

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

## Interim guidance

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## 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 and updated as a result of another extraordinary SAGE meeting on 5 October 2021. It was further updated based on additional discussions at the extraordinary SAGE meeting on 19 January 2022 with regards to the revised WHO Prioritization Roadmap which now also includes considerations for booster doses.

Declarations of interests were collected from all external contributors, assessed for any conflicts of interest and appropriate measures taken. 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<sup>1</sup> 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 (1). 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 (2). 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 make COVID-19 vaccines available at scale and equitably across all countries.

As sufficient vaccine supply will not be immediately available to immunize all who could benefit from it, countries are recommended to use the WHO Prioritization Roadmap (3) and the WHO Values Framework (4) as guidance for their prioritization of target groups. As long as vaccine supplies are very limited, the Roadmap recommends that priority be given initially to high priority-use groups which include older persons, health workers and immunocompromised persons. As more vaccine becomes available, additional priority groups should be vaccinated as outlined in the WHO Prioritization Roadmap (3), taking into account national epidemiological data and other relevant considerations.

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<sup>1</sup> The recommendations contained in this publication are based on the advice of independent experts, who have considered the best available evidence, a risk–benefit analysis, and other factors, as appropriate. This publication may include recommendations on the use of medicinal products for an indication, in dosage form, dose regimen, population or other use parameters that are not included in the approved labelling. Relevant stakeholders should familiarize themselves with applicable national, legal, and ethical requirements. WHO does not accept any liability for the procurement, distribution and/or administration of any product for any use.

## Vaccine performance

Sinovac-CoronaVac, is an aluminium-hydroxide-adjuvanted, inactivated whole virus vaccine. A large phase 3 trial in Brazil showed that 2 doses of Sinovac-CoronaVac, 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 dose. No COVID-19-related deaths occurred in the vaccinated group; there was 1 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. More detailed data on the efficacy and safety of Sinovac-CoronaVac can be found in the background document (5). The data reviewed by WHO support the conclusion that the known benefits of Sinovac-CoronaVac outweigh the risks that are known or considered possible.

### Post-introduction data

A prospective national cohort study from Chile involving 10.2 million persons aged 16 years and older, was conducted from 2 February to 1 May 2021. Among persons who received 2 doses, the adjusted vaccine effectiveness was 65.9% (95% CI: 65–66%) for the prevention of COVID-19; 88% (95% CI: 87–88%) for the prevention of hospitalization; 90% (95% CI: 89–91%) for the prevention of intensive care unit (ICU) admission; 86% (95% CI: 85–88%) for the prevention of COVID-19-related death. These data were generated when gamma and alpha variants were circulating (6).

**Older persons:** Early post-introduction observational data from Chile suggested satisfactory vaccine effectiveness of Sinovac-CoronaVac vaccine across all age groups in the first few months of roll-out. The adjusted vaccine effectiveness for the fully immunized group of individuals aged 60 years and older (2 doses,  $\geq 14$  days after the second dose) was 67% (95% CI: 65–68%) for COVID-19; 85% (95% CI: 84–86%) for hospitalization; 89% (95% CI: 88–91%) for ICU admission; and 87% (95% CI: 85–88%) for COVID-19-related death (6). Subsequent data from Brazil and Chile have shown lower vaccine effectiveness in older persons, particularly among those older than 80 years, when compared to younger adults. Furthermore, neutralizing antibody levels and seroconversion rates were lower in persons aged 60 years and older, and there was a more rapid decline in seropositivity over 6 months compared to persons aged 18–59 years (7, 8).

**Booster including heterologous boosters:** In a study in Brazil in adults who had received 2 doses of Sinovac-CoronaVac 6 months previously, a third homologous dose of Sinovac-CoronaVac was compared with a third heterologous dose of either a recombinant adenoviral vectored vaccine (Ad26.COV2.S, Janssen), or an mRNA vaccine (BNT162b2, Pfizer-BioNTech), or a recombinant adenoviral-vectored ChAdOx1 nCoV-19 vaccine (AZD1222, AstraZeneca). Heterologous regimens had anti-spike IgG responses at day 28 that were superior to homologous booster responses: geometric mean ratios (heterologous vs homologous) were 6.7% (95% CI: 5.8–7.7%) for Ad26.COV2.S; 13.4% (95% CI: 11.6–15.3%) for BNT162b2; and 7.0% (95% CI: 6.1–8.1%) for ChAdOx1 nCoV-19 (9). However, all four vaccines administered as a third dose induced a significant increase in binding and neutralizing antibodies, which could improve protection against infection. Heterologous boosting resulted in more robust immune responses than homologous boosting which might enhance protection.

A prospective national cohort of 11.2 million persons aged 16 years and older in Chile to assess the effectiveness of Sinovac-CoronaVac, AZD1222, or BNT162b2 vaccine booster doses in individuals who completed their primary vaccination schedule with Sinovac-CoronaVac, compared to unvaccinated individuals, showed the following findings: the adjusted vaccine effectiveness against symptomatic COVID-19 was 79% (95% CI: 77–81%) for a 3-dose schedule with Sinovac-CoronaVac; 97% (95% CI: 96–97%) for a BNT162b2 booster dose; and 93% (95% CI: 93–94%) for an AZD1222 booster dose. The adjusted vaccine effectiveness against hospitalization, ICU admission, and COVID-19-related deaths was 86%, 92%, and 87% (respectively) for a 3-dose schedule with Sinovac-CoronaVac; 96%, 96%, and 97% for the BNT162b2 booster; and 98%, 99%, and 98% for the AZD1222 booster. Delta was the predominant circulating variant in Chile at the time the study was conducted (10).

### Intended use

Persons aged 18 years and older (for prioritization of subpopulations refer to the WHO Prioritization Roadmap (3)).

### Administration

The recommended primary vaccine series is 2 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 2–4 weeks. WHO recommends an interval of 4 weeks. 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 2 doses.

## Booster doses

Booster doses are administered to a vaccinated population that has completed a *primary vaccination series* when, with time, the immunity and clinical protection has fallen below a rate deemed sufficient in that population. The objective of a booster dose is to restore vaccine effectiveness.

In accordance with the WHO Prioritization Roadmap, a booster dose is recommended for the highest and high priority-use groups (e.g. older adults, health workers, persons with comorbidities), administered 4–6 months after the completion of the primary series. Countries with moderate-to-high rates of primary series coverage in higher priority-use groups should usually prioritize available resources to first achieve high booster dose coverage rates in higher priority-use groups before offering vaccine doses to lower priority-use groups.<sup>2</sup>

If more than 6 months have elapsed since the completion of the primary series, the booster dose should be given at the earliest opportunity. Either homologous or heterologous booster doses can be used.

## Interchangeability with other COVID-19 vaccines (heterologous schedules)

WHO supports a flexible approach to using different EUL COVID-19 vaccine products for different doses (heterologous schedule), and considers a total of 2 doses of any combination of EUL COVID-19 vaccines (e.g. 1 dose of Sinovac-CoronaVac and 1 dose of another EUL COVID-19 vaccine) to be a complete primary series. Heterologous vaccination should only be implemented with careful consideration of current vaccine supply, vaccine supply projections, and other access considerations, alongside the potential benefits and risks of the specific products being used (11).

## Heterologous booster

Immunogenicity and vaccine effectiveness is superior with a heterologous booster (COVID-19 vaccine from a different vaccine platform) following a primary vaccine series with Sinovac-CoronaVac, compared to a homologous booster (9, 10). Any of the EUL COVID-19 vaccines (mRNA vaccines, or the viral vectored vaccines) can be used as a booster dose following a primary series with Sinovac-CoronaVac (11).

## Co-administration with other vaccines

For adults, based on several co-administration studies of COVID-19 vaccines and inferred from co-administration studies of other adult vaccines, COVID-19 vaccines may be given concomitantly, or any time before or after, other adult vaccines including live-attenuated, inactivated, adjuvanted, or non-adjuvanted vaccines (12). When administered concomitantly, the vaccines should be injected in separate sites, preferably different extremities. For children and adolescents, evidence from co-administration studies is currently insufficient to make a recommendation for concomitant administration with COVID-19 vaccines.

## 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 ( $\geq$  grade 4) hypersensitivity and anaphylaxis reactions caused by Sinovac-CoronaVac were recorded in clinical trials, but have been observed occasionally post-authorization. As for all COVID-19 vaccines, Sinovac-CoronaVac should be administered 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 (i.e. with a body temperature  $>38.5^{\circ}\text{C}$ ) 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.

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<sup>2</sup> In some circumstances, there may be a relatively close trade-off in optimizing the impact of vaccine use between offering booster doses to older adults to avert more hospitalizations and deaths versus offering primary series doses to the remaining adults, adolescents, and children, that depend on country conditions, including supply and rollout timelines, past epidemic dynamics and infection-induced immunity, vaccine product, vaccine effectiveness, and waning of protection.

## Vaccination of specific populations

### **Persons aged 60 years and older**

The risk of severe disease and death due to COVID-19 increases steeply with age. Older adults are identified as a priority-use group in the WHO SAGE Prioritization Roadmap. Vaccination is recommended for older persons without an upper age limit. In accordance with the Roadmap, a booster dose is recommended for the highest and high priority-use groups, such as older adults, administered 4–6 months after completion of the primary series.

### **Persons with comorbidities**

Certain comorbidities such as diabetes, hypertension, obesity and neurodevelopmental and neurodegenerative conditions have been identified as increasing the risk of severe COVID-19 disease and death. Vaccination is recommended for persons with comorbidities that have been identified as increasing the risk of severe COVID-19, in line with the WHO Prioritization Roadmap (13).

### **Children and adolescents below 18 years of age**

Most children and adolescents are at very low risk of severe COVID-19. Sinovac-CoronaVac has not yet obtained EUL for the age indication below 18 years of age, although a phase 2 paediatric study has been completed. Until EUL for this age group has been approved, vaccination of individuals below 18 years of age with this vaccine is not routinely recommended.

### **Pregnant women**

Pregnant women with COVID-19 are at higher risk of developing severe disease, with increased risk of ICU admission and invasive ventilation, compared to non-pregnant women of reproductive age. COVID-19 in pregnancy is associated with an increased risk of preterm birth and of neonates requiring neonatal intensive care, and may also be associated with an increased risk of maternal mortality (14, 15). Pregnant women who are aged 35 years and older, or have high body mass index, or have an existing comorbidity such as diabetes or hypertension, are at particular risk of serious outcomes from COVID-19.

Developmental and reproductive toxicology (DART) studies have not shown harmful effects of the vaccine in pregnant animals and their foetuses. Available data from clinical trials are insufficient to assess vaccine safety or efficacy of Sinovac-CoronaVac in pregnancy. 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. Emerging post-introduction pharmacovigilance data have not identified any pregnancy-related safety concerns (16). 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.

WHO has identified pregnant women as a priority-use group for COVID-19 vaccination, given their increased risk of severe outcomes. 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.

### **Breastfeeding women**

WHO recommends the same use of Sinovac-CoronaVac in breastfeeding and non-breastfeeding women. This is based on the following considerations: breastfeeding offers substantial health benefits to breastfeeding women and their breastfed children; and vaccine effectiveness in breastfeeding women is expected to be similar to that 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. WHO does not recommend discontinuing breastfeeding after vaccination.

### **Moderately and severely immunocompromised persons, including persons living with HIV with CD4 cell count of <200 cells/μl**

Moderately and severely immunocompromised persons (ICPs) are at higher risk of severe COVID-19, regardless of age, although increasing age remains an important co-factor. For purposes of this interim recommendation, moderately and severely immunocompromised persons include those with active cancer, transplant recipients, immunodeficiency, and active treatment with immunosuppressives. It also includes people living with HIV with a current CD4 cell count of <200 cells/μl, evidence of an

opportunistic infection, not on HIV treatment, and/or with a detectable viral load (i.e. advanced HIV disease).<sup>3</sup> For more details, see the WHO Interim recommendations for an extended primary vaccination series in immunocompromised persons (17).

Available data for WHO EUL COVID-19 vaccine products suggest that vaccine effectiveness and immunogenicity are lower in ICPs compared to persons without immunocompromising conditions (17). Emerging evidence suggests that an additional dose included in an extended primary series enhances immune responses in ICPs. Reactogenicity data on an additional (third) dose given to ICPs, where reported, have generally been similar to those observed for the standard primary series of the vaccine being administered. Given the significant risk of severe COVID-19 for ICPs, if infected, WHO considers that the benefits of an additional (third) dose in an extended primary series outweigh the risks based on available data, although additional safety monitoring is required.

WHO recommends an extended primary series including an additional (third) dose for ICPs aged 18 years and older. Available evidence (17) suggests that an additional (third) dose should be given 1–3 months after the second dose in the standard primary series. If more than 3 months have elapsed since the second dose in the primary series, the additional (third) dose should be given at the earliest opportunity. The most appropriate timing for the additional dose may vary depending on the epidemiological setting and the extent and timing of immune suppressive therapy, and should be discussed with the treating physician. Heterologous boosters should be considered.

Given the limited vaccine effectiveness in this population, a booster (fourth) dose, administered 3–6 months after the additional (third) dose, may be considered.

Given that protection may remain inadequate in a portion of immunocompromised persons even after the administration of an additional dose, WHO further recommends that close contacts (in particular caregivers) of such individuals should be vaccinated if eligible (according to the product-specific vaccines that have received EUL). Additional public health and social measures at household level to protect immunocompromised persons are also warranted depending on the local epidemic circumstances.

### **Persons living with HIV who are stable on antiretroviral therapy**

Persons living with human immunodeficiency virus (PLWH) may be at higher risk of severe COVID-19. Persons living with HIV were not included in the Sinovac-CoronaVac trials. It is possible that immune responses to the vaccine may be reduced, which may lower clinical effectiveness. Studies in PLWH are underway. In the interim, given that the vaccine is nonreplicating, persons living with HIV that is well controlled (e.g. current CD4 count >200 cells/μl and/or viral suppression), and 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.

### **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. Data from the pooled analyses indicate that the vaccine is safe in people with evidence of prior SARS-CoV-2 infection. With the emergence of Omicron, reinfections after infection appear to be more common. Hybrid immunity is superior to immunity induced by vaccine or infection alone (18). The optimal time interval between infection and vaccination is not yet known. Persons with laboratory-confirmed SARS-CoV-2 infection before primary series vaccination may choose to delay vaccination for 3 months. Persons with breakthrough infections following any dose could also consider delaying the next dose by 3 months. When more data on duration of immunity after natural infection become available, the length of this time period may be revised as well as the number of doses needed.

### **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 as per government advice. The optimal minimum interval between a natural infection and vaccination is not yet known. An interval of 3 months or more could be considered.

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<sup>3</sup> **Active cancer:** Active immunosuppressive treatment for solid tumour or hematologic malignancy (including leukaemia, lymphoma, and myeloma), or within 12 months of ending such treatment. **Transplant recipients:** Receipt of solid organ transplant and taking immunosuppressive therapy; receipt of stem cell transplant (within 2 years of transplantation, or taking immunosuppressive therapy). **Immunodeficiency:** Severe primary immunodeficiency; chronic dialysis. **HIV/AIDS** with a current CD4 count of <200 cells/μl and/or lacking viral suppression. **Immunosuppressives:** Active treatment causing significant immunosuppression (including high-dose corticosteroids), alkylating agents, antimetabolites, transplant-related immunosuppressive drugs, cancer chemotherapeutic agents, tumour-necrosis factor (TNF) blockers, and other drugs that are significantly immunosuppressive; or treatment in the previous 6 months of immunosuppressive chemotherapy or radiotherapy.



## **Persons who previously received passive antibody therapy for COVID-19**

In people who have previously received monoclonal antibodies or convalescent plasma as part of COVID-19 treatment, vaccination does not need to be delayed. Although some reduction in vaccine-induced antibody titers was observed in people who previously received antibody products, the clinical significance of this reduction is unknown, and the balance of benefits versus risks favours proceeding with vaccination, even considering the possibility of diminished vaccine effectiveness in this situation.

### **Special settings**

Vaccine use should be prioritized in persons in settings with high population densities, such as refugee and detention camps, prisons and slums, where physical distancing is not implementable, as outlined in the WHO Prioritization Roadmap (3), 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 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 vaccination with Sinovac-CoronaVac.

#### **Role of vaccines among other preventive measures**

As recent data suggest limited effect of the vaccine on transmission, particularly against Omicron, it is advisable that public health and social measures to reduce SARS-CoV-2 transmission continue, including use of well fitted face masks, physical distancing, handwashing, appropriate ventilation and other measures as appropriate in particular settings, depending on the COVID-19 epidemiology and potential risks of emerging variants. Each country is facing a different situation in the pandemic depending on several factors including the intensity of SARS-CoV-2 circulation, amount of population level immunity, capacities to respond and agility to adjust measures. As the pandemic continues and the virus evolves, policy adjustments related to SARS-CoV-2 public health and social measures, will be needed. Government advice on public health and social measures should continue to be followed by vaccinated individuals, as well as those who have not yet been vaccinated.

Country strategies related to COVID-19 control should be designed to facilitate children's participation in education and other aspects of social life, regardless of vaccination (19).

#### **Community engagement and effective communication**

Community engagement and effective communication (including risk communication) are essential to the success of COVID-19 vaccination programmes. The decisions and processes for vaccination prioritization should be transparent and based on shared values, the best available scientific evidence, and appropriate representation and input by affected parties. Furthermore, communication needs to be strengthened on the mechanism of action of inactivated vaccines; efficacy and safety data derived from clinical trials and post-marketing studies; background mortality, maternal and neonatal outcomes; and rates of adverse events of special interest (AESI) in priority-use groups for vaccination. 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, such as 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.

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