Evidence Summary on COVID-19 Vaccine *Sinopharm* for the prevention of COVID-19

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Background

Background

On 10 September 2021, the Philippine Food and Drug Administration (FDA) released the Emergency Use Authorization (EUA) for *COVID-19 Vaccine Sinopharm (Beijing)* to the Philippine Department of Health. The FDA has also released an EUA for *COVID-19 Vaccine Sinopharm (Wuhan)* on 17 August 2021 and *COVID-19 Vaccine Sinopharm (Hayat-Vax)* on 07 October 2021. According to the Philippine FDA (05 November 2021), the vaccine technology, active ingredient and formulation of these three Sinopharm vaccines are identical. The differences of these applications were only on manufacturing site, stability studies, and summary lot protocol and packaging details. Of the three products of *COVID-19 Vaccine Sinopharm* with an EUA from the Philippine FDA, only *COVID-19 Vaccine Sinopharm (Beijing)* was included in the World Health Organization Emergency Use Listing (WHO-EUL) on 07 May 2021.

To date, *Sinopharm (Beijing)* has been given an EUA for the adult population in 68 countries, while *Sinopharm (Wuhan)* has been given an EUA in only two countries - China and the Philippines. Basic information on *Sinopharm* is provided below:

Table 1.1 Characteristics of *Sinopharm*

	Sinopharm (Beijing) **(HB02 strain)**	***Sinopharm (Wuhan)*** **(WIV04 strain)**	***Sinopharm (Hayat-Vax)*** **(HB02 strain)**
Trade name	COVID-19 Vaccine (Vero Cell), Inactivated	COVID-19 Vaccine (Vero Cell), Inactivated	SARS-CoV-2 Vaccine (Vero Cell), Inactivated
Other name	COVID-19 Vaccine Sinopharm	COVID-19 Vaccine Sinopharm (Wuhan)	COVID-19 Vaccine (Vero Cell), Inactivated [Hayat-Vax] (Vial)
Manufacturer/s	Sinopharm/China National Pharmaceutical Group/ Beijing Institute of Biological Products (BIBP) Co., Ltd.	Sinopharm/China National Pharmaceutical Group/ Wuhan Institute of Biological Products Co., Ltd	G42 Pharmaceutical Manufacturing LLC [Abu Dhabi; UAE]
Vaccine platform	Inactivated COVID-19 Vaccine (Vero Cell)	Inactivated COVID-19 Vaccine (Vero Cell)	Inactivated COVID-19 Vaccine (Vero Cell)
Dose strength and administration	2 doses, 0.5 mL each, 21-28 days apart	2 doses, 0.5 mL each, 21-28 days apart	2 doses, 0.5mL each, 21 to 28 days apart
Route of administration	Intramuscular (IM)	Intramuscular (IM)	Intramuscular (IM)
Drug delivery system	Suspension for injection	Suspension for injection	Suspension for injection
Storage condition	Storage temperature: 2° to 8 °C	Storage temperature: 2° to 8 °C	Storage temperature: 2° to 8 °C

	Shelf-life: 6 months	Shelf-life: 6 months	Shelf-life: 6 months
Mechanism of action	The antibodies against the SARS-CoV-2 can be produced after vaccination, to prevent the COVID-19 disease caused by the SARS-CoV-2 virus.	The antibodies against the SARS-CoV-2 can be produced after vaccination, to prevent the COVID-19 disease caused by the SARS-CoV-2 virus.	The antibodies against the SARS-CoV-2 can be produced after vaccination, to prevent the COVID-19 disease caused by the SARS-CoV-2 virus.
Contraindications	1) Individuals who are allergic to any component (including excipients) of this product 2) Individuals who have had allergic reactions to vaccines before (acute allergic reaction, angioneurotic edema, dyspnea, etc.) 3) Individuals with uncontrolled epilepsy or other progressive nervous system diseases, and with a history of Guillain Barre Syndrome.	1) Individuals who are allergic to any component (including excipients) of this product 2) Individuals who have had allergic reactions to vaccines before (acute allergic reaction, angioneurotic edema, dyspnea, etc.) 3) Individuals with uncontrolled epilepsy or other progressive nervous system diseases, and with a history of Guillain Barre Syndrome.	1) Individuals who are allergic to any component (including excipients) of this product 2) Individuals who have had allergic reactions to vaccines before (acute allergic reaction, angioneurotic edema, dyspnea, etc.) 3) Individuals with uncontrolled epilepsy or other progressive nervous system diseases, and with a history of Guillain Barre Syndrome.
PHL EUA status	Released as of 10 September 2021 https://www.fda.gov.ph/wp-content/uploads/2021/09/EUA-DOH-procured-Sinopharm-Website.pdf	Released as of 19 August 2021 https://www.fda.gov.ph/wp-content/uploads/2021/08/EUA-Sinopharm-2-World-Traders-Website.pdf	Released as of 07 October 2021 https://www.fda.gov.ph/wp-content/uploads/2021/10/EUA-Sinopharm-Hayat-Vax-Website.pdf
PHL FDA EUA indication	For active immunization for the prevention of COVID-19 caused by SARS-CoV-2 in individuals 18 years old and above	For active immunization for the prevention of COVID-19 caused by SARS-CoV-2 in individuals 18 years old and above	For active immunization for the prevention of COVID-19 caused by SARS-CoV-2 in individuals 18 years old and above
WHO EUL status	EUL listed as of 07 May 2021 https://www.who.int/publications/i/item/WHO-2019-nCoV-vaccines-SAGE_recommendation-BIBP-2021.1	Ongoing assessment as of 11 November 2021	Not in the EUL as of 29 October 2021

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 ***Sinopharm* as primary homologous vaccination** in the 2022 COVID-19 Vaccination Program to reduce COVID-19 cases, severe infection, and deaths?

Recommendations *(as of 29 November 2021)*

The HTAC recommends the inclusion of *Sinopharm* in the Philippine National Deployment and Vaccination Plan for COVID-19 Vaccines for the general population aged 18 years and above, given that it has passed the safety, efficacy and other criteria of HTAC and 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:

Criterion	HTAC Judgment
Can Sinopharm significantly reduce the magnitude and severity of COVID-19 in the general population?	**Yes**. *Sinopharm* has the potential to reduce the disease burden by averting a significant number of symptomatic infections assuming sufficient vaccine coverage.
Is Sinopharm safe and efficacious for the general population?	**Yes,** it is efficacious for preventing symptomatic COVID-19 and any infection (including asymptomatic cases) in the general population aged 18 years and above, based on high certainty of evidence. It is likely that *Sinopharm* also provides protection against severe COVID-19, based on low certainty of evidence (Al Kaabi et al., 2021). *Sinopharm* has demonstrated low rates of breakthrough infection and protection against severe COVID-19, hospitalization and death due to COVID-19 among the general population (Al Hosani et al., 2021; Badano et al., 2021; Jahromi et al. 2021). Currently, there is no data on the efficacy or effectiveness of *Sinopharm* against variants of concern. **Yes**, the safety profile of *Sinopharm* is acceptable based on short-period follow-up (moderate to high certainty of evidence). However, further follow-up data is needed to establish the longer-term safety profile. Real world studies and safety reports also showed an acceptable safety profile of *Sinopharm.*
Is Sinopharm affordable and feasible to use in a national immunization program for the general population?	**Yes,** it is affordable. The share of the cost to implement vaccination using *Sinopharm* will constitute 0.86% of the total allocated budget for vaccination (Php 711 M of the Php82.5 B total budget) and will cover 0.52% of the 97 million target vaccinees for primary homologous vaccination. **Yes**, it is feasible as there are no significant challenges in vaccine implementation using *Sinopharm* in terms of storage, transport, and handling.
Does Sinopharm reduce out-of-pocket (OOP) expenses of households due to COVID-19?	**Yes.** Based on current evidence, Sinopharm 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 Sinopharm possess the characteristics that are	**Yes.** Based on short-term outcomes, Sinopharm possesses most of the characteristics desired by key

desired by key stakeholders?	stakeholders for its use among the general population 18 years and above.
Does Sinopharm reduce or not further add to existing inequities in the health system?	**Yes**. Because of non-stringent logistic requirements, Sinopharm will not aggravate health inequities related to inoculation of recipients residing in isolated and disadvantaged locations. However, there is currently limited evidence on the efficacy and effectiveness of *Sinopharm* as a primary vaccine in special populations such as the older population and individuals with comorbidities.

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; and
- 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.

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

- 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 other 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 *Sinopharm*

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

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

- Appendix 1: Review on Sinopharm by the Philippine Living Clinical Practice Guidelines Group
- Appendix 2: Risk of Bias Assessment Method (LCPG Group)
- Appendix 3: GRADE Table (HTAC Appraisal)
- Appendix 4: Risk of Bias Assessment (LCPG Group Appraisal)
- Appendix 5: Risk of Bias Assessment (COVID-NMA)
- Appendix 6: Risk of Bias Assessment (HTAU Appraisal)
- Appendix 7: Costing table

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

Evaluation Criteria	Question	Current Evidence	HTAC specification
CRITERION 1			
1. Responsiveness to magnitude and severity	Can *Sinopharm* significantly reduce the magnitude and severity of COVID-19?	**Responsiveness to the magnitude and severity of COVID 19 in the Philippines** As of 19 November 2021, the total number of cases has exceeded more than 248 million cases and breached the 5.0 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 2,753,312 cases with total deaths reported at 46,698 as of 19 November 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, obesity, 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., 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	The vaccine can potentially reduce the COVID-19 disease burden (health, social and economic impact). Trends in COVID-19 morbidity, mortality and hospitalization rates

		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**: *Sinopharm* 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 *Sinopharm* 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, reviews from the following organizations were synthesized: 1) Philippine Living Clinical Practice Guidelines Group (LCPG Group) with date of last search on 29 Oct 2021; 2) the International Vaccine Access Center (IVAC) of the Johns Hopkins Bloomberg School of Public Health and World Health Organization as of 29 Oct 2021; and 3) COVID-NMA as of 03 Nov 2021. Overall, there were 10 studies - one Phase III RCT, three real world effectiveness studies, and 6 studies that evaluated immunogenicity - included in the review that evaluated the efficacy, effectiveness, and immunogenicity of *Sinopharm*. **Evidence from trials** ***Efficacy outcomes*** ***Description of evidence*** Overall, the reference reviews detected one Phase III clinical trial that established the efficacy and safety of *Sinopharm*. The multi-site trial included 40,411 randomized participants with 26,924 participants who received the vaccine (13,459 participants received the WIV04 formulation; while 13,465 participants received the HB02 formulation). The interim results of this Phase III clinical trial are available in the publication by Al Kaabi et al. (2021) and the WHO SAGE Background Document. *Sinopharm (Wuhan)* was not included in the review of the WHO SAGE; hence, we will present the findings from the publication of Al Kaabi et al. (2021) below. Table 1.2.1 below details the characteristics of Al Kaabi et al., 2021. TABLE 1.2.1. STUDY CHARACTERISTICS OF THE PHASE III RCT (AL KAABI ET AL., 2021) ON THE EFFICACY AND SAFETY OF *SINOPHARM* (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, hospitalization due to COVID-19; **at least 80% reduction** of death due to COVID-19

Al Kaabi et al., 2021 UAE, Egypt, Bahrain, Jordan Phase III RCT, Published	
Population	Healthy adults, >18 years; older population (>60 years) recruited late in the study N=40,411

Intervention	Two doses of inactivated SARS-CoV-2 (WIV04 or HB02 strain) in aluminum hydroxide adjuvant
	- Intervention arm 1: Sinopharm *Wuhan* WIV04 strain (WIBP), 200WU/dose in 0.5ml, 2 doses with dosing interval of 21 days (+7)
	  - N=13,470 (13,066 received dose 2)
	- Intervention arm 2: Sinopharm *Beijing* HB02 strain (BIBP), 4ug vp/dose in 0.5ml, 2 doses with dosing interval of 21 days (+7)
	  - N=13,470 (13,086 received dose 2)

Comparator	Aluminum adjuvant, 0.5ml, 2 doses with dosing interval of 21 days (+7) N=13,471 (13,071 received dose 2)
Outcomes	*Efficacy outcomes* - VE against symptomatic COVID-19 - VE against severe COVID-19 and deaths - VE against asymptomatic infection - VE against infection after first dose, before second dose *Immunogenicity outcomes* - Anti-SARS-CoV-2 neutralizing antibody protective level against COVID-19 - Occurrence of ADE/VED after immunization - 4-fold increase rate, GMT and GMI of anti-SARS-COV-2 neutralizing antibody after full course of immunization *Safety outcomes* - Incidence of any adverse reactions/events within 30 mins after each dose - Incidence of solicited adverse reactions within 7 days - Incidence of unsolicited adverse reaction with d8-21 after first dose and d8-28 after 2nd dose - Incidence of serious adverse events from D1 to 12 months
Follow-up period	Median (range): 77 days (1-121)

Key findings

Risk of Bias

		The HTAC rated the risk of bias (*RoB)* of Al Kaabi et al. (2021) as *not serious* for symptomatic COVID-19, asymptomatic COVID-19, and any SARS-CoV-2 infection. Meanwhile the HTAC rated severe COVID-19 to have *serious* RoB as this outcome requires a follow up longer than the minimum interim follow up period.
		
		Results of the trial on clinical efficacy
		The results of the Phase III clinical trial (Al Kaabi et al., 2021) reported the vaccine efficacy of *Sinopharm* for the outcomes symptomatic COVID-19, severe COVID-19, any SARS-CoV-2 infection, symptomatic COVID-19 after the first dose, symptomatic COVID-19 in older adults, and asymptomatic COVID-19. The GRADE rating by the HTAC for these outcomes are in Appendix 3. In summary, Al Kaabi et al. (2021) reported the following:
		For critical outcomes:
		- Using *Sinopharm* (14 days after dose 2), compared to placebo, reduces the risk for:
		  - Symptomatic COVID-19 by **72.8% (95% CI: 58.1 to 82.4)** for the WIV04 formulation and **78.1% (95% CI: 64.8 to 86.3)** for the HB02 formulation, based on high certainty of evidence.
		- As for its efficacy against severe COVID-19 (≥14 days after dose 2), there were **zero events in both the WIV04 and HB02 vaccine groups** (N of WIV04=12,743; N of HB02=12,726) and 2 events in the placebo group (N=12,737). Thus, protection against severe COVID-19 remains to be demonstrated. This outcome had a low certainty of evidence.
		- **No mortality due to COVID-19** occurred during the follow-up period of the study.
		
		For important outcomes:
		- Using *Sinopharm* (14 days after dose 2), compared to placebo, reduces the risk for:
		  - Any SARS-CoV-2 infection (including asymptomatic cases) by **64.0% (95%CI: 48.8 to 74.7)** for the WIV04 formulation and 73.5% (95%CI: 60.6 to 82.2) for the HB02 formulation, based on high certainty of evidence.
		  - Symptomatic COVID-19 after the first dose, before the second dose by 50.3% (95%CI: 33.6 to 62.7) for the WIV04 formulation, and 65.5% (95%CI: 52.0 to 75.1) for the HB02 formulation, based on high certainty of evidence.
		- VE against asymptomatic COVID-19 was not reported in the trial; however, the study identified 16 cases of asymptomatic infection in the WIV04 group, 10 cases in the HB02 group, and 21 in the placebo group. These events were included in the calculation of VE against any infection (symptomatic and asymptomatic cases). This outcome had a high certainty of evidence..
		- The older population age ≥60 years were recruited late into the study, comprising only a small proportion of the study population (N of WIV04=213; N of HB02=201) and had a shorter follow-up period. There were no incident cases of COVID-19 in this population for both the vaccine and placebo	

groups; hence, vaccine efficacy was not calculated.

Immunogenicity outcomes

Description of evidence

Overall, the reference reviews detected: one network meta-analysis (Rogliani et al., 2021) on neutralizing antibodies which included one trial on *Sinopharm* (Xia et al., 2021a); and, two clinical trials (Feng et al., 2021 and Guo et al., 2021). The table 1.2.2 below details the characteristics of the studies.

Table 1.2.2. Study characteristics of evidence on immunogenicity outcomes of *Sinopharm* from trials

Author Year Country Study Design	Population	Intervention	Control	Outcomes
Rogliani et al, 2021 Network meta-analysis [published]	Healthy adults	COVID-19 Vaccines	Candidate SARS-CoV-2 vaccines and with respect to baseline	Neutralizing antibodies
Xia et al., 2021 China Phase I/II trial [published]	Healthy adults aged 18-80 years old ● 18-59 years ● ≥60 years	*Sinopharm* (HB02 strain) ● Phase I ○ 2-dose ○ 2, 4, and 8 µg ○ 28 day interval ● Phase II ○ 1-dose 8 µg ○ 2-dose 4 µg with 14, 21, or 28 day interval	Placebo	Neutralizing antibodies Adverse reactions (local, systemic, serious)
Feng et al., 2021 China RCT [preprint]	18-59 years old in the occupational high risk population (N = 809)	*Sinopharm* (strain not specified) 4µg at 14, 21, or 28 day intervals	Baseline titers	Neutralizing antibodies Adverse reactions (solicited, unsolicited, serious)
Guo et al., 2021 China Phase I/II trial [published]	Individuals ≥18 years: 18-59 years (N=784) ≥60 years (N=336) ● Phase I (n=24 per	*Sinopharm-Wuhan* (WIV04 strain) ● Phase I ○ 3-dose of 2.5, 5,	Placebo (0.5mg aluminum hydroxide)	Neutralizing antibodies and specific IgG binding antibody titres Adverse events

	group) ● Phase II (n=60 per group)	or 10µg on day 0/28/56 ● Phase II ○ 1-dose of 10µg ○ 2-dose of 5µg on day 0/14 or day 0/21 ○ 3-dose of 2.5, 5, or 10µg on day 0/28/56		(solicited local and systemic ARs, and unsolicited AEs)

Key findings

In the network meta-analysis, it was found that *Sinopharm* had a very large effect as indicated by its standard mean difference of 2.27 (95% CI: 1.80 to 2.75) on the level of neutralizing antibodies similar to *AstraZeneca, Pfizer, and Sputnik V,* based on the trial by Xia et al (2021). On the other hand, the Feng et al. (2021) trial evaluated neutralizing antibody response in populations with high risk occupations. The study evaluated immunogenic response at 14, 21, or 28 day intervals, wherein all three cohorts exhibited 100% seroconversion. However, it was found that those in the 21- and 28-day interval groups induced significantly higher neutralizing antibody levels compared to those in the 14-day interval group. The Phase II trial of Guo et al. (2021) saw higher seroconversion rates and higher antibody titers in the 2-dose cohort using 5µg with a 21-day interval compared to the 1-dose cohort using 10µg or the 2-dose cohort with a 14-day interval. As expected, the three-dose cohorts had a better immunogenicity profile at 28 days and 90 days after the whole vaccination course compared to the other vaccination regimens included in the study. However, the authors concluded that this may result in inadequate vaccine supply for more people; hence, it was recommended to proceed to Phase III trials using the two-dose 5µg regimen with a longer dosing interval.

Evidence from real world studies

Effectiveness outcomes

Description of evidence

Overall, the reference reviews detected 3 real world studies on the effectiveness of *Sinopharm* - a retrospective cohort study (Al Hosani et al., 2021), a prospective cohort study (Badano et al., 2021) and a case series (Jahromi et al., 2021). Characteristics of the three studies are detailed in Table 1.2.3 below.

Table 1.2.3. Study characteristics of Badano et al., 2021, Jahromi et al., 2021, and Al Hosani et al., 2021(LCPG Group, 2021)

Author Year Country Study Design	Population	Intervention	Comparator	Outcomes
Badano et al., 2021 Argentina Longitudinal observational study (comparison of vaccinated individuals with or without prior SARS-CoV-2 infection) preprint	Healthcare workers with or without exposure to SARS-COV-2 (N = 82)	2 doses of *Sinopharm* (strain not specified)	No comparator for effectiveness results	Number of cases of infection after vaccination Immunogenicity
Jahromi et al., 2021 Bahrain Case series, published	Members of an extended family (N=54)	Partially vaccinated with *Sinopharm* (n=26) Fully vaccinated with *Sinopharm* (n=20) (2 other subjects included in the case series were vaccinated with another vaccine)	Unvaccinated (n=8)	Number of cases of infection, hospitalization, and death for the fully vaccinated, partially vaccinated, and unvaccinated
Al Hosani et al., 2021 UAE Retrospective cohort, preprint	Individuals ≥15 years with prior exposure to COVID-19 N=176,640	*Sinopharm BBIBP-CorV* Partially vaccinated (n=21,768) Fully vaccinated (n=62,931)	Unvaccinated group (n=91,941)	Admission to hospital general ward, critical admission, and death 14 days after vaccination

Key findings

Risk of bias

Badano et al., 2021 had 'serious' ROB while Jahromi et al., 2021 had 'very serious' ROB, based on the appraisal performed by the LCPG Group. Both studies had high ROB in the following domains: randomization, allocation concealment, blinding of participants, blinding of assessors, selective reporting, and follow-up. Since both

		studies had an observational study design, additional assessment on confounders was done. Both studies did not adjust for the following pre-identified confounders: age, exposure risk, and comorbidities. Jahromi et al. was downgraded further due to its case series study design with very few participants. Details of the LCPG Group appraisal tool for observational studies is presented in Appendix 2 while the results of ROB of Jahromi et al. (2021) and Badano et al. (2021) are detailed in Appendix 4. Lastly, Al Hosani et al., 2021 had 'serious' ROB, based on the appraisal performed by HTAU. The rating was based on the high ROB due to the observational study design, selective reporting, and the adjustment of confounders. The study controlled for age and exposure risk but the risk assessment based on comorbidities was not assessed. Refer to Appendix 6 for the ROB appraisal of Al Hosani et al. (2021). *Results of clinical effectiveness* Vaccine effectiveness was reported only by Al Hosani et al. (2021), while effectiveness results from Badano et al. (2021) and Jahromi et al. (2021) were limited to the number of breakthrough infections after vaccination with *Sinopharm*. Among the 82 healthcare workers who received the *Sinopharm* vaccine in the study by Badano et al. (2021), 8 participants had a breakthrough infection: 4 participants got infected more than 14 days after the first dose, 2 participants immediately after the second dose, and 2 participants more than 14 days after the second dose. All participants had mild COVID-19. Meanwhile, of the 54 family members included in the case series of Jahromi et al. (2021), 20 were fully vaccinated with *Sinopharm,* 26 were partially vaccinated while 8 were unvaccinated. Nearly all members included in the case series developed an infection (20/20 fully vaccinated, 23/26 partially vaccinated, and 8/8 unvaccinated. Among those with breakthrough infection, 43% (10/23) of the partially vaccinated required hospitalization while this occurred in only 5% (1/20) of the fully vaccinated. Among the unvaccinated group, three were hospitalized and the only death in the study occurred in this group. Al Hosani et al. (2021) reported the vaccine effectiveness of *Sinopharm,* 14 days after the second dose for the following outcomes: - VE against hospitalization: 80% (95% CI: 78 to 81.4) - VE against critical care admission: 92.2% (95% CI: 89.7 to 94.1) - VE against death: 97.1% (95% CI: 83 to 99.9) ***Immunogenicity outcomes***	

Description of evidence

Overall, the review by the LCPG Group detected 4 real world studies evaluating the immunogenicity of *Sinopharm* (Badano et al., 2021; Jeewandara et al., 2021; Holt et al., 2021; Ariamanesh et al., 2021). Details on Badano et al. (2021) may be found in Table 1.2.3. Table 1.2.4 below details the characteristics of the other included real-world studies.

Table 1.2.4. Study characteristics of evidence on immunogenicity of *Sinopharm* from real-world studies

Author Year Country Study Design	Population	Intervention	Control	Outcomes
Jeewandara et al., 2021 Sri Lanka Observational [preprint]	Seronegative individuals (N = 282)	*Sinopharm* 2 doses (strain not specified)	Antibodies of naturally infected individuals	Immunogenicity (seroconversion)
Holt et al., 2021 Abu Dhabi Prospective cohort [published]	Hemodialysis patients with positive antibodies and negative baseline titers (N=142)	*Sinopharm* 2 doses (HB02 strain), 21 day interval	Hemodialysis patients with negative antibodies and negative baseline titers (N=128)	Immunogenicity (anti-spike antibodies, neutralizing antibodies)
Ariamanesh et al., 2021 Iran Observational [preprint]	Adult patients with cancer (N=364)	*Sinopharm* 2 doses (HB02 strain), 21 day interval	Baseline titers	Immunogenicity (neutralizing antibodies, anti-S IgG)

Key findings

Immunogenicity results from the Badano et al. (2021) and Jeewandara et al. (2021) studies exhibited generally high seroconversion rates in the study population of the respective studies. For the Badano et al. (2021) study, 100% seroconversion for anti-S IgG was observed after the second dose signifying a significant increase in titers after the second dose from that of the first dose. However, a significant drop in titers was observed after 3 months from 377 IU/mL after the second dose to 125.4 IU/mL three months after the second dose but in spite of the significant drop, the titers were still higher compared to pre-vaccination. In the Jeewandara et al. (2021) study, 95% seroconversion

		was observed with lower seroconversion rates for individuals older than 60 years old (93.3%) compared to younger individuals at 20-39 years old (98.9%). As for the difference in seroconversion with those diagnosed with comorbidities, no significant difference was observed. Meanwhile, the Holt et al. (2021) and Ariamanesh et al. (2021) looked into the immunogenicity of a primary series of *Sinopharm* in immunocompromised populations such as hemodialysis patients (Holt et al., 2021) and cancer patients (Ariamanesh et al., 2021). The Holt et al. (2021) study used *Sinopharm (HBO2 strain)* wherein 50% of the study population were found to be positive with anti-spike antibodies, and 53% were found to be positive with neutralizing antibodies 15 days after the second dose. On the other hand, the Ariamanesh et al. (2021) study observed 80.7% of its study population to be seropositive for neutralizing antibodies after two doses of *Sinopharm*, and 77.1% of its study population was seropositive for anti-S IgG two months after the second dose. It was also observed in the Ariamanesh et al. (2021) study that the rate of seroconversion was higher in patients younger than 60 years old. Seroconversion rate was also found to be higher in patients with breast cancer (93.3%) and upper GI cancer (94.7%). Meanwhile, the lowest rates were found in patients with hematologic malignancies (61.9%). Additionally, antibody response was higher in those receiving radiotherapy alone or endocrine therapy (97%) compared to those in chemotherapy (83.5%). **HTAC Judgment**: Based on one Phase III RCT, *Sinopharm* passed the preferred vaccine efficacy threshold (i.e., at least 60% VE) against symptomatic COVID-19 for the general population aged 18 years and above more than 14 days after the second dose. It is likely that *Sinopharm* also provides protection against severe COVID-19 and death due to COVID-19. Based on real world effectiveness studies, *Sinopharm* passed the preferred vaccine effectiveness threshold (i.e., at least 80% VE) against severe COVID-19, hospitalization, and death due to COVID-19; and demonstrated effectiveness against hospitalization and death in cases of breakthrough infections.	
	What is the efficacy and effectiveness of *Sinopharm* in terms of: reducing incidence of symptomatic and severe COVID-19, hospitalization due to COVID-19 and	For the evidence on efficacy and effectiveness against variants of concern, reviews from the following organizations were synthesized: 1) Philippine Living Clinical Practice Guidelines Group (LCPG Group) with date of last search on 29 Oct 2021; 2) the International Vaccine Access Center (IVAC) of the Johns Hopkins Bloomberg School of Public Health and World Health Organization as of 29 Oct 2021; and 3) COVID-NMA as of 03 Nov 2021. Overall, there were 2 studies included in the review that evaluated the immunogenicity of *Sinopharm* against variants of concern - one trial and one real world study. There were no studies included in the review that reported the efficacy or effectiveness against variants of concern. ***Evidence from clinical trials***	**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

	death due to COVID-19 caused by variants of concern in the general population and vulnerable populations (i.e., older adults aged 60 and above, with comorbidities)?	***Efficacy outcomes*** There were no clinical trials detected in the reference reviews that reported efficacy of *Sinopharm* against variants of concern. ***Immunogenicity outcomes*** ***Description of evidence*** There was one trial (Huang et al., 2021) that evaluated the neutralizing activity of serum samples from 12 participants of the Phase III trial who were vaccinated with *Sinopharm* against the Beta variant (501Y.V2) versus the Wuhan or D614G strain. Serum from the trial participants were extracted 28 days after dose 2. ***Key findings*** Huang et al. (2021) used 12 random serum samples from the participants of the Phase III trial extracted 28 days after the second dose. All samples showed preserved neutralization against the Beta variant. However, there was a 1.6-fold reduction in GMTs against the Beta variant compared to the Wuhan strain. ***Evidence from Real World Studies*** ***Effectiveness outcomes*** There were no real world studies detected in the reference reviews that reported effectiveness of *Sinopharm* against variants of concern. ***Immunogenicity outcomes*** ***Description of Evidence*** There was one real world study (Jeewandara et al., 2021) that evaluated the anti-RBD antibodies and IFN-gamma titers in serum samples from 282 individuals vaccinated with *Sinopharm* who were seronegative at baseline. Immune response of vaccinated sera against the Alpha, Beta, and Delta variants was compared to the Wuhan strain. Serum from the trial participants were extracted 2 weeks after dose 2. ***Key Findings*** The study involved 282 vaccinees with no evidence of previous infection. Overall, seroconversion rate for anti-RBD antibodies was 95%. However, at 2 weeks after dose 2 of *Sinopharm*, the participants showed significantly lower titers to Alpha (1.3-fold reduction), Beta (10-fold) and Delta (1.38-fold) compared to the Wuhan reference strain. There was also a noted increase in T and B cell response at 2 weeks after dose 2, but less than those observed with some other vaccines.	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

		HTAC Judgment: Currently, there is no data on the efficacy or effectiveness of *Sinopharm* against variants of concern. However, available evidence from an immunogenicity study showed lower neutralizing antibodies and anti-RBD antibodies against the Alpha, Beta, and Delta variants compared to the Wuhan reference strain.	

	What is the duration of protection of the *Sinopharm* in terms of reducing the incidence of symptomatic and severe COVID-19, hospitalization due to COVID-19 and death due to COVID-19?	For the evidence on duration of protection of *Sinopharm* primary vaccination, reviews from the following organizations were synthesized: 1) Philippine Living Clinical Practice Guidelines Group (LCPG Group) with date of last search on 29 Oct 2021; 2) the International Vaccine Access Center (IVAC) of the Johns Hopkins Bloomberg School of Public Health and World Health Organization as of 29 Oct 2021; and 3) COVID-NMA as of 03 Nov 2021. Overall, there was 1 retrospective study included in the reviews that evaluated the duration of protection of *Sinopharm*. ***Evidence from Real World Studies*** ***Description of Evidence*** There was 1 study (Al Hosani et al., 2021) identified from the reviews that evaluated the effectiveness of the *Sinopharm* over time based on **cumulative risk** from inclusion in the study up to more than 200 days of follow-up. Characteristics of the study have been previously described in Table 1.2.3. ***Key Findings*** *Risk of bias* The HTAC rated the *RoB* of Al Kaabi et al. (2021) as *not serious* for solicited adverse events, unsolicited adverse events, local adverse events, and systemic adverse events. Meanwhile the HTAC rated serious adverse events and death to have *serious* RoB as these outcomes require a follow-up longer than the minimum interim follow up period. *Results of duration on protection* Al Hosani et al., 2021 analysed cumulative risk for hospital admission, critical admission, and death over time. The analysis showed that the cumulative risk of the fully vaccinated group for hospitalization, critical admission, and death remained low compared to the cumulative risk of the unvaccinated and partially vaccinated throughout the entire study period or up to almost 250 days since entering the study. However, the analysis of the cumulative risk over time of these outcomes was presented as graphs. Further, the values for incidence risk over time were not reported in the study and thus cannot be verified. The overall vaccine effectiveness against hospital admission, critical admission, and death reported for one time point has been previously discussed in the section on vaccine effectiveness of *Sinopharm*. **HTAC Judgment:** Based on the graphs presented in one real-world study (Al Hosani et al., 2021), *Sinopharm* maintained a low cumulative risk of hospitalization, critical admission, and death compared to the cumulative risk of the unvaccinated and partially vaccinated throughout the entire study period (up to 250 days). However, the values of vaccine effectiveness over time and/or cumulative risk of hospitalization, critical admission, and death over time were not reported in the available publication.	Minimum acceptable duration of protection: confers at least 6 months protective immunity Preferred: ≥1-year protective immunity *Duration of protection shall be assessed and re-assessed on an interim basis based on the best available data at the time of evaluation Reduction of severe allergy and other contraindications

<table>
<tr>
<td></td>
<td>What is the safety of Sinopharm 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 Syndrome, Capillary Leak Syndrome, Immune Thrombocytopenia)</td>
<td>
For the evidence on safety, the following reviews on Sinopharm were considered: 1) Philippine Living Clinical Practice Guidelines Group (LCPG Group) with date of last search on 29 Oct 2021; 2) the International Vaccine Access Center (IVAC) of the Johns Hopkins Bloomberg School of Public Health and World Health Organization as of 29 Oct 2021; and 3) COVID-NMA as of 03 Nov 2021. Overall, there were 10 studies (four RCTs and six real world studies), 1 guidance document and 1 local NRA report detected and were included in the review.

Safety data from clinical trials
Description of Evidence
Overall, the reference review by the LCPG Group detected four clinical trials - the main Phase III clinical trial (Al Kaabi et al., 2021); one Phase 4 RCT (Feng Y. et al., 2021) and 2 Phase I/II RCT (Xia et al., 2021; Guo et al., 2021) that examines the safety of Sinopharm. Table 1.2.5 below describes the characteristics of the mentioned studies.

TABLE 1.2.5. STUDY CHARACTERISTICS OF EVIDENCE ON SAFETY OUTCOMES OF SINOPHARM FROM TRIALS
<table>
<tr><th>Author Year
Country
Study Design</th><th>Population</th><th>Intervention</th><th>Control</th><th>Outcomes</th></tr>
<tr>
<td>Al Kaabi et al., 2021

UAE, Egypt, Bahrain, Jordan
Phase III RCT, Published</td>
<td>Healthy adults, >18 years; older population (>60 years) recruited late in the study
N=40,411

Safety set
N= 40,388</td>
<td>Two doses of inactivated SARS-CoV-2 (WIV04 or HB02 strain) in aluminum hydroxide adjuvant
- WIV04 strain (WIBP), 200WU/dose in 0.5ml, 2 doses with dosing interval of 21 days (+7)
- N=13,470 (13,066 received dose 2)
- HB02 strain (BIBP), 4ug vp/dose in 0.5ml, 2 doses with dosing interval of</td>
<td>Aluminum adjuvant, 0.5ml, 2 doses with dosing interval of 21 days (+7)
N=13,471 (13,071 received dose 2)</td>
<td>Efficacy outcomes
Immunogenicity outcomes
Safety outcomes
- Incidence of any adverse reactions/events within 30 mins after each dose
- Incidence of solicited adverse reactions within 7 days
- Incidence of unsolicited adverse reaction with d8-21 after first dose and d8-28 after 2nd dose
- Incidence of serious</td>
</tr>
</table>
</td>
<td>Local and systemic reactions are tolerable, self-limiting and do not require hospitalization. No serious adverse events were caused by the vaccine.

Short term outcomes (e.g., reactogenicity and allergic reactions, SAEI): at least 2 months
Long term outcomes (e.g., serious AEs, all-cause mortality, SAEI, Vaccine-associated enhanced disease): at least 1 year</td>
</tr>
</table>

				21 days (+7) - N=13,470 (13,086 received dose 2)		adverse events from D1 to 12 months
		Xia et al., 2021 China Phase I/II trial [published]	Healthy adults aged 18-80 years old ● 18-59 years ● ≥60 years Safety set n= 96 *(n= 24 in 2 μg cohort; n= 24 in 4 μg cohort; n= 24 in 8 μg cohort and 24 in the placebo cohort)*	*Sinopharm* (HB02 strain) ● Phase I ○ 2-dose ○ 2, 4, and 8μg ○ 28 day interval ● Phase II ○ 1-dose 8 μg ○ 2-dose 4 μg with 14, 21, or 28 day interval	Placebo	Neutralizing antibodies Adverse reactions (local, systemic, serious)
		Feng et al., 2021 China RCT [preprint]	18-59 years old in the occupational high risk population (N = 809) Safety set n=809 *(n=270 in day 0,14 cohort; n=270 in day 0,21 cohort and n=269 in day 0,28 cohort)*	*Sinopharm* (strain not specified) 4μg at 14, 21, or 28 day intervals	Baseline titers	Neutralizing antibodies Adverse reactions (solicited, unsolicited, serious)
		Guo et al., 2021 China Phase I/II trial [published]	Individuals ≥18 years: 18-59 years (N=784) ≥60 years (N=336) ● Phase I (n=24 per group) ● Phase II (n=60 per group) Safety set n= 1120 *(n=672 in the*	*Sinopharm-Wuhan* (WIV04 strain) ● Phase I ○ 3-dose of 2.5, 5, or 10μg on day 0/28/56 ● Phase II ○ 1-dose of 10μg ○ 2-dose of 5μg on day 0/14 or	Placebo (0.5mg aluminum hydroxide)	Neutralizing antibodies and specific IgG binding antibody titres Adverse events (solicited local and systemic reactions, and unsolicited AEs)

	three-dose cohort; n=112 in the day 0, 14 two-dose cohort; ; n=112 in the day 0, 21 two-dose cohort;; n=112 in the day 0, 28 two-dose cohort; and ; n=112 in the one-dose cohort)	day 0/21 ○ 3-dose of 2.5, 5, or 10µg on day 0/28/56		

Key findings

Risk of bias

Based on the rating of LCPG, Al Kaabi et al., 2021 had 'some concerns' on its ROB due to its short follow-up period. The study had low ROB for the following domains: randomization, allocation concealment, blinding of participants, blinding of assessors, and selective reporting. Meanwhile Feng Y. et al., 2021 had an overall rating of 'serious ROB' due to a high ROB rating in the follow-up domain and unclear rating on the allocation concealment, blinding of participants and carer/assessors domains. Xia et al., 2021a had an overall rating of 'not serious'. Lastly, COVID-NMA rated Guo et al., 2021 with 'some concerns' on its ROB due to some concerns on the randomization domain (unclear allocation concealment). The HTAC also performed a GRADE assessment on the safety outcomes of Al Kaabi et al., 2021. Refer to Appendix 3 for the GRADE appraisal by HTAC and Appendices 4 to 5 for the ROB appraisal of these studies.

Results of clinical safety

Below are the key findings on its safety and the rating of evidence:

- **Local adverse reactions**
  - Based on high certainty of evidence, Al Kaabi et al., 2021 reported similar rates of local reactions among the WIV04 (25.6%), HB02 (20.7%) and placebo groups (29.9%). The relative risk for local adverse reactions compared to placebo is 0.71 (0.68- 0.74) in the HB02 group and 0.88 (0.85- 0.92) in the WIV04 group.
- **Systemic adverse reactions**
  - Based on high certainty of evidence, Al Kaabi et al., 2021 reported similar rates of systemic reactions among the WIV04 (27.4.6%), HB02 (28.3%) and placebo groups (27.8%). The relative risk for systemic adverse reactions compared to placebo is 1.02 (0.98- 1.06)in the HB02 group and 0.99 (0.95- 1.03) in the WIV04 group.

- **Adverse reactions**
  - Feng Y. et al., 2021 reported an overall incidence of adverse reactions at 4.07% in the days 0 and 14 vaccination cohort group; 4.81% in the days 0 and 21 vaccination cohort group; and 3.72% in the days 0 and 28 vaccination cohort group. Solicited adverse reactions were reported by 3.21% within 7 days after injection, and 0.99% reported unsolicited adverse reactions within 28 days in the trial. No significant differences were found in the occurrence of solicited and unsolicited adverse reactions among the three groups.
  - Guo et al., 2021 reported the following results for adverse reactions in the the three-dose, two-dose and one-dose cohorts:

Three-dose regimen (Days 0, 28 and 56)								
	Younger adults (aged 18-59 years old)				Older adults (≥60 years old)			
	2.5 µg (n=84)	5 µg (n=84)	10 µg (n=84)	placebo (n=84)	2.5 µg (n=84)	5 µg (n=84)	10 µg (n=84)	placebo (n=84)
Total adverse reactions	12 (14.3%)	18 (21.4%)	21 (25%)	14 (16.7%)	4 (4.8%)	13 (15.5%)	6 (7.1%)	14 (16.7%)

- The proportion of adverse reactions was similar between vaccine and placebo groups (p value >0.099), except that the proportion of total adverse reactions was higher among those in the placebo group compared with the 2.5 µg group. (p value = 0.042). Also, the proportion of adverse reactions was higher in the 5 µg group compared with 2.5 µg or 10 µg group (p value= 0.012) among older adults receiving three doses, (p value= 0.012).

	Younger adults (aged 18-59 years old)							
	Two-dose regimen (Days 0 and 14)		**Two-dose regimen (Days 0 and 21)**		**Two-dose regimen (Days 0 and 28)**		**One- dose regimen (Days 0 and 14)**	
	5 µg (n=84)	placebo (n=28)	5 µg (n=84)	placebo (n=28)	5 µg (n=84)	placebo (n=28)	10 µg (n=84)	placebo (n=28)
Total adverse reactions	5 (6.0%)	4 (14.3%)	16 (19.1%)	5 (17.9%)	17 (17.9%)	9 (32.1%)	9 (10.7%)	3 (10.7%)

		● No statistically significant differences of incident adverse reactions were observed between vaccine and placebo groups (p value >0.099); however, incidence rates of total and injection-site adverse reactions were lower among 5 mg days 0 and 14 group compared with 5 mg days 0 and 21/28 groups (p value <0.013). ● **Adverse events** ■ Xia et al., 2021a reported overall rates of adverse events of 47% in the vaccination group (across all dosing regimens) vs 29% in the placebo group with no significant differences between groups (p value=0.16): ● In the 2 µg cohort, the overall adverse event rate is 50%, vs 38% of the placebo, with no significant difference (p value = 0.69). ● In the 4 µg cohort, the overall adverse event rate is 46%, vs 25% of the placebo, with no significant difference (p value = 0.42). ● In the 8 µg cohort, the overall adverse event rate is 46%, vs 25% of the placebo, with no significant difference (p value = 0.42). ● **Serious adverse events** ■ Al Kaabi et al., 2021 reported a total of 201 serious adverse events: 0.4% in the HB02 group, 0.5% in the WIV04 group and 0.6% in the control group, based on low certainty of evidence. Rates of serious adverse events were similar among the three groups. The relative risk for serious adverse events compared to placebo is 0.76 (95% CI: 0.54 to 1.06) in the HB02 group and 0.83 (95% CI: 0.59 to 1.15) in the WIV04 group. ■ Al Kaabi et al., 2021 reported two serious adverse events with possible causality with the HB02 formulation of the vaccine: ● A case of demyelinating disease developing in a 50 year old man after the first dose ● A case of severe emesis in a 35-year old woman after the second dose. ■ Guo et al., 2021 reported that a total of 68 serious adverse events from 20 participants occurred during the follow-up of median 306 days after the first vaccine dose, but none were judged to be related to the vaccination. ***Safety data from Real World Evidence*** ***Description of Evidence*** Overall, the reference reviews detected six real world studies, 1 guideline and 1 local NRA report examining the real world safety of *Sinopharm*. Among the studies, two are cross-sectional surveys (Abu-Halaweh et al., 2021 and Saeed et al., 2021[preprint]) which looked at safety in the general population. One prospective study (Liu T. et al., 2021) reported on the safety of the vaccine in healthcare workers. Lastly, three studies looked at the real world safety of	

Sinopharm among immunocompromised individuals - two reported on safety of the vaccine in patients with multiple sclerosis (MS) (Etemadifar et al., 2021 [preprint], prospective study; Sahraian et al., 2021, cross-sectional survey) and one cross-sectional survey (Ariamanesh et al., 2021) reported on safety of the vaccine in cancer patients. Characteristics of the studies are detailed in Table 1.2.6.

Table 1.2.6. Study characteristics of evidence on safety of *Sinopharm* from real-world studies

Author Year Country Study Design	Population	Intervention	Control	Outcomes
Abu-Halaweh et al., 2021 Jordan Cross-sectional survey	Adults 18 and above (N=1004) vaccinated with either *Sinopharm* or *Pfizer-BioNTech*	*Sinopharm Vaccine* (Strain not specified)	*Pfizer-BioNTech vaccine*	Local adverse reactions Systemic adverse reactions adverse medical events
Saeed et al., 2021[preprint] UAE Cross-sectional survey	Adults 18 and above (N=1080)	One or 2 doses of *Sinopharm* (Strain not specified)	None	Local adverse reactions Systemic adverse reactions
Liu T. et al., 2021 China Prospective cohort	Healthcare workers (N=406)	2 doses of *Sinopharm* with a 28 day interval	Antiphospholipid antibody and anti-PF4-heparin antibody levels before vaccination	Thrombotic events Antiphospholipid antibody and anti-PF4-heparin antibody levels
Etemadifar et al., 2021 [preprint], Iran Prospective study	Patients with multiple sclerosis (Vaccinated : 517) (Unvacc : 174)	2 doses of *Sinopharm* (Strain not specified)	Unvaccinated	MS relapse Local adverse reactions Systemic adverse reactions adverse medical events

Sahraian et al., 2021. Iran Cross-sectional survey	Patients with multiple sclerosis (N=583)	1 dose of*Sinopharm* (Strain not specified)	None	MS relapse Local adverse reactions Systemic adverse reactions adverse medical events
Ariamanesh et al., 2021 Iran Observational [preprint]	Adult patients with cancer (N=364)	*Sinopharm* 2 doses (strain not specified)	Baseline	Local ARs Systemic ARs

Key findings

Risk of bias

Based on the appraisal of the LCPG, overall, all studies (Abu-Halaweh et al., 2021 and Saeed et al., 2021[preprint]; Liu T. et al., 2021; Etemadifar et al., 2021 [preprint]; Sahraian et al., 2021; Ariamanesh et al., 2021) had 'serious' ROB rating due to high ROB in the randomization, allocation concealment, blinding of participants, carer/assessor and follow up domains, and non-adjustment of confounding factors.

Safety results

General population

- **Local adverse reactions**
  - Abu-Halaweh et al., 2021 reported that frequencies of local adverse reactions are significantly lower in participants who received *Sinopharm* (17.7%; 14.8%) compared to participants who received *Pfizer-BioNTech* (50.3%; 44.2%) after the first and second dose. Local adverse events decreased after the second dose compared to after the first dose in both vaccine groups. The most common local adverse event for both groups is pain at the injection site.
  - Saeed et al., 2021 [preprint] reported pain in the injection site as one of the most common adverse reactions after both 1st and second doses. All the side effects in both doses were more prevalent among the participants ≤ 49-year-old group.
- **Systemic adverse reactions**
  - Abu-Halaweh et al., 2021 reported that frequencies of systemic adverse reactions are significantly lower in participants who received *Sinopharm* (17.5%; 22%) compared to participants who received

		Pfizer-BioNTech (30.2%; 31.2%) after the first and second dose. The most common systemic adverse event for both groups is general weakness. ○ Saeed et al., 2021 [preprint] reported fatigue and headache as two of the most common systemic adverse reactions after the 1st dose and fatigue, lethargy, headache, and tenderness were most common after the second dose. All the side effects in both doses were more prevalent among the participants ≤ 49-year-old group. Immunocompromised individuals ● Etemadifar et al., 2021 [preprint], reported that among individuals with MS, 16.2% of the vaccinated participants experienced at least one post-vaccination neurological symptom, among which, motor symptoms and vertigo were more common. Six participants experienced MS relapse during the at risk period but there was no significant difference between relapse rates of vaccinated and unvaccinated subjects in the year prior. ● Sahraian et al., 2021 reported that among individuals with MS, no serious adverse events were reported. At least one complaint (mostly transient) was reported by 350 (60%) of vaccine recipients. Constitutional symptoms (malaise, fatigue, fever, shivering, & generalized body pain) (51%) and headache (9%) were the most reported complaints. Only five recipients (0.9%) reported MS relapse after vaccination. MS worsening was a minor incident related to fever. ● Ariamanesh et al., 2021 reported that among cancer patients, the most common local adverse event is pain at the injection site, and fever as the most common systemic adverse event. Healthcare workers ● Liu T. et al., 2021 reported that 32.76% (133/406) of participants experienced local adverse reactions; 38.18% (155/406) experienced systemic adverse reactions and 6.40% (26/406) had other adverse events post vaccination ● Liu T. et al., 2021 also determined the incidence of thrombotic events and to determine any change in the presence of autoantibodies pre and post vaccination. After an eight-week follow up, no thrombotic event occurred. No significant difference was noted in the presence of all 10 autoantibodies between pre and post vaccination samples. Seven cases presented with anti-PF4 heparin antibodies but none of them exhibited any sign of thrombotic disorder. Local safety reports ● As of the October 24, 2021 report of the Philippine FDA, there were 86 adverse events associated with *Sinopharm* out of the 750,978 doses administered locally. Five of these were classified as serious, with no	

		further description of the cases given. The top reported events were pyrexia (25.6%), cough (15.1%) dizziness (13.95%) and headache (13.95%). Adverse events of interest The WHO SAGE background document reported the following adverse events of interest: ● Two cases of Bell's palsy in the trial, one in the placebo group and one in the *Sinopharm* group. ● One thrombotic event was reported among the 29,240 trial participants in the vaccine group. This was in a 50 year old man who had prior history of blood clots before vaccination and suffered abdominal pains 7 days after the first dose of *Sinopharm*, confirmed to be due to thrombus. **HTAC judgment:** The safety profile of *Sinopharm* is acceptable based on short-period follow-up based on short-period follow-up. However, further follow-up data is needed to establish the longer-term safety profile.	
	Does the *Sinopharm* 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 *Sinopharm* in terms of decreased occurrence of symptomatic COVID-19, severe COVID-19, and deaths outweigh the known short-term risks. Real world evidence showed that *Sinopharm* has potential benefit due to its low breakthrough infection rates after vaccination and protection against severe COVID-19, hospitalization and death due to COVID-19. **HTAC Judgment:** *Sinopharm* passed the benefit/risk profile for the general population based on efficacy, effectiveness, and safety data.	Favorable benefit/risk profile
CRITERION 3			

3. Affordability and viability	*Is Sinopharm affordable?*	According to the Department of Finance (DOF), the price of *Sinopharm* offered to the Philippine government is within the price range for which *Sinopharm* is available in various markets globally. Based on the prices reflected in the UNICEF COVID-19 Vaccine Market Dashboard, the price per dose of *Sinopharm* offered to the Philippine government is lower than the price range for which it is available among low to middle income countries. Based on the number of doses of *Sinopharm* included in the National Government procurement portfolio, costing analysis was conducted using the *Sinopharm* (details of the costing assumptions and scenarios are provided in Appendix 7). The unit cost of the vaccine used in the analysis was based on the latest price offered to the government 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. The total cost of the primary vaccination roll-out with *Sinopharm* for 500,000 vaccinees is at around **Php 711.13 M**. **HTAC Judgment:** Based on the costing analysis, *Sinopharm* is considered affordable.	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 Sinopharm?	The potential budget impact to the national government of the use of *Sinopharm* as primary homologous series was calculated at **Php 711.13 M**. It is estimated to consume **0.86%** of the 2021 total government budget for vaccines (Php 711M of the Php 82.5 B total budget) for **0.52%** of the 97M target vaccines for primary homologous vaccination. **HTAC Judgment:** The share of the cost of the *Sinopharm* to the total vaccine budget is considered not proportionate to the share of the population to be vaccinated using the said vaccine.	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.

<table>
<tr><td></td><td>Does Sinopharm represent good value for money in terms of preventing COVID-19 morbidity and mortality?</td><td>Sinopharm in a primary homologous series represents good value for money in terms of reducing the incidence of any SARS-CoV-2 infection and symptomatic COVID-19 in the general population aged 18 years and older (including older adults aged ≥60 years and individuals with comorbidities), and likely, reducing the incidence of severe COVID-19, hospitalization and deaths.

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: The HTAC deems that the health, economic, and social benefits of using Sinopharm mitigate the negative impacts of COVID-19, such as deaths, medical costs, loss of productivity, social disruption and unprecedented challenges in the health system.</td><td>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.</td></tr>
<tr><td colspan="4">CRITERION 4</td></tr>
<tr><td>4. Household Financial Impact</td><td>Will Sinopharm reduce or not add further to the out-of-pocket expenses of Filipino households?</td><td>As mandated by Philhealth Circular 2021-0014, Philhealth Circular 2020-0012, and Philhealth Circular 2020-0009, the following benefit packages with corresponding case rates related to COVID-19 are available for the general population:
1. Home Isolation Package for asymptomatic and mild cases (C19HI) = Php 5,917.00
2. Community Isolation Package for symptomatic and confirmed cases (C19CI): Case rate = Php 22,499.00
1. Mild COVID-19 pneumonia for elderly and with comorbidities (C19IP1): Case rate= Php 43,997.00
2. Moderate COVID-19 pneumonia (C19IP2): Case rate= Php 143, 267.00
3. Severe COVID-19 pneumonia (C19IP3): Case rate= Php 333,519.00
4. 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 1.2.7 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 1.2.7. 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)</th><th rowspan="2">Average % Coverage
[proportion of</th></tr><tr><th>Range of Hospitalization</th><th>Median Hospitalization</th></tr></table></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>

		Cost *[PHP]*	**Cost** *[PHP]*	*[PHP]*	*financial coverage out of the total bill]*
Mild COVID-19 *[C19IP1]*	1,688	₱0 to ₱1,751,629.51	₱74,988.62	₱30,991.62	61.90%
Moderate COVID-19 *[C19IP2]*	7,488	₱0 to ₱326,482,781.10	₱206,294.29	₱63,027.29	70.16%
Severe COVID-19 *[C19IP3]*	2,226	₱0 to ₱5,404,430.74	₱399,404.39	₱65,885.39	76.31%
Critical COVID-19 *[C19IP4]*	762	₱0 to ₱6,574,031.60	₱850,472.44	₱64,088.44	80.12%

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

HTAC Judgment: Based on current evidence, *Sinopharm* 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 Sinopharm possess the characteristics desired by key stakeholders (i.e., policy- and decision makers, health*	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 *Sinopharm*. 1) **Safe and efficacious** for the general population (aged 18 years and older) and for some vulnerable groups like the	The vaccine possesses all or most of the characteristics desired by key stakeholders Qualitative responses will contextualize the Filipino

	workers, program managers and/or implementers, patient groups, CSOs, communities, general public)? ● *Safety* ● *Efficacy* ● *Transparency in the regulatory/approval process and information on the vaccines* ● *Availability* ● *Potential for high and equitable coverage* ● *Ease in logistical and implementation requirements* ● *Cost-efficiency to the government* ● *Public acceptability* ● *Availability of mechanisms to compensate vaccine recipients for*	older population and individuals with comorbidities. - Evidence: *Sinopharm* is efficacious in preventing symptomatic COVID-19, and likely severe COVID-19 and deaths in the general population 18 years and above. Additionally, based on real world evidence, *Sinopharm* has demonstrated protection against severe COVID-19, hospitalization and death due to COVID-19. Short-term safety of *Sinopharm* among individuals 18 years and older is acceptable. Further follow-up data is needed to establish longer-term safety. 2) Underwent a **transparent regulatory process** of being evaluated and approved by health authorities - Evidence: *Sinopharm* underwent the usual regulatory process of the FDA Philippines. The Philippine FDA has issued an EUA for Sinopharm (Hayat-Vax) on 19 August 2021, for Sinopharm (Beijing) on 10 September 2021, and for Sinopharm (Wuhan) on 07 October 2021 for its use among individuals 18 years old and above. 3) **Potential for high and equitable coverage across the population** - Evidence: *Sinopharm* can be made more available since vaccine handling and storage are within the capacity of the RHUs. 4) **Ease in logistics and administration** - Evidence: *Sinopharm* can be stored for 6 months at 2-8°C in cold chain facilities that are present in most RHUs. The vaccine is a suspension for injection that does not require dilution at the vaccination site which may simplify implementation of the vaccine especially in community settings. 5) **Cost-effectiveness** - Evidence: The health, economic, and social benefits of using *Sinopharm* mitigate the negative impact of COVID-19, such as deaths, medical costs, loss of productivity, social disruption, and unprecedented challenges in the health system. 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	experience and may impact on implementation strategy

	any untoward event following vaccination ● *Appropriateness of the vaccine to special at-risk groups and patients with comorbidities*	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 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. d. Based on the national survey conducted by the Social Weather Station from 27 to 30 September 2021 among 1,500 Filipino adults: - 64% of adult Filipinos are willing to get vaccinated (25% who already received 2 doses of COVID-19 vaccines, 10% who already received 1 dose of COVID-19 vaccine, 23% unvaccinated individuals who responded that they will surely get vaccinated, and 6% who responded that they will probably get vaccinated). This is 9 points above the 55% willingness in June 2021 and twice as high compared to the results of the May 2021 survey. - In the same survey, willingness to get vaccinated increased in all areas compared to the June 2021 survey results. The proportion of willing respondents increased from 76% to 87%, 54% to 65%, 48% to 56%, and 48% to 54% in Metro Manila, Balance Luzon (i.e. areas in Luzon outside Metro Manila), Visayas, and Mindanao, respectively. The proportion of those uncertain and unwilling also decreased in all geographical areas, when compared to results in June 2021.	

		- The percentage of vaccinated respondents also increased from 10% in June 2021 to 35% in the September 2021 survey. - Willingness to be vaccinated among elementary, junior high school, and college graduates also increased since the survey in June 2021. For elementary graduates, those willing to get a COVID-19 vaccine increased from 49% to 59%. Junior high school graduates' willingness increased from 59% to 68%. Among college graduates, those willing to get a COVID-19 vaccine increased from 71% to 83%. Non-elementary graduates' willingness to be vaccinated increased from 27% to 36%, however, this group is still the least willing to get vaccinated. - 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 Phase III clinical trial enrolled individuals 18 years and above. Currently, there is limited data from the trial on the use of the vaccine for special at-risk groups such as the older population, patients with comorbidities, 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. The WHO recommendations (28 Oct 2021) on the use of this vaccine in the older population, patients with comorbidities, and other special populations are detailed below. *For older populations:* - According to the WHO interim guidance on the use of this vaccine, the efficacy of the vaccine in participants 60 years and older cannot be estimated in the phase 3 clinical trial available. Observational data suggest a	

		vaccine effectiveness across all age-groups of more than 80%, including persons aged ≥ 60 years. Supportive immunogenicity data together with observational data suggest that the vaccine is likely to have a protective effect in older persons, although whether at an equivalent level as in younger adults needs to be shown. Likewise, although safety data from clinical trials are limited, there are no theoretical reasons to believe that the vaccine has a different safety profile on older than in younger younger populations for which there is evidence specific to this vaccine hence it is recommended for older persons. - Given increasing evidence on lower immunogenicity and vaccine effectiveness in older persons aged 60 and above, WHO recommends an additional dose for this population for countries that have already achieved high vaccine coverage with the primary vaccine series in high-priority groups. Implementation should follow the WHO prioritization map, particularly the ≥80 year age group, followed by individuals aged ≥60 years. However, the WHO recommends that countries that have not yet achieved high vaccine coverage should focus on achieving this target before implementation of the additional dose. *For populations with comorbidities:* - According to the WHO interim guidance on the use of this vaccine, there is limited data to determine vaccine efficacy among participants with comorbidities included in the trial. However, previous experience with other vaccines with the same platform indicates that vaccine effectiveness in populations with comorbidities , except for immunocompromised patients, is likely to be similar or slightly lower than in persons of the same age without comorbidities. Considering the favourable benefit-risk assessment, the WHO recommends it for persons with comorbidities. *For pregnant women* - Completed developmental and reproductive toxicity studies in animals have not demonstrated harmful effects of the vaccine in pregnancy. - Vaccine effectiveness in pregnant women is expected to be similar to non-pregnant women in similar age groups. - In the interim, WHO recommends vaccination in pregnant women when the benefits of vaccination outweigh the potential risks. Risks of COVID-19 in pregnancy, the likely benefits of vaccination, and the limited safety data in pregnant women should be considered. *For lactating women* - Vaccine effectiveness in lactating women is expected to be similar to other adults. However, currently, there is no evidence on the potential benefits and risks of the vaccine on breastfed children. - In the interim, as the vaccine is not a live virus, it is biologically and clinically unlikely to pose a risk to the	

		breastfeeding child, and is therefore recommended for lactating women. *For children and adolescents below the age of 18 years* - As of the date of the WHO recommendation, individuals below 18 years of age were not recommended to be vaccinated with this vaccine based on the lack of efficacy and safety data for this population. However, since then, the Phase I/II trial on the use of the vaccine in the pediatric population was released. The trial was found to be safe and well-tolerated at all tested dose levels in participants aged 3–17 years. The vaccine has also elicited robust humoral immune responses against SARS-CoV-2 infection after the two dose regimen. *For 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. - Available data show 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. *For 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. *For 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. **HTAC Judgment:** Based on short-term outcomes, *Sinopharm* possesses most of the characteristics desired by key stakeholders for its use among the general population 18 years and above.	
CRITERION 6			
6.Responsiveness to equity	*How will Sinopharm and its use impact*	There is limited evidence from the Phase III RCT and real world studies on the efficacy and effectiveness of *Sinopharm* in older adults ≥60 years and in individuals with comorbidities. However, the Phase III RCT reported no incident cases of	Ideally, health interventions can be

	pre-COVID-19 and COVID-generated health and socioeconomic inequities? *Which groups might be unfairly disadvantaged in relation to the COVID-19 disease burden and delivery of the Sinopharm?*	COVID-19 among the elderly population included in the trial. *Sinopharm* can be stored at normal cold storage conditions (2 to 8°C). This can make vaccine distribution in geographically isolated and disadvantaged areas possible. **HTAC Judgment:** Because of non-stringent logistic requirements, *Sinopharm* will not aggravate health inequities related to inoculation of recipients residing in isolated and disadvantaged locations. However, there is currently limited evidence on the efficacy and effectiveness of *Sinopharm* as a primary vaccine in special populations such as the older population and individuals with comorbidities.	fairly adopted and distributed/ implemented for eligible populations without aggravating existing health inequities especially for vulnerable sectors of our society.

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- Philippine Living Clinical Practice Guidelines Group (LCPG Group)
- Philippine Insurance Corporation (PhilHealth)

Appendix 1. Review on Sinopharm by the Philippine Living Clinical Practice Guidelines Group

Link: https://docs.google.com/document/d/1kHxaIcpu7nqdFTk28ozzeYOH5OhSu7OU/edit

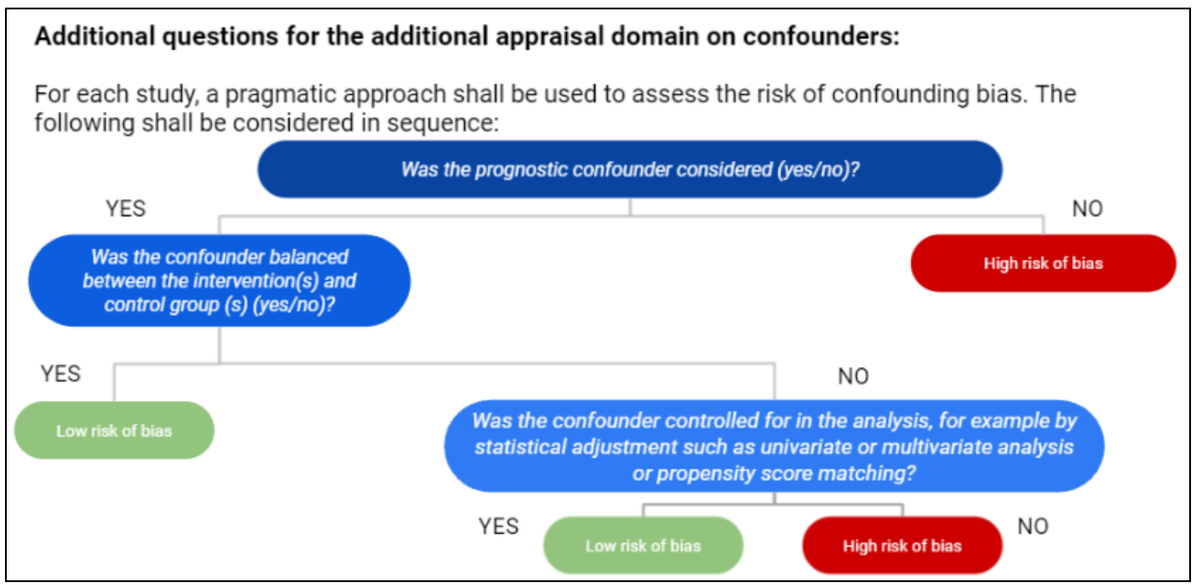
Appendix 2. Risk of Bias Assessment Method (LCPG Group)

The LCPG group conducted a Risk of Bias Assessment of the included RCTs using the Cochrane Risk of Bias Tool 2. Meanwhile, for observational studies, the LCPG Group developed an appraisal tool which was composed of two parts:

Part 1: The Cochrane Risk of Bias Tool 1 with the following domains

- Randomization
- Allocation concealment
- Blinding of Participants
- Blinding of Investigators
- Blinding of Assessors
- Missing outcomes/follow up
- Selecting reporting

Part 2: Assessment of confounders terms of age, exposure risk, and comorbidities using the following algorithm to determine the study's assessment, balance, and control for these confounders.



Appendix 3. GRADE Table (HTAC Appraisal)

Efficacy and effectiveness

Efficacy Outcome		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(at >14 days after dose2)	1 RCT	**Not serious**	**Not assessed**	**Not serious**	**Not serious**	**None**	26/12743 [a] 21/12726 [b]	95/ 12737	72.8[a] (58.1-82.4 78.1[b] (64.8-86.3)	**++++ High**
2 : Severe COVID-19 infection, seronegative at baseline(at >14 days after dose2)	1 RCT	**Serious** *Short ffup*	**Not assessed**	**Not serious**	**Serious** *Low number of events*	**None**	0/12743 [a] 0/12726 [b]	2/12737	100% (NE)	**++ Low**
3. Asymptomatic COVID-19 infection, seronegative at baseline (at >14 days after dose2)	1 RCT	**Not serious**	**Not assessed**	**Not serious**	**Not serious**	**None**	16/12727 [a] 10/12713 [b]	21/12722	Not reported	**++++ High**
4. Any COVID-19 infection, seronegative at baseline (at >14 days after dose2)	1 RCT	**Not serious**	**Not assessed**	**Not serious**	**Not serious**	**None**	42/12727 [a] 31/12713 [b]	116/12722	64.0 [a] (48.8-74.7) 73.5 [b] (60.6-82.2)	**++++ High**
5. Symptomatic COVID-19 infection after first dose, before the second dose	1 RCT	**Not serious**	**Not assessed**	**Not serious**	**Not serious**	**None**	43/12727 [a] 27/12713 [b]	43/12722	50.3% [a] (33.5-62.7) 65.5% [b] (52.0-75.1%)	**++++ High**

Safety

Safety Outcome		Quality Assessment					Summary of Findings			
		Risk of Bias	Inconsistency	Indirectness	Imprecision	Other considerations	Vaccine [1]	Control [1]	Relative Risk (95%CI)	Certainty
1: Solicited adverse reaction	4 RCT[1]	**Not serious**	**Not serious**	**Not serious**	**Not serious**	**None**	5595/13464 (41.6%) [a] 5270/13471 (39.1%) [b]	5935/13453 (44.1%)	0.94 (0.92- 0.97)[a] 0.89 (0.86- 0.91)[b]	**++++ High**
2: Local adverse reaction	4 RCT[1]	**Not serious**	**Not serious**	**Not serious**	**Not serious**	**None**	3450/13464 (25.6%) [a] 2786/13471 (20.7%) [b]	3906/13453 (29.9%)	0.88 (0.85- 0.92)[a] 0.71 (0.68- 0.74)[b]	**++++ High**
3: Systemic adverse reaction	4 RCT[1]	**Not serious**	**Not serious**	**Not serious**	**Not serious**	**None**	3695/13464 (27.4%) [a] 3810/13471 (28.3%) [b]	3743/13453 (27.8%)	0.99 (0.95- 1.03)[a] 1.02 (0.98- 1.06)[b]	**++++ High**
4. Unsolicited adverse event (28d)	4 RCT[1]	**Not serious**	**Not serious**	**Not serious**	**Not serious**	**None**	2162/13464 (16.1%) [a] 2094/13464 (15.5%) [b]	2075/13453 (15.4%)	1.04 (0.99- 1.10)[a] 1.01 (0.95- 1.07)[b]	**++++ High**
5: Serious adverse event	4 RCT[1]	**Serious** *Short ffup*	**Not serious**	**Not serious**	**Serious (wide CI)**	**None**	64/13464 (0.5%) [a] 59/13471 (0.4%) [b]	78/13453 (0.6%)	0.83 (0.59 to 1.15)[a] 0.76 (0.54 to 1.06)[b]	**++ Low**
8: Death	4 RCT[1]	**Serious** *Short ffup*	**Not serious**	**Not serious**	**Not serious**	**None**	No events	No events	No events	No events

1 – values from the Phase 3 trials only a – WIV04/WIBP b – HBO2/BiBP c – unspecified strain

Appendix 4. Risk of Bias Assessment (LCPG Group Appraisal)

Study ID	Design	Randomization	Allocation Concealment	Blinding Particip	Blinding Carer/ Assessor	Followup	Selective Reporting	Others	Age	Comorbidities	Exposure	Confounding	OVERALL
Abu-Halaweh (Jordan)	Prospective cohort	HiGH	HiGH	HiGH	HiGH	HiGH	UNCLEAR	NA	HiGH	HiGH	HiGH	HiGH	SERIOUS
Al Kaabi (UAE, Egypt)	RCT Ph3	LOW	LOW	LOW	LOW	HiGH	LOW	NA	NA	NA	NA	NA	SOME CONCERNS
Ariamanesh (Iran)	Single cohort	HiGH	HiGH	HiGH	HiGH	HiGH	UNCLEAR	NA	HiGH	HiGH	HiGH	HiGH	SERIOUS
Badano (Argentina)	Single cohort	HiGH	HiGH	HiGH	HiGH	HiGH	UNCLEAR	NA	HiGH	HiGH	HiGH	HiGH	SERIOUS
Drulovic (Serbia)	Single cohort	HiGH	HiGH	HiGH	HiGH	HiGH	UNCLEAR	HiGH	HiGH	HiGH	HiGH	HiGH	VERY SERIOUS
Etemadifar (Iran)	Prospective cohort	HiGH	HiGH	HiGH	HiGH	HiGH	UNCLEAR	HiGH	HiGH	HiGH	HiGH	HiGH	SERIOUS
Feng (China)	RCT Ph4	LOW	UNCLEAR	UNCLEAR	UNCLEAR	HiGH	LOW	NA	NA	NA	NA	NA	SERIOUS
Ferecii (Hungary)	prospective cohort	HiGH	HiGH	HiGH	HiGH	HiGH	UNCLEAR	NA	HiGH	HiGH	HiGH	HiGH	SERIOUS
Holt (UAE)	Prospective cohort	HiGH	HiGH	HiGH	HiGH	HiGH	UNCLEAR	NA	NA	NA	NA	NA	SERIOUS
Huang (China)	Single cohort	HiGH	HiGH	HiGH	UNCLEAR	UNCLEAR	UNCLEAR	HiGH	HiGH	HiGH	HiGH	HiGH	SERIOUS
Jahromi (Bahrain)	Single cohort	HiGH	HiGH	HiGH	HiGH	HiGH	UNCLEAR	HiGH	HiGH	HiGH	HiGH	HiGH	VERY SERIOUS
Jeewandara (Sri Lanka)	Single cohort	HiGH	HiGH	HiGH	UNCLEAR	LOW	UNCLEAR	NA	HiGH	HiGH	HiGH	HiGH	SERIOUS
Liu (China)	Single cohort	HiGH	HiGH	HiGH	HiGH	HiGH	UNCLEAR	NA	HiGH	HiGH	HiGH	HiGH	SERIOUS
Liu Y (China)	Single cohort	HiGH	HiGH	HiGH	HiGH	LOW	UNCLEAR	NA	HiGH	HiGH	HiGH	HiGH	SERIOUS
Saeed (UAE)	Single cohort	HiGH	HiGH	HiGH	HiGH	HiGH	UNCLEAR	NA	HiGH	HiGH	HiGH	HiGH	SERIOUS
Sahraian (Iran)	Single cohort	HiGH	HiGH	HiGH	HiGH	HiGH	UNCLEAR	NA	HiGH	HiGH	HiGH	HiGH	SERIOUS
Xia1 (China)	RCT Ph 1/2 (Adult)	LOW	LOW	LOW	LOW	LOW	UNCLEAR	NA	NA	NA	NA	NA	NOT SERIOUS

Xia2 (China)	RCT Ph 1/2 (Children)	LOW	LOW	LOW	LOW	LOW	UNCLEAR	NA	NA	NA	NA	NA	NOT SERIOUS

Appendix 5. Risk of Bias Assessment (COVID-NMA)

For RCTs, the COVID-NMA Living review group conducted using the Cochrane Risk of Bias 2 tool. For phase I/II studies, risk of bias was assessed for safety outcomes only.

Trial ChiCTR2000031809
Publication Guo W, EClinicalMedicine, 2021
Primary outcome on the report: 7-day adverse reactions; neutralizing antibody titres and specific IgG binding antibody titres measured on days 28 and 90 after the whole-course vaccination
Note: The risk of bias by domain corresponds to the highest risk of bias among outcomes by domain. The overall risk of bias corresponds to the overall highest risk of bias assessed among outcomes.

Bias	Author's judgement	Support for judgement
Randomization	**Some concerns**	Quote: "Sequential computer-generated randomization numbers were assigned to participants, and stratified block randomization by age and doses was adopted (block size 8)." Comment: Allocation sequence random. Unclear allocation concealment. Imbalances in baseline characteristics appear to be compatible with chance. Risk assessed as some concerns
Deviations from intervention	**Low**	Quote: "Participants, investigators, and laboratory personnel were blinded to the intervention allocation." Comment: Blinded study (participants and personnel/carers) Data for the outcome were analyzed using intention-to-treat analysis. As we are assessing the effect of assignment to intervention, the analysis method performed on these safety outcomes, was considered appropriate Risk assessed to be low for the outcomes: Neutralizing antibody GMT. Specific antibody GMT. Local adverse events. Systemic adverse events. Adverse events. Serious adverse events.
Missing outcome data	**Low**	Comment: 1120 participants randomized; 1120 participants analyzed for safety; 1113 participants analyzed for immunogenicity. Data available for all or nearly all participants randomized. Risk assessed to be low for the outcomes: Neutralizing antibody GMT. Specific antibody GMT. Local adverse events. Systemic adverse events. Adverse events. Serious adverse events.

Measurement of the outcome	**Low**	Comment: Method of measuring the outcome is probably appropriate. Measurement or ascertainment of outcome probably does not differ between groups. Blinded study (outcome assessor). Risk assessed to be low for the outcomes: Neutralizing antibody GMT. Specific antibody GMT. Local adverse events. Systemic adverse events. Adverse events. Serious adverse events.
Selection of the reported results	**Low**	Comment: The protocol, statistical analysis plan and registry (prospective, dated 2020-04-11) were available. Outcomes pre-specified. Results were not selected from multiple outcome measurements or analyses of the data. Trial analyzed as pre-specified. Risk assessed to be low for the outcomes: Neutralizing antibody GMT. Specific antibody GMT. Local adverse events. Systemic adverse events. Adverse events. Serious adverse events.
Overall risk of bias	**Some concern**	

Appendix 6. Risk of Bias Assessment (HTAU Appraisal)

The appraisal of Al Hosani et al. (2021) was conducted by the HTAU. The method used by the LCPG Group for the appraisal of observational studies was adopted for this appraisal. Refer to Appendix 2 for the details on the appraisal tool used.

STUDY	Al Hosani et al., 2021	
STUDY DESIGN	Retrospective cohort	
DOMAINS	**REVIEWER JUDGMENT (HIGH / UNCLEAR / LOW / NA)**	**SUPPORT FOR JUDGMENT**
RANDOMIZATION	High	No randomization
ALLOCATION CONCEALMENT	High	No allocation concealment
BLINDING OF PARTICIPANTS	High	No blinding
BLINDING OF INVESTIGATORS	High	No blinding
BLINDING OF ASSESSORS	High	No blinding
MISSING OUTCOMES / FOLLOW-UP	Low	Cases with missing or incomplete data were excluded from the analysis (n=38,300) Excluded cases with an event before evaluation period (14 days post-vaccination) Follow-up was more than 200 days of observation period (based on Figure 3)
SELECTIVE REPORTING	High	Protocol not available. Methods stated outcome of interest which were the outcomes presented in the results; values for incidence risk over time were not reported
Overall ROB	High	
ASSESSMENT OF CONFOUNDING FACTORS		

AGE	A	Yes	Table 3 Multivariate analysis based on Cox proportional hazard regression models (Table 3) corroborated the unadjusted findings and reached the same qualitative conclusions. with respect to vaccine effectiveness for the three outcomes under consideration. Additionally, subjects aged 30-59 years old and those above 60 years experienced significantly higher risk for all outcomes compared with those below 30 years old.
	B	Yes	Table 1. Balanced for all age groups except for the age group 15-19
	C	Yes	Table 3. Multivariate analysis based on Cox proportional hazard regression model to confirm unadjusted findings
EXPOSURE RISK	A	Yes	All participants had prior exposure to COVID (all participants were positive, the study evaluated the outcomes after being positive)
	B	Yes	
	C	N/A	
COMORBIDITIES	A	No	"risk assessment based on comorbidities could not be assessed, another limitation of the study"
	B	No	
	C	No	
OVERALL FOR CONTROL OF CONFOUNDERS		**Low**	
OVERALL APPRAISAL		**Serious**	High ROB due to study design but low ROB for control of confounders

Appendix 7. Costing table

Cost of implementing *Sinopharm*

In projecting the costs for implementing the COVID-19 Vaccination program in 2022 using *Sinopharm,* the following cost items were identified in calculating for the total resource requirement: *Sinopharm* and vaccine consumables; logistics (hauling and storage); and operations (recruitment and training of vaccinators). The source of these costs was derived from the DOH - Disease Prevention and Control Bureau's (DPCB) overall vaccine budget plan. Overall, the projected cost of vaccine and consumables, logistics and operations to vaccinate 500,000 Filipinos with *Sinopharm* is Php 711,134,959.49.

For the sources of cost value inputs, we used the unit cost of vaccines based on the price offered to the government (as disclosed in confidence by DOF). Meanwhile, the cost inputs (i.e., cost items, cost values and resource utilization) to estimate the cost of consumables, logistics and operations were all referenced from the DOH-NIP and the manufacturer. The calculations were also consulted and aligned with the DOH-NIP.

The paragraphs below will detail the costing calculation for cost components.

Vaccine and Consumables

The total cost of vaccines and consumables for 500,000 Filipinos will amount to Php 558,976,000.00. This amount takes into account 1% estimated wastage of vaccines and cost of two doses of *Sinopharm* for every vaccinee, as well as the 10% estimated wastage for vaccine consumables. Vaccine consumables include injection devices and safety collector boxes. As for personal protective equipment (PPE) of the vaccination team, these costs will be incurred by the LGU as this will be incorporated in their routine vaccination program.

Logistics

Included under logistics are hauling and storage costs. Hauling cost includes the rental cost of transport boxes that can contain 400 vials each box. Given a weight of 31.4 kg per box, the total cost for hauling *Sinopharm* is estimated at Php 152,127,513.00. This amount also includes a 1% valuation cost. For storage, it is estimated to cost Php 504 per cubic meter per month of storage, resulting in a storage cost of Php 31,446.46 per month. The overall cost for logistics is estimated to be at Php 152,158,959.46.

Operations

Operations cost includes mobilization, hiring costs, as well as training for vaccine implementation. However, since COVID-19 Vaccination in 2022 is expected to be incorporated in the routine immunization program of LGUs, operations costs shall be incurred by the LGU.

Table A3.1 summarizes the resource requirement costs and assumptions in the roll-out of *Sinopharm* in the Philippines in 2022.

Table A3.1. Resource requirement costs in the roll-out of *Sinopharm* in the Philippines in 2022

Description	Cost	Assumptions/Notes	Source
Vaccine and Vaccine Consumables	**Php 558,976,000.00**	For two doses, with 1% wastage for vaccines; consumables include syringes and safety collector boxes, with 10% wastage for vaccine consumables *(estimated costs for vaccinating 500,000 Filipinos based on identified target primary vaccinees for 2022)*	DOF, DPCB
Logistics	**Php 152,158,959.46**	This includes hauling and storage costs. *(estimated costs for vaccinating 500,000 Filipinos based on identified target primary vaccinees for 2022)*	DPCB
Operations	**Php 0**	Operations cost will be incurred by the LGUs as this will be incorporated in their routine vaccination program.	DPCB
TOTAL COST	**Php 711.13 M**		
PROPORTION OF THE COST TO THE 2022 TOTAL COVID-19 VACCINATION BUDGET	**0.86%** **[Allocated from 2021 budget]**		

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

Based on the projected calculations, the total cost of rolling out vaccination with *Sinopharm* for 500,000 Filipinos would amount to Php 711,134,959.46. This would entail utilization of 0.86% of the total allocated budget for vaccination while the roll out using *Sinopharm* will cover 0.52% of the target vaccinees for primary homologous vaccination.