CoronaVac®, produced by Sinovac Life Sciences Co. Ltd., a World Health Organization recommended vaccine through the Emergency Use Listing procedure

Variation to extend the age indication to children and adolescents from 3 to 17 years of age

Abstract

SARS-CoV-2 vaccine (Vero cell) Inactivated - CoronaVac™, was submitted to the World Health Organization (WHO) for evaluation under the Emergency Use Listing (EUL) procedure by Sinovac Life Science Co., Ltd., P.R. China (Sinovac). This vaccine is a whole virion vaccine inactivated with Beta-propiolactone (BPL). The purified inactivated SARS-CoV-2 antigen bulk is adsorbed with Aluminum Hydroxide as the adjuvant. On 01 June 2021 the vaccine received recommendation for Emergency Use Listing.

The Vaccine received conditional marketing approval by the National Medical Products Administration (NMPA), P.R. China for one year starting 9 February 2021. A list of 21 countries that have been granted an approval for emergency use of the product was provided by Sinovac on 8 March 2021.

The manufacturer submitted a variation to extend the age indication to include children and adolescents from 3 to 17 years of age. Based on the review of data by WHO and the positive opinion received from the National Medical Products Administration (NMPA), which is the WHO regulatory authority of record for this vaccine, this variation was added to the EUL recommendation.

These findings were prepared by the product evaluation group (report finalized on 22 September 2022 and discussed by the technical advisory group for emergency use listing (TAG-EUL).

1 Introduction

1.1.1 The SINOVAC SARS-CoV2 Vaccine

COVID-19 Vaccine Sinovac is a whole virion vaccine inactivated with BPL,. SARS-CoV-2 virus from the working seed lot is grown in Vero cells. After propagation, the virus is harvested, inactivated, purified and

sterile filtered as vaccine bulk. The SARS-CoV-2 bulk is adsorbed with Aluminum hydroxide, formulated to become final bulk, which is then filled into vials or syringes to become COVID-19 Vaccine.

The finished product vaccine is a single dose with no preservative, 0.5 mL aqueous (milky-white) suspension which can be deposited due to precipitation and can be dispersed by shaking. No clumps/particles shall be found after shaking. The CoronaVac™ vaccine is designed to be stored and transported at 2-8°C, protected from light and freezing must be avoided.

The vaccine is for intramuscular injection and the recommended schedule for immunization is 2 doses with an interval of 2 to 4 weeks. The vaccine is indicated for prevention of symptomatic Covid-19 in individuals 18 to 59 years of age.

2 Assessment process

This evaluation took into consideration data submitted by Sinovac, in November 2021 and August 2022. Annex XX indicates the list of studies (published and unpublished) that were used for the assessment.

The NRA of reference for WHO for this COVID-19 Vaccine Sinovac submission is the NMPA.

3 Scientific Review

3.1 Clinical overview

The main points from the different conducted studies considered for the decision about the acceptance of the use of CoronaVac for primary immunization in children and adolescents from 3 to 17 years of age are as follows:

3.1.1 Study Corona 03

The study objectives were the following:

- Phase I Clinical Trial: To evaluate the safety, tolerance and preliminary immunogenicity of different dosage vaccine in healthy children and adolescents aged from 3 to 17 years.
- Phase II Clinical Trial: To evaluate the safety and immunogenicity of different dosage vaccine in healthy children and adolescents aged from 3 to 17 years and to determine the appropriate dosage for further clinical evaluation.

The phase I study included 72 participants, and the phase II study, 480. Low- (300 SU/0.5 mL and medium- (600 SU/0.5 mL) dosages were studied, compared to placebo.

According to the summary prepared by the applicant (in italic):

[…] COVID-19 vaccine (CoronaVac) developed by Sinovac Life Science Co., Ltd. was well tolerated, safe and induced humoral responses in children and adolescents aged 3-17 years. The safety profiles were similar in both vaccine groups. Among the two doses evaluated [300 SU and 600 SU/0.5 mL]*, the neutralizing antibody titres induced by medium-dosage vaccine were higher than those of the low-dosage vaccine. The results support the further study and*

use of the medium-dosage CoronaVac in population aged 3-17 years. Neutralizing antibody level decreased over time. Compared with 28 days and 3 months after the second dose, the GMT of neutralizing antibody at 6 months after the second dose had a significant downward trend. However, the antibody level at 6 months after the second dose in this age group was higher than that in the elderly people aged 60 years and above as well as adults aged 18-59 years

Comment**:** The neutralizing antibody titers were low compared to those observed with COVID-19 vaccines of other platforms, but comparable or even superior to those observed in adults. The safety data raised no concerns about the use of this vaccine in this age group,

3.1.2 Study Corona 13

According to information extracted from the study report,

The main objective of this trial [was] *to evaluate the safety of the investigational vaccine. Randomized, double-blinded and placebo-controlled study design is applied. A total of 500 adolescents and children aged 3-17 (including 100 subjects aged 3-5, 200 subjects aged 6-11 and 200 subjects aged 12-17 respectively) were selected. Each age group was randomly divided into 2 groups according to the ratio of 3:1. According to the D0/28 immunization schedule, they were vaccinated with 2 doses of medium-dosage vaccine (600SU) or placebo respectively.*

The clinical trial showed that the vaccine had good safety and tolerance from full-course inoculation according to the D0/28 schedule to Day 28 after the full-course immunization, which was equivalent to the data of placebo group. […] *The adverse reactions were dominated by Grade 1 with incidence of 14.4%. The incidence of Grade 2 adverse reactions was 6.80%, and that of Grade 3 adverse reactions was only 0.60%. No serious adverse reactions occurred. The incidence of adverse reactions in the second dose was lower than that in the first dose.*

[…] *The incidence of adverse reactions in subjects aged 3-5 was significantly higher than that in subjects aged 6-11 and 12-17, which was mainly due to the high incidence of fever and pain at the vaccination site. The incidence of fever in subjects aged 3-5, 6-11 and 12-17 was 16.00%, 3.50% and 2.00% respectively; the incidence of pain at the vaccination site was 11.00%, 7.50% and 9.00% respectively*.

Comment**:** The observed safety profile is acceptable. Attention should be given to post-approval AEFI data in the 3 to 5 years age group.

3.1.3 Multicenter Chile and South Africa studies

Preliminary data on the Sinovac sponsored trials conducted in Chile and South Africa

See below summary of the findings and comments on "the final report of the 'Multicenter, double blind, randomized, placebo-controlled, phase 3 clinical study to evaluate the efficacy, immunogenicity, and safety of a vaccine against COVID19 (Vero cell), inactivated (CoronaVac®) in children and adolescents from 6 months to 17 years of age' (PedCoronaVac03CL)."

3.1.3.1 Chile vaccine effectives study

The preliminary report "Estimation of SARS-CoV-2 vaccine effectiveness among the pediatric population in Chile", from a study conducted by the Ministry of Health of Chile.

See below summary of the findings and comments on the two papers from the Ministry of Health of Chile.

3.1.3.2 Phase III multicenter study

The final report of the 'Multicenter, double blind, randomized, placebo-controlled, phase 3 clinical study to evaluate the efficacy, immunogenicity, and safety of a vaccine against COVID19 (Vero cell), inactivated (CoronaVac®) in children and adolescents from 6 months to 17 years of age' (PedCoronaVac03CL).

Sinovac indicated that:

The phase 3 clinical trial (Protocol No. PRO-nCOV-3002) has been initiated to evaluate the efficacy, immunogenicity and safety of CoronaVac® in 14,000 children and adolescents aged 6 months to 17 years. The trial was launched in South Africa and Chile on 10th September, 2021. In Malaysia, the enrollment was initiated on 11th November, 2021, and 11th December in Philippines. As of 10th March, 2022, which is the cut-off date of efficacy analysis, a total of 10,880 subjects were enrolled (Vaccine group: 5,833; Placebo group: 5,047). As of now, a total of 11,351 subjects were enrolled, including 4,504 in South Africa, 1,481 in Chile, 1,652 in Malaysia, and 3,714 in Philippines; a total of 125 confirmed cases were reported in the case monitoring period; and till now, over 600 RT-PCR positive subjects were observed. Results of preliminary efficacy analysis indicated that, the efficacy of CoronaVac® on moderate or hospitalized cases was favorable. However, the protection against mild COVID-19 case caused by Omicron was relatively low, which is supporting the rationality of booster immunization to counter the emerging variants (especially the variant BA.2), the interim analysis report for this study is shared as Annex 1. Hence, Sinovac decided to initiate the booster vaccination in this study to evaluate the immunogenicity, safety and efficacy of CoronaVac®. As of now, the booster protocol has been finalized and submitted to South Africa, Malaysia and Philippines. The approved protocol will be submitted to WHO once we got approval from these countries

The findings of the interim analysis of this study summarized by the applicant:

<u>Efficacy results</u>

Results of efficacy analysis indicated that, the efficacy of CoronaVac® on moderate (VE 40.31%, with fever) or hospitalized cases (75.22%) was higher than that of against mild cases (17.23%). Besides, our results showed that vaccine efficacy was also affected by different Omicron subtype (BA.1 and BA.2). A better efficacy against Omicron BA.1 (45.97%) than Omicron BA.2 (18.48%) was observed, suggesting a cross protection of between prototype and Omicron BA.1. In terms of efficacy, the protection of CoronaVac® against hospitalized COVID-19 case caused by Omicron was favorable, however, the protection of CoronaVac® against mild COVID-19 case caused by Omicron was relatively low, which is supporting the rationality of booster immunization to counter the emerging variants.

<u>Safety and immunogenicity results for children aged 6-35 months</u>

<u>Safety</u>: The safety profile subjects aged 6-35 months was favorable, with or without previous exposure to SARS-CoV-2. The overall incidence rate of ARs within 28 days of each vaccination was 29.7% (60/202), 33.62% in vaccine group and 25.74% in placebo group, respectively, without significant difference. The most common AR was fever, cough, diarrhea, vaccination site pain and vomiting, without significant difference between the groups. Adverse reactions were mainly of Grade 1, no Grade 3 and above adverse reactions was reported during study period. No SAE related with vaccine was reported.

Immunogenicity: A high seropositive rate was observed, 116 (65.91%) participants were seropositive before vaccination, indicating a very high prevalence of COVID-19 in South Africa for this population. 28 days after two doses of vaccination, the GMT of neutralizing antibody in vaccine group and placebo group were 743.55 and 43.45, respectively. Stratified by baseline neutralizing antibody (positive/negative), the GMT of neutralizing antibody in seronegative subjects and seropositive subjects were 234.38 and 1138.79, respectively, suggesting that investigational vaccine has good immunogenicity in eliciting both priming immune response and anamnestic immune response.

Conclusion: In conclusion, this study showed satisfactory safety and immunogenicity of CoronaVac® in children aged 6~35 months using a 0,28 days immunization schedule, regardless for immune-naïve children or previously infected children. In terms of efficacy, the protection of CoronaVac® against hospitalized COVID-19 case caused by Omicron was favorable, and the booster immunization needs to be introduced to counter the emerging variants.

Comment: This analysis is useful because it provides some data on protection against early subvariants of the Omicron variant of concern (VOC). The data support acceptable efficacy against hospitalization, but poor efficacy against mild COVID-19 cases, and poor protection against subvariant BA.2. The applicant acknowledges the limited efficacy of CoronaVac® against Omicron subvariants in the 6-35 years age group and suggests that a booster dose should be required for children who are primarily immunized with that vaccine. The safety data support that the vaccine is safe for this age group.

3.1.4 Post-approval effectiveness data

3.1.4.1 3-5 years of age

Jara A, Undurraga EA, Zubizarreta JR, et al. Effectiveness of CoronaVac in children 3–5 years of age during the SARS-CoV-2 Omicron outbreak in Chile. **Nature Medicine** 2022; 38:1377-1380.

Abstract
The outbreak of the B.1.1.529 lineage of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) (Omicron) has caused an unprecedented number of Coronavirus Disease 2019 (COVID-19) cases, including pediatric hospital admissions. Policymakers urgently need evidence of vaccine effectiveness in children to balance the costs and benefits of vaccination campaigns, but, to date, the evidence is sparse. Leveraging a population-based cohort in Chile of 490,694 children aged 3–5 years, we estimated the effectiveness of administering a two-dose schedule, 28 days apart, of Sinovac's inactivated SARS-CoV-2 vaccine (CoronaVac). We used inverse probability-weighted survival regression models to estimate hazard ratios of symptomatic COVID-19, hospitalization and admission to an intensive care unit (ICU) for children with complete immunization over non-vaccination, accounting for time-varying vaccination exposure and relevant confounders. The study was conducted between 6 December 2021 and 26 February 2022, during the Omicron outbreak in Chile. The estimated vaccine effectiveness was 38.2% (95% confidence interval (CI), 36.5–39.9) against symptomatic COVID-19, 64.6% (95% CI, 49.6–75.2) against hospitalization and 69.0% (95% CI, 18.6–88.2) against ICU admission. The effectiveness against symptomatic COVID-19 was modest; however, protection against severe disease was high. These results support vaccination of children aged 3–5 years to prevent severe

illness and associated complications and highlight the importance of maintaining layered protections against SARS-CoV-2 infection.

3.1.4.2 6-16 years of age

Jara A, Undurraga EA, Flores JC, et al. Effectiveness of an inactivated SARS-CoV-2 vaccine in children and adolescents: a large-scale observational study. SSRN preprint. https://ssrn.com/abstract=4035405. (Posted online on February 15, 2022).

Abstract

Background: Policymakers urgently need evidence to adequately balance the costs and benefits of mass vaccination against Covid-19 across all age groups, including children and adolescents.

Methods: We used a large prospective national cohort of about two million children and adolescents 6 to 16 years to estimate the effectiveness of an inactivated SARS-CoV-2 vaccine (CoronaVac) in preventing Covid-19 cases, hospitalizations, and admission to intensive care unit (ICU). We compared the risk of individuals treated with a complete primary immunization schedule (two doses, 28 days apart) with the risk of unvaccinated individuals during the follow-up period. The study was conducted in Chile from June 27, 2021, to January 12, 2022. We used inverse probability-weighted survival regression models to estimate hazard ratios of complete immunization over the unvaccinated status, accounting for time-varying vaccination exposure and adjusting for relevant demographic, socioeconomic, and clinical confounders.

Findings: The estimated adjusted vaccine effectiveness for the inactivated SARS-CoV-2 vaccine in children aged 6 to 16 years was 74·5% (95% CI, 73·8–75·2), 91·0% (95% CI, 87·8–93·4), 93·8% (95% CI, 87·8–93·4) for the prevention of Covid-19, hospitalization, and ICU admission, respectively. For the subgroup of children 6-11 years, the vaccine effectiveness was 75·8% (95% CI, 74·7–76·8) for the prevention of Covid-19 and 77·9% (95% CI, 61·5–87·3) for the prevention of hospitalization.

Interpretation: Our results suggest that a complete primary immunization schedule with the inactivated SARS-CoV-2 vaccine provides an effective protection against severe Covid-19 disease for children 6-16 years.

3.1.5 Vaccine effectiveness in Hong Kong

In addition to the data from the cohort study in Chile, the applicant provided data of a real-world study conducted by a group of Hong Kong. In the response to WHO the applicant states that:

> *The SARS-CoV-2 Omicron BA.2 subvariant replaced BA.1 globally in early 2022, and caused an unprecedented tsunami of cases in Hong Kong, resulting in the collapse of elimination strategy. Vaccine effectiveness (VE) of BNT162b2 and CoronaVac against BA.2 is unclear. Therefore, a group of Hong Kong experts utilize an ecological design incorporating population-level vaccine coverage statistics and territory-wide case-level SARS-CoV-2 infection surveillance data and investigate the VE against infection during the Omicron BA.2 wave between January 1 to April 19, 2022, in Hong Kong for children and adolescents. The estimated VE was 33.0% for 1 dose of BNT162b2 in children aged 5–11 and 40.8% for 2 doses of CoronaVac in children aged 3–11. It is also estimated that 54.9% and 86.8% are the VE for 2*

and 3 doses of BNT162b2, and 55.0% and 92.0% are the VE for 2 and 3 doses of CoronaVac in adolescents aged 12–18. The findings from this study support preserved VE against infection by variants of concerns for children and adolescents in settings with extremely low levels of prior SARS-CoV-2 circulation.

Comment: The findings of the Chilean cohort support the effectiveness of CoronaVac® against hospitalization in the 6-16 years age group and, to a lesser extent, also in the 3 to 5 years-old children. The data from Hong Kong, during an outbreak of COVID-19 caused by the BA.2 subvariant of the Omicron VOC show that CoronaVac® was better effective in adolescents (from 12 years of age) than in children from 3-11 years, in whom vaccine effectiveness was ~41%.

3.1.6 Updated post-approval safety data

According to AEFI Analysis Report among the Population Aged 3-17 Years, 23 732 AEFI cases were reported in mainland China from May 28, 2021 and July 17, 2022, and 1303 AEFI cases were reported from overseas, mainly from Brazil, Chile and Indonesia. The conclusion of the report was the following:

This AEFI analysis suggests that our COVID-19 vaccine CoronaVac® has an overall good safety profile among the population aged 3-17 years on the Chinese mainland and the population aged 0-17 years in countries/regions outside Chinese mainland. AEFIs collected among the population aged 3-17 years on the Chinese mainland focused on common symptoms as pyrexia, asthenia, dizziness, etc., and new AEFI symptoms were mainly crying, upper respiratory tract infection, acute lymphocytic leukaemia, etc., of which most were non-serious symptoms. In addition, most of AESI symptoms were non-serious. AEFIs collected among the population aged 0-17 years in countries/regions outside Chinese mainland focused on common symptoms as pyrexia, headache, vomiting, etc., and new AEFI symptoms were mainly nasopharyngitis, loss of consciousness, pain etc., of which most were non-serious symptoms. No AESI symptoms had been identified as confirmed signals and risks in signal detection and risk evaluation process in and outside Chinese mainland. Overall, no risks related to vaccination are identified for the time being, and we will be monitoring all the time.

Comment: No additional safety concerns have been raised by the data obtained from passive surveillance.

4 Conclusion

The original data used to support the approval of CoronaVac® in children and adolescents 3-17 years of age in China was limited to immunogenicity and safety from a phase I/II trial (Corona 03) and additional safety data from another trial (Corona 13), both conducted in China. Although antibody response to the vaccine was observed and considered superior to that obtained in the trials conducted in adults (comparison between different studies), the neutralizing antibody levels were not impressive when compared to those observed with COVID-19 vaccines of different platforms.

The vaccine has shown to be safe in clinical trials conducted in China and other countries, and available post-authorization AEFI surveillance data are also reassuring. Clinical trial data from South Africa, Chile, Malaysia and The Philippines, which are more recent in time, include information when early subvariants of the Omicron VOC were already circulating. Interim efficacy data from that trial and effectiveness data from Chile and Hong Kong show that CoronaVac® is more effective to prevent hospitalization than mild cases, which has also been shown in adults, is apparently more effective in adolescents than young children, and has decreased effectiveness against the most recent studied Omicron subvariant, BA.2, which is not any longer the dominant SARS-CoV-2 variant currently circulating.

CoronaVac has been approved for use in children 3-5 years of age in several countries. When this vaccine was approved for this age group in Chile, the Delta VOC was dominant, while the vaccine was deployed to Chile when the Omicron variant had already arrived. A possible explanation for the lower effectiveness in the 3-5 years age group compared to older children and adolescents in that country is its late deployment.

Effectiveness of CoronaVac against the BA.2 subvariant has been shown to be inferior to what was observed with BA.1, which may indicate a still lower effectiveness of the vaccine against newer dominant Omicron subvariants due to antibody evasion. Lower effectiveness of CoronaVac in younger children as an age-related issue is also a possibility; limited available data prevents a definite conclusion about that hypothesis.

Notwithstanding its limitations pointed out above, and the paucity of available COVID-19 vaccine approved for use in children, the potential benefits of CoronaVac® can be considered to outweigh its risks in adolescents and in children from 3 years of age.