases, and 266 Theta (P.3) variant cases detected out of the 9,725 samples sequenced. Meanwhile, there were 116, 72, 4 and 2 deaths reported for Alpha, Beta, Delta, and Theta variants cases respectively. There were no reported deaths for the Gamma variant. The DOH emphasized the importance of enhanced and immediate response for areas with detected Delta variant cases and with case spikes with the premise that there may be ongoing local transmission already. Table 1. presents the total number of cases caused by variants of concerns and variants classified as alert for further monitoring.

Table 1. Local epidemiological data on variants of concern and variants classified as alert for further monitoring as of 28 July 2021.

Variants of Concern	Total cases (%)	Total deaths (%)
Alpha (B.1.1.7)	1,856 (19.08%)	117 (1.20%)
Beta (B.1.351)	2,146 (22.07%)	74 (0.76%)
Delta (B.1.617.2)	216 (2.22%)	8 (0.08%)

Gamma (P.1)	2 (0.02%)	0
Variants classified as alert for further monitoring	**Total cases (%)**	**Total deaths (%)**
Theta (P.3)	266 (2.74%)	3 (0.03%)

HTAC JUDGMENT *1.1. Can the SARS-CoV-2 Vaccine (Vero cell), Inactivated [CoronaVac] significantly reduce the magnitude and severity of COVID-19?*	
Version 1 (as of 08 April 2021)	**Version 2 (as of 30 July 2021)**
Yes. *SARS-CoV-2 Vaccine (Vero cell), Inactivated [CoronaVac]* has the potential to reduce the disease burden by averting a significant number of symptomatic infections and deaths assuming sufficient vaccine coverage.	No revision.

Criterion 2: Clinical efficacy and safety

New supporting evidence are added for **Criterion 2 - Clinical efficacy/effectiveness and safety:**

2.1. ***What is the efficacy of SARS-CoV-2 Vaccine (Vero cell), Inactivated [CoronaVac] in terms of reducing the incidence and/or severity of COVID-19 in the general and vulnerable populations?***

CURRENT EVIDENCE:

CLINICAL TRIAL DATA ON EFFICACY

Efficacy against COVID-19

Description of evidence considered

As for the review of updated efficacy trials for this vaccine, we reviewed the trials in the (1) WHO Background document; and, (2) any other new or updated trials that were published beyond their review date.

- As for the trials reviewed by the WHO, the following studies were reviewed as part of their evidence base in recommending this vaccine (WHO Interim

Recommendation for the Use of the Inactivated COVID-19 Vaccine, CoronaVac, developed by Sinovac; 01 June 2021):

- Phase III clinical trial in Brazil (Palacios et al., 2021) [preprint]
- Phase III clinical trial in Indonesia (unpublished)
- Phase III clinical trial in Turkey (unpublished)

These trials have been reviewed by the HTAC in the development of the version 1 of the Evidence Summary which served as evidentiary basis for its recommendation. Based on our review, the only new data reported in the WHO background document that was not included in these three trials was the additional subgroup analysis in the Brazil trial (Palacios et al., 2021) *[n=12,408, healthcare workers]* on vaccine efficacy against symptomatic COVID-19 in populations with hypertension. Symptomatic COVID-19 in this study was defined as the presence of at least two type A symptoms lasting for at least 2 days, or at least one type B symptom, or radiologic characteristics of COVID-19 vaccine, with positive PCR test of COVID-19 (including saliva sample). Type A symptoms include fever (axillary temperature ≥37.5ºC), chills, sore throat, fatigue, nasal congestion or runny nose, muscle pain, headache, nausea or vomiting, diarrhea). Type B symptoms include cough lasting for at least 2 days, loss of smell or taste (for at least 2 days), shortness of breath or difficulty breathing.

- As for new and updated trials beyond the WHO review, one published trial (Tanriover et al., 2021) on the safety and efficacy of *SARS-CoV-2 Vaccine (Vero cell), Inactivated [CoronaVac]* was detected. The trial was a double-blind, randomized, placebo-controlled Phase III clinical trial evaluating the safety and efficacy of *SARS-CoV-2 Vaccine (Vero cell), Inactivated [CoronaVac]* in Turkey. The trial randomized 10,218 participants aged 18-59 years with no history of COVID-19 (Intervention = 6650; Control = 3568) in two consecutive cohorts (K1 and K2). The K1 cohort (Intervention = 458; Control = 461) was composed of healthcare workers working in COVID-19 and non-COVID-19 areas, while the K2 cohort (Intervention = 6188; Control = 3107) included members of the general population. The participants received either *SARS-CoV-2 Vaccine (Vero cell), Inactivated [CoronaVac]* containing 3 µg SARS-CoV-2 virion or placebo containing all ingredients of the vaccine except the virus in a 1:1 allocation in the K1 cohort and 2:1 allocation in the K2 cohort. The injections were given in two doses 14 days apart. The study had a short median follow-up period (from the date of randomization to the date of unmasking) of 43 days as the trialists had to discontinue masking when the vaccination programme using *SARS-CoV-2 Vaccine (Vero cell), Inactivated [CoronaVac]* in Turkey began. In this trial, symptomatic COVID-19 was defined in the trial as having a positive RT-PCR test and at least one of the following symptoms for 2 days or more fever or chills; cough; dyspnoea; fatigue; muscle or body

pain; headache; new loss of sense of smell or change in taste; sore throat; nasal congestion or rhinorrhoea; nausea or vomiting; and diarrhea

As such the Turkey trial (Tanriover et al., 2021) shall be the main clinical trial evidence of this evidence summary. The additional analysis on vaccine efficacy in hypertensive participants in the Brazil trial (Palacios et al. 2021) was also noted.

Key findings from the efficacy trials

Turkey trial (Tanriover et al., 2021)

Critical outcomes:

- Using *SARS-CoV-2 Vaccine (Vero cell), Inactivated [CoronaVac]* compared to placebo, reduces the risk of symptomatic COVID-19 at least 14 days after the second dose by **83.5% (95% CI 65.4 to 92.1)**, based on high certainty of evidence.
- There were zero events of hospitalization due to COVID-19 at least 14 days after the second dose in 6,559 participants in the intervention group versus 6 events in 3,470 participants in the control group. Protection against hospitalization due to COVID-19 remains to be demonstrated, based on low certainty of evidence.
- There were no fatalities due to COVID-19 that occurred in both the intervention and control arms of the trial.

Important outcomes:

- Using *SARS-CoV-2 Vaccine (Vero cell), Inactivated [CoronaVac]* compared to placebo reduces the risk of symptomatic COVID-19 14 to 27 days after the first dose by **46.4% (95%CI: 0.4–71.2)**, based on low certainty of evidence.
- A total of 9 asymptomatic cases were detected, 3 in the vaccine arm and 6 in the placebo arm. Vaccine efficacy for this outcome was not reported nor can it be computed.

Appendix 3 details the GRADE rating for the outcomes reviewed from the Turkey trial.

Brazil trial (Palacios et al., 2021)

As mentioned above, the outcomes reported in the WHO background document have already been considered and reported in the ES V1 and the only new data reported in the background document was the subgroup analysis of its vaccine efficacy against symptomatic COVID-19 in the population with hypertension. There were zero events of symptomatic COVID-19 at least 14 days after the second dose in 335 participants with hypertension in the intervention group versus 7 events in 330 participants in the control group.

For the primary outcome vaccine efficacy against symptomatic COVID-19 at least 14 days after the second dose, the Brazil trial found that *SARS-CoV-2 Vaccine (Vero cell), Inactivated [CoronaVac]* had an efficacy of 50.65% (95% CI: 35.94 to 61.98), as reported in the ES V1, while the Turkey trial found a higher vaccine efficacy of 83.5% (95% CI 65.4 to 92.1). WHO noted that the difference in vaccine efficacy estimates may have been influenced by important features in the trials including risk of disease among participants, case detection particularly of mild cases, and circulation of variants of concern that may reduce efficacy. Particularly, the participants in the Brazil trial were all frontline healthcare workers treating patients with COVID-19 who have relatively high exposure to SARS-CoV-2. On the other hand, the participants in the Turkey trial were primarily from the general population and only 10% of the trial participants were healthcare workers. WHO also mentioned that healthcare workers are more likely to be tested for SARS-CoV-2 infection leading to a higher ascertainment of COVID-19 cases in those with mild symptoms. Thus, the lower vaccine efficacy estimate against symptomatic COVID-19 in the Brazil trial (Palacios et al. 2021) compared to that in the Turkey trial (Tanriover et al. 2021) may be attributed to the higher detection of COVID-19 cases in its trial population.

Apart from the trial population, the HTAC also notes the difference in the attack rate in the unvaccinated population of the Brazil and Turkey trials that may have affected the vaccine efficacy for the primary outcome. The Brazil trial had a higher incidence rate of symptomatic COVID-19 at least 14 days after the second dose in the placebo group of 22.34 cases per 100 person-years while the Turkey trial had an incidence rate of 192.3 per 1000 person-years or 19.23 per 100 person-years.

CLINICAL TRIAL DATA ON IMMUNOGENICITY

Immunogenicity against COVID-19

This section shall discuss the comparative immunogenicity data among patients aged 18-59 years versus patients aged 60 years and above which was part of the evidence base of the WHO in recommending this vaccine for older adults.

The WHO background document cited the following clinical trials which evaluated immunogenicity for the age groups 18-59 years old and ≥60 years old to support the use of *SARS-CoV-2 Vaccine (Vero cell), Inactivated [CoronaVac]* in these age groups:

- Phase I/II trial among 18-59 years old in China (Zhang et al., 2021) [published]
- Phase I/II trial among ≥ 60 years old in China (Wu et al., 2021) [published]
- Phase III trial in China [unpublished]
- Phase III trial in Chile (Bueno et al., 2021) [preprint]

The two Phase I/II trials from China, and the Chile Phase III trial were already examined in

the Evidence Summary version 1 but were not discussed in detail. Meanwhile, the previous HTAC review did not cover the immunobridging Phase III trial in China [unpublished]. However, there is currently limited information on this immunobridging trial. Hence, only the results of the Phase I/II trials in China (Zhang et al. 2021; Wu et al., 2021) and the Phase III trial in Chile (Bueno et al. 2021 preprint) shall be covered in this section of the evidence summary. Below are the description and key findings for each of these trials:

- **Phase I/II trials in China** [Zhang, et al., 2021; Wu et al, 2021]
  Study characteristics:
  - *18-59 years old (Zhang, et al., 2021) [published]:* A Phase I/II randomized, double-blind placebo-controlled clinical trial *(N=144 in Phase I, N=600 for Phase II)* that evaluated the safety and immunogenicity of *SARS-CoV-2 Vaccine (Vero cell), Inactivated [CoronaVac]* in SARS-CoV-2 antibody-negative, polymerized chain reaction (PCR)-negative healthy individuals aged 18-59 years. Its Phase I trial enrolled 72 participants while its Phase II trial enrolled 120 participants per dosing schedule for the evaluation of immunogenicity. Phase I trial evaluated two dosages (3 µg and 6 µg per dose) vs. placebo in two vaccination schedules - emergency vaccination schedule (day 0 and day 14) and routine vaccination schedule (day 0 and day 28). Meanwhile, Phase II trial evaluated four vaccination schedules - two emergency vaccination schedules (day 0/14 and day 0/14/42) and two routine vaccination schedules (day 0/28 and day 0/28/56). Immunogenicity data for both 18 to 59 year and ≥60 year age groups is only available for the 0/28 schedule. Data using the 0/14 schedule is only available for the 18-59 year age group, while the results for the 0/14/42 and 0/28/56 schedules were not reported in Zhang et al. (2021) and in the WHO background document. Hence, the only comparative data to be presented here are for the analysis of the 0/28 schedule for which 24 participants for Phase I and 118 participants for Phase II were evaluated in the 3 µg dose. Zhang et al. (2021) used micro cytopathogenic effect assay to measure neutralizing antibody titers to live SARS-CoV-2.
  - *≥60 years old (Wu et al, 2021) [published]:* A Phase I/II randomized, double-blind placebo-controlled clinical trial [*N=422 (Intervention group =348; Control group =74)]* that evaluated the safety and immunogenicity of *SARS-CoV-2 Vaccine (Vero cell), Inactivated [CoronaVac]* with a 14-day and 28-day dosing interval in healthy older adults aged 60 years and above. Its Phase I enrolled 72 participants per dosing schedule in a dose escalation study evaluating the 3 µg and 6 µg doses. In Phase II, there were 300 participants enrolled per dosing schedule and allocated to 3 dosing groups (1.5 µg, 3 µg, and 6 µg). Immunogenicity data for both 18 to 59 year and ≥60 year age groups is only available for the 0/28 schedule. Hence, the only comparative data to be presented here are for the analysis of the 0/28 schedule to which 24 participants for Phase I and 98 participants for Phase II were evaluated in the 3 µg dose. This study has already been covered in the initial version of this

evidence summary but key findings are still presented below for comparison with the immunogenicity data from the Phase I/II trial in China for the 18-59 year age group. Wu et al. (2021) used micro cytopathogenic effect assay to measure neutralizing antibody titers to live SARS-CoV-2.

Findings

- For the 18-59 year age group, seropositivity peaked 28 days after the second dose at 83% (95% CI: 62-95) for Phase I and at 97% (95% CI: 93-100) for Phase II. Meanwhile, for participants aged 60 years old and above, high seropositivity rates were also observed at 28 days after the second dose during Phase I [SR: 100% (95% CI: 86 to 100)] and during the Phase II trial [seropositivity rate or SR: 98% (95% CI: 93 to 100)]. Further, the seropositivity and neutralizing antibody titer are indicated in Table 2. below.

Table 2. Seropositivity rates and geometric mean titer of neutralizing antibodies in the 18-59 year-old (Zhang et al., 2021) and 60 year-old age groups (Wu et al., 2021) in the Phase I/II trials in China

		China Phase I trial		China Phase II Trial	
		18-59 (0,28) N=24 *(Zhang et al, 2021)*	≥60 yo (0,28) N=24 *(Wu et al, 2021)*	18-59 yo (0,28) N=118 *(Zhang et al, 2021)*	≥60 yo (0,28) N=98 *(Wu et al, 2021)*
Before vaccination	Seropositive (%) (95% CI)	0 (0-14)	0 (0 to 14)	0 (0-3)	0 (0 to 4)
	GMT (95% CI)	2 (2-2)	2 (2 to 2)	2 (2-2)	2 (2 to 2)
28 days after dose 2	Seropositive (%) (95% CI)	83 (63-95)	100 (86 to 100)	97 (93-100)	98 (93 to 100)
	GMT (95% CI)	19 (13-27)	55 (39 to 78)	44 (37-52)	42 (35 to 51)

- **Phase III trial in Chile** (Bueno et al., 2021) [preprint]

Study Characteristics:

- 18-59 years old and ≥60 years old (Bueno et al., 2021) [preprint]: A multicenter Phase III trial *[N=434 (Intervention group = 270; Control group = 164)]* on healthcare workers aged 18 years and older. A subgroup of participants were assigned to the immunogenicity arm, which was randomized in a 3:1 ratio to receive either *SARS-CoV-2 Vaccine (Vero cell), Inactivated [CoronaVac]* or placebo. A total of 190 participants were included in the immunogenicity subgroup. Of these, 32 participants were 18 to 59 years old (23 were assigned to the vaccine arm and 9 to the placebo arm).

Meanwhile 17 participants aged 60 years old and above (14 were assigned to the vaccine arm and 3 to the placebo arm) were included in the immunogenicity subgroup. Antibody and cell-mediated immunity results were assessed. For the neutralizing anti-S1-RBD antibody, they used SARS-CoV-2 surrogate virus neutralization test (sVNT) kit.

- The study had a very small sample size. Only 23 samples from vaccinated individuals 18-59 years old and 10 samples from the ≥60 years age group were evaluated. Out of 434 participants, 190 were included in the immunogenicity arm. Neither the inclusion criteria nor the reason for incomplete reporting was mentioned in the interim results for the immunogenicity arm. The sample size calculation was also not indicated as the study protocol was unavailable to confirm these missing information. Lastly, the report is still a non-peer reviewed preprint article as of the date of this review, and the final manuscript is yet to be published.
- The findings from this trial for this population have already been reviewed in the initial HTAC recommendation but were not included in the initial evidence summary.

***Findings*:**

- There was no seroconversion in both the 18-59 year and ≥60 year groups 14 days after the first dose, and neutralizing anti-S1-RBD antibodies were not detected.
- Seropositivity rates at 14 days after the second dose in the 18-59 year age group is higher (94%) compared to that of the ≥60 years age group (90%). However, the geometric mean of neutralizing anti-S1-RBD antibody titres was higher in the ≥60 years age group [GMT: 39 (95% CI: 10 to 163)] compared to the 18-59 years age group [GMT: 16 (95% CI: 10 to 26)].
- Seropositivity and GMTs at 28 days after the second dose were higher in the ≥60 years age group [SR: 100%; GMT: 49 (95% CI: 22 to 106)] compared to the response in the 18 to 59 years age group [SR: 96%; GMT: 18 (9 to 33)].

Table 3. Seropositivity rates and geometric mean titer of neutralizing antibodies in the 18-59 year-old and 60 year-old age groups in the Phase III trial in Chile (Bueno et al. 2021) [preprint]

		18-59 years old N=23	≥60 years old N=10
14 days after dose 1	Seropositive (%) (95% CI)	Not detected	Not detected
	GMT (95% CI)	Not detected	Not detected
14 days after dose 2	Seropositive (%) (95% CI)	94.0 (Not reported)	90.0 (Not reported)

	GMT (95% CI)	16.3 (10.3 to 25.9)	39.4 (9.5 to 163.4)
28 days after dose 2	Seropositive (%) (95% CI)	95.7 (Not reported)	100 (Not reported)
	GMT (95% CI)	17.5 (9.2 to 33.2)	48.5 (22.2 to 106.0)

Immunogenicity against new variants

The WHO background document noted the subset analysis of Palacios et al. (2021) evaluating the vaccine efficacy of *SARS-CoV-2 Vaccine (Vero cell), Inactivated [CoronaVac]* against emerging variants of concern:

- Serum samples from 45 vaccinees were used to determine neutralization titers against SARS-CoV-2 B.1.1.28 variant and its sub-lineages gamma (P.1) and zeta (P.2). Among the vaccinees, 71% seroconverted for B.1.1.28, 68.9% for the gamma variant, and 80.0% for zeta variant. GMTs across the three variants were not significantly different.

REAL WORLD DATA ON EFFECTIVENESS

This section shall discuss effectiveness of *SARS-CoV-2 Vaccine (Vero cell), Inactivated [CoronaVac]* in the real world setting which were not covered in the previous review as pharmacovigilance data were only available at that time.

Effectiveness against COVID-19

The WHO background document cited two studies evaluating the effectiveness of the *SARS-CoV-2 Vaccine (Vero cell), Inactivated [CoronaVac]* - one study evaluating the real world effectiveness (de Faria et al., 2021) and an updated, published report (Jara et al., 2021) of the preliminary effectiveness report (Araos, 2021) cited by the WHO.

In addition to these studies reviewed by WHO, real world effectiveness reports from Indonesia (Ministry of Health Indonesia, 2021 [press release]), Uruguay (Ministry of Public Health Uruguay, 2021 [preliminary report]), and Thailand (Ministry of Thailand, 2021 [press release]) were also found. However, these reports were excluded due to the following reasons:

- Ministry of Health Indonesia, 2021 [press release]: The press release reported that 128,000 health workers were included in the analysis of vaccine efficacy against symptomatic COVID-19, reducing treatment for COVID-19, and reducing death due to COVID-19. However, the time point at which these outcomes were measured was not specified. The attack rate per group was presented, however, the number of events per group was not included in the report. Lastly, the 95% confidence interval of the vaccine effectiveness estimates were not reported. In addition, there was no full report that is accessible for appraisal.

- Ministry of Public Health Uruguay, 2021 [preliminary report]: The preliminary report presented vaccine effectiveness in reducing COVID-19 cases and deaths 14 days after the second dose. However, the report did not present the total number of participants included in the study as well as the number of events per group. In addition, there was no full report that is accessible for appraisal.
- Ministry of Health Thailand (2021) [press release]: The data cannot be extracted due to unavailability of an accurate translated version of the document.

Study characteristics

- The cohort study of de Faria et al., 2021 [pre-print] among health care workers (N=65,706) in São Paulo, Brazil estimated the number of cases expected in the month following vaccination, based on COVID-19 cases in the previous six months, as well as the mobility trends in the general population for the indicated period. Participants were vaccinated on 18-21 January 2021 and 14-16 February 2021. Observed case numbers were compared to the estimated case numbers for the succeeding 2 to 5 weeks after the second dose. The study noted the following limitations: first, the study is a preliminary evaluation and did not measure severity of disease and death. Secondly, the peak of cases among HCWs in a hospital preceded the peak of cases in the city of São Paulo resulting in the investigators excluding data from 2020 epidemiological weeks 9 through 23 in their predictive model. Lastly, the results for 2021 epidemiological weeks 10-12 (3-5 weeks after vaccination) should be interpreted with caution, as the numbers of cases in the city of São Paulo in these weeks were outside the range variation observed during parameter estimation of the Poisson regression model. Further, HTAU also noted the following limitations: first, there was no mention of adjusting for confounding variables that may have affected the results of the study. Moreover, the effectiveness estimates from this study were derived from a regression model designed using COVID-19 case data from the healthcare workers and general population. Lastly, the report is still a non-peer reviewed preprint and the final manuscript is yet to be published.
- Jara et al. (2021) is a prospective national cohort study in Chile that included 16 years old and above who are affiliated with the public national health care system [Fondo Nacional de Salud (FONASA)] which includes 80% of the Chilean population. Of the 11,820,292 affiliated with FONASA, 10,187,720 were included in the cohort study from 02 February to 01 May 2021. Of these, 41% are fully vaccinated. The study noted the following limitations: first, being observational by design, this study is subjected to confounding and adjusted the analyses for relevant variables that could afffect vaccine effectiveness, such as age, sex, underlying medical conditions, region of residence, and nationality. The study also addressed differences in health care access by restricting the analysis to persons who had undergone diagnostic testing, and found results that were

consistent with those of the main analysis. They also noted risk for selection bias. Further, given the study's short follow up period (3 months), late outcomes may have not yet developed in persons infected near the end of the study and thus was not included. Effectiveness estimates against severe disease and death should be interpreted with caution. Lastly, ICUs in Chile were operating at 93.5% of average capacity (67.5% COVID-19 patients), therefore effectiveness estimates for protection vs. ICU admission might be underestimated, and estimates for protection vs. death might be overestimated.

Findings

- Effectiveness against COVID-19 in the general population:
    - Jara et al. (2021) reported an adjusted vaccine effectiveness of *SARS-CoV-2 Vaccine (Vero cell), Inactivated [CoronaVac]* in the general population who are fully immunized (≥14 days after the second dose) with the following effectiveness estimates:
        - Effectiveness against laboratory confirmed COVID-19 (RT-PCR assay or antigen test): 65.9% (95% CI: 65.2 to 66.6)
        - Effectiveness against hospitalization due to COVID-19: 87.5% (95% CI: 86.7 to 88.2)
        - Effectiveness against ICU admissions due to COVID-19: 90.3% (95% CI: 89.1 to 91.4)
        - Effectiveness against death due to COVID-19: 86.3% (95% CI: 84.5 to 87.9) .

- Effectiveness against COVID-19 among 16 to 59 year-old and ≥ 60 year old age groups:
    - Jara et al. (2021) also performed subgroup analyses on the adjusted vaccine effectiveness of *SARS-CoV-2 Vaccine (Vero cell), Inactivated [CoronaVac]* in 16-59 year old age group and in 60 years old and above age group who are fully immunized (≥14 days after the second dose) with the following effectiveness estimates:
        - Effectiveness against laboratory confirmed COVID-19:
            - 16-59 years old: 63.5% (95% CI: 62.39 to 64.57)
            - ≥60 years old: 66.6% (95% CI: 65.4 to 67.8)
        - Effectiveness against hospitalization due to COVID-19:
            - 16-59 years old: 91.86% (95% CI: 90.22 to 93.23)
            - ≥60 years old: 85.3% (95% CI: 84.3 to 86.3)
        - Effectiveness against ICU admission due to COVID-19:
            - 16-59 years old: 94.59% (95% CI: 92.18 to 96.26)
            - ≥60 years old: 89.2% (95% CI: 87.6 to 90.6)
        - Effectiveness against death related to COVID-19:
            - 16-59 years old: 85.79% (95% CI: 69.61 to 93.36)
            - ≥60 years old: 86.5% (95% CI: 84.6 to 88.1)

Table 4. Adjusted vaccine effectiveness estimates for *SARS-CoV-2 Vaccine (Vero cell), Inactivated [CoronaVac]* from a prospective national cohort study in Chile

		All ages		16-59 years		Adults ≥ 60 years	
		Partial Immunization	Full Immunization	Partial Immunization	Full Immunization	Partial Immunization	Full Immunization
Jara et al. 2021 (Chile)	Laboratory-confirmed COVID-19	15.5 (14.2 to 16.8)	65.9 (65.2 to 66.6)	17.11 (15.52 to 18.68)	63.50 (62.39 to 64.57)	9.7 (6.9 to 12.4)	66.6 (65.4 to 67.8)
	Hospitalization	37.4 (34.9 to 39.9)	87.5 (86.7 to 88.2)	42.58 (38.88 to 46.06)	91.86 (90.22 to 93.23)	35.0 (31.3 to 38.6)	85.3 (84.3 to 86.3)
	ICU admission	44.7 (40.8 to 48.3)	90.3 (89.1 to 91.4)	44.63 (38.85 to 49.87)	94.58 (92.18 to 96.26)	44.5 (38.7 to 49.7)	89.2 (87.6 to 90.6)
	Death	45.7 (40.9 to 50.2)	86.3 (84.5 to 87.8)	42.01 (25.60 to 54.80)	85.79 (69.61 to 93.36)	45.8 (40.4 to 50.7)	86.5 (84.6 to 88.1)

Note: Partial immunization ≥ 14 days after dose 1; Full immunization ≥ 14 days after dose 2.

- Effectiveness against confirmed symptomatic COVID-19 based on weeks after the second dose
    - de Faria et al., 2021: Vaccine effectiveness was estimated to be at 50.7% (95% CI: 33.3% to 62.5%) during the second week after vaccination, increasing up to 73.8% (95% CI: 57.0% to 84.8%) in the fifth week post-vaccination. However, according to WHO, a general caveat to be taken with this analysis is the multiple assumptions on the comparability of disease trends and predictions between health care workers and non-health care workers. Further, the total number of cases observed during the observation period did not decrease following vaccination, though this took place in the context of a significant increase in cases in Sao Paulo, Brazil. The estimates for vaccine effectiveness for this study are detailed in Table 5.

Table 5. Vaccine effectiveness estimates for *SARS-CoV-2 Vaccine (Vero cell), Inactivated [CoronaVac]* based on vaccination in a cohort of health care workers in Sao Paulo, Brazil

Weeks after second dose	Vaccine effectiveness (95% CI)
2	50.7% (33.3-62.5)
3	51.8% (30.0-66.0)
4	68.4% (51.0-80.8)

5	73.8% (57.0-84.8)

- Effectiveness against symptomatic COVID-19 after the first and second dose
    - The national cohort study in Chile (Jara et al. 2021) showed that vaccine effectiveness after the second dose [VE: 65.9 (95% CI: 65.2 to 66.6) is higher compared to its effectiveness after the first dose [VE: 15.5 (95% CI: 14.2 to 16.8)] which supports completion of the two-dose vaccination regimen.

Effectiveness against new variants

The WHO background document noted one study (Hitchings et al., 2021) evaluating the vaccine effectiveness of *SARS-CoV-2 Vaccine (Vero cell), Inactivated [CoronaVac]* against emerging variants of concern.

Study characteristics

- Hitchings et al. (2021) [preprint] is a matched test-negative control study (N=786; case = 393; control= 393) which assessed vaccine effectiveness of *SARS-CoV-2 Vaccine (Vero cell), Inactivated [CoronaVac]* against symptomatic COVID-19 among healthcare workers in Manaus, Brazil, at the time when the gamma (P.1) variant was identified in 75% of isolates genotyped through surveillance. Hitchings et al., 2021 was cited in the WHO recommendation as the basis for the vaccine's benefit against variants. However, the reported vaccine effectiveness is inconclusive given the wide confidence interval. The study noted the following limitations: firstly, high seroprevalence in Manaus prior to the vaccination campaign due to prior natural infection may have led to underestimation of the VE estimate among seropositive individuals. If vaccine uptake were lower among those previously infected, this would exacerbate such a downward bias. Sensitivity analysis was done, but precision remained low. Further, effectiveness against the Gamma variant cannot be directly assessed as the samples were not routinely sequenced. The investigators noted however that the study was conducted at the epicentre for Gamma variant emergence and during an epidemic when surveillance of the general population identified the variant in 66% of genotyped samples. The study authors also noted that the estimates may be subject to unmeasured and residual confounding, as vaccinated individuals may have better access to RT-PCR and antigen testing compared to unvaccinated individuals. Lastly since the median time from second dose to sample collection date was 14 days among those who have received two doses, the study was unable to assess any changes in effectiveness over longer follow-up times, and the estimate may represent effectiveness at the peak of antibody titre following vaccination. The WHO background document also noted that because of the declining outbreak, most cases occurred before a second dose was received. Earlier, the region had been affected by a large outbreak that is estimated to have infected 76% of the population. Thus,

these results may not be generalizable to a largely unexposed population. Further, the assessment team also noted that the report is still a non-peer-reviewed preprint and the final manuscript is yet to be published.

Findings

- Effectiveness against symptomatic COVID-19 caused by Gamma variant
    - In the context of significant gamma variant transmission, adjusted vaccine effectiveness against symptomatic COVID-19 disease14 days after the first dose of *SARS-CoV-2 Vaccine (Vero cell), Inactivated [CoronaVac]* was 49.6% (95% CI: 11.3 to 71.4) and an adjusted vaccine effectiveness of 36.8% (95% CI: -54.9 to 74.2) 14 days after the second dose based on the study by Hitchings et al. (2021). These data suggest that the gamma variant can escape neutralization antibodies elicited during infection or immunization.

IMMUNOGENICITY DATA FROM OBSERVATIONAL STUDIES

The WHO background document noted one immunogenicity study (Souza et al., 2021) evaluating the vaccine effectiveness of *SARS-CoV-2 Vaccine (Vero cell), Inactivated [CoronaVac]* against emerging variants of concern.

Study characteristics

- Souza et al. (2021) (published) evaluated for antibody neutralization against the B lineage and two gamma variants (P. 1/28 and P.1/30) from isolates of nasopharyngeal and bronchoalveolar lavage samples of patients in Brazil using plasma from 74 blood donors (21 donors who recently had COVID-19 and 53 *SARS-CoV-2 Vaccine (Vero cell), Inactivated [CoronaVac]* vaccinees (18 samples collected from individuals 20-23 days after dose 1; 20 samples collected 17-38 days after dose 2; and 15 samples from individuals who received 2 doses during phase 3 of the vaccine collected 134-260 days after the second dose. The SARS-CoV-2 samples of the gamma variant were confirmed to be positive by RT-PCR and confirmed to be classified as being infected with the gamma variant by viral genome sequencing. The study noted the following limitations: only neutralizing antibodies were assessed which is not the only contributing factor to immune response. Memory T cell or B cell responses might also reduce disease severity. Further, HTAU noted the following study limitations: firstly, a small number of participants (N = 74) was included in the study, hence the results of this study may not be generalizable. Moreover, although details from where the plasma samples used in the study were given, details for the selection of donor participants were not included in the published article.

Findings

- Souza et al, 2021 (published) evaluated antibody neutralization against the B lineage and two gamma variants (P.1/28 and P.1/30) in terms of median virus neutralization titre (VNT_{50}) and plaque reduction neutralization ($PRNT_{50}$) with the

following values:

- Plasma from previously SARS-CoV-2- infected participants showed an 8.6 times lower neutralizing capacity against the gamma variant than against the B lineage.
    - VNT_{50}:260 (IQR 160-400) against the B lineage isolate
    - VNT_{50} :30 (IQR <20 to 45) against the P. 1/28 isolate
    - VNT_{50} :30 (IQR <20 to 40) against the P. 1/30 isolate
    - $PRNT_{50}$:1:640 against the B lineage isolate
    - $PRNT_{50}$ 1:25 against the P. 1/28 isolate
    - $PRNT_{50}$:1:23 against the P. 1/30 isolate

- Plasma samples from vaccinated individuals from the Brazilian vaccination program collected 20-23 days after a single dose had VNT_{50} .Efficient neutralization of gamma variant isolates was not seen as VNT_{50} measured were near or below the limit of detection
    - VNT_{50} 20 (IQR 20 to 30) against B lineage isolate
    - VNT_{50} : <20 (lower than the limit of detection) against the gamma variants
    - $PRNT_{50}$: 1:20 against the B lineage isolate
    - no neutralizing activity (below the limit of detection) against the gamma variants
- Plasma samples from vaccinated individuals from the Brazilian vaccination program collected 17-38 days after two doses showed a significant decrease in neutralizing capacity against the gamma variant than against the B lineage.
    - VNT_{50} : 75 (IQR <20-263) against B lineage isolate
    - VNT_{50} : 24 (IQR <20 to 25) against the P. 1/28 isolate
    - VNT_{50} : 28 (IQR <20 to 25) against the P. 1/30 isolate
    - $PRNT_{50}$: 1:80 against the B lineage isolate
    - $PRNT_{50}$: <1:20 against the gamma variants
- Plasma samples collected 134-260 days after the second dose from phase 3 trial participants had VNT_{50} which were near or below the limit of detection, thus, statistical significance could not be reached in the comparison of the B lineage and the gamma variant.
    - VNT_{50}:20 (IQR <20 to 30) against B lineage isolate
    - VNT_{50} : <20 (lower than the limit of detection) against the gamma variants
    - $PRNT_{50}$: 1:20 against the B lineage isolate
    - no neutralizing activity (below the limit of detection) against the gamma variants

Additionally, two studies by Hu et al. (2021) [preprint] and Acevedo et al., 2021 [preprint] discuss the efficacy of *SARS-CoV-2 Vaccine (Vero cell), Inactivated [CoronaVac]* against emerging variants of concern.

- Hu et al., 2021 [preprint]
  Study characteristics: A study conducted in Chonqing, China evaluating SARS-CoV-2 cell entry mediated by the delta (B.1.617) and alpha (B.1.1.7) variants. The study also compared the neutralizing ability of monoclonal antibodies from convalescent sera to the neutralizing antibodies elicited by *SARS-CoV-2 Vaccine (Vero cell), Inactivated [CoronaVac].* With regard to the activity of *SARS-CoV-2 Vaccine (Vero cell), Inactivated [CoronaVac]* against the delta (B.1.617) variant, the study compared the neutralization potency of COVID-19 vaccine-elicited antibodies against D614G, alpha (B.1.1.7), and delta (B.1.617) spike pseudotyped viruses. Serum was collected from twenty patients with COVID-19 obtained from February to October 2020 and twenty individuals who received two doses of *SARS-CoV-2 Vaccine (Vero cell), Inactivated [CoronaVac]*, obtained 7 to 14 days after the administration of the second dose of the vaccine. The dosing schedule of the vaccine used in this study was not specified. We also note that a small number of participants was included in the study, hence the results of this study may not be generalizable. The study noted the following limitations: the study included only a small sample size.The investigators mentioned that the study does not analyze for the mutations that may alter neutralization by modulation of its Spike function rather than its antigenicity. Further, the assessment team noted the following study limitations: the dosing schedule used in the study was not specified. This study did not mention where the vaccinee sera samples were obtained, how the samples were chosen nor how the sample size was calculated. The study protocol is also unavailable to confirm these missing information. Another limitation of the trial was that it only focused on pseudovirus-based antibody neutralization in cell culture. Mutations present in D614G, the alpha and delta variants were only synthesized and introduced to the SARS-CoV-2 spike pseudotyped viruses. Lastly, the report is still a non-peer reviewed preprint and the final manuscript is yet to be published.
  Findings: Among the collected sera from 20 *SARS-CoV-2 Vaccine (Vero cell), Inactivated [CoronaVac]* vaccinees, 19 of the vaccinees' sera had substantial serum neutralizing activity against D614G Spike pseudotyped viruses. Comparing the activity against D614G, 35% (7/20) of the post-vaccination sera were found to have activity that decreased below the threshold against the alpha variant (B.1.1.7), and 65% (13/20) were decreased below the threshold against the delta variant (B.1.617). On the average, neutralization potency of the *SARS-Cov-2 Vaccine (Vero cell), Inactivated [CoronaVac]*-elicited serum was reduced 2.5-fold for the delta variant (B.1.617) variant (GMT: 36), compared to D614G (GMT: 89), and it was reduced 1.6-fold for the alpha variant (B.1.1.7) (GMT: 55) compared to D614G.

- Acevedo et al., 2021 [preprint]

Study characteristics: A study evaluating the infectivity and immune escape of the alpha (B.1.1.7), gamma (P.1), and lambda (C.37) variants measured by a pseudotyped virus neutralization assay using the plasma samples from 79 healthy healthcare workers in Chile that have received two doses of *SARS-CoV-2 Vaccine (Vero cell), Inactivated [CoronaVac]* at 28 days apart. Pseudotyped viruses carrying different SARS-CoV-2 spike proteins from the wild type (Wuhan-1 reference lineage), D641G mutation, and the alpha (B.1.1.7), gamma (P.1), and lambda (C.37) variants were prepared. Plasma samples from vaccinated participants were obtained a median of 95 days after the second dose. We also note that a small number of participants was included in the study, hence the results of this study may not be generalizable. HTAU noted the following study limitations: the study had a small sample size of 79 plasma samples from vaccinated healthcare workers. The trial did not report how the samples were chosen among the two study sites nor how the sample size was calculated. The study protocol is also unavailable to confirm missing information.. Lastly, the report is still a non-peer reviewed preprint and the final manuscript is yet to be published.

Findings: The analysis of 3,695 SARS-CoV-2 sequences from Chile as of 24 June 2021 demonstrated that the lambda (C.37) and gamma (P.1) variants were the dominant circulating variants in the past months, accounting for 79% of the sequences. The study found that the mutations present in the lambda variant (C.37) of the virus has the largest impact on the increase and infectivity of the virus and decrease in neutralizing capacity elicited by the vaccine. Compared to the wild type, there was an observed 1.37 times (95% CI: 1.20 to 1.55), 2.03 times (95% CI: 1.71 to 2.41), 2.33 times (95% CI: 1.95 to 2.80), and 3.05 times (95% CI: 2.57 to 3.61) reduction in the inhibitory dilution mean titer (ID_{50} i.e. reciprocal of serum dilution giving 50% inhibition of the viral infection) for the D614G mutation, alpha (B.1.1.7), gamma (P.1), and lambda (C.37) variant, respectively. The results from the neutralization assay of the pseudotyped viruses using plasma samples of vaccinated healthcare workers are detailed in Table 6.

Table 6. 50% inhibitory dilution (ID_{50}) mean titer for the pseudoviruses carrying different spike proteins and the decrease in geometric mean titer when compared to the wild type pseudovirus.

	ID_{50} Mean titer (95% CI)	**Reduction factor of ID_{50} titer (95% CI)**
Wild type	191.46 (154.9 to 227.95)	Reference
D614G mutation	153.92 (115.68 to 192.16)	1.37 (1.20 to 1.55)
Alpha variant (B.1.1.7)	124.73	2.03 (1.71 to 2.41)

	(86.2 to 163.2)	
Gamma variant (P.1)	104.57 (75.02 to 134.11)	2.33 (1.95 to 2.80)
Lambda variant (C.37)	78.75 (49.8 to 107.6)	3.05 (2.57 to 3.61)

HTAC JUDGMENT

2.1. What is the efficacy of SARS-CoV-2 Vaccine (Vero cell), Inactivated [CoronaVac] in terms of reducing the incidence and/or severity of COVID-19 in the general and vulnerable populations?

Version 1 (as of 08 April 2021)	Version 2 (as of 30 July 2021)
SARS-CoV-2 Vaccine (Vero cell), Inactivated [CoronaVac] passed the minimum acceptable VE threshold against symptomatic COVID-19.	*SARS-CoV-2 Vaccine (Vero cell), Inactivated [CoronaVac]* passed the minimum acceptable VE threshold against symptomatic COVID-19. Additionally, based on real-world effectiveness data, the vaccine has also demonstrated clinical benefits in reducing the risk of symptomatic COVID-19, hospitalization due to COVID-19, death due to COVID-19 in the general population including older adults (≥60 years old). The WHO noted that current evidence from observational studies together with immunogenicity results suggest that *SARS-CoV-2 Vaccine (Vero cell), Inactivated [CoronaVac]* is likely to have a protective effect in older persons, although whether at an equivalent level as in younger adults remains to be shown in further studies. Current evidence on immunogenicity against variants of concern is inadequate. More studies of better quality are anticipated to establish more conclusive evidence on *SARS-CoV-2 Vaccine (Vero cell), Inactivated [CoronaVac]'s* effectiveness variants of concern.

2.2. *What is the duration of protection of the SARS-CoV-2 Vaccine (Vero cell), Inactivated [CoronaVac in terms of reducing the incidence and/or severity of COVID-19?*

HTAC JUDGMENT *2.2. What is the duration of protection of the SARS-CoV-2 Vaccine (Vero cell), Inactivated [CoronaVac] in terms of reducing the incidence and/or severity of COVID-19?*	
Version 1 (as of 08 April 2021)	**Version 2 (as of 30 July 2021)**
Cannot be assessed based on current data	Cannot be assessed based on current data

2.3. *What are the safety issues and incidence of adverse events caused by COVID-19 SARS-CoV-2 Vaccine (Vero cell), Inactivated [CoronaVac]?*

CURRENT EVIDENCE:
CLINICAL TRIAL DATA ON SAFETY

Description of evidence considered

As for the review of updated safety trials for this vaccine, we reviewed the trials in the (1) WHO Background document; and, (2) any other new or updated trial that was published beyond their review date.

- As for the trials reviewed by the WHO, the following studies were reviewed as part of their evidence base in recommending this vaccine (WHO Interim Recommendation for the Use of the Inactivated COVID-19 Vaccine, CoronaVac, developed by Sinovac; 01 June 2021):
    - Phase III clinical trial in Brazil (Palacios et al., 2021) [preprint]
    - Phase III clinical trial in Indonesia (unpublished)
    - Phase III clinical trial in Turkey (unpublished)
    - Phase III clinical trial in China (unpublished)

  The Phase III trials in Brazil, Indonesia, and Turkey have been reviewed by the HTAC in the development of the version 1 of the Evidence Summary which served as evidentiary basis for its recommendation. Based on our review, the only new data are the safety data from an unpublished Phase III trial in China (2021)[*N=1,040 (single-arm; 25% of participants ≥60 years old)*] However, results of this trial were not included given the limited information available on this trial.

- As for new and updated trials beyond the WHO review, Tanriover et al. (2021) was a double-blind, randomized, placebo-controlled Phase III clinical trial evaluating the safety and efficacy of *SARS-CoV-2 Vaccine (Vero cell),*

Inactivated [CoronaVac] in healthcare workers and the general population in Turkey. Characteristics of this trial were detailed in the previous section.

- As such, Tanriover et al., 2021) shall compose the clinical trial evidence for safety of this evidence summary.

Key findings from Tanriover et al. 2021

Short term outcomes:

Using *SARS-CoV-2 Vaccine (Vero cell), Inactivated [CoronaVac]*, compared to placebo increases the risk of:

- Systemic adverse events by **1.11** times **(95% CI: 1.01 to 1.21)** based on high certainty of evidence.
- Local adverse events by **1.86** times **(95%CI: 1.27 to 2.52)** based on high certainty of evidence.

Long term outcomes:

- *SARS-CoV-2 Vaccine (Vero cell), Inactivated [CoronaVac]* shows inconclusive safety for serious adverse events **[RR: 0.64 (95% CI: 0.20 to 2.11)]**, based on low certainty of evidence.
- There were no fatalities, regardless of cause, that occurred in both the intervention and control arms of the trial.

REAL WORLD DATA ON SAFETY

General AEs from select National Regulatory Authorities (NRAs)

The LCPG review noted reports from selected regulatory agencies regarding the real world safety status of *SARS-CoV-2 Vaccine (Vero cell), Inactivated [CoronaVac]*. The DOH-HTA Unit then updated the data from these regulatory agencies (Date of last search: 15 July 2021).

Adverse events

- Philippine FDA - 7,044,592 administered with the first dose and 5,093,246 administered with the second dose as of 01 August 2021 (Source: FDA Philippines, 2021)
    - 21,446 adverse events reports
        - 724 reports were classified as serious
        - Severe allergic reaction rate was rare
        - Most common adverse events by system organ class were examinations (i.e., increase in blood pressure, heart rate), followed by general symptoms and reactions in the administration site, neurological symptoms, skin symptoms, respiratory symptoms, gastrointestinal symptoms, and musculoskeletal symptoms.
        - The top reported events are increase in blood pressure, headache, vaccination/injection site pain, pyrexia, dizziness, rash, cough, malaise, pruritus, and nasopharyngitis.
- China - A total of 35.8 million doses have been administered as of 14 March 2021 (Source: WHO, 2021)

    - 6,638 adverse events reports, with an overall reporting rate of 18.5 AEFI per 100,000 doses administered
        - 64% general reactions, 14% abnormal reactions, 13% coincidental, 5% psychogenic, and 4% undetermined
        - Of the 5,427 AEFIs for which causality with *SARS-CoV-2 Vaccine (Vero cell), Inactivated [CoronaVac]* cannot be ruled out, symptoms and diagnosis were available for severity determination for 4,990. 49 cases were classified as serious.
        - Of the serious adverse reactions, there were 6 cases of anaphylactic shock, 5 cases of Henoch-Schonlein purpura, 4 cases of facial paralysis, 3 cases of laryngeal edema, 3 cases of demyelination, 3 cases of cerebral hemorrhage, 2 cases of Guillain-Barré syndrome, and one case each of thrombocytopenic purpura, peripheral neuropathy, intracranial hemorrhage, syncope, septic shock, meningitis, sensation of foreign body (laryngeal), multiorgan dysfunction syndrome, autonomic nervous system imbalance, sudden hearing loss, hemorrhagic disorder, conversion disorder, nephrotic syndrome, tubulointerstitial nephritis, and subacute thyroiditis.
- Hong Kong - 2,253,000 doses administered as of 31 July 2021 (Source: Government of the Hong Kong Special Administrative Region, 2021)
    - 2,242 cumulative AEFI reports have been received from those vaccinated with *SARS-CoV-2 Vaccine (Vero cell), Inactivated [CoronaVac]*
    - Between the period of 1 July to 31 June 2021, 45 hospitalizations were reported for those vaccinated with *SARS-CoV-2 Vaccine (Vero cell), Inactivated [CoronaVac]* and there were 2 deaths that occurred among those vaccinated with *SARS-CoV-2 Vaccine (Vero cell), Inactivated [CoronaVac]* but none have been linked to the vaccine.
    - The most frequently reported events among those vaccinated with *SARS-CoV-2 Vaccine (Vero cell), Inactivated [CoronaVac]* are dizziness, rash, chest discomfort, numbness, and chest pain.
- Chile - A total of 5,350,038 doses of *SARS-CoV-2 Vaccine (Vero cell), Inactivated [CoronaVac]* have been administered as of 10 March 2021. (Source: Jara et al. 2021).
    - 2,584 adverse events were notified to the Chilean Institute of Public Health.
    - 122 notifications reported were classified as serious.
    - 15 post-vaccination notifications which resulted in death occurred with *SARS-CoV-2 Vaccine (Vero cell), Inactivated [CoronaVac]*. However, after evaluation, there are no patterns in causes of death that may indicate a vaccine safety problem against SARS- CoV- 2.

Adverse events of Special Interest

Myocarditis and Pericarditis

As of writing, there have been no reports of myocarditis or pericarditis following vaccination with *SARS-CoV-2 Vaccine (Vero cell), Inactivated [CoronaVac].*

Bell's Palsy

As of 31 July 2021, 2,253,000 doses of *SARS-CoV-2 Vaccine (Vero cell), Inactivated [CoronaVac]* has been administered in HongKong. The Hong Kong Department of Health Safety Monitoring Report (as of 31 July 2021) reported 83 cases of Bell's Palsy following immunization of the said vaccine, yielding a reporting rate of 0.004% or 3.7 cases per 100,000 doses administered. All reported cases of Bell's Palsy were deemed not serious. The Hong Kong Advisory Panel conducted a meeting on 14 July 2021 to review the benefit-risk balance of *SARS-CoV-2 Vaccine (Vero cell), Inactivated [CoronaVac].* They identified a signal risk of Bell's palsy after receiving the vaccine and deemed the incidence as very rare. The package insert of the vaccine has already been updated to include this information. Based on their judgment, the identified risks associated with *SARS-CoV-2 Vaccine (Vero cell), Inactivated [CoronaVac]* were addressed by provision of relevant information and that the overall benefit-risk profile remains favorable.

Thrombosis with Thrombocytopenia Syndrome

As of writing, there have been no reports of thrombosis with thrombocytopenia syndrome following vaccination with *SARS-CoV-2 Vaccine (Vero cell), Inactivated [CoronaVac].*

Capillary Leak Syndrome

As of writing, there have been no reports of capillary leak syndrome following vaccination with *SARS-CoV-2 Vaccine (Vero cell), Inactivated [CoronaVac].*

Cerebral Venous Sinus Thrombosis

As of writing, there have been no reports of cerebral venous sinus thrombosis following vaccination with *SARS-CoV-2 Vaccine (Vero cell), Inactivated [CoronaVac].*

Immune thrombocytopenia

As of writing, there have been no reports of immune thrombocytopenia following vaccination with *SARS-CoV-2 Vaccine (Vero cell), Inactivated [CoronaVac].*

HTAC JUDGMENT

2.3. What are the safety issues and incidence of adverse events caused by SARS-CoV-2 Vaccine (Vero cell), Inactivated [CoronaVac]?

Version 1 (as of 08 April 2021)	Version 2 (as of 30 July 2021)
Short-term safety of *SARS-CoV-2 Vaccine (Vero cell), Inactivated [CoronaVac]* is acceptable. However, further follow-up data is needed to establish longer-term safety.	Based on the current evidence from the phase 3 clinical trials, short-term safety of *SARS-CoV-2 Vaccine (Vero cell), Inactivated [CoronaVac]* is acceptable. However, further follow-up data is needed to establish longer-term safety.

	In terms of safety, trials which included both 18 to 59 and ≥60 age groups generally showed that adverse event rates are lower in older adults compared to the young adult population. While Bell's Palsy is considered a rare adverse event following immunization with *SARS-CoV-2 Vaccine (Vero cell), Inactivated [CoronaVac]* based on the analysis of the HK Department of Health, the HTAC deems that the benefits of vaccination outweigh the the risks as all reported cases of Bell's Palsy were deemed not serious.

2.4. Does COVID-19 SARS-CoV-2 Vaccine (Vero cell), Inactivated [CoronaVac] provide a highly favorable benefit/risk profile in the context of observed vaccine efficacy?

CURRENT EVIDENCE:

Based on the efficacy data from the phase 3 clinical trials in Brazil and Turkey, and real world effectiveness studies, clinical benefits in terms of decreased occurrence of symptomatic COVID-19 and reduced risk of hospitalization due to COVID-19 outweigh the known short-term risks.

In terms of safety, long-term safety outcomes are still inconclusive. The HK Department of Health reported a potential association between the use of the vaccine and Bell's palsy after 38 reports of the said adverse event. All cases were not serious hence, the benefits of vaccination outweigh the risks.

HTAC JUDGMENT *2.4. Does SARS-CoV-2 Vaccine (Vero cell), Inactivated [CoronaVac] provide a highly favorable benefit/risk profile in the context of observed vaccine efficacy?*	
Version 1 (as of 08 April 2021)	**Version 2 (as of 30 July 2021)**
PASSED	PASSED

Details on the additional clinical evidence are located in the Appendices 2, 3, and 4.

Criterion 3: Affordability and Viability

Costing revisions were necessary to reflect the changes in the number of target vaccines, cost of vaccine consumables, logistics, and operations. Refer to Appendix 5 for details in the costing analysis findings presented here.

3.1 Is SARS-CoV-2 Vaccine (Vero cell), Inactivated [CoronaVac] affordable?

EVIDENCE CONSIDERED

Version 1 (as of 08 April 2021)	Version 2 (as of 30 July 2021)
Based on the projected calculations, the total cost of rolling out vaccination with *SARS-CoV-2 Vaccine (Vero cell), Inactivated [CoronaVac]* for 25M Filipinos in 2021 (i.e., target vaccinees for this vaccine profile identified in the vaccination roll out plan) will amount to Php 39,457,905,333.33.	Based on the projected calculations, the total cost of rolling out vaccination with *SARS-CoV-2 Vaccine (Vero cell), Inactivated [CoronaVac]* for 12.5M Filipinos in 2021 (i.e., target vaccinees for this vaccine profile identified in the vaccination roll out plan) will amount to Php 19,406,565,735.17.

HTAC JUDGMENT

3.1. Is SARS-CoV-2 Vaccine (Vero cell), Inactivated [CoronaVac] affordable?

Version 1 (as of 08 April 2021)	Version 2 (as of 30 July 2021)
The vaccine is affordable since the budget for the purchase and use of *SARS-CoV-2 Vaccine (Vero cell), Inactivated [CoronaVac]* for the target number of vaccinees has been allocated.	No revision.

3.2 What are the budget implications of using SARS-CoV-2 Vaccine (Vero cell), Inactivated [CoronaVac]?

EVIDENCE CONSIDERED

Version 1 (as of 08 April 2021)	Version 2 (as of 30 July 2021)

The total cost of vaccination per individual, which accounts for other costs such as consumables, hauling and storage, and operations, was computed at Php 1,578.32. The potential budget impact of the use of *SARS-CoV-2 Vaccine (Vero cell), Inactivated [CoronaVac]* to the national government to cover 25 million Filipinos was calculated at about Php 39,457,905,333.33. It is estimated that 47.83% of the total allocated budget for vaccination will go to 36% of the 70 million target vaccinees for 2021.	The total cost of vaccination per individual, which accounts for other costs such as consumables, hauling and storage, and operations, was computed at Php 1,552.53. The potential budget impact of the use of *SARS-CoV-2 Vaccine (Vero cell), Inactivated [CoronaVac]* to the national government to cover 12.5 million Filipinos was calculated at about Php 19,406,565,735.17. It is estimated that 23.52% of the total allocated budget for vaccination will go to 17.86% of the 70 million target vaccinees for 2021.

HTAC JUDGMENT

3.2. What are the budget implications of using SARS-CoV-2 Vaccine (Vero cell), Inactivated [CoronaVac]?

Version 1 (as of 08 April 2021)	Version 2 (as of 30 July 2021)
The share of the cost of the *SARS-CoV-2 Vaccine (Vero cell), Inactivated [CoronaVac]* to the total vaccine budget is considered not proportionate to the share of the population to be vaccinated using the said vaccine.	No revision.

3.3. *Does the SARS-CoV-2 Vaccine (Vero cell), Inactivated [CoronaVac] represent good value for money in terms of:*

- *preventing COVID-19 mortality*
- *lowering hospitalization (moderate, severe and critical cases)*
- *lowering incidence of symptomatic (mild) and asymptomatic cases (RT-PCR confirmed cases)?*

EVIDENCE CONSIDERED

Version 1 (as of 08 April 2021)	Version 2 (as of 30 July 2021)
Whether *SARS-CoV-2 Vaccine (Vero cell), Inactivated [CoronaVac]* good value for money in terms of preventing COVID-19 mortality, lowering hospitalization (moderate, severe, and critical cases), and lowering the incidence of symptomatic (mild) and asymptomatic cases (RT-PCR confirmed cases) cannot be fully assessed at the moment. Rough estimates of the vaccination cost per case averted are high. However, HTAC has bases to conclude that these will be offset by averted healthcare costs (i.e., total COVID-19-related PhilHealth claims, out of pocket expenditures), economic gains (i.e., in terms of recovery in GDP), and social gains.	*SARS-CoV-2 Vaccine (Vero cell), Inactivated [CoronaVac] represents good value for money in terms of lowering symptomatic COVID-19, including hospitalization due to COVID-19, and COVID-19 related deaths based on real world evidence. Protection is also expected in 60 years old and above given the real world evidence of effectiveness and immunogenicity seen in this age group.* Whether *SARS-CoV-2 Vaccine (Vero cell), Inactivated [CoronaVac]* represents good value for money in terms of lowering asymptomatic cases (RT-PCR confirmed cases) cannot be fully assessed at the moment. Rough estimates of the vaccination cost per case averted are high. However, HTAC has bases to conclude that these will be offset by averted healthcare costs (i.e., total COVID-19-related PhilHealth claims, out of pocket expenditures), economic gains (i.e., in terms of recovery in GDP), and social gains.

HTAC JUDGMENT

3.3. Does the SARS-CoV-2 Vaccine (Vero cell), Inactivated [CoronaVac] represent good value for money in terms of:

- *preventing COVID-19 mortality*
- *lowering hospitalization (moderate, severe and critical cases)*
- *lowering incidence of symptomatic (mild) and asymptomatic cases (RT-PCR confirmed cases)?*

Version 1 (as of 08 February 2021)	Version 2 (as of 30 July 2021)
The HTAC deems that the health, economic, and social benefits of the vaccination program using *SARS-CoV-2 Vaccine (Vero cell), Inactivated*	The HTAC deems that the health, economic, and social benefits of the vaccination program using *SARS-CoV-2 Vaccine (Vero cell), Inactivated*

[CoronaVac] outweigh the negative impacts such as deaths due to COVID-19, medical costs, loss of productivity, social disruption and unprecedented challenges in the health system.	*[CoronaVac]* mitigate the negative impacts such as deaths due to COVID-19, medical costs, loss of productivity, social disruption and unprecedented challenges in the health system.

Criterion 4: Household financial impact

The HTAC notes the additional evidence regarding the household financial impact of COVID-19 illness.

4.1. *Will the SARS-CoV-2 Vaccine (Vero cell), Inactivated [CoronaVac] reduce or not add further to the out-of-pocket expenses of Filipino households?*

EVIDENCE CONSIDERED

V1 (as of 08 April 2021)	V2 (as of 30 July 2021)
<u>For mild COVID-19 pneumonia:</u> ● PhilHealth has issued the following packages and case rates related to mild COVID-19: - Isolation Package (C19CI): Php 22,499.00 - Mild COVID-19 pneumonia for elderly and with comorbidities (C19IP1): Php 43,997.00 ● Looking at the actual PhilHealth claims as of January 2021, the isolation package amounted to a median cost of **Php 22,499,** while claims for mild COVID-19 pneumonia for elderly and those with comorbidities amounted to a median cost of **Php 43,997.** ● Reviewing the hospital bills data collected by PhilHealth as of January 2021, the median amount spent by patients for isolation is at **Php 22,499** while mild cases among elderly and those with comorbidities is at **Php 60,020.25.**	**<u>For mild COVID-19 pneumonia:</u>** ● PhilHealth has issued the following packages and case rates related to mild COVID-19: - Isolation Package (C19CI): Php 22,499.00 - Mild COVID-19 pneumonia for elderly and with comorbidities (C19IP1): Php 43,997.00 ● Looking at the actual PhilHealth claims as of January 2021, the isolation package amounted to a median cost of **Php 22,499,** while claims for mild COVID-19 pneumonia for elderly and those with comorbidities amounted to a median cost of **Php 43,997.** ● Reviewing the hospital bills data collected by PhilHealth as of January 2021, the median amount spent by patients for isolation is at **Php 22,499** while mild cases among elderly and those with comorbidities is at **Php 60,020.25.**

- From the same dataset, the calculated median out-of-pocket spending for patients with mild COVID-19 pneumonia is at **Php 16,023.25.** Meanwhile, the median out-of-pocket reported for patients availing an isolation package is 0.

For moderate COVID-19 pneumonia:

- PhilHealth has issued benefit package C19IP2 for moderate COVID-19 pneumonia with a case rate of Php 143, 267.
- Looking at the actual PhilHealth claims for moderate COVID-19 pneumonia as of January 2021, they amounted to a median of **Php 143, 267.00**.
- Reviewing the hospital bills data collected by PhilHealth as of January 2021, the median amount spent by patients with moderate COVID-19 is at **Php 234, 925.13**.
- From the same dataset, the calculated median out-of-pocket spending for patients with moderate COVID-19 pneumonia is at **Php 63,371.3**.

For severe COVID-19 pneumonia:

- PhilHealth has issued benefit package C19IP3 for severe COVID-19 pneumonia with a case rate of Php 333,519.
- Looking at the actual PhilHealth claims for severe COVID-19 pneumonia as of January 2021, they amounted to a median of **Php 333,519.00**.
- Reviewing the hospital bills data collected by PhilHealth as of January 2021, the median amount spent by patients with severe COVID-19 pneumonia is at **Php 388,904.20**.
- From the same dataset, the calculated median out-of-pocket spending for patients with

- From the same dataset, the calculated median out-of-pocket spending for patients with mild COVID-19 pneumonia is at **Php 16,023.25.** Meanwhile, the median out-of-pocket reported for patients availing an isolation package is 0.

For moderate COVID-19 pneumonia:

- PhilHealth has issued benefit package C19IP2 for moderate COVID-19 pneumonia with a case rate of Php 143, 267.
- Looking at the actual PhilHealth claims for moderate COVID-19 pneumonia as of January 2021, they amounted to a median of **Php 143, 267.00**.
- Reviewing the hospital bills data collected by PhilHealth as of January 2021, the median amount spent by patients with moderate COVID-19 is at **Php 234, 925.13**.
- From the same dataset, the calculated median out-of-pocket spending for patients with moderate COVID-19 pneumonia is at **Php 63,371.3**.

For severe COVID-19 pneumonia:

- PhilHealth has issued benefit package C19IP3 for severe COVID-19 pneumonia with a case rate of Php 333,519.
- Looking at the actual PhilHealth claims for severe COVID-19 pneumonia as of January 2021, they amounted to a median of **Php 333,519.00**.
- Reviewing the hospital bills data collected by PhilHealth as of January 2021, the median amount spent by patients with severe COVID-19 pneumonia is at **Php 388,904.20**.
- From the same dataset, the calculated median out-of-pocket spending for patients with

severe COVID-19 pneumonia is at **Php 388,903.20**.	severe COVID-19 pneumonia is at **Php 388,903.20**.
Interim results from the clinical trials have shown its clinical benefit in decreasing the risk of symptomatic COVID-19. It may reduce the risk of hospitalization due to COVID-19.	Interim results from the clinical trials and real-world effectiveness data have shown its clinical benefit in decreasing the risk of symptomatic COVID-19. Additionally, real-world effectiveness data on the vaccine likely shows clinical benefits in reducing the risk of hospitalization and death due to COVID-19.

HTAC JUDGMENT *4.1. Will the SARS-CoV-2 Vaccine (Vero cell), Inactivated [CoronaVac] reduce or not add further to the out-of-pocket expenses of Filipino households?*	
Version 1 **(as of 08 April 2021)**	**Version 2** **(as of 30 July 2021)**
Based on current evidence, *SARS-CoV-2 Vaccine (Vero cell), Inactivated [CoronaVac]* has the potential to reduce out-of-pocket expenses of Filipino households due to averted isolation, treatment and hospitalization costs.	Interim results from the clinical trials and real-world effectiveness data have shown its clinical benefit in decreasing the risk of symptomatic COVID-19. Additionally, real-world effectiveness data on the vaccine likely shows clinical benefits in reducing the risk of hospitalization and death due to COVID-19 (Jara et al., 2021).

Criterion 5: Social impact

The HTAC notes the additional evidence regarding the public acceptability of COVID-19 vaccines and availability of mechanisms to manage any untoward serious adverse reactions following vaccination. Other evidence considered in ES V1 for this criterion remains valid.

5.1. ***Does the SARS-CoV-2 Vaccine (Vero cell), Inactivated [CoronaVac] possess the characteristics desired by key stakeholders (i.e. on public acceptability)?***

EVIDENCE CONSIDERED

V1 (as of 08 April 2021)	V2 (as of 30 July 2021)
1) Safe and efficacious for the general population (18 years old and older) and for some vulnerable groups like the older population and individuals with comorbidities. - Evidence: Clinical trial shows acceptable safety profile for known short-term risks and efficacy to reduce risk of symptomatic COVID-19, and may reduce the risk of severe COVID-19 and hospitalization due to COVID-19. There is insufficient efficacy and safety data for populations aged 60 and older and the Asian population. Trials are ongoing to provide more conclusive evidence on the efficacy and safety for these special populations.	**1) Safe and efficacious for the general population (18 years old and older) and for some vulnerable groups like the older population and individuals with comorbidities.** - Evidence: The Phase III clinical trials conducted in Brazil and Turkey show acceptable safety profile for known short-term risks and efficacy to reduce the risk of symptomatic COVID-19, and may reduce the risk of severe COVID-19 and hospitalization due to COVID-19. As for the protection conferred by the vaccine in the older population aged ≥60 years, the WHO noted that current evidence from observational studies together with immunogenicity results suggest that *SARS-CoV-2 Vaccine (Vero cell), Inactivated [CoronaVac]* is likely to have a protective effect in older persons, although whether at an equivalent level as in younger adults is yet to be known in further studies. Currently, there is still insufficient efficacy and safety data from trials for the Asian population. According to the WHO, trials are ongoing to provide more conclusive evidence on the efficacy, effectiveness, safety, and immunogenicity of *SARS-CoV-2 Vaccine (Vero cell), Inactivated [CoronaVac]* in special populations including the older population, persons with rheumatic diseases, persons living with HIV, breast or lung cancer patients receiving chemotherapy, and persons with chronic liver disease.
2) Underwent a transparent regulatory process of being evaluated and approved by health authorities - Evidence: The *SARS-CoV-2 Vaccine (Vero cell), Inactivated [CoronaVac]* underwent the usual regulatory process of the FDA Philippines. However, this review had to consider unpublished, non-peer reviewed data. To date, no	**2) Underwent a transparent regulatory process of being evaluated and approved by health authorities** - - Evidence: The *SARS-CoV-2 Vaccine (Vero cell), Inactivated [CoronaVac]* underwent the usual regulatory process of the FDA Philippines. The Philippine FDA does not object to the

stringent regulatory agency has issued EUA on this vaccine.

6) Public acceptability

- Evidence: No brand-specific study has been conducted to provide evidence for this characteristic. Based on a series of focus group discussions (FGD) conducted by HTAC, there were expressed reservations towards China-produced vaccines. However, in the concluding discussion, the participants emphasized the transparency of regulatory process and consideration for shortage of supply.

7) Availability of mechanisms to compensate vaccine recipients for any untoward event 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.

expansion of its target population to include individuals aged 60 years and older as stated in a letter dated 07 April 2021.

6) Public acceptability

- Evidence: Based on the national survey conducted by the Social Weather Station from 28 April to 02 May 2021:

    - 63% of the 1,200 respondents aged 18 years and above picked the United States as one of their preferred country sources of vaccines. This was followed by China which was selected by 19% of the respondents. Meanwhile, 13% of the respondents also opted for the United Kingdom, 12% included Russia, and 3% picked India as one of their preferred country sources of vaccines.

The certainty of the evidence provided by published and real world data that support the favorable recommendation, if appropriately communicated, will increase public acceptability of vaccines.

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

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

- Evidence: The Phase III clinical trial conducted in Brazil included healthcare workers 18 years and older, who are healthy and/or have underlying medical conditions that can be controlled by medication.

Elderly population:

- The *SARS-CoV-2 Vaccine (Vero cell), Inactivated [CoronaVac]* shows inconclusive vaccine efficacy in the older population of 60 years and above [VE: 51.11% (95% CI: -166.93 to 91.04)] (N = 632; 5.10% of the trial population), based on very low certainty of evidence.
- In terms of safety, using *SARS-CoV-2 Vaccine (Vero cell), Inactivated [CoronaVac]*, compared to placebo increases the risk of local AEs by 1.70 times (95%CI: 1.34 to 2.15), based on moderate certainty of evidence. However, its safety profile for the following outcomes are inconclusive: AEs related to vaccination [RR: 1.13 (95% CI: 0.97 to 1.31)], based on low certainty of evidence; and systemic AEs [RR: 0.97 (95% CI: 0.80 to 1.17)], based on low certainty of evidence.

With stable comorbidities:

- The reported vaccine efficacy for the population with stable comorbidities is 48.93% (95% CI:

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 to special at-risk groups and patients with comorbidities

- Evidence: The Phase III clinical trials evaluating the safety and efficacy of *SARS-CoV-2 Vaccine (Vero cell), Inactivated [CoronaVac]* enrolled individuals aged 18 years and older. The current efficacy and safety data demonstrate protection in persons with obesity. Although the older population enrolled in the clinical trials was insufficient to draw conclusions from the Phase III clinical trials, real world evidence showed that *SARS-CoV-2 Vaccine (Vero cell), Inactivated [CoronaVac]* provides protection against symptomatic COVID-19 in adults aged 60 years and older.

Currently, there is limited data from the trials on the use of the vaccine for pregnant and lactating women, persons living with HIV, immunocompromised individuals, and persons who have previously received antibody therapy for the treatment of COVID-19. The updated WHO interim recommendations (24 May 2021) on the use of the vaccine in the older population, patients with comorbidities, and other special populations are detailed below.

Adults aged 60 years and above:

26.57 to 64.49) (N = 6.925; 55.86% of the trial population), based on low certainty of evidence.
- The reported vaccine efficacy for the obese population is 74.86% (95%CI: 53.73 to 86.35) (proportion in the trial population not mentioned), based on moderate certainty of evidence.
- The trial did not report specific safety analysis for this subpopulation.

Evidence for efficacy and safety are insufficient for the following populations: individuals aged below 18 years and 60 years and above, individuals with uncontrolled comorbidities, and those who are immunocompromised, pregnant, and lactating women.

- Data from post-introduction observational studies and immunogenicity studies suggest that *SARS-CoV-2 Vaccine (Vero cell), Inactivated [CoronaVac]* is likely to have a protective effect in older persons.
- WHO recognizes that there are no theoretical reasons to believe that the vaccine has a different safety profile in older adults compared to younger adults.
- Based on currently available evidence, WHO recommends the use of *SARS-CoV-2 Vaccine (Vero cell), Inactivated [CoronaVac]* in persons aged 60 years and older.

<u>*Persons with comorbidities:*</u>
- Vaccine efficacy has been demonstrated among trial participants with obesity and hypertension while the number of participants with other comorbidities are too small to draw firm conclusions. Considering the favourable benefit-risk assessment, vaccination with *SARS-CoV-2 Vaccine (Vero cell), Inactivated [CoronaVac]* is recommended for this special population.

<u>*Pregnant women:*</u>
- Evidence for efficacy and safety are insufficient to assess vaccine-associated risks in pregnancy.
- The *SARS-CoV-2 Vaccine (Vero cell), Inactivated [CoronaVac]* is an inactivated vaccine with an adjuvant that is routinely used in many other vaccines with documented good safety profile, including in pregnant women.
- No safety issues were noted from the developmental and

reproductive toxicology studies conducted in animals.
- The WHO interim recommendation for pregnant women to receive the vaccine remains on the condition that the benefit of protection from COVID-19 outweigh the potential vaccine risks.

Lactating women:
- Vaccine efficacy in lactating women is expected to be similar to other adults.
- Currently, there is no evidence on the potential benefits or risks of the vaccine on breastfed children.
- Since the vaccine is not a live virus, WHO recommends vaccination in lactating women who are part of the recommended groups for vaccination. Discontinuing breastfeeding after vaccination is not recommended.

Persons living with HIV:
- PLHIV were not included in the clinical trials; however, studies including this special population are forthcoming.
- In the interim, as *SARS-CoV-2 Vaccine (Vero cell), Inactivated [CoronaVac]* is nonreplicating, WHO still recommended vaccination for PLHIV who are part of the recommended groups for vaccination.

Immunocompromised persons:
- Currently, the available data is insufficient to assess vaccine efficacy or vaccine-associated risks in severely immunocompromised persons including those receiving immunosuppresant therapy.
- Meanwhile, as *SARS-CoV-2 Vaccine (Vero cell), Inactivated [CoronaVac]* is nonreplicating, WHO still recommended

vaccination for immunocompromised persons who are part of the recommended groups for vaccination.

Persons who have previously had SARS-CoV-2 infection:

- Vaccination should be offered regardless of personal history of SARS-CoV-2 infection. Hence, testing (i.e., viral or serological) for prior infection is not necessary for decision making regarding vaccination.
- In the context of limited vaccine supply, persons with PCR-confirmed SARS-CoV-2 infection in the last 6 months may choose to delay vaccination given that symptomatic reinfection within 6 months after an initial natural infection is uncommon. However, in settings where variants of concern are circulating, earlier immunization after natural infection may be advisable due to higher risk of symptomatic reinfection.

Persons with current acute COVID-19:

- Individuals with acute PCR-confirmed COVID-19 should not be vaccinated until after full recovery from the acute illness and meeting the criteria for discontinuation of isolation. The optimal minimum interval between a natural infection and vaccination is not yet known.

Persons who previously received passive antibody therapy for COVID-19:

- Currently, there is no data on the safety or efficacy of vaccination in individuals who have received monoclonal antibodies or convalescent plasma as treatment for COVID-19.
- Vaccination should be deferred

for at least 90 days to avoid interference of the antibody therapy with the immune response elicited by vaccination.

Children and adolescents below the age 18 years:

- For most children and adolescents the disease profile is less severe.
- There is currently no efficacy or safety data for children or adolescents below the age of 18 years, although a phase 2 paediatric study is under way. Until such data are available, vaccination of individuals below 18 years of age is not routinely recommended.

The assessment team notes the publication of Han et al. (2021), a Phase I/II trial on the safety, tolerability, and immunogenicity of *SARS-CoV-2 Vaccine (Vero cell), Inactivated [CoronaVac]* among children and adolescents aged 3 to 17 years. However, at the time of writing this report, the WHO has not released an updated recommendation to include vaccination of children aged 3-17 years old. Further, the EUA issued by the Philippine FDA does not cover this population.

HTAC JUDGMENT *5.1 Does the SARS-CoV-2 Vaccine (Vero cell), Inactivated [CoronaVac] possess the characteristics desired by key stakeholders (i.e. on public acceptability)?*	
Version 1 **(as of 08 April 2021)**	**Version 2** **(as of 30 July 2021)**
Based on short-term outcomes, *SARS-CoV-2 Vaccine (Vero cell), Inactivated [CoronaVac]* possesses most of the characteristics desired by key stakeholders.	No revision.

Criterion 6: Responsiveness to equity

6.1. How will the SARS-CoV-2 Vaccine (Vero cell), Inactivated [CoronaVac] and its use impact pre-COVID and COVID-generated health and socioeconomic inequities?

6.2. Which groups might be unfairly disadvantaged in relation to the COVID-19 disease burden and delivery of the SARS-CoV-2 Vaccine (Vero cell), Inactivated [CoronaVac]?

EVIDENCE CONSIDERED

V1 (as of 08 April 2021)	V2 (as of 30 July 2021)
SARS-CoV-2 Vaccine (Vero cell), Inactivated [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 Brazil Phase III trial. There may be issues/gaps in access for special and vulnerable populations such as individuals below 18 years old and those with allergy to one of the components of the vaccine. *SARS-CoV-2 Vaccine (Vero cell), Inactivated [CoronaVac]* can be stored at normal cold storage conditions (2 to 8 degrees Celsius). This will make vaccine distribution more logistically feasible which in turn does not aggravate inequities for patients living in geographically isolated and disadvantaged areas. Compared to other new vaccines, the price per dose and the logistical and operational cost of *SARS-CoV-2 Vaccine (Vero cell), Inactivated [CoronaVac]* allow it to be utilized widely.	*SARS-CoV-2 Vaccine (Vero cell), Inactivated [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, *SARS-CoV-2 Vaccine (Vero cell), Inactivated [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. In terms of its protective effect in older adults, a national prospective cohort study in Chile observed a vaccine effectiveness of 66.6% (95% CI: 65.4% to 67.8%) in older adults (≥60 years old). There may be issues/gaps in access for special and vulnerable populations such as individuals below 18 years old and those with allergy to one of the components of the vaccine. *SARS-CoV-2 Vaccine (Vero cell), Inactivated [CoronaVac]* can be stored

at normal cold storage conditions (2 to 8 degrees Celsius). This will make vaccine distribution more logistically feasible which in turn does not aggravate inequities for patients living in geographically isolated and disadvantaged areas. Compared to other new vaccines, the price per dose and the logistical and operational cost of *SARS-CoV-2 Vaccine (Vero cell), Inactivated [CoronaVac]* allow it to be utilized widely.

HTAC JUDGMENT

6.1. How will the SARS-CoV-2 Vaccine (Vero cell), Inactivated [CoronaVac] and its use impact pre-COVID and COVID-generated health and socioeconomic inequities?

6.2. Which groups might be unfairly disadvantaged in relation to the COVID-19 disease burden and delivery of the SARS-CoV-2 Vaccine (Vero cell), Inactivated [CoronaVac]?

Version 1 (as of 08 April 2021)	Version 2 (as of 30 July 2021)
Because of non-stringent logistic requirements, *SARS-CoV-2 Vaccine (Vero cell), Inactivated [CoronaVac]* does not aggravate health inequities related to inoculation of recipients residing in isolated and disadvantaged locations. However, the evidence on the efficacy and safety of the vaccine among individuals aged 60 years and above are insufficient. Trials are ongoing to provide more conclusive evidence on the efficacy and safety for older adults. The trial population also did not include important vulnerable groups such as individuals with impaired immune systems, and pregnant and lactating women.	Because of non-stringent logistic requirements, *SARS-CoV-2 Vaccine (Vero cell), Inactivated [CoronaVac]* does not aggravate health inequities related to inoculation of recipients residing in isolated and disadvantaged locations. New evidence based on real-world effectiveness data demonstrated clinical benefits in reducing risk of symptomatic COVID-19, hospitalization due to COVID-19, death due to COVID-19, in older adults (≥60 years old). In terms of safety, trials which included both 18 to 59 and ≥60 age groups generally showed that adverse event rates are lower in older adults compared to the young adult population.

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Appendix 1. HTAC Evidence Summary on SARS-CoV-2 Vaccine (Vero Cell), Inactivated [CoronaVac] *[Version 1 dated 09 April 2021]*

Access link:

https://drive.google.com/file/d/1NvHbNKPVg7Y8dbbG9Ovnfz2UzFqR9k88/view?usp=sharing

Appendix 2. Table of Additional RCTs *(from WHO report)*

Additional RCTs	Key Findings
Palacios et al. (2021)[preprint]	Efficacy: ● Symptomatic COVID-19 in population with hypertension (≥14 days after the second dose): There were zero events of symptomatic COVID-19 at least 14 days after 2nd dose in 335 participants in the intervention group versus 7 events in 330 participants in the control group.
Tanriover et al. (2021)	Efficacy: ● VE against symptomatic COVID-19 at least 14 days after second dose: **83.5% (95% CI 65.4 to 92.1)** ● Hospitalization due to COVID-19 at least 14 days after second dose: ● There were zero events of hospitalization due to COVID-19 at least 14 days after the second dose in 6,559 participants in the intervention group versus 6 events in 3,470 participants in the control group. ● Death due to COVID-19: There were no fatalities due to COVID-19 that occurred in both the intervention and control arms of the trial. ● VE against symptomatic COVID-19 at least 14 to 27 days after first dose: **46.4% (95%CI: 0.4–71.2)** ● A total of 9 asymptomatic cases were detected, 3 in the vaccine arm and 6 in the placebo arm. Safety: ● Relative risk of systemic adverse events: 1.11 (95% CI: 1.01 to 1.21) ● Relative risk of local adverse events: 1.86 (95% CI: 1.28 to 2.52)

	● Relative risk of serious adverse events: 0.64 (95% CI: 0.20 to 2.11) ● There were no fatalities, regardless of cause, that occurred in both the intervention and control arms of the trial.
Bueno et al. (2021)[preprint]	Immunogenicity: ● Seropositivity rates 14 days after the second dose in the 18-59 year age group is higher compared to that of the 60 years and above age group. However, the geometric mean of neutralizing antibody titers was higher in the 60 years and above age group compared to the 18-59 years age group. ● Seropositivity and GMTs at 28 days after the second dose were higher in the 60 years and above age group compared to the response in the 18 to 59 years age group.

Appendix 3. GRADE Table

EFFICACY OUTCOMES										
OUTCOME	**Quality Assessment** *Note: The study design and number of studies column were collapsed since the input for these columns are the same across all outcomes*					**Summary of Findings**			**Certainty**	**Importance**
	Risk of bias	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**CoronaVac/N**	**Placebo n/N**	**Effect Size (95% CI)**		
TURKEY TRIAL (Tanriover et al. 2021)										
1. VE against symptomatic COVID-19 *(at least 14 days after 2nd dose)*	**Not serious (Low RoB)**	N/A	**Not serious**	**Not serious**	None	9/6559 (0.14%)	32/3470 (0.92%)	**VE: 83.5%** (65.4 to 92.1)	⊕⊕⊕⊕ HIGH	**CRITICAL**
2. VE against hospitalization related to COVID-19 *(at least 14 days after 2nd dose)*	**Not serious (Low RoB)**	N/A	**Serious** (needs longer follow up)	**Serious** (CI not estimable)	None	0/6559 (0.0%)	6/3470 (0.17%)	**VE: 100%** (not estimable)	⊕⊕◯◯ LOW	**CRITICAL**
3. VE against symptomatic COVID-19 *(14 days to 27 days after 1st dose)*	**Serious** (High ROB due to selective reporting)	N/A	**Not serious**	**Serious** (Wide CI)	None	Not reported	Not reported	**VE: 46.4%** (95% CI: 0.4 to 71.2)	⊕⊕◯◯ LOW	**IMPORTANT**

SAFETY OUTCOMES

OUTCOME	Quality Assessment *Note: The study design and number of studies column were collapsed since the input for these columns are the same across all outcomes*					Summary of Findings			Certainty	Importance
	Risk of bias	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**CoronaVac/N**	**Placebo n/N**	**Effect Size (95% CI)**		
TURKEY TRIAL [(Tanriover et al. 2021)]										
1. Serious adverse events	**Not Serious** (Unclear ROB due to selection and detection bias)	N/A	Serious (needs longer follow up)	Serious (Crosses null value)	None	6/6646 (0.09%)	5/3568 (0.14%)	**RR: 0.64** (0.20 to 2.11)	⊕⊕◯◯ LOW	**CRITICAL**
2. Systemic adverse events	**Not Serious** (Unclear ROB due to selection and detection bias)	N/A	Not serious	Not serious	None	1179/6646 (17.74%)	571/3568 (16.00%)	**RR: 1.11** (1.01 to 1.21)	⊕⊕⊕⊕ HIGH	**CRITICAL**
3. Local Adverse events	**Not Serious** (Unclear ROB due to selection and detection bias)	N/A	Not serious	Not serious	None	180/6646 (2.71%)	52/3568 (1.46%)	**RR: 1.86** (1.27 to 2.52)	⊕⊕⊕⊕ HIGH	**IMPORTANT**

Appendix 4. Table of real world evidence *(from WHO report)*

EFFECTIVENESS AGAINST COVID-19

Table 1. Two studies that provided real world evidence on the effectiveness of *SARS-CoV-2 Vaccine (Vero cell), Inactivated [CoronaVac]*

Outcomes	Population	Key Findings	Interpretation
Vaccine Effectiveness (VE) against Symptomatic COVID-19	**Healthcare workers**	de Faria, et al., 2021 - unpublished [Sao Paulo, Brazil]: • VE on 3rd week after dose 2: 51% (95% CI: 22 to 63) • VE on 6th week after dose 2: 74% (95% CI: 57 to 85)	There is a 74% reduction in the risk of symptomatic COVID-19 infection (VE) among HCWs in the sixth week after dose 2 vaccination in Brazil.
VE against Deaths due to COVID-19	**Older Population (≥ 60 years old)**	Jara et al., 2021 - published [Chile] • VE for fully immunized patients (≥14 days after the dose 2): 86.5% (95% CI: 84.6 to 88.1) • VE for partially immunized patients (≥14 days after the dose 1): 45.8% (95% CI: 40.4 to 50.7)	There is a 45.8% reduction in the risk of deaths due to COVID among the population aged 60 years and above at least 14 days after dose 1 of the vaccine. Meanwhile, VE increases to 86.5% reduction in risk of deaths due to COVID-19 in the same population in Chile ≥14 days after dose 2.

EFFECTIVENESS AGAINST NEW COVID-19 VARIANTS

Table 2. Four studies that provided real world evidence on the effectiveness of *SARS-CoV-2 Vaccine (Vero cell), Inactivated [CoronaVac]* caused by variants of concern

Outcomes	Population	Key Findings	Interpretation
Symptomatic COVID-19	**Healthcare workers**	Hitchings et al., 2021 - preprint [Brazil] Gamma Variant (P. 1)	Two dose effectiveness against symptomatic COVID-19 caused by the gamma variant is 36%.

		• Adjusted VE 14 days after dose 1: 49.6% (95% CI: 11.3 to 71.4) • Adjusted VE 14 days after dose 2: 36% (95% CI: -54.9 to 74.2) • adjusted OR 0-13 days after first dose: 2.11 (95% CI: 1.36-3.27)	

IMMUNOGENICITY AGAINST NEW COVID-19 VARIANTS

Table 3.Three studies that provided real world evidence on the immunogenicity of *SARS-CoV-2 Vaccine (Vero cell), Inactivated [CoronaVac]* caused by variants of concern

Outcomes	Population	Key Findings	Interpretation
Serum neutralization	**General population**	Souza et al., 2021 - preprint [Brazil] Antibody neutralizing capacity of plasma from previously SARS-CoV-2- infected participants • VNT_{50} 260 (160-400) against the B lineage isolate • VNT_{50} 30 (IQR <20 to 45) against the P. 1/28 isolate • VNT_{50} 30 (IQR <20 to 40) against the P. 1/30 isolate • $PRNT_{50}$ 1:640 against the B lineage isolate • $PRNT_{50}$ 1:25 against the P. 1/28 isolate • $PRNT_{50}$ 1:23 against the P. 1/30 isolate Antibody neutralizing capacity of plasma from participants collected 20 - 28 days after a single dose of the vaccine • VNT_{50} 20 (IQR 20 to 30) against B lineage isolate • VNT_{50} <20 (lower than the limit of detection) against the gamma variants • $PRNT_{50}$ 1:20 against the B lineage isolate • no neutralizing activity (below the limit of detection) against the gamma variants Antibody neutralizing capacity of plasma from participants	Plasma from previously SARS-CoV-2- infected participants showed an 8.6 times lower neutralizing capacity against the gamma variant than against the B lineage. Plasma samples from participants after a single dose had VNT_{50} which were near or below the limit of detection, thus, statistical significance could not be reached in the comparison of the B lineage and the gamma variant. Plasma samples from participants after two doses

		collected 17-38 days after the second dose of the vaccine ● VNT_{50} 75 (IQR <20-263) against B lineage isolate ● VNT_{50} 24 (IQR <20 to 25) against the P. 1/28 isolate ● VNT_{50} 28 (IQR <20 to 25) against the P. 1/30 isolate ● $PRNT_{50}$ 1:80 against the B lineage isolate ● $PRNT_{50}$ <1:20 against the gamma variants Antibody neutralizing capacity of plasma from participants collected 134-260 days after receiving booster vaccination ● VNT_{50} 20 (IQR 20 to 30) against B lineage isolate ● VNT_{50} <20 (lower than the limit of detection) against the gamma variants ● $PRNT_{50}$ 1:20 against the B lineage isolate ● no neutralizing activity (below the limit of detection) against the gamma variants Hu et al., 2021 - preprint [China] Number of participants that had neutralizing activity below the threshold: ● Alpha (B.1.1.7 variant): 7/20 (35%) ● Delta (B.1.617) variant: 13/20 (65%) Compared to the virus with the D614G mutation (GMT: 89), neutralization potency of the vaccine decreased by the ff factors: ● Delta variant: 2.5-fold reduction (GMT: 36) ● Alpha variant: 1.6-fold reduction (GMT: 55)	showed a significant decrease in neutralizing capacity against the gamma variant than against the B lineage. Plasma samples from phase 3 trial participants had VNT_{50} which were near or below the limit of detection, thus, statistical significance could not be reached in the comparison of the B lineage and the gamma variant. Compared to the D614G mutation and the alpha variant, the delta variant shows more resistance to antibody neutralization.
	Healthcare workers	Acevedo et al., 2021 - pre-print [Chile] Compared to the wild type (Wuhan-1 lineage), the ID50 titers for the SARS-CoV-2 pseudoviruses decreased by the ff factors: ● D614G mutation: 1.37 (1.20 to 1.55)	Mutations present in the spike protein of the Lambda variant of interest confer increased infectivity and immune escape from neutralizing antibodies elicited by CoronaVac.

		• Alpha variant: 2.03 (1.71 to 2.41) • Gamma variant: 2.33 (1.95 to 2.80) • Lambda variant: 3.05 (2.57 to 3.61)	

Appendix 5. Updated costing table

Description	Cost	Assumptions/Notes	Source
Vaccine and Vaccine Consumables	**Php 18,462,489,166.67**	For two doses, with 5% wastage; consumables include syringes, personal protective equipment *(estimated costs for vaccinating 12,500,000 Filipinos based on identified target vaccinees for this brand)*	DOF DPCB
Logistics	**Php 110,743,048.50**	For 2°C to 8°C vaccine storage temperature only. This includes hauling and storage costs. *(estimated costs for vaccinating 12,500,000 Filipinos based on identified target vaccinees for this brand)*	DOF
Operations	**Php 833,333,520.00**	This does not include yet cost of their testing, transportation of vaccinators, or any other costs necessary for mobilization and service delivery. Note that the duration of activity provided by DPCB was 24 days. Cost of hiring additional staff (depending on demand) is not considered in this costing. *(estimated costs for vaccinating 12,500,000 Filipinos based on identified target vaccinees for this brand)*	DPCB
TOTAL COST	**Php 19,406,565,735.17**		
TOTAL VACCINATION COST PER INDIVIDUAL	Php 1,552.53		

Acronym: **DPCB:** Disease Prevention and Control Bureau | **DOF:** Department of Finance