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

Interim guidance

First issued 8 January 2021
Updated 15 June 2021
Updated 19 November 2021
Updated 21 January 2022
Updated 18 August 2022

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)*, consecutively updated during its extraordinary meeting on 27 May 2021 *(2)* further updated in writing on 19 November 2021, 19 January 2022 and last updated at the extraordinary SAGE meeting on 11 August 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[1] refer to the mRNA vaccine BNT162b2, manufactured by Pfizer and BioNTech. The International non-proprietary name 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).

[1] The recommendations contained in this publication are based on the advice of independent experts, who have considered the best available evidence, a risk–benefit analysis and other factors, as appropriate. This publication may include recommendations on the use of medicinal products for an indication, in a dosage form, dose regimen, population or other use parameters that are not included in the approved labelling. Relevant stakeholders should familiarize themselves with applicable national legal and ethical requirements. WHO does not accept any liability for the procurement, distribution and/or administration of any product for any use.

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 BNT162b2 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 remains an urgent global need to make COVID-19 vaccines available and deploy them at scale and equitably across all countries. Countries are recommended to use the WHO Prioritization Roadmap *(8)* and the WHO Values Framework *(9)* as guidance for their prioritization of target groups. The WHO Prioritization Roadmap recommends that priority of vaccine use be given to the highest priority-use groups (health workers, older persons, persons with moderate to severe immunocompromising conditions), and high priority-use groups (persons with comorbidities, teachers, pregnant women etc). Within the capacity of programmes and vaccine availability, additional priority-use groups should be vaccinated as outlined in the WHO Prioritization Roadmap (4), taking into account national epidemiological data and other relevant considerations.

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% Confidence Interval (CI): 89 to 93%) 7 days post dose 2 against symptomatic SARS-CoV-2- infection with the ancestral strain in persons aged 16 years and above, based on a median follow-up of six 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 *(12)*. However, there is waning of protection against infection and mild disease with time since vaccination, and lower neutralization activity has been observed against Delta, and even more markedly against Omicron, waning of protection has been less against severe disease *(13, 14)*. 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 that is expected to confer extended protection against COVID-19, including against variants of concern. 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, with no new safety concerns identified in the those who received a booster and with no increased reactogenicity or unusual adverse events or other safety findings.

<u>Interval between dose 1 and dose 2</u>

Vaccine effectiveness was significantly higher against both infection and hospitalization with a longer 7–8-week interval between doses versus the manufacturer-specified 3–4-week interval *(15)*. An inter-dose interval of 8 weeks or longer was associated with a lower risk of myocarditis compared to the 4-week interval *(16)*.

<u>Waning of vaccine effectiveness over time and performance of a second booster</u>

COVID-19 vaccine effectiveness (VE) can be reduced by newly emerging variants or sublineages that evade vaccine-induced immunity or because of increasing time since vaccination. A second booster can enhance VE. A relative vaccine effectiveness of 62% (95% CI: 50 to 74) against severe COVID-19, and 74% (95% CI: 50 to 90) against COVID-19 related death comparing 3 dose recipients to 4 dose recipients was documented *(17)*
VE against COVID-19-associated hospitalization 7-119 days and ≥120 days after receipt of dose 3 was 92% (95% CI: 91 to 93%) and 85% (95% CI: 81 to 89%), respectively, during the BA.1 period, compared with 69% (95% CI: 58 to 76%) and 52% (95% CI: 44 to 59%), respectively, during the BA.2/BA.2.12.1 period. Among adults aged ≥50 years, VE against

COVID-19-associated hospitalization ≥120 days after receipt of dose 3 was 55% (95% CI: 46 to 62%) and ≥7 days (median = 27 days) after a fourth dose was 80% (95% CI: 71 to 85%) during BA.2/BA.2.12.1 predominance *(18)*.
Among registrants who reported homologous vaccination, injection site and systemic reactions were less frequent after the second booster dose than after the first booster dose *(19)*.

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*(20)*. Only limited safety data are available for this age group because of the small size of the trial.

A Phase 3 trial was completed in children aged 5-11 years and showed similar immunogenicity and reactogenicity as in young adults. Safety data in these age groups are limited to Phase 3 trial data and data from early roll-out. 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 *(21)*.

A Phase 3 trial in 4,526 children aged 6 months to 4 years was conducted, initially with a 2-dose schedule, with a protocol amendment to a 3-dose schedule. The interval between the first two doses was 3 weeks. The median interval between doses 2 and 3 in the trial was 16 weeks among children aged 6–23 months and 11 weeks among children aged 2–4 years *(22)*. Vaccine efficacy ≥7 days after dose 3 was 80.0% (95% CI ; 23% to 95%) in preventing symptomatic, laboratory-confirmed COVID-19 with and without evidence of previous SARS-CoV-2 infection, based on infection in three vaccine recipients and seven placebo recipients, none of whom were hospitalized. In the immune-bridging analysis, the measure of immune response to 3 doses (3 µg each) of the Pfizer-BioNTech COVID-19 vaccine in children aged 6 months–4 years without evidence of previous SARS-CoV-2 infection was at least as high as the response observed in persons aged 16–25 years who had received 2 doses (30 µg each) of the Pfizer-BioNTech COVID-19 vaccine, with a geometric mean ratio (GMR) for 50% neutralizing antibody titre of 1.19 (95% CI: 1.00–1.43) for children aged 6–23 months and 1.30 (95% CI: 1.13–1.50) for children aged 2–4 years, satisfying the non-inferiority criteria.
Among vaccine recipients aged 6 months–4 years, reactogenicity, defined as solicited local injection site or systemic signs or symptoms during the 7 days after vaccination, were common (47.8% reported any local reaction, and 63.8% reported any systemic reaction); most reactions were mild to moderate, but less frequent in children aged 6 months–4 years (64%) than in children aged 5–11 years (86%). The most commonly reported grade 3 or higher reactions among vaccine recipients aged 6–23 months were fever (4%) and irritability (1%), and among recipients aged 2–4 years, fatigue (1%) and fever (2%). These were more common after the second dose versus the first dose.

Intended use according to the vaccine label

Persons aged 6 months and older.

WHO recommendation for use

For prioritization by age and other considerations, please see the WHO Prioritization Roadmap *(8)*. Healthy children and adolescents belong to the lowest priority-use group, children and adolescents with comorbidities belong to the medium priority-use group, and children and adolescents with moderate to severe immunocompromising conditions belong to the highest priority-use group.

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 to 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.

For infants and children aged 6 months to 4 years, the recommended schedule is three doses (3µg, 0.2 ml each): a schedule of two doses 3 weeks apart followed by a third dose at least 8 weeks after the second dose are according to the label. However, countries could consider extending the interval between the first and second dose up to 8 weeks.

Additional doses to the primary series

Additional doses of the vaccine may be needed as part of an extended primary vaccination series for target populations where the immune response following the standard primary series is likely to be insufficient. Emerging evidence suggests that immunocompromised individuals mount a lower immune response after a standard primary series compared to those without immunocompromising conditions. Therefore, for immunocompromised persons who have received a standard 2-dose primary series of BNT162b2, WHO recommends an additional dose, see under "Immunocompromised persons".

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, the first booster dose is recommended for the highest priority-use groups (i.e. older adults, persons with moderate to severe immunocompromising conditions, and health workers), 4-6 months after the completion of the primary series. Once high booster dose coverage has been achieved in the highest priority-use group or booster dose uptake slows considerably in the highest priority-use groups, countries should also consider a booster for lower priority-use groups.[2] If more than 6 months have elapsed since completion of the primary series, the booster dose should be given at the earliest opportunity.

To further reduce the risk of severe disease, deaths and disruptions of health services, WHO recommends countries should consider a second booster dose 4-6 months after the first booster dose for all older persons (age specific cut-off should be defined by countries based on local COVID-19 epidemiology), all persons with moderate and severe immunocompromising conditions, regardless of age, adults with comorbidities that put them at higher risk of severe disease, pregnant women and health workers (https://www.who.int/publications/i/item/WHO-2019-nCoV-vaccines-SAGE-good-practice-statement-second-booster).

Heterologous vaccines (e.g COVID-19 vaccines using platforms other than mRNA) and variant-adapted vaccines (once they have received regulatory approval) can be used for first and second boosters.

For children below the age of 12, there is currently no recommendation for booster doses except for children with immunocompromising conditions. If more data become available for the need of booster doses in this age group, this recommendation will be updated.

Interchangeability with other COVID-19 vaccines (heterologous schedules)

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 vaccines 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. 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*(23)*.

[2] In some circumstances, there may be a relatively close trade-off in optimizing the impact of vaccine use between offering booster doses to older adults to avert more hospitalizations and deaths versus offering primary series doses to the remaining adults, adolescents, and children, that depend on country conditions, including supply and roll-out timelines, past epidemic dynamics and infection-induced immunity, vaccine product, vaccine effectiveness, and waning of protection.

Heterologous booster

In adults and adolescents, 30 µg may be used as a booster dose following a completed primary series using any other EUL COVID-19 vaccine platform.

Co-administration with other vaccines

Based on several co-administration studies of COVID-19 vaccines and inferred from co-administration studies of other adult vaccines, COVID-19 vaccines may be given concomitantly, or any time before or after, other adult vaccines including live attenuated, inactivated, adjuvanted, or non-adjuvanted vaccines *(24)*. When administered concomitantly, the vaccines should be injected in separate sites, preferably different extremities. Continued pharmacovigilance monitoring is recommended.

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 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. In October 2021, the Global Advisory Committee on Vaccine Safety (GACVS) COVID-19 subcommittee concluded that the benefits of 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 relevant to their epidemiological and social context when developing their COVID-19 immunisation policies and programmes *(25)*.

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 COVID-19 infection 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 6 months -17 years of age

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

For healthy children and adolescents, COVID-19 is rarely lethal. MIS-C and post-acute COVID sequelae are rare, but may occur even after mild or asymptomatic infection. Children can experience significant morbidity but most infections are self-limiting, with only a small proportion requiring hospitalization.

Countries contemplating vaccinating children should consider the benefit-risk, affordability, epidemiological situation, programmatic trade-offs, national childhood vaccination programmes and opportunity costs, seroprevalence rates, and community acceptance. It is of utmost importance for children to continue to receive the recommended childhood vaccines for other infectious diseases.

In accordance with the WHO Prioritization Roadmap, the priority remains to prevent deaths by achieving high vaccine coverage (primary series and boosters) in the highest and high priority-use groups.

Pregnant persons

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*(26)*. It may also be associated with an increased risk of maternal mortality *(26)*. 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. A growing body of post-introduction vaccine pharmacovigilance data have not identified any acute safety problems, with obstetric outcomes including spontaneous abortion and neonatal outcomes similar to reported background rates *(27-29)*. COVID-19 mRNA vaccines are immunogenic in pregnant women, and initial post-introduction vaccine effectiveness studies have shown high effectiveness of BNT162b2 in pregnant women, similar to effectiveness in nonpregnant people *(30)*. Further, emerging evidence demonstrates that vaccination with mRNA vaccines during pregnancy is associated with a reduced risk of severe COVID-19 in young infants *(31)*.

WHO recommends the use of BNT162b2 in pregnant individuals. WHO has identified pregnant women as a high priority-use group for COVID-19 vaccination, given their increased risk of severe outcomes.

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

Breastfeeding persons

Breastfeeding offers substantial health benefits to breastfeeding women and their breastfed children. Vaccine effectiveness is expected to be similar in breastfeeding persons as in other adults. In addition, vaccine-elicited antibodies are found in breast milk following vaccination of breastfeeding women, suggesting possible neonatal as well as maternal protection *(32)*. 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. 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 .[3] For more details, see *(33)*.

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 *(33)*. The emerging evidence suggests that an additional dose included in an extended primary series enhances immune responses in some ICPs*(34)*. 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 *(33)* 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.

A first and second booster dose (fourth and fifth doses) given 4-6 months after the previous dose is recommended for all 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.

[3] **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. **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 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. Within 6 months after an initial natural infection, available data have shown that symptomatic reinfection is uncommon. 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 persons who are in-between doses, should not be vaccinated until after they have recovered from acute illness and the criteria for discontinuation of isolation have been met. The optimal minimum interval between a natural infection and vaccination is not yet known. Given that the additional benefit may be limited if vaccination is given too soon after natural infection, typically an interval of 3 months or more could be considered.

Persons who previously received passive antibody therapy for COVID-19

In people who have previously received monoclonal antibodies or convalescent plasma as part of COVID-19 treatment, vaccination does not need to be delayed. Although some reduction in vaccine-induced antibody titres was observed in people who previously received antibody products, the clinical significance of this reduction is unknown, and the balance of benefits vs. risks favours proceeding with vaccination, even when considering the possibility of diminished vaccine effectiveness in this situation.

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 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. Data show some reduction in neutralization activity of BNT162b2 against the Beta variant, as well as against Delta, and more marked reduction against Omicron. These 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. Variant-updated vaccines are currently in development *(35, 36)*.

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. Currently, antibody testing is not routinely 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 *(37)*.

Other programmatic considerations

Countries should consider broader integration of COVID-19 vaccination into primary health care through national immunization programmes.

WHO recommends that countries consider co-administration of COVID-19 vaccines with seasonal influenza vaccines, whenever feasible, dependent on seasonality. The known risk of serious illness for older adults and many other priority groups infected either with influenza virus or SARS-CoV-2 is substantial. Other adult vaccines may also be co-administered with COVID-19 vaccines as WHO aims for a life course approach for the implementation of COVID-19 vaccines. Such a programmatic approach will help to reach higher uptake of vaccines, increase efficiency and protect stretched health care systems.

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 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.

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 *(38)*
  - 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 doses;
  - vaccine effectiveness in relation to new virus variants of concern;
  - 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 in unvaccinated populations
  - impact on enabling in-person schooling for children and adolescents
  - impact of third and fourth doses (first and second boosters)
  - impact of additional boosters in immunocompromised persons
- 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 pneumococcal vaccines, to adults and older persons, and routine childhood vaccinations in younger persons;
  - 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.

Table of updates

Update 18 August 2022

Section	Rationale for update
Paediatric age indication	Reflects recent authorization of the age indication from age 6 months upwards.
Interchangeability between vaccine products and platforms	Both homologous and heterologous schedules are encouraged.
Booster doses	Booster doses (third dose) is recommended 4-6 months after the 2nd dose, given increasing evidence of waning of vaccine effectiveness over time, further compounded by lower vaccine effectiveness against Omicron and Delta that can be restored with a third dose.
Second booster doses	2nd booster doses (fourth dose) is recommended 4-6 months after the last dose in certain subpopulations at high risk.
Pregnant persons	Updated section given increasing body of evidence of safety, immunogenicity and vaccine effectiveness in pregnant persons
Co-administration	In adults and adolescents, co-administration with any live or non-live vaccines is permissible

Update 19 January 2022

Section	Rationale for update
Pediatric age indication	Reflects recent authorization of the age indication from age 5 years upwards.
Interchangeability between vaccine products and platforms	Both homologous and heterologous schedules are encouraged.
Booster doses	Booster doses (third dose) is recommended 4-6 months after the 2nd dose, given increasing evidence of waning of vaccine effectiveness over time, further compounded by lower vaccine effectiveness against Omicron and Delta that can be restored with a third dose.
Immunocompromised persons	Updated regarding the need for a third and fourth dose in certain immunocompromised populations.
SARS-CoV-2 variants	This section has been updated to reflect the latest data with regards to the circulation of variants of concern and evidence on the impact on immunogenicity and effectiveness of the vaccine, in particular Omicron.

Update 19 November 2021

Section	Rationale for update
Additional dose	Reflects recent authorization of a third dose to immunocompromised individuals with certain underlying conditions.
Interchangeability between vaccine products and platforms	Mix-and-match studies remain limited, but recent evolving evidence led to an update in this section.
Pregnant and breastfeeding women	Text was updated to reflect more recent evidence on vaccination of pregnant women. Given the increasing evidence on safety and effectiveness of this vaccine in pregnant women, WHO now recommends the use of BNT162b2 vaccine in pregnant women.
Immunocompromised persons	Updated regarding the need for a third dose in certain immunocompromised populations.
SARS-CoV-2 variants	This section has been updated to reflect the latest data with regards to the circulation of variants of concern and evidence on the impact on immunogenicity and effectiveness of the vaccine

Update 15 June 2021

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).

Funding source

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

Acknowledgements

This document was developed in consultation with:

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

WHO: Annelies Wilder-Smith, Joachim Hombach, Melanie Marti, Shalini Desai, Katherine O'Brien.

References

1. WHO. Extraordinary meeting of the Strategic Advisory Group of Experts on Immunization (SAGE) - 5 January 2021. (https://www.who.int/news-room/events/detail/2021/01/05/default-calendar/extraordinary-meeting-of-the-strategic-advisory-group-of-experts-on-immunization-(sage)---5-january-2021, accessed 19 November 2021).
2. WHO. Extraordinary meeting of the Strategic Advisory Group of Experts on Immunization (SAGE) – 27 May 2021. (https://www.who.int/news-room/events/detail/2021/05/27/default-calendar/extraordinary-meeting-of-the-strategic-advisory-group-of-experts-on-immunization-(sage)-27-may-2021, accessed 28 May 2021).
3. Extraordinary meeting of the Strategic Advisory Group of Experts on Immunization (SAGE) – 11 August 2022 (www.who.int/news-room/events/detail/2022/08/11/default-calendar/extraordinary-meeting-of-the-strategic-advisory-group-of-experts-on-immunization-(sage)-11-august-2022, accessed 12 August 2022).
4. WHO. Background document on the mRNA vaccine BNT162b2 (Pfizer-BioNTech) against COVID-19: background document to the WHO interim recommendations for use of the Pfizer–BioNTech COVID-19 vaccine, BNT162b2, under emergency use listing, 14 January 2021. Geneva: World Health Organization; 2021 (https://www.who.int/publications/i/item/background-document-on-mrna-vaccine-bnt162b2-(pfizer-biontech)-against-covid-19.
5. WHO. Annexes to the recommendations for use of the Pfizer–BioNTech vaccine BNT162b2 against COVID-19. (https://www.who.int/publications/i/item/WHO-2019-nCoV-vaccines-SAGE-recommendation-BNT162b2-GRADE-ETR-annexes, accessed 19 November 2021).
6. Guidance for the development of evidence-based vaccination recommendations. https://www.who.int/immunization/sage/Guidelines_development_recommendations.pdf. 2020.
7. WHO. Evidence to recommendations for COVID-19 vaccines: evidence framework: a framework to inform the assessment of evidence and formulation of subsequent COVID-19 vaccine recommendations, 10 December 2020. Geneva: World Health Organization; 2020 (https://www.who.int/publications/i/item/WHO-2019-nCoV-SAGE-Framework-Evidence-2020-1, accessed 27 May 2021).
8. WHO. WHO SAGE roadmap for prioritizing uses of COVID-19 vaccines. (https://www.who.int/publications/i/item/who-sage-roadmap-for-prioritizing-uses-of-covid-19-vaccines-in-the-context-of-limited-supply, accessed 20 January 2022).
9. WHO SAGE values framework for the allocation and prioritization of COVID-19 vaccination. 2020 (www.who.int/publications/i/item/who-sage-values-framework-for-the-allocation-and-prioritization-of-covid-19-vaccination, accessed 4 June 2021).
10. Thomas SJ, Moreira ED, Kitchin N, Absalon J, Gurtman A, Lockhart S et al. Safety and Efficacy of the BNT162b2 mRNA Covid-19 Vaccine through 6 Months. New England Journal of Medicine. 2021;385:1761-73. doi: 10.1056/NEJMoa2110345.
11. Parry, H.; Bruton, R.; Stephens, C.; Brown, K.; Amirthalingam, G.; Hallis, B.; et al. Extended interval BNT162b2 vaccination enhances peak antibody generation in older people.: medRxiv; (https://www.medrxiv.org/content/10.1101/2021.05.15.21257017v1.
12. International Vaccine Access Center, Health JHBSoP, and, Organization WH. Results of COVID-19 Vaccine Effectiveness Studies: An Ongoing Systematic Review. 2021 (https://view-hub.org/sites/default/files/2021-10/COVID19%20VE%20Studies_Forest%20Plots_1.pdf, accessed 5 July 2022).
13. Goldberg Y, Mandel M, Bar-On YM, Bodenheimer O, Freedman L, Haas EJ et al. Waning Immunity after the BNT162b2 Vaccine in Israel. New England Journal of Medicine. 2021. doi: 10.1056/NEJMoa2114228.
14. Rosenberg ES, Dorabawila V, Easton D, Bauer UE, Kumar J, Hoen R et al. COVID-19 Vaccine Effectiveness by Product and Timing in New York State. medRxiv. 2021:2021.10.08.21264595. doi: 10.1101/2021.10.08.21264595.
15. Skowronski DM, Febriani Y, Ouakki M, Setayeshgar S, El Adam S, Zou M et al. Two-Dose Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) Vaccine Effectiveness With Mixed Schedules and Extended Dosing Intervals: Test-Negative Design Studies From British Columbia and Quebec, Canada. Clinical Infectious Diseases. 2022:ciac290. doi: 10.1093/cid/ciac290.
16. Buchan SA, Seo CY, Johnson C, Alley S, Kwong JC, Nasreen S et al. Epidemiology of Myocarditis and Pericarditis Following mRNA Vaccination by Vaccine Product, Schedule, and Interdose Interval Among Adolescents and Adults in Ontario, Canada. JAMA network open. 2022;5:e2218505-e. doi: 10.1001/jamanetworkopen.2022.18505.
17. Magen O, Waxman JG, Makov-Assif M, Vered R, Dicker D, Hernán MA et al. Fourth Dose of BNT162b2 mRNA Covid-19 Vaccine in a Nationwide Setting. N Engl J Med. 2022. doi: 10.1056/NEJMoa2201688.
18. Link-Gelles R, Levy M, Gaglani M, Irving S, Stockwell M, Dascomb K et al. Effectiveness of 2, 3, and 4 COVID-19 mRNA Vaccine Doses Among Immunocompetent Adults During Periods when SARS-CoV-2 Omicron BA.1 and

BA.2/BA.2.12.1 Sublineages Predominated — VISION Network, 10 States, December 2021–June 2022. 2022;71:931–9. doi: http://dx.doi.org/10.15585/mmwr.mm7129e1.

19. Hause A, Baggs J, Marquez P, Abara W, Baumblatt J, Blanc P et al. Safety Monitoring of COVID-19 mRNA Vaccine Second Booster Doses Among Adults Aged ≥50 Years — United States, March 29, 2022 – July 10, 2022. . MMWR Morb Mortal Wkly Rep. 2022;71:971-76. doi: http://dx.doi.org/10.15585/mmwr.mm7130a4.

20. Frenck RW, Klein NP, Kitchin N, Gurtman A, Absalon J, Lockhart S et al. Safety, Immunogenicity, and Efficacy of the BNT162b2 Covid-19 Vaccine in Adolescents. N Engl J Med. 2021. doi: 10.1056/NEJMoa2107456.

21. Administration FaD. CBER assessment of a single booster dose of the Pfizer-BioNTech COVID-19 Vaccine (0.3 mL) administered to individuals 16 to 17 years of age after completion of a primary vaccination series with the Pfizer-BioNTech COVID-19 Vaccine or COMIRNATY. 2022 (https://www.fda.gov/media/154869/download.

22. Vaccines and Related Biological Products Advisory Committee Meeting June 15, 2022. FDA Briefing Document.EUA amendment request for Pfizer-BioNTech COVID-19 Vaccine for use in children 6 months through 4 years of age (https://www.fda.gov/media/159195/download, accessed 2 August 2022).

23. Interim recommendations for heterologous COVID-19 vaccine schedules.(https://www.who.int/publications/i/item/WHO-2019-nCoV-vaccines-SAGE-recommendation-heterologous-schedules, accessed 11 January 2022).

24. Izikson R, Brune D, Bolduc J, Bourron P, Fournier M, Moore T et al. Safety and immunogenicity of a high-dose quadrivalent influenza vaccine administered concomitantly with a third dose of the mRNA-1273 SARS-CoV-2 vaccine in adults ≥ 65 years of age: a Phase II, open-label study. 2021. doi: doi: https://doi.org/10.1101/2021.10.29.21265248.

25. COVID-19 subcommittee of the WHO Global Advisory Committee on Vaccine Safety (GACVS): updated statement regarding myocarditis and pericarditis reported with COVID-19 mRNA vaccines. 27 October 2021. (www.who.int/news/item/27-10-2021-gacvs-statement-myocarditis-pericarditis-covid-19-mrna-vaccines-updated, accessed 2 November 2021).

26. Allotey J, Fernandez S, Bonet M, Stallings E, Yap M, Kew T et al. Clinical manifestations, risk factors, and maternal and perinatal outcomes of coronavirus disease 2019 in pregnancy: living systematic review and meta-analysis. BMJ. 2020;370:m3320. doi: 10.1136/bmj.m3320.

27. Shimabukuro TT, Kim SY, Myers TR, Moro PL, Oduyebo T, Panagiotakopoulos L et al. Preliminary Findings of mRNA Covid-19 Vaccine Safety in Pregnant Persons. N Engl J Med. 2021. doi: 10.1056/NEJMoa2104983.

28. Zauche LH, Wallace B, Smoots AN, Olson CK, Oduyebo T, Kim SY et al. Receipt of mRNA Covid-19 Vaccines and Risk of Spontaneous Abortion. New England Journal of Medicine. 2021. doi: 10.1056/NEJMc2113891.

29. Kharbanda EO, Haapala J, DeSilva M, Vazquez-Benitez G, Vesco KK, Naleway AL et al. Spontaneous Abortion Following COVID-19 Vaccination During Pregnancy. JAMA. 2021;326:1629-31. doi: 10.1001/jama.2021.15494.

30. Dagan N, Barda N, Biron-Shental T, Makov-Assif M, Key C, Kohane IS et al. Effectiveness of the BNT162b2 mRNA COVID-19 vaccine in pregnancy. Nature Medicine. 2021;27:1693-5. doi: 10.1038/s41591-021-01490-8.

31. Halasa NB, Olson SM, Staat MA, Newhams MM, Price AM, Pannaraj PS et al. Maternal Vaccination and Risk of Hospitalization for Covid-19 among Infants. New England Journal of Medicine. 2022;387:109-19. doi: 10.1056/NEJMoa2204399.

32. Perl SH, Uzan-Yulzari A, Klainer H, Asiskovich L, Youngster M, Rinott E et al. SARS-CoV-2-Specific Antibodies in Breast Milk After COVID-19 Vaccination of Breastfeeding Women. JAMA. 2021;325:2013-4. doi: 10.1001/jama.2021.5782.

33. WHO. Interim recommendations for an extended primary series with an additional vaccine dose for COVID-19 vaccination in immunocompromised persons. 2021 (https://www.who.int/publications/i/item/WHO-2019-nCoV-vaccines-SAGE_recommendation-immunocompromised-persons.

34. Hall VG, Ferreira VH, Ku T, Ierullo M, Majchrzak-Kita B, Chaparro C et al. Randomized Trial of a Third Dose of mRNA-1273 Vaccine in Transplant Recipients. N Engl J Med. 2021;385:1244-6. doi: 10.1056/NEJMc2111462.

35. Organization. WH. Interim statement on decision-making considerations for the use of variant updated COVID-19 vaccines. 2022 (https://www.who.int/news/item/17-06-2022-interim-statement-on-decision-making-considerations-for-the-use-of-variant-updated-covid-19-vaccines.

36. Organization WH. Interim statement on the composition of current COVID-19 vaccine. 2022 (https://www.who.int/news/item/17-06-2022-interim-statement-on--the-composition-of-current-COVID-19-vaccines.

37. WHO, UNICEF, UNESCO. Considerations for school-related public health measures in the context of COVID-19: annex to considerations in adjusting public health and social measures in the context of COVID-19, 14 September 2020. Geneva: World Health Organization; 2020 (https://apps.who.int/iris/handle/10665/334294.

38. Brighton Collaboration Draft Myocarditis Definition (Version_1.4.2_30.May.2021). (https://brightoncollaboration.us/myocarditis-case-definition-update/, accessed 7 June 2021).

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.

© World Health Organization 2022. Some rights reserved. This work is available under the CC BY-NC-SA 3.0 IGO licence.

WHO reference number: WHO/2019-nCoV/vaccines/SAGE_recommendation//BNT162b2/2022.2