Interim recommendations for use of the Pfizer–BioNTech COVID-19 vaccine, BNT162b2, under Emergency Use Listing

Interim guidance

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World Health Organization

Background

This interim guidance has been developed on the basis of the advice issued by the Strategic Advisory Group of Experts (SAGE) on Immunization at its extraordinary meeting on 5 January 2021 *(1)* and updated during its extraordinary meeting on 27 May 2021 *(2)* further updated on 19 November 2021 and on 19 January 2022 *(3)*.

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

The guidance is based on the evidence summarized in the background document on mRNA vaccine BNT162b2 (Pfizer-BioNTech) against COVID-19 *(4)* and further updated based on new data derived from scientific publications.

Annexes *(5)* which include GRADE and evidence-to-recommendations (ETR) tables have also been updated to reflect the updated recommendations. All referenced documents are available on the SAGE COVID-19 webpage: https://www.who.int/groups/strategic-advisory-group-of-experts-on-immunization/covid-19-materials.

These interim recommendations refer to the mRNA vaccine BNT162b2, manufactured by Pfizer and BioNTech. The International nonproprietary name (INN) is Tozinameran. The vaccine is also known as Pfizer-BioNTech COVID-19 Vaccine or Comirnaty. In the subsequent text the vaccine will be referred to as BNT162b2.

On 31 December 2020, BNT162b2 was granted WHO's Emergency Use Listing (EUL).

Methods

SAGE applies the principles of evidence-based medicine and has set in place a thorough methodological process for issuing or updating recommendations *(6)*. Specifically for COVID-19 vaccines, a detailed description of the methodological processes can be found in the SAGE evidence framework for COVID-19 vaccines. This framework is intended to offer guidance for considering data emerging from clinical trials in support of issuing vaccine-specific evidence-based recommendations *(7)*.

General goal and strategy for the use of the mRNA vaccine BNT162b2 against COVID-19 (Pfizer–BioNTech)

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.

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 *(8)* and the WHO Values Framework *(9)* as guidance for their prioritization of target groups. As long as vaccine supplies are very limited (see WHO Prioritization Roadmap), the Roadmap recommends that priority be given initially to health workers at high risk and older people with and without comorbidities. As more vaccine becomes available, additional priority groups should be vaccinated as outlined in the WHO Prioritization Roadmap *(8)*, taking into account national epidemiological data and other relevant considerations. Also, as a matter of global equity, as long as many parts of the world are facing extreme vaccine shortages, WHO recommends that countries that have achieved high vaccine coverage (primary series and boosters) in their high-risk populations prioritize global sharing of COVID-19 vaccines through the COVAX facility before proceeding to vaccination of children and adolescents who are at low risk for severe disease.

Vaccine performance

BNT162b2 is an mRNA vaccine against COVID-19. In the randomized trial of the vaccine, a two-dose regimen of BNT162b2 given 21 days apart conferred 91% protection (95% CI 89–93%) 7 days post dose 2 against symptomatic SARS-CoV2- infection with the ancestral strain in persons aged 16 years and above, based on a median follow-up of two months *(10)*. Similar vaccine efficacy (generally 90 to 100%) was observed across subgroups, defined by age, sex, race, body mass index and comorbidities. Immunogenicity, in terms of neutralizing antibodies, is increased with a longer inter-dose interval to 12 weeks *(11)*, highlighting that extended inter-dose intervals will result in a good immune response, including in older adults.

Multiple studies have shown that post-introduction effectiveness of two doses is consistent with findings from the Phase 3 trials in the general population with very high protection against hospitalization and death *(12, 13)* and moderate vaccine impact against transmission *(14)*. However, with the emergence of Variants of Concern (VoC) since the ancestral strain, lower vaccine effectiveness has been observed, in particular with regards to mild breakthrough infections *(15)* and impact on transmission *(16)*. Protection against severe disease and hospitalizations remains high for the Delta variant although some waning (<10%) is also observed after several months *(17-19)*, with more marked waning (>30%) against mild infections six months after completion of the primary series *(19)*. For the Omicron variant, which is antigenically the most distant VoC from the ancestral strain, vaccine effectiveness against severe and mild disease after two doses is lower compared to Delta, and waning is more rapid *(20, 21)*.

Booster doses:

Re-enrolling unblinded participants from the phase 1 and phase 3 trials, a booster dose of BNT162b2 was administered approximately 6 months after completing the two-dose regimen. A third dose induces a strong and broad immune response. Overall, the safety profile associated with a third dose of BNT162b2 at 30 µg, administered approximately 6 months after completing the two-dose regimen, is very similar to the safety profile of the initial regimen itself. No new safety concerns were identified in study participants who received a booster, including no increased reactogenicity, nor unusual adverse events, nor other safety findings. Booster doses restore vaccine effectiveness against Delta and Omicron, but waning of VE is observed for Omicron even after the booster dose.

Children and adolescents:

A trial in adolescents aged 12-15 years showed a vaccine efficacy against symptomatic SARS-CoV-2 infection of 100% (95% CI 75–100%) from 7 days after dose 2 *(22)*. Multisystem inflammatory syndrome in children (MIS-C) is a severe postinfectious hyperinflammatory condition, which generally occurs 2–6 weeks after a typically mild or asymptomatic infection with SARS-CoV-2. A post-introduction study in the U.S. using a test-negative case-control design amongst hospitalized patients aged 12–18 years showed a VE of 91% (95% CI = 78%–97%) against MIS-C *(23)*.

A Phase 3 trial was completed in children aged 5-11 years and showed similar immunogenicity and reactogenicity as in young adults. Efficacy against symptomatic disease was 90.7% (CI 67.7; 98.3). No cases of myocarditis were reported among 3,082 trial participants aged 5–11 years with ≥7 days of follow-up after receipt of dose 2, although the study was not powered to assess the risk for myocarditis. Early post-introduction safety data from the U.S. show that the risk of myocarditis is lower in this age group compared to adolescents. No post-introduction vaccine effectiveness studies for the age group 5-11 years are currently available.

Intended use

Persons aged 5 years and above (for prioritization of different population groups see WHO Prioritization Roadmap *(13)*).

Administration

The recommended schedule is two doses (30 µg, 0.3 ml each for all persons aged 12 years and above; 10 µg, 0.2 ml each for children aged 5- 11 years) given intramuscularly into the deltoid muscle. WHO recommends that the second dose should be provided 4-8 weeks after the first dose, preferentially 8 weeks as a longer interval between doses is associated with higher vaccine effectiveness and potentially lower risk of myocarditis/pericarditis.

Booster doses

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

In accordance with the WHO Prioritization Roadmap, a booster dose is recommended for the highest priority-use groups (e.g. older adults and health workers) 4-6 months after the completion of the primary series. If more than 6 months have elapsed since the completion of the primary series, the booster dose should be given at the earliest opportunity.

Once high booster dose coverage has been achieved in the highest priority-use group, countries may also consider a booster for other lower priority-use groups. The need for, and timing of, booster doses for children aged 5-11 years has not yet been determined.

Interchangeability with other COVID-19 vaccines

Using 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 COVID-19 vaccine platforms for different doses (heterologous schedule), and considers two doses of any EUL COVID-19 vaccine to be a complete primary series. With heterologous schedules, the order of the vaccines administered may affect immune response levels. For example, a first dose mRNA vaccine followed by ChAdOx1-S [recombinant] vaccine is less immunogenic compared to first dose ChAdOx1-S [recombinant] vaccine followed by an mRNA vaccine *(24)*. A booster with BNT162b2 following a primary series with another platform often led to superior neutralizing antibody titres. 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. Interim recommendations on the use of heterologous schedules are available *(25)*.

Co-administration with inactivated influenza vaccines

Evidence on co-administration of BNT162b2 vaccine with inactivated influenza vaccine suggests that neither adverse events and reactogenicity, nor immunogenicity are increased as a result of co-administration. The BNT162b2 vaccine can be co-administered with inactivated influenza vaccines as per the interim recommendations *(26)*. Different arms for injection should be used when both vaccines are delivered during the same visit.

Co-administration with other vaccines

No co-administration data are available for other inactivated vaccines or live vaccines and a minimum interval of 14 days between administration of this vaccine and any other vaccines is recommended. This recommendation will be updated as data on co-administration with other vaccines become available.

Contraindications

A history of anaphylaxis to any component of the vaccine is a contraindication to vaccination. If anaphylaxis occurs after the first dose, a second 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, but counselling should be given about the potential risk of anaphylaxis and the risks 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, BNT162b2 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 BNT162b2 should be administered only in settings where anaphylaxis can be treated. Until more data are available with regard to anaphylaxis after BNT162b2 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 BNT162b2 does not contain eggs or gelatine, there is no contraindication or precaution to vaccination for persons with allergies to any food substances.

Myocarditis is a very rare adverse event that has been reported after receipt of mRNA COVID-19 vaccines. The observed risk is highest in males aged 12–29 years, and higher after the second dose. Available data suggest that the immediate course of myocarditis and pericarditis following vaccination is generally mild and responds to treatment. In a study in Denmark, of 3 482 295 individuals vaccinated with BNT162b2 (Pfizer-BioNTech), 48 developed myocarditis or myopericarditis within 28 days from the vaccination date compared with unvaccinated individuals (adjusted hazard ratio 1.34 (95% confidence interval 0.90 to 2.00); absolute rate 1.4 per 100 000 vaccinated individuals within 28 days of vaccination (95% confidence interval 1.0 to 1.8) *(27)*. As presented to the U.S. Advisory Committee on Immunization Practices (ACIP) on 5 January 2022, of 18 707 169 doses administered to children and adolescents ages 12–15 years, there were 265 reports of myocarditis, 90% of which were in males. In the U.S., reporting rates were substantially lower amongst ages 5–11 years compared with ages 12–15 and 16–17 years.

In October 2021, the Global Advisory Committee on Vaccine Safety (GACVS) COVID-19 subcommittee concluded that the mRNA COVID-19 vaccines have clear benefits in all age groups in reducing hospitalizations and deaths due to COVID-19. Countries should consider the individual and population benefits of immunisation as it pertains to their epidemiological and social context when developing their COVID-19 immunisation policies and programmes *(28)*.

Vaccinated individuals should be instructed to seek immediate medical attention if they develop symptoms indicative of myocarditis or pericarditis, such as new onset and persisting chest pain, shortness of breath, or palpitations following vaccination. It is important to rule out other potential causes of myocarditis and pericarditis, including natural infection from SARS-CoV-2 and other viral aetiologies.

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

Vaccination of specific populations

Older people

The risk of severe COVID-19 and death increases steeply with age. Post-introduction studies have shown high vaccine effectiveness and good safety profiles in this age group, including very old persons. Vaccination is recommended for older persons without an upper age limit.

Persons with comorbidities

Certain comorbidities have been identified as increasing the risk of severe COVID-19 disease and death. Vaccination is recommended for persons with comorbidities that have been identified as increasing the risk of severe COVID-19, in alignment with the WHO Prioritization Roadmap.

Children and adolescents 5-17 years of age

Children 5-17 years of age 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 usually a mild disease. Children can experience significant morbidity such as MIS-C even after mild or asymptomatic infection, but this is rare. In accordance with the WHO Prioritization Roadmap, WHO recommends that countries consider using BNT162b2 in children aged 5- 17 years only when high vaccine coverage (primary series and boosters) has been achieved in the higher priority-use groups.

Countries should consider the individual and population benefits of immunising children and adolescents in their specific epidemiological and social context when developing their COVID-19 immunisation policies and programmes *(29)*.

Pregnancy

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 disease in pregnancy is also associated with an increased risk of preterm birth, and of neonates requiring neonatal intensive care *(30, 31)*. It may also be associated with an increased risk of maternal mortality *(32-34)*. Pregnant women who are older (age 35 years and above), or have high body mass index, or have an existing comorbidity such as diabetes or hypertension, are at particular risk of severe outcomes from COVID-19.

Developmental and reproductive toxicology (DART) studies of BNT162b2 have not shown harmful effects in pregnant animals and their offspring. Clinical trial data on safety and immunogenicity in pregnancy are limited. However, a growing body of post-introduction vaccine pharmacovigilance data has not identified any acute safety problems, with obstetric outcomes including spontaneous abortion and neonatal outcomes similar to reported background rates *(35-37)*. Data from small studies have demonstrated that COVID-19 mRNA vaccines are immunogenic in pregnant women and that vaccine-elicited antibodies are transported to infant cord blood and breast milk, suggesting possible neonatal as well as maternal protection *(38, 39)*.

WHO recommends the use of BNT162b2 in pregnant individuals. Pregnant individuals should be informed that they can receive the vaccine and be provided with information about the increased risks of COVID-19 in pregnancy, the likely benefits of vaccination, and the current limitations of safety data. WHO does not recommend pregnancy testing prior to vaccination. WHO does not recommend delaying pregnancy or terminating pregnancy because of vaccination

Breastfeeding

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. Data are not available on the potential benefits or risks of the vaccine to breastfed children. However, as BNT162b2 is not a live virus vaccine and the mRNA does not enter the nucleus of the cell and is degraded quickly, it is biologically and clinically unlikely to pose a risk to the breastfeeding child. On the basis of these considerations, WHO recommends the use of BNT162b2 in breastfeeding women as for other adults. 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 risk increases with age. Moderately and severely immunocompromised persons include those with active cancer, transplant recipients, immunodeficiency, and active treatment with immunosuppressives. They also include people living with HIV who have 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 .[a] For more details, see *(40)*.

[a] **Active cancer:** Active immunosuppressive treatment for solid tumor 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.

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 *(40)*. The emerging evidence suggests that an additional dose included in an extended primary series enhances immune responses in some ICPs *(41)*. Reactogenicity data of an additional (third) dose given to ICPs, where reported, have generally been similar to those observed for the standard primary series of the vaccine being administered. Given the significant risk of severe COVID-19 for ICPs, if infected, WHO considers that the benefits of an additional (third) dose in an extended primary series outweigh the risks based on available data, though additional safety monitoring is required.

WHO recommends an extended primary series including an additional (third) dose (30 µg) for ICPs aged 12 years and above, and 10 µg for ICPs aged 5 to 11 years. Available evidence *(40)* suggests that an additional (third) dose should be given 1-3 months after the second dose in the standard primary series in order to increase protection as quickly as possible in ICPs. If more than 3 months have elapsed since the second dose in the primary series, the additional (third) dose should be given at the earliest opportunity. The most appropriate timing for the additional dose may vary depending on the epidemiological setting and the extent and timing of immune suppressive therapy, and should be discussed with the treating physician.

Given the emergence of Omicron, a booster (fourth) dose 4-6 months after the additional dose may be considered for ICPs.

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

Persons living with HIV who are stable on Antiretroviral Therapy

Persons living with HIV may be at higher risk of severe COVID-19. HIV-positive persons whose infection is well controlled with highly active antiretroviral therapy should be vaccinated. Information and, where possible, counselling about vaccine safety and efficacy in immunocompromised persons should be provided to inform individual benefit–risk assessment. It is not necessary to test for HIV infection prior to vaccine administration.

Persons who have previously had SARS-CoV-2 infection

Vaccination should be offered regardless of a person's history of symptomatic or asymptomatic SARS-CoV-2 infection. Viral or serological testing for prior infection is not recommended for the purpose of decision-making about vaccination. Data from the pooled analyses indicate that the vaccine is safe in people with evidence of prior SARS-CoV-2 infection. Available data have shown that symptomatic reinfection is uncommon within 6 months after an initial natural infection. The optimal time interval between a natural infection and vaccination is not yet known. 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 6-month period. However, emerging data indicate that symptomatic reinfection may occur sooner in settings where variants of concern are circulating. In these settings, earlier immunization after infection is advisable, e.g. within 90 days following natural infection. When more data on duration of immunity after natural infection in relation to variants of concern become available, the length of this time period may be revised.

Persons with current acute COVID-19

Persons with acute PCR-confirmed COVID-19, including 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, but an interval of 3-6 months could be considered (see above).

Immunosuppressives: Active treatment causing significant immunosuppression (including high-dose corticosteroids), alkylating agents, antimetabolites, transplant-related immunosuppressive drugs, cancer chemotherapeutic agents, tumor-necrosis factor (TNF) blockers, and other drugs that are significantly immunosuppressive or have received in the previous 6 months immunosuppressive chemotherapy or radiotherapy

Persons who previously received passive antibody therapy for COVID-19

Currently there are no data on the safety or efficacy of vaccination in persons who received monoclonal antibodies or convalescent plasma as part of COVID-19 treatment. Hence, as a precautionary measure, vaccination should be deferred for at least 90 days after such treatment 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 is not implementable, should be prioritized for vaccination as outlined in the WHO Prioritization Roadmap, taking into account national epidemiological data, vaccine supply, and other relevant considerations.

As noted in the WHO Prioritization Roadmap, national programmes should give special consideration to groups who are disproportionately affected by COVID-19 or who 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 currently available antibody tests for SARS-CoV-2 assess levels of IgM and/or IgG to the spike or the nucleocapsid protein. The vaccine contains mRNA that encodes the spike protein; thus, a positive test for spike protein IgM or IgG could indicate either prior infection or prior vaccination. To evaluate for evidence of prior infection in an individual who has received BNT162b2, a test that specifically evaluates IgM or IgG to the nucleocapsid protein should be used. A positive nucleocapsid protein-based assay indicates prior infection. Antibody testing is not currently recommended to assess immunity to COVID-19 following BNT162b2 vaccination.

Role of vaccines among other preventive measures

As there is not yet sufficient evidence of the extent of vaccine impact on transmission, non-pharmaceutical interventions must continue, including use of face masks, physical distancing, handwashing, and other measures based on the epidemiology of SARS-CoV-2 and vaccine coverage rates. Government advice on non-pharmaceutical interventions should continue to be followed by vaccinated individuals, as well as those who have not yet been vaccinated. This advice will be updated as information on the impact of vaccination on virus transmission and indirect protection in the community has been better assessed.

Countries' strategies related to COVID-19 control should be designed to facilitate children's participation in education and other aspects of social life *(42)*.

Community engagement and effective communication

Community engagement and effective communication (including risk communication) are essential to the success of COVID-19 vaccination programmes. Prioritization decisions should be made through transparent processes that are based on shared values, the best available scientific evidence, and appropriate representation and input by affected parties. Furthermore, communication about the mechanism of action of mRNA vaccines, and efficacy and safety data derived from clinical trials and post-marketing studies, needs to be strengthened. Strategies should include: (1) culturally acceptable and linguistically accessible communications regarding COVID-19 vaccination made freely available; (2) active community engagement and involvement of community opinion leaders and trusted voices to improve awareness and understanding of such communications, and (3) 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

BNT162b2 currently requires ultra-cold-chain distribution and storage conditions that will be challenging in many country settings. The maximum permissable storage period of the unopened thawed vial at 2–8 °C (i.e. in a standard fridge after removal from deep-

freeze conditions) is one month (31 days). Updates on storage duration can be obtained from: https://extranet.who.int/pqweb/vaccines/vaccinescovid-19-vaccine-eul-issued

When assessing the feasibility of deploying BNT162b2, immunization programmes should consider the cold-chain requirements, the current minimum number of doses per shipment, the need to administer a whole batch of vaccine within a short timeframe after removal from cold storage, and the need to ensure bundling with an adequate independent supply of the correct diluent. Conditions must be met to avoid exposure of vials to sunlight and ultraviolet light. When scheduling vaccination for occupational groups, e.g. health workers, consideration should be given to the reactogenicity profile of BNT162b2 observed in clinical trials, leading to time off work in the 24-48 hours following vaccination.

Appropriate medical treatment to manage anaphylaxis must be immediately available. Hence, this vaccine should only be administered in settings with the necessary resources and trained health workers, and in settings that allow for at least 15 minutes of post-vaccination observation.

Recommendations on addressing current knowledge gaps through further research

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

- Safety surveillance and monitoring:
  - serious adverse events including myocarditis *(43)*;
  - cases of multisystem inflammatory syndrome following vaccination, cases of COVID-19 following vaccination that result in hospitalization or death;
  - rates of myocarditis after booster doses;
  - rates of myocarditis by age and sex;
  - background rates of AESIs (including myocarditis), maternal and neonatal outcomes, and mortality in groups prioritized for vaccination.
- Vaccine effectiveness:
  - vaccine effectiveness in relation to time interval between the first and second dose;
  - vaccine effectiveness in relation to new virus variants;
  - studies to investigate whether this vaccine reduces SARS-CoV-2 transmission and viral shedding;
  - assessment and reporting of breakthrough infections and virus sequence information;
  - head-to-head studies with other vaccines on extent and duration of immunity using standardized neutralization, T-cell and mucosal immunity assays;
  - vaccine effectiveness against post-COVID-19 conditions;
  - indirect protection against unvaccinated populations;
  - impact on enabling in person-schooling for children and adolescents.
- Subpopulations:
  - prospective studies on the safety in pregnant and lactating women;
  - safety data on vaccination in immunocompromised persons, including persons living with HIV and persons with