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

Interim guidance

3 November 2021

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.

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 recommendations1 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 develop effective and safe vaccines and to make them available at scale and equitably across all countries. The main immediate goal of vaccination against COVID-19, especially in low- and middle-income countries with limited supply of vaccines, is to protect against severe COVID-19 and death.

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 (3). 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

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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.
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 (3).

For the phase 3 trial of the BBV152 vaccine, participants aged ≥18 years were recruited. An interim analysis was conducted including data to May 17, 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 (VE) against COVID-19 of any severity, 14 or more days post dose 2, was 78% (95% CI: 65–86). In adults aged <60 years, VE was 79% (95% CI: 66–88); and in those aged ≥60 years it was 68% (95% CI: 8–91). There was 1 case of severe COVID-19 in the vaccinated group versus 15 in the placebo group (VE 93% [95% CI: 57–99]). VE 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, including those aged ≥60 years (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 (4). 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.

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 (5) and the WHO Values Framework (6) as guidance for prioritized vaccine use, based on population subgroup. As long as vaccine supplies are very limited, in settings with community transmission (stage I in the WHO Prioritization Roadmap), the Roadmap recommends that priority be given initially to health workers and older people with and without comorbidities. As more vaccine becomes available, additional target groups should be vaccinated (5), taking into account national epidemiological data, and vaccine-specific characteristics, as outlined in vaccine product information approved by regulatory authorities, and other relevant considerations.

**Intended use**

Persons aged 18 years and above.

**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 dose 2 is inadvertently administered less than 4 weeks after dose 1, dose 2 does not need to be repeated. If administration of dose 2 is delayed beyond 4 weeks, it should be given at the earliest possible opportunity. It is recommended that all vaccinated individuals receive 2 doses.

**Additional doses**

Additional doses of a vaccine may be needed as part of an *extended primary series* for target populations where the immune response following the standard primary series is deemed likely to be insufficient. The objective of including an additional dose in the primary series is to increase the proportion of individuals who are protected against disease (7). Emerging evidence suggests that older adults and immunocompromised individuals mount a lower immune response after a standard primary series compared to younger individuals and those without immunocompromising conditions. Therefore, for immunocompromised persons who have received a standard 2-dose primary series of BBV152, WHO recommends an additional (third) dose (see “Immunocompromised persons” below).

The benefit of an additional dose has been assessed largely using the same vaccine product as for the first 2 doses (homologous doses) (8). Evolving evidence suggests that a heterologous series (using a different COVID-19 vaccine platform, such as an mRNA or viral-vectorized vaccine, for the third dose) may be more immunogenic than a homologous series. However, data on safety, immunogenicity, and effectiveness are currently limited as to the relative merits of heterologous versus homologous additional doses. Advice as to whether the additional third dose should be a homologous or heterologous vaccine will be updated once more data are available.
In situations of interrupted vaccine supply used for the primary series, or for countries with access to COVID-19 vaccines from another vaccine platform with WHO emergency use listing (EUL), a heterologous third dose can be considered.2

**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 (7). The objective of a booster dose is to restore vaccine effectiveness. For BBV152, the need for, and timing of, booster doses is being assessed. Recommendations with regards to booster doses will be updated as data become available.

**Interchangeability with other COVID-19 vaccines**

Limited data are available on using a first dose of BBV152 and a second dose of a different COVID vaccine in the primary series. It is currently recommended that the same product be used for both doses. Recommendations may be updated as further information becomes available. If different COVID-19 vaccines are inadvertently administered in the 2 doses, no additional doses of either vaccine are recommended at this time.

**Coadministration with other vaccines**

Data gaps remain for coadministration of BBV152 vaccine with other vaccines. The limited evidence on coadministration of COVID-19 vaccines with inactivated influenza vaccines (derived mainly from coadministration studies with other COVID-19 vaccines) suggests that adverse events and reactogenicity are not increased as a result of coadministration. BBV152 can be coadministered with inactivated influenza vaccines. Different arms for injection should be used when both vaccines are delivered during the same visit. Continued pharmacovigilance monitoring is recommended.

No coadministration data are available for live-attenuated influenza vaccines given with COVID-19 vaccines. Data gaps also remain for coadministration of BBV152 vaccine with other vaccines. There should be a minimum interval of 14 days between administration of the BBV152 vaccine and vaccines other than coadministered inactivated influenza vaccines. This recommendation will be updated as data on coadministration with other vaccines, including live-attenuated influenza vaccines, become available.

**Contraindications**

A history of anaphylaxis to any component of this 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 vaccine administration, BBV152 should be given 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 (9).

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

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2 Additional doses to the primary series, with either a homologous or heterologous vaccine product, are currently considered off-label use.
Vaccination of specific populations

Populations for which clinical trial and/or post-introduction data exist

Persons aged 60 years and older

The risk of severe COVID-19 and death increases steeply with age. Of participants in the phase 3 trial, only 11% were aged ≥60 years. The vaccine showed efficacy against COVID-19 of any severity in this age group but with a wide confidence interval (VE 68% [95% CI: 8.0–90.0]) that is likely due to a small sample size. The trial data indicate that the vaccine has an acceptable safety profile for this age group. Post-introduction vaccine effectiveness studies are not yet available, but over 77 million doses of the vaccine have been used in India and vaccine effectiveness studies are anticipated. WHO recommends the vaccine for use in persons aged ≥60 years.

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. The clinical trial demonstrated that the vaccine has similar safety and only slightly reduced efficacy profiles in persons with various underlying medical conditions that place them at increased risk for severe COVID-19. The comorbidities studied in the clinical trials included cardiovascular disease, respiratory disease, diabetes, liver disease and obesity. Vaccination is recommended for persons with comorbidities that have been identified as increasing the risk of severe COVID-19.

Populations for which limited or no data exist from the clinical trials

Children and adolescents less than 18 years of age

Most children and adolescents are at very low risk of severe COVID-19. Safety and immunogenicity data are currently being generated for those aged <18 years. Until such data are available, vaccination of individuals in this age group 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 admission and invasive ventilation, compared to non-pregnant women of reproductive age. COVID-19 in pregnancy is also associated with an increased risk of preterm birth and of neonates requiring neonatal intensive care. It may also be associated with an increased risk of maternal mortality (10, 11). Pregnant women who are older (aged ≥35 years), 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.

Preliminary reproductive toxicity 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 sub-study 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 this 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 increased risk of severe outcomes. WHO recommends the use of BBV152 vaccine in pregnant women if 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; 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 (8). 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 (8).

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 (8). 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. Given the relatively small population of individuals covered by this additional dose recommendation, the impact on vaccine supply is expected to be limited.

Available evidence (8) suggests that an additional (third) dose should be given at least 1 month, and within 3 months, after dose 2 in the standard primary series in order to increase protection as quickly as possible in ICPs. If more than 3 months have elapsed since dose 2 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.

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 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. Data on administration of the vaccine are

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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.
currently insufficient to allow assessment of vaccine efficacy or safety for persons living with HIV. 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 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 benefit 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. Within 6 months after an initial natural infection, available data show that symptomatic reinfection due to the same variant is uncommon. Given limited vaccine supply, persons with PCR-confirmed SARS-CoV-2 infection in the preceding 6 months may therefore choose to delay vaccination until near the end of this period.

However, emerging data indicate that symptomatic reinfection may occur in settings with new, circulating variants of concern (VOCs) that are associated with markedly reduced protection conferred by previous natural infection and reduced vaccine efficacy. In these settings, earlier immunization is advisable, for example, within 90 days after natural infection. When more data become available on duration of immunity after natural infection and against different virus variants, the length of this time period may be revised.

**Persons with current acute COVID-19**

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

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

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

**Special settings**

Persons in settings 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 (5), 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 variants**

SARS-CoV-2 undergoes evolution (https://www.who.int/en/activities/tracking-SARS-CoV-2-variants/). Some new VOCs, may be associated with higher transmissibility, disease severity, risk of reinfection, or a change in antigenic composition resulting in lower vaccine effectiveness.

Data from the phase 3 clinical trial included individuals infected with VOCs such as Alpha, Delta and Kappa. Numbers were too low for VE estimates for Alpha. VE 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.
In view of these findings, WHO currently recommends the use of BBV152 vaccine according to the WHO Prioritization Roadmap (5), even if VOCs are present in the country. Countries should conduct a benefit–risk assessment according to the local epidemiological situation including the extent of circulating VOCs. Countries using the vaccine in the presence of variants of interest and VOCs are encouraged to monitor vaccine effectiveness, in particular to capture data on the frequency and severity of any breakthrough infections due to variants.

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

**SARS-CoV-2 tests**

Prior receipt of the vaccine will not affect the results of SARS-CoV-2 nucleic acid amplification or antigen tests for diagnosis of acute/current SARS-CoV-2 infection. However, it is important to note that 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**

In view of insufficient evidence to date of an effect of the vaccine on transmission, public health and social measures must continue, including use of 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. Government advice on public health and social measures should continue to be followed by both vaccinated and unvaccinated individuals. This advice will be updated as information on the impact of vaccination on virus transmission and indirect protection in the community is assessed.

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.

**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 about the mechanism of action of vector-based vaccines needs to be strengthened, along with 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 °C to +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 °C to +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 (12, 13). 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.
Interim recommendations for use of the Bharat Biotech BBV152 COVAXIN® vaccine against COVID-19

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 VE against variants of concern.

- Post introduction safety surveillance and monitoring (though 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 (11):
  - in relation to new virus variants;
  - in persons aged ≥60 years;
  - in persons with comorbidities;
  - against severe COVID-19;
  - in relation to time interval between the first and second 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 aged <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.

- Correlates of protection and of duration of immunity.

- Vaccination logistics:
  - immunogenicity and safety studies of coadministration with other vaccines, including influenza and pneumococcal vaccines, to adults and older persons;
  - safety, immunogenicity, and impact of a delayed second dose;
  - interchangeability and “mix and match” studies within and across COVID-19 vaccine platforms.

- Virus variants:
  - global surveillance of virus evolution and the impact of virus variants on vaccine effectiveness to support update of vaccines;
  - modelling to determine the trade-offs in the use of vaccines with reduced effectiveness against emergent variants;
  - effectiveness studies against virus variants.
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WHO continues to monitor the situation closely for any changes that may affect this interim guidance. Should any factors change, WHO will issue a further update. Otherwise, this interim guidance document will expire 2 years after the date of publication.

**References**


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