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 15 March 2021 (1) and updated during its extraordinary meeting on 27 May 2021 (2).

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 (3) and the background paper on COVID-19 disease and vaccines (4).

Annexes 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 (5). 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 (6).

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.

BNT162b2 is an mRNA vaccine against COVID-19. A two-dose regimen of BNT162b2 given 21 days apart conferred 95% protection (95% CI 90.3–97.6%) 7 days post dose 2 against symptomatic SARS-CoV2- infection in persons aged 16 and above, based on a median follow-up of two months (7). Similar vaccine efficacy (generally 90 to 100%) was observed across subgroups, defined by age, sex, race, body mass index and comorbidities. Post-introduction studies from Israel have shown high vaccine

effectiveness from 7 days after dose 2 (with an inter-dose interval of 3 weeks): for documented infection 92% (95% CI 88–95%); for symptomatic COVID-19, 94% (95% CI 87–98%); for hospitalization 87% (95% CI 55–100%); and for severe disease, 92% (95% CI 75–100%) (4). A recent trial in adolescents 12-15 years of age showed a vaccine efficacy against symptomatic SARS-CoV-2 infection of 100% (95% CI 75–100%) from at least 7 days after dose 2[a]. Only limited safety data are available for this age group given the small sample size of the trial.

The data reviewed by WHO support the conclusion that the known and potential benefits of BNT162b2 outweigh the known and potential risks. 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 (stage I in the WHO Prioritization Roadmap), in settings with community transmission, 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 in the 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.

Intended use

Persons aged 12 years and above.

Administration

The recommended schedule is two doses (30 µg, 0.3 ml each) given intramuscularly into the deltoid muscle. An interval of 21–28 days between the doses is recommended. If the second dose is inadvertently administered less than 21 days after the first, the dose does not need to be repeated. If administration of the second dose is inadvertently delayed it should be given as soon as possible thereafter, according to the manufacturer's instructions.

Considerations for deferring the second dose in settings with limited vaccine supply

WHO acknowledges that a number of countries face exceptional circumstances of vaccine supply constraints combined with a high disease burden. Some countries have therefore considered delaying the administration of the second dose to allow for a higher initial coverage with one dose. This is based on the observation that efficacy has been shown to start from day 12 after the first dose and reached about 89% between days 14 and 21, at the time when the second dose was given. No data on longer term efficacy for a single dose of BNT162b2 currently exist from Phase 3 trials, as the trial participants received 2 doses with an interval between doses in the trial ranging from 19 to 42 days. Neutralizing antibody responses were shown to be modest after the first dose and increase substantially after the second dose, and the second dose increased the efficacy against symptomatic disease to 95%. Post second dose studies showed that immunogenicity in terms of neutralizing antibodies is increased with a longer inter-dose interval to 12 weeks (10) highlighting that extended inter-dose intervals will result in a good immune response, even in older adults.

Some countries have chosen an inter-dose interval of 12 weeks. Based on post-introduction vaccine effectiveness studies from these countries, data on persistence of post dose 1 effectiveness are currently available up to 10 weeks in the context of the ancestral virus and the variant of concern Alpha (B 1.1.7) (11). Evidence on the impact of variants of concern other than Alpha (B1.1.7) on first and second dose vaccine effectiveness is only just emerging. Effectiveness after a single dose of vaccine against COVID-19 associated with Delta (B 1.617.2) was lower than that against Alpha (B.1.1.7), whilst two dose effectiveness was similar for these two variants (12). These data highlight the importance of providing a second dose of vaccine in the context of circulating variants of concern that may lower the effectiveness of a single dose.

Countries should take into account the following factors when considering deferral of the second dose beyond 3 to 6 weeks after the first dose: During an initial period of limited vaccine supply, prioritizing distribution of first doses of vaccine to as many highly vulnerable individuals as possible will avert more deaths than covering fewer such people with two doses - so long as the effectiveness of a single dose against COVID-19 mortality is at least half that of two doses and does not wane below this level before receipt of the second dose. The optimal interval before offering second doses depends not only on vaccine effectiveness and

[a] unpublished data on phase 2/3 randomized controlled trial (RCT) in adolescents 12-15 years, obtained from sponsor Pfizer-BioNTech.

waning but also on population vaccine coverage, supply projections, pre-existing naturally acquired immunity and country-specific vaccine prioritization plans (13-16). Furthermore, for settings with substantial circulation of variants of concern which have been shown to have reduced single doses effectiveness, the importance of providing the most vulnerable groups with 2 doses must be considered.

In conclusion, for countries that have not yet achieved high vaccine coverage rates in the high-priority groups who are experiencing a high incidence of COVID-19 cases combined with vaccine supply constraints, WHO recommends that such countries should focus on achieving a high first dose coverage in the high priority groups by extending the inter-dose interval up to 12 weeks.

Booster doses

There is currently no evidence on the need for a booster dose or booster doses of the vaccine after the current two-dose vaccine series is complete. The need for and timing of homologous, heterologous or variant-adapted booster doses will be evaluated as further data accumulate.

Interchangeability with other vaccines

It is currently recommended that the same product should be used for both doses. If different COVID-19 vaccine products are inadvertently administered in the two doses, no additional doses of either vaccine are recommended at this time. Heterologous (mix-and-match) studies are ongoing with regards to the interchangeability of this vaccine with other COVID-19 vaccines. Preliminary results from a heterologous priming schedule where BNT162b2 was given as the second dose following a first dose of ChAdOx1-S [recombinant] vaccine showed a slightly increased but acceptable reactogenicity with superior or similar immunogenicity results, thus supporting the use of such a heterologous priming schedule in settings where the second dose for the ChAdOx1-S [recombinant] vaccine is not available due to vaccine supply constraints or other concerns (17, 18).

Recommendations will be updated as further information becomes available on interchangeability between vaccine products and platforms.

Co-administration with other vaccines

There should be a minimum interval of 14 days between administration of this vaccine and any other vaccine against other conditions, until 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. 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.

A possible causal association with very rare cases of myocarditis in young men (16–24 years of age) is currently being investigated.

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

Vaccination of specific populations

Populations for which supportive data are available from phase 2/3 clinical trials and post introduction vaccine effectiveness studies.

Older people

The risk of severe COVID-19 and death increases steeply with age. Data from the phase 3 trial indicate that the efficacy and safety of the vaccine are comparable across all age groups (above the age of 16). Persons above the age of 85 years and very frail older persons were not included in the clinical trials. The safety and immunogenicity data obtained in a large subset of older people with and without comorbidities suggest that the benefits of vaccination outweigh the potential risks. Post introduction vaccine effectiveness studies have shown high 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. Phase 2/3 clinical trials have demonstrated that the vaccine has similar safety and efficacy profiles in persons with various underlying medical conditions, including those that place them at increased risk for severe COVID-19. The comorbidities studied in phase 2/3 clinical trials include hypertension; diabetes; asthma; and pulmonary, liver and kidney disease; as well as chronic (stable and controlled) infection with human immunodeficiency virus (HIV), hepatitis C virus (HCV) and hepatitis B virus (HBV). 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 below the age of 16 years

For children and adolescents COVID-19 is rarely severe. Evidence suggests that adolescents, particularly older adolescents, are as likely to transmit SARS-CoV-2 as adults. WHO recommends that countries should consider using BNT162b2 in children aged 12 to 15 only when high vaccine coverage with 2 doses has been achieved in the high priority groups as identified in the WHO Prioritization Roadmap.

Children 12-15 years of age with comorbidities that put them at significantly higher risk of serious COVID-19 disease, alongside other high-risk groups, may be offered vaccination.

There are currently no efficacy or safety data for children below the age of 12 years. Until such data are available, individuals below 12 years of age should not be routinely vaccinated.

Populations for which limited or no data exist from phase 2/3 clinical trials

Pregnant women

Evidence suggests that pregnant women with COVID-19 (second and third trimester) are at higher risk of developing severe disease compared to non-pregnant women of reproductive age. COVID-19 in pregnancy has also been associated with an increased risk of preterm birth and of neonates requiring neonatal intensive care. 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 serious outcomes from COVID-19.

Completed developmental and reproductive toxicology (DART) studies in animals have not shown harmful effects of the vaccine in pregnancy. Clinical trial data on safety and immunogenicity in pregnancy are not currently available but are being collected. Post-introduction vaccine pharmacovigilance data thus far have not identified any acute safety problems, with a reactogenicity and

adverse events profile similar to that reported in the absence of pregnancy. Based on previous experience with other vaccine use during pregnancy, the effectiveness of BNT162b2 in pregnant women is expected to be comparable to that observed for non-pregnant women in similar age groups. 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 (19, 20). As data from additional studies become available, recommendations will be updated accordingly.

In the interim, WHO recommends the use of BNT162b2 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, 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.

Lactating women

Breastfeeding offers substantial health benefits to lactating women and their breastfed children. Vaccine effectiveness is expected to be similar in lactating 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 lactating women as in other adults. WHO does not recommend discontinuing breastfeeding because of vaccination.

Persons living with HIV

Persons living with HIV may be at higher risk of severe COVID-19. Among the phase 2/3 clinical trial participants with well controlled HIV, there were no reported differences in safety signals. HIV-positive persons who are well controlled on highly active antiretroviral therapy and are part of a group recommended for vaccination can be vaccinated. Available data on administration of the vaccine are currently insufficient to allow assessment of vaccine efficacy or safety for persons living with HIV who are not well controlled on therapy. It is possible that the immune response to the vaccine may be reduced, which may alter its effectiveness. In the interim, given that the vaccine is not a live virus, persons living with HIV who are part of a group recommended for vaccination may be vaccinated. Information and, where possible, counselling about vaccine safety and efficacy profiles 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.

Immunocompromised persons

Immunocompromised persons are at higher risk of severe COVID-19. Available data are currently insufficient to assess vaccine efficacy or vaccine-associated risks in severely immunocompromised persons. It is possible that the immune response to the vaccine may be reduced, which may alter its effectiveness. In the interim, given that the vaccine is not a live virus, immunocompromised persons who are part of a group recommended for vaccination may be vaccinated. Information and, where possible, counselling about vaccine safety and efficacy profiles in immunocompromised persons should be provided to inform individual benefit–risk assessment.

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 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 6-month period. However, emerging data indicate that symptomatic reinfection may occur in settings where variants of concern are circulating that are associated with markedly reduced vaccine effectiveness (for example Beta B1.351). 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 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 occurrence 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. The optimal minimum interval between a natural infection and vaccination is not yet known.

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 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 [4], taking into account national epidemiological data, vaccine supply and other relevant considerations.

As noted in the WHO Prioritization Roadmap, national programmes should give special consideration to groups that are disproportionately affected by COVID-19 or that face health inequities as a result of social or structural inequities. Such groups should be identified, barriers to vaccination should be addressed, and programmes should be developed to enable equitable access to vaccines.

Other considerations

SARS-CoV-2 variants

SARS-CoV-2 viruses undergo evolution. Variants of concern may have higher transmissibility, disease severity, risk of reinfection, or a change in antigenic composition resulting in lower vaccine effectiveness. Preliminary data show some reduction in neutralization activity of BNT162b2 against the Beta (B1.351) variant, as well as against Gamma (P1) and Delta (B1.617.2), and less marked reduction against Alpha (B.1.1.7). Vaccine effectiveness after 2 doses against symptomatic SARS-CoV-2 infection with the Beta (B.1.351) variant has been estimated as 75.0% (95% CI 70.5–78.9%) (21). BNT162b2 was estimated to be 88% (95% CI 78.2–93.2%) effective against symptomatic disease from the Delta (B.1.617.2) variant after the second dose, compared to 93% (95%CI 90.4–95.5%) effectiveness against the Alpha (B.1.1.7) variant after the second dose (12). These preliminary findings highlight the urgent need for a coordinated approach for surveillance and evaluation of variants and their potential impact on vaccine effectiveness. WHO will continue to monitor the 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 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 (22).

Community engagement, effective communication, and legitimacy

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 storage period of the unopened thawed vial at 2–8 °C (i.e. in a normal fridge after taking out of deep-freeze conditions) is one month (31 days).

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 time frame 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.

In considering the programme implications of implementing these recommendations, particular attention should be given to equity, including the feasibility, acceptability, and effectiveness of the programme in resource-constrained settings (for example, how to ensure ultra-cold chain storage and the need to be able to provide treatment for anaphylaxis).

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 (23), thromboembolic events, thrombosis with thrombocytopenia syndrome (TTS), anaphylaxis and other serious allergic reactions, Bell`s palsy, and transverse myelitis
  - cases of multisystem inflammatory syndrome following vaccination, cases of COVID-19 following vaccination that result in hospitalization or death;
  - background rates of AESIs (including myocarditis, thromboembolic events and TTS), 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;
  - vaccine effectiveness over time and whether protection can be prolonged by booster doses;
  - booster studies with heterologous vaccines;
  - 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 autoimmune disease.
- 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, as currently implemented by certain countries;
  - interchangeability and "mix and match" studies within and across COVID-19 vaccine platforms;
  - stability of vaccine under alternative cold-chain distribution and storage conditions.
- 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 for the use of vaccines with reduced effectiveness against emergent variants;
  - Booster studies with updated vaccine formulations.

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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.

Table of updates

Section	Rationale for update
Considerations for deferring the second dose in settings with limited vaccine supply	Post-introduction vaccine effectiveness studies in countries that have implemented an inter-dose interval longer than per emergency use authorization (up to 12 weeks) have shown a high public health impact. This observation combined with additional immunological data support that countries facing a high incidence of COVID-19 combined with severe vaccine supply constraints could consider delaying the second dose up to 12 weeks in order to achieve a higher first dose coverage in high priority populations.
Interchangeability between vaccine products and platforms	Mix-and-match studies remain limited, but recent evolving evidence led to an update in this section.
Paediatric age indication	A Phase 3 trial in children aged 12-15 years showed high efficacy and good safety in this age group, leading to an extension of the previous age indication from 16 years onwards down to age 12 onwards.
Children and adolescents below the age of 16 years	The following statement was added: For children and adolescents COVID-19 is rarely severe. Evidence suggests that adolescents, particularly older adolescents, are as likely to transmit SARS-CoV-2 as adults. WHO recommends that countries should consider using BNT162b2 in children aged 12 to 15 only when high vaccine coverage with 2 doses has been achieved in the high priority groups as identified in the WHO Prioritization Roadmap. Children 12-15 years of age with comorbidities that put them at significantly higher risk of serious COVID-19 disease, alongside other high-risk groups, may be offered vaccination. There are currently no efficacy or safety data for children below the age of 12 years. Until such data are available, individuals below 12 years of age should not be routinely vaccinated.
Pregnant and lactating women	Text was updated as reassuring data on safety and immunogenicity in pregnancy has become available since the first Issue of this Recommendation.
Role of vaccines among other preventive measures	The following statement was added: “Countries’ strategies related to COVID-19 control should be designed to facilitate children’s participation in education and other aspects of social life.”.
SARS-CoV-2 variants	This section has been added to reflect the latest data with regards to the circulation of variants of concern and evidence on the impact on effectiveness of the vaccine.
Vaccination logistics	Based on additional storage studies, the storage period of the unopened thawed vial at 2–8 °C (i.e. in a normal fridge after taking out of deep-freeze conditions) has been extended from five days to one month (31 days).

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