Interim recommendations for the use of inactivated COVID-19 vaccines

Interim guidance

31 August 2023

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 various extraordinary meetings since January 2021 (Strategic Advisory Group of Experts on Immunization (who.int)).

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

The guidance should be considered along with the broader COVID-19 policy advice to WHO Member States and in particular the advice on how to reach the COVID-19 vaccination targets.

These interim recommendations on the inactivated vaccine platform for COVID-19 vaccines[1] summarize previous interim recommendations for inactivated COVID-19 vaccines (Table 1).

Table 1. **Summary information on current inactivated COVID-19 vaccines**

Vaccine name	Manufacturer [a]	Adjuvant composition	Regulatory authority[b]	Intended use (age range)	Administration		References
					Dosage[c]	Interval	
BBV152 COVAXIN	Bharat Biotech	• Aluminium hydroxide • Toll-like receptor (TLR) 7/8 agonist Imidazo quinolin gallamide (IMDG)[d]	EUL	≥12 yrs[e,f]	2 doses	4 weeks	Annexes to the interim recommendations for use of the Bharat Biotech BBV152 COVAXIN® vaccine against COVID-19 (who.int) Background document on the Bharat Biotech BBV152 COVAXIN® (COVID-19) vaccine (who.int)

[1] 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 a 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 name	Manufacturer [a]	Adjuvant composition	Regulatory authority[b]	Intended use (age range)	Administration		References
					Dosage[c]	Interval	
BIBP (Beijing Institute of Biological Products Co-Ltd)	China National Biotec Group (CNBG), Sinopharm	• Aluminium hydroxide	EUL	≥3 yrs	2 doses	3–4 weeks	Annexes to the interim recommendations for use of the inactivated COVID-19 vaccine BIBP developed by China National Biotec Group (CNBG), Sinopharm, 7 May 2021 (who.int) Background document on the inactivated COVID-19 vaccine BIBP developed by China National Biotec Group (CNBG), Sinopharm, 7 May 2021 (who.int)
CoronaVac	Sinovac	• Aluminium hydroxide	EUL	≥3 yrs[g,h]	2 doses	4 weeks	Annexes to the recommendations for use of the Sinovac-CoronaVac vaccine against COVID-19: Grading of evidence, Evidence to recommendation tables (who.int) Background document on the inactivated vaccine Sinovac-CoronaVac against COVID-19 (who.int)
Valneva VLA2001	Valneva Austria GmbH	• Aluminium hydroxide • TLR9 agonist adjuvant cytosine-phospho-guanine (CpG 1018)	SRA	18–50 yrs	2 doses	4 weeks	Annexes to the interim recommendations for use of the Valneva VLA2001 vaccine against COVID-19 (who.int) Background document on the Valneva VLA2001 vaccine against COVID-19 (who.int)

[a] Some of the manufacturers listed in the table may be updating the antigen composition of their COVID-19 vaccines to include the most recent SARS-CoV-2 variants (see: Statement on the antigen composition of COVID-19 vaccines (who.int).

[b] EUL: WHO Emergency Use Listing; SRA: stringent regulatory authority.

[c] Further information regarding dosage per age category is provided in the text below.

[d] IMDG and alum are adjuvants added to the vaccine to enhance immunogenicity. IMDG is a novel adjuvant which has not been used in any previous vaccine. Studies generally demonstrate that TLR7/8 agonists enhance Th1 responses and inhibit Th2 responses which is considered beneficial for COVID-19 vaccines. In addition, CD8 T-cell responses may be increased when using TLR7/8 agonists as adjuvants.

[e] See: https://www.bharatbiotech.com/images/covaxin/covaxin-pack-insert.pdf.

[f] See: https://www.bharatbiotech.com/images/covaxin/covaxin-smpc.pdf.

[g] See: https://www.hsa.gov.sg/docs/default-source/hprg-tpb/psar/coronavac-covid-19-vaccine-package-insert-(syringe).pdf.

[h] See: https://extranet.who.int/pqweb/sites/default/files/documents/Status_COVID_VAX_29May2023.pdf.

Inactivated vaccines platforms have been used in the production of vaccines against diseases such as seasonal influenza, pertussis, and diphtheria as well as COVID-19. Inactivated (or killed) vaccines cannot replicate; they are formulated with an adjuvant to increase immunogenicity and usually require more than one dose to elicit a durable immune response.

In the subsequent text, these vaccines will be referred to as inactivated COVID-19 vaccines. Future interim recommendations will include additional inactivated COVID-19 vaccines should such vaccines be licensed. In cases where a recommendation differs by product, product-specific names will be used. Timing, frequency and target populations for booster doses are derived from the revised March 2023 WHO prioritization roadmap on the use of COVID-19 vaccines *(1)*.

Methods

SAGE applies the principles of evidence-based medicine and has established thorough methodological processes for issuing or updating recommendations *(2)*. Specifically for COVID-19 vaccines, a detailed description of these processes can be found in the SAGE evidence framework for COVID-19 vaccines which provides guidance for considering data emerging from clinical trials in support of issuing vaccine-specific evidence-based recommendations *(3)*.

The guidance is based on the evidence-to-recommendation tables developed for inactivated vaccines, GRADEing on product-specific vaccine performance and new data derived from scientific publications (Table 1). All referenced documents are available on the SAGE COVID-19 webpage.

Evidence on vaccine effectiveness, in particular Omicron-specific vaccine effectiveness studies, can be accessed on the International Vaccine Access Center (IVAC)'s View-hub website (COVID vaccines | ViewHub (view-hub.org)), including weekly literature tables, forest plots, neutralization plots, and methods used.

General goal and strategy for the use of the inactivated vaccines against COVID-19

The COVID-19 pandemic has caused significant morbidity and mortality worldwide, as well as major social, educational and economic disruptions. Globally, population-level immunity has increased significantly, due to substantial, increasing vaccine use and infection-induced immunity, or a combination of both (hybrid immunity). Most countries have lifted most or all public health and social measures, and while the SARS-CoV-2 virus continues to circulate, the third year of the COVID-19 pandemic has seen a significant reduction in rates of hospitalization, admission to intensive care units and mortality across all age groups. This is due to a number of factors including increasing population-level immunity from infection and/or vaccination, and earlier testing and access to COVID-19 therapeutics. Nonetheless, certain subgroups continue to be at greater risk of severe disease and mortality and account for most of the ongoing COVID-19-related mortality; thus, even a minor decrease in vaccine effectiveness with time in vulnerable subgroups translates into a rise in cases of severe disease and death.

While vaccine effectiveness remains substantial and relatively well maintained over time against severe disease from Omicron, protection against mild disease and infection is lower than against pre-Omicron variants of concern and declines rapidly with time since the last vaccination. Older adults and people with comorbidities continue to be at greatest risk of severe disease and mortality due to Omicron and make up most of the deaths. In such vulnerable persons, even a minor decrease in vaccine effectiveness over time translates into a rise in severe disease and deaths.

WHO SAGE roadmap on uses of COVID-19 vaccines in the context of Omicron and substantial population immunity

Countries are recommended to use the WHO prioritization roadmap *(1)* and the WHO values framework *(4)* as guidance for prioritizing target groups. The WHO prioritization roadmap defines three priority-use groups: high, medium and low. WHO recommends that vaccine use be prioritized to the high priority-use groups (i.e. older persons, adults with multiple significant comorbidities or severe obesity, younger adults with significant comorbidities or severe obesity, persons with moderate to severe immunocompromising conditions (regardless of age), pregnant adults and adolescents, and frontline health workers). The medium priority-use group includes adults who do not fall into high-priority use groups, and children and adolescents with comorbidities and severe

obesity. Healthy children and adolescents are in the low priority-use group.[2] Within the capacity of programmes and vaccine availability, additional priority-use groups should be vaccinated as outlined in the WHO prioritization roadmap *(1)* taking into account national epidemiological data and other relevant considerations.

Administration and dosage

Administration of the primary vaccine series

The recommended vaccination schedule is two doses given intramuscularly into the deltoid muscle. WHO recommends that the second dose should be provided at least 4 weeks after the first dose.

BBV152 COVAXIN inactivated COVID-19 vaccine:

For individuals aged 12 years and above, the schedule is 2 doses (0.5 ml each) given intramuscularly.

BIBP inactivated COVID-19 vaccine:

For individuals aged 3 years and above, the schedule is 2 doses (0.5 ml each) given intramuscularly.

CoronaVac inactivated COVID-19 vaccine:

For individuals aged 3 years and above, the schedule is 2 doses (0.5 ml each) given intramuscularly.

Valneva inactivated COVID-19 vaccine:

For individuals aged 18–50 years, the schedule is 2 doses (0.5 ml each) given intramuscularly.

Booster doses

First booster doses are recommended at 6–12 months after the completion of the primary series.

Second and additional booster doses:

WHO recommends that for all older adults and adults with significant comorbidities or severe obesity (high priority-use group), second and additional booster doses should be given at an interval of 12 months after the previous dose. The age cut-off is to be decided by countries but is often 50–60 years.

For a subgroup of the high priority-use group (i.e. persons with the highest risk of severe disease and death, such as those who are very old and frail, those with multiple significant comorbidities, those with severe immunocompromising conditions, and those in long-term care facilities), an interval of 6 months after the previous dose should be considered, given that even a minor reduction in vaccine effectiveness after 6 months could translate into substantial mortality.

For healthy non-elderly adults (medium priority-use groups) and healthy children and adolescents aged below 18 years (low priority-use group), additional booster doses are not routinely recommended.

Further information on booster doses in priority-use groups is available in the WHO prioritization roadmap *(1)*.

[2] Healthy children and adolescents belong to the low priority-use group; children and adolescents with comorbidities belong to the medium priority-use group; and children and adolescents with moderate to severe immunocompromising conditions belong to the high priority-use group.

Interchangeability with other COVID-19 vaccines (heterologous schedules)

Use of the same vaccine for all doses (homologous schedule) is considered standard practice based on the substantial safety, immunogenicity, and efficacy data available; however, WHO supports a flexible approach to using different vaccines for different doses (heterologous schedule) *(5)*. Heterologous schedules may enhance immunogenicity.

Co-administration with other vaccines

WHO recommends that countries consider co-administration of COVID-19 vaccines (including variant-containing vaccines) with seasonal influenza vaccines *(6)*, whenever epidemiologically justified. 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 at any time before or after other vaccines for adults and adolescents, including live-attenuated, inactivated, adjuvanted, or non-adjuvanted vaccines. The same applies to maternal immunization for vaccines recommended during pregnancy.

When administered concomitantly, the vaccines should be injected in separate sites, preferably different extremities. Continued pharmacovigilance monitoring is recommended. WHO aims for a life-course approach for the implementation of all vaccines including COVID-19 vaccines. Such a programmatic approach will help to achieve a higher uptake of vaccines, increase the efficiency of vaccine roll-out and protect stretched health-care systems.

Contraindications

A history of anaphylaxis to any component of the vaccine is a contraindication to vaccination. If anaphylaxis occurs after any dose, a subsequent dose of the vaccine should not be administered.

Precautions

A history of anaphylaxis to any other vaccine or injectable therapy (i.e. intramuscular, intravenous, or subcutaneous vaccines or therapies) is not a contraindication to vaccination; however, for such persons, a risk assessment should be conducted by a health professional. It remains uncertain if there is an increased risk of anaphylaxis with use of inactivated COVID-19 vaccines, but counselling should be given about the potential risk which should be weighed against the benefits of vaccination. Such persons should be observed for 30 minutes after vaccination in health-care settings where anaphylaxis can be immediately treated.

In general, persons with an immediate non-anaphylactic allergic reaction to the first dose (such as urticaria, angioedema or respiratory symptoms) without any other symptoms (cough, wheezing, stridor), that occur within 4 hours of administration) should not receive additional doses, unless recommended after review by a health professional with specialist expertise. However, subject to individual risk–benefit assessment, inactivated COVID-19 vaccines could be provided under close medical supervision if it is the only available vaccine for persons at high risk of severe COVID-19.

As a small number of anaphylactic reactions have also been reported in vaccinees without a history of anaphylaxis, WHO recommends that inactivated COVID-19 vaccines be administered only in settings where anaphylaxis can be treated. Until more data are available regarding anaphylaxis after inactivated COVID-19 vaccination, all vaccinees should be observed for at least 15 minutes after vaccination.

Food, insect venom and contact allergies and allergic rhinitis, eczema and asthma are not considered a contraindication to vaccination. The vial stoppers are not made with natural rubber latex, and there is no contraindication or precaution to vaccination for persons with a latex allergy. In addition, as inactivated COVID-19 vaccines do not contain eggs or gelatine, there is no contraindication or precaution to vaccination for persons with allergies to these food substances.

Anyone with an acute febrile illness (body temperature over 38.5 ºC) should postpone vaccination until they are afebrile.

Vaccination of specific populations

Children and adolescents aged 6 months to 17 years

Children aged 6 months to 17 years with comorbidities that put them at higher risk of serious COVID-19 disease should be offered vaccination.

For healthy children and adolescents, COVID-19 is rarely lethal. Multisystem inflammatory syndrome in children (MIS-C) is a rare condition associated with SARS-CoV-2 infection. MIS-C *(7)* and post-COVID-19 conditions have decreased in the Omicron era. Children can experience significant morbidity but most infections are self-limiting, with only a small proportion requiring hospitalization. The benefit and cost–effectiveness of vaccinating healthy children and adolescents are substantially lower than for vaccinating high and medium priority-use groups and compared with most other vaccine preventable diseases in childhood.

Countries contemplating vaccinating children should consider the national disease burden in this age group, the benefit–risk, cost–effectiveness, other health and programmatic priorities, and opportunity costs. Additional booster doses are not routinely recommended in this age group. It is paramount that children continue to receive the recommended childhood vaccines for other infectious diseases.

In accordance with the WHO prioritization roadmap *(1)*, the priority remains to prevent deaths by achieving high vaccine coverage (primary series and boosters) in the high priority-use groups.

Pregnant adults and adolescents

Pregnant adults and adolescents are a high priority-use group because of the potential adverse effects of COVID-19 on the pregnant adult or adolescent, the foetus, and the infant. Although the risk of severe disease in the Omicron era is less than that in the pre-Omicron era *(8)*, pregnant women[3] with COVID-19 continue to be at higher risk of severe maternal morbidity and/or adverse pregnancy outcomes such as preterm birth *(9-11)*. They may also have an increased risk of maternal mortality *(9, 10)*. COVID-19 in pregnancy has also been associated with increased risks of neonates being born having low birth weight and requiring neonatal intensive care *(10)*. Pregnant women who are older (aged 35 years and above) or who have a high body mass index or an existing comorbidity, such as diabetes or hypertension, are at particularly high risk of severe outcomes from COVID-19.

Developmental and reproductive toxicology (DART) studies of inactivated COVID-19 vaccines have not shown harmful effects in pregnant animals and their offspring. A growing body of post-introduction vaccine pharmacovigilance data and observational studies has not identified any acute safety problems, with no increased risk of adverse obstetric outcomes, including spontaneous abortion, and neonatal outcomes following vaccination during pregnancy *(12-14)*. COVID-19 inactivated vaccines are immunogenic in pregnant women *(15, 16)*. Vaccine effectiveness studies have shown high effectiveness of COVID-19 vaccines in pregnant women, similar to effectiveness in nonpregnant people *(17, 18)*. During the Omicron era, COVID-19 vaccination, including booster dose, given to pregnant adults and adolescents protects them against severe disease and hospitalization, particularly when the last dose was received within the previous 4–5 months *(19)*. Further, vaccination with COVID-19 vaccines during pregnancy is associated with a reduced risk of severe COVID-19 in young infants *(20)*. Even during Omicron predominance, the incidence of hospitalization for COVID-19 was lower during the first 6 months of life among infants of vaccinated (and especially boosted) mothers, compared to infants of unvaccinated mothers *(21)*. The burden of severe COVID-19 in infants aged below 6 months is overall low, but nevertheless higher than in children aged 6 months to 5 years *(22)*.

The recommendation for pregnant adults and adolescents is to receive the primary series and booster vaccination as soon as possible. An additional booster dose should be given once during pregnancy if the last dose was administered more than 6 months prior. For this additional booster dose, vaccination in the mid-second trimester is preferred to optimize protection of the pregnant woman, the foetus, and the infant. However, the vaccine can be safely given at any time during pregnancy to avoid missing opportunities to vaccinate.

[3] Some studies on COVID and pregnancy refer to "pregnant women", and others to "pregnant people". While most people who are, or can become, pregnant are cisgender women or adolescent girls who were born and identify as female, this guidance is also intended for transgender men and other gender diverse people who can become pregnant. All uses of the terms "pregnant women" and "mothers" in the guidance are intended to be inclusive of all those who are pregnant or give birth.

WHO does not recommend pregnancy testing prior to vaccination. WHO does not recommend delaying pregnancy or terminating pregnancy because of vaccination.

Breastfeeding adults and adolescents

Breastfeeding offers substantial health benefits to breastfeeding women and their breastfed children. Vaccine effectiveness is expected to be similar in breastfeeding women as in other adults. In addition, vaccine-elicited antibodies are found in breast milk following vaccination of breastfeeding women, suggesting possible neonatal as well as maternal protection *(23)*. As an inactivated COVID-19 vaccine 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 because of 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 their age, although risk increases with age. Moderately and severely immunocompromised persons include those with active cancer, transplant recipients, immunodeficiency, and those receiving active treatment with immunosuppressives. Also included are 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.[4] Further information is available in WHO's Interim recommendations for an extended primary series for ICPs *(24)*.

Available data for COVID-19 vaccine products suggest that vaccine effectiveness and immunogenicity are lower in ICPs than in persons without immunocompromising conditions *(24, 25)*. The emerging evidence suggests that an additional dose included in an extended primary series enhances immune responses in some ICPs *(25)*. Reactogenicity data of an additional dose given to ICPs, where reported, have generally been similar to those observed for the standard primary series of the vaccine being administered.

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. Booster doses given 6 months after the previous dose are recommended for all ICPs.

Given that protection may remain inadequate in a portion of immunocompromised persons even after the administration of additional doses, WHO further recommends that close contacts and caregivers of such individuals should be vaccinated if eligible. Additional public health and social measures at household level to protect immunocompromised persons are also warranted depending on the local epidemic circumstances.

[4] **Active cancer:** Active immunosuppressive treatment for solid tumour or hematologic malignancy (including leukemia, 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** 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 blockers, and other drugs that are significantly immunosuppressive, or have received in the previous 6 months immunosuppressive chemotherapy or radiotherapy.

Funding source

SAGE members and SAGE working group members do not receive any remuneration from the Organization for any work related to the SAGE. The SAGE secretariat is funded through core contributions to WHO.

Acknowledgements

This document was developed in consultation with:

External: Current members of the Strategic Advisory Group of Experts on Immunization (SAGE) and the SAGE Working Group on COVID-19 Vaccines.

WHO: W. Roodly Archer, Annelies Wilder-Smith, Joachim Hombach, Melanie Marti, Katherine O'Brien.

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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.

WHO reference number: WHO/2019-nCoV/vaccines/SAGE_recommendation/inactivated/2023.1