Evidence Summary on *Covovax* for the prevention of COVID-19

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Background

On 17 November 2021, the Philippine Food and Drug Administration (FDA) released the Emergency Use Authorization (EUA) for *Covovax*. As of 11 November 2021, *Covovax* is still under the evaluation process of the WHO Emergency Use Listing (EUL)/Prequalification (PQ) and is yet to have released recommendations. To date, *Covovax,* also known as NVX-CoV2373, has been given an EUA for the adult population in Indonesia (as of 1 November 2021) and Philippines (as of 17 November). Currently, *Covovax* has yet to be authorized under EUA in the US where it was developed, and in India where it is manufactured and tested in a Phase II/III clinical trial. Basic information on *Covovax* is provided below:

Table 1.1 Characteristics of *Covovax*

Trade name	SARS-CoV-2 rS Protein Nanoparticle Vaccine (Covovax)
Other name	NVX-CoV2373 COVID-19 Vaccine
Manufacturer/s	Serum Institute of India Private Limited
Vaccine platform	Protein subunit (rS Protein Nanoparticle Vaccine)
Dose strength and administration	2 doses, 0.5 mL each, not less than 21 days apart
Route of administration	Intramuscular (IM)
Drug delivery system	Colorless to slightly yellow, clear to mild opalescent, free to practically free from visible particles, suspension for injection.
Storage condition	Store at temperatures between 2° to 8 °C. Do not freeze. Keep vials on the outer carton to protect from light
Mechanism of action	*NVX-2372* is a recombinant vaccine adjuvanted with the saponin-based Matrix-M1™ adjuvant for the prevention of disease caused by SARS-CoV-2. SARS-CoV-2 recombinant (r) spike (S) protein nanoparticle vaccine (SARS-CoV-2 rS) is constructed from the full-length, wild-type SARS-CoV-2 S glycoprotein (GP) based upon the GenBank gene sequence MN908947, nucleotides 21563-25384, from the 2019 SARS-CoV-2 genome. The S protein is a type 1 trimeric glycoprotein of 1,273 amino acids that is produced as an inactive S0 precursor. The S-gene was codon optimised for expression in Spodoptera frugiperda (Sf9) insect cells. The SARS-CoV-2 rS nanoparticle vaccine is intended for administration with Matrix-M1 adjuvant, which is a saponin-based adjuvant that has previously been shown to enhance the immunogenicity of other nanoparticle vaccines in nonclinical and clinical studies (Novavax Phase III Clinical Study Protocol, 2020)
Contraindications	Persons who have hypersensitivity to the active substance or to any of the excipients of this vaccine. (Novavax Press Release, 01 November 2021)
PHL EUA status	Released as of 17 November 2021
PHL FDA EUA indication	SARS-CoV-2 rS Protein Nanoparticle Vaccine (Covovax), is indicated for active immunization of individuals >18 years old for the prevention of coronavirus disease 2019 (COVID-19) caused by SARS-CoV-2.
WHO EUL status	Ongoing evaluation process (as of 22 November 2021)

The product information/fact sheet for healthcare providers is available here.

Pursuant to the role of the Health Technology Assessment Council (HTAC) to develop coverage recommendations particularly in the selection and financing of COVID-19 vaccines for the COVID-19 Vaccine Implementation for 2022, this assessment follows the HTAC evaluation framework to assess COVID-19 vaccines using the following criteria: (1) responsiveness to magnitude and severity; (2) clinical efficacy and safety; (3) affordability and viability; (4) household financial impact; (5) social impact; and (6) responsiveness to equity.

Policy Question

The HTAC aims to answer the policy question:
Should the DOH use ***Covovax* as primary homologous vaccination** in the 2022 COVID-19 Vaccination Program to reduce COVID-19 cases, severe infection, and deaths?

Recommendations *(as of 09 December 2021)*

The HTAC recommends the DOH financing and inclusion of *Covovax* in the Philippine National Deployment and Vaccination Plan for COVID-19 among the general population aged 18 years and above because it has passed the HTAC criteria of (a) responsiveness to disease magnitude and severity, (b) clinical efficacy and safety, (c) affordability and viability, (d) household financial impact, (e) social impact, and, (f) responsiveness to equity; provided that there is sufficient budget to cover its implementation after pending supply negotiations in 2022.

The HTAC considered the following criteria in formulating its recommendation for the vaccine:

Criteria	HTAC Judgment *(as of 09 December 2021)*
Can Covovax significantly reduce the magnitude and severity of COVID-19 in the general population?	**Yes**. *Covovax* has the potential to reduce the disease burden by averting a significant number of symptomatic infections including severe COVID-19 assuming sufficient vaccine coverage.
Is Covovax safe and efficacious for the general population?	**Yes**, *Covovax* is efficacious in preventing symptomatic COVID-19 among the general population aged 18 years and older up to at least 7 days after the second dose based on one published Phase III RCT (Heath et al., 2021). Additionally, *Covovax* passed the HTAC-specified preferred vaccine efficacy threshold against symptomatic COVID-19 caused by the Alpha variant for the general population ≥18 years based on the same published Phase III trial (Heath et al., 2021). We note that one preprint Phase III trial (Dunkle et al., 2021) supplements the findings of the published Phase III trial. However, based on one study, *Covovax* did not pass the preferred vaccine efficacy threshold against symptomatic COVID-19 caused by the Beta variant (Shinde et al., 2021). **Yes,** the short-term safety profile of *Covovax* is acceptable, based on clinical trial evidence. Further follow-up data and real world safety data are needed to establish longer-term safety. *Covovax* also passed the benefit/risk profile assessment in the general population based on efficacy, and short term safety data.

Is Covovax affordable and feasible to use in a national immunization program for the general population?	The affordability of *Covovax* cannot be assessed due to lack of information on prices offered to ASEAN countries and on the allocated budget and indicative volumes for procurement of this vaccine from the Department of Finance (DOF). However, the computed cost per vaccinee using Covovax is within the range of the costs of vaccines in the National Government Procurement Portfolio.
Does Covovax reduce out-of-pocket (OOP) expenses of households due to COVID-19?	**Yes.** Based on current evidence, *Covovax* has the potential to reduce out-of-pocket expenses in the general population due to averted costs of isolation and treatment of mild, moderate, and severe COVID-19.
Does Covovax possess the characteristics that are desired by key stakeholders?	**Yes,** based on short-term outcomes, *Covovax* possesses most of the characteristics desired by key stakeholders for its use among the general population 18 years and above.
Does Covovax reduce or not further add to existing inequities in the health system?	**Yes,** because of its non-stringent logistic requirements, *Covovax* does not aggravate health inequities related to inoculation of recipients residing in isolated and disadvantaged locations. Trial evidence has demonstrated the safety and efficacy of *Covovax* among the vulnerable population such as older adults ≥65 years and individuals with comorbidities. However, the trial population did not include important vulnerable groups such as individuals with impaired immune systems, pregnant and lactating women, and healthcare workers. Further, there are no real world studies on the safety and effectiveness of *Covovax* among these vulnerable groups.

In the development of this recommendation, the HTA Council has appraised and considered the evidence review of the Philippine COVID-19 Living Clinical Practice Guidelines Group on the following sub-themes of evidence on COVID-19 vaccines:

- Effectiveness and safety to the general population
- Efficacy and effectiveness against variants of concern in the general population

The HTA Council further emphasizes the need to enforce strict conditions for the emergency use of health products to safeguard against eventualities:

- Transparency and accountability in the processes of allowing emergency use of health products, especially for the public health response;
- Continuous collection of safety and effectiveness data in the context of clinical trials and actual use in the real world;
- Close monitoring of recipients and safeguards for expected and unexpected adverse events that may arise from the use of health products under an EUA;
- National coordination of the emergency use under the Philippine FDA and the DOH;
- Cascading of complete information to vaccinees and healthcare providers on potential risks and benefits, and securing of informed consent with regard to receiving the intervention; and

Finally, the HTAC recommends the conduct of research to address the current gaps in evidence with regard to the use of the *Covovax*:

- Real-world effectiveness in the Philippine context particularly focused on the following knowledge gaps:
    - Effectiveness in reducing COVID-19 cases, hospitalizations and deaths, and preventing outbreaks and transmission of disease across the population
    - Effectiveness in reducing asymptomatic infection
    - Duration of protection
    - Impact of the timing and number of doses received
    - Probable need for booster dosing
    - Differences in the effectiveness of the vaccine among special populations (i.e., elderly, individuals with comorbidities, pregnant and lactating women, immunocompromised patients)
    - Effectiveness of the vaccine against emerging SARS-CoV-2 viral strains
- Continuous safety surveillance and monitoring of all adverse events especially severe allergic reactions, Bell's palsy, serious adverse events such as thrombosis thrombocytopenia syndrome (TTS), myocarditis and adverse events of special interest (AESI) following vaccination
    - Across the general population
    - In special populations: elderly, patients with comorbidities, pregnant and lactating women, immunocompromised individuals
- Randomized controlled trials should also be done among populations not currently included in clinical trials: children below 18 years of age
- Best practices, challenges, and barriers in implementation across different localities
- Monitoring of unexpected or additional costs associated with vaccine implementation.

Current Evidence on *NVX-CoV2373 COVID-19 Vaccine (Covovax)*

The table below summarizes the appraisal of available evidence on *Covovax* based on the HTAC evaluation framework.

In addition, the following appendices are provided for further details:

- Appendix 1: LCPG Report on Clinical Efficacy, Effectiveness and Safety
- Appendix 2: Risk of Bias Assessment by LCPG and HTAC
- Appendix 3: HTAC GRADE table

Table 1.2 Key Findings in the Current Evidence Considered for the HTAC Evaluation of *Covovax*

Evaluation Criteria	Question	Current Evidence	HTAC specification
CRITERION 1			
1. Responsiveness to magnitude and severity	*Can Covovax significantly reduce the magnitude and severity of COVID-19?*	**Responsiveness to the magnitude and severity of COVID 19 in the Philippines** As of 13 December 2021, the total number of cases has exceeded more than 269 million cases and breached the 5.3 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 2,836,803 cases with total deaths reported at 50,341 as of 13 December 2021. Based on the latest DOH-Epidemiology Bureau data (as of 05 November 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) who have the highest case fatality rate (CFR) at 6.94% and comprise around 62.36% of COVID-19 deaths. In addition, vulnerable individuals with existing comorbidities such as chronic kidney disease (CKD), liver disease, chronic obstructive pulmonary disease (COPD), obesity, other pulmonary, cardiovascular and cerebrovascular diseases have CFRs reported at around 75.35% to 94.90%. The DOH Philippines has also reported the detection of four variants of concern (i.e., Alpha, Beta, Gamma, and Delta), two variants of interest (i.e., Eta, Lambda), and one variant on alert for further monitoring (i.e., Theta) in the country. As of 03 October 2021, there were a total of 3,387 Delta (B.1.617.2) variant cases, 3,229 Beta (B.1.351) variant cases, 2,847 Alpha (B.1.1.7) variant cases, 3 Gamma (P.1) variant cases, 480 Theta (P.3) variant cases, and 1 Lambda (C.37) variant case detected out of the 15,652 samples sequenced. Meanwhile, as of 13 September 2021, there were 129, 95, 26 and 5 deaths reported for Alpha, Beta, Delta, and Theta variants cases, respectively. There were no reported deaths for the Gamma, Eta, and Lambda variants. For those infected with the Delta variant, 142 of these cases were unvaccinated, 33 were partially vaccinated, and 63 were fully vaccinated. The vaccination status of the remaining 1,035 cases of Delta variant are still for verification. For the other variants of concern and interest, verification is ongoing with respect to their vaccination status. 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. COVID-19 has led to significant disruptions not only in the delivery of other priority health services (e.g.,	The vaccine can potentially reduce the COVID-19 disease burden (health, social and economic impact). Trends in COVID-19 morbidity, mortality and hospitalization rates.

		immunization, maternal and child health, noncommunicable diseases) but also in the social and economic life of the nation by arresting the growth of the economy, displacing migrant and local workers, loss of jobs, and food insecurity (NEDA, 2020; PSA 2020; TESDA, 2020). Social safety nets for the poorest and other vulnerable sectors have not been enough to compensate for these losses (TESDA, 2020). The lockdowns and community quarantines have also been shown to have an impact on the mental health of Filipinos and have affected how common Filipino households adjust under the new normal, unable to visit and freely enjoy quality time with members of their families, as captured in some focus group discussions conducted by the HTAC and the HTA Unit. Locally-contextualized modelling studies are needed for more accurate projections of the potential impact of vaccination along with other interventions, under different scenarios. These can better inform decision-making. **HTAC Judgment**: *Covovax* has the potential to reduce the disease burden by averting a significant number of symptomatic infections including severe COVID-19 assuming sufficient vaccine coverage.	
CRITERION 2			
2. Clinical efficacy, effectiveness and safety	*What is the **efficacy and effectiveness** of Covovax in terms of: reducing incidence of: symptomatic and severe COVID-19, hospitalization due to COVID-19 and death due to COVID-19 in the general population and vulnerable populations (i.e., older adults aged 60 and above, with comorbidities)?*	For the evidence on efficacy, the following reviews on *Covovax* were considered: 1) Philippine Living Clinical Practice Guidelines Group (LCPG Group) review (updated as of 15 November 2021) 2) International Vaccine Access Center (IVAC) of the Johns Hopkins Bloomberg School of Public Health and World Health Organization review as of 12 November 2021; and 3) COVID-NMA living review as of 12 November 2021. Overall, there were 5 studies detected - three evaluated the efficacy while the other two evaluated the immunogenicity of *Covovax* which covered the general, elderly, and immunocompromised population. There were no studies included in the reference reviews that evaluated the efficacy of *Covovax* among healthcare workers. **Evidence from trials** ***Efficacy outcomes*** ***Description of evidence*** Overall, the reference reviews detected two Phase III randomized control trials (RCT) (Heath et al., 2021; Dunkle et al., 2021) and one Phase IIa/b RCT (Shinde et al. 2021) that reported efficacy outcomes for *Covovax*. Details of the trials are presented in Table 1.2.1 below. Table 1.2.1. Study characteristics of the Phase IIb and Phase III RCTs on *Covovax* (LCPG Group, 2021)	The vaccine achieves the following efficacy parameters: **Preferred VE: ≥70% reduction** in the risk of symptomatic infection with vaccination versus no vaccination **Minimum acceptable VE (point estimate): at least 60% reduction** of symptomatic COVID-19; **at least 80% reduction** of severe COVID-19,

Author Year Country Study Design	Population	Intervention	Control	Outcomes
Heath et al., 2021 United Kingdom Phase III RCT [published]	Adults 18-84 years old, healthy or with stable medical condition N=15,187	2 doses 5ug *Covovax*, 21 days apart	Placebo, 21 days apart	VE against symptomatic mild, moderate, or severe COVID-19, ≥7 days after dose 2 Follow-up: 98 days after dose 2
Dunkle et al., 2021 United States and Mexico Phase III RCT [preprint]	Adults ≥18 years old, healthy or with stable medical condition N=29,949	2 doses 5ug *Covovax*, 21 days apart	Placebo, 21 days apart	Preventing the first episode of RT-PCR confirmed symptomatic mild, moderate, severe COVID-19, ≥7 days after dose 2 Follow up (efficacy): 4 months Follow-up (safety): median 2 months
Shinde et al., 2021 South Africa Phase IIa/b RCT [published]	18-84 years healthy HIV-negative or HIV-positive participants who are medically stable Total population =4,387 Seronegative at baseline = 2,684 HIV-positive = 6% of 2,684	2 doses 5ug Covovax	Placebo, 21 days apart	VE against symptomatic COVID-19 ≥7 days after dose 2 Follow up (efficacy): 45 days after dose 2 Follow up (safety): 35 days after dose 1

Key findings

Risk of bias

The HTAC rated the risk of bias (*RoB)* of Heath et al. (2021) and Dunkle et al. (2021) as *not serious* for symptomatic COVID-19 more than 7 days after 2nd dose, symptomatic COVID-19 after the first dose, before the second dose, symptomatic COVID-19 in older adults (≥65 yo)and symptomatic COVID-19 in population with comorbidities. Meanwhile the HTAC rated severe COVID-19 to have *serious* RoB as

hospitalization due to COVID-19; **at least 80% reduction** of death due to COVID-19.

		this outcome requires a follow up longer than the minimum interim follow up period. Details on the RoB assessment of these studies are presented in Appendix 2. *Results of the trial on clinical efficacy* The results of the Heath et al., 2021 and Dunkle et al., 2021 studies reported the vaccine efficacy of *Covovax* for the critical and important outcomes presented below. Certainty of evidence was assessed using the GRADE approach by the HTAC. Details on the GRADE assessment are presented in Appendix 3. For critical outcomes: Using *Covovax* (at least 7 days after the second dose), compared to placebo, reduces the risk for: ● Symptomatic COVID-19 in participants who were SARS-CoV-2 negative at baseline ○ by 89.7% (95% CI 80.2 to 94.6), based on moderate certainty of evidence (Heath et al., 2021) ○ by 90.4% (95% CI 82.9 to 94.6), based on moderate certainty of evidence (Dunkle et al., 2021) As for its efficacy against severe COVID-19 (at least 7 days after the second dose): ● There were **zero events in the vaccine group** as reported by Heath et al. (2021) (N=7,020) and 5 events in the placebo group (N=7,019) [VE: 90.9% (-0.64, 100)], based on very low certainty of evidence. ● Similarly, there were **zero events in the vaccine group** in the study by Dunkle et al. (2021) (N=17,312) and 4 events in the placebo group (N=8,140) [VE: 100% (34.6, 100%)], based on very low certainty of evidence. Thus, protection against severe COVID-19 remains to be demonstrated. For important outcomes: Using *Covovax* (at least 7 days after dose 2), compared to placebo, reduces the risk for: ● Symptomatic COVID-19 infection after the first dose, before the second dose by 83.4% (95% CI 73.6 to 89.5), based on moderate certainty of evidence (Heath et al., 2021). ● Symptomatic COVID-19 infection in older adults (≥65 years) who were seronegative at baseline by 88.9% (95% CI: 20.2 to 99.7), based on moderate certainty of evidence (Heath et al., 2021). ● Symptomatic COVID-19 infection of adults with pre-existing medical conditions	

- by 90.9% (95% CI: 70.4 to 97.2), based on moderate certainty of evidence (Heath et al., 2021)
- by 90.8% (95% CI: 79.2 to 95.9), based on moderate certainty of evidence (Dunkle et al., 2021)

The Phase IIa/b trial (Shinde et al., 2021) reported a VE against symptomatic COVID-19 of 49.4% (95% CI: 6.1 to 72.8) for SARS-CoV-2 seronegative individuals, regardless of HIV status. For its efficacy against symptomatic COVID-19 in HIV-positive individuals, there were 4 events in 76 participants in the intervention group versus 2 events in 72 participants in the control group. Protection against symptomatic COVID-19 in HIV positive adults remains to be demonstrated. The trial had several limitations including its small sample size of 2,684 participants in the primary efficacy outcome analysis, only 6% of which were HIV positive participants. The study also had a short follow up period of 45 days after the second dose. Lastly, there was no information on the CD4 count of HIV-patients nor subgroup analysis by CD4 count.

Immunogenicity outcomes

Description of evidence

Overall, there were two RCTs detected examining the immunogenicity of *Covovax*. One study is a Phase II trial preprint included in the LCPG and COVID-NMA review (Formica et al., 2021), while the other study is a published Phase I/II RCT (Keech et al., 2021) on *Covovax* included in the LCPG and COVID-NMA living systematic review. Details of the trials are presented in Table 1.2.2 below.

Table 1.2.2. Study characteristics of the Phase I and II RCTs on *Covovax*

Author Year Country Study Design	Population	Intervention	Control	Outcomes
Formica et al., 2021 [preprint] United States Phase II Trial	Adults 18-84 years old, healthy or with stable medical condition (N=1288)	2 doses 5ug and 25ug Covovax	Placebo	Immunogenicity - Antispike IgG titers and seropositivity - Neutralizing antibodies
Keech et al., 2021 [published]	Healthy adults, 18-59 years old (N=133)	2 doses 5ug and 25ug Covovax	Placebo	Immunogenicity - Anti-spike titers

Australia Phase I/II Trial				at days 0,7,21,28 and 35 - Neutralizing antibodies

Key findings

Results of the immunogenicity trials

In the Phase II RCT (Formica et al., 2021), it was reported that the geometric mean titer increased 14 days after the second dose (day 35) compared to placebo across age groups. The older population (60 to 84 years old) had significantly lower immunogenic response compared to the younger population (18 to 59 years old). Nevertheless, high seroconversion rates were still achieved after two doses in the older population (60 to 84 years old), and the antibody titers in the sera of the vaccinated older population were still higher than the titers in the placebo arm. Table 1.2.3 below summarizes the results of the study.

Table 1.2.3. Geometric Mean Titers of Anti-Spike Protein Binding IgG Response reported from the Phase II trial on vaccination with *Covovax* (Formica et al., 2021)

	Overall (≥18 to 84 years old)			Younger population (18 to 59 years old)			Older population (60 to 84 years old)		
	5ug	25ug	Placebo	5ug	25ug	Placebo	5ug	25ug	Placebo
Geometric Mean titer (95% CI)	44,420.9 (37,929.1 to 52,023.8)	46,459.3 (40,839.4 to 52,852.5)	126.1 (114.0 to 139.4)	65,019.1(55,484.8 to 76191.9)	58,773.8 (51,611.7 to 66, 929.8)	123.9 (109.0 to 140.9)	28,136.6 (21,616.6 to 36,623.3	32,871.2 (26,189.5 to 41,257.5)	127.8 (109.2 to 149.6)
Geometric mean fold rise relative to baseline (95% CI)	385.6 (325.5 to 456.8)	384.9 (334.7 to 442.7)	1.0 (1.0 to 1.1)	538.6 (442.1 to 656.2)	464.7 (395.2 to 546.4)	1.1 (1.0 to 1.2)	257.7 (197.1 to 336.9)	286.3 (226.6 to 361.8)	1.0 (0.9 to 1.1)

Seroconversion rate (%) (95% CI)	98.3% (95.8 to 99.5)	99.6% (97.7 to 100.0)	1.3% (0.3 to 3.6)	99.2% (95.7 to 100.0)	100% (97.3 to 100)	1.5% (0.2 to 5.2)	97.4% (92.5 to 99.5)	99.0% (94.8 to 100.0)	0.9% (0.0 to 5.1)

In the Phase I/II RCT (Keech et al., 2021), it was seen that the geometric mean titers increase over time among the 4 groups of varying dosing of the intervention (Groups B,C,D,E) compared to placebo (Group A). Table 1.2.4 below summarizes the results of the study.

Table 1.2.4. Geometric Mean Titer IgG response reported from the Phase I/II on vaccination with *Covovax* (Keech et al., 2021)

	Keech et al., 2021 **Phase I/II** MNT_{99} [GMT (95 CI)]				
	Group A Placebo	**Group B 25-ug doses of Covovax**	**Group C 5-µg doses of rSARS-CoV-2 plus Matrix-M1**	**Group D 25-µg doses of rSARS-CoV-2 plus Matrix-M1**	**Group E single 25-µg dose of rSARS-CoV-2 plus Matrix-M1 followed by a single dose of placebo**
Day 0	108.5 (91.6 to 128.4)	115.6 (97.5 to 137.1)	113.6 (97.8 to 132.0)	114.3 (92.8 to 140.7)	104.9 (95.1 to 115.6)
Day 7	110.4 (89.9 to 135.7)	122.7 (100.5 to 149.8)	131.8 (107.6 to 161.4)	160.5 (113.0 to 227.8)	180.8 (122.0 to 267.8)
Day 21	109.7 (90.4 to 133.2)	189.2 (117.6 to 304.5)	1984.2 (1405.8 to 2800.7)	1 2625.9 (1579.4 to 4365.6)	3317.2 (2202.4 to 4996.2)
Day 28	110.6 (89.7 to 136.3)	206.9 (138.9 to 308.1)	15318.8 (9486.8 to 24736.0)	20429.2 (11974.4 to 34853.6)	3503.2 (2378.4 to 5160.1)

Day 35	113.5 (93.6 to 137.6)	575.5 (331.7 to 998.5)	63160.4 (47117.3 to 84666.0)	47521.0 (33803.7 to 66804.6)	2932.0 (1987.7 to 4324.8)

Evidence from real world studies

As the vaccine has just been recently approved by 2 NRAs, there were no real world studies detected by the LCPG for the clinical effectiveness and immunogenicity of *Covovax*.

HTAC Judgment: *Covovax* passed the HTAC-specified preferred vaccine efficacy threshold against symptomatic COVID-19 for the general population aged 18 years and older, including older adults and individuals with comorbidities based on one published Phase III trial (Heath et al., 2021). We note that one preprint Phase III trial (Dunkle et al., 2021) supplements the findings of the published Phase III trial.

*What is the **efficacy and effectiveness** of Covovax in terms of: reducing incidence of symptomatic and severe COVID-19, hospitalization due to COVID-19 and death due to COVID-19 **caused by variants** of concern in the general population and vulnerable populations (i.e., older adults aged 60 and below, with comorbidities)?*

For the evidence on efficacy and effectiveness against variants of concern, the following reviews on *Covovax* were considered: 1) Philippine Living Clinical Practice Guidelines Group (LCPG Group) review (updated as of 15 November 2021) 2) International Vaccine Access Center (IVAC) of the Johns Hopkins Bloomberg School of Public Health and World Health Organization review as of 12 November 2021; and 3) COVID-NMA living review as of 12 November 2021. Overall, there were 4 studies detected - 3 trials and 1 real world study - that evaluated the efficacy, effectiveness and immunogenicity of *Covovax* against variants of concern which covered the general, elderly, and immunocompromised population. There were no studies included in the reference reviews that evaluated the efficacy of *Covovax* against variants of concern among healthcare workers.

Evidence from trials

Efficacy outcomes

Description of evidence

Overall, the reference reviews detected two Phase III randomized control trials (RCT) on the efficacy of *Covovax* against the Alpha variant, and one Phase II RCT on the efficacy of *Covovax* against the Beta variant. The two Phase III RCTs (Heath et al. 2021; Dunkle et al. 2021) and one Phase IIa/b RCT (Shinde et al. 2021) have both been discussed in the efficacy and effectiveness subsection. Details of the trials are presented in Table 1.2.5 below.

Table 1.2.5. Randomized control trials on the efficacy of *Covovax* against variants of concern

Author Year	Study Duration	Population	Intervention	Comparator	Outcome

Preferred VE: ≥70% reduction in the risk of symptomatic infection with vaccination versus no vaccination

Minimum acceptable VE (point estimate): at least 60% reduction of symptomatic COVID-19; **at least 80% reduction** of severe COVID-19, hospitalization due to COVID-19; **at least 80% reduction** of death due to COVID-19

Country Study Design					
Heath et al., 2021 United Kingdom *Phase III RCT*	September 28, 2020 to November 28, 2020	Adults 18-84 years old, healthy or with stable medical condition N=15,187	2 doses 5ug Covovax	Placebo	Clinical efficacy against Alpha variant
Dunkle et al., 2021 [preprint] United States Mexico *Phase III RCT*	December 27, 2021 to April 19, 2021	Healthy adults N = 29,582	2 doses Covovax	Placebo	Clinical efficacy against Alpha variant
Shinde et al., 2021 South Africa Phase IIa/b RCT	August 17, 2020 to January 25, 2021	18-84 years healthy HIV-negative or HIV-positive participants who are medically stable N=4,387	2 doses 5ug Covovax	Placebo	Clinical efficacy against Beta variant

Key findings

Risk of bias

The HTAC rated the *RoB* of Heath et al. (2021) and Dunkle et al. (2021) as *not serious* for any COVID-19 Alpha variant infection.

Clinical Efficacy Results

The Heath et al., 2021 study found that vaccine efficacy of *Covovax* against symptomatic COVID-19 infection caused by Alpha variant with onset at least 7 days after dose 2 is at 86.3% (95% CI 71.3 to 93.5) upon post hoc analysis. On the other hand, one preprint of study (Dunkle et al., 2021) found vaccine efficacy of *Covovax* against COVID-19 infection caused by Alpha to be at 93.6% (95% CI 81.7 to 97.8). The results of both Phase III trials are based on moderate certainty of evidence. On the other

hand, Shinde et al., 2021 showed decreased efficacy against the Beta variant, with a vaccine efficacy of 43.0% (95 CI: -9.8 to 70.4).

Immunogenicity outcomes

Description of Evidence

The LCPG Group review detected one study (Shen et al., 2021) which evaluated the immunogenicity outcomes of *Covovax* against the Beta strain compared to the D614G reference strain. Details of the study are presented in Table 1.2.6 below.

Table 1.2.6. Study characteristics of the real world study on immunogenicity outcomes of *Covovax* against variants of concern (LCPG Group, 2021)

Author Year Country Study Design	Population	Intervention	Comparator	Outcome
Shen et al., 2021 United States *Comparative cohort* N=23	Randomly selected sera from convalescent persons and vaccine recipients from the Phase I/II trial	Covovax	Moderna	Immunogenicity against Beta vs reference strain D614G

Key Findings

Immunogenicity results

The Shen et al., 2021 study reveals a 6.8 to 14.5-fold reduction in antibody titers with the Beta strain compared to D614G. These results were derived from the sera of 23 *Covovax* recipients, taken 14 days after their second dose.

Evidence from Real World Studies

The LCPG Group review did not detect any real-world studies that examined the effectiveness of *Covovax* against VOC. This shall be updated once new clinical evidence has been reviewed.

HTAC Judgment: *Covovax* passed the HTAC-specified preferred vaccine efficacy threshold against symptomatic COVID-19 caused by the Alpha variant for the general population aged 18 years and older, based on one published Phase III trial (Heath et al., 2021). We note that one preprint Phase III trial (Dunkle et al.,

		2021) supplements the findings of the published Phase III trial. On the other hand, *Covovax* did not pass the preferred vaccine efficacy threshold against symptomatic COVID-19 caused by the Beta variant (Shinde et al., 2021). One immunogenicity study showed reduction in the neutralization activity against the Beta variant (Shen et al., 2021).	
	What is the duration of protection of the Covovax in terms of reducing the incidence of symptomatic and severe COVID-19, hospitalization due to COVID-19 and death due to COVID-19?	There were no studies included in the reference reviews that reported on the duration of protection of *Covovax* as the vaccine has just been recently approved by 2 NRAs; thus there were no real world studies measuring clinical outcomes at different time points as of publication of this review. Data on the duration of protection will be assessed as more evidence becomes available. **HTAC Judgment:** Cannot be assessed based on current data	Minimum acceptable duration of protection: confers at least 6 months protective immunity Preferred: ≥1-year protective immunity
	What is the safety of Covovax in terms of: serious adverse events, all-cause mortality systemic reactogenicity local reactogenicity special adverse events of interest (i.e. Bell's palsy, Myocarditis/Pericarditis, Thrombosis with Thrombocytopenia	For the evidence on safety, the following reviews on *Covovax* were considered: 1) Philippine Living Clinical Practice Guidelines Group (LCPG Group) review (updated as of 15 November 2021) 2) International Vaccine Access Center (IVAC) of the Johns Hopkins Bloomberg School of Public Health and World Health Organization review as of 12 November 2021; and 3) COVID-NMA living review as of 12 November 2021. Overall, they have detected four randomized control trials that evaluated the safety of *Covovax* which covered the general and elderly population. There were no studies included in the reference reviews that evaluated the safety of *Covovax* among healthcare workers and immunocompromised population. As there are only two countries which have approved *Covovax* (Indonesia and Philippines) which both approved it in November 2021, real world safety data are not yet available. ***Safety data from clinical trials*** ***Description of Evidence*** There were 4 RCTs - two Phase III (Heath et al, 2021; Dunkle et al, 2021); one Phase I/II (Keech et al,	Local and systemic reactions are tolerable, self-limiting and do not require hospitalization. No serious adverse events were caused by the vaccine. **Short term outcomes** (e.g., reactogenicity and allergic reactions, SAEI): at least 2 months

	Syndrome, Capillary Leak Syndrome, Immune Thrombocytopenia)	2021), and one Phase II (Formica et al, 2021) trial that were identified in the LCPG review. Of the four studies, two (Formica et al, 2021; Dunkle et al, 2021) were preprint articles. All of the four studies have been previously discussed in the section on the efficacy and effectiveness of *Covovax*. The studies are detailed in Table 1.2.7 below. Table 1.2.7. Characteristics of studies that reported on the safety of *Covovax* ***Key findings***	**Long term outcomes** (e.g., serious AEs, all-cause mortality, SAEI, Vaccine-associated enhanced disease): at least 1 year

Author Year Country Study Design	Population	Intervention	Control	Outcomes
Heath et al., 2021 UK Phase III RCT	18-84 years (N = 15,187) ≥65 years: 27.9% With comorbidities: 44.6%	NVX-CoV2372 5ug; 2 doses, 21 days apart	Placebo	Solicited and unsolicited local and systemic AE
Dunkle et al., 2021 USA and Mexico Phase III RCT	Healthy adults ≥18 years (N = 29,949) ≥65 years: 12.6%	NVX-CoV2372 5ug; 2 doses, 21 days apart	Placebo	Solicited local and systemic AEs up to 7 days, unsolicited AEs up to 28 days, SAEs, AESIs, MAAEs
Keech et al., 2021 Australia Phase I/II RCT	Healthy adults 18-59 years old (N = 133)	NVX-CoV2373, 5ug and 25 ug, with or without Matrix M1 adjuvant, 2 doses, 21 days apart	Placebo	Reactogenicity at 7 days Adverse events through day 35
Formica et al., 2021 Australia and USA Phase II RCT	18-84 years; with stable medical condition N= 1288 randomized	NVX-CoV2373, 5ug and 25 ug, with or without Matrix M1 adjuvant, 2 doses, 21 days apart	Placebo	Reactogenicity at 7 days Unsolicited AEs Serious AEs

Risk of bias

The HTAC rated the *RoB* of Heath et al. (2021) and Dunkle et al. (2021) as *not serious for* local, systemic, unsolicited, and severe adverse events. Meanwhile, the HTAC rated *serious RoB* for serious adverse events, and deaths.

Results of clinical safety

Short-term outcomes:

The LCPG group noted that solicited local and systemic adverse events were more frequent in the vaccine group versus placebo. Most reported solicited adverse events were mild to moderate grade and transient. The most common systemic AE were headache, myalgia, and fatigue while the most common local AE was injection site pain. Rates of reported AEs were higher in the younger age group compared to the older age group and after the second dose compared to the first dose. The relative risk of short-term safety outcomes are detailed in Table 1.2.8.

Long-term outcomes:

Rates of unsolicited adverse events were slightly higher in the vaccine group but the difference was not statistically significant. Serious adverse events, medically-attended adverse events, discontinuation and death rates were low and similar across the vaccine group and placebo group. One related serious adverse event (myocarditis) was reported in one vaccine recipient, which occurred 3 days after the second dose. The relative risks of long-term safety outcomes are detailed in Table 1.2.8.

Table 1.2.8. Reported safety outcomes in the Phase III RCTs (Heath et al., 2021, Dunkle et al., 2021)

	Covovax *(%participants who experienced the AE)*	**Placebo** *(%participants who experienced the AE)*	**Relative Risk** *(RR, 95% CI)*	**Certainty of Evidence (HTAC Appraisal)**
Short term outcomes				
Local reactogenicity	57.6% (D1)[a] 76.6% (D2)[a] 58.0% (D1)[b] 78.9% (D2)[b]	17.9% (D1)[a] 51.2% (D2)[a] 21.1% (D1)[b] 21.7% (D2)[b]	3.2 (2.8 to 3.7)[a] 1.5 (1.4 to 1.6)[a] 2.7 (2.6 to 2.9)[b] 3.6 (3.5 to 3.8)[b]	+++ Moderate (preprint study)[b]
Systemic reactogenicity	45.7% (D1)[a] 64.0% (D2) [a]	36.3% (D1)[a] 30.0% (D2)[a]	1.3 (1.1 to 1.4) (D1)[a] 2.1 (1.6 to 2.9) (D2)[a]	+++ Moderate

			47.66% (D1) [b] 69.47% (D2) [b]	40.00% (D1)[b] 35.87% (D2) [b]	1.19 (1.16 to 1.23)[b] 1.94 (1.88 to 2.0)[b]	(preprint study)[b]
		Unsolicited AEs (28 days)	25.3% [a] 21.79% [b]	20.5% [a] 18.21% [b]	1.2 (1.2 to 1.3)[a] 1.20 (1.14 to 1.26)[b]	+++ Moderate (preprint study)[b]
		Long term outcomes				
		Serious AE	0.5% [a] 1.16%[b]	0.5% [a] 1.30%[b]	1.0 (0.65 to 1.54)[a] 0.89 (0.72 to 1.10)[b]	+ Very Low (serious RoB, serious imprecision, preprint study)[b]
		Death	2/7569 (0.02%)[a]	1/7570 (0.01%)[a]	2.0 (0.18 to 22.1)[a]	++ Low (serious RoB, serious imprecision)

[a]Heath et al. (2021) [b]Dunkle et al. (2021)

Safety data from real world evidence

There were no studies included in the reference reviews that reported on the safety of *Covovax* as the vaccine has just been recently approved by 2 NRAs and thus there were no real world studies evaluating the safety of *Covovax* as of publication of this review. This shall be updated once post-authorization safety evidence is available.

HTAC Judgment: Short-term safety of *Covovax* is acceptable. Further follow-up data is needed to establish longer-term safety.

	Does Covovax provide a highly favorable benefit/risk profile in the context of observed vaccine effectiveness?	Trial evidence in the general population shows that the clinical benefits of *Covovax* in terms of decreased occurrence of symptomatic COVID-19 (Heath et al., 2021 & Dunkle et al., 2021) outweigh the known short-term risks. Two trials (Heath et al., 2021 & Dunkle et al., 2021) demonstrated that the vaccine also showed efficacy against the Alpha variant. Meanwhile, one study (Shinde et al., 2021) showed that *Covovax* did not pass the HTAC vaccine efficacy threshold against symptomatic COVID-19 caused by the Beta variant. **HTAC Judgment:** *Covovax* passed the benefit risk profile assessment in the general population based on	Favorable benefit/risk profile

		efficacy and short term safety data.	
CRITERION 3			
3. Affordability and viability	*Is Covovax affordable?*	Based on the prices reflected in the UNICEF COVID-19 Vaccine Market Dashboard, the price per dose of *Covovax* offered to the Philippine government is higher compared to the procurement cost of the COVAX Advance Market Commitment (AMC) but below the cost in Denmark, a high income country. There was no information on the price offered to other ASEAN countries or other lower-middle income countries. According to the DOF and DPCB, there are currently no ongoing negotiations for the procurement of *Covovax,* therefore, the target number of vaccinees (based on indicative volumes) using this vaccine cannot be determined at the moment. Thus, only the cost of implementation of *Covovax* per vaccinee can be computed. The unit cost of the vaccine used in the analysis was based on the latest price offered to the LGUs as disclosed in confidence by DOF. The additional cost of consumables and logistics were sourced from the DOH National Immunization Program. Meanwhile, the operations cost will not incur additional cost to the NIP anymore since COVID-19 vaccinations are now incorporated in the routine vaccination programs of the LGUs. Based on the costing calculations, the estimated total cost of the primary vaccination roll-out with *Covovax* per individual vaccinee is at **Php 1,082.77.** **HTAC Judgment:** Cannot be assessed due to lack of information on prices offered to ASEAN countries and on the allocated budget and indicative volumes for the vaccine from the Department of Finance (DOF). However, the computed cost per vaccinee is within the range of the cost of vaccines in the National Government Procurement Portfolio.	Affordability will be measured using the sufficiency of the allocated amount to achieve vaccination targets. **The vaccine unit cost is comparable with those in other ASEAN countries.* **The vaccine implementation cost is a reasonable and acceptable allocation of resources.*

	What are the budget implications of using the Covovax?	Due to the lack of information on the indicative volumes for *Covovax,* the potential budget impact to the national government of the use of this vaccine as primary homologous series and its proportionality to the target vaccinees cannot be determined. **HTAC Judgment:** Cannot be assessed due to lack of information on the indicative volumes for *Covovax* .	Proportionality of the size of the population to be vaccinated versus the cost. The share of the cost to implement the COVID-19 vaccine within the total vaccination budget is not too disproportionate to the share of the population to be vaccinated using the said vaccine in the total population to be vaccinated.
	Does Covovax represent good value for money in terms of preventing COVID-19 morbidity and mortality?	*Covovax* can potentially represent good value for money in terms of reducing the incidence of any symptomatic COVID-19 in the general population aged 18 years and older, including older adults aged ≥65 years and individuals with comorbidities. **HTAC Judgment:** HTAC deems that *Covovax* has potential to represent good value for money based on its ability to avert health and socioeconomic costs due to COVID-19.	The HTAC deems that the health, economic, and social benefits of the vaccination program outweigh the costs. The vaccine is a cost-effective/ efficient allocation of resources.
CRITERION 4			

<table>
<tr>
<td>4. Household Financial Impact</td>
<td>Will Covovax reduce or not add further to the out-of-pocket expenses of Filipino households?</td>
<td>As mandated by Philhealth Circular 2021-0014 and Philhealth Circular 2020-0009, the following benefit packages with corresponding case rates related to COVID-19 are available for the general population:
1. Isolation Package for asymptomatic and mild cases (C19CI): Case rate = Php 22,499.00
2. Mild COVID-19 pneumonia for elderly and with comorbidities (C19IP1): Case rate= Php 43,997.00
3. Moderate COVID-19 pneumonia (C19IP2): Case rate= Php 143, 267.00
4. Severe COVID-19 pneumonia (C19IP3): Case rate= Php 333,519.00
5. Critical COVID-19 pneumonia (C19IP4): Case rate= Php 786,384.00

Based on Philhealth data, there were a total of 12,164 hospitalization claims from April 15, 2020 to August 10, 2021 for the general population aged 15-59 years old. Table 1.2.9 below summarizes the cost of COVID-19 illness (inferred from total hospital bill) and out-of-pocket-expenses incurred by patients belonging to the general population at different levels of severity. The mean financial coverage ranged from 61.90% to 80.12%. Financial coverage was seen to increase with severity of the COVID-19 disease.

Table 1.2.9. Philhealth data on COVID-19 Hospitalization Costs and Claims
<table>
<tr><th rowspan="2">Severity
[Benefit package]</th><th rowspan="2">Total Number of Paid Claims</th><th colspan="2">Total Hospital Bill</th><th rowspan="2">Out-of-Pocket Payment (Median)
[PHP]</th><th rowspan="2">Average % Coverage
[proportion of financial coverage out of the total bill]</th></tr>
<tr><th>Range of Hospitalization Cost
[PHP]</th><th>Median Hospitalization Cost
[PHP]</th></tr>
<tr><td>Mild COVID-19
[C19IP1]</td><td>1,688</td><td>₱0 to ₱1,751,629.51</td><td>₱74,988.62</td><td>₱30,991.62</td><td>61.90%</td></tr>
<tr><td>Moderate COVID-19
[C19IP2]</td><td>7,488</td><td>₱0 to ₱326,482,781.10</td><td>₱206,294.29</td><td>₱63,027.29</td><td>70.16%</td></tr>
<tr><td>Severe COVID-19
[C19IP3]</td><td>2,226</td><td>₱0 to ₱5,404,430.74</td><td>₱399,404.39</td><td>₱65,885.39</td><td>76.31%</td></tr>
<tr><td>Critical COVID-19
[C19IP4]</td><td>762</td><td>₱0 to ₱6,574,031.60</td><td>₱850,472.44</td><td>₱64,088.44</td><td>80.12%</td></tr>
</table>
Meanwhile, there were a total of 15,119 community isolation claims recorded by PhilHealth from 2020 to</td>
<td>The adoption of the vaccine can reduce out-of-pocket spending of individuals and families due to averted COVID-19 disease and/or hospitalization.</td>
</tr>
</table>

		August 2021 for asymptomatic and mild cases, however, there was no data on age indicated in the Philhealth data. The median cost of COVID-19 isolation recorded was Php 22,449.00, while the median claims cost was also at PHP 22,449.00. Therefore, the median out-of-pocket-expenses for community isolation is at Php 0.00 and the median financial coverage is at 100%. **HTAC Judgment**: Based on current evidence, *Covovax* has the potential to reduce out-of-pocket expenses in the general population due to averted costs of isolation and treatment of mild, moderate, and severe COVID-19.	
CRITERION 5			
5. Social Impact	*Does Covovax possess the characteristics desired by key stakeholders (i.e., policy- and decision makers, health workers, program managers and/or implementers, patient groups, CSOs, communities, general public)?* ● *Safety* ● *Efficacy* ● *Transparency in the regulatory/approval process and information on the vaccines* ● *Availability*	Based on the results of the focus group discussions conducted by the HTAC among *healthcare workers, patient groups, civil society organizations and community leaders* from low- and high-prevalence areas, the results from the deliberations in congressional inquiries on the COVID-19 vaccination roadmap, public hearings, and consultations with government decision-makers and implementers, the following are the **important and desirable attributes of COVID-19 vaccines** and the corresponding evidences for the *Covovax.* 1) **Safe and efficacious** for the general population (aged 18 years and older) and for some vulnerable groups like the older population and individuals with comorbidities. - Evidence: *General population* *Covovax* is effective in preventing symptomatic COVID-19 in the general population 18 years and above, including individuals ≥ 65 years old and those with comorbidities based on one published Phase III trial (Heath et al., 2021). Additionally, based on the same published trial evidence, *Covovax* has demonstrated protection against symptomatic COVID-19 caused by the Alpha variant. We note that one preprint Phase III trial (Dunkle et al., 2021) supplements the findings of the published Phase III trial. Meanwhile, one study (Shinde et al. 2021) showed that *Covovax* did not pass the HTAC threshold against symptomatic COVID-19 caused by the Beta variant. Shinde et al. 2021 inconclusive vaccine efficacy for symptomatic COVID-19 in the HIV-positive population. Based on trial evidence, short-term safety of *Covovax* among individuals 18 years and older is acceptable. Further follow-up data and real world safety data are needed to establish longer-term safety. 2) Underwent a **transparent regulatory process** of being evaluated and approved by health authorities - Evidence: *Covovax* underwent the usual regulatory process of the FDA Philippines. The Philippine FDA issued an EUA for the vaccine on 17 November 2021 for its use among 18 years old and above.	The vaccine possesses all or most of the characteristics desired by key stakeholders Qualitative responses will contextualize the Filipino experience and may impact on implementation strategy

	● *Potential for high and equitable coverage* ● *Ease in logistical and implementation requirements* ● *Cost-efficiency to the government* ● *Public acceptability* ● *Availability of mechanisms to compensate vaccine recipients for any untoward event following vaccination* ● *Appropriateness of the vaccine to special at-risk groups and patients with comorbidities*	3) **Potential for high and equitable coverage across the population** - Evidence: *Covovax* can be made more available since vaccine handling and storage are within the capacity of the RHUs. 4) **Ease in logistics and administration** - Evidence: *Covovax* can be stored at 2 to 8 degrees Celsius which is present in most RHUs. 5) **Cost-effective** - Evidence: The health, economic, and social benefits of using *Covovax* mitigate the negative impact of COVID-19, such as deaths, medical costs, loss of productivity, social disruption, and unprecedented challenges in the health system. However, the budget implications of *Covovax* cannot be assessed at the moment due to lack of information on the indicative volumes for *Covovax*. 6) **Public acceptability** - Evidence: a. Based on a national survey conducted by Pulse Asia Research Inc. from June 7 to 16, 2021 among 2,400 Filipino adults 18 years and older: - Willingness to receive any available COVID-19 vaccine increased from 16% in February 2021 to 43% in June 2021. - Across geographic areas and socio-economic groups, 'concern about vaccine safety' remains as the most cited reason for being disinclined to get the vaccine or undecided regarding vaccination. Other reasons for vaccine hesitancy include: concerns about efficacy, the belief that vaccines are not needed to combat COVID-19, and concerns about the vaccine not being free and expensive. b. Based on the survey conducted by the DSWD from May 24 to June 4, 2021 among 349 beneficiaries of the Pantawid Pamilyang Pilipino Program (4Ps) and 378 city/municipal links (C/ML): - Only 41% of 4Ps beneficiaries were willing to receive a COVID-19 vaccine, 37.2% were undecided, while 21.8% were unwilling. The most common reasons behind unreceptiveness to receive a COVID-19 vaccine were pre-existing conditions, perception that the vaccine development was rushed, and concern on side effects. - 69% of C/ML respondents were willing to receive a COVID-19 vaccine while 20.9% were undecided and 10.1% who were unwilling. Reasons behind unreceptiveness to take a COVID-19	

		vaccine include having pre-existing conditions and the perception that the vaccine development was rushed. - In both groups, unwillingness was addressed through availability of information and accounts of effects and experiences of those who have already been vaccinated. c. Based on a national survey conducted by the Social Weather Station from June 23 to 26, 2021 among 1,200 Filipino adults 18 years and older: - The proportion of surveyed Filipinos who are willing to be vaccinated increased from 32% in May 2021 to 45% in the latest SWS survey (June 2021). - In the same survey, willingness to get vaccinated increased in all areas compared to results in May 2021. The proportion of willing respondents increased from 41% to 49%, 28% to 46%, 32% to 41%, and 34% to 42% in Metro Manila, Balance Luzon, Visayas, and Mindanao, respectively. The proportion of those uncertain and unwilling also decreased in all geographical areas, when compared to results in May 2021. - Willingness to be vaccinated among elementary, junior high school, and college graduates also increased since the survey in May 2021. Among elementary graduates, those willing to get a COVID-19 vaccine increased from 25% to 41% while among junior high school graduates, willingness increased from 34% to 49%. Among college graduates, those willing to get a COVID-19 vaccine increased from 50% to 53%. Meanwhile, willingness to be vaccinated decreased in non-elementary graduates from 25% in May 2021 to 23% in June 2021. d. Based on the national survey conducted by the Social Weather Station from 28 April to 02 May 2021 among 1,200 Filipino adults: - 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: Evidence: Republic Act 11525 or the COVID-19 Vaccination Program Act of 2021 establishes the COVID-19 National Vaccine Indemnity Fund to provide funds and authorize PhilHealth to pay	

		compensation to any person inoculated through the vaccination program, in the case of death and permanent disability. In response to RA 11525, PhilHealth released PhilHealth Circular No. 2021-0007 last 17 June 2021. The circular, otherwise known as the "Implementing Guidelines on the Coverage of COVID-19 Vaccine Injury due to Serious Adverse Effects (SAEs) following immunization resulting in hospitalization, permanent disability or death under the COVID-19 National Vaccine Indemnity Fund (The COVID-19 Vaccine Injury Compensation Package), aims to provide coverage for cases of hospital confinement, permanent disability, or death due to SAEs from the use of COVID-19 vaccines administered through the COVID-19 vaccination program.
		
		8) Appropriateness of the vaccine to special at-risk groups and patients with comorbidities
		- Evidence: The interim results from the two Phase III clinical trials (Heath et al., 2021; Dunkle et al., 2021) enrolled individuals 18 years and above. The current evidence for special populations allow it to be used for the following special at-risk groups:
		  - VE against symptomatic COVID-19 in older population ≥65 years:
		  - Heath et al. (2021) [27% of participants]: **88.9% (95% CI: 20.2 to 99.7)**
		  - Dunkle et al. (2021) [11.8% of participants]: VE among older adults ≥65 years **cannot be estimated** as there were only four cases of COVID-19 at the time of data cutoff.
		  - VE against symptomatic COVID-19 in patients with comorbidities
		  - Heath et al. (2021) [44.6% of participants]: **90.9% (95% CI: 70.4 to 97.2)**
		  - Dunkle et al. (2021) [47.3% of participants]: **90.8% (95% CI: 79.2 to 95.9)**
		  - VE against symptomatic COVID-19 among HIV-positive adults (Shinde et al., 2021)
		  - 4 events of symptomatic COVID-19 in 76 participants in the intervention group versus 2 events in 72 participants in the control group
		  - Protection against symptomatic COVID-19 in HIV positive adults remains to be demonstrated.
		
		Currently, there is limited data from the trial on the use of the vaccine for pregnant and lactating women, children below 18 years old, persons living with HIV, immunocompromised individuals, and persons who have previously received antibody therapy for the treatment of COVID-19. Further, the WHO is yet to release their recommendation on the use of *Covovax* in these special populations.
		
		HTAC Judgment: Based on short-term outcomes, *Covovax* possesses most of the characteristics desired by key stakeholders for its use among the general population 18 years and above, and among patients with comorbidities.	

CRITERION 6			
6. Responsiveness to equity	*How will Covovax and its use impact pre-COVID-19 and COVID-generated health and socioeconomic inequities?* *Which groups might be unfairly disadvantaged in relation to the COVID-19 disease burden and delivery of Covovax?*	Based on one published Phase III RCT (Heath et al., 2021), *Covovax* demonstrated an efficacy against symptomatic COVID-19 of **88.9% (95% CI 20.2 to 99.7)** in older adults ≥ 65 years, and an efficacy of **90.8% (95% CI: 79.2 to 95.9)** to **90.9% (95% CI: 70.4 to 97.2)** in individuals with comorbidities. We note that one preprint Phase III trial (Dunkle et al., 2021) supplements the findings of the published Phase III trial for its efficacy against symptomatic COVID-19 among individuals with comorbidities. Meanwhile, the efficacy of *Covovax* against symptomatic COVID-19 among HIV-positive adults was evaluated in one Phase IIa/b RCT (Shinde et al. 2021). There were 4 events of symptomatic COVID-19 in 76 participants in the intervention group versus 2 events in 72 participants in the control group. Protection against symptomatic COVID-19 in HIV positive adults remains to be demonstrated. There were no studies included in the reference reviews that evaluated the efficacy of *Covovax* among healthcare workers. 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**.** *Covovax* can be stored at normal cold storage conditions (2 to 8°C). This will make vaccine distribution more logistically feasible which in turn does not aggravate inequities for patients living in geographically isolated and disadvantaged areas. **HTAC Judgment:** Because of non-stringent logistic requirements, *Covovax* will not aggravate health inequities related to inoculation of recipients residing in isolated and disadvantaged locations. Based on trial evidence, *Covovax* may be used for older adults ≥65 years and persons with comorbidities as trial evidence has demonstrated its safety and efficacy among these vulnerable groups. Protection provided by *Covovax* against symptomatic COVID-19 for HIV-positive individuals remains to be demonstrated. However, the trial population did not include important vulnerable groups such as individuals with impaired immune systems, pregnant, lactating women, and healthcare workers. Currently, there are no real world studies reporting clinical outcomes of *Covovax* as the vaccine has just been recently approved by 2 NRAs. Hence, the effectiveness and safety of *Covovax* among these vulnerable groups in the real world setting cannot be evaluated.	Ideally, health interventions can be fairly adopted and distributed/ implemented for eligible populations without aggravating existing health inequities especially for vulnerable sectors of our society.

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- National Clinical Practice Guidelines Group (NCPG Group)
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Appendix 1: LCPG Report on Clinical Efficacy, Effectiveness, and Safety

https://docs.google.com/document/d/1yaDY3V5a-4oMAaRuW7fjxHhVN0tf8GIe/edit?usp=sharing&ouid=109297663583909516719&rtpof=true&sd=true

Appendix 2a: Risk of Bias Assessment (LCPG Group, 2021)

Table A1.1. Risk of Bias Assessment of Included Studies

Study ID	Design	Randomization	Allocation Concealment	Blinding Particip	Blinding Carer/ Assessor	Followup	Selective Reporting	Others	Age	Comorbidities	Exposure	Confounding	OVERALL
Formica	RCT	LOW	LOW	LOW	LOW	LOW	LOW	NA	NA	NA	NA	NA	LOW
Keech	RCT	LOW	LOW	LOW	LOW	LOW	LOW	NA	NA	NA	NA	NA	LOW
Shinde	RCT	LOW	LOW	LOW	LOW	HIGH [b]	UNCLEAR	NA	NA	NA	NA	NA	LOW
Shen	Comparative cohort, immuno	HIGH	HIGH	UNCLEAR	UNCLEAR	LOW	UNCLEAR	NA	HIGH	HIGH	HIGH	HIGH	HIGH

a - interim report b - interim report, safety data not reported for all

Appendix 2b: Risk of Bias Assessment (HTAC, 2021)

Study ID	Design	Randomization	Allocation Concealment	Blinding Particip	Blinding Carer/ Assessor	Followup	Selective Reporting	Others	Age	Comorbidities	Exposure	Confounding	OVERALL
Heath	RCT	LOW	LOW	UNCLEAR	LOW	LOW	LOW	NA	NA	NA	NA	NA	LOW
Dunkle	RCT	LOW	LOW	LOW	LOW	LOW	LOW	NA	NA	NA	NA	NA	LOW

Appendix 3: GRADE Table (HTAC)

Table A1.2. Summary of Findings Table for the Efficacy of NVX-CoV2373

Efficacy Outcome (at ≥7 days after dose2)	N Study design	Quality Assessment					Summary of Findings			Certainty
		Risk of Bias	Inconsistency	Indirectness	Imprecision	Other considerations	Vaccine n/N (%)	Control n/N (%)	Vaccine Efficacy (CI)	
1: Symptomatic COVID-19 infection, seronegative at baseline	2 RCT	**Not serious**	**Not serious**	**Not serious**	**Not serious**	**Serious** *Dunkle et al., 2021 is a preprint and Covovax has no WHO EUL*	10/7020 (0.1%)[a] 14/17312 (0.08%)[b]	96/7019 (1.4%)[a] 63/8140 (0.78%)[b]	89.7% (80.2, 94.6)[a] 90.4% (82.9, 94.6)[b]	**+++ Moderate**
2 : Severe COVID-19 infection,	2 RCT	**Serious** *(short ffup)*	**Not serious**	**Not serious**	**Serious** *wide CI [a,b] and crosses the null value [a]*	**Serious** *Dunkle et al., 2021 is a preprint and Covovax has no WHO EUL*	0/7020 (0%)[a] 0/17312(0%)[b]	5/7019 (.07%)[a] 4/8140(4.2%)[b]	90.9% (-0.64, 100)[a] 100% (34.6, 100%)[b]	**+ Very Low**
3. Symptomatic COVID-19 infection after first dose, before the second dose	1 RCT	**Not Serious**	**Not assessed**	**Not serious**	**Not serious**	**Serious** *Lack of reporting per arm/ selective reporting*	not reported	not reported	83.4% (73.6, 89.5)[a]	**+++ Moderate**
4. Symptomatic COVID-19 infection, older adults (>=65yo), seronegative at baseline	1 RCT	**Not Serious**	**Not assessed**	**Not serious**	**Serious**	**None**	1/1953 (0.05%)[a]	9/1957 (0.5%)[a]	88.9 (20.2, 99.7)[a]	**+++ Moderate**
5. Symptomatic COVID-19 infection, with pre-existing medical condition	2 RCT	**Not Serious**	**Not serious**	**Not serious**	**Not serious**	**Serious** *Dunkle et al., 2021 is a preprint and Covovax has no WHO EUL*	3/3117 (0.09%)[a] 7/8109 (0.08%)[b]	33/3143 (1.0%)[a] 34/3910 (0.9%)[b]	90.9 (70.4, 97.2)[a] 90.8 (79.2, 95.9)[b]	**+++ Moderate**
6. Any COVID-19 infection, B.1.1.7/Alpha variant	2 RCTs	**Not Serious**	**Not assessed**	**Not serious**	**Not serious**	**Serious** *Dunkle et al., 2021 is a preprint and Covovax has no WHO EUL*	8/7020 (0.1%)[a] 4/17312 (0.02%)[b]	58/7020 (0.8%)[a] 27/8140 (0.33%)	86.3 (71.3, 93.5)[a] 93.6% (81.7, 97.8)[b]	**+++ Moderate**

a – Heath b - Dunkle

Table A1.3. Summary of Findings Table for the Safety of NVX-CoV2373

Safety Outcome	N Study design	Quality Assessment					Summary of Findings			Certainty
		Risk of Bias	Inconsistency	Indirectness	Imprecision	Other considerations	Vaccine	Control	Relative Risk (95%CI)	
1: Local adverse reaction	2 RCT	**Not serious**	**Not assessed**	**Not serious**	**Not serious**	**Serious** *Dunkle et al., 2021 is a preprint and Covovax has no WHO EUL*	57.6% (D1)[a] 76.6% (D2)[a] 58.0% (D1)[b] 78.9% (D2)[b]	17.9% (D1)[a] 51.2% (D2)[a] 21.1% (D1)[b] 21.7% (D2)[b]	3.2 (2.8, 3.7)[a] 1.5 (1.4, 1.6)[a] 2.7 (2.6 to 2.9)[b] 3.6 (3.5 to 3.8)[b]	**+++ Moderate**
2: Systemic adverse reaction	2 RCT	**Not serious**	**Not serious**	**Not serious**	**Not serious**	**Serious** *Dunkle et al., 2021 is a preprint and Covovax has no WHO EUL*	45.7% (D1)[a] 64.0% (D2) [a] 47.66% (D1)[b] 69.47% (D2) [b]	36.3% (D1)[a] 30.0% (D2)[a] 40.00% (D1)[b] 35.87% (D2) [b]	1.3 (1,1, 1.4)[a] 2.1 (1.6, 2.9)[a] 1.19 (1.16 to 1.23)[b] 1.94 (1.88 to 2.0) [b]	**+++ Moderate**
3. Unsolicited adverse event (28d)	2 RCT	**Not serious**	**Not serious**	**Not serious**	**Not serious**	**Serious** *Dunkle et al., 2021 is a preprint and Covovax has no WHO EUL*	25.3% [a] 21.79% [b]	20.5% [a] 18.21% [b]	1.2 (1.2, 1.3)[a] 1.20 (1.14 to 1.26)[b]	**+++ Moderate**
4. Severe adverse event	1 RCT	**Not Serious**	**Not serious**	**Not serious**	**Serious** *(wide CI)*	**None**	1.0%[a]	0.8%[a]	1.2 (0.85, 1.65)[a]	**+++ Moderate**
5: Serious adverse event	2 RCT	**Serious** *(short ffup)*	**Not serious**	**Not serious**	**Serious** *(wide CI)*	**Serious** *Dunkle et al., 2021 is a preprint and Covovax has no WHO EUL*	0.5% [a] 1.16%[b]	0.5% [a] 1.30%[b]	1.0 (0.65,1.54)[a] 0.89 (0.72 to 1.10)[b]	**+ Very Low**
6: Death	1 RCT	**Serious** *(short ffup)*	**Not assessed**	**Not serious**	**Serious** *(wide CI)*	**None**	0.02%[a]	0.01%[a]	2.0 (0.18, 22.1)[a]	**++ Low**

a – Heath b – Dunkle