

# Interim recommendations for use of the Moderna mRNA-1273 vaccine against COVID-19

Interim guidance

25 January 2021



## Background

This interim guidance has been developed on the basis of the advice issued by the Strategic Advisory Group of Experts on Immunization (SAGE) at its extraordinary meeting on 21 January 2021 [1].

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 summarised in the Background document on mRNA-1273 vaccine (Moderna) against COVID-19 and the Background paper on Covid-19 disease and vaccines. Both of these documents are available on the SAGE Covid-19 webpage: <https://www.who.int/groups/strategic-advisory-group-of-experts-on-immunization/covid-19-materials>.

## Methods

SAGE applies the principles of evidence-based medicine and has set in place a thorough methodological process for issuing and updating recommendations [2]. A detailed description of the methodological processes as they apply to COVID-19 vaccines can be found in the SAGE evidence framework for COVID-19 vaccines. This framework contains guidance on considering data emerging from clinical trials in relation to the issuance of vaccine-specific evidence-based recommendations [3].

## Goal and strategy for the use of the Moderna mRNA-1273 vaccine against COVID-19

The COVID-19 pandemic has caused significant morbidity and mortality throughout the world, as well as major social, educational and economic disruptions. There is an urgent global need for effective and safe vaccines and to make them available at scale and equitably across all countries.

The mRNA-1273 vaccine against COVID-19 developed by Moderna (Moderna COVID-19 vaccine) has been shown to have an efficacy of 94.1%, based on a median follow-up of two months. High efficacy was maintained across all age groups (above 18 years), and was not affected by sex or ethnicity. The data reviewed by WHO at this time support the conclusion that the known and potential benefits of mRNA-1273 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 [4] and the WHO Values Framework (5) as guidance for their prioritization of target groups. When 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. Protecting high-risk health workers has a threefold purpose: (i) to protect the individual health workers; (ii) to protect critical essential services during the COVID-19 pandemic, and (iii) to prevent onward transmission to vulnerable people. Protecting older people will have the greatest public health impact in terms of reducing the number of deaths. As more vaccine becomes available, additional priority groups should be vaccinated as outlined in the WHO Prioritization Roadmap [4], taking into account national epidemiological data and other relevant considerations.

**Intended use**

Persons aged 18 years and above.

**Administration**

The recommended schedule is two doses (100 µg, 0.5 ml each) given intramuscularly into the deltoid muscle. An interval of 28 days between doses is recommended. If the second dose is inadvertently administered less than 28 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. It is currently recommended that individuals receive no more than two doses in total.

**Considerations for modifications to vaccine dose schedules**

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. This is based on the observation that efficacy has been shown to be 91.9%, starting 14 days after the first dose, with a median follow-up time of 28 days. There appears to be protection against COVID-19 disease following one dose; however, there is insufficient information about longer-term protection beyond 28 days after a single dose, as most trial participants received two doses. It is of note that neutralizing antibody responses were modest after the first dose and increased substantially after the second dose.

Countries experiencing such exceptional circumstances may consider delaying the administration of the second dose as a pragmatic approach to maximizing the number of individuals benefiting from a first dose while vaccine supply continues to increase. WHO's recommendation at present is that, if judged necessary, the interval between doses may be extended to 42 days. The evidence base for this extension is not strong, but this was the longest interval for any participants in the primary efficacy analyses of the phase 3 trial, though the great majority received the second dose after a shorter interval [6]. It is anticipated that additional data on extending the interval will become available shortly from use of the vaccine in public health vaccination programmes. This recommendation will be updated if required in the light of these data. Countries should ensure that any programme adjustments to dose intervals do not affect the likelihood of receiving the second dose of the same vaccine.

WHO does not recommend halving the dose to 50 µg until supporting evidence is available.

**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 booster doses will be evaluated as further data accumulate.

**Interchangeability with other vaccines**

No data are available on the interchangeability of this vaccine with other mRNA vaccines or other COVID-19 vaccine platforms. 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. Recommendations may be updated as further information becomes available on interchangeability.

**Co-administration with other vaccines**

There should be a minimum interval of 14 days between administration of this vaccine and any other vaccine, 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. mRNA-1273 vaccine should not be administered to individuals with a history of anaphylaxis to polyethylene glycol (PEG), a component of the vaccine. If anaphylaxis occurs after the first dose, a second dose of mRNA-1273 vaccine or of mRNA-BNT162b2 (Pfizer) 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 considered as a precaution but not a contraindication to vaccination. For such persons, a risk assessment should be conducted by a health professional with specialist expertise in allergic disorders. Such individuals may still receive vaccination. It remains uncertain if there is an increased risk of anaphylaxis, but they should be counselled 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 should not receive additional doses, unless recommended after review by a health professional with specialist expertise. For the purposes of this guidance, an immediate non-anaphylactic allergic reaction is defined as any signs or symptoms, such as urticaria, angioedema or respiratory symptoms without any other symptoms (cough, wheezing, stridor), that occur within 4 hours of administration. However, subject to individual risk–benefit assessment, mRNA-1273 could be provided under close medical supervision if it is the only available option 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 mRNA-1273 vaccine should be administered only in settings where anaphylaxis can be treated. Until more data and insights are available with regard to anaphylaxis after mRNA-1273 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 precaution. 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 mRNA-1273 does not contain eggs or gelatine, there is no contraindication or precaution to vaccination for persons with allergies to any food substances.

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

## Vaccination of specific populations

### Populations for which supportive data are available from phase 2/3 clinical trials

#### 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 18). Vaccination is recommended for older persons.

#### Persons with comorbidities

Certain comorbidities have been identified as increasing the risk of severe COVID-19 disease and death. The phase 3 clinical trial 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 the phase 3 clinical trial included chronic lung disease, significant cardiac disease, severe obesity, diabetes, liver disease and human immunodeficiency virus (HIV) infection. Vaccination is recommended for persons with such comorbidities that have been identified as increasing the risk of severe COVID-19.

### Populations for which limited or no data exist from the phase 3 clinical trial

#### Extremely frail older persons and persons above the age of 95

Extremely frail older persons and persons above the age of 95 years were not included in the clinical trials. However, 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. Vaccination is recommended for older persons without an upper age limit. For very frail older persons with a life expectancy anticipated to be less than 3 months, an individual risk–benefit assessment will need to be conducted.

### **Children and adolescents below the age of 18 years**

There are currently no efficacy or safety data for children or adolescents below the age of 18 years. Until such data are available, individuals below 18 years of age should not be vaccinated with this vaccine.

### **Pregnant women**

Pregnant women are at higher risk of severe COVID-19 compared with women of childbearing age who are not pregnant, and COVID-19 has been associated with an increased risk of preterm birth. The available data on mRNA-1273 vaccination of pregnant women are insufficient to assess vaccine efficacy or vaccine-associated risks in pregnancy. However, it should be noted that the mRNA-1273 vaccine is not a live virus vaccine, and the mRNA does not enter the nucleus of the cell and is degraded quickly.

Developmental and reproductive toxicology (DART) studies in animals have not shown harmful effects in pregnancy. Further studies are planned in pregnant women in the coming months. As data from these studies become available, recommendations on vaccination will be updated accordingly. In the interim, WHO recommends not to use mRNA-1273 in pregnancy, unless the benefit of vaccinating a pregnant woman outweighs the potential vaccine risks, such as in health workers at high risk of exposure and pregnant women with comorbidities placing them in a high-risk group for severe COVID-19. Information and, if possible, counselling on the lack of safety and efficacy data for pregnant women should be provided.

WHO does not recommend pregnancy testing prior to vaccination. WHO does not recommend delaying pregnancy following vaccination.

### **Lactating women**

Breastfeeding offers substantial health benefits to lactating women and their breastfed children. Vaccine efficacy is expected to be similar in lactating women as in other adults. However, there are no data on the safety of COVID-19 vaccines in lactating women or on the effects of mRNA vaccines on breastfed children. As the mRNA-1273 vaccine 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, a lactating woman who is part of a group recommended for vaccination, e.g. health workers, should be offered vaccination on an equivalent basis. WHO does not recommend discontinuing breastfeeding after vaccination.

### **Persons living with HIV**

Persons living with HIV may be at higher risk of severe COVID-19. Among the phase 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 with autoimmune conditions**

No data are currently available on the safety and efficacy of mRNA-1273 in persons with autoimmune conditions, although these persons were eligible for enrolment in the clinical trials. Persons with autoimmune conditions who have no contraindications to vaccination may be vaccinated.

**Persons with a history of Bell's palsy**

Cases of Bell's palsy were reported following vaccination in participants in the manufacturer's clinical trial. However, there is currently no conclusive evidence that these cases were causally related to vaccination. Post-authorization safety surveillance will be important to assess any possible causal association. In the absence of such evidence, persons with a history of Bell's palsy may receive mRNA-1273 unless they have a contraindication to vaccination.

**Persons who have previously had SARS-CoV-2 infection**

Vaccination may 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. Available data from the phase 3 trials indicate that mRNA-1273 is safe in people with evidence of prior SARS-CoV-2 infection. The added protection of vaccinating previously infected individuals is yet to be established. Despite the potential for reinfection, currently available data indicate that symptomatic reinfection within 6 months after an initial infection is rare. Thus, persons with PCR-confirmed SARS-CoV-2 infection in the preceding 6 months may choose to delay vaccination until near the end of this period. 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**

Vaccination of persons with acute COVID-19 should be deferred until they have recovered from acute illness and the criteria for discontinuation of isolation have been met.

**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.

In the current period of very limited vaccine supply, preferential vaccination of international travellers would counter the principle of equity. Because of this and the lack of evidence on whether vaccination reduces the risk of transmission, WHO currently does not recommend COVID-19 vaccination of travellers (unless they are also part of a high-risk group or in epidemiological settings identified in the WHO Prioritization Roadmap [4]). As vaccine supply increases, these recommendations will be revisited.

## 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 the mRNA-1273 vaccine, 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 mRNA-1273 vaccination.

### Role of vaccines among other preventive measures

As there is not yet any evidence of an effect of the vaccine 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 in particular settings. 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 is assessed.

### 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: (i) culturally acceptable and linguistically accessible communications regarding COVID-19 vaccination made freely available; (ii) active community engagement and involvement of community opinion leaders and trusted voices to improve awareness and understanding of such communications, and (iii) inclusion of diverse and affected stakeholder opinions in decision-making. Such efforts are especially important in subpopulations who may be unfamiliar with or distrustful of health care systems and immunization.

### Vaccination logistics

The mRNA-1273 COVID-19 vaccine is provided as a frozen suspension at  $-25^{\circ}\text{C}$  to  $-15^{\circ}\text{C}$  in a multidose vial containing 10 doses. The vaccine must be thawed prior to administration. After thawing, 10 doses (0.5 ml each) can be withdrawn from each vial. Vials can be stored refrigerated at  $2-8^{\circ}\text{C}$  for up to 30 days prior to withdrawal of the first dose. Unopened vials may be stored for up to 12 hours in cool storage or at room temperature ( $8-25^{\circ}\text{C}$ ). After the first dose has been withdrawn, the vial should be held between  $2^{\circ}\text{C}$  and  $25^{\circ}\text{C}$  and discarded after 6 hours.

When assessing the feasibility of deploying the mRNA-1273 vaccine, immunization programmes should consider the cold-chain requirements. Conditions must be met to avoid exposure of vials to sunlight and ultraviolet light.

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

When scheduling vaccination for occupational groups, e.g. health workers, consideration should be given to the reactogenicity profile of mRNA-1273 vaccine observed in clinical trials, occasionally leading to time off work in the 24-48 hours following vaccination.

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 cold-chain storage and the need to be able to provide treatment for anaphylaxis).



## Recommendations on addressing current knowledge gaps through further surveillance and research

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

- **Safety surveillance and monitoring**
  - serious adverse events, anaphylaxis and other serious allergic reactions, Bell's palsy, cases of multisystem inflammatory syndrome following vaccination, cases of COVID-19 following vaccination that result in hospitalization or death.
- **Vaccine effectiveness**
  - vaccine effectiveness over time and whether protection can be prolonged by booster doses;
  - studies to investigate whether this vaccine reduces SARS-CoV-2 transmission and viral shedding;
  - assessment and reporting of vaccination failures and virus sequence information.
- **Subpopulations**
  - prospective studies on the safety of mRNA-1273 vaccine in pregnant and lactating women;
  - randomized controlled trials on efficacy and safety of vaccination in children below the age of 18 years;
  - 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;
  - stability of vaccine under alternative cold-chain distribution and storage conditions;
  - effectiveness of the proposed strategies for the prevention and management of anaphylactic reactions;
  - interchangeability and “mix and match” studies within and across COVID-19 vaccine platforms.
- **Other considerations**
  - global surveillance of virus evolution and the impact of virus mutants on vaccine effectiveness, to support update of vaccines if needed;
  - head-to-head studies with other vaccines on extent and duration of immunity using standardized neutralization, T-cell and mucosal immunity assays.

## References

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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.

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