Interim recommendations for use of the Bharat Biotech BBV152 COVAXIN® vaccine against COVID-19

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 meeting on 5 October 2021 and 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 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.

These interim recommendations[1] refer to the BBV152 (COVAXIN®) vaccine against COVID-19 manufactured by Bharat Biotech.

The guidance is based on the evidence presented in the Background document on the BBV152 COVAXIN® vaccine against COVID-19 developed by Bharat Biotech, and the annexes which include the GRADE and Evidence to Recommendation tables. Both documents are available on the SAGE COVID-19 webpage: https://www.who.int/groups/strategic-advisory-group-of-experts-on-immunization/covid-19-materials.

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 may be found in the SAGE evidence framework for COVID-19 vaccines *(2)*. This framework contains guidance on considering data emerging from clinical trials and post-introduction effectiveness and safety monitoring.

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

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 WHO Prioritization Roadmap recommends that priority of vaccine use be given initially to health workers and older people with and without comorbidities *(3)*. As more vaccine becomes available,

[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 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.

additional priority-use groups should be vaccinated as outlined in the Roadmap *(3)*, taking into account national epidemiological data and other relevant considerations.

Vaccine performance

The Bharat Biotech vaccine (BBV152) is a whole virion inactivated SARS-CoV-2 antigen adsorbed to alum and formulated with a toll-like receptor (TLR) 7/8 agonist Imidazo quinolin gallamide (IMDG) and the preservative 2-phenoxyethanol *(5)*. The vaccine is given in 2 doses, separated by 4 weeks. Inactivated vaccines have been used for diseases such as seasonal influenza, polio, and hepatitis A. Inactivated vaccines cannot replicate and therefore cannot infect individuals. IMDG and alum are adjuvants added to enhance immunogenicity. IMDG is a novel adjuvant which has not been used in any previous vaccine. Studies generally demonstrate that TLR 7/8 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 TLR 7/8 agonists as adjuvants *(5)*.

For the phase 3 trial of the BBV152 vaccine, participants aged 18 years and older were recruited. An interim analysis was conducted including data to 17 May 2021, when the median follow-up period (14 or more days post dose 2), was 99 days. During the follow-up period, the Delta variant was the predominantly circulating virus. Vaccine efficacy against COVID-19 of any severity, 14 or more days post dose 2, was 78% (95% confidence interval [CI]: 65–86%). In adults aged less than 60 years, vaccine efficacy was 79% (95% CI: 66–88%); and in those aged 60 years and older it was 68% (95% CI: 8–91%). There was 1 case of severe COVID-19 in the vaccinated group versus 15 cases in the placebo group (vaccine efficacy 93% [95% CI: 57–99%]). Vaccine efficacy against asymptomatic SARS-CoV-2 infection was 64% (95% CI: 29–82%).

BBV152 vaccine demonstrated an acceptable safety and reactogenicity profile in adults aged 18 years and older, including those aged 60 years and older (including those with comorbidities associated with an increased risk of progressing to severe/critical COVID-19). In line with other inactivated vaccines, hypersensitivity reactions following immunization with BBV152 were rare and usually non-serious. Severe allergic (anaphylactic) reactions have not been reported in BBV152 clinical studies to date.

More detailed data on the efficacy, effectiveness and safety of this vaccine can be found in the background document on BBV152 vaccine *(6)*. The data reviewed by WHO support the conclusion that the known benefits of BBV152 vaccine outweigh the risks that are known or considered possible. Therefore, WHO recommends the use of BBV152 in those aged 18 years and older.

Duration of protection and booster doses

In a continuation of the phase 2 trial, participants were rerandomized to receive a third (booster) dose of BBV152 or placebo. No vaccine efficacy data are available for this trial. Immunological testing for neutralizing antibodies against homologous and heterologous SARS-CoV-2 variants (Alpha, Beta and Delta) increased 19-fold to 97-fold after a third dose. No safety concerns were identified *(7)*.

Variants of concern

Data from the phase 3 clinical trial included individuals infected with circulating variants of concern such as Alpha, Delta and Kappa. Numbers were too low for vaccine efficacy estimates for Alpha. Vaccine efficacy against all variant-related COVID-19 disease was 71% (95% CI: 50–84%) with an efficacy of 90% (95% CI: 30–100%) against Kappa, and 65% (95% CI: 33–83%) against Delta.

Two published studies provide information on the vaccine effectiveness of BBV152 during the Delta wave in India. The first study used a test negative design among vaccinated health workers at a tertiary care centre in Delhi. The adjusted vaccine effectiveness of BBV152 against symptomatic COVID-19 in participants with no previous history of SARS-CoV2 infection after 2 doses administered at least 14 days before PCR testing was 47% (95% CI 29–61%) *(8)*. The second study was a retrospective cohort study also conducted among health workers in Delhi. Participants were individuals who had been previously infected by SARS-CoV2 (PCR confirmed) and then divided into groups by vaccination status. Among those who had received 2 doses of BBV152, the vaccine effectiveness against reinfection with symptomatic disease was 87% (95% CI, 76–93%) *(9)*.

Intended use according to the vaccine label

Persons aged 18 years and older.

WHO recommendation for use

For prioritization by age and other considerations, please see the WHO Prioritization Roadmap *(3)*.

Administration

The recommended primary vaccine series is 2 doses (0.5 ml each dose) given intramuscularly into the deltoid muscle. According to the manufacturer's product label, the vaccine can be administered with an interval of 4 weeks. If the second dose is inadvertently administered less than 4 weeks after the first dose, the second 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 2 doses.

Booster doses

Booster doses are administered to a vaccinated population that has completed a primary vaccination series when, with time, vaccine effectiveness 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 *(3)*, a booster dose is recommended for the highest priority-use groups (e.g. older adults, health workers, persons with comorbidities), administered 4–6 months after 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.[2]

If more than 6 months have elapsed since completion of the primary series, the booster dose should be given at the earliest opportunity.

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 BBV152 vaccine 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 *(10)*.

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 *(11)*. 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 BBV152 vaccine is a contraindication to its use. People who have an anaphylactic reaction following the first dose of BBV152 vaccine should not receive a second dose of the same vaccine.

Precautions

No severe allergic reactions or anaphylaxis caused by BBV152 vaccine have been recorded in the context of clinical trials; however rare cases of anaphylaxis have been reported following use in national vaccination programmes. As for all COVID-19 vaccines,

[2] 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.

BBV152 should be administered under health-care supervision, with the appropriate medical treatment available in case of allergic reactions, and an observation period ensured of 15 minutes after vaccination.

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. For such persons, a risk assessment should be conducted by a health professional. Such individuals should be observed for 30 minutes after vaccination in health-care settings where anaphylaxis can be immediately treated *(12)*.

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

Vaccination of specific populations

Persons aged 60 years and older

The risk of severe COVID-19 and death increases steeply with age. WHO recommends BBV152 vaccine for use in persons aged 60 years and older. In accordance with the WHO Prioritization 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 and death. Vaccination is recommended for persons with such comorbidities that have been identified as increasing the risk of severe COVID-19, in line with the WHO Prioritization Roadmap *(3)*.

Children and adolescents below 18 years of age

Most children and adolescents are at very low risk of severe COVID-19. BBV152 vaccine has not yet obtained EUL for the age indication below 18 years, although a phase 2/3 paediatric study has been completed *(13)*. Until EUL for this age group has been approved, vaccination of individuals below 18 years of age with this vaccine is not recommended.

Pregnant women

Pregnant women with COVID-19 are at higher risk of developing severe disease, with increased risk of intensive care unit (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 an existing comorbidity, such as diabetes or hypertension, are at particular risk of serious outcomes from COVID-19.

Developmental and reproductive toxicity (DART) studies have not shown harmful effects of the vaccine in pregnant animals and their foetuses. Available data on vaccination of pregnant women with BBV152 vaccine are insufficient to assess vaccine safety or efficacy in pregnancy; studies in pregnant women are planned, including a pregnancy substudy and a pregnancy registry. The TLR 7/8 adjuvant IMDG has not been used in any other licensed vaccine and the only safety data specific to this antigen come from the BBV152 vaccine safety profile, which does not include data on pregnant women. Post-marketing safety data from India, where over 120 000 pregnant women have received the BBV152 vaccine, found only minor adverse events related to the vaccine, but data on neonatal outcomes have not yet been collected. On the basis of previous experience with use of other inactivated vaccines used during pregnancy, the effectiveness of BBV152 vaccine 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 the increased risk of severe outcomes. WHO recommends the use of BBV152 vaccine 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 BBV152 vaccine 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 or risks of the BBV152 vaccine to breastfed children. However, as BBV152 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 age, although increasing age remains an important co-factor *(16)*. 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).[3] For more details, see the WHO Interim recommendations for an extended primary vaccination series in immunocompromised persons *(16)*.

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 *(16)*. Emerging evidence suggests that an additional vaccine 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, based on available data, the benefits of an additional (third) dose in an extended primary series outweigh the risks, 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 *(16)* suggests that an additional (third) dose should be given at least 1–3 months, after the second dose in the standard primary series in order to increase protection as quickly as possible in ICPs. 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.

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

Information and, where possible, counselling about the limitations surrounding data on administration of an additional dose to ICPs should be provided to inform individual benefit–risk assessment.

Given that protection may remain inadequate in a portion of ICPs, even after administration of an additional dose, WHO further recommends that close contacts (particularly 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 ICPs are also warranted, depending on 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. Data on the safety and immunogenicity of 2 doses of BBV152 vaccine in PLWH have not yet been studied. 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, persons

[3] **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.

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 with the standard primary series of 2 doses. Information and, where possible, counselling about vaccine safety and efficacy profiles should be provided to inform individuals on the potential benefits and risks. 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 prior infection appear to be common. Hybrid immunity is superior to immunity induced by vaccine or infection alone *(17)*. 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 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, including persons who are in-between doses, 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 infection and vaccination is not yet known. An interval of 3 months could be considered.

Persons who have 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*(18)*.

Special settings

Persons in settings such as refugee and detention camps, prisons, slums, and other settings with high population densities where physical distancing cannot be implemented, should be prioritized for vaccination, as outlined in the WHO Prioritization Roadmap *(3)*, taking into account national epidemiological data, vaccine supply and other relevant considerations.

As noted in the 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 enable 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 antibody tests currently available 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 at an individual level is not currently recommended to assess immunity to COVID-19 following vaccination with BBV152.

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 minimize disruption to children's participation in education and other aspects of social life *(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 vector-based 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 (AESIs) in groups prioritized for vaccination. Strategies should include: (i) culturally-acceptable and linguistically-accessible communications regarding COVID-19 vaccination, made freely available; (ii) active community engagement and the 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 BBV152 vaccine is presented as a 10-dose vial (5 ml per dose) delivered in cartons each containing 10 multidose vials. Unopened multidose vials should be stored at a temperature of 2–8 °C and should not be frozen. Frozen vaccine supply should be discarded according to national policy. The vaccine must be protected from light and well shaken before use. Opened vials should be kept at 2–8 °C during the immunization session and discarded within 6 hours of opening (first puncture) or at the end of the session, whichever comes first *(20, 21)*. Each vial comes with a vaccine vial monitor (VVM7) on the vial label.

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.

In considering the implications of implementing these recommendations in vaccine programmes, 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 post-authorization monitoring activities and research. Particularly pressing research needs for BBV152 vaccine include documenting the duration of protection, reproductive toxicology studies, safety in pregnancy, and vaccine efficacy against variants of concern.

- Post introduction safety surveillance and monitoring (through passive surveillance systems in all countries, and active surveillance systems wherever possible) should address:
  - all serious adverse events (e.g. death; life-threatening event requiring in-patient hospitalization; a persistent or significant disability/incapacity; a congenital anomaly/birth defect; or a medical event considered important by the health-care provider), including thromboembolic events, thrombosis with thrombocytopenia syndrome, anaphylaxis and other serious allergic reactions, Bell's palsy, transverse myelitis;
  - cases of multisystem inflammatory syndrome following vaccination; or 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 vaccination;
  - vaccine safety assessment in the context of phase 4 studies, particularly in older persons and persons with comorbidities.
- Vaccine effectiveness *(15)*:
  - Correlates of protection and of duration of immunity;
  - in relation to new virus variants;
  - in persons aged 60 years and older;
  - in persons with comorbidities;
  - against severe COVID-19;
  - in relation to time interval between the first and second dose, and second and booster dose;
  - over time and whether protection can be prolonged by additional doses;
  - against post-COVID-19 conditions
  - in pregnancy
  - studies to investigate whether BBV152 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 the vaccine in pregnant and breastfeeding women;
  - immunogenicity and safety studies in persons below the age of 18 years;
  - safety data on vaccination in ICPs, including persons living with HIV and persons with autoimmune disease;
  - studies to assess the need for and timing of additional doses in persons where vaccine may result in lower immunogenicity, such as ICPs, 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.

Table of Updates:

Update 15 March 2022

Section	Rationale for update
Vaccine performance	Updated to reflect post-introduction studies in India.
Booster doses	Given lower vaccine effectiveness against variants of concern, particularly Omicron, the need and timing of booster doses was updated.
Heterologous schedules	Updated to reflect the increasing evidence that heterologous boosters provide superior immunogenicity.
Pregnant women	Updated to reflect final DART study results.

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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.

References

1. WHO. Guidance for the development of evidence-based vaccination recommendations. 2017 (https://www.who.int/immunization/sage/Guidelines_development_recommendations.pdf, accessed 28 May 2021).
2. WHO. Evidence to recommendations for COVID-19 vaccines: evidence framework: a framework to inform the assessment of evidence and formulation of subsequent COVID-19 vaccine recommendations, 10 December 2020. Geneva: World Health Organization; 2020 (https://www.who.int/publications/i/item/WHO-2019-nCoV-SAGE-Framework-Evidence-2020-1, accessed 27 May 2021).
3. WHO SAGE roadmap for prioritizing uses of COVID-19 vaccines. (https://www.who.int/publications/i/item/who-sage-roadmap-for-prioritizing-uses-of-covid-19-vaccines-in-the-context-of-limited-supply, accessed 20 January 2022).
4. WHO SAGE values framework for the allocation and prioritization of COVID-19 vaccination. 2020 (www.who.int/publications/i/item/who-sage-values-framework-for-the-allocation-and-prioritization-of-covid-19-vaccination, accessed 4 June 2021).
5. Ganneru B, Jogdand H, Daram VK, Das D, Molugu NR, Prasad SD et al. Th1 skewed immune response of whole virion inactivated SARS CoV 2 vaccine and its safety evaluation. iScience. 2021;24. doi: 10.1016/j.isci.2021.102298.
6. WHO. Background document on the Bharat Biotech BBV152 COVAXIN® vaccine against COVID-19. 2021 (https://www.who.int/publications/i/item/WHO-2019-nCoV-vaccines-SAGE-recommendation-bbv152-covaxin-background, accessed 15 October 2021).
7. Vadrevu KM, Ganneru B, Reddy S, Jogdand H, Raju D, Praturi U et al. Persistence of immunity and impact of a third (booster) dose of an inactivated SARS-CoV-2 vaccine, BBV152; a phase 2, double-blind, randomised controlled trial. medRxiv. 2022:2022.01.05.22268777. doi: 10.1101/2022.01.05.22268777.
8. Desai D, Khan AR, Soneja M, Mittal A, Naik S, Kodan P et al. Effectiveness of an inactivated virus-based SARS-CoV-2 vaccine, BBV152, in India: a test-negative, case-control study. Lancet Infect Dis. 2021. doi: 10.1016/s1473-3099(21)00674-5.

9. Malhotra S, Mani K, Lodha R, Bakhshi S, Mathur VP, Gupta P et al. SARS-CoV-2 Reinfection Rate and Estimated Effectiveness of the Inactivated Whole Virion Vaccine BBV152 Against Reinfection Among Health Care Workers in New Delhi, India. JAMA Netw Open. 2022;5:e2142210. doi: 10.1001/jamanetworkopen.2021.42210.
10. WHO. Interim recommendations for heterologous COVID-19 vaccination schedules. (https://www.who.int/news/item/16-12-2021-interim-recommendations-for-heterologous-covid-19-vaccine-schedules, accessed 21 Dec 2021).
11. Izikson R, Brune D, Bolduc J, Bourron P, Fournier M, Moore T et al. Safety and immunogenicity of a high-dose quadrivalent influenza vaccine administered concomitantly with a third dose of the mRNA-1273 SARS-CoV-2 vaccine in adults ≥ 65 years of age: a Phase II, open-label study. 2021. doi: doi: https://doi.org/10.1101/2021.10.29.21265248.
12. WHO. Brief overview of anaphylaxis as an adverse event following immunization (AEFI) and practical guidance on its identification, case management and response in a primary care setting. 2021 (https://www.who.int/publications/i/item/anaphylaxis-aefi-management-and-response, accessed 20 December 2021).
13. Vadrevu KM, Reddy S, Jogdand H, Ganneru B, Mirza N, Tripathy VN et al. Immunogenicity and safety of an inactivated SARS-CoV-2 vaccine (BBV152) in children from 2 to 18 years of age: an open-label, age-de-escalation phase 2/3 study. medRxiv. 2021:2021.12.28.21268468. doi: 10.1101/2021.12.28.21268468.
14. Chinn J, Sedighim S, Kirby KA, Hohmann S, Hameed AB, Jolley J et al. Characteristics and Outcomes of Women With COVID-19 Giving Birth at US Academic Centers During the COVID-19 Pandemic. JAMA Network Open. 2021;4:e2120456-e. doi: 10.1001/jamanetworkopen.2021.20456.
15. Allotey J, Stallings E, Bonet M, Yap M, Chatterjee S, Kew T et al. Clinical manifestations, risk factors, and maternal and perinatal outcomes of coronavirus disease 2019 in pregnancy: living systematic review and meta-analysis. BMJ. 2020;370:m3320. doi: 10.1136/bmj.m3320.
16. WHO. Interim recommendations for an extended primary series with an additional vaccine dose for COVID-19 vaccination in immunocompromised persons. (https://www.who.int/publications/i/item/WHO-2019-nCoV-vaccines-SAGE_recommendation-immunocompromised-persons, accessed 15 March 2022).
17. Bates Timothy A, McBride Savannah K, Leier Hans C, Guzman G, Lyski Zoe L, Schoen D et al. Vaccination before or after SARS-CoV-2 infection leads to robust humoral response and antibodies that effectively neutralize variants. Science Immunology.0:eabn8014. doi: 10.1126/sciimmunol.abn8014.
18. Benschop RJ, Tuttle JL, Zhang L, Poorbaugh J, Kallewaard NL, Vaillancourt P et al. The effect of anti-SARS-CoV-2 monoclonal antibody, bamlanivimab, on endogenous immune response to COVID-19 vaccination. medRxiv. 2021:2021.12.15.21267605. doi: 10.1101/2021.12.15.21267605.
19. WHO, UNICEF, UNESCO. Considerations for school-related public health measures in the context of COVID-19: annex to considerations in adjusting public health and social measures in the context of COVID-19, 14 September 2020. Geneva: World Health Organization; 2020 (https://apps.who.int/iris/handle/10665/334294, accessed 15 March 2022).
20. WHO Policy Statement: Multi-dose Vial Policy (MDVP). WHO Policy (www.who.int/immunization/documents/general/WHO_IVB_14.07/en/, accessed 16 July 2021). WHO Policy Statement: Multi-dose Vial Policy (MDVP).
21. Product Information Leaflet, Bharat Biotech COVAXIN. 2021.

WHO reference number: WHO/2019-nCoV/vaccines/SAGE_recommendation/BBV152/2022.1