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

Interim guidance
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World Health Organization

Background[1]

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)*, was updated at another extraordinary SAGE meeting on 27 May 2021 *(2)*, and further updated on 19 November 2021 and 23 February 2022.

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 here is based on the evidence summarized in the Background document on the Moderna mRNA-1273 vaccine against COVID-19 *(3)*.

Annexes *(4)* 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-1273 vaccine, manufactured by Moderna. The vaccine is also known as COVID-19 Vaccine Moderna. In some countries, the vaccine is known under the trade name of "Spikevax". In the subsequent text the vaccine will be referred to as mRNA-1273. On 30 April 2021, mRNA-1273 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 and updating recommendations *(5)*. 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 *(6)*. This framework contains guidance

[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.

on considering data emerging from clinical trials in relation to the issuance of vaccine-specific evidence-based recommendations.

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.

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 *(7)* and the WHO Values Framework *(8)* as guidance for their prioritization of target groups. As long as vaccine supplies are very limited (see WHO Prioritization Roadmap), the Roadmap recommends that priority of vaccine use be given initially to health workers and older people with and without comorbidities. As more vaccine becomes available, additional priority-use groups should be vaccinated, as outlined in the WHO Prioritization Roadmap *(7)*, taking into account national epidemiological data and other relevant considerations.

Vaccine performance

The initial results of the phase 3 trial in persons aged ≥18 years, conducted in 2020, showed an efficacy in preventing COVID-19 of any severity of COVID-19 of 94% *(9)*. After a median follow-up of 5.3 months at the end of the blinded phase of the trial, vaccine efficacy in preventing COVID-19 was 93% (95% confidence interval [CI]: 91–95%); in preventing severe disease, efficacy was 98% (95% CI: 93–100%); and in preventing asymptomatic infection, 63% (95% CI: 57–69%) *(10)*. Antibody levels declined but remained high throughout this period. The geometric mean titre was lower in those aged ≥56 years than in trial participants aged 18–55 years *(11)*. Several studies have shown that the mRNA-1273 vaccine is effective in preventing symptomatic laboratory confirmed COVID-19 (pooled effectiveness = 89.2% [95% CI: 82.0–98.6%]); hospitalizations (pooled effectiveness = 94.8% [95% CI: 93.1–96.1%]); and deaths (pooled effectiveness = 93.8% [95% CI: 91.5–95.4%]) *(12)*.

Interval between dose 1 and dose 2

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 *(13)*. An inter-dose interval of 8 weeks or longer was associated with a lower risk of myocarditis compared to the 4-week interval *(14)*.

Duration of protection and booster doses

Vaccine effectiveness against any PCR-confirmed infection in a study in the Czech Republic declined from 90% (95% CI: 89–91%) at 0–2 months, to 65% (95% CI: 63–67%) at 7–8 months after receipt of the second dose. Vaccine effectiveness against hospital admissions and deaths declined at significantly lower rates: at around 15% and 10% respectively during the first 6–8 months after dose 2. The administration of a booster dose returned protection to a rate equal to, or above, the estimates in the first 2 months after dose 2 *(15)*.

Administration of a booster dose of 50 µg at least 6 months after the 100 µg mRNA-1273 primary series increased neutralizing antibody titres by 13-fold, 1 month after vaccination compared to pre-booster levels *(16)*. The reactogenicity and adverse event profile observed after the booster dose was generally similar to that observed following dose 2 of the initial 2-dose regimen, which suggests no potentiation of reactogenicity or any new safety signals arising from administration of a third dose.

Variants of concern:

Delta: A large, post-licensure study conducted in southern California in the United States of America, showed that the effectiveness of a 2-dose regimen of mRNA-1273 against Delta infection was 79.8% (95% CI: 67.4–87.5%) and waned slowly over 9–12 months to 57.5% (95% CI: 50.4–63.6%), while the effectiveness following a booster dose was high (94.0% [(95% CI: 92.3–95.4%]) and durable through ~6 months *(17)*. The effectiveness of 2 and 3 doses against hospitalization with Delta were both more than 98%. A post-introduction observational study among 3689 adults aged ≥18 years who were hospitalized in the United States during 11 March to 15 August, 2021, which included the Delta variant surge, showed vaccine effectiveness against hospitalizations of 93% (95% CI: 91–95%) *(18)*. The effectiveness against mild infections in health workers was 91% (95% CI: 81–96%) during the months preceding the emergence of the Delta variant and declined to 66% (95% CI: 26–84%) when the Delta variant became the predominant virus strain, which could reflect waning immunity or reduced effectiveness because of Delta variant prevalence, or both *(19)*.

Omicron: A large, post-licensure study conducted in southern California during December 2021, when Omicron surged, showed that the effectiveness of a 2-dose regimen of mRNA-1273 against Omicron infection was 42.8% (95% CI: 33.8–50.7%) and quickly declined from day 91 to the end of the observation period (>270 days). Vaccine effectiveness against infection after a booster dose rose to 67.9% (95% CI: 65.8–69.9%). The effectiveness of 2 and 3 doses against hospitalization with Omicron was 74.8% (95% CI: 2.4–93.5%) and 99.7% (95% CI: 82.2–100.0%), respectively *(17)*. In the United Kingdom, vaccine effectiveness against *symptomatic* Omicron variant infections after 2 doses of mRNA-1273 declined from around 65% to 70%, 2–4 weeks after dose 2, to around 10% by 25 weeks after dose 2. In the period 2–4 weeks after a booster dose of mRNA-1273, effectiveness ranged from around 60% to 75%, dropping to 25% to 40%, 15 or more weeks after the booster dose *(20)*.

Children and adolescents:

A phase 2/3 trial of mRNA-1273 in adolescents aged 12–17 years (2489 vaccine recipients and 1243 placebo recipients) showed that the vaccine was well tolerated, immunogenic, and efficacious, leading to an extension of the previous age indication from 18 years down to 12 years in some countries *(21)*. Cases of symptomatic COVID-19 were few in the trial, but vaccine efficacy using a modified case definition was 93% (95% CI: 48–100%). Immunogenicity and the reactogenicity profiles were similar to those previously shown for young adults *(21)*.

A phase 2 study of the vaccine in children aged 6 months to 11 years was recently completed, but results have not yet been published.

Intended use according to the vaccine label

Persons aged 12 years and older.

WHO recommendation for use

For prioritization by age and other considerations, please see the WHO Prioritization Roadmap*(7)*.

Administration

The schedule, as per manufacturer specification, is 2 doses (100 µg, 0.5 ml each), given intramuscularly into the deltoid muscle, 4 weeks apart.

WHO recommends that the second dose should be administered 4–8 weeks after the first dose; an interval of 8 weeks between doses is preferred as this interval is associated with higher vaccine effectiveness and lower risk of myocarditis.

However, these considerations should be balanced against the need to achieve quick protection, in particular for high risk groups, in settings of high transmission intensity and circulating variants of concern.

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 in that population. The objective of a booster dose is to restore vaccine effectiveness.

In accordance with the WHO Prioritization Roadmap, a booster dose (*50 µg at 0.25 ml, i.e. half the dose used in the primary series*) is recommended for the highest and high priority-use groups (i.e. older adults, health workers, persons with comorbidities), administered 4–6 months after completion of the primary series. Countries with moderate-to-high rates of primary series coverage in higher priority-use groups should usually prioritize available resources to first achieve high booster dose coverage rates in higher priority-use groups before offering vaccine doses to 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.

Interchangeability with doses of other COVID-19 vaccines (heterologous schedules)

WHO supports a flexible approach to using different EUL COVID-19 vaccine products for different doses (heterologous schedule), and considers a total of 2 doses of any combination of EUL COVID-19 vaccines (e.g. 1 dose of mRNA-1273 vaccine, and 1 dose of another EUL COVID-19 vaccine) to be a complete primary series. Heterologous vaccination (including boosters) 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.

Heterologous booster

A 50 µg dose of mRNA-1273 vaccine may be used as a booster dose following a completed primary series using any other EUL COVID-19 vaccine platform *(22)*.

Co-administration with vaccines other vaccines

Evidence on co-administration of mRNA-1273 vaccine with inactivated influenza vaccine suggests that neither adverse events and reactogenicity nor immunogenicity are increased as a result of co-administration *(23)*. The mRNA-1273 vaccine can be co-administered with inactivated influenza vaccines. Different arms for injection should be used when both vaccines are delivered during the same visit. Continued pharmacovigilance monitoring is recommended.

No co-administration data are available for other live or inactivated vaccines. There should be a minimum interval of 14 days between administration of this vaccine and all other vaccines except influenza vaccine. This recommendation will be updated as data on co-administration with other vaccines, including live vaccines, become available.

[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.

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 considered as a precaution but 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, 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.

In the United States anaphylaxis occurred at a rate of 2.5 cases per million mRNA-1273 doses administered *(24)*. As a small number of anaphylactic reactions have also been reported in vaccinees without a history of anaphylaxis, WHO recommends that mRNA-1273 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.

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 gelatin, 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 18–39 years (with the highest risk in males aged 18–24 years), and highest within a few days after dose 2. In the United States, out of 64 million total doses (doses 1 and 2) of mRNA-1273 vaccine administered to persons aged ≥18 years (as of 13 January 2022), 359 cases of myocarditis were reported during 0–7 days following vaccination that met the case CDC working definition *(25)*, with an estimated 32.2 excess cases reported per 1 million second doses. Most cases of myocarditis resolve without treatment but no long-term follow-up data are yet available.

Data from the United Kingdom and Canada of mRNA vaccines suggest that rates of myocarditis/pericarditis are lower with an extended interval between the first and second dose of mRNA vaccine primary series *(26)*. According to Moderna`s global safety database, rates of myocarditis/ myopericarditis are lower following the third dose compared to the second dose, and lower among adolescents than young adults.

In October 2021, the Global Advisory Committee on Vaccine Safety (GACVS) COVID-19 subcommittee concluded that mRNA COVID-19 vaccines have clear benefits in all age groups in reducing hospitalizations and deaths due to COVID-19. The favourable benefit–risk increases with increasing age. Countries should consider the individual and population benefits of immunization relevant to their epidemiological and social context when developing their COVID-19 immunization policies and programmes *(27)*.

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.

Development of myocarditis or pericarditis after any dose of mRNA-1273 vaccine is considered a precaution to subsequent doses of COVID-19 vaccine. Until additional safety data are available, individuals who develop myocarditis or pericarditis after a dose of mRNA-1273 vaccine should generally not receive additional doses of any COVID-19 vaccine, unless recommended after review by a health professional with specialist expertise.

In persons with an acute febrile illness (body temperature over 38.5 ºC) vaccination should be postponed until they are afebrile.

Vaccination of specific populations

Older persons

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. Post-introduction vaccine effectiveness studies have shown high effectiveness and good safety profiles in older persons. Vaccination is recommended for older persons without an upper age limit.

Persons with comorbidities

Vaccination is recommended for persons with such comorbidities that have been identified as increasing the risk of severe COVID-19, in line with the WHO Prioritization Roadmap *(7)*.

Children and adolescents below the age of 18 years

Children aged 12–17 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 severe. Some children develop multisystem inflammatory syndrome, even after mild or asymptomatic infection. In accordance with the WHO Prioritization Roadmap, WHO recommends that countries could consider using mRNA-1273 in children aged 12–17 years, only when high vaccine coverage (primary series and booster doses) has been achieved in the higher priority-use groups *(23)*.

A phase 2 trial for children aged 6–12 years was recently completed and is currently under review by regulatory authorities. Until this age indication has received emergency use authorization or listing, children aged <12 years should not be routinely vaccinated with the mRNA-1273 vaccine.

Pregnant women

Pregnant women with COVID-19 are at higher risk of developing severe disease, with increased risk of intensive care unit admission and invasive ventilation, compared to non-pregnant women of reproductive age. COVID-19 in pregnancy is also associated with an increased risk of preterm birth, and of neonates requiring neonatal intensive care. It may also be associated with an increased risk of maternal mortality *(28-30)*. Pregnant women who are older (aged ≥35 years), 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 mRNA-1273 have not shown harmful effects in pregnant animals and their offspring. Clinical trial data on safety and immunogenicity in pregnancy are limited. However, a growing body of post-introduction vaccine pharmacovigilance data has not identified any acute safety problems, with obstetric outcomes including spontaneous abortion and neonatal outcomes similar to reported background rates *(31-33)*. Based on previous experience with other vaccine use during pregnancy, the effectiveness of mRNA-1273 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 neonatal as well as maternal protection *(34-36)*.

WHO recommends the use of mRNA-1273 in pregnant individuals. Pregnant individuals should be informed that they can receive the vaccine and provided with information about the increased risks of COVID-19 in pregnancy, the likely benefits of vaccination, and the current limitations of safety data. WHO does not recommend pregnancy testing prior to vaccination. WHO does not recommend delaying pregnancy or terminating pregnancy because of vaccination.

Breastfeeding persons

Breastfeeding offers substantial health benefits to breastfeeding women and their breastfed children. Vaccine effectiveness is expected to be similar in breastfeeding women as in other adults. Data are not available on the potential benefits or risks of the vaccine to breastfed children. However, as mRNA-1273 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. Several small studies show that mRNA vaccine-elicited antibodies are found in breast milk, which might help protect breastfeeding infants. On the basis of these considerations, WHO recommends the use of mRNA-1273 in breastfeeding women as in non-breastfeeding individuals. WHO does not recommend discontinuing breastfeeding because of vaccination.

Moderately and severely immunocompromised persons, including persons living with HIV with CD4 cell count of <200 cells/µl

Moderately and severely immunocompromised persons (ICPs) are at higher risk of severe COVID-19, regardless of age, although increasing age remains an important co-factor. For purposes of this interim recommendation, moderately and severely immunocompromised persons include those with active cancer, transplant recipients, immunodeficiency, and active treatment with immunosuppressives. It also includes people living with HIV with a current CD4 cell count of <200 cells/µl, evidence of an opportunistic infection, not on HIV treatment, and/or with a detectable viral load (i.e. advanced HIV disease).[3] For more details, see the WHO Interim recommendations for an extended primary vaccination series in immunocompromised persons *(37)*.

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 *(37)*. The emerging evidence suggests that an additional dose included in an extended primary series enhances immune responses in some ICPs *(38)*. Reactogenicity data of an additional (third) dose given to ICPs, where reported, have generally been similar to those observed for the standard

[3] **Active cancer:** Active immunosuppressive treatment for solid tumour or hematologic malignancy (including leukaemia, lymphoma, and myeloma), or within 12 months of ending such treatment. **Transplant recipients**: Receipt of solid organ transplant and taking immunosuppressive therapy; receipt of stem cell transplant (within 2 years of transplantation, or taking immunosuppressive therapy). **Immunodeficiency:** Severe primary immunodeficiency; chronic dialysis. **HIV** 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

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) full 100 µg dose for ICPs. Given the emergence of the Omicron variant, a booster (fourth) 50 µg dose 3–6 months after the additional (third) dose should be considered.

Available evidence *(37)* 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. 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 course of the disease, and should be discussed with the treating physician.

Information and, where possible, counselling about the limitations around the data on administration of an additional dose to ICPs should be provided to inform individual benefit–risk assessment.

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

Persons living with HIV who are stable on Antiretroviral Therapy

Persons living with HIV may be at higher risk of severe COVID-19. 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.

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.