Evidence Summary on *CoronaVac COVID-19 Vaccine* for children 6 to 17 years old

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Background

In February 2021, the Philippine FDA released the initial EUA for the use of *CoronaVac* in adults ages 18 years to 59 years old. The age group was eventually expanded to include individuals aged 60 and above on 07 April 2021. On 24 May 2021, the World Health Organization Strategic Advisory Group of Experts (WHO SAGE) released their interim recommendation for the use of *CoronaVac* wherein they recommended the use of the said vaccine in persons aged 18 years and above.

On 09 April 2021, the Health Technology Assessment Council (HTAC) first released its recommendation for the emergency use of *CoronaVac* as the primary vaccine in the country for the healthy population, 18 to 59 years of age. This recommendation was then updated on 30 July 2021 to expand the target population to include older adults aged 60 years old and above.

On 11 March 2022, the Philippine Food and Drug Administration (FDA) updated its Emergency Use Authorization (EUA) for the use of *CoronaVac* to include children ages 6 to 17 years old. According to the Philippine FDA, the use of *CoronaVac* for children aged 6 years and older will use the same formulation and will follow the same dose strength and dosing interval as that used for adults i.e., 2 doses of 600 SU/0.5mL per dose, 4 weeks apart. As of this writing, *CoronaVac* has been granted EUA for use in children in 13 other countries specifically for the following age groups:

- 6 months to 17 months: HongKong (3-dose schedule)
- 3 to 17 years old: China, Cambodia, Chile, Colombia, Brazil, Ecuador
- 5 to 17 years old: Dominican Republic, Malaysia
- 6 to 17 years old: Thailand, Indonesia
- 12 to 17 years old: Myanmar
- 16 to 17 years old: Zimbabwe

On 11 August 2022, the WHO released an updated interim statement on the COVID-19 vaccination for children, stating that children with comorbidities and severe immunocompromising conditions should be offered vaccination. They also noted that COVID-19 vaccines with WHO Emergency Use Listing (EUL) that have undergone clinical trials in children and adolescents are safe and effective in preventing disease. However, despite having completed trials in children and being approved by Chinese authorities, *CoronaVac* has yet to receive WHO EUL for its use in children. The WHO maintains that countries should consider the individual and population benefits of immunizing children and adolescents in their specific epidemiological and social context when developing their COVID-19 immunization policies and programs.

Table 1.1 Characteristics of *CoronaVac*

Trade name	SARS-CoV-2 Vaccine (Vero Cell), Inactivated [CoronaVac]
Other name	*CoronaVac*
Manufacturer/s	Sinovac Life Sciences Co., Ltd.
Vaccine platform	Inactivated vaccine
Dose strength and administration	• Children aged 6 to 11 years old: 2 doses of 600 SU/0.5 mL suspension for injection (IM) • Adolescents aged 12 to 17 years old: 2 doses of 600 SU/0.5 mL suspension for injection (IM) • Adults aged 18 years old and above: 2 doses of 600 SU/0.5 mL suspension for injection (IM)

	• Immunocompromised population aged 18 years old and above: 3 doses of 600 SU/0.5 mL suspension for injection (IM)
Route of administration	Intramuscular (IM)
Drug delivery system	Opalescent aqueous suspension in one-dose or two-dose vials.
Storage condition	Store at 2° to 8°C. Protect from light. Do not freeze. One dose vial: 12 months; Two-dose vial: 6 months
Mechanism of action	*Inactivated strain of SARS-CoV-2 created from vero -cells to induce immune response (Mascellino et al., 2021)*
Contraindications	• People with history of allergic reaction to *CoronaVac* or other inactivated vaccine, or any component of CoronaVac (active or inactive ingredients, or any material used in the process); • Previous severe allergic reactions to the vaccine (e.g. acute anaphylaxis, angioedema, dyspnea, etc); • People with severe neurological conditions (e.g. transverse myelitis, Guillain-Barre syndrome, demyelinating diseases, etc); • Patients with uncontrolled chronic diseases
PHL EUA status	• Released on 22 February 2021 • Updated on 07 April 2021 to include senior citizens in the target population • Updated on 15 November 2021 to include its indication for booster vaccination among adults 18 years and above • Updated on 11 March 2022 to expand the indication to individuals aged 6 and above
PHL FDA EUA indication	This product is suitable for clinically healthy people aged 6 years old and above susceptible to virus.

The product information/fact sheet is available here.

Pursuant to the role of the Health Technology Assessment Council (HTAC) which is to develop recommendations 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, viability and feasibility; (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 finance ***CoronaVac COVID-19 Vaccine for the pediatric population ages 6 - 17 years old*** as part of the 2022 COVID-19 Vaccination Program to reduce COVID-19 cases, severe infection, and deaths?

Recommendations *(as of 05 October 2022)*

The **HTAC is not recommending government financing of *CoronaVac* for primary vaccination series for children aged 6 to 11 years old because of the unsatisfactory benefit-risk profile** based on currently available evidence on clinical efficacy and effectiveness against Omicron variant and short term safety data.

However, for children ages 6 to 11 years old with contraindications to receiving currently available mRNA vaccines (eg. anaphylaxis to the first dose of mRNA vaccine or previous allergy to PEG), the HTAC recommends using available supplies of *CoronaVac* as an alternative based on the evidence that *CoronaVac* shows lower risk of having severe adverse events (SAEs) compared to mRNA vaccines.

Meanwhile, **for children ages 12 to 17 years, the HTAC recommends using available supplies of *CoronaVac* as an alternative for mRNA vaccines due to its acceptable benefit-risk profile** based on currently available clinical effectiveness against the Omicron variant and short-term safety data.

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

Criteria	HTAC Judgment for 6 to 11 years old *(as of 05 October 2022)*	HTAC Judgment for 12 to 17 years old *(as of 05 October 2022)*
What is the magnitude and severity of COVID-19 in children ages 6 to 17 years old? *Is COVID-19 a public health priority?*	The global burden of COVID-19 contributed by children aged 6 to 17 years old cannot be ascertained as children experience milder symptoms and asymptomatic presentations leading to less probability of being tested and more unreported cases (WHO, 2021). In the Philippines, trends of cases in children are similar to other age groups, with a rise in cases from July to August 2022. A decrease in cases was observed in early September 2022 but an increase is being observed again in late September 2022. Meanwhile, Case Fatality Rates (CFRs) in children remained relatively the same over time, which is consistent in other age groups as well. In terms of hospitalization, currently, the effect of variants in this age group cannot be established due to limited sequencing capacity in the country. Only one (1) new case of MIS-C was reported in the 12-17 year-old age group from March to July 2022 and no new case of MIS-C was then reported from July to August 2022 based on passive surveillance of the SALVACION registry. It is noted that studies of hospitalized children with SARS-CoV-2 Omicron infection in Hong Kong showed more severe illness with neurologic manifestations and croup compared to children with influenza and parainfluenza. In terms of transmission, children have significantly lower possibility to transmit SARS-CoV-2 to their family members. Specifically for Omicron, there is no significant difference in the household secondary attack rate between child and adult contacts. There are no local studies on post-COVID-19 conditions. US data shows that this post-COVID-19 condition appears to be less common in children than in adults. Based on the above, there is no apparent increase in the burden of COVID-19 among children aged 6 to 17 years old, as of the writing of this report (07 September 2022).	
Is CoronaVac safe and efficacious for the pediatric population ages 6 to 17 years old? *Can CoronaVac*	**Yes,** based on limited trial data and real-world post-marketing safety surveillance, the short-term safety of 2-dose primary series of *CoronaVac* in children aged 6-17 years is acceptable. However, further follow-up data is needed to establish longer-term safety. Evidence on clinical efficacy of C*oronaVac* in children aged 6 to 17 years old showed that VEs against the Omicron variant did not pass HTAC specifications, based on very low certainty of evidence (Sinovac Life Sciences Co., Ltd., 2022). • **Symptomatic COVID-19 (6 to 11 yo):** 22.11% (95% CI: -26.74 to 52.52) • **Symptomatic COVID-19 (12-17 yo):** 19.97% (95% CI: -77.45 to 64.59)	

significantly reduce the magnitude and severity of COVID-19 in children ages 6 to 17 years old?	• **Severe COVID-19(6 mo to 17 yo):** 75.29% (95% CI: -149.70 to 99.50)
	
	In terms of **v**accine effectiveness during the Omicron-dominant period and the Delta-dominant period, there were varying results.
	• A real-world study in Chile during the Delta dominant period (Jara et al., 2022, preprint) showed passing VE against hospitalization due to COVID-19 [VE: 91.0% (95% CI: 87.7 to 93.4)] in children aged 6 to 16 years old, based on high certainty of evidence.
	• Meanwhile, in terms of the Omicron variant:
	  ○ Florentino, et al. 2022 (published) showed that VEs against Omicron variant in children aged 6 to 11 years old did not pass HTAC specifications based on moderate to very low certainty of evidence:
	  ■ Symptomatic COVID-19 39.8% (95% CI: 33.7 to 45.4)
	  ■ Hospitalization due to COVID-19: 59.2% (95% CI: 11.3 to 84.5)
	  ■ ICU admission due to COVID-19 20.9 (95% CI: -177.2 to 85.0)]
	  ○ Lau et al., 2022 (preprint), a test-negative design study showed that:
	  ■ In children aged 3 to 11 yo, VE against infection of *CoronaVac* at least 14 days after the second dose did not pass the HTAC specifications for symptomatic COVID-19 [VE: 40.8% (95% CI: 12.8 to 59.5)]. However, it was noted vaccination in children aged 3 to 11 yo was implemented during the Omicron variant and while the study was already being conducted. Longer follow-up period is needed to establish the effectiveness of the vaccine in this age group.
	  ■ In adolescents aged 12 to 17 yo, VE against infection of *CoronaVac* at least 14 days after the second dose passed the HTAC specifications for symptomatic COVID-19 [VE: 55% (38.2 to 67.2)].
	
	In terms of immunogenic response is acceptable:
	• Phase III trial by Soto et al., 2022 (preprint) showed that *CoronaVac* induces an immune response in children aged 6 to 17 years old. However, there was a decrease in neutralizing antibody and T-cell response against Delta variant compared to the wild-type strain. For the Omicron variant, there is a decrease in neutralizing antibodies but an increase in T-cell response.
	• Immunobridging study by Rosa Duque et al., 2022 (published, variant not specified) showed that *CoronaVac* induces an immune response in adolescents aged 11 to 17 years old that is either non-inferior or superior compared to the immune response of adults.
	• Phase II trial by Leung et al., 2022 (preprint, wild-type) showed enhanced immune response in adolescents aged 11 to 17 yo after the second dose of *CoronaVac* compared to before vaccination.	

Does CoronaVac provide a highly favorable benefit/risk profile in the context of observed vaccine efficacy, effectiveness and safety in individuals aged 6 to 17	Among children aged 6 to 11 years old, the 2-dose primary series of *CoronaVac* has an **unsatisfactory benefit-risk** profile based on currently available evidence on clinical efficacy and effectiveness against the Omicron variant and short-term safety data. However, for children aged 6 to 11 years old with mRNA vaccine contraindication (eg. anaphylaxis to the first dose of mRNA vaccine or previous allergy to PEG), *CoronaVac* may be given.	Among children aged 12 to 17 years old, the 2-dose primary series of *CoronaVac* has an acceptable benefit-risk profile based on currently available clinical effectiveness against the Omicron variant and short-term safety data.

years old?		
Is CoronaVac affordable and feasible to use in a national immunization program for the pediatric population ages 6 to 17 years old? Does CoronaVac represent good value for money in terms of preventing COVID-19 morbidity and mortality?	Implementing 2-dose primary series using *CoronaVac* for children aged 6 to 11 years old with mRNA vaccine contraindications and adolescents aged 12 to 17 years old will not incur additional budget impact as existing doses will be used for this vaccination strategy. A 2-dose primary series of *CoronaVac* for children aged 6 to 11 years old with mRNA vaccine contraindications and adolescents aged 12 to17 years old may represent good value for money as it is likely to be effective based on limited evidence.	
Does CoronaVac reduce out-of-pocket (OOP) expenses of households due to COVID-19?	Based on current evidence, 2-dose primary series of *CoronaVac* for children aged 6 to 11 years old with mRNA vaccine contraindications and adolescents aged 12 to 17 years old has the potential to reduce out-of-pocket expenses due to averted costs of isolation and treatment of mild, moderate, and severe COVID-19.	
Does CoronaVac possess the characteristics that are desired by key stakeholders?	Given the available clinical evidence, ease in logistics and ability to allow for equitable coverage, and availability of FDA EUA, *CoronaVac* possesses most of the characteristics desired by key stakeholders for its use as a 2-dose primary series for children aged 6 to 11 years old with mRNA vaccine contraindications and adolescents aged 12 to 17 years old. However, currently there is no information on public acceptability of CoronaVac as the primary series for pediatric vaccination. Furthermore, *CoronaVac* does not have a WHO EUL for the pediatric population.	
Does CoronaVac reduce or not further add to existing inequities in the health system?	The HTAC reiterates the importance of the following measures in the success of the implementation of COVID-19 primary series for the adolescent population: ● emphasis on strategies to increase primary series in children <12 years old and first booster vaccination coverage among priority groups ● ensure that information, education, and communication (IEC) and other vaccination-related documents are accessible and comprehensible (i.e., translated into the local language of the target population) Vaccination of the adolescent population shall be rolled out following the country's prioritization criteria, cognizant of the following: ● burden of COVID-19 in the priority groups, especially those with comorbidities; ● sufficient supply to cover the all other vaccination strategies in the pipeline along with second booster (remaining primary and 1st booster for adult population)	

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, the International Vaccine Access Center (IVAC) of the Johns Hopkins Bloomberg School of Public Health and World Health Organization review, COVID-NMA living review and review of global and local data pertaining to the epidemiology of 6 to 17 year-old children with COVID-19.

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

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

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

- 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., individuals with comorbidities, 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
- Best practices, challenges, and barriers in implementation across different localities
- Monitoring of unexpected or additional costs associated with vaccine implementation.

Current Evidence on *CoronaVac COVID-19 Vaccine*

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

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

- Appendix 1A: Risk of Bias Assessment Methodology

- Appendix 1B: Risk of Bias Assessment Results by HTAC
- Appendix 2: GRADE Table

Table 1.2 Key Findings in the Current Evidence Considered for the HTAC Evaluation of *CoronaVac for the pediatric population*

<table>
<tr><th>Evaluation Criteria</th><th>Question</th><th>Current Evidence</th><th>HTAC specification</th></tr>
<tr><td colspan="4">CRITERION 1</td></tr>
<tr><td>1. Responsiveness to magnitude and severity</td><td>What is the magnitude and severity of COVID-19 in children ages 6 to 17 years old?

Is COVID-19 a public health priority?</td><td>Local epidemiologic data on children ages 6 to 17 years old versus older age groups
In the pediatric population, the DOH Philippines recorded a total of 274,639 COVID-19 cases in the pediatric population ages 6-17 years old (6-11 y.o. children: 116,660 cases; 12-17 y.o. adolescents: 157,979 cases) as of 17 September 2022. A rise in cases in children was observed from June to August 2022. A decrease in cases was observed in early September 2022 but an increase is being observed again in late September 2022. This trend is consistent across all age groups. In terms of risk of infection, children in the 6-17 years age group have the second to the lowest rate of cases per total at-risk population at 1.06% (6-11 yo: 0.88%; 12-17 yo: 1.24%). This is much lower compared to the adult and elderly population (4.84% for 18-59 years old and 5.10% for 60 years old and above) and slightly more than the population below 6 years old (0.82%).

Evidence on risk of hospitalization, severe disease, MIS-C and death among children ages 6 -17 years old
The SALVACION REGISTRY recorded a total of 3,306 local cases in children aged less than 18 years old with 1,522 cases (46.04%) from the 6-17 age group (as of 20 August 2022). In terms of severity, the majority of the cases in children ages 6-11 years old were mild cases (45.86%; 321/700), followed by asymptomatic (24.00%; 168/700) and moderate cases (18.00%; 126/700).The remaining were severe (5.43%; 38/700) and critical cases (4.43%; 31/700). The same trend was also seen in adolescents aged 12-17 years old. Most of the cases were mild (42.46%; 349/822), asymptomatic (28.22%; 232/822), and moderate cases (18.00%; 148/822). The remaining were severe (5.96%; 49/822) and critical cases (4.38%; 36/822). Lastly, a total of 5 cases (4 in children; 1 in adolescents) were of unknown severity. Distribution of cases by severity and age group can be seen below.

Table 1.1. Distribution of COVID-19 cases in children and adolescents by severity
<table>
<tr><th></th><th>Mild</th><th>Asymptomatic</th><th>Moderate</th><th>Severe</th><th>Critical</th><th>Unknown</th></tr>
<tr><td>No. of cases in children 6-11 years old (%) N=700</td><td>321 (45.86)</td><td>168 (24.00%)</td><td>126 (18.00)</td><td>38 (5.43)</td><td>31 (4.43)</td><td>4 (0.57)</td></tr>
</table>
</td><td>The vaccine can potentially reduce the COVID-19 disease burden (health, social and economic impact).

Trends in COVID-19 morbidity, mortality and hospitalization rates.</td></tr>
</table>

No. of cases in adolescents **12-17 years old (%) N=822**	349 (42.46)	232 (28.22%)	148 (18.00)	49 (5.96)	36 (4.38)	1 (0.12)	

Of the 1,522 cases reported, 96 (6.31%) deaths were reported, comprising 38 children and 58 adolescents. In terms of hospitalization, 1,341 (88.11%) cases were reported. Cases of hospitalization are slightly higher in adolescents at 732 cases compared to children at 609 cases. The trend in the proportion of hospitalized cases with and without comorbidities remained relatively the same from March to August 2022 (without comorbidities: 41.90% to 42.29%; with comorbidities: 57.71% to 58.10%).

In terms of MIS-C, a total of 19 cases were reported. From March to July 2022, only 1 new MIS-C case in the 12 to 17 age group was reported around July 2022 and no new case of MIS-C was then reported by August 2022.

This registry has some limitations such as: (1) the registry is a voluntary, passive surveillance database, as such not all cases in children and adolescents are accounted for, and (2) cases reported may be confirmed or probable COVID-19 cases.

DOH Data Drop since February 2022 has shown a consistent trend in CFRs showing that children aged 6 to 11 years and adolescents aged 12 to 17 years have the lowest CFRs across all ages. Based on their latest data (17 September 2022), the case fatality rates (CFR) in children aged 6-11 (0.16%) and adolescents aged 12-17 (0.19%) (0.18%, overall) are less than the CFRs of both the population below 6 years (0.67%) and the adult population (18-59 years old: 0.76%; ≥ 60 years old: 7.34%).

In their interim statement on COVID-19 vaccination in children, the WHO (11 August 2022) stated that COVID-19 cases in children and adolescents are typically less severe and results in fewer deaths compared to older age groups. This is supported by global data showing that cases in children below 5 years old represent 0.11% and children ages 5-14 years old represent 0.089% of the total deaths globally. WHO noted that milder symptoms and asymptomatic presentations may mean less frequent care seeking in these groups, thus children and adolescents tend to be tested less and cases may go unreported.

Evidence on variants of concern (VoC)

In the latest WHO Weekly Epidemiological Update for COVID-19 (21 September 2022), the dominant variant

		globally remains to be the Omicron variant, comprising 99.0% (119,458/120,617) of the sequences uploaded to the Global Initiative on Sharing Avian Influenza Data (GISAID) from 19 August 2022 to 19 September 2022. Among the Omicron subvariants, comparison of the sequences shows that BA.5 subvariant continue to be dominant globally, with a prevalence of 76.6%. Other subvariants present are BA.4 (7.5%), BA.2.75 (1.26%) and BA.3, BA.2 and BA.1 (less than 1%). Locally, as of August 15 to September 15, 2022, 291 samples taken by convenience and purposive sampling from children and adolescents 6 to 17 years old tested positive for VoCs (total number of samples tested was not available). Local trends showed that Omicron continues to be the dominant VoC at 100% (291/291) prevalence among children aged 6 to 17 years old. Among the Omicron subvariants, BA.5 is the dominant subvariant at 96.56% (281/291) followed by other BA sub lineages e.g. B.1.1.529 (2.06%; 6/291) and lastly BA.4 (1.37%; 4/291). Majority of the COVID-19 cases caused by VoCs have already recovered and among the active cases, most have mild or moderate disease severity. In terms of the effect of VoCs in hospitalized cases, results of a study (Tso et al., 20220) from Hong Kong which analyzed hospitalized cases from the fifth COVID-19 wave during the Omicron dominant period in the country showed that BA.2 infection in children younger than 11 years old can lead to severe hospitalization and complications such as neurological involvements, severe upper respiratory tract infections, admissions in the pediatric intensive care unit (PICU) and even death due to encephalitis caused by SARS-CoV-2. The study also found that compared to influenza and parainfluenza, an omicron infection can cause the following: ● 2.7 times more deaths than influenza and 4.7 times more than parainfluenza ● 1.6 times more neurological complications than influenza and 1.9 times more than parainfluenza ● 2.0 times more croup than influenza but no difference to parainfluenza and ● 2.1 times more ICU admissions than influenza but no difference to parainfluenza It is noteworthy however that there is insufficient evidence to observe this trend in hospitalization and severe complications in the Philippines. ***Evidence on transmission among children*** A systematic review by Chen et al., 2022 determined the transmissibility of SARS-CoV-2 in children with the emergence of new variants. Results showed that children as index case have significantly lower possibility to transmit SARS-CoV-2 to their family members as compared to adults as index case [13 studies: RR = 0.64 (95% CI: 0.50–0.81, I^2 = 96%)]. In terms of transmission from any family member as the index case, results showed that with the Omicron variant, household Secondary Attack Rate (SAR) of child contacts was at 0.56 (95% CI:	

		0.51-0.61). This is significantly higher as compared to the SAR of child contacts against other variants (Alpha: 0.42, Delta: 0.35, Wild-type: 0.20). Subgroup analyses in the different pediatric age groups showed no significant difference in susceptibility between children younger and older than 12 years [11 studies: RR = 1.12 (95% CI: 0.90–1.39, I^2 = 77%)]. It was also noted that during the Omicron-dominant period, transmission from any household member as index case showed no significant difference in the household SAR between child and adult contacts [2 studies: RR= 1.09 (95% CI: 0.88–1.35, I^2 =74%)]. ***Post COVID-19 conditions*** Data from the US CDC on post-COVID conditions in children showed that long COVID conditions appear to be less common in children than in adults. The WHO in their interim statement also stated that although children can indeed experience prolonged clinical symptoms, the frequency and characteristics of these conditions are still under investigation, and to date they appear to be less frequent compared to adults. A national survey in the UK showed that only around 7-8% of children with COVID-19 reported prolonged symptoms greater than 12 weeks. The most common symptoms of post COVID-19 among children are similar to adults which include fatigue, headache, insomnia, trouble concentrating, muscle and joint pain, and cough. In terms of impact on quality of life, limitations of physical activity, feeling distressed about symptoms, mental health challenges, decreased school attendance/participation are observed. **HTAC Judgment**: The global burden of COVID-19 contributed by children aged 6 to 17 years old cannot be ascertained as children experience milder symptoms and asymptomatic presentations leading to less probability of being tested and more unreported cases (WHO, 2021). In the Philippines, trends of cases in children are similar to other age groups, with a rise in cases from July to August 2022. A decrease in cases was observed in early September 2022 but an increase is being observed again in late September 2022. Meanwhile, CFRs in children remained relatively the same over time, which is consistent in other age groups as well. In terms of hospitalization, currently, the effect of variants in this age group cannot be established due to limited sequencing capacity in the country. Only one (1) new case of MIS-C was reported in the 12-17 year-old age group from March to July 2022 and no new case of MIS-C was then reported from July to August 2022 based on passive surveillance of the SALVACION registry. It is noted that studies of hospitalized children with SARS-CoV-2 Omicron infection in Hong Kong showed more	

		severe illness with neurologic manifestations and croup compared to children with influenza and parainfluenza. In terms of transmission, children have significantly lower possibility to transmit SARS-CoV-2 to their family members. Specifically for Omicron, there is no significant difference in the household secondary attack rate between child and adult contacts. There are no local studies on post COVID-19 conditions. US data shows that this post COVID-19 condition appears to be less common in children than in adults. Based on the above, there is no apparent increase in burden of COVID-19 among children aged 6 to 17 years old, as of writing of this report (28 September 2022).	
CRITERION 2			
2. Clinical efficacy, effectiveness, and safety	*What is the **efficacy and effectiveness** of CoronaVac in terms of: reducing the incidence of symptomatic and severe COVID-19, hospitalization due to COVID-19, and death due to COVID-19 in children ages 6 to 17 years old?*	For the evidence on efficacy, effectiveness, and immunogenicity of *CoronaVac* among children ages 6 to 17 years, the following latest available reviews were considered: International Vaccine Access Center (IVAC) of the Johns Hopkins Bloomberg School of Public Health and World Health Organization review of COVID-19 vaccines in general as of 04 August 2022; Philippine Society of Allergy, Asthma, and Immunology as of 04 August 2022; Philippine Living Clinical Practice Guidelines Group (LCPG Group) review on COVID-19 vaccines in the pediatric population (updated as of 04 January 2022); and, COVID-NMA review of COVID-19 vaccines in general as of 28 June 2022 (last search date of review: 03 November 2021). Additionally, trial reports and real world evidence from the manufacturer dossier submission to the Philippine FDA and independently retrieved preprints from medRxiv were also considered. Overall, there is one Phase III trial (Sinovac Life Sciences Co Ltd. 2022 [unpublished]) with vaccine efficacy outcomes and a total of four trials that reported immunogenicity outcomes (Wu et al., 2022 [unpublished]; Soto et al., 2022 [preprint], Rosa Duque et al., 2022 [published]; Leung et al., 2022 [preprint]). Three real world effectiveness studies (Jara et al., 2022 [preprint], Lau et al., 2022 [preprint], Florentino et al., 2022 [published]) were also reviewed. **EVIDENCE FROM TRIALS** ***Efficacy outcomes*** ***Description of evidence***	The vaccine achieves the following efficacy parameters: **Symptomatic COVID-19:** ● **Preferred VE:** point estimate is **≥70%** and a confidence interval lower limit of **≥50%** ● **Critical or minimum acceptable VE:** point estimate is **≥50%** and a

One preliminary report of a Phase III RCT (Sinovac Life Sciences Co., Ltd., 2022) conducted in four countries (South Africa, Malaysia, Philippines and Chile) during Delta and Omicron dominant periods reported efficacy outcomes for *CoronaVac* in children ages 6 to 17 years old. The study characteristics are presented below.

Table 2.1. Study characteristics of the interim Phase III RCT on *CoronaVac*

Author Year Country Study Design	Population	Intervention	Comparator	Outcomes
Sinovac Life Sciences Co., Ltd., 2022 South Africa, Malaysia, Philippines, & Chile Phase III RCT 10 September 2021 to 15 April 2022 Dominant variant: Omicron	Children and adolescents, aged 6 months to 17 years old **Enrolled Population** N=10,880 **Efficacy Analysis Population** 6-11 years old: N= 2,165 12-17 years old: N= 1,684	Children and adolescents, vaccinated with 2 doses of *CoronaVac,* given 28 days apart **Enrolled Population** N=5,833 **Efficacy Analysis Population** 6-11 years old: n=1,088 12-17 years old: n=849	Children and adolescents, receiving 2 doses of placebo, given 28 days apart **Enrolled Population** N=5,047 **Efficacy Analysis Population** 6-11 years old: n= 1,077 12-17 years old: n= 835	VE against symptomatic COVID-19, 14 days after dose 2 *(6 to 11 yo and 12 to 18 yo)* VE against hospitalization due to COVID-19, 14 days after dose 2 *(6 months to 17 years old, no age disaggregation)* VE against Omicron (BA.1, BA.2, unspecified subvariant), 14 days after dose 2 *(6 months to 17 years old, no age disaggregation)* **Follow up period:** *CoronaVac* group: 50.68 days after 14

confidence interval lower limit of **≥30%**

Severe COVID-19, and hospitalization due to COVID-19:

- **Preferred VE:** point estimate is **≥90%** and a confidence interval lower limit of **≥70%**
- **Critical or Minimum acceptable VE:** point estimate is **70-80%** and a confidence interval lower limit of **≥ 50%**

					days of receiving dose 2 Placebo group: 50.51 days after 14 days of receiving placebo	

Key Findings

Risk of Bias

The HTAC rated the overall RoB of Sinovac Life Sciences Co. Ltd., 2022 as "High" due to its short (<2 months) follow up period. Details on the RoB assessment of the trial is reflected in Appendix 1B.

Results of efficacy studies

The results of Sinovac Life Sciences Co., Ltd., 2022 on the vaccine efficacy of *CoronaVac* against symptomatic COVID-19 and hospitalization due to COVID-19 in children ages 6 months to 17 years old are reported below. There were no reported severe cases and deaths due to COVID-19. Certainty of evidence was assessed using the GRADE approach by the HTAC. Details on the GRADE assessment are presented in Appendix 2.

Vaccine efficacy of CoronaVac (14 days after the 2nd dose) among children aged 6 to 17 years old are as follows. The VEs, however, are inconclusive due to negative values in the lower confidence interval (CI) limits, and wide confidence intervals. The VEs also did not pass the HTAC specifications (i.e. more than 30% lower CI limit).

- **VE *against symptomatic COVID-19***
  - 6-11 years old: 22.11% (95% CI: -26.74 to 52.52), based on very low certainty of evidence
  - 12-17 years old: 19.97% (95% CI: -77.45 to 64.59), based on very low certainty of evidence

- ***VE against hospitalization due to COVID-19***
  - 6 months to 17 years old (no age disaggregation)**:** 75.29% (95% CI: -149.70 to 99.50), based on very low certainty of evidence
- ***VE against infection due to Omicron***
  - 6 months to 17 years old, (no age disaggregation)

- BA.1 variant: 50.40% (95% CI: -6.72 to 78.28), based on very low certainty of evidence
- BA.2 variant: 22.20% (95% CI: -41.00 to 57.58), based on very low certainty of evidence
- Unspecified variant: 0.78% (95% CI: -1,268.83 to 92.81), based on very low certainty of evidence

Immunogenicity outcomes

Description of evidence

Overall, there were four studies that evaluated the immunogenicity of *CoronaVac* - one Phase III RCT (Soto et al., 2022) [preprint]; two Phase II nonrandomized trials (Rosa Duque et al., 2022 [published]; Leung et al., 2022 [preprint]) and one unpublished Phase I/II RCT (Wu et al., 2022). The trials generally included children and adolescents aged 3 to 17 years old. Details of the trials are presented below.

Table 2.2. Study characteristics of trials with immunogenicity outcomes of *CoronaVac vaccination in the pediatric population*

Author Year Country Study Design	Population	Intervention	Comparator	Outcomes
Wu et al., 2022 [unpublished update of Han et al.] China Phase I/II RCT 31 October 2020 to May 2022 Dominant variant: not specified	Healthy children and adolescents aged 3-17 years old N=552 (N, phase 1= 72; N, phase 2= 480)	1.5 µg *CoronaVac* [days 0, and 28] n, Phase 1=36 n, Phase 2=192 3.0 µg *CoronaVac* [days 0, and 28] n, Phase 1=36 n, Phase 2=192 *Note: 3.0 µg CoronaVac is the approved dose by the PH FDA.*	Aluminum hydroxide only [days 0, 28] N, Phase 2=96	Neutralising antibody response to live SARS-CoV-2 at 28 days after the second injection ***Follow up period:*** *12 months after dose 2*

			Soto et al., 2022 [preprint] Chile Interim Phase III RCT 10 September 2021 to 31 December 2021 Dominant variant: D614G strain, Delta, and Omicron	Healthy children ages 3-17 years old N=963	2 doses of 3µg *CoronaVac,* 28 days apart n, immunogenicity = 92	Pre-vaccination titers n=148 *Note: The trial only included children and adolescents who received CoronaVac*	IgG anti-S1-RBD of SARS-CoV-2 [in WHO converted geometric mean units] versus unspecified variant Neutralizing antibodies by sVNT [in WHO converted GMU] versus unspecified variant Neutralizing antibodies by cVNT [in WHO converted GMU] versus D614G strain Neutralizing antibodies against SARS-CoV-2 VOCs (D614G strain, Delta, Omicron) SARS-CoV-2 specific T cell responses (D614G strain, Delta, Omicron) IL-2 and IFN-γ cytokines secretion versus unspecified variant ***Follow-up period:*** *4 weeks after dose 2*	

		Rosa Duque et al., 2022 [published] Hong Kong Interim Phase II nonrandomized trial Enrollment period: 27 April 2021 to 23 October 2021 Dominant variant: not specified	11-17 year old children and >18 year old adults N, children = 239 N, adults = 288	Immunogenicity titers among children ages 11-17 years old n, 2 doses CoronaVac = 123 n, 2 doses Pfizer-BioNTech = 116	Immunogenicity titers among adult participants n, 2 doses *CoronaVac* = 141 n, 2 doses *Pfizer-BioNTech* = 147	Humoral immune response titers versus wild type strain Cellular immune response titers versus wild type strain ***Follow-up period:*** *28 days after dose 2*
		Leung et al., 2022 [preprint] Hongkong Interim Phase II non-randomized trial Enrollment period: 31 January 2022 Dominant variant: Omicron	Adolescents ages 11 to 17 years old N=60	Titers after dose 2 n=60 **Dosing Interval:** Primary Series: 28 to 35 days after dose 1	Titers before vaccination n=60 *Note: The trial only included children and adolescents who received CoronaVac*	IgG anti-S1-RBD of SARS-CoV-2 versus wild type strain ACE2-Blocking antibody versus wild type strain T cell response versus versus wild type strain ***Follow up period:*** ***T0:*** *before vaccination* ***T1:****: 4 weeks after dose 2* ***T2:****15 weeks after dose 2*

Key findings

Results of the immunogenicity trials

The Phase I/II RCT (Wu et al., 2022) showed that GMT decreased after 28 days after dose 2, with GMT at 12 months only at 21.7 versus the baseline GMT at 28 days after dose 2 at 142.2 (GMR = 0.15).

Seroconversion rate decreased from 100.0% at 3 months after dose 2 to 87.1% 10 months after dose 2. The seroconversion rate then increased again at 12 months after dose 2 (93.1%). Details on the immunogenicity outcomes reported in the trial are presented in Table 2.3 below.

Table 2.3. Geometric mean neutralization titers (GMT) and seroresponse rate in children ages 3-17 yo reported in the Wu et al., 2022 Phase I/II trial

Timepoints	**GMT**	**GMR** *(vs GMT 28 days after dose 2)* *[HTAD computation]*	**Seroconversion rate (%)**
28 days after dose 2	142.2	Reference	100.0
3 months after dose 2	110.5	0.78	100.0
6 months after dose 2	27.2	0.19	95.7
10 months after dose 2	20.8	0.15	87.1
12 months after dose 2	21.7	0.15	93.1

Meanwhile, the Phase III RCT (Soto et al., 2022 [preprint]) measured the immune response elicited by *CoronaVac* in children ages 3 to 17 years at 28 days after the second dose. Of the 963 participants enrolled in the study, humoral and cellular immunogenicity outcomes were measured for 92 participants who received two doses of *CoronaVac*. Humoral immunity was measured by the induction of IgG antibodies against RBD-S1 of SARS-CoV-2 and neutralizing antibodies, while cellular immunity was measured by the induction of CD4+ and CD8+ T cells and the secretion of the cytokines IL-2 and IFN-ɣ. Humoral and cellular response against of *CoronaVac* against the Omicron and Delta variant as compared to previous strains (i.e. D614 G strain) were also measured before vaccination and four weeks after the second dose. The following were the key findings from the evaluation of immunogenicity outcomes from

the study:

Humoral immune response

- ***IgG against RBD-S1 of SARS-CoV-2 (variant unspecified)***
  At 4 weeks after the second dose, the total IgG against RBD-S1 of SARS-CoV-2 significantly increased in both the 3-11 year age group and the 12-17 year age group, compared to the baseline pre-immune IgG titers ($p<0.0001$). There was no significant difference in the IgG titers between age groups at 4 weeks after the second dose. The resulting GMTs and seropositivity in both age groups are detailed in Table 2.4 below.

  Table 2.4. Total IgG anti S1-SARS-CoV-2 (variant unspecified) GMU in participants ages 3-11 years and 12-17 years before vaccination and at 4 weeks after the second dose (Soto et al., 2022)

Outcome	**Age 3-11 years**		**Age 12-17 years**	
	Antibody levels(95% CI)	**Seropositivity (n/N)**	**Antibody levels (95% CI)**	**Seropositivity (n/N)**
***Total IgG anti S1- SARS-CoV-2* [in WHO converted geometric mean units]**				
Before vaccination (Pre-immune)	3.77 (CI not reported)	Not reported	6.52 (CI not reported)	Not reported
At 4 weeks after dose 2	964.9 (503-1,850)	96% (24/25)	680.6 (371-1,245)	94.5% (34/36)

- ***Neutralizing antibodies (D614G strain)***
  The neutralizing antibody titers, measured by either the conventional virus neutralization test (cVNT) and surrogate virus neutralization test (sVNT), significantly increased in both the 3-11 year age group and the 12-17 year age group, at 4 weeks after the second dose ($p<0.0001$). A significant difference was observed in neutralizing antibodies between age groups (p-value<0.005). The resulting GMTs and seropositivity in both age groups are detailed in Table 2.5. below.

Table 2.5. Neutralizing antibody against D614G strain measured by sVNT (GMU) and cVNT (GMT) in participants ages 3-11 years and 12-17 years before vaccination and at 4 weeks after the second dose (Soto et al., 2022)

Outcome	Age 3-11 years		Age 12-17 years	
	Antibody levels (95% CI)	**Seropositivity (n/N)**	**Antibody levels (95% CI)**	**Seropositivity (n/N)**
***Neutralizing antibodies (sVNT)* [in WHO converted geometric mean units (GMU)]**				
Before vaccination (Pre-immune)	16.40 (CI not reported)	Not reported	16.40 (CI not reported)	Not reported
At 4 weeks after dose 2	713.1 (565.8-898.8)	100% (55/55)	492.2 (342-708.3)	100% (37/37)
***Neutralizing antibodies (cVNT)* [in GMT]**				
Before vaccination (Pre-immune)	3.43 (CI not reported)	Not reported	2.89 (CI not reported)	Not reported
At 4 weeks after dose 2	GMT: 128.0 (74.8-219.2)	100% (27/27)	GMT: 34.02 (18.1-64.0)	88.2% (30/34)

- ***Neutralization capacity and seropositivity against Delta and Omicron variant compared to D614G***
  Relative to the D614G strain, there was a 1.9-fold reduction in neutralization capacity against Delta and a 15.8-fold reduction against the Omicron variant. There was also a substantial decrease in seropositive individuals against the Omicron variant, compared to the seropositivity rates against the Delta and D614G strains. Thus, the study mentioned that a possible booster dose of *CoronaVac* may be required in children and adolescents although this remains to be determined. There was no significant difference (no p-value reported) in the response against the VOCs when comparing between the 3-11 years and 12-17 years age groups. The resulting GMTs and seropositivity against the VOCs are detailed in Table 2.6 below.

Table 2.6. Neutralizing antibody titers against SARS-CoV-2 variants in children ages 3-11 years and

12-17 years (Soto et al., 2022)

	SARS-CoV-2 variants		
	D614G Strain	**Delta variant**	**Omicron variant**
Neutralizing antibodies (in GMT): 3 to 17 yo			
GMT (95% CI)	265.4 (213.1-330.5)	141.6 (113.6-176.5)	16.81 (14.0-20.3)
Fold-reduction/increase vs. D614 G strain	Reference	1.9 fold reduction	15.8 fold reduction
Seropositivity (n/N)	100% (88/88)	97.7% (86/88)	45.5% (40/88)

Cellular immune response

- ***CD4+ T cell activation***
  There was an observed significant increase in the activation of CD4+ T cells in children ages 12-17 upon stimulation for all peptides (S, R, M, and N) evaluated 4 weeks after dose 2. Meanwhile, for those aged 3-11 years, a significant increase in CD4+ T cells 4 weeks after dose 2 was found upon stimulation with the S and N peptides only. CD4+ T cell response is detailed in Table 2.7.

Table 2.7. CD4+ T cell activation in participants aged 3-11 years and 12-17 years before vaccination and at 4 weeks after the second dose (Soto et al., 2022)

Timepoints	**Age 3-11 years**				**Age 12-17 years**			
	MP S	**MP R**	**MP M**	**MP N**	**MP S**	**MP R**	**MP M**	**MP N**
Baseline	0.01	0.003	0.003	0.002	0.007	0.008	0.012	0.013
4 weeks after dose 2	0.079	0.037	0.019	0.046	0.083	0.083	0.062	0.062
p-value	p<0.05	p-value not reported (not significant)	p-value not reported (not significant)	p<0.05	p<0.005	p<0.0001	p<0.005	p<0.005

- ***CD8+ T cell activation***
  As compared to the pre-immune levels, only participants ages 3-11 years showed an increase in CD8+ T cells upon stimulation with the CD8A peptide ($p<0.05$). There was no significant increase observed in CD8+ T cells for participants aged 12-17 years upon stimulation with the CD8A and CD8B peptides or for participants ages 3-11 years upon stimulation with the CD8B. CD8+ T cell response is detailed in Table 2.8.

Table 2.8. CD8+ T cell activation in participants ages 3-11 years and 12-17 years before vaccination and at 4 weeks after the second dose (Soto et al., 2022)

Timepoints	Age 3-11 years		Age 12-17 years	
	MP CD8A	MP CD8B	MP CD8A	MP CD8B
Baseline	1.35	0.56	1.65	1.31
4 weeks after dose 2	3.74	0.69	1.93	2.08
p-value	p<0.05	p-value not reported (not significant)	p-value not reported (not significant)	p-value not reported (not significant)

- ***Secretion of the cytokines IL-2 and IFN-γ***
  There was an observed significant increase in IL-2 secretion but no increase in IFN-γ production upon stimulation with the S, R, M, and N peptides for adolescents aged 12-17 years. Meanwhile, children ages 3-11 years had a significant increase in both IL-2 and IFN-γ secretion in response to the S, M, and N peptides. Findings for these outcomes are detailed in Table 2.9.

Table 2.9. IL-2 and IFN-γ secretion in response to S, R, M, and N peptides among participants ages 3-11 years and 12-17 years before vaccination and at 4 weeks after the second dose (Soto et al., 2022)

	Age 3-11 years	Age 12-17 years

Secretion of the cytokines IL-2

Timepoints	MP S	MP R	MP M	MP N	MP S	MP R	MP M	MP N
Baseline	23.3	22	17.07	17.77	33.57	55.78	33.76	36.17
4 weeks after dose 2	94.84	53.04	50.84	147.5	102.4	95.31	84.59	144.3
p-value	p<0.005	p-value not reported (not significant)	p<0.5	p<0.001	p<0.005	p<0.5	p<0.001	p<0.005

Secretion of the cytokines IFN-γ

Timepoints	MP S	MP R	MP M	MP N	MP S	MP R	MP M	MP N
Baseline	153.9	259	33.52	40.83	71.35	450.6	52.98	50.04
4 weeks after dose 2	1877	766	785	1553	503.9	759.5	114.6	357
p-value	p<0.5	p-value not reported (not significant)	p<0.5	p<0.005	p-value not reported (not significant)	p-value not reported (not significant)	p-value not reported (not significant)	p-value not reported (not significant)

- ***T cell response against variants of concern***
  There was a significant reduction (1.67-fold; p-value <0.05) in CD4+ T cells against the Delta variant while there was a significant increase (1.63-fold; p-value <0.05) in response against the Omicron variant, compared to the response against the D614G strain. There was no significant difference in the T-cell response against the VOCs between children aged 3-11 years old and adolescents aged 12-17 years old. The findings of the evaluation of T cell responses against the

VOCs are detailed in Table 2.10.

Table 2.10. T-cell response against SARS-CoV-2 variants in children ages 3-11 years and 12-17 years (Soto et al., 2022)

	SARS-CoV-2 variant		
	Wild type	**Delta variant**	**Omicron variant**
T-cell Response (CD4+ T cells, %): 3-17 yo			
CD4+ T cells %	0.144	0.086	0.234
Fold-reduction/ increase vs. D614G strain	Reference	1.67 fold reduction	1.63 fold increase
p-value (VoC vs D614G)	N/A	<0.05	<0.05
T-cell Response (CD4+ T cells, %): 3-11 yo vs 12-17 yo			
3-11 years	0.164	0.097	0.303
12-17 years	0.125	0.074	0.165
p-value	p-value not reported (not significant)	p-value not reported (not significant)	p-value not reported (not significant)

The Phase II nonrandomized immunobridging trial by Rosa Dugue et al. (2022) [published] compared the immune response of two doses of *CoronaVac* in adolescents aged 11-17 years (n=239) and adults aged 18-67 years (n=288). Humoral immune response was measured by SARS-CoV-2 S IgG, S-RBD IgG by enzyme-linked immunosorbent assay (ELISA), surrogate virus neutralization test (sVNT), plaque reduction neutralization test (PRNT), S IgG avidity, and S IgG Fcg receptor IIIa (FcgRIIIa)-binding on ELISA. Meanwhile, the following outcomes were measured to evaluate the cellular immune response: Interferon-ɣ (IFN-ɣ)$^{+}$, interleukin-2 (IL-2)$^{+}$, CD4^{+} and CD8^{+} T cell responses specific to S, N, and M.

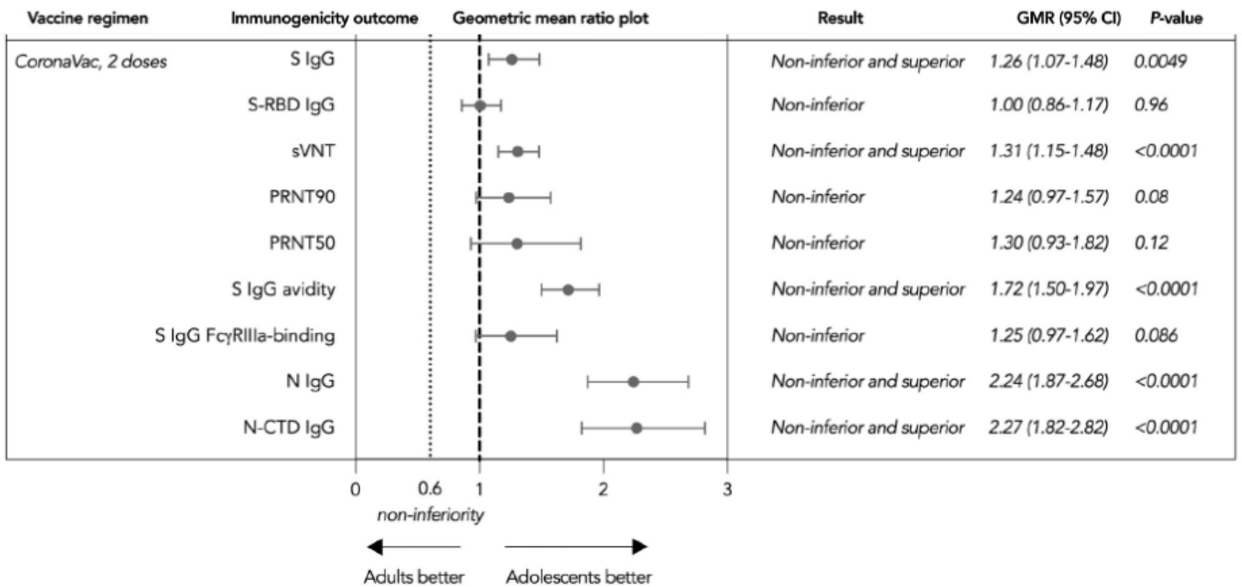
Immunobridging is achieved when the following endpoints are met:

- non-inferior: point estimate >0.6 and lowerbound >0.6
- non-inferior and superior: point estimate >0.6 and lower bound >1

Humoral immune response

Compared to adults, the humoral immune response by *CoronaVac* in adolescents was non-inferior for all humoral immunogenicity outcomes, with immune response in adolescents being superior over those of adults in 5 out of 9 outcomes. The GMRs for each immunogenicity outcome were reported with the 95% CI and were tested for non-inferiority at the margin of 0.60. Meanwhile, outcomes were considered superior if the lower bound of the 95% CI for the GMR with the comparator was more than 1. The humoral immunogenicity outcomes of adolescents, compared to adults are detailed in the figure below.

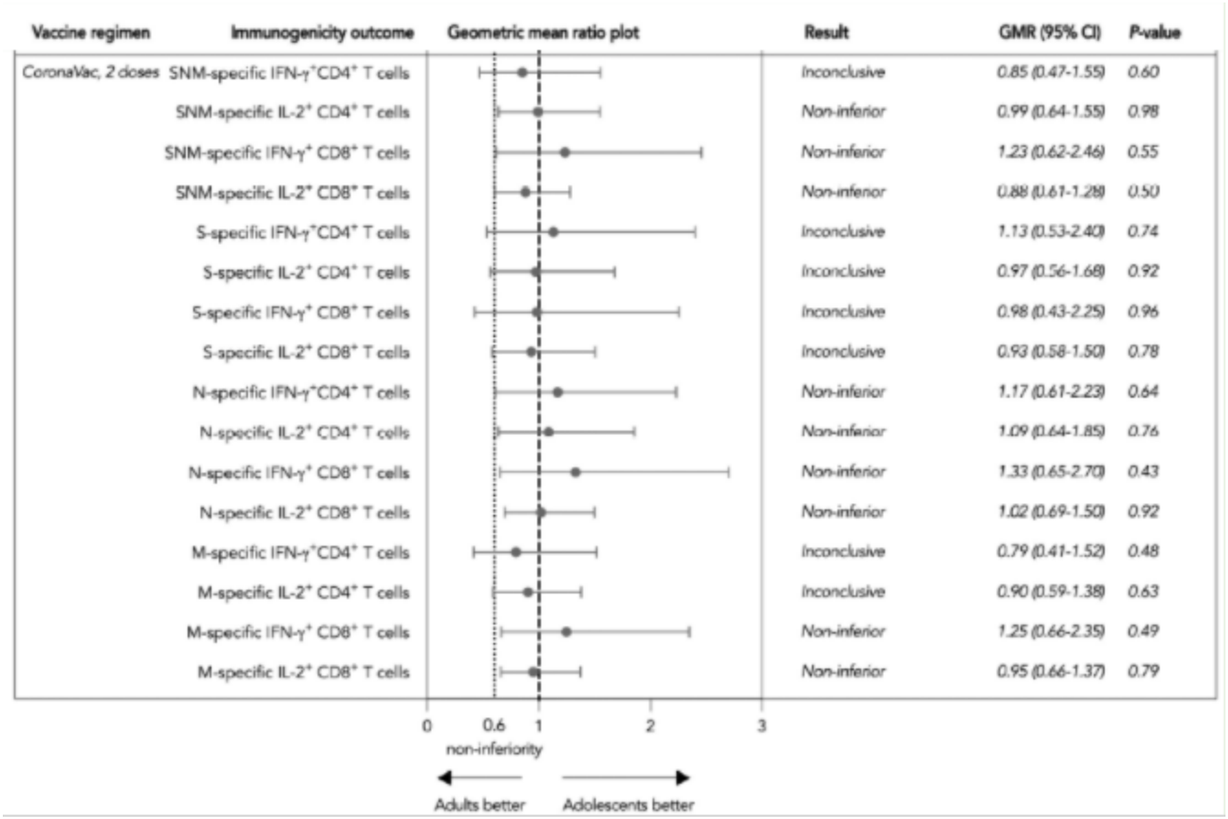
Figure 1. Humoral immunogenicity outcomes in adolescents vs. adults (Rosa Duque et al.,2022)



Cellular immune response

Compared to adults, the cellular immune response of adolescents who received two doses of *CoronaVac* were non-inferior in 9 out of 16 cellular immunogenicity outcomes. Meanwhile, the other cellular immune response outcomes were inconclusive since the 95% CI limits were out of the non-inferiority margin of 0.60 and 1 respectively (lower bound <0.6 and upper bound >1). The cellular immunogenicity outcomes of adolescents, compared to adults are detailed in the figure below.

Figure 2. Cellular immunogenicity outcomes in adolescents vs. adults (Rosa Duque et al.,2022)



The Phase II nonrandomized trial by Leung et al., 2022 [preprint] measured the immune response of 2 doses of *CoronaVac* among adolescents aged 11 to 17 years old (N=60) at different timepoints (before vaccination, 4 weeks after dose 2 and 15 weeks after dose 2). Humoral immunity was assessed by the S-RBD IgG titers and through the ACE2-blocking antibody response measured using surrogate virus neutralization test (sVNT). On the other hand, cellular immunity was measured by the induction of SMN-specific IFN-ɣ+ and IL-2+, CD4+ and CD8+ T cells.

Humoral Immune Response

In adolescents aged 11 to 17 years old, S-RBD IgG and ACE2-blocking antibody significantly increased 4 weeks after the second dose. However, at 15 weeks after the second dose, both S-RBD IgG and ACE2-blocking antibody significantly decreased as compared to the humoral immune responses 4 weeks after the second dose. The values for GMT and sVNT % inhibition are detailed in Table 2.11.

Table 2.11. Humoral immune response in participants ages 11 to 17 years old before vaccination, 4 weeks after dose 2 and 15 weeks after dose 2 (Leung et al., 2022)

Timepoints	**S-RBD IgG** (GMT)	**ACE2-blocking antibody** (sVNT Inhibition %)
pre-dose 1	0.25	15.0%
4 weeks after dose 2	1.31	77.7%
15 weeks after dose 2	0.82	36.6%
p-value *(pre-dose 1 vs 2 weeks after dose 2)*	p<0.0001	p<0.0001
p-value *(4 weeks after dose 2 vs 15 weeks after dose 2)*	p<0.001	p<0.0001

Cellular Immune Response

In adolescents aged 11 to 17 years old, T-cell responses were preserved from 4 weeks after dose to 15

weeks after dose 2. The values for T-cell responses are detailed in Table 2.9.

Table 2.9. Cellular immune response in participants ages 11 to 17 years old before vaccination, 4 weeks after dose 2 and 15 weeks after dose 2 (Leung et al., 2022)

Timepoints	% SMN-specific IFN-γ+ CD4+ Tcell	% SMN-specific IL-2+ CD4+ Tcell	% SMN-specific IFN-γ+ CD8+ Tcell	% SMN-specific IL-2+ CD8+ Tcell
pre-dose 1	0.017	0.016	0.017	0.015
4 weeks after dose 2	0.074	0.067	0.044	0.044
15 weeks after dose 2	0.028	0.038	0.054	0.023
p-value *(pre-dose 1 vs 2 weeks after dose 2)*	p<0.05	p<0.001	p-value not reported (not significant)	p<0.05
p-value *(4 weeks after dose 2 vs 15 weeks after dose 2)*	p-value not reported (not significant)	p-value not reported (not significant)	p-value not reported (not significant)	p-value not reported (not significant)

EVIDENCE FROM REAL WORLD STUDIES

Vaccine Effectiveness outcomes

Description of evidence

Overall, there were three real world studies (Jara et al., 2022; Florentino et al., 2022; Lau et al., 2022) evaluating the effectiveness of *CoronaVac* in children aged 6 to 17 years old detected by the reference reviews. Of which, one study was conducted during the Delta-dominant period (Jara et al. (2022) while two studies were conducted during the Omicron-dominant period (Florentino et al., 2022; Lau et al., 2022). The characteristics of the studies are presented in Table 2.10 below.

Table 2.10. Study characteristics of real world studies evaluating effectiveness of *CoronaVac* vaccination in the pediatric population

Author Year Country	Population	Intervention	Control	Outcomes

Study Design				
Jara et al. (2022) [Preprint] Chile Prospective cohort 27 June 2021 to 12 January 2022 Delta	Children ages 6 to 16 years old N=1,976,344; n, Children with at least 1 comorbidity: n=250,269 (12.66%)	Children ages 6 to 16 years old vaccinated with *CoronaVac* (2 doses, 28 days apart, *dosage strength not specified)* n: 1 dose: 138,041 2 doses: 1,219,805 3 doses: 134,137	Unvaccinated children ages 6 to 16 years old n=274,042	VE against confirmed COVID-19 VE against hospitalization VE againstICU admission *Note: Did not estimate VE against fatal outcomes because no deaths have been observed in the cohort as of January 12, 2022* ***Follow-up period:*** *Approximately 120 million person-days in the intervention group (~98 days)*
Florentino et al., 2022 [published] Brazil Test-negative study 21 January 2022 to 15 April 2022 Omicron	Children 6 to 11 years old Symptomatic infection: N= 197,958 Hospital admission: N= 108,871	Children 6 to 11 years old vaccinated with at least 1 dose of *CoronaVac* Symptomatic Infection: n= 55,298 Hospital admission: n= 38,520	Unvaccinated children 6 to 11 years old Symptomatic infection: n= 142,660 Hospital admission: n= 70, 351	VE against symptomatic infection VE against hospital admission VE against ICU admission ***Follow up period:*** *43 days after dose 2*

Lau et al., 2022 [preprint] Hong Kong Test-negative study 1 January to 19 April 2022 Omicron BA.2	Children and adolescents ages 3 to 18 years old N=510,187 3 to 11 yo: 434,891 12 to 18 yo: 75,296	Children and adolescents ages 3 to 18 years old vaccinated with *CoronaVac* 3 to 11 yo: n= 252,918 Dose 1: 118,678 Dose 2: 132,200 Dose 3: 40 12 to 18 yo: n= 61,320 Dose 1: 12,138 Dose 2: 41,878 Dose 3: 7,286	Unvaccinated children ages 3 to 18 years old: n= 195, 967 3 to 11 yo: 181,973 12 to 18 yo: 13,994	VE against infection, at least 14 days after dose 2 ***Follow up period:*** *3 to 11 years old, dose 2: 25 (SD: 20) days* *12 to 18 years old, dose 2: 64 (SD: 54) days*

Key findings

Risk of bias:

Jara et al., 2022 [preprint], Florentino et al., 2022 [published], and Lau et al. 2022 [preprint] did not perform randomization and blinding due to them being observational studies. Florentino et al. controlled for all pre-identified confounders (age, exposure risk, comorbidities) while Jara et al. did not control for only one confounder (exposure risk). Hence, their overall RoB rating was "Serious". Meanwhile, Lau et al. was rated as "Very Serious" as it did not control for two pre-identified confounders (exposure risk and comorbidities). Details on the RoB assessments are reflected in Appendix 1B, while the GRADE assessments for specific outcomes are shown in Appendix 2.

Results of effectiveness studies

Against Delta variant:

Using *CoronaVac* (14 days after the 2nd dose) among children aged 6 to 16 years old compared to those unvaccinated, **passed the HTAC specifications for:**

- **Confirmed COVID-19: 74.5% (95% CI: 73.8 to 75.2)** based on high certainty of evidence (Jara et al. 2022)
- **Hospitalization: 91.0% (95% CI: 87.8 to 93.4)** based on high certainty of evidence (Jara et al. 2022)

		• **ICU admission**: **93.8% (95% CI: 85.7 to 97.3)** based on high certainty of evidence (Jara et al., 2022) *Against Omicron variant:* Using *CoronaVac* (14 days after the 2nd dose) among the pediatric population compared to those unvaccinated **passed the HTAC specifications for any SARS-CoV-2 infection in 12 to 18 years old** by **55.0% (95% CI: 38.2 to 67.2)** based on low certainty of evidence (Lau et al., 2022) Using *CoronaVac* (14 days after the 2nd dose) among the pediatric population compared to those unvaccinated, **did not pass the HTAC specifications for the following outcomes:** • **Any SARS-CoV-2 infection in 3 to 11 years old** by **40.8% (95% CI: 12.8 to 59.5)** based on very low certainty of evidence (Lau et al., 2022) • **Symptomatic infection in 6 to 11 years old** by **39.8% (95% CI: 33.7 to 45.4)** based on moderate certainty of evidence (Florentino et al., 2022) • **Hospitalization due to COVID-19 in 6 to 11 years old** by **59.2% (95% CI: 11.3 to 84.5)** based on low certainty of evidence (Florentino et al., 2022) Meanwhile, using *CoronaVac* (14 days after the 2nd dose) among the pediatric population compared to those unvaccinated had **inconclusive results** in terms of **ICU admission** in 6 to 11 years old [VE: **20.9% (95% CI: −177.2 to 85.0)]** based on very low certainty of evidence (Florentino et al., 2022) ***Immunogenicity outcomes*** There were no real world studies detected by the reference reviews for the immunogenicity of *CoronaVac* in the pediatric population ages 6 to 17 years old. **HTAC Judgment**: Evidence on clinical efficacy of *CoronaVac* in children aged 6 to 17 years old showed that VEs against the Omicron variant did not pass HTAC specifications, based on very low certainty of evidence (Sinovac Life Sciences Co., Ltd., 2022). In terms of vaccine effectiveness during the Omicron-dominant period and the Delta-dominant period, there were varying results: • A real world study in Chile during Delta dominant period (Jara et al., 2022, preprint) showed passing VE	

		against hospitalization due to COVID-19 in children aged 6 to 16 years old, based on high certainty of evidence. Meanwhile, in terms of the Omicron variant: ● Florentino, et al. 2022 (published) showed that VEs against symptomatic COVID-19, hospitalization due to COVID-19, and ICU admission in children aged 6 to 11 years old did not pass HTAC specifications based on moderate to very low certainty of evidence. ● Lau et al., 2022 (preprint), a test negative design study showed that: ○ In children aged 3 to 11 yo, VE against infection at least 14 days after the second dose of *CoronaVac* did not pass the HTAC specifications for symptomatic COVID-19. However, it was noted vaccination in children aged 3 to 11 yo was implemented during the Omicron variant and while the study was already being conducted. Longer follow up period is needed to establish the effectiveness of the vaccine in this age group. ○ In adolescents aged 12 to 17 yo, VE against infection at least 14 days after the second dose of *CoronaVac* passed the HTAC specifications for symptomatic COVID-19. Immunogenic response is acceptable: ● Phase III trial by Soto et al., 2022 (preprint) showed that *CoronaVac* induces immune response in children aged 6 to 17 years old. However, there was a decrease in neutralizing antibody and T-cell response against Delta variant compared to wild-type strain. For the Omicron variant, there is a decrease in neutralizing antibodies but an increase in T-cell response. ● Immunobridging study by Rosa Duque et al., 2022 (published, variant not specified) showed that *CoronaVac* induces an immune response in adolescents aged 11 to 17 years old that is either non inferior or superior compared to the immune response of adults. ● Phase II trial by Leung et al., 2022 (preprint, wild-type) showed enhanced immune response in adolescents aged 11 to 17 yo after the second dose of *CoronaVac* compared to before vaccination.	
	*What is the **duration of protection** of the CoronaVac in terms of reducing the incidence of symptomatic and severe COVID-19, hospitalization due to COVID-19 and death*	Four studies (Sinovac Life Sciences Co. Ltd., 2022 [unpublished]; Lau et al., 2022 [preprint]; Florentino et al., 2022 [published]; Jara et al., 2022 [preprint]) assessed the efficacy and effectiveness of 2-dose primary series of *CoronaVac* in children and adolescents ages 6-17 years old. Of which, only Jara et al. (2022) was conducted during the Delta-dominant period and the rest were conducted during the Omicron-dominant period. In addition to these, two studies (Leung et al., 2022; Wu et al., 2022) with immunogenicity outcomes for duration of protection were also reviewed. ***Description of Evidence*** Description of these studies are reported in the efficacy/effectiveness section.	**Minimum acceptable duration of protection:** confers at least 6 months protective immunity **Preferred**: ≥1-year protective immunity

	due to COVID-19 in children ages 6 to 17 years old?	***Key Findings*** Any SARS-CoV-2 infection/ Confirmed COVID-19 One study (Jara et al., 2022) reported a passing VE against confirmed COVID-19 against the Delta variant for children ages 6 to 16 years old with a follow up period of approximately 98 days after the second dose, which did not pass the minimum HTAC specification (at least 6 months). One study (Lau et al., 2022) reported a failing VE against any SARS-CoV-2 infection against the Omicron variant for children ages 3 to 11 years old with a follow up period of 25 days after the second dose and a passing VE against any infection in adolescents aged 12 to 17 years old with a follow up period of 64 days after the second dose. Follow up periods for both populations did not pass the minimum HTAC specification (at least 6 months). Symptomatic COVID-19 One trial (Sinovac Life Sciences Co. Ltd., 2022) and one observational study (Florentino et al., 2022) reported failing VE against symptomatic infection (vs Omicron). These studies follow up periods ranging from 43 days to 64.68 days after the second dose which did not pass the minimum HTAC specification (at least 6 months). Hospitalization due to COVID-19 Three studies reported VE against hospitalization. Of which, two (Sinovac Life Sciences Co. Ltd., 2022; Florentino et al., 2022) were conducted during the Omicron-dominant period and one (Jara et al., 2022) was conducted during the Delta-dominant period. Both studies conducted during the Omicron dominant period had VEs that did not pass HTAC specifications. However, the other real world study (Jara et al., 2022) conducted during the Delta-dominant period had VE against hospitalization that passed HTAC specifications. These studies had follow-up periods ranging from 43 days to 98 days after the second dose which did not pass the minimum HTAC specification (at least 6 months). ICU Admission due to COVID-19 Two studies reported VE against ICU admission. Of which, one study (Florentino et al., 2022) reported ICU admission against Omicron which did not pass HTAC specifications. However, the other study (Jara et al., 2022) conducted during the Delta-dominant period had passing VE. These studies follow-up periods ranging from 43 days to approximately 98 days after the second dose which did not pass the minimum HTAC specification (at least 6 months).	

		Immunogenicity Two studies with immunogenicity outcomes for duration of protection were reviewed. Study by Leung et al. (2022) showed that in children ages 11 to 17 years old, humoral response decreased 4 weeks after second dose of *CoronaVac* while no decline in cellular response was observed 15 weeks after second dose. Another study by Wu et al. (2022) showed that GMT of neutralizing antibodies declined 3 months after the second dose. Longest follow-up period for immunogenicity studies is 12 months after the second dose. Data on the duration of protection of *CoronaVac* among children ages 6-17 years will be assessed as more evidence becomes available. **HTAC Judgment:** Cannot be assessed based on current clinical limited evidence. However, it was noted that one immunogenicity study with a 12-month follow up period showed that immune response declines 3 months after the second dose (Wu et al. 2022).	
	*What is the **safety** of CoronaVac in children ages 6 to 17 years old 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,*	For the evidence on the safety of *CoronaVac* among children ages 6 to 17 years, the following latest available reviews were considered: Philippine Living Clinical Practice Guidelines Group (LCPG Group) review on COVID-19 Vaccines in the pediatric population (updated as of 04 January 2022); International Vaccine Access Center (IVAC) of the Johns Hopkins Bloomberg School of Public Health and World Health Organization review on COVID-19 vaccines in general as of 02 September 2022; and, COVID-NMA review of trials and real world evidence on COVID-19 vaccines in general as of 03 November 2021. Additionally, trial reports and real world evidence from the manufacturer dossier submission to FDA and independently retrieved preprints from medRxiv were also considered. To supplement these, a targeted search for safety surveillance reports was also done among countries with EUA on *Coronavac* for the pediatric population. These included the Ministries of Health and National Regulatory Agencies of 13 countries (China, Hong Kong, Cambodia, Chile, Colombia, Dominican, Thailand, Ecuador, Malaysia, Indonesia, Brazil, Myanmar, Zimbabwe). Overall, there were a total of 4 trials (i.e. Han et al, 2021, Zhao, 2021, Soto et al., 2022, Rosa Duque et al., 2022) and 3 real world safety surveillance reports detected in the reference reviews and dossier submission that reported the safety of *CoronaVac* among children ages 6-17 years old. We note that one interim Phase III report (Sinovac Life Sciences Co. Ltd., 2021) that was examined by the Philippine FDA was excluded due the absence of disaggregated data for the vaccine and placebo arms. ***SAFETY DATA FROM CLINICAL TRIALS***	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, AESI): at least 2 months **Long term outcomes** (e.g., serious AEs, all-cause mortality, AESI, Vaccine-associated

Multisystem Inflammatory Syndrome in Children [MIS-C] Post Vaccination)

Description of Evidence

The reference reviews detected 4 trials on safety - 1 preprint of a Phase III RCT (Soto et al., 2022) and 1 published of Phase II nonrandomized trial (Rosa Duque et al., 2022), which are the same trials presented in the efficacy section of this evidence summary, 1 published Phase I/II RCT (Han et al, 2021), which is the earlier, published version of Wu et al. (Wu et al. did not report safety outcomes), and 1 unpublished preliminary clinical trial report (Phase IIb RCT (Zhao, 2021). Details of the studies are presented in Table 1.2.5 below.

Table 2.12 Study characteristics of clinical trials that reported the safety of *CoronaVac* among children aged 6 to 17 years.

Author, Year Country Study Design	Population	Intervention	Comparator	Outcomes
Phase I/II RCTs				
Han et al, 2021 [published] China Phase I/II RCT Start of enrollment: Phase 1: October 31, 2020 Phase 2: December 12, 2020 Data cut-off: June 2021	Healthy children and adolescents aged 3-17 years old *N=550* N, Phase 1 = 71 N, Phase 2 = 479	1.5 ug *CoronaVac* Vaccine, 2 doses, 28 days apart n, Phase 1 = 27 n, Phase 2 = 192 3.0 ug *CoronaVac* Vaccine, 2 doses, 28 days apart n, Phase 1 = 26 n, Phase 2 = 191 *Note: 3.0 µg CoronaVac is the approved dose by the PH FDA.*	Aluminum hydroxide only, 2 doses, 28 days apart n, Phase 1 = 18 n, Phase 2 = 96	- Any vaccine-related adverse events (adverse reactions) within 28 days after each injection - Serious adverse events (SAEs) and any abnormal changes in laboratory measurements at day 3 after each dose ***Follow-up period:*** *28 days after each dose*
Zhao, 2021	Healthy children and	600 SU or 0.5ml	Placebo, 2 doses, 28	- Adverse reactions

enhanced disease): at least 1 year

		[unpublished] China Phase IIb RCT Study Initiation Date: May 3, 2021 Date of report: July 2021	adolescents aged 3-17 years *N=500*	*CoronaVac,* 2 doses, 28 days apart n= 375 *(368 participants completed 2-dose vaccination)*	days apart n= 125 *(124 participants completed 2-dose vaccination)*	(ARs) up to 28 days after dose 2 - Serious adverse events (SAEs) up to 6 months after dose 2 ***Follow-up period:*** *At least 56 days after enrollment*
		<u>Rosa Duque et al., 2022</u> [published] Hong Kong Interim Phase II nonrandomized trial Enrollment period: 27 April 2021 to 23 October 2021 Dominant variant: not specified	11-17 year old children and ≥18 year old adults N, children = 239 N, adults = 288	Children ages 11-17 years old n, 2 doses CoronaVac = 123 n, 2 doses Pfizer-BioNTech = 116	Adult (>18 year old) n, 2 doses *CoronaVac* = 141 n, 2 doses *Pfizer-BioNTech* = 147	- Any unsolicited adverse events within 28 days of vaccination - Local adverse reactions - Systemic adverse reactions - Serious adverse reactions (SAE) ***Follow-up period:*** *28 days after vaccination*
		Phase III RCTs				
		<u>Soto et al., 2022</u> [preprint] Chile Interim Phase III RCT September 10, 2021 to December 31,	Healthy children ages 3-17 years old N=963	2 doses of 3µg (600 SU) *CoronaVac,* 28 days apart Safety set Dose 1: 3-11 years old:	None	- Local and systemic immediate (within 30 minutes) and non-immediate (within 7 days) adverse events

2021		n= 653 12-17 years old: n= 46 Dose 2: 3-11 years old: n= 336 12-17 years old: n= 45		- Any adverse events until 28 days after each dose - SAEs and AESIs within 12 months after the 2nd dose ***Follow-up period:*** *28 days after each dose*	

Key findings

Risk of bias

The HTAC rated the RoB of Han et al., 2021 [published] as 'Unclear' due to an 'unclear' RoB rating in the domains incomplete safety outcome data and allocation concealment. Meanwhile, the study of Zhao, 2021 [unpublished] and Soto et al., 2022 [preprint] were rated to be of 'High' RoB. For specific domains, Zhao, 2021 [unpublished] was rated high RoB due to incomplete outcome data, while Soto et al., 2022 [preprint] was rated 'high' RoB due to lack of blinding for investigators, incomplete outcome data, and selective reporting. Lastly, the study of Rosa Duque et al., 2022 [published] was rated to be of 'High' overall RoB due to 'High' RoB rating in the domains random sequence generation, allocation concealment, blinding of participants, personnel and outcome assessment and an 'unclear' rating for the domain incomplete outcome data. Details on the RoB assessment of this study is reflected in Appendix 3B.

Results of clinical safety

In terms of safety results, all four studies (Han et al, 2021 [published]; Zhao, 2021 [unpublished]; Soto et al., 2022 [preprint]; and Rosa Duque et al., 2022 [published]) reported short-term and long-term safety outcomes. Han et al, 2021 [published] and Zhao, 2021 [unpublished] compared the safety and reactogenicity of two doses of *CoronaVac* versus placebo. The study by Rosa Duque et al., 2022 [published], on the other hand, compared the safety outcomes reported among adolescents after two doses of *CoronaVac* versus *Pfizer-BioNTech.* Meanwhile, Soto et al., 2022 [preprint] only reported safety data for participants ages 3-17 years who received two doses of *CoronaVac*.

		Short-term safety outcomes: ● ***Any adverse events (AEs):*** *Phase I/II trials:* - Han et al (2021) [published] reported at least one AE in 29% (63/217) participants within 28 days of with 3.0 µg (600SU/0.5mL) of *CoronaVac* which is not significantly higher than rates observed in placebo group (24%; 27/114) and the lower dose (1.5µg) of *CoronaVac* (26%; 56/219) (p-value = 0.55). Most of the AEs were mild (grade 1) and moderate (grade 2) in severity and only 2 out of 550 (<1%) had grade 3 AEs. In terms of age group, 18% (37/204) of participants aged 6-11 reported cases of AEs while 35% (72/203) of participants aged 12-17 exhibited AEs. Most of the AEs occurred within 7 days after vaccination, and participants recovered within 48 hours. The study also reported no significant difference in the prevalence of other solicited (p=0.28) or unsolicited (p=0.52) AEs among the three (Phase 1, Phase 2, placebo) groups except for the higher prevalence of injection site pain in both the 1.5ug and 3ug dose groups compared to placebo (p=<0.0001). - Zhao (2021) [unpublished] reported no significant difference (p=0.6344) between the overall incidence of adverse events in the vaccine arm (25.87%, 97/375) and the placebo arm (23.2%, 29/125). - Rosa Duque et al. (2022) [published] reported 8 (6.50%) grade 1 unsolicited adverse events within 28 days of vaccination in the healthy adolescent from the healthy safety population who received *CoronaVac* (n=123). There were no grade 2 or grade 3 adverse events among healthy adolescents who received *CoronaVac.* ● ***Local reactogenicity:*** *Phase I/II trials:* - Han et al (2021) [published] reported a significantly higher incidence (p=<0.0001) of pain in the injection site in both vaccine dose groups (1.5 µg group: 16%, 36/219; and 3.0 µg group: 16%, 35/217) than in the placebo group (2%, 2/114). There were no significant differences in the incidence of other reported injection site adverse reactions such as swelling (p=0.50), induration (p=0.20), erythema (p=0.60), and pruritus (p=0.64). - Zhao (2021) [unpublished] reported a significantly higher (p=0.0289) incidence of local adverse reactions in the vaccine arm (10.67%, 40/375) than in the placebo arm (4.0%, 5/125). All adverse reactions occurred within 0-7 days after administration of the product. No reactions were reported within 30 minutes after vaccination in the vaccine	

		arm. Of all reported adverse reactions, the most frequently reported was pain at the injection site, with an incidence of 10.40% (39/375) in the vaccine arm and 4.0% (5/125) in the placebo arm (p=0.0285). - Rosa Duque et al. (2022) [published] reported that among adolescents in the healthy safety population, pain at the injection site was the most common adverse reaction reported for both *CoronaVac* and *Pfizer-BioNTech*. Among adolescents receiving *CoronaVac*, 54.5% experienced pain in injection after the first dose and 52.9% after the second dose. It is also noted that this adverse reaction was observed for those who received *CoronaVac* (n=123) significantly less than *Pfizer-BioNTech* (n=116) (p-value<0.0001). *Phase III trials:* - Soto et al., (2022) [preprint] reported both immediate (i.e. within 30 minutes of vaccination) and non-immediate local reactions (i.e. within 7 days after each dose). In terms of immediate adverse events, the most reported local reaction was local pain at 3.8% and 1.7% after the first and second dose, respectively, in children ages 3 to 11 years old. While for adolescents (12 to 17 years old), the rate for local pain was 2.2% and 8.2% after the first and second dose, respectively. Other local reactions i.e., redness, induration, pruritus and swelling were reported in ≤2% of the participants. In terms of non-immediate adverse events, the most reported local reaction was local pain at 15% and 8% after the first and second dose, respectively, in children ages 3 to 11 years old. While for adolescents (12 to 17 years old), the rates for local pain was 25% after each dose. There was a significantly higher frequency of injection site pain, both immediate (p=0.002791) and non-immediate (p=0.0063) in adolescents than children after the second dose. Most local AEs resolved after 2 days. ● ***Systemic reactogenicity:*** *Phase I/II trials:* - Han et al (2021) [published] reported no significant differences in all collected systemic adverse reactions across the three treatment arms: fever (p=0.93), cough (p=0.47), headache (p=0.82), anorexia (p=0.92), diarrhea (p=0.16), nausea (p=0.89), mucocutaneous eruption (p=1.00), vomiting (p=0.85), muscle pain (p=0.08), fatigue (p=1.00), hypersensitivity (p=0.21). - Zhao (2021) [unpublished] reported no significant difference (p=0.53) between the incidence of systemic adverse reactions in the vaccine arm (11.47%, 43/375) and the	

		placebo arm (13.6%, 17/125). All adverse reactions occurred within 0-7 days after administration of the product. No reactions were reported within 30 minutes after vaccination in the vaccine arm. Of all reported adverse reactions, the second most frequently reported was fever, with an incidence of 5.87% (22/375) in the vaccine arm and 4.0% (5/125) in the placebo arm. - Rosa Duque et al. (2022) [published] reported that as compared to *Pfizer-BioNTech*, *CoronaVac* was associated with less systemic adverse reactions which include headache, myalgia, nausea, diarrhoea, vomiting, arthralgia, chills, fever, reduced appetite and abdominal pain. Further, less participants had antipyretics use after either dose of *CoronaVac* than *Pfizer-BioNTech*. *Phase III trials:* - Soto et al., (2022) [preprint] reported both immediate (i.e. within 30 minutes of vaccination and non-immediate local reactions (i.e. within 7 days after each dose). In terms of immediate adverse events, systemic AEs were more frequent in adolescents than in children (less than 1% of the 3 to 11 years age group reported systemic AE). Headaches were reported in adolescents (12 to 17 yo) at a rate of 2.2% and 1.2% after the first and second dose, respectively. No other AE was reported after the first dose while one adolescent reported auto-limited pruritus (skin mucosal abnormality) after the second dose. In terms of non-immediate adverse events, headache and fever were the most common AE reported in adolescents and children, respectively. Fever was reported in 9% and 7% of children after the first and second dose, respectively. Headache was reported in 6% and 4% of adolescents after the first and second dose, respectively. The severity of AEs were mostly grade 1 (62% to 79%) and grade 3 AEs were reported by 1.7% to 2.7% of the population. Further, no grade 4 AE was reported. Long-term outcomes: ● ***Serious adverse events (SAEs):*** *Phase I/II trials:* - As of the study data cutoff, Han et al (2021) [published] observed one serious adverse event of pneumonia that occurred in the placebo group. The event was considered by the investigators to be unrelated to the vaccination. However, it is noted that the median follow-up period from full vaccination to the date of the report is unclear and was not indicated in the manuscript. - Zhao, (2021) [unpublished] reported that there were no serious adverse events that	

occurred during the study period. However, it is noted that the median follow-up period from full vaccination to the date of the report is unclear and was not indicated in the manuscript.

- Rosa Duque et al. (2022) [published] reported that there were no serious adverse events that occurred during the study period for both *CoronaVac* and *Pfizer-BioNTech*. However, the median follow-up period was not indicated.

Phase III trials:

- Soto et al., (2022) [preprint] reported one serious AE in the trial, a 3 year-old participant who was hospitalized due to influenza A infection. However, Soto et al. noted that this SAE is not related to the vaccine.

SAFETY DATA FROM REAL WORLD EVIDENCE

Out of the 13 other countries reported to have issued EUA for the use of *CoronaVac* in the pediatric population, 5 countries (Chile, China, Hong Kong, Ecuador and Malaysia) were detected to have available safety surveillance reports. Of these, 4 countries (Chile, China, HongKong and Malaysia) have safety data specific to the pediatric population while 1 country (Ecuador) did not report specific AEFI analysis for the pediatric population. The 8 other countries (Brazil, Cambodia, Colombia, Dominican Republic, Myanmar, Thailand and Zimbabwe) that were reviewed did not have available or accessible reports.

Description of Evidence

The four safety surveillance reports detected via targeted search were from Chile (collected by Pharmacovigilance Subdepartment of Chilean Institute of Public Health (SDFV-ISP), China (Sinovac AEFI analysis submission), Hong Kong (Hong Kong Drug Office Monitoring) and Malaysia (National Pharmaceutical Regulatory Agency). The characteristics of these surveillance reports are indicated in Table 2.12 below:

Table 2.13. Characteristics of safety surveillance reports from countries implementing pediatric vaccination.

Agency/Author/ Presenter [Period of Observation]	Reporting system	Population (N)	Intervention	Limitations

		Chile SDFV-ISP [01 March 2021 to 21 May 2022]	Electronic reporting systems: Vigilancia de Errores Programaticos (ESAVI-EPRO), Reaccion Adversa de Medicamentos (RED-RAM), Automated Reaccion Adversa de Medicamentos (NOTI-RAM-ESAVI), and manual reporting via email	**3-17 years old:** 5,158,963 *CoronaVac* doses administered as of 21 May 2022	*CoronaVac* 0.5mL/dose, 2 doses 14-28 days apart	• Reported outcomes do not have disaggregation for 6 to 17 years old vaccinees as the report available for the pediatric population is for 3 -17 years old • Events Supposedly Attributable to Vaccination and Immunization (ESAVI), are events that do not always correspond to proven adverse reactions. Causality is not yet established. • This is a passive surveillance system; hence, it may not account for all people who experience an adverse event in the country since not all events in the population are reported.
		China Sinovac AEFI Analysis Report [company submission, unpublished] [February 5, 2021 - February 20, 2022]	Chinese Center for Disease Control and Prevention Adverse Event Following Immunization (AEFI) monitoring system and Marketing Department, Sinovac	N= more than 256,000,000 doses of *CoronaVac* (includes children 3-17 years old)	*CoronaVac* 0.5mL/dose, 2 doses 14-28 days apart	• Investigation on causality of reports is still ongoing. Relation of all AESIs to the vaccine is yet to be determined. • The total number of administered doses per age group (i.e., 3-5, 6-11, 12-17) is unknown. The denominator used for the reporting rates for each age group is the total number of doses for children ages 3-17 years.
		Hong Kong Drug Office Monitoring [1June - 31 July	COVID-19 Vaccine Adverse Event on-line Reporting System	N (19 and below) = 1,803,200 doses *CoronaVac* and *Pfizer* doses administered	*CoronaVac* 0.5mL/dose, 2 doses 14-28 days apart	• Reported outcomes did not disaggregate results for 6 to 17 years old vaccinees as the report available is for 19 years old and below.

2022]		as of 31 July 2022		• Reported outcomes did not disaggregate results per vaccine brand.
Malaysia National Pharmaceutical Regulatory Agency [**5 to 11 yo:** 7 March 2022 - 10 June 2022 **12 to 17 yo:** 20 September 2021 - 10 June 2022]	NPRA Adverse Drug Reaction (ADR)/AEFI Reporting System	**5 to 11 years old:** N= 2,702,653 doses *CoronaVac* and *Pfizer* doses administered as of 10 June 2022 **12 to 17 years old:** N=5,867,031 doses *CoronaVac* and *Pfizer* doses administered as of 10 June 2022	*CoronaVac* 0.5mL/dose, 2 doses 14-28 days apart	• Reported outcomes did not disaggregate results per vaccine brand.

Key Findings

Safety results

The results from the safety surveillance studies among the vaccinated pediatric population with ages ranging from 6 years old to 17 years old are reported in Table 2.13. below:

Table. 2.14. Results of safety surveillance reports from countries implementing pediatric vaccination.

	Chile SDEV-ISP	**China** Sinovac AEFI Analysis Report [company submission]	**Hong Kong** Drug Office Monitoring	**Malaysia** National Pharmaceutical Regulatory Agency

		All Adverse events *(Reporting rate: reports per 100,00 doses administered)*	**<u>3-11 years old</u>** **Reporting rate =** 11.13 **<u>12-17 years old</u>** **Reporting rate =** 9.91	**<u>3-17 years old</u>** **No. of reports =** 21,692 **Reporting Rate =** 8.47 **<u>6-11 years old</u>** **No. of reports =** 9,848 (45.40% of reported AEs) **Reporting Rate =** 3.84 **<u>12-17 years old</u>** **No. of reports =** 5,033 (23.20% of reported AEs) **Reporting Rate =** 1.96	**<u>19 and below</u>** **Reporting rate =** 32.7	**<u>5 to 11 years old:</u>** **Reporting rate** = 14.6 **<u>12 to 17 years old:</u>** **Reporting rate** = 20.8	
		Serious Adverse Events (SAE) *(Reporting rate, reports per 100,00 doses administered))*	**<u>3-17 years old</u>** **Reporting rate** = 1.32 after dose 1 = 1.60 after dose 2 = 0.81	**<u>3-17 years old</u>** **No. of reports =** 477 (2.20% of reported AEFIs) **Reporting Rate =** 0.19 **<u>6-11 years old</u>** **No. of reports =** 215 (45.07% of reported SAEs) **Reporting Rate =** 0.08 **<u>12-17 years old</u>** **No. of reports =** 189 (39.62% of reported SAEs) **Reporting Rate =** 0.07	Not reported	**<u>5 to 11 years old:</u>** **Reporting rate =** 0.9 **<u>12 to 17 years old:</u>** **Reporting rate** = 1.4	
		Non-serious AEs	**<u>3-17 years old</u>** **Reporting rate** = 9.48	**<u>3-17 years old</u>** **No. of reports** =	Not reported	**<u>5 to 11 years old:</u>** **Reporting rate:** 13.7	

		(Reporting rate: reports per 100,00 doses administered)	after dose 1 = 13.20 after dose 2 = 4.37	21,215 (97.80%) **Reporting Rate =** 8.28		**<u>12 to 17 years old:</u>** **Reporting rate**= 19.4
		Local AEs *(Reporting rate: reports per 100,00 doses administered)*	**<u>3-17 years old</u>** • Injection site reaction: 3.20 • Itching: 1.92 • Urticaria: 1.38 • Skin rash: 0.64	**<u>6-17 years old</u>** **No. of reports =** 4,290 No reporting rate reported	Not reported	Not reported
		Systemic AEs *(Reporting rate: reports per 100,00 doses administered)*	**<u>3-17 years old</u>** • Vomiting: 1.57 • Headache: 1.55 • Fever: 1.22 • Nausea: 1.03 • Syncope: 0.83 • General discomfort: 0.76	**<u>6-17 years old</u>** **No. of reports =** 14,020 No reporting rate reported	Not reported	Not reported
		Death *(Reporting rate: reports per 100,00 doses administered)*	Not reported	**<u>6-17 years old</u>** **No. of reports =** 16 (3 indeterminate; 11 coincidental/not related; 1 abnormal reaction) **<u>3-17 years old</u>** **Reporting Rate =** 0.09	Not reported	Not reported
		Adverse Event of Special Interest (AESI): Note: All reports were for age groups 3-17 years old.				

		Guillain-Barre Syndrome *(Reporting rate: reports per 100,00 doses administered)*	**<u>3-17 years old</u>** **Reporting rate** = 0.04	**<u>3-17 years old</u>** **No. of reports =** 18 (14 serious) **Reporting Rate =** 0.007 Related to the vaccine : 8 cases	Not reported	Not reported	
		Bell's palsy *(Reporting rate: reports per 100,000 doses administered)*	**<u>3-17 years old</u>** **Reporting rate** = 0.00	**<u>3-17 years old</u>** **No. of reports =** 9 (all non-serious) **Reporting Rate =** 0.004 Related to the vaccine : 2 cases	Not reported	Not reported	
		Sudden hearing loss *(Reporting rate: reports per 100,00 doses administered)*	Not reported	**<u>3-17 years old</u>** **No. of reports =** 11 (3 serious) **Reporting Rate =** 0.004 Related to the vaccine : 3 cases	Not reported	Not reported	
		Thrombocytopenic purpura *(Reporting rate: reports per 100,00 doses administered)*	Not reported	**<u>3-17 years old</u>** **No. of reports =** 35 (19 serious) **Reporting Rate =** 0.014 Related to the vaccine : 12 cases	Not reported	Not reported	

		Myelitis *(Reporting rate: reports per 100,00 doses administered)*	Not reported	**<u>3-17 years old</u>** **No. of reports =** 2 (1 serious) **Reporting Rate =** 0.001 Related to the vaccine : 1 case	Not reported	Not reported
		Demyelination *(Reporting rate: reports per 100,00 doses administered)*	Not reported	**<u>3-17 years old</u>** **No. of reports =** 10 **(**7 serious) **Reporting Rate =** 0.004 Related to the vaccine : 7 cases	Not reported	Not reported
		Immune thrombocytopenia *(Reporting rate: reports per 100,00 doses administered)*	**<u>3-17 years old</u>** **Reporting rate** = 0.02	**<u>3-17 years old</u>** **No. of reports =** 13 (4 serious) **Reporting Rate =** 0.005 Related to the vaccine : 4 cases	Not reported	Not reported
		Myocarditis *(Reporting rate: reports per 100,00 doses administered)*	**<u>3-17 years old</u>** **Reporting rate** = 0.02	**<u>3-17 years old</u>** **No. of reports =** 18 (7 serious) **Reporting Rate =** 0.007 Related to the vaccine : 1 case	Not reported	Not reported
		Venous thrombosis limb *(Reporting rate: reports per 100,00*	Not reported	**<u>3-17 years old</u>** **No. of reports =** 1 (causality to be determined) **Reporting Rate =** 0.0005	Not reported	Not reported

		doses administered)				
		Anaphylactic shock *(Reporting rate: reports per 100,00 doses administered)*	**<u>3-17 years old</u>** **Reporting rate** = 0.12	**<u>3-17 years old</u>** **No. of reports =** 32 (22 serious) **Reporting rate =** 0.012 Related to the vaccine : 31 cases	Not reported	Not reported
		Laryngeal edema *(Reporting rate: reports per 100,00 doses administered)*	Not reported	**<u>3-17 years old</u>** **No. of reports =** 7 (5 serious) **Reporting rate =** 0.003 Related to the vaccine : 7 cases	Not reported	Not reported
		Henoch-Schonlein purpura *(Reporting rate: reports per 100,00 doses administered)*	Not reported	**<u>3-17 years old</u>** **No. of reports =** 291 (144 serious) **Reporting rate =** 0.114 Related to the vaccine : 138 cases	Not reported	Not reported
		Seizures (Focal Seizures and Tonic/clonic seizures). *(Reporting rate: reports per 100,00 doses*	**<u>3-17 years old</u>** **Reporting rate** = 0.70	**<u>3-17 years old</u>** **No. of reports =** 40 (7 serious) **Reporting rate =** 0.016 Related to the vaccine : 3 cases	Not reported	Not reported

		administered)				
		Thromboembolism (thrombosis, thromboembolism and embolism.) *(Reporting rate: reports per 100,00 doses administered)*	**<u>3-17 years old</u>** **Reporting rate** = 0.06	Not reported	Not reported	Not reported
		Stroke *(Reporting rate: reports per 100,00 doses administered)*	**<u>3-17 years old</u>** **Reporting rate** = 0.00	Not reported	Not reported	Not reported
		Herpes Zoster *(Reporting rate: reports per 100,00 doses administered)*	**<u>3-17 years old</u>** **Reporting rate** = 0.02	Not reported	Not reported	Not reported
		Pericarditis *(Reporting rate: reports per 100,00 doses administered)*	**<u>3-17 years old</u>** **Reporting rate** = 0.00	Not reported	Not reported	Not reported
		Vasculitis *(Reporting rate:*	**<u>3-17 years old</u>** **Reporting rate** = 0.02	Not reported	Not reported	Not reported

		reports per 100,00 doses administered) [redacted]	
		* from Chilean Ministry of Health Report as of 7 September, 2022. **HTAC Judgment:** Based on limited trial data and real world post-marketing surveillance, the short-term safety of *CoronaVac* in children ages 6 to 17 years old is acceptable. However, further follow-up data is needed to establish longer-term safety.	
	*Does CoronaVac provide a highly favorable **benefit/risk profile** in the context of observed vaccine effectiveness and safety?* *Can CoronaVac significantly reduce the magnitude and severity of COVID-19 in children ages 6 to 17 years old?*	The following table summarizes the evidence on efficacy, effectiveness, and safety of 2-dose primary series of *CoronaVac* among children and adolescents ages 6 to 17 years old.	Favorable benefit/risk profile

Outcome	6 to 11 years old	12 to 17 years old
Efficacy (vs Omicron)	Evidence on clinical efficacy (Sinovac Life Sciences Co. Ltd., 2022) of *CoronaVac* in children ages 6 to 17 years old showed that VEs (any SARS-CoV-2 infection, symptomatic COVID-19 and hospitalization due to COVID-19) against Omicron variant did not pass HTAC specifications.	
Effectiveness (vs Delta)	Real world study during the Delta dominant period (Jara et al., 2022) showed passing VE against confirmed COVID-19, hospitalization and ICU admission due to COVID-19 in children ages 6 to 16 years old.	
Effectiveness (vs Omicron)	Study by Florentino et al. (2022) showed that vaccine effectiveness (symptomatic COVID-19, hospitalization and ICU admission due to COVID-19) against the Omicron variant in children ages 6 to 11 year old did not pass HTAC	[redacted]

			specifications.		
			Study by Lau et al. (2022) also showed that VE against SARS-CoV-2 infection in children 3 to 11 years old did not pass HTAC specifications for symptomatic COVID-19.	However, a study by Lau et al. (2022) showed that VE against SARS-CoV-2 infection in children 12 to 17 years old passed HTAC specifications for symptomatic COVID-19.	
			Immunogenicity	Phase III trial by Soto et al., 2022 (preprint) showed that CoronaVac induces immune response in children aged 3 to 11 years old.	• Phase III trial by Soto et al., 2022 (preprint) and Phase II trial by Leung et al., 2022 (preprint, wild-type) showed that *CoronaVac* induces immune response in children aged 12 to 17 years old. • Immunobridging study by Rosa Duque et al., 2022 (published, variant not specified) showed that *CoronaVac* induces an immune response in adolescents aged 11 to 17 years old that is either non inferior or superior compared to the immune response of adults.
			Safety	Short-term safety of 2-dose primary series of *CoronaVac* in children ages 6 to 11 years old is acceptable. It is also noted that in	Short-term safety of 2-dose primary series of *CoronaVac* in adolescents ages 12 to 17 years old is acceptable. Further follow-up

			children 6-11 yo, safety data shows very rare severe adverse events (e.g., anaphylaxis, myocarditis and thromboembolic events). Thus, *CoronaVac* can be given as an alternative for children aged 6-11 years old with mRNA vaccine contraindication (eg. anaphylaxis to the first dose of mRNA vaccine or previous allergy to PEG). Further follow-up data is needed to establish long-term safety.	data is needed to establish long-term safety.	

HTAC Judgment:

For children aged 6 to 11 yo	For adolescents aged 12 to 17 yo
Among children aged 6 to 11 years old, 2-dose primary series of *CoronaVac* has an unsatisfactory benefit-risk profile based on currently available evidence on clinical efficacy and effectiveness against the Omicron variant and short term safety data. However, for children aged 6-11 years old with mRNA vaccine contraindication (eg. anaphylaxis to the first dose of mRNA vaccine or previous allergy to PEG), *CoronaVac* may be given.	Among children ages 12 to 17 years old, 2-dose primary series of *CoronaVac* has an acceptable benefit-profile based on currently available clinical efficacy and effectiveness against Omicron variant and short-term safety data.

CRITERION 3

3. Affordability, viability and feasibility	*What are the current best practices, challenges and measures used to address challenges related to the implementation of COVID-19 Vaccines in the pediatric population (5-17 years old), which can be applicable to the implementation of CoronaVac in children ages 6 to 17 years old?* *How will the vaccination for the pediatric population be DIFFERENT with the use of CoronaVac compared to other vaccines for the pediatric population?* *Are there any foreseen advantages and barriers specific to the use of CoronaVac in the pediatric population? How are these*	Based on a series of consultation with the Public Health Operations Center (PHOC) [*formerly known as National Vaccine Operations Center (NVOC)*] and selected DOH Centers for Health Development (CHDs), information on real world experience during the current roll out of COVID-19 vaccines in children ages 5-11 years old using *Pfizer-BioNTech* and adolescents 12-17 years old using both *Pfizer-BioNTech and Moderna*, and plans for the future roll out of *CoronaVac* for children and ages adolescents 6-17 years old were gathered (as of September 2022). ***Best Practices in the Implementation of COVID-19 Vaccination for Children (5 to 17 years old)*** *5-11 years old COVID-19 vaccinations* ● ***Utilizing festive strategies in vaccination sites:*** Regional offices noted the use of mascots and playgrounds to encourage children to get vaccinated. Incentives such as food and free accommodations to park were also distributed. ● ***Coordination with the Department of Education (DepEd):*** Schools were also used as vaccination sites for children. DepEd's plan to conduct face-to-face classes encouraged parents to have their children vaccinated for safety reasons. ● ***Availability of guidelines:*** According to regional offices, implementers find it helpful that the pediatric vaccination guidelines were readily available which contributed to the clarity of implementation and a well prepared roll-out. ● ***Transparent reporting of AEFIs:*** According to PHOC, side effects for the pediatric population were less as compared to adults and these AEFIs were documented and properly reported. ● ***Confidence to get vaccinated***: Unlike adults, children are used to getting vaccinated as they are the target population of routine EPI immunization. ● ***Confidence of healthcare workers:*** Healthcare workers were also more confident because of their experience with the adolescent roll-out. ● ***Vaccination rollout during weekends:*** Vaccination was extended until weekends in some vaccination sites to accommodate children with parents/guardians that are unavailable during weekdays. ● ***Experts, healthcare workers and LGUs encouraging the vaccination of the pediatric population***: Testimonials from experts and DOH personnel who got their children vaccinated were used to promote pediatric vaccination efforts. Ceremonial giving of vaccines to pediatric family members of health workers and local chief executives were conducted to encourage parents to have their children vaccinated as well. The pediatric society such as the Philippine Pediatric Society (PPS) and private sectors also supported the roll-out. *Common best practices for 5-11 and 12-17 year old COVID-19 vaccinations* ● ***Available and accessible vaccination sites:*** Vaccinations were conducted at the mega-sites such as	There are no significant barriers and if there are, the plans to address the barriers are clearly reflected in the vaccine roadmap and other relevant documents.

	foreseen barriers planned to be managed?	malls, temporary posts, mobile buses, and house visits to accommodate the vaccinees and their guardians, to ensure that standard public health measures are maintained, and to actually encourage children, especially the younger ones, to get vaccination. These strategies also allowed parents and children to be vaccinated together at one site. ● ***Stringent documentary requirements:*** Documentation from the accompanying parent/guardian was required to provide proof of affiliation to the pediatric vaccinee. Obtaining informed consent from the parent/guardian and assent from the child were strictly implemented prior to vaccination. ● ***Stringent screening process:*** The rollout for the pediatric population was tailored to ensure that vaccinees with comorbidities, including those with a history of conditions that were considered AESIs associated with vaccination (e.g. myocarditis and pericarditis) are identified and educated properly. ● ***Presence of medical specialists at the vaccination site:*** Aside from the usual AEFI teams present in vaccination sites, the on-site supervision of pediatricians and allergologists during vaccination of the pediatric population facilitated the timely and appropriate management of AEFIs (vs the on-call visit of the specialists for the adult vaccination). ***Challenges in the Current Implementation of COVID-19 Vaccination for Children (5 to 17 years old)*** *5-11 years old COVID-19 vaccinations* ● ***Low Vaccination Turnout****:* The PHOC reported that some factors might have lowered the turnout of vaccinees. These factors include conflict with the schedule of guardians since vaccination is usually held on weekdays, and diminished sense of urgency to vaccinate children due to DepEd's non requirement of vaccination for face to face classes. The DOH explained though that we cannot require vaccination for face to face classes until sustainable supply of vaccines for the pediatric population is ensured. ● ***Vaccine Hesitancy:*** PHOC experienced an unexpected increase in vaccine hesitancy during the rollout of vaccination for children ages 5 to 11 years compared to when they were rolling out for adolescents. Identified causes of hesitancy include the spread of fake news, including authenticity of AEFI reporting, and resurfacing of the *Dengvaxia* controversy. An increased presence of anti-vaccine groups was also noticed, with some going as far as picketing outside vaccination sites. These circumstances have also made public communication difficult. ● ***Lengthier Vaccination Time for Pediatric Populations:*** PHOC noted that vaccination time is longer for the pediatric population compared to adult vaccination time. This was attributed to the following reasons: more complicated obtainment of children's assent; and the need for a more exhaustive assessment and screening prior to vaccination, which take longer to per form.	

		• ***Preference for Another Vaccine Platform:*** Given that the current implementation of vaccination for children and adolescents uses mRNA vaccines, a new vaccine platform, there are anecdotal statements expressing that parents are hesitant to get their children vaccinated as they still prefer more traditional vaccine platforms such as inactivated vaccines. • ***Refusal of children to get vaccinated:*** During vaccination, some children refuse to give assent to get vaccinated, and to some extent cry loudly while at the vaccination site. Implementers express that in these certain situations, the children were sent home without getting the vaccine and may have to return some other time. These types of scenarios might also affect other children waiting when they see others in distress. <u>*12-17 years old COVID-19 vaccinations*</u> • ***Compliance to stringent documentary requirements in certain situations:*** Compliance was difficult with regard to the documentary requirements (e.g. proof of affiliation to the child) and the presence of the parent/guardian. This was especially true for children of OFWs. • ***Inadvertent vaccination using vaccines with no EUA for pediatric use:*** The PHOC previously received a few reports of inadvertent vaccination using vaccines that do not have an EUA for pediatric use at the time (e.g., *AstraZeneca* and *CoronaVac*). This administration error happened during the National Vaccination Days (NVDs) where there were no special lanes for the pediatric age group. • ***Cold chain requirement:*** Most LGUs, particularly in Region VI, still do not have the capacity to store *Pfizer-BioNTech* at ultra-low temperatures. The central storage of this vaccine is still at the Provincial Health Offices (PHO) or municipalities that have ultra-low temperature freezers (ULTFs). This causes delays and complications in the delivery of *Pfizer-BioNTech* to the LGUs and vaccination sites. • ***Insufficient human resource:*** Vaccination teams were limited which caused HCWs to become more fatigued leading to more errors toward the end of the day. This was observed especially during the NVDs where the turnout was twice or thrice the crowd when the rollout started. <u>*Common challenges for 5-11 and 12-17 year old COVID-19 vaccinations*</u> • ***Limited vaccine supply and delays in delivery****:* For the vaccines for the 5 to 11 year old population, manufacturers cannot keep up with the high demand due to global rollout of vaccination for children leading to 3 days to 1 week delay in the delivery of vaccines. Similarly, in the 12-17 vaccination, there were challenges with limited distribution/freight capacity. The quantity of vaccines that can be directly delivered to provinces is limited to the capacity of the aircraft. Further, some aircrafts do not have the capacity to transport dry ice, which is required to maintain the cold chain requirements of *Pfizer-BioNTech*. Hence, the vaccine cannot reach certain areas in the country (e.g. Bicol region).	

		Measures to Address Challenges in the Current Implementation of COVID-19 Vaccination for Children The key informants have noted the following observed measures to address these challenges. These will be carried on for the *CoronaVac* rollout in children ages 6-17 years old : *5-11 years old COVID-19 vaccinations* ● ***Fast dissemination of accurate information on vaccines:*** Different mechanisms of proper information dissemination were promptly implemented in both local level (e.g. conduct of town hall meetings, prompt release of communications) and national level (e.g. use of social media) to counter the spread of fake news. ● ***Providing Incentives:*** Different incentivization mechanisms were given to children who got vaccinated (e.g. giving candies and lollipops, seeing dogs while being vaccinated, festive mall environment, free access to a waterpark). This strategy also helped to encourage other children to get vaccinated. ● ***Improving health education to lessen vaccine hesitancy among parents and their children:*** Implementers produce more public-friendly and easy to understand information materials to help explain to parents and children the need to get vaccinated and what to expect. ● ***Ensuring fast response to AEFIs:*** All principals concerned are informed such that all directives to address concerns, manage, and finance AEFI cases related to COVID-19 vaccination were quick. ● ***Require assent from children****:* Assent of children who will be vaccinated and consent from their parents is included in the guidelines. Crying and hesitation of the child is considered dissent. Parents are encouraged to get their children vaccinated however they also advised not to force their children to get vaccinated. According to the regional offices, hesitant children are encouraged to stay on site and observe to see that the process is easy. ● ***Online pre-registration:*** Online pre-registration systems were utilized to facilitate more efficient assessment of children at the vaccination site and shorten waiting time in the administration of multi-dose vials. ● ***Rollout during weekends***: Weekend schedules for vaccinations were made available to avoid conflicts with the parents' work schedule during the weekdays. ● ***Testimonials from health experts, DOH officials, and parents***: Testimonials from health experts, DOH officials, and parents who got their children vaccinated were published to encourage other parents to get their children vaccinated. *12-17 years old COVID-19 vaccination* ● ***Allowing use of alternatives for required documents****:* Requirements prior to vaccination were tweaked	

		during the rollout to facilitate compliance. As an alternative to proof of affiliation, certification from the barangay captain was also accepted. A different guardian (e.g. neighbor, grandparent) was allowed to take the child to the vaccination site provided that they present an informed consent form and authorization note signed by the parent. ● ***Hiring of additional pharmacist****:* To prevent errors in the preparation and administration, additional pharmacists were hired to ensure dedicated roles wherein the pharmacist is in charge of dilution and preparation of the vaccine while the vaccinator is solely in charge of administration. *Common measures to address challenges for 5-11 and 12-17 year old vaccination* ● ***Timely strategic planning and forecasting with implementers***: PHOC is constantly communicating with implementers (CHDs, LGUs and PHOs) to provide guidance in managing the distribution of vaccines given the limited vaccine supply and delays in delivery. Updates on new arrivals of supply and match with stocks on hand to consider possible readjustment of implementation are regularly provided. Alternative scenarios for adjusted vaccine arrival are also explained. ***PHOC Plans for the Implementation of CoronaVac for children*** For the implementation of *CoronaVac* in children ages 6 to 17 years old, the PHOC expressed that they will follow their general plan to shift from mega vaccination sites to the establishment of temporary vaccination posts and house to house vaccinations to bring the vaccines closer to people. The PHOC noted the following foreseen advantages in vaccinating children ages 6 to 17 years old using *CoronaVac:* ● ***Easier implementation:*** *CoronaVac* does not require special preparation techniques, and is not sensitive to movements during transport unlike *Pfizer-BioNTech*. Further, *CoronaVac* comes in smaller packs which allows for easier distribution at the CHD and LGU level compared to *Pfizer-BioNTech.* ● ***Improvement of vaccination coverage:*** *CoronaVac* can be used for both adults and children in the households which is ideal given that vaccination efforts will shift to house to house vaccination *Coronavac* roll out can also improve vaccination coverage in GIDAs because of ease in logistics and more lenient storage requirements. ● ***Additional vaccine option for children:*** *CoronaVac* will provide an additional option for parents and children who are hesitant to receive mRNA vaccines. ● ***Addition to the vaccine supply:*** Adding another vaccine in the portfolio can ramp-up current vaccination efforts for children aged 5-11 years old since the currently approved pediatric vaccine is *Pfizer-BioNTech*	

		which has limited and staggered supply. On the other hand, PHOC recognizes the following foreseen barriers and challenges in vaccinating children ages 6 to 17 years old using *CoronaVac:* ● ***Inadvertent vaccine administration:*** Given that *Pfizer-BioNTech* and *CoronaVac* slightly differ in their target pediatric population i.e. *Pfizer-BioNTech* can be given to children ages 5 to 17 years old while *CoronaVac* can only be given to children ages 6 to 17 years old, inadvertent administration of *CoronaVac* for 5-year old children might occur. ● ***Limitation of indication:*** There is uncertainty as to whether *CoronaVac* can be used for children with comorbidities as the EUA issued by PH FDA specified that the vaccine is indicated for healthy children. Clinical trials (Han et al., Zhao, Soto et al., Sinovac et al.) excluded children with comorbidities i.e., children with asthma, severe neurological conditions, severe chronic diseases, confirmed or suspected HIV, congenital malformations, autoimmune disease, cancer, thyroid disease, and coagulopathies. Given the exclusion criteria of these studies, children with comorbidities still may have been included in trials (e.g. children with stable comorbidities). However, as the proportion of children with comorbidities included in trials is not reported, the appropriateness of using the vaccine for this subgroup cannot be assured. Meanwhile, the package insert published in HongKong's government website only stated the vaccine is contraindicated to individuals with severe neurological conditions or uncontrolled severe chronic diseases. ● ***CoronaVac-related queries and hesitations: Questions and comparisons with other vaccines used for children:*** ○ Questions as to why a lower dose of *Pfizer-BioNTech* is given to children while *CoronaVac* has the same dose strength for adults and children may arise. ○ The public often compares vaccine brands which may be disadvantageous to *CoronaVac* as Filipinos prefer vaccines from the USA (e.g. *Pfizer-BioNTech* and *Moderna)* over vaccines from China like *CoronaVac* (SWS, 2021). Further, it was noted that some healthcare workers also advocate for their preferred vaccine brands. ○ The public often asks whether Phase III trials are available for the vaccine brands. Currently, there are no published Phase III trials for the use of *CoronaVac* in children. ○ The public also asks whether a certain vaccine brand is in the WHO emergency use listing (EUL). Currently, *CoronaVac* is yet to obtain WHO EUL for children. Further, due to this, children vaccinated with *CoronaVac* might not be able to travel to countries requiring vaccination with WHO EUL vaccines, leading to missed opportunities (student exchange programs, family vacations etc).	

		To address the aforementioned foreseen barriers, the PHOC has planned the following measures: ● ***Separation of Schedule for Different Brands:*** To prevent inadvertent administration of vaccines, a separate schedule for *Pfizer-BioNTech* and *CoronaVac* will be implemented. ● ***Consultation with Experts:*** PHOC is consulting with experts to determine whether *CoronaVac* can be used for children with comorbidities. ● ***Effective communication:*** Messaging to the public is currently being improved by developing IEC materials that are more visual so that parents and children (especially for those who cannot read yet) can understand information being relayed. This measure will aim to address the public's concern regarding vaccine brand comparisons, the difference between mRNA and inactivated vaccines, and information on clinical evidence such as Phase III trials and real world studies. ● ***English translation for CoronaVac packaging*:** English translation of important details in packaging such as manufacturing date and expiration date will be carried out to address confusion reported by some healthcare personnel with vaccine labels that are printed in foreign languages. These labels on boxes and vials should be consistent. **HTAC Judgment:** Rollout of primary series among children aged 6 to 11 years old with mRNA vaccine contraindications and adolescents aged 12 to 17 years old is viable and feasible using the best practices, and lessons learned from the ongoing implementation of vaccination in this age group using mRNA vaccines. Further, *CoronaVac* is easier to implement than current vaccines for the pediatric population.	

	Is CoronaVac for pediatric vaccination (6 to 17 years old) affordable?	Based on the prices reflected in the UNICEF COVID-19 Vaccine Market Dashboard, the price per dose of *CoronaVac* offered to the Philippine government is within the price range for which it is available among low to middle income countries. **HTAC Judgment:** *CoronaVac* is considered affordable and within the range of price at which it is available in other low-middle income countries.	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 CoronaVac in children ages 6 to 17 years old?	The DOH has no plans to procure COVID-19 vaccines (including *CoronaVac*) and will use existing supplies for the primary series vaccination of children aged 6 to 17 years old using *CoronaVac*, thus its use for the aforementioned age group will not incur additional budget impact. **HTAC Judgment:** Implementing 2-dose primary series of *CoronaVac* for children aged 6 to 11 years old with mRNA vaccine contraindications and adolescents aged 12 to 17 years old will not incur additional budget impact as existing doses will be used for this vaccination strategy.	Proportionality of the size of the population to be vaccinated versus the cost. The share of the cost to implement the COVID-19 vaccine within the total vaccination budget is not too disproportionate to the share of the population to be vaccinated using the said vaccine in the total population to be vaccinated.
	Does CoronaVac represent good value for money in terms of preventing COVID-19 morbidity and mortality in the pediatric population (6 to 17 years old)?	In children aged 6 to 11 years old, two-dose primary series of *CoronaVac* may not represent good value for money due to the low clinical efficacy and effectiveness. However, for children aged 6 to 11 years old with contraindications to mRNA vaccines, *CoronaVac* may represent good value for money due to the lower risk of severe adverse reaction compared to mRNA vaccination (e.g., anaphylaxis, myocarditis and thromboembolic events) and risk of SARS-CoV-2 infection compared to when no vaccine will be given. For adolescents aged 12 to 17 years old, two-dose primary series of *CoronaVac* represents good value for money in terms of providing some protection against any SARS-CoV-2 infection caused by Omicron variant (Lau, et. al.) and against hospitalization due to COVID-19 caused by Delta variant (Jara, et. al.). 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:** A 2-dose primary series of *CoronaVac* for children aged 6 to 11 years old with mRNA vaccine contraindications	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.

		and adolescents aged 12 to 17 years old may represent good value for money as it is likely to be effective based on limited evidence.	
CRITERION 4			
4. Household Financial Impact	*Will pediatric vaccination with CoronaVac reduce or not add further to the out-of-pocket expenses of Filipino households?*	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. Note that these also cover the pediatric population as there are no separate benefit packages for this subgroup. 1. Home Isolation Package for asymptomatic and mild cases (C19HI) = ₱ 5,917.00 2. Community Isolation Package for symptomatic and confirmed cases (C19CI): Case rate= ₱ 22,499.00 3. Mild COVID-19 pneumonia for elderly and with comorbidities (C19IP1): Case rate= ₱ 43,997.00 4. Moderate COVID-19 pneumonia (C19IP2): Case rate= ₱ 143, 267.00 5. Severe COVID-19 pneumonia (C19IP3): Case rate= ₱ 333,519.00 6. Critical COVID-19 pneumonia (C19IP4): Case rate= ₱ 786,384.00 Meanwhile, children of healthcare workers are eligible to the full financial risk protection (i.e. no cap in terms of case rate) for hospitalization due to COVID-19 (C19FRP) as mandated by PhilHealth Circular 2020-0011. Based on PhilHealth data, there were a total of 1,299 hospitalization claims for the pediatric population ages 6 to 17 years old from the first quarter of 2020 to the third quarter of 2022. The table below summarizes the cost of COVID-19 (inferred from total hospital bill) and out-of-pocket expenses incurred by patients belonging to the pediatric population 6 to 17 years old at different levels of severity. The mean financial coverage for hospitalization across the different levels of severity ranged from 66.70% (mild COVID-19) to 86.33% (critical COVID-19). Financial coverage generally increased with severity of the COVID-19 disease. Table 4.1. Philhealth data on COVID-19 Hospitalization Costs and Claims in the Pediatric Population 6-17 years old	The adoption of the vaccine can reduce out-of-pocket spending of individuals and families due to averted COVID-19 disease and/or hospitalization.

Severity *[Benefit package]*	Case Rate	Total Number of Paid Claims	Total Isolation / Hospital Cost		Out-of-Pocket Payment		Average % of Financial Coverage *[proportion of financial coverage out of the total bill]*
			Range of Hospitalization Cost	Median Hospitalization Cost	Range of Out-of-Pocket Payment	Median Out-of-Pocket Payment	
Mild COVID-19 *[C19IP1]*	₱ 43,997.00	501	₱3,764.50 to ₱1,751,629.51	₱64,996.30	₱0.00 to ₱1,707,632.51	₱22,691.00	66.70%
Moderate COVID-19 *[C19IP2]*	₱ 143, 267.00	647	₱3,490.00 to ₱2,126,347.17	₱145,558.45	₱0.00 to ₱1,983,080.17	₱11,749.75	81.73%
Severe COVID-19 *[C19IP3]*	₱ 333,519.00	99	₱27,434.56 to ₱1,345,333.85	₱353,353.67	₱0.00 to ₱1,011,814.85	₱41,467.10	79.63%
Critical COVID-19 *[C19IP4]*	₱ 786,384.00	38	₱129,455.79 to ₱5,737,449.44	₱577,017.21	₱0.00 to ₱4,951,065.44	₱6,896.74	86.33%
Full Financial Risk Protection *[C19FRP]*	No cap	14	₱14,710.00 to ₱3,236,743.07	₱165,931.24	₱0.00 to ₱1,095,392.87	₱26,375.76	77.44%

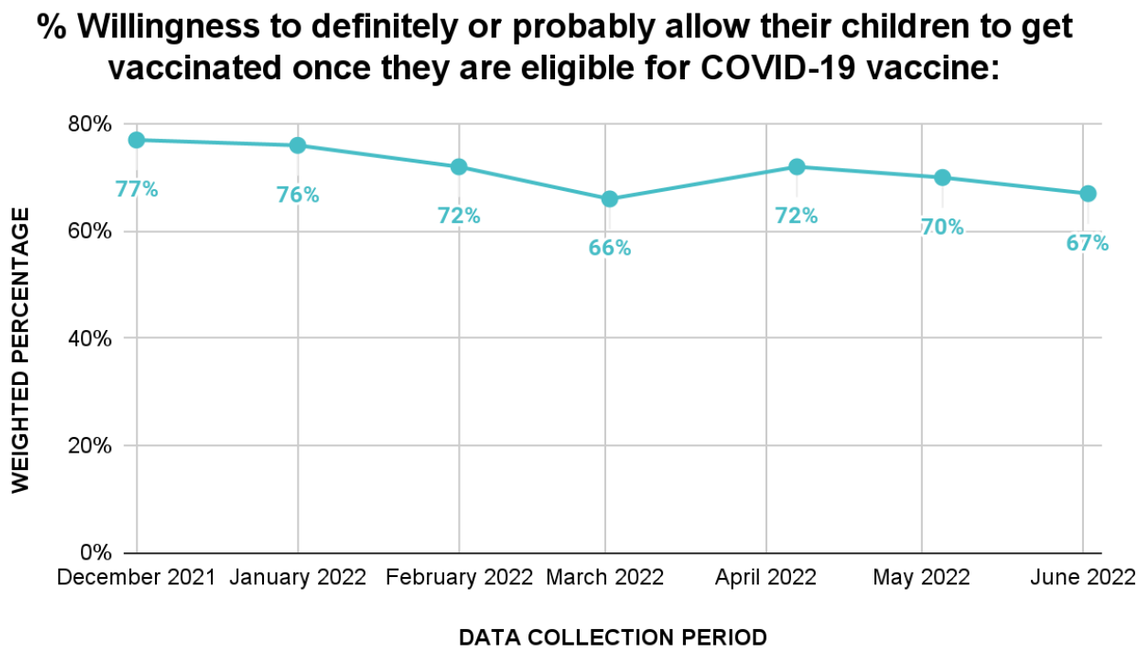
Meanwhile, there were a total of 1,124 community isolation claims recorded by PhilHealth for asymptomatic and mild cases for pediatric patients 6 to 17 years old, using the same dataset. The median cost of community isolation based on bills recorded was ₱20,309.30, while the median claims cost was at ₱ 22,449.00. Therefore, the median out-of-pocket expenses for community isolation is at ₱ 0.00 (₱0.00 to ₱310,778.92). The mean financial coverage is at 95.40%. Meanwhile, there were 9 claims for home isolation in pediatric patients ages 6 to 17 years old. The median cost of isolation was ₱2,975.00, with ₱0.00 out-of-pocket cost resulting in a mean

		financial coverage of 100%. The out-of-pocket expenses reflected above only represents medical costs shouldered by patients and their families. Other non-medical costs such as transportation, food, and productivity loss of the parents of these children were not incorporated due to lack of data. In addition, the above costing of household costs did not include the treatment/ management cost of other family members within the household who had likely contracted COVID-19. Considering these other incurred costs shouldered by households further increases the potential of the vaccine to reduce out-of-pocket expenses of households due to COVID-19. **HTAC Judgment**: Based on current evidence, 2-dose primary series of *CoronaVac* for children aged 6 to 11 years old with mRNA vaccine contraindications and adolescents aged 12 to 17 years old has the potential to reduce out-of-pocket expenses due to averted costs of isolation and treatment of mild, moderate, and severe COVID-19.	
CRITERION 5			
5. Social Impact	*Does pediatric vaccination with CoronaVac possess the characteristics desired by key stakeholders (i.e., policy- and decision-makers, health workers, program managers and/or implementers, patient groups, CSOs, communities, general public)?* • *Safety* • *Efficacy* • *Transparency in the*	Based on the results of the focus group discussions conducted in the context of vaccinating the adult population by the HTAC among *healthcare workers, patient groups, civil society organizations and community leaders* from low- and high-prevalence areas, the results from the deliberations in congressional inquiries on the COVID-19 vaccination roadmap, public hearings, and consultations with government decision-makers and implementers, the following are the important and desirable attributes of COVID-19 vaccines and the corresponding evidence for *CoronaVac* specifically in children ages 6 to 17 years old. 1) **Safe and efficacious** - *please refer to Criteria 2: Clinical Efficacy, Effectiveness, and Safety* 2) Underwent a **transparent regulatory process** of being evaluated and approved by health authorities - Evidence: *CoronaVac* underwent the usual regulatory process of the FDA Philippines. The Philippine FDA updated the EUA for the vaccine on 11 March 2022 to expand its use among children 6 to 17 years old. 3) **Potential for high and equitable coverage across the population** - Evidence: *CoronaVac* can be stored at 2 to 8 degrees Celsius which is present in most RHUs.Therefore, *CoronaVac* can be made more available since vaccine handling and storage are within the capacity of the RHUs. - The Philippine Pediatric Society (PPS) and Pediatric Infectious Disease Society of the Philippines (PIDSP)	The vaccine possesses all or most of the characteristics desired by key stakeholders Qualitative responses will contextualize the Filipino experience and may impact on implementation strategy

	regulatory/approval process and information on the vaccines • *Availability* • *Potential for high and equitable coverage* • *Ease in logistical and implementation requirements* • *Cost-efficiency to the government* • *Public acceptability* • *Availability of mechanisms to compensate vaccine recipients for any untoward event following vaccination* • *Appropriateness of the vaccine to special at-risk groups and patients with comorbidities*	released a joint position statement (published 4 February 2022) reiterating its recommendation last 17 January 2022 for the vaccination of children ages 5 to 11 years old against COVID-19. The updated statement emphasizes the risk of children from acquiring severe illnesses due to COVID-19 such as Multisystem Inflammatory Syndrome in Children (MIS-C) and post-covid conditions such as "long COVID". Prioritization of children in the age group who have comorbidities and children of healthcare frontliners was also recommended. As for children ages 12 to 17 years old, the PPS and PIDSP had previously released a joint position statement (published 6 September 2021) which recommended vaccinating children aged 12 years old and above once there is sufficient coverage in the adult priority groups. As of writing of this report, the PPS and PIDSP has not released an updated statement on COVID-19 pediatric vaccination. 4) **Ease in logistics and administration** - Evidence: *CoronaVac* can be stored at 2 to 8 degrees Celsius which is present in most RHUs.Therefore, *CoronaVac* can be made more available since vaccine handling and storage are within the capacity of the RHUs. Further, according to the updated EUA from PH FDA (11 March 2022), the shelf life of the single dose vial of *CoronaVac* was extended from 6 months to 12 months while the two-dose vial remains to have a 6-month shelf life. Both of these vial preparations will be used for the vaccination of children aged 6-17 years old. Based on PHOC's experience, the implementation of *CoronaVac* in the adult population was generally manageable to roll out due to its temperature requirement. Other details of implementation of *CoronaVac* for the pediatric population are presented in *Criteria 3: Affordability, Viability, and Feasibility.* 5) **Cost-effective** *- please refer to Criteria 3: Affordability, Viability, and Feasibility* 6) **Public acceptability** **General Public's Acceptability of Administration of COVID-19 Vaccination for the Pediatric Population** ***Global and Regional View of Vaccine Acceptance and Related Behaviors (Johns Hopkins Center for Communication Programs, WHO GOARN)*** A global survey conducted by Johns Hopkins Center for Communication Programs and the World Health Organization's (WHO) Global Outbreak Alert and Response Network (GOARN) on the acceptability of pediatric vaccination across different countries (which included data specific to the Philippines) was found (End of data collection: 25 June 2022). The survey asked parents of children under 18 years old if they will choose to vaccinate their oldest child under age 18 when eligible. In the Philippines, the acceptability of parents to vaccinate their children below 18 years old had a downward trend but	

remained relatively high (67% as of June 2022). The age range of the children of the respondent parents were not specified and no disaggregated data for the response of parents of children ages 6-17 years old.

Figure 3. Results of survey on acceptability of parents to vaccinate their children below 18 years old in the Philippines.



The COVID-19 pandemic in children and young people during 2020-2021: A complex discussion on vaccination (Rudan et al. 2021)

An editorial paper by Rudan et al. published on 25 December 2021, presented the complex debate on the COVID-19 vaccination of children and young people.

As cited in Rudan et al. (2021) the European Center for Disease Prevention and Control suggested that decisions on pediatric vaccination should consider the vaccine uptake in older age groups, the incidence of COVID-19 in the general population, and practical issues concerning availability and access to vaccines globally.

Meanwhile, Rudan stated that proponents of mass vaccination in children suggest that vaccinating children will improve children and adolescent's well-being and mental health allowing them to resume education and social interactions which are important to their development. They suggested that this will also prevent the pediatric population from becoming a pocket of the population wherein COVID-19 would continue to circulate freely leading to mutation of the virus into new variants.

Rudan et al.'s paper also highlighted that ethical concerns would need to be carefully documented and addressed. Notable concerns include specific situations and needs of children with developmental disorders and chronic conditions, health inequities and vaccine hesitancy. Vaccination willingness and hesitancy should first be assessed before attempting vaccination. The following surveys were conducted among caregivers of minors to assess caregiver's willingness to vaccinate their minor children.

Table 5.1. Surveys on Willingness to Vaccinate Children Cited in Rudan et al. 2021

Author (Year)	Study Period	Country	Survey participants	Vaccination willingness and hesitancy
Goldman et al. (2020)	26 to 31 March 2020	US, Canada, Israel, Japan, Spain , and Switzerland *COVID-19 Parental Attitude Study (COVIPAS)*	1,541 caregivers Median age of children: 7.5 years old	● Willing to vaccinate their children once vaccine is available: 65% ○ Most common reason for willingness: Protection of their child (62%) ○ Most common reason for hesitancy: Vaccine's novelty

					(52%)	
			Teasdale et al. (2021)	9 March, 2021 to 2 April 2021	US *(nationwide)*	2,074 parents/ caregivers of children ≤12 years	• Willing to vaccinate their children once vaccine is available: 49% ○ Primary reasons for hesitancy: Safety and lack of need for vaccines • Lower income and less education were associated with greater parental vaccine hesitancy.
			Ruggiero et al. (2021)	November 2020 to January 2021	US *(nationwide)*	427 parents of children (aged 1–18 years; 34.1% have children ages 4 to 8 yo; 25.1% have children ages 8 to 12 yo)	• Willing to vaccinate their children: 49.45%
			Szilagyi et al (2021)	February to March 2021	US *(nationwide)*	1,745 parents of children (<5 years: 24%, 5 to 10 years: 36%, 11 to 18 years: 40%)	• Likelihood of child COVID-19 vaccination: ○ Very likely : 28% ■ High among parents of older children ■ High among parents with bachelor's degree or higher education ■ Among those had already received or were likely to receive a COVID-19 vaccine

					■ Had Democratic affiliation ○ Somewhat likely : 18% ○ Somewhat unlikely: 9% ○ Very Unlikely: 33% ○ Unsure 12% Concerns were centered around vaccine safety and side effects	
			Teasdale et al. (2021)	9 March to 11 April 2021	US *(New York City)*	1,119 primary caregivers of a child ≤ 12 years of age	● Plans to vaccinate their children (≤12 years): 61.9% ● Unsure: 23.3% ● No plans to vaccinate their children:14.8% ○ Most common reason for hesitancy: Vaccine safety and effectiveness (81.2%) ● Vaccinated parents and parents intended to get themselves vaccinated: 67.3% ○ Pediatric vaccine hesitancy is strongly tied to parental vaccine hesitancy.	
			Zhang et al (2020)	1 to 7 September 2020	China	2,053 factory workers, guardians of children <18 years old	● Willing to vaccinate their children: 72.6%	
			Yang et al (2021)	7 to 19 February 2020	China	12,872 questionnaires guardians of children aged 0–6 years old	● Willing to vaccinate their children: 70.87%	
			Wan et al	December	China	468 parents of 3–6	● Willing to vaccinate their	

			(2021)	2020 to February 2021		year old children	children: 86.75% ○ Most common reason for willingness: Worried about their children being infected in the future (78.57%) ● Hesitant to vaccinate their children: 13.25% ○ Most common reason for hesitancy: Did not believe in the safety of vaccines (67.74%)
			Feng et al (2021)	30 November, 2020 to 31 January 2021	China	3,703 guardians of children <18 years old	● Willing to vaccinate their children: 84.0%
			Wang et al (2021)	September 2020 to April 2021	China	914 guardians of children with special disease (congenital heart disease, preterm birth, others) Mean age of children: 1.4 years old *Face-to-face questionnaire interview*	● Willing to vaccinate their children with special diseases: 49.9%
			Brandstetter et al (2021)	5 to 28 May 2020	Europe *(Data used is from KUNO-Kids health study which is a multipurpose birth cohort study*	612 parents with children ages 1.5 - 5 years old	● Intended to vaccinate their children: 51% ● Parents intended to get themselves vaccinated: 58%

		situated in Germany)		
Montalti et al (2021)	December 2020 to January 2021	Italy	5054 parents/ guardians of children aged <18 years old	● Willing to vaccinate their children: 60.4% ● Considering: 29.6% ● Hesitant to vaccinate their children: 9.9%
Choi et al (2021)	25 May to 3 June 2021	South Korea	226 parents of children ≤18 years old and 117 children 10 -18 years old	● Children willing to get vaccinated: 49.6% ● Parents willing to have their children be vaccinated: 64.2% ○ Factors associated intention to vaccinate: ■ High confidence in the safety of the vaccines ■ Willingness to vaccinate themselves ■ Awareness of the need to vaccinate children against COVID-19

Social impact of the COVID-19 pandemic and pandemic response on children and adolescents

According to the WHO Interim Statement on COVID-19 vaccination for children and adolescents (11 August 2022), children and teenagers have been disproportionately impacted by COVID-19 control measures. The disturbance of educational services caused by school closings, which also raised emotional distress and mental health problems, is one of the most significant indirect consequences. Children who are unable to attend school and who are socially isolated are more prone to maltreatment, sexual violence, adolescent pregnancy, and child marriage, all of which increase the likelihood that they will miss out on further schooling and have poor pregnancy outcomes.

Further, social isolation places children at risk of potential for predatory behavior from adults related to spending more time online, cyberbullying from other children, and disruption in physical activities and routines.

		7) Availability of mechanisms to manage any untoward serious adverse reactions following vaccination - 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 in special at-risk groups and patients with comorbidities** - The updated WHO interim statement (11 August 2022) on COVID-19 vaccination for children recognized that COVID-19 vaccines with WHO EUL that conducted clinical trials in the pediatric population are safe and effective in children and adolescents. Although *CoronaVac* has received EUL for adults, they have not yet received WHO EUL for the use in children. - In the updated WHO SAGE Roadmap for prioritizing uses of COVID-19 vaccines, the WHO recommends vaccinating children only when high vaccine coverage (i.e., 40 to 70%) both for primary series and booster vaccination has been achieved in higher priority-use groups (i.e., older adults, healthcare workers, immunocompromised persons, adults with comorbidities, pregnant women, teachers and other essential workers, disadvantaged sociodemographic subpopulations at higher risk of severe COVID-19, and remaining adults). The WHO also recommended for countries to consider the individual and population benefits of vaccinating this age group based on country-specific epidemiologic and social context. **HTAC Judgment:** Given the available clinical evidence, ease in logistics and ability to allow for equitable coverage, and availability of FDA EUA, *CoronaVac* possesses most of the characteristics desired by key stakeholders for its use as a 2-dose primary series for children aged 6 to 11 years old with mRNA vaccine contraindications and adolescents aged 12 to 17 years old. However, currently there is no information on public acceptability of *CoronaVac* as the primary series for pediatric vaccination. Furthermore, *CoronaVac* does not have a WHO EUL for the pediatric population.	

<table>
<tr><th colspan="4">CRITERION 6</th></tr>
<tr>
<td>6. Responsiveness to equity</td>
<td>How will CoronaVac and its use impact pre-COVID-19 and COVID-generated health and socioeconomic inequities?

Which groups might be unfairly disadvantaged, in relation to the COVID-19 disease burden and delivery of CoronaVac?</td>
<td>As of this writing, there are three brands with Philippine FDA EUA for the pediatric population aged 6 to 17 years old [Pfizer-BioNTech (also approved for 5 yo), Moderna, and CoronaVac], with two brands currently being rolled out for the pediatric population 12-17 years old - Pfizer-BioNTech and Moderna. In terms of implementation, only Pfizer-BioNTech is being rolled out in children aged 6 to 11 years old, while both Pfizer-BioNTech and Moderna are being given to adolescents aged 12 to 17 years old.

CoronaVac can be stored at normal cold storage conditions (2 to 8 degrees Celsius). This will make vaccine distribution more logistically feasible which in turn does not aggravate existing inequities for individuals living in geographically isolated and disadvantaged areas (GIDAs). Compared to other new vaccines, the price per dose and the logistical and operational cost of CoronaVac allow it to be utilized widely.

As of September 07, 2022, 4,760,687 (43.70%) out of the 10,895,015 target children ages 5 to 11 years old have already received a full regimen of COVID-19 vaccines (i.e., Pfizer-BioNTech). Meanwhile in the 12 to 17 age group, 9,879,933 (110.79%) out of the total target 8,917,833 have received a full regimen of COVID-19 vaccines (i.e, Pfizer-BioNTech and Moderna).

The overall vaccination coverage in the Philippines for the primary series and booster dose, by age group as of 07 September 2022, are as follows:
<table>
<tr><th rowspan="2">WHO Prioritization groups</th><th rowspan="2">Age Group</th><th colspan="3">Philippine COVID-19 Vaccination Coverage</th></tr>
<tr><th>Primary Series</th><th>1st Booster Dose</th><th>2nd booster dose</th></tr>
<tr><td></td><td>Across all age groups</td><td>93.01%</td><td>23.41%</td><td>3.03%</td></tr>
<tr><td rowspan="2">Highest to Medium Priority Use</td><td>18-59 years old</td><td>103.27%</td><td>30.56%</td><td>3.37%</td></tr>
<tr><td>60 years and older</td><td>78.15%</td><td>28.51%</td><td>8.04%</td></tr>
<tr><td rowspan="2">Medium to Lowest Priority Use</td><td>5 to 11 years old</td><td>43.70%</td><td>0% (not yet eligible)</td><td>0% (not yet eligible)</td></tr>
<tr><td>12 to 17 years old</td><td>110.79%</td><td>7.22%</td><td>0% (not yet eligible)</td></tr>
</table>
</td>
<td>Ideally, health interventions can be fairly adopted and distributed/ implemented for eligible populations without aggravating existing health inequities especially for vulnerable sectors of our society.</td>
</tr>
</table>

		The WHO emphasized in their interim statement (11 August 2022) on vaccination in children that although benefit-risk assessments clearly show the benefit of vaccinating all age groups including children and adolescents in reducing the number of infections, hospitalizations and deaths due to COVID-19, the direct health benefit of vaccinating healthy children is lower compared with adults. On the other hand, vaccinating children and adolescents do not only provide direct health benefits. The lessening of disruptions in school for children and maintenance of their overall well-being, health and safety are also important factors. Finally, the WHO still reiterates their former position that before the consideration of implementing vaccination in children and adolescents, attaining high coverage for primary and booster doses in highest and high priority-use groups such as older adults should be pursued. **HTAC Judgment:** The HTAC reiterates the importance of the following measures in the success of the implementation of COVID-19 primary series for the adolescent population: ● emphasis on strategies to increase primary series in children <12 years old and first booster vaccination coverage among priority groups ● ensure that information, education, and communication (IEC) and other vaccination-related documents are accessible and comprehensible (i.e., translated into the local language of the target population) Vaccination of the adolescent population shall be rolled out following the country's prioritization criteria, cognizant of the following: ● burden of COVID-19 in the priority groups, especially those with comorbidities; ● sufficient supply to cover all the other vaccination strategies in the pipeline along with the second booster (remaining primary and 1st booster for adult population).	

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Appendix 1A: Risk of Bias (RoB) Assessment Methodology

RoB for RCTs

The Cochrane RoB1 tool was used in the RoB of the included RCTs. Therefore, the overall RoB rating of RCTs corresponds to its overall rating using the Cochrane ROB1 tool. Figure A4.1 below summarized the ROB1 method on assessment of overall RoB.

Figure A4.1. *Possible approach for summary assessments of the risk of bias for each important outcome (across domains) within and across studies (Higgins, et al., 2017)*

OVERALL Risk of bias of the study	Interpretation	RoB rating per domain
Low risk of bias	Plausible bias unlikely to seriously alter the results	Low risk of bias for all key domains
Unclear risk of bias	Plausible bias that raises some doubt about the results	Unclear risk of bias for one or more key domains
High risk of bias	Plausible bias that seriously weakens confidence in the results	High risk of bias for one or more key domains

RoB for Observational studies

Meanwhile, the appraisal of real world evidence (i.e., observational studies) is composed of two parts as adopted from the LCPG assessment method: (1) Cochrane RoB1 tool as (2) some additional questions to appraise an additional domain - control of prespecified confounders by LCPG, namely, age, exposure risk, and comorbidities.

DESCRIPTION OF THE TOOLS AND RATING ALGORITHM

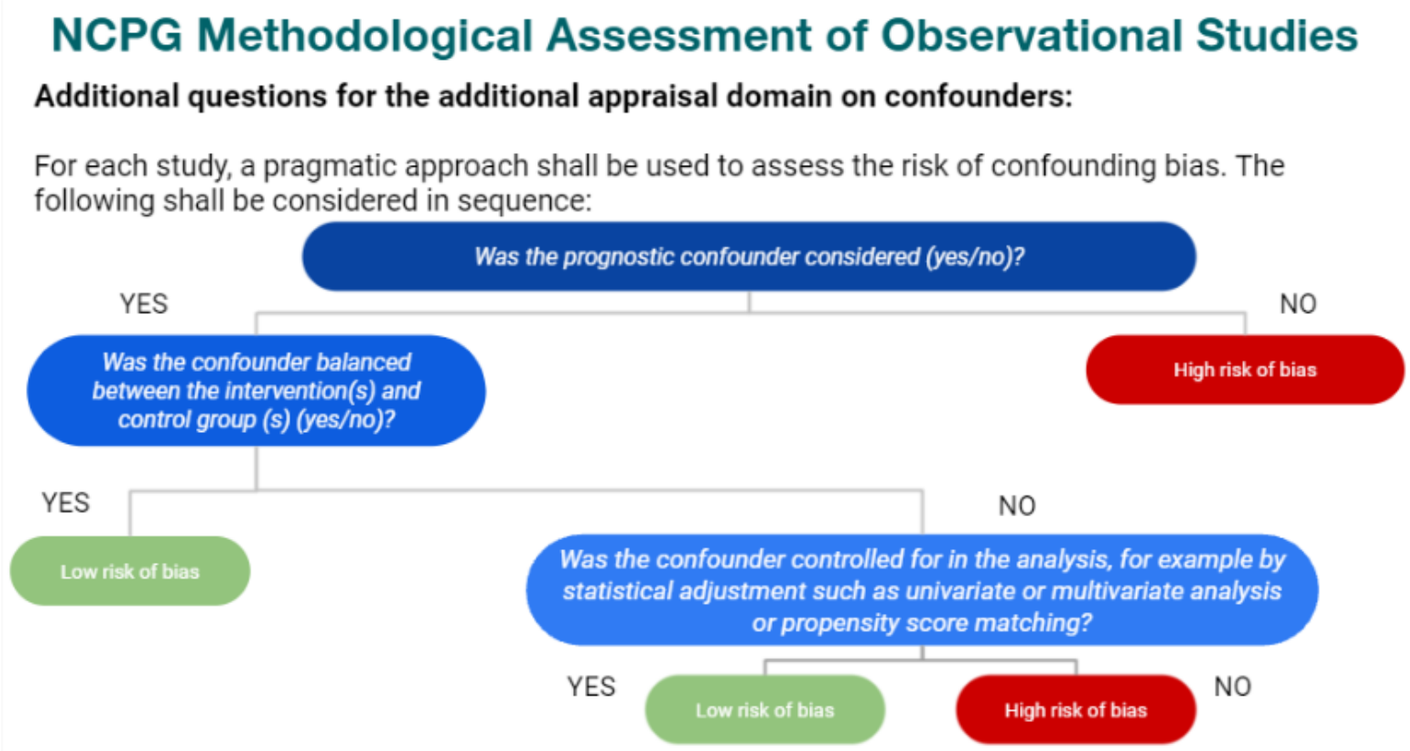
Part 1: Cochrane RoB1 Tool

- please refer to algorithm in the RoB for RCT section

Part 2: Control for Confounders

- please refer to Figure A4.2 below for the set of questions in assessment control for confounders.

Figure A4.2. Methodological Assessment of Observational by the COVID-19 Living CPG group (2021)



Note: Assessment for control of confounders should be performed for each pre-specified confounding variable (i.e., age, comorbidities, exposure risk).

ALGORITHM FOR OVERALL CONTROL OF CONFOUNDERS for RWE

Confounder Variables Controlled (i.e. age, comorbidity, exposure risk)	Overall RoB rating for Control on Confounders
3 Low RoB, 0 High RoB	**LOW**
2 Low RoB, 1 High RoB *	**LOW ***
1 Low RoB, 2 High RoB	**HIGH**
0 Low RoB, 3 High RoB	**HIGH**

** Note: LCPG follows the majority rather than the worst case for the assessment of overall RoB on confounders.*

OVERALL RoB RATING ALGORITHM FOR EACH RWE STUDY

Overall RoB rating in RoB1 tool	Overall RoB rating for Control on Confounders	Overall RoB of RWE
High	High	Very Serious
High	Low	Serious
Unclear	High	Very Serious
Unclear	Low	Serious
Low	High	Serious
Low	Low	Not Serious

Appendix 1B: Risk of Bias (RoB) Assessment Results

Appraisal of RCTs

RCTs on efficacy outcomes

Author Year	Study Design	ROB1 Domains							
		Randomization	Allocation concealment	Blinding of Participants	Blinding of Investigators	Blinding of Assessors	Incomplete Outcome Data	Selective reporting	OVERALL ROB1 ASSESSMENT
Sinovac Life Sciences Co., Ltd., 2022	Phase III RCT	Low	Low	Low	Low	Low	High	Low	**High**

RCTs on safety outcomes

Author Year	Study Design	ROB1 Domains							
		Randomization	Allocation concealment	Blinding of Participants	Blinding of Investigators	Blinding of Assessors	Incomplete Outcome Data	Selective reporting	OVERALL ROB1 ASSESSMENT
Han et al., 2021 [published]	Phase I/II RCT	Low	Unclear	Low	Low	Low	Unclear	Low	**UNCLEAR**
Zhao, 2021 [unpublished]	Phase IIb RCT	Low	Low	Low	Low	Low	High	Low	**HIGH**
Soto et al., 2022 [preprint]	Ongoing Phase III RCT	Unclear	Unclear	Unclear	High	Unclear	High	High	**HIGH**
Rosa Duque et al., 2022 [preprint]	Phase II Nonrandomized trial	High	High	High	High	High	Unclear	Low	**HIGH**

Observational studies on effectiveness outcomes

Author Year	Outcome	Study Design	ROB1 Domains								Control for Confounders				OVERALL ROB
			Randomization	Allocation concealment	Blinding of Participants	Blinding of Investigators	Blinding of Assessors	Incomplete Outcome Data	Selective reporting	OVERALL ROB1 ASSESSMENT	Age	Exposure Risk	Comorbidities	OVERALL CONTROL OF CONFOUNDERS	
Jara et al., 2022 [preprint].	VE against confirmed COVID-19, hospitalization and ICU admission due to COVID-19 6-16 yo	Prospective cohort	High	High	High	High	High	Low	Unclear	**HIGH**	Low	High	Low	**LOW**	**SERIOUS**
Florentino et al., 2022 [published]	VE against symptomatic COVID-19, hospitalization and ICU admission due to COVID-19 6-11 yo	Test-negative study	High	High	High	High	High	High	Unclear	**HIGH**	Low	Low	Low	**LOW**	**SERIOUS**
Lau et al., 2022 [preprint]	VE against any SARS-CoV-2 infection, 14 days after dose 2 3-11 yo	Test-negative study	High	High	High	High	High	High	Unclear	**HIGH**	Low	High	High	**HIGH**	**VERY SERIOUS**
	VE against any SARS-CoV-2 infection, 14 days	Test-negative study	High	High	High	High	High	Low	Unclear	**HIGH**	Low	HIgh	High	**HIGH**	**VERY SERIOUS**

	after dose 2 12-17 yo														

Observational studies on safety outcomes

Not applicable.

Appendix 2: GRADE TABLE

Quality assessment							Summary of Findings			Certainty	Importance
Outcome	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Vaccine n/N (%)**	**Control n/N (%)**	**Vaccine Efficacy (95% CI)**		
EFFICACY											
Sinovac Life Sciences Co. Ltd., 2022											
VE against symptomatic COVID-19 <u>after dose 2</u> **6-11 yo**	1 RCT	Serious (Short follow up period)	Cannot be assessed	Not Serious	Very Serious (Wide CI, crosses null)	Unpublished report	32/1,088 (2.94%)	41/1,077 (3.81%)	**VE:** 22.11 (-26.74 to 52.52)	⊕◯◯◯ **VERY LOW**	CRITICAL
VE against symptomatic COVID-19 <u>after dose 2</u> 12-17 yo	1 RCT	Serious (Short follow up period)	Cannot be assessed	Not Serious	Very Serious (Wide CI, crosses null)	Unpublished report	13/849 (1.53%)	16/835 (1.92%)	**VE:** 19.97 (-77.45 to 64.59)	⊕◯◯◯ **VERY LOW**	CRITICAL
VE against hospitalization due to COVID-19 <u>after dose 2</u> not disaggregated by age group (6 mos- 17yrs)	1 RCT	Serious (Short follow up period)	Cannot be assessed	Serious (evidence not specific to age group of interest)	Very Serious (Wide CI, crosses null)	Unpublished report	1/2,511 (0.04%)	4/2,479 (0.16%)	**VE:** 75.29 (-149.70 to 99.50)	⊕◯◯◯ **VERY LOW**	CRITICAL
VE against symptomatic COVID-19 caused by B.1.1.529/OMICRON BA.1 variant <u>after dose 2</u> not disaggregated by age	1 RCT	Serious (Short follow up period)	Cannot be assessed	Serious (evidence not specific to age group of interest)	Very Serious (Wide CI, crosses null)	Unpublished report	11/2,511 (0.44%)	22/2,479 (0.89%)	**VE:** 50.40 (-6.72 to 78.28)	⊕◯◯◯ **VERY LOW**	IMPORTANT

group (6 mos- 17yrs)											
VE against symptomatic COVID-19 caused by B.1.1.529/OMICRON BA.2 variant <u>after dose 2</u> not disaggregated by age group (6 mos- 17yrs)	1 RCT	Serious (Short follow up period)	Cannot be assessed	Serious (evidence not specific to age group of interest)	Very Serious (Wide CI, crosses null)	Unpublished report	22/2,511 (0.88%)	28/2,479 (1.13%)	**VE:** 22.20 (-41.00 to 57.58)	⊕◯◯◯ **VERY LOW**	IMPORTANT
VE against symptomatic COVID-19 caused by B.1.1.529/OMICRON (unspecified) variant <u>after dose 2</u> not disaggregated by age group (6 mos- 17yrs)	1 RCT	Serious (Short follow up period)	Cannot be assessed	Serious (evidence not specific to age group of interest)	Very Serious (Wide CI, crosses null)	Unpublished report	2/2,511 (0.08%)	2/2,479 (0.08%)	**VE**: 0.78 (-1,268.83 to 92.81)	⊕◯◯◯ **VERY LOW**	IMPORTANT
EFFECTIVENESS											
Jara et al., 2022											
VE against confirmed COVID-19 <u>after dose 2</u> 6-16 yo	Observational study	Serious (lack of randomization, allocation concealment, and blinding)	Cannot be assessed	Not Serious	Not Serious	Preprint, non-peer reviewed (Large magnitude of effect, no plausible confounding, no dose-response gradient)	2,998/ 1,219,805 (0.2%)	8,684/ 2,274,042 (3.2%)	**VE:** 74.5% (73.8 to 75.2)	⊕⊕⊕⊕ **High**	CRITICAL

VE against hospitalization <u>after dose 2</u> 6-16 yo	Observational study	Serious (lack of randomization, allocation concealment, and blinding)	Cannot be assessed	Not Serious	Not Serious	Preprint, non-peer reviewed (Very large magnitude of effect, no plausible confounding, no dose-response gradient)	16/ 1,219,805 (0.0%)	181/ 2,274,042 (0.1%)	**VE:** 91.0% (87.8 to 93.4)	⊕⊕⊕⊕ **High**	CRITICAL
VE against ICU admission <u>after dose 2</u> 6-16 yo	Observational study	Serious (lack of randomization, allocation concealment, and blinding)	Cannot be assessed	Not Serious	Not Serious	Preprint, non-peer reviewed (Very large magnitude of effect, no plausible confounding, no dose-response gradient)	1/ 1,219,805 (0.0%)	28/ 2,274,042 (0.0%)	**VE:** 93.8% (85.7 to 97.3)	⊕⊕⊕⊕ **High**	CRITICAL
Florentino et al., 2022											
VE against symptomatic infection <u>after dose 2</u> 6-11 yo	Observational study	Serious (short follow up period)	Cannot be assessed	Not Serious	Not Serious	Published (Magnitude of effect not large, no plausible confounding, no dose-response gradient)	524/7,357 (7.12%)	72,737/ 142,660 (50.99%)	VE: 39.8 (33.7 to 45.4)	⊕⊕⊕◯ **MODERATE**	CRITICAL
VE against hospital admission <u>after dose 2</u> 6-11 yo	Observational study	Serious (short follow up period)	Cannot be assessed	Not Serious	Very Serious (Wide CI, lower limit of CI <30%)	Published (Large magnitude of effect , no plausible confounding, no dose-response gradient)	6/6,839 (0.09%)	428/ 70,351 (0.61%)	VE: 59.2 (11.3 to 84.5)	⊕⊕◯◯ **LOW**	CRITICAL

VE against ICU admission <u>after dose 2</u> 6-11 yo	Observational study	Serious (short follow up period)	Cannot be assessed	Not Serious	Very Serious (Wide CI, crosses null)	Published (Magnitude of effect not large, no plausible confounding, no dose-response gradient)	2/6,835 (0.03%)	88/70,011 (0.13%)	VE: 20.9 (-177.2 to 85.0)	⊕◯◯◯ **VERY LOW**	CRITICAL
Lau et al., 2022											
VE against any SARS-CoV-2 infection, 14 days <u>after dose 2</u> 3-11 yo	Observational study	Very Serious (lack of randomization and blinding; short follow up; insufficient control for confounding)	Cannot be assessed	Not Serious	Very Serious (Wide CI; lower CI <30%)	Preprint (Very large magnitude of effect , no plausible confounding, no dose-response gradient)	533/ 134,200 (0.40%)	47,758/ 181,973 (26.24%)	**VE:** 40.8 (12.8 to 59.5)	⊕◯◯◯ **VERY LOW**	CRITICAL
VE against any SARS-CoV-2 infection, 14 days <u>after dose 2</u> 12-18 yo	Observational study	Very Serious (lack of randomization and blinding; insufficient control for confounding)	Cannot be assessed	Not Serious	Serious (Wide CI)	Preprint (Very large magnitude of effect , no plausible confounding, no dose-response gradient)	1,945/ 41,878 (4.64%)	6,565/ 13,994 (46.91%)	**VE:** 55.0 (38.2 to 67.2)	⊕⊕◯◯ **LOW**	CRITICAL

CI: confidence interval; **RR:** risk ratio

Explanations:

a. Observational studies were judged to have serious RoB. It is noted that the tool used has inherent bias against observational studies. This is remedied with GRADEPro adjusting the overall GRADE rating via ROBINS-I