Interim recommendations for use of the inactivated COVID-19 vaccine, CoronaVac, developed by Sinovac

Interim guidance

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World Health Organization

Background

This interim guidance has been developed on the basis of the advice issued by the Strategic Advisory Group of Experts (SAGE) on Immunization at its extraordinary meeting on 29 April 2021 (1).

Declarations of interests were collected from all external contributors and assessed for any conflicts of interest. Summaries of the reported interests can be found on the SAGE meeting website and SAGE Working Group website.

The guidance is based on the evidence in the background document on the Sinovac-CoronaVac (COVID-19) vaccine and the annexes which include the GRADE and Evidence to Recommendation tables. Both these documents are available on the SAGE COVID-19 webpage: https://www.who.int/groups/strategic-advisory-group-of-experts-on-immunization/covid-19-materials.

These interim recommendations refer to the inactivated vaccine against COVID-19 developed by Sinovac. The trade name of the vaccine is CoronaVac. In the subsequent text the vaccine will be referred to as Sinovac-CoronaVac.

Methods

SAGE applies the principles of evidence-based medicine and has set in place a thorough methodological process for issuing and updating recommendations (2). A detailed description of the methodological processes as they apply to COVID-19 vaccines can be found in the SAGE evidence framework for COVID-19 vaccines (3). This framework contains guidance on data emerging from clinical trials in relation to the issuance of vaccine-specific evidence-based recommendations.

General goal and strategy for use of Sinovac-CoronaVac vaccine

The COVID-19 pandemic has caused significant morbidity and mortality throughout the world, as well as major social, educational and economic disruptions. There is an urgent global need to develop effective and safe vaccines and to make them available at scale and equitably across all countries.

Sinovac-CoronaVac, is an aluminium-hydroxide-adjuvanted, inactivated whole virus vaccine. A large phase 3 trial in Brazil showed that two doses, administered at an interval of 14 days, had an efficacy of 51% (95% confidence interval (CI): 36–62%) against symptomatic SARS-CoV-2 infection, 100% (95% CI:17–100%) against severe COVID-19, and 100% (95% CI: 56–100%) against hospitalization starting 14 days after the second vaccination. No COVID-19-related deaths occurred in the vaccinated group; there was one COVID-19-related death in the placebo group. Vaccine efficacy was maintained in groups with and without comorbidities and irrespective of previous SARS-CoV-2 infection. The median duration of follow-up was 73 days. Interim vaccine efficacy data from phase 3 trials in Indonesia of 65.3% (95% CI: 20.0–85.1%) and Turkey of 83.5% (95% CI: 65.4–92.1%) against symptomatic SARS-CoV-2 infection support protection across settings.

Preliminary and not yet peer-reviewed findings from a post-introduction cohort study in Chile that involved about 2.5 million individuals aged 16 and over that had received two doses and 2.1 million that received one dose to date suggest vaccine effectiveness against symptomatic disease starting 14 days after the second dose to be 67% (95% CI: 65–69%) against symptomatic SARS-CoV-2 infection, 85% (95% CI: 83–87%) against hospitalization and 80% (95% CI: 73–86%) against death. Protection 14 days after first dose up to administration of the second dose was limited.

Preliminary findings from another vaccine effectiveness study in Manaus, Brazil using the test-negative design estimated effectiveness to be 49.6% (95% CI 11.3–71.4%) following at least one dose in the context of broad circulation of the P.1 variant (4).

Vaccine effectiveness assessed in a cohort of health workers in Sao Paulo, Brazil was 50.7% (95% CI: 33.3-62.5%) two weeks after the second dose, in the context of circulating variants of concern (mainly P1) (5).

More detailed data on the efficacy, effectiveness and safety of this vaccine can be found in the background document on Sinovac-CoronaVac. The data reviewed by WHO support the conclusion that the known benefits of Sinovac-CoronaVac outweigh the risks that are known or considered possible. As sufficient vaccine supply will not be immediately available to immunize all who could benefit from it, it is recommended that countries use the WHO Prioritization Roadmap (6) and the WHO Values Framework (7) as guidance for their prioritization of target groups. As long as vaccine supplies are very limited (stage I in the WHO Prioritization Roadmap), in settings with community transmission, the Roadmap recommends that priority be given initially to health workers and older people with and without comorbidities. As more vaccine becomes available, additional priority groups should be vaccinated as outlined in the WHO Prioritization Roadmap (6), taking into account national epidemiological data, vaccine-specific characteristics as outlined in product information approved by regulatory authorities, and other relevant considerations.

Intended use

Persons aged 18 years and above.

Administration

The recommended schedule is two doses (0.5 ml) given intramuscularly into the deltoid muscle. According to the manufacturer's product label, the vaccine can be administered with an interval of 2 to 4 weeks. WHO recommends an interval of 2 to 4 weeks. If the second dose is administered less than 2 weeks after the first, the dose does not need to be repeated. If administration of the second dose is delayed beyond 4 weeks, it should be given at the earliest possible opportunity. It is recommended that all vaccinated individuals receive two doses.

Booster doses

The need for, and timing of, additional doses is being assessed in clinical trials.

Interchangeability with other COVID-19 vaccines

No data are available on the interchangeability of doses of this vaccine with other COVID-19 vaccines. It is currently recommended that the same product should be used for both doses. Recommendations may be updated as further information becomes available.

Co-administration with other vaccines

There should be a minimum interval of 14 days between administration of this vaccine and any other vaccine against other conditions. This recommendation may be amended as data on co-administration with other vaccines become available.

Contraindications

A history of anaphylaxis to any component of the vaccine is a contraindication to vaccination. People who have an anaphylactic reaction following the first dose of this vaccine should not receive a second dose of the same vaccine.

Precautions

No severe (≥ grade 4) hypersensitivity and anaphylaxis reactions caused by Sinovac-CoronaVac have been recorded in clinical trials but were occasionally observed post-authorization. As for all COVID-19 vaccines, Sinovac-CoronaVac should be given under health care supervision, with the appropriate medical treatment available in case of allergic reactions. As a precautionary measure, an observation period of 15 minutes after vaccination should be ensured.

Anyone with an acute febrile illness (body temperature over 38.5 ºC) should postpone vaccination until they are afebrile. However, the presence of a minor infection, such as a cold, or low-grade fever should not delay vaccination.

Vaccination of specific populations

Populations for which limited or no data exist

Adults aged 60 years and above

The representation of participants aged 60 years or over in the clinical trials was insufficient, and there were few cases of COVID-19 in either the vaccine or the control group in this age category; thus the vaccine efficacy could not be determined from the clinical trials. However, seropositivity rates induced by Sinovac-CoronaVac in older persons were similar to those in younger adults and neutralizing antibody titres were lower than those in the younger adult age group.

Recent preliminary post-introduction observational data from Chile suggested consistent vaccine effectiveness across all age-groups. In persons aged 60 years and over, vaccine effectiveness starting 14 days after dose 2 was 67.4 (95% CI: 64.6–69.6%) doses against symptomatic SARS-CoV-2 infection, 83.3% (95%CI 80.4–85.8%) against hospitalisations, and 83% (95%CI: 76.4–87.7%) against death. These observational data together with immunogenicity results suggests that Sinovac-CoronaVac is likely to have a protective effect in older persons, although whether at an equivalent level as in younger adults remains to be shown in further studies.

While data on vaccine safety from the phase 3 clinical trial are very limited, there are no theoretical reasons to believe that the vaccine has a different safety profile in older adults than in younger adults for which there is evidence specific to this vaccine. The currently available trial and post-introduction data indicate that the vaccine is safe in older adults.

The risk of severe disease and death due to COVID-19 increases steeply with age. Older adults are identified as a priority group in the WHO SAGE Prioritization Roadmap. Based on all currently available evidence, WHO recommends the vaccine for use in persons aged 60 years and older. To make this recommendation more robust and evidence based, additional data should be generated on the safety and effectiveness of the vaccine in this age group.

Persons with comorbidities

Certain comorbidities have been identified as increasing the risk of severe COVID-19 disease and death. Vaccine efficacy was demonstrated among participants with obesity and those who had hypertension ; the numbers of participants with other comorbidities were too small to allow firm conclusions to be drawn. Considering the favourable benefit-risk assessment, vaccination is recommended for persons with comorbidities that have been identified as increasing the risk of severe COVID-19.

Children and adolescents below the age of 18 years

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

Pregnant women

Evidence suggests that pregnant women with COVID-19 are at higher risk of developing severe disease compared to non-pregnant women of reproductive age. COVID-19 in pregnancy has also been associated with an increased risk of preterm birth and of neonates requiring intensive care. Pregnant women who are aged 35 years or older, or who have high body mass index or an existing comorbidity, such as diabetes or hypertension, are at particular risk of serious outcomes from COVID-19.

The available data on Sinovac-CoronaVac in pregnant women are insufficient to assess vaccine efficacy or vaccine-associated risks in pregnancy. However, developmental and reproductive toxicology (DART) studies in animals have not shown harmful effects in pregnancy. In addition, this vaccine is an inactivated vaccine with an adjuvant that is routinely used in many other vaccines with a documented good safety profile, including in pregnant women. On the basis of previous experience with use of other inactivated vaccines used during pregnancy, the effectiveness of Sinovac-CoronaVac in pregnant women is expected to be comparable to that observed in non-pregnant women of similar age. Studies should be conducted to evaluate safety and immunogenicity in pregnant women.

In the interim, WHO recommends the use of Sinovac-CoronaVac in pregnant women when the benefits of vaccination to the pregnant woman outweigh the potential risks. To help pregnant women make this assessment, they should be provided with information about the risks of COVID-19 in pregnancy, the likely benefits of vaccination in the local epidemiological context, and the current limitations of the safety data in pregnant women. WHO does not recommend pregnancy testing prior to vaccination. WHO does not recommend delaying pregnancy or terminating pregnancy because of vaccination.

Lactating women

Breastfeeding offers substantial health benefits to lactating women and their breastfed children. Vaccine effectiveness is expected to be similar in lactating women as in other adults. Data are not available on the potential benefits and risks of the vaccine to breastfed children. However, as Sinovac-CoronaVac is not a live virus vaccine, it is biologically and clinically unlikely to pose a risk to the breastfeeding child. On the basis of these considerations, WHO recommends the use of Sinovac-CoronaVac in lactating women as in other adults. WHO does not recommend discontinuing breastfeeding after vaccination.

Persons living with HIV

Persons living with HIV may be at higher risk of severe COVID-19. Persons living with HIV were not included in the trials. Data on administration of the vaccine are currently insufficient to allow assessment of vaccine efficacy for persons living with HIV. It is possible that the immune response to the vaccine may be reduced, which may lower its clinical effectiveness. Studies in persons living with HIV are under way. In the interim, given that the vaccine is nonreplicating, persons living with HIV who are part of a group recommended for vaccination may be vaccinated. Information and, where possible, counselling should be provided to inform individual benefit–risk assessment. It is not necessary to test for HIV infection prior to vaccine administration.

Immunocompromised persons

Immunocompromised persons are at higher risk of severe COVID-19. Available data are currently insufficient to assess vaccine efficacy or vaccine-associated risks in severely immunocompromised persons, including those receiving immunosuppressant therapy. It is possible that the immune response to the vaccine may be reduced, which may lower its clinical effectiveness. In the interim, given that the vaccine is nonreplicating, immunocompromised persons who are part of a group recommended for vaccination may be vaccinated with CoronaVac. Information and, where possible, counselling about the limitations around the data in immunocompromised persons should be provided to inform individual benefit–risk assessment.

Persons who have previously had SARS-CoV-2 infection

Vaccination should be offered regardless of a person's history of symptomatic or asymptomatic SARS-CoV-2 infection. Viral or serological testing for prior infection is not recommended for the purpose of decision-making about vaccination. Available data show that, in the 6 months after an initial natural infection, symptomatic reinfection is uncommon. If vaccine supply is limited, persons who have had SARS-CoV-2 infection in the preceding 6 months, confirmed by polymerase chain reaction (PCR), may therefore choose to delay vaccination until near the end of this period. However, emerging data indicate that the risk of symptomatic reinfection is higher in settings where variants of concern dominate. In these settings earlier immunization after natural infection may be advisable. When more data on duration of immunity after natural infection become available, the recommendation on the length of this time period may be revised.

Persons with current acute COVID-19

Persons with acute PCR-confirmed COVID-19 should not be vaccinated until after they have recovered from acute illness and the criteria for discontinuation of isolation have been met. The optimal minimum interval between a natural infection and vaccination is not yet known.

Persons who previously received passive antibody therapy for COVID-19

Currently there are no data on the safety or efficacy of vaccination in persons who received monoclonal antibodies or convalescent plasma as part of COVID-19 treatment. As a precautionary measure, vaccination should be deferred for at least 90 days to avoid interference of the antibody treatment with vaccine-induced immune responses.

Special settings

Persons in settings with high population densities, such as refugee and detention camps, prisons and slums, where physical distancing is not implementable, should be prioritized for vaccination as outlined in the WHO Prioritization Roadmap (4), taking into account national epidemiological data, vaccine supply and other relevant considerations.

As noted in the WHO Prioritization Roadmap, national programmes should give special consideration to groups that are disproportionately affected by COVID-19 or that face health inequities as a result of social or structural inequities. Such groups should be identified, barriers to vaccination should be addressed, and programmes should be developed to allow equitable access to vaccines.

Other considerations

SARS-CoV-2 variants

SARS-CoV-2 viruses undergo evolution. Some new virus variants may be associated with higher transmissibility, disease severity, risk of reinfection, or a change in antigenic composition resulting in lower vaccine effectiveness.

The phase 3 clinical trial was conducted in Brazil at the time when a variant from the P.2 lineage was predominant. The variant of concern, P.1, was just emerging and not yet frequent. The other variants of concern, such as the B.1.1.7 and the B1.351 variants, were not circulating in Brazil at the time of the trial.

In an observational study, the estimated effectiveness of Sinovac-CoronaVac in health workers in Manaus, Brazil, where P.1 accounted for 75% of SARS-CoV-2 samples genotyped as part of surveillance at the peak of the epidemic in January 2021, was 49.6% (95% CI, 11.3–71.4%) against symptomatic infection (4). A post-introduction cohort study in Chile in the context of circulating B.1.1.7 and P.1 demonstrated high vaccine effectiveness against hospitalizations and deaths. No information yet available regarding B.1.617.

WHO currently recommends the use of Sinovac-CoronaVac according to the WHO Prioritization Roadmap (4), even if variants are present in the country. Countries should conduct a benefit–risk assessment according to the local epidemiological situation including the extent of circulating virus variants. Countries using the vaccine in the presence of variants are encouraged to monitor vaccine effectiveness, in particular to capture data on the frequency and severity of any breakthrough infections due to variants.

There is an urgent need for a coordinated approach to surveillance and evaluation of variants and their potential impact on vaccine effectiveness. WHO will continue to monitor the situation; as new data become available, recommendations will be updated accordingly.

SARS-CoV-2 tests

Prior receipt of the vaccine will not affect the results of SARS-CoV-2 nucleic acid amplification or antigen tests for diagnosis of acute/current SARS-CoV-2 infection. However, it is important to note that currently available antibody tests for SARS-CoV-2 assess levels of IgM and/or IgG to the spike or the nucleocapsid protein. The vaccine contains inactivated SARS-CoV-2 virus, which elicits an immunological response to the spike and nucleocapsid protein; thus, a positive result in a test for spike protein IgM or IgG or a test that specifically evaluates IgM or IgG to the nucleocapsid protein could indicate either prior infection or prior vaccination. Antibody testing is not currently recommended to assess immunity to COVID-19 following Sinovac-CoronaVac vaccination.

Role of vaccines among other preventive measures

As there is not yet sufficient evidence of an effect of the vaccine on transmission, nonpharmaceutical interventions must continue, including use of face masks, physical distancing, handwashing and other measures as appropriate in particular settings, depending on the COVID-19 epidemiology and potential risks of emerging variants. Government advice on nonpharmaceutical interventions should continue to be followed by vaccinated individuals, as well as those who have not yet been vaccinated. This advice will be updated as information on the impact of vaccination on virus transmission and indirect protection in the community is assessed.

Community engagement, effective communication, and legitimacy

Community engagement and effective communication (including risk communication) are essential to the success of COVID-19 vaccination programmes. Prioritization decisions should be made through transparent processes that are based on shared values, the best available scientific evidence, and appropriate representation and input by affected parties. Furthermore, communication about the mechanism of action of inactivated vaccines, and efficacy and safety data derived from clinical trials and post-marketing studies, as well as background mortality, maternal and neonatal outcomes and rates of adverse events of special interest (AESI) in groups prioritized for vaccination, needs to be strengthened. Strategies should include: (i) culturally acceptable and linguistically accessible communications regarding COVID-19 vaccination made freely available; (ii) active community engagement and involvement of community opinion leaders and trusted voices to improve awareness and understanding of such communications; and (iii) inclusion of diverse and affected stakeholder opinions in decision-making. Such efforts are especially important in subpopulations who may be unfamiliar with or distrustful of health care systems and immunization.

Vaccination logistics

The vaccine is provided as a refrigerated liquid formulation stored at 2–8 °C in a multidose vial containing 40 doses (0.5 ml each). The vials should be protected from light.

In order to improve the traceability of biological medicinal products, the name and the batch number of the administered product should be clearly recorded in patient records.

When scheduling vaccination for occupational groups, e.g. health workers, consideration should be given to the reactogenicity profile of Sinovac-CoronaVac observed in clinical trials, which may occasionally lead to time off work in the 24–48 hours following vaccination.

In considering the programme implications of implementing these recommendations, particular attention should be given to equity, including the feasibility, acceptability, and effectiveness of the programme in resource-constrained settings.

Recommendations on addressing current knowledge gaps through further research

WHO recommends the following post-authorization monitoring activities and research.

- Safety surveillance and monitoring:
  - serious adverse events, including thromboembolic events, thrombosis with thrombocytopenia syndrome (TTS), anaphylaxis and other serious allergic reactions, Bell`s palsy, transverse myelitis;
  - cases of multisystem inflammatory syndrome following vaccination, cases of COVID-19 following vaccination that result in hospitalization or death;
  - background rates of AESIs (including thromboembolic events), maternal and neonatal outcomes, and mortality in groups prioritized for vaccination;
  - vaccine-associated enhanced disease and vaccine-associated enhanced respiratory disease following immunization;
  - vaccine safety assessment in the context of phase IV studies, particularly in older persons and persons with comorbidities
- Vaccine effectiveness (8):
  - vaccine effectiveness in relation to new virus variants;
  - vaccine effectiveness in persons 60 years and above;
  - vaccine effectiveness in persons with comorbidities;
  - vaccine effectiveness against severe COVID-19;
  - vaccine effectiveness in relation to time interval between the first and second dose;
  - vaccine effectiveness over time and whether protection can be prolonged by booster doses;
  - vaccine effectiveness against post-COVID-19 conditions
  - studies to investigate whether this vaccine reduces SARS-CoV-2 transmission and viral shedding;
  - assessment and reporting of breakthrough infections and virus sequence information;
  - head-to-head studies with other vaccines on extent and duration of immunity using standardized neutralization, T-cell and mucosal immunity assays;
  - booster studies with homologous and heterologous vaccines.

  Subpopulations:
  - prospective studies on the safety of this vaccine in pregnant and lactating women;
  - immunogenicity and safety studies in persons below the age of 18 years;
  - safety data on vaccination in immunocompromised persons, including persons living with HIV and persons with autoimmune disease;
  - studies to assess the need for and timing of booster doses in persons where vaccine may result in lower immunogenicity, such as immunocompromised persons, persons living with HIV, and older persons.
- Vaccination logistics:
  - immunogenicity and safety studies of co-administration with other vaccines, including influenza and pneumococcal vaccines, to adults and older persons;
  - safety, immunogenicity, and impact of a delayed second dose;
  - interchangeability and “mix and match” studies within and across COVID-19 vaccine platforms.
- Virus variants:
  - global surveillance of virus evolution and the impact of virus variants on vaccine effectiveness to support update of vaccines;
  - modelling to determine the trade-offs in the use of vaccines with reduced effectiveness against emergent variants;
  - effectiveness studies against virus variants.

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WHO continues to monitor the situation closely for any changes that may affect this interim guidance. Should any factors change, WHO will issue a further update. Otherwise, this interim guidance document will expire 2 years after the date of publication.

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