Background document on the mRNA-1273 vaccine (Moderna) against COVID-19

Background document to the WHO Interim recommendations for use of the mRNA-1273 vaccine (Moderna)

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World Health Organization

Contents

Background

This background document has been prepared by the Strategic Advisory Group of Experts (SAGE) on Immunization Working Group on COVID-19 Vaccines to inform the discussions of SAGE at its 21 January 2021 extraordinary meeting (1), which resulted in the issuance of the 25 January 2021 WHO Interim recommendations for use of the Moderna mRNA-1273 vaccine against COVID-19.

Both recommendations and background document are available on the SAGE Covid-19 webpage: https://www.who.int/groups/strategic-advisory-group-of-experts-on-immunization/covid-19-materials.

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.

Methods

SAGE applies the principles of evidence-based medicine and has set in place a thorough methodological process for issuing or updating recommendations (2). 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 (3).

General considerations on mRNA vaccines

The advantage of RNA-based vaccines is their potential for rapid development and reduced side effects. mRNA-based vaccines avoid the risk of integration with the host cell genome and are able to produce pure viral protein. mRNA is transiently expressed, therefore allowing protein to be made within the cell. . Lipid nanoparticle (LNP)-formulated mRNA vaccine technology allows the delivery of precise genetic information together with an adjuvant effect to antigen-presenting cells. It is molecularly well defined, free from materials of animal origin, and synthesized by an efficient, cell-free in vitro transcription process from DNA templates. The technology associated with this vaccine is also capable of bypassing time-consuming standardization processes, thus speeding up its commercial production. The fast and highly scalable mRNA manufacturing and LNP formulation processes enable rapid production of many vaccine doses, making it suitable for rapid vaccine development and pandemic vaccine supply.

Characteristics of COVID-19 vaccine mRNA-1273 (Moderna)

Moderna's mRNA-1273 COVID-19 vaccine is an LNP-encapsulated mRNA vaccine expressing the prefusion-stabilized spike glycoprotein. It was developed by Moderna and the Vaccine Research Center at the National Institute of Allergy and Infectious Diseases (NIAID) in the USA.

Vaccine composition and storage

The vaccine contains a synthetic mRNA (single-stranded, 5'-capped) encoding the prefusion-stabilized spike glycoprotein (S) of SARS-CoV-2 virus. The vaccine also contains the following ingredients: lipids (SM-102, 1,2-dimyristoyl-rac-glycero-3-methoxypolyethylene glycol-2000 (PEG2000-DMG), cholesterol, and 1,2-distearoyl-sn-glycero-3-phosphocholine (DSPC)), tromethamine, tromethamine hydrochloride, acetic acid, sodium acetate, and sucrose. The Moderna COVID-19 vaccine is supplied as a frozen suspension, at between –25 ºC and –15 ºC (–13 ºF and 5 ºF), in a multidose vial containing 10 doses.

The vaccine is a white to off-white, sterile, preservative-free frozen suspension for intramuscular injection. The vaccine must be thawed prior to administration. After thawing, a maximum of 10 doses (0.5 ml each) can be withdrawn from each vial. Vials can be stored refrigerated at 2–8 °C (36–46 °F) for up to 30 days prior to first use. Unopened vials may be stored at 8–25 °C (46–77 °F) for up to 12 hours. After the first dose has been withdrawn, the vial should be held at 2–25 °C (36–77 °F) and discarded after 6 hours.

Vaccine dosing

The Moderna COVID-19 vaccine, mRNA-1273 (100 µg), is administered intramuscularly as a series of two doses (0.5 ml each), given 28 days apart.

Efficacy of the Moderna mRNA-1273 COVID-19 vaccine

Trial population

The pivotal phase 3 registration trial of the vaccine was conducted in 99 centres across the United States of America and involved about 30 000 participants aged 18 years or older with no known history of SARS-CoV-2 infection, but whose location or circumstances put them at appreciable risk of acquiring COVID-19 (4). Participants were healthy or had stable pre-existing

medical conditions. In total, 25% (7512 of 30 351) were aged 65 years or over (mean age: 70.6 years; range: 65–95 years) and 16.7% (5065 of 30 351) were under 65 years and at risk of severe COVID-19 illness (mean age: 49.0 years; range: 18–64 years). The vaccine was administered in 2 doses separated by one month. The median age at vaccination was 51 years. Participants were randomized equally between vaccine and placebo groups. Women who were pregnant or breastfeeding were excluded. At entry to the trial, 2.2% of participants had serological or virological evidence of a past SARS-CoV-2 infection. Most were white (79%) and similar numbers of males and females were included. The median body mass index was 28.1. The primary analysis of the trial results was conducted when participants had been followed for a median of 64 days after the second vaccine dose; at that time, 61% had been followed for more than 56 days.

Efficacy against COVID-19

The primary endpoint was specified as efficacy against symptomatic COVID-19, starting 14 days after the second dose, among participants who were seronegative at trial entry. Efficacy was evaluated for those subjects who received the second dose 21-42 days after the first dose. There were 196 cases that met this definition, 11 in the vaccinated group and 185 in the placebo group. Vaccine efficacy (VE) was estimated as 94.1% (95% confidence interval (CI) 89.3–96.8%).

Analyses were also conducted including all cases from the time of the first dose. Adjusting for person–years, the VE and 95% CI are: from dose 1 to dose 2: 84.7% (65.8–94.2%); from dose 2 to 14 days after dose 2: 100% (78.6%, NE). There was no evidence of efficacy until approximately 14 days after the first dose.

In the period 14 or more days after the second vaccine dose, no significant variations in the estimates of vaccine efficacy were apparent when the primary analyses were stratified according to sex, age, race and ethnic group, or for those at high risk of severe COVID-9. In particular, among those aged 65 years or older there were 4 cases in the vaccinated group and 29 cases in the placebo group (VE 86.4%, 95% CI 61.4–95.2%), based on a stratified Cox model.

Efficacy against severe COVID-19

A total of 30 cases of severe COVID-19 occurred in trial participants 14 or more days after the second dose, all in the placebo group (VE=100%, 95% CI 86.9–100%; adjusting for person-years, the 95% CI is 87.0%, NE.

Summary

The vaccine was highly efficacious against laboratory-confirmed COVID-19 from 14 days after the second vaccine dose until the end of the follow-up period, which was, on average, about two months after the second dose. Evidence of efficacy emerged from about 12 days after the first vaccine dose. No evidence of variation in efficacy was found in the various subgroups that were analysed, including, importantly, those likely to be at higher risk of severe COVID-19, e.g. those over 65 years. The estimates of efficacy were very high. Efficacy against severe COVID-19 was also very high, with all 30 cases occurring 14 or more days after the second dose being in the placebo group.

Safety of the Moderna mRNA-1273 COVID-19 vaccine

In the phase 3 trial, safety data were collected from 30 351 participants who received at least one dose of the vaccine (n = 15 185) or placebo (n = 15 166). 87.9% of study participants were followed up for at least 28 days after dose 2, and the median follow-up time for all participants was 9 weeks after dose 2 (4).

The safety data supported a favorable safety profile. Reactogenicity symptoms, defined as solicited local injection site or systemic reactions during the seven days after vaccination, were frequent, mostly mild to moderate and short-lived after dosing for both adult age groups. Reactogenicity and adverse events (AEs) were generally milder and less frequent in participants in the older group (≥65 years of age) and tended to increase in frequency and severity after the second dose.

The vaccine's AE profile did not suggest any specific safety concerns. Severe adverse reactions occurred in 0.2–9.7% of participants, were more frequent after dose 2 than after dose 1, and were generally less frequent in older adults (≥65 years of age). The incidence rates of serious adverse events (SAEs), deaths, and discontinuations due to AEs were low and comparable for both the vaccine and placebo groups. There were no specific safety concerns identified in subgroup analyses by age, sex, race, ethnicity, medical comorbidities, or prior SARS-CoV-2 infection at enrolment. Of note, persons with a known history of COVID-19 were excluded from the trial. However, the trial collected nasopharyngeal swabs and serology on the day of enrollment and some persons were positive at that time based on those results, but had no symptoms.

Adverse events

Adverse events occurring within 28 days following each vaccination were reported by 23.9% (n = 3632) of participants who received the vaccine and 21.6% (n = 3277) of participants who received placebo. The most common adverse reactions in participants 18 years of age and older were pain at the injection site (92.0%), fatigue (70.0%), headache (64.7%), myalgia (61.5%), arthralgia (46.4%), chills (45.4%), nausea/vomiting (23.0%), axillary swelling/tenderness (19.8%), fever (15.5%),

swelling at the injection site (14.7%), and erythema at the injection site (10.0%). The median duration for pain was 2–3 days. The highest rates of pain were in participants aged 18–64 years after dose 2, with 90.1% reporting any pain and 4.6% reporting grade 3 pain. The median duration for fatigue in vaccine recipients was 2 days after any dose. The highest rates of fatigue were reported by participants aged 18–64 years after the second dose, with 67.6% reporting any fatigue, 10.6% reporting grade 3, and one participant reporting grade 4 (after dose 1).

Delayed localized injection site reaction with onset after 7 days was more frequent in the vaccine group than in the placebo group and mostly occurred after the first dose.

Adverse events of special interest (that would potentially require longer follow-up)

Lymphadenopathy-related events

Lymphadenopathy-related events were reported by 173 (1.1 %) vaccine recipients and 95 (0.63 %) placebo recipients. These events included lymphadenopathy (axillary swelling and tenderness of the vaccination arm), lymphadenitis, lymph node pain, vaccination-site lymphadenopathy and axillary mass. These were plausibly related to vaccination.

The median duration of lymphadenopathy following any dose was 1–2 days, and fewer than 1% reported grade 3 axillary swelling or tenderness. Lymphadenopathy was more frequently observed in participants aged 18–64 years after dose 2, with 16.0% reporting any severity lymphadenopathy and 0.4% reporting grade 3 lymphadenopathy.

Bell's palsy

There were three reports of Bell's palsy in the vaccine group and one in the placebo group. In the vaccine recipients, the events occurred 22, 28, and 32 days after dose 2. One event was a serious adverse event (reported as resolving), one case has resolved and one is ongoing. In the placebo group, the event occurred 17 days after dose 1. Causality assessment is confounded by predisposing factors in all the participants. The usual incidence of Bell`s palsy is 15–30 per 100 000 per year. The observed frequency of reported Bell's palsy in the vaccine group is consistent with the expected background rate in the general population. An association between COVID-19 and Bell's palsy has been reported. Currently available information on Bell's palsy is insufficient to determine a causal relationship with the vaccine. Surveillance for cases of Bell's palsy with deployment of the vaccine in larger populations is required. Bell`s palsy has been addressed in the manufacturer's risk management plan.

Hypersensitivity-related events

A total of 233 events (1.5%) occurred in the vaccine group and 166 events (1.1%) in the placebo group. The hypersensitivity-related events included injection site rash, injection site urticaria and maculopapular rash. There is a plausible relationship to vaccination of these events.

No anaphylactic or severe hypersensitivity reactions with close temporal relation to the vaccine were reported during the trial.

Serious adverse events

The frequency of serious adverse events was low (1.0% in the vaccine group and 1.0% in the placebo group), without meaningful imbalances between the two groups.

As of 3 December 2020, there had been 13 deaths in total, with 6 in the vaccine group and 7 in the placebo group. No causal relationship was determined.

The SAEs thought to be related to the vaccine included intractable nausea and vomiting in a 65-year-old one day after the second dose. Two subjects, who were 46 and 51 years old, reported facial swelling one and two days after the second dose, respectively. Both subjects had prior dermal fillers.

Special populations

Pregnancies

Women were screened for pregnancy prior to each vaccination and were excluded or discontinued from vaccination if there was a positive test. As of 2 December 2020, 13 pregnancies (6 in the vaccine group and 7 in the placebo group) had been reported.

The pregnancy outcomes in the placebo group included one spontaneous abortion and one elective abortion. The other outcomes are not known to date and the pregnant women are being followed.

A combined developmental and perinatal/postnatal reproductive toxicity study of the vaccine in rats concluded that the vaccine at a dose of 100 µg, given prior to mating and during gestation periods, did not have any adverse effects (including on female reproduction, fetal/embryonal development, or postnatal development).

Summary

The safety data supported a favourable safety profile. Reactogenicity was mostly mild to moderate, less frequent and severe in adults aged 65 years and over than in younger adults and generally more frequent after the second dose in both age groups. No safety concerns were identified in subgroup analyses by age, sex, race, ethnicity, comorbidities and health risks for severe COVID-19.

Delayed localized injection site reaction with onset after 7 days was more frequent in the vaccine group than in the placebo group and mostly seen after the first dose.

Lymphadenopathy-related events were more frequent in the vaccine group than the placebo group and were plausibly related to vaccination. Hypersensitivity-related events were more frequent in the vaccine group than the placebo group. No anaphylactic or severe hypersensitivity reactions with temporal relation to vaccination were reported during the trial. Three cases of Bell's palsy were reported in vaccine recipients, and one in placebo recipients. Although there is no clear basis upon which to conclude a causal relationship at this time, further surveillance for Bell's palsy is required as part of the risk management plan.

Reference

1. Extraordinary meeting of the Strategic Advisory Group of Experts on Immunization (SAGE) - 21 January 2021 (https://www.who.int/news-room/events/detail/2021/01/21/default-calendar/extraordinary-meeting-of-the-strategic-advisory-group-of-experts-on-immunization-(sage)---21-january-2021, accessed 29 January 2021).
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4. Baden LR, El Sahly HM, Essink B, Kotloff K, Frey S, Novak R et al. Efficacy and safety of the mRNA-1273 SARS-CoV-2 vaccine. N Engl J Med. 2020 Dec 30:NEJMoa2035389. doi: 10.1056/NEJMoa2035389. Epub ahead of print.

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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.

Annexes

Annexes 1–6 contain tables that summarize the grading of recommendations, assessment, development and evaluations (GRADE). Annexes 7–9 contain the SAGE evidence-to-recommendation framework tables (ETR tables). The ETR tables are based on the DECIDE Work Package 5: Strategies for communicating evidence to inform decisions about health system and public health interventions. Evidence to a recommendation (for use by a guideline panel) (www.decide-collaboration.eu/, accessed 11 January 2021).

Annex 1. GRADE table: Efficacy of mRNA-1273 COVID-19 vaccine in adults

Population : Adults (18–64 years)

Intervention: Two doses of mRNA-1273 vaccine

Comparison: Placebo/ no vaccination

Outcome : COVID-19 (PCR-confirmed)

What is the efficacy of two doses of mRNA-1273 vaccine compared with placebo in preventing PCR-confirmed COVID-19 in adults (18–64 years)?				
			Rating	Adjustment to rating
Quality Assessment	No. of studies/starting rating		1/ RCT(1, 2)	4
	Factors decreasing confidence	Limitation in study design[a]	Not serious[b]	0
		Inconsistency	Not serious	0
		Indirectness	Not serious	0
		Imprecision	Not serious	0
		Publication bias	Not serious	0
	Factors increasing confidence	Large effect	Not applicable	0
		Dose-response	Not applicable	0
		Antagonistic bias and confounding	Not applicable	0
	Final numerical rating of quality of evidence			4
Summary of findings	Statement on quality of evidence			Evidence supports a high level of confidence that the true effect lies close to that of the estimate of the effect on the health outcome (level 4, or ⊕⊕⊕⊕).
	Conclusion			We are very confident that 2 doses of mRNA-1273 vaccine are efficacious in preventing PCR-confirmed COVID-19 in adults (18–64 years).

References