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

DRAFT

Prepared by the Strategic Advisory Group of Experts (SAGE) on Immunization Working Group on COVID-19 vaccines

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Contents

General considerations on mRNA vaccines

The messenger ribonucleic acid (mRNA) vaccine platform has advantages as a pandemic-response strategy, given its efficiency in immunogen design and manufacturing. As mRNA is a non-infectious, non-integrating platform, there is no potential risk of infection or insertional mutagenesis. Additionally, mRNA is degraded by normal cellular processes. Efficient *in vivo* delivery can be achieved by formulating mRNA into carrier molecules, allowing rapid uptake and expression in the cytoplasm. mRNA is the minimal genetic vector; therefore, anti-vector immunity is avoided, and mRNA vaccines can be administered repeatedly. 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 of 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. Two mRNA vaccines have received Emergency Use Authorization, the BNT162b2 vaccine by BioNTech and Pfizer, and the COVID-19 vaccine (mRNA-1273) by Moderna.

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

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

Vaccine composition and storage

The vaccine contains a synthetic mRNA- single-stranded, 5'-capped messenger RNA-encoding the pre-fusion 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 provided as a frozen suspension [stored between -25º to -15ºC (-13º to 5ºF)] multi-dose 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 between 2° to 8°C (36° to 46°F) for up to 30 days prior to first use. Unopened vials may be stored between 8° to 25°C (46° to 77°F) for up to 12 hours. After the first dose has been withdrawn, the vial should be held between 2° to 25°C (36° to 77°F) and discarded after 6 hours.

Vaccine dosing

The Moderna COVID-19 Vaccine, mRNA-1273 (100µg) 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 Phase 3 pivotal registration trial of the vaccine was conducted at sites in 99 centres across the United States and involved in total about 30,000 participants aged 18 years or older with no known history of SARS-CoV-2 infection but whose locations or circumstances put them at appreciable risk of acquiring COVID-19 (1). Participants were healthy or had stable pre-existing medical conditions. In total, 25% (7512/30351) were aged 65 years or over (mean age: 70.6 years; range: 40-95 years) and 16.7% (5065/30351) participants were under 65 years and at risk of severe Covid-19 illness (mean age: 49.0 years; range: 18-79 years). The vaccine was administered in 2 doses separated by 28 days. The median age at vaccination was 51 years. Participants were randomised equally between vaccine and placebo groups. Women who were pregnant or breast-feeding were excluded. 2.2% of participants had serological or virological evidence of a past SARS-CoV-2 infection at entry to the trial. 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 and 61% had more than 56 days of follow-up.

Efficacy against Covid-19

The primary endpoint was specified as efficacy against symptomatic Covid-19 at least 14 days after the second dose among participants who were seronegative at trial entry. There were 196 cases who met this definition, with 11 cases in the vaccinated group and 185 in the placebo group with the estimate of vaccine efficacy (VE) being 94.1% (95% confidence interval (CI) 89.3% - 96.8%).

Analyses were also conducted including all cases from the time of the first dose. There was evidence of protection both between the first (14 days after receipt of dose 1) and receipt of the second doses (VE=84.8%, 95% CI 66.1% - 94.2% - 7 cases in vaccine group, 46 cases in placebo group) and between the second dose and 14 days after the second dose (VE=100%, 95% CI 78.6% - 100% - 0 cases in vaccine group, 19 cases in placebo group). More detailed analyses indicated that there was no evidence of efficacy until approx. 12 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 into 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%).

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 were in the placebo group (VE=100%, 95% CI 86.9% - 100%).

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 2 months

after the second dose. Evidence of efficacy emerged from about 12 days after the first vaccine dose. No evidence of variations in efficacy were found in the various subgroups that were analysed and, importantly, in subgroups of participants likely to be at higher risk of severe Covid-19, including 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 was collected from 30,351 participants ≥18 years of age, randomized 1:1 to vaccine or placebo, who received at least one dose of the vaccine (n=15,185) or placebo (n=15,166). 87.9% of study participants had at least 28 days of follow-up after Dose 2, and the median follow-up time for all participants was 9 weeks (>2 months) after Dose 2 (1).

The safety data supported a favorable safety profile. Reactogenicity symptoms, defined as solicited local injection site or systemic reactions during the 7 days after vaccination, were frequent and 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) compared with the younger group (18 to <65 years of age) and tended to increase after the second dose.

The vaccine's AE profile did not suggest any specific safety concerns. Severe adverse reactions occurred in 0.2% to 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) as compared to younger adults. The incidence 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 enrollment.

Adverse Events

Adverse events, that occurred within 28 days following each vaccination, were reported by 23.9% (n=3,632) of participants who received the vaccine and 21.6% (n=3,277) 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 durations for pain were 2-3 days. The highest rates of pain were in participants 18 to <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 18 to 64 years after the second dose, with 67.6% reporting any fatigue, 10.6% reporting Grade 3, and 1 participant reporting Grade 4 (after Dose 1).

Delayed localized injection site reaction with onset after 7 days was more frequent in the vaccine group compared to the placebo group and mostly seen 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 %) of vaccine recipients and 95 (0.63 %) of placebo recipients. These events included lymphadenopathy (axillary swelling and tenderness of the vaccination arm), lymphadenitis, lymph node pain, vaccination-site lymphadenopathy, injection-site lymphadenopathy, and axillary mass. These were plausibly related to vaccination.

The median duration of lymphadenopathy following any dose was 1 to 2 days, and <1% reported Grade 3 axillary swelling/tenderness. Lymphadenopathy was more frequently observed in participants 18 to 64 years of age 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 vaccination. One event was a serious adverse event (reported as resolving), one case has resolved and one is ongoing. In the placebo recipients, 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 15-30/100,000/year. The observed frequency of reported Bell's palsy in the vaccine group is consistent with the expected background rate in the general population and 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 into larger populations is a requirement and Bell`s palsy has been addressed in the risk management plan.

Hypersensitivity-related events

233 events (1.5%) occurred in the vaccine arm and 166 events (1.1%) in the placebo arm. The hypersensitivity related events included injection site rash, injection site urticaria and maculo-papular 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 arm and 1.0% in the placebo arm), without meaningful imbalances between study arms.

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

The SAE's thought to be related to the vaccine (as per the FDA) include intractable nausea and vomiting in a 65 year old 1 day post the second dose. Two subjects, who were 46 and 51 years old,

reported facial swelling one and two days post 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 December 2, 2020, 13 pregnancies (6 in the vaccine and 7 in the placebo group) have been reported.

The pregnancy outcomes in the placebo group include spontaneous abortion and an 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 developmental).

Summary

The safety data supported a favorable safety profile. Reactogenicity was mostly mild to moderate, less frequent and severe in adults ≥65 years than in younger adults and generally more frequent after the second dose in age groups. There were no safety concerns identified in subgroup analyses by age, sex, race, ethnicity, comorbidities and health risks for severe COVID-19, and prior SARS-CoV-2 infection

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

Lymphadenopathy events were more frequent in the vaccine group compared with placebo and are plausibility related. Hypersensitivity-related events were more frequent in the vaccine group compared with placebo. 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

References

1. 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.

Annexes

Note:

The annexes contain the grading of recommendations, assessment, development and evaluations – *GRADE tables* (Annex 1 to 6) and the SAGE evidence-to-recommendation framework tables – *ETR tables* (Annex 7-9). 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 thatof 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).

[a] For the risk of bias assessments using the revised Cochrane risk-of-bias tool for randomized trials (RoB 2), please see www.covid-nma.com/vaccines.

[b] Data on long-term protection emerging from the ongoing phase 2/3 clinical trial remain limited, as trial data have so far been reported only for a follow-up of approximately 2 months. This was considered as not constituting a limitation that would lead to downgrading of the evidence. SAGE will continue to review any emerging data and adjust its quality assessment as required.

Annex 2: GRADE table: Safety of mRNA-1273 COVID-19 vaccine in adults

Population : Adults (18–64 years)

Intervention: One or two doses of mRNA-1273 vaccine

Comparison: Placebo/ no vaccination

Outcome : Serious adverse events following immunization

What is the risk of serious adverse events following mRNA-1273 vaccination compared with placebo in adults (18–64 years)?

			Rating	Adjustment to rating
Quality Assessment	No. of studies/starting rating		2/ RCT (1-3)	4
	Factors decreasing confidence	Limitation in study design[a]	Serious[b]	-1
		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			**3**
Summary of Findings	**Statement on quality of evidence**			**Evidence supports a moderate level of confidence that the true effect lies close to that of the estimate of the effect on the health outcome (level 3, or ⊕⊕⊕).**
	Conclusion			We are moderately confident that the risk of serious adverse events following one or two doses of mRNA-1273 vaccine in adults (18–64 years) is low.

[a] For the risk of bias assessments using the revised Cochrane risk-of-bias tool for randomized trials (RoB 2), please see www.covid-nma.com/vaccines.

[b] Downgraded for limitations in follow-up time of clinical trial, which may not allow detection of adverse events occurring several months after vaccination. Not adequately powered to detect rare adverse events. These may emerge only when large populations have been vaccinated.

Annex 3: GRADE table: Efficacy of mRNA-1273 COVID-19 vaccine in older adults

Population : Older adults (≥65 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 older adults (≥65 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	0
		Inconsistency	Not serious	0
		Indirectness	Not serious[b]	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 confident that 2 doses of mRNA-1273 vaccine are efficacious in preventing PCR-confirmed COVID-19 in older adults (≥65 years).

[a] For the risk of bias assessments using the revised Cochrane risk-of-bias tool for randomized trials (RoB 2), please see www.covid-nma.com/vaccines.

[b] Of the trial participants, approximately 25% were aged over 65 years. Data on long-term protection emerging from the ongoing phase 2/3 clinical trial remain limited, as trial data have so far been reported only for a follow-up of approximately 2 months. This was considered as not constituting a limitation that would lead to downgrading of the evidence. SAGE will continue to review any emerging data and adjust its quality assessment as required.

Annex 4: GRADE table: Safety of mRNA-1273 COVID-19 vaccine in older adults

Population : Older adults (≥65 years)

Intervention: One or two doses of mRNA-1273 vaccine

Comparison: Placebo/ no vaccination

Outcome : Serious adverse events following immunization

What is the risk of serious adverse events following mRNA-1273 vaccination compared with placebo in older adults (≥65 years)?				
			Rating	Adjustment to rating
Quality Assessment	No. of studies/starting rating		2/ RCT(1;2;4)	4
	Factors decreasing confidence	Limitation in study design[a]	Serious[b]	-1
		Inconsistency	Not serious	0
		Indirectness	Not serious[c]	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			**3**
Summary of Findings	**Statement on quality of evidence**			**Evidence supports a moderate level of confidence that the true effect lies close to that of the estimate of the effect on the health outcome (level 3, or ⊕⊕⊕).**
	Conclusion			We are moderately confident that the risk of serious adverse events following one or two doses of mRNA-1273 vaccine in older adults (≥65 years) is low.

[a] For the risk of bias assessments using the revised Cochrane risk-of-bias tool for randomized trials (RoB 2), please see www.covid-nma.com/vaccines.

[b] Downgraded for limitations in follow-up time of clinical trial, which may not allow detection of adverse events occurring several months after vaccination. Not adequately powered to detect rare adverse events. These may emerge only when large populations have been vaccinated.

[c] Of the participants within the RCT, approximately 25% were aged over 65 years. This was considered as not constituting a limitation that would lead to downgrading of the evidence.

Annex 5: GRADE table: Efficacy of mRNA-1273 COVID-19 vaccine in individuals with underlying conditions

Population : Individuals with comorbidities or health states that increase risk for severe COVID-19

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 individuals with comorbidities or health states that increase risk for severe COVID-19?				
			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	0
		Inconsistency	Not serious	0
		Indirectness	Serious[b,c]	-1
		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			**3**
Summary of Findings	**Statement on quality of evidence**			**Evidence supports a moderate level of confidence that the true effect lies close to that of the estimate of the effect on the health outcome (level 3, or ⊕⊕⊕).**
	Conclusion			We are moderately confident that 2 doses of mRNA-1273 vaccine are efficacious in preventing PCR-confirmed COVID-19 in individuals with comorbidities or health states that increase risk for severe COVID-19 as included in the clinical trial. No data were obtained on vaccination of pregnant or breastfeeding women, or persons who were immunocompromised.

[a] For the risk of bias assessments using the revised Cochrane risk-of-bias tool for randomized trials (RoB 2), please see www.covid-nma.com/vaccines.

[b] Underlying comorbidities included diabetes, chronic lung disease, severe obesity, significant cardiovascular disease, liver disease, or infection with HIV. Around 46% of the trial population were either obese or affected by co-morbidities. Data on long-term protection emerging from the ongoing phase 2/3 clinical trial remain limited, as trial data have so far been reported only for a follow-up of approximately 2 months. This was considered as not constituting a limitation that would lead to downgrading of the evidence. SAGE will continue to review any emerging data and adjust its quality assessment as required.

[c] Trial excluded pregnant and breastfeeding women, and persons who were immunocompromised.

Annex 6: GRADE table: Safety of mRNA-1273 COVID-19 vaccine in individuals with underlying conditions

Population : Individuals with comorbidities or health states that increase risk for severe COVID-19

Intervention: One or two doses of mRNA-1273 vaccine

Comparison: Placebo/ no vaccination

Outcome : Serious adverse events following immunization

What is the risk of serious adverse events following mRNA-1273 vaccination compared with placebo in individuals with comorbidities or health states that increase risk for severe COVID-19?

			Rating	Adjustment to rating
Quality Assessment	No. of studies/starting rating		1/ RCT(1;2)	4
	Factors decreasing confidence	Limitation in study design[a]	Serious[b]	-1
		Inconsistency	Not serious	0
		Indirectness	Serious[c]	-1
		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			**2**
Summary of Findings	**Statement on quality of evidence**			**Evidence supports a limited level of confidence that the true effect lies close to that of the estimate of the effect on the health outcome (level 2, or ⊕⊕).**
	Conclusion			We have low confidence in the quality of evidence. Limited data are available on the risk of serious adverse events in individuals with comorbidities or health states that increase risk for severe COVID-19 following vaccination with mRNA-1273 vaccine.

[a] For the risk of bias assessments using the revised Cochrane risk-of-bias tool for randomized trials (RoB 2), please see www.covid-nma.com/vaccines.

[b] Downgraded for limitations in follow-up time of clinical trial, which may not allow detection of adverse events occurring several months after vaccination. Not adequately powered to detect rare adverse events. These may emerge only when large populations have been vaccinated.

[c] Trial excluded pregnant and breastfeeding women, and persons who were immunocompromised.

Annex 7: SAGE evidence-to-recommendation framework: mRNA-1273 mRNA vaccine use in adults

Question: Should mRNA-1273 vaccine be administered to adults to prevent COVID-19?
Population: Adults (18–64 years)
Intervention: Two doses of mRNA-1273 vaccine
Comparison(s): No vaccination/placebo
Outcome: COVID-19 (PCR-confirmed)

Background: On 31 December 2019, WHO was alerted to several cases of pneumonia of unknown origin in Wuhan City, Hubei Province, China. The cause was found to be a novel coronavirus, SARS-CoV-2. The disease caused by this novel virus has been named COVID-19. The outbreak of COVID-19 was declared a public health emergency of international concern in January 2020. The disease has since spread, with an enormous impact on the health and well-being of individuals and populations worldwide. It has further caused major disruptions to various sectors of society and the economy across the globe.

	CRITERIA	JUDGEMENTS				RESEARCH EVIDENCE	ADDITIONAL INFORMATION
PROBLEM	Is the problem a public health priority?	*No* ☐	*Un-certain* ☐	*Yes* ☒	*Varies by setting* ☐	The cumulative number of COVID-19 cases globally has surpassed 88 828 387 with more than 1 926 635 deaths. Cases have been found in 190 different countries or territories throughout the world (status 11 January 2021). There has been collateral damage to other public health programmes.	The COVID-19 situation is evolving rapidly; the most recent epidemiological situation can be found on the following website: https://covid19.who.int/table
BENEFITS & HARMS OF THE OPTIONS	<u>Benefits of the intervention</u> Are the desirable anticipated effects large?	*No* ☐	*Un-certain* ☐	*Yes* ☒	*Varies* ☐	Primary efficacy analysis shows that mRNA-1273 vaccine is 95.6% efficacious (95%CI: 90.6–97.9%) in individuals aged 18–64 years against COVID-19 beginning 14 days after the second dose.(1;2)	Phase 1 trial data showed seroconversion of all participants by day 15, independent of dosage used. The study showed immunogenicity of the mRNA-1273 vaccine, binding antibody IgG concentrations and SARS-CoV-2 neutralizing titres in sera increased with dose level (25, 100 and 250 µg) and after a second dose. Further, two doses of either 25 or 100 µg of mRNA-1273 vaccine elicited robust CD4+ T-cell response. CD8+ T-cell responses were elicited at low levels after the second dose in the 100 µg group. (3)

						A phase 2a trial showed that the immune response as assessed by binding antibody IgG and neutralizing antibodies after 2 doses were comparable in the two groups assessed (50-µg and 100-µg).(1)
	<u>Harms of the intervention</u> Are the undesirable anticipated effects small?	*No* ☐	*Un-certain* ☒	*Yes* ☐	*Varies* ☐	Data from over 30 420 participants demonstrate that mRNA-1273 vaccine was well tolerated across all populations. Solicited systemic adverse events occurred more often in the mRNA-1273 group than in the placebo group after both the first dose (8320/15168 (54.9%), vs. 6399/15155 (42.2%)) and the second dose (11652/14677 (79.4%), vs. 5323/14566 (36.5%)), with severity increasing after the second dose. Both solicited injection-site and systemic adverse events were more common among younger participants (18 to 64 years of age) than among older participants (⩾65 years of age). The frequency of grade 3 adverse events in the placebo group (202/15166 (1.3%)) was similar to that in the vaccine group (234/15185 (1.5%)), as were the frequencies of medically attended adverse events (1465/15166 (9.7%) vs. 1372/15185 (9.0%)) and serious adverse events (89/15166 and 93/15185 (0.6% in both groups)). There are no long-term safety data available yet and follow-up time remains limited. After country implementation of vaccination programmes using mRNA vaccines in the United Kingdom and the USA, cases of anaphylactic reactions to the vaccine were observed in people with and without a history of anaphylactic reactions to other antigens (5).	

	Balance between benefits and harms	*Favours intervention* ☒ | *Favours comparison* ☐ | *Favours both* ☐ | *Favours neither* ☐ | Unclear ☐	Efficacy data suggest benefit, and short-term safety data suggest minimal harms. Further ongoing studies are being undertaken as part of post-marketing surveillance.	
	What is the overall quality of this evidence for the critical outcomes?	Effectiveness of the intervention: *No included studies* ☐ | *Very low* ☐ | *Low* ☐ | *Moderate* ☐ | *High* ☒ Safety of the intervention: *No included studies* ☐ | *Very low* ☐ | *Low* ☐ | *Moderate* ☒ | *High* ☐	Please see the related GRADE tables.	
VALUES & PREFERENCES	How certain is the relative importance of the desirable and undesirable outcomes?	*Important uncertainty or variability* ☐ | *Possibly important uncertainty or variability* ☒ | *Probably no important uncertainty or variability* ☐ | *No important uncertainty or variability* ☐ | *No known undesirable outcomes* ☐	Available scientific evidence on the relative importance of the intervention, as well as the relative weights that the target population attributes to the desirable (i.e. protection conferred by the vaccine) and the undesirable outcomes (i.e. the currently reported safety signals), vary. There may also be variability around acceptance of novel product platforms for mRNA vaccines, which may represent a source of uncertainty/variability. Different population groups may have different opinions regarding the weights assigned to desirable and undesirable outcomes.	
	Values and preferences of the target population: Are the desirable effects large relative to	*No* ☒ | *Probably No* ☐ | *Uncertain* ☐ | *Probably Yes* ☐ | *Yes* ☒ | *Varies* ☒	Available scientific evidence suggests that target population probably assigns more weight to the desirable effects than to the undesirable effects related to COVID-19 vaccination in general. Targeted information campaigns should assess this aspect.	

	undesirable effects?						
RESOURCE USE	Are the resources required small?	*No* ☒	*Un-certain* ☐	*Yes* ☐	*Varies* ☐	Considerable resources will be needed to ensure the implementation of a COVID-19 vaccination programme, especially given: (i) that COVID-19 vaccination is likely to be prioritized for populations (e.g. health care workers, older adults) without pre-existing robust immunization programmes in many settings, and (ii) the urgency of vaccination roll-out worldwide, which may necessitate additional surge resources to accelerate implementation with adequate infection prevention and control procedures in the context of COVID-19. Resources required include, but are not restricted to, human resources, vaccine costs, logistics, cold-chain capacity, planning and coordination, training, social mobilization and communications, and immunization safety surveillance.	An estimated US$15.9 billion is needed for the vaccines pillar (COVAX) of the Access to COVID-19 Tools Accelerator (ACT-A) for 2020–21, in order to deliver 2 billion doses by the end of 2021. This does not include all delivery costs in all countries participating in COVAX, bilateral procurement deals, or research and development investments outside of COVAX (6). The World Bank has approved a financing window of up to US$12 billion to support low- and middle-income countries in purchasing and distributing vaccine (7).
	Cost-effectiveness	*No* ☐	*Un-certain* ☐	*Yes* ☐	*Varies* ☒	Formal global cost-effectiveness analyses have not been conducted, but the emerging evidence indicates that the benefits, including the impact on recovery of the global economy, are likely to outweigh the cost of COVID-19 vaccination in general. Cost-effectiveness analyses should be conducted at country level; cost-effectiveness of COVID-19 vaccination may vary by country depending on COVID-19 burden, comparator interventions assessed, analysis perspective, and local cost-effectiveness thresholds used.	The global economy is estimated to be losing US$375 billion per month due to the coronavirus pandemic. G20 countries have invested approximately US$10 trillion in domestic economic stimulus to mitigate the economic consequences of reduced business activity and unemployment due to the pandemic. Initial estimates suggest that COVID-19 vaccination will provide substantial economic value in terms of averted morbidity and mortality costs and averted GDP losses (6;8-13).
EQUITY		*Increa-sed*	*Un-certain*	*Reduced*	*Varies*	Equity and ethical considerations are critical. SAGE has produced a Values Framework (14),	Vaccine nationalism is seen as a threat to reducing health inequity, in

	What would be the impact on health inequities?	☒	☐	☐	☐		which offers guidance on the fair allocation of COVID-19 vaccines based on six core ethical principles that should guide distribution. If distributed fairly, COVID-19 vaccines may have considerable impact on reducing health inequities. Storage and distribution of mRNA-1273 vaccines lies at -20°C. Once thawed, it can be kept in a refrigerator for up to 30 days. This requirement is not shared by many other vaccine platforms. This cold chain capacity is not currently available in many low- and middle-income-countries, and in some regions of high-income countries, particularly in hard-to-reach or otherwise already disadvantaged communities. If other vaccines with less demanding storage requirements are not made available, or if vaccines that are feasible and available to deliver are less efficacious or less safe, health inequities will result and existing health inequities may be exacerbated.	particular as high-income countries have arranged bilateral contracts with manufacturers. This has led to the establishment of the Access to COVID-19 Tools (ACT) Accelerator and within this, the COVAX facility, which aims to ensure equitable access to vaccines for its participating member states most of whom do not have bilateral contracts (15).
ACCEPTABILITY	Which option is acceptable to key stakeholders (e.g. ministries of health, immunization managers)?	*Inter-vention* ☒	*Com pari son* ☐	*Both* ☐	*Neit her* ☐	*Un-clear* ☐	No scientific evidence is available. As vaccination is an eagerly awaited tool to combat the COVID-19 pandemic, it is assumed that key stakeholders, in particular ministries of health and immunization managers, are strongly in favour of it.	The fact that 190 economies are participating in COVAX suggests a very high acceptability of COVID-19 vaccination in general, though not necessarily of this vaccine in particular.
	Which option is acceptable to target group?	*Inter-vention*	*Com pari son*	*Both*	*Neit her*	*Un-clear*	Vaccine acceptability varies between (sub-) population groups and may be correlated with the perceived risk posed by the disease. In a global survey (19 countries) of acceptance rates in the general population of any COVID-19 vaccine	WHO has worked with an external expert group to develop tools to understand public intentions to get a COVID-19 vaccine. The survey and interview guides are targeted

		☒ ☐ ☐ ☐ ☐	product, 71.5% of participants reported that they would be very or somewhat likely to take a COVID-19 vaccine. Acceptance rates ranged from almost 55% to 87% (16). Acceptability of COVID-19 vaccination is currently being assessed by international polls (www.yougov.co.uk and www.ipsos.com).	towards populations prioritized for COVID-19 vaccines: adults and health workers. Gathering and using quality data on the behavioural and social drivers of vaccination will enable programmes to design, target and evaluate interventions to achieve greater impact with more efficiency, and to examine trends over time. The tools measure four domains that influence vaccine uptake: what people think and feel about vaccines; social processes that drive or inhibit vaccination; individual motivations (or hesitancy) to seek vaccination; and practical factors involved in seeking and receiving vaccination. Assessing all domains will enable more comprehensive planning and evaluation. Publication is expected imminently.
FEASIBILITY	Is the intervention feasible to implement?	*No* *Probably No* *Uncertain* *Probably Yes* *Yes* *Varies* ☐ ☐ ☐ ☐ ☐ ☒	Cold chain requirements and logistics may not be available in all settings, in particular in low- and middle-income-countries, and is expensive and time-consuming to establish.	The combination of the product's logistic features and its reactogenicity makes mass workplace vaccination, which will be intended for this vaccine in many settings, more difficult. In particular, if many health workers are vaccinated at the same time, several may be unable to work the next day because of mild post-vaccination immune responses.
Balance of consequences		Undesirable consequences *clearly outweigh* desirable consequences in most settings	Undesirable consequences *probably outweigh* desirable consequences in most settings	The balance between desirable and undesirable consequences *is closely balanced or uncertain*	Desirable consequences *probably outweigh* undesirable consequences in most settings	Desirable consequences *clearly outweigh* undesirable consequences in most settings

	☐	☐	☐	☐	☒
Type of recommendation	We recommend the intervention ☐	We suggest considering recommendation of the intervention ☐ Only in the context of rigorous research ☒ Only with targeted monitoring and evaluation ☐ Only in specific contexts or specific (sub)populations		We recommend the comparison ☐	We recommend against the intervention and the comparison ☐
Recommendation (text)	Vaccination with mRNA-1273 is recommended in persons aged 18 and above. The recommended schedule is two doses (100 µg, 0.5 ml each) given intramuscularly into the deltoid muscle. An interval of 28 days between the 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.				
Implementation considerations	Before implementation, countries should consider whether they have adequate logistic and cold-chain capacity in place to ensure vaccine distribution and administration under the mentioned requirements. In countries where various immunization stakeholders have a crucial role in vaccine distribution, information and open discussion will be required before the vaccine is deployed.				
Monitoring and evaluation	WHO recommends the following post-authorization monitoring activities: • vaccine effectiveness over time; • ongoing collection of safety data in vaccine recipients; • surveillance for COVID-19 among vaccinated individuals, looking for vaccine-induced enhanced disease (possibly as vaccine-induced antibody levels decline); • safety data from inadvertently vaccinated pregnant women during trials and post-authorization; • safety data from pregnant women who receive vaccine because they are members of prioritized groups, e.g. health workers; • prospective studies on the safety of mRNA-1273 in pregnant women; • impact on infants of vaccination of breastfeeding mothers; • safety data on vaccination in immunocompromised persons, including persons living with HIV and persons with autoimmune disease;				

	• impact of delayed second dose as currently implemented by certain countries.
Research priorities	WHO recommends the following research activities: • immunogenicity and safety studies of co-administration with other vaccines, including influenza and pneumococcal vaccines, to adults and older persons; • studies to demonstrate whether this vaccine reduces SARS-CoV-2 transmission and viral shedding; • clinical trials on the efficacy and safety of vaccination of children below the age of 18 years; • 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; • global surveillance of virus evolution and the impact of virus mutants on vaccine effectiveness to support possible update of vaccines if needed; • head-to-head studies with other vaccines on extent and duration of immunity using standardized neutralization assays and mucosal immunity assays.

Annex 8: SAGE evidence-to-recommendation framework: MRNA-1273 mRNA vaccine use in older adults

Question: Should mRNA-1273 vaccine be administered to older adults to prevent COVID-19?
Population: Older adults (≥65 years)
Intervention: Two doses of mRNA-1273 vaccine
Comparison(s): No vaccination/Placebo
Outcome: COVID-19 (PCR-confirmed)

Background: On 31 December 2019, WHO was alerted to several cases of pneumonia of unknown origin in Wuhan City, Hubei Province, China. The cause was found to be a novel coronavirus, SARS-CoV-2. The disease caused by this novel virus has been named COVID-19. The outbreak of COVID-19 was declared a public health emergency of international concern in January 2020. The disease has since spread with an enormous impact on the health and well-being of individuals and populations worldwide. It has further caused major disruptions to various sectors of society and the economy across the globe.

	CRITERIA	JUDGEMENTS				RESEARCH EVIDENCE	ADDITIONAL INFORMATION
PROBLEM	Is the problem a public health priority?	*No* ☐	*Un-certain* ☐	*Yes* ☒	*Varies by setting* ☐	The cumulative number of COVID-19 cases globally has surpassed 88 828 387 with more than 1 926 635 deaths. Cases have been found in 190 different countries or territories throughout the world (status 11 January 2021). There has been collateral damage to other public health programmes. Older adults are particularly affected by COVID-19 and bear a significantly higher risk of severe COVID-19 outcomes and death.	The COVID-19 situation is evolving rapidly; the most recent epidemiological situation can be found on the following website: https://covid19.who.int/table
BENEFITS & HARMS OF THE OPTIONS	<u>Benefits of the intervention</u> Are the desirable anticipated effects large?	*No* ☐	*Un-certain* ☐	*Yes* ☒	*Varies* ☐	Of the trial participants, approximately 24% were aged 65 years or older. Primary efficacy analysis shows that mRNA-1273 is 86.4% efficacious (95%CI: 61.4–95.2%) in individuals aged 65 years and older. Primary efficacy analysis shows that mRNA-1273 vaccine is 95.6% efficacious (95%CI: 90.6–97.9%) in individuals aged 18–64 years against COVID-19 beginning 14 days after the second dose.(1;2)	Phase 1 trial data showed seroconversion of all participants by day 15, independent of dosage used. The study showed immunogenicity of the mRNA-1273 vaccine, binding antibody IgG concentrations and SARS-CoV-2 neutralizing titres in sera increased with dose level (25, 100 and 250 µg) and after a second dose. Further, two doses of either 25 or 100 µg of mRNA-1273 vaccine elicited

						robust CD4+ T-cell response. CD8+ T-cell responses were elicited at low levels after the second dose in the 100 µg group. (3) A phase 2a trial showed that the immune response as assessed by binding antibody IgG and neutralizing antibodies after 2 doses were comparable in the two groups assessed (50-µg and 100-µg).(1)
	<u>Harms of the intervention</u> Are the undesirable anticipated effects small?	*No* ☐	*Un-certain* ☒	*Yes* ☐	*Varies* ☐	Data from over 30 420 participants demonstrate that mRNA-1273 vaccine was well tolerated across all populations. Solicited systemic adverse events occurred more often in the mRNA-1273 group than in the placebo group after both the first dose (8320/15168 (54.9%), vs. 6399/15155 (42.2%)) and the second dose (11652/14677 (79.4%), vs. 5323/14566 (36.5%)), with severity increasing after the second dose. Both solicited injection-site and systemic adverse events were more common among younger participants (18 to 64 years of age) than among older participants (⩾65 years of age). In those 65 years and over, the frequency of grade 3 adverse events in the placebo group (70/3750 (1.9%)) was similar to that in the vaccine group (78/3770 (2.1%)), as were the frequencies of medically attended adverse events (414/3750 (11.0%) vs. 381/10.1 (10.1%)) and serious adverse events 43/3750 (1%) and 39/3770 (1.1%). There are no long-term safety data available yet and follow-up time remains limited.	

	Balance between benefits and harms	*Favours inter-vention* ☒ | *Favours com-parison* ☐ | *Favours both* ☐ | *Favours neither* ☐ | Unclear ☐	Efficacy data suggest benefit, and short-term safety data suggest minimal harm. Further ongoing studies are being undertaken as part of post-marketing surveillance.	
	What is the overall quality of this evidence for the critical outcomes?	Effectiveness of the intervention *No included studies* ☐ | *Very low* ☐ | *Low* ☐ | *Mod-erate* ☐ | *High* ☒ Safety of the intervention *No included studies* ☐ | *Very low* ☐ | *Low* ☐ | *Mod-erate* ☒ | *High* ☐	Please see the related GRADE tables.	
VALUES & PREFERENCES	How certain is the relative importance of the desirable and undesirable outcomes?	*Important uncertainty or variability* ☐ | *Possibly important uncertainty or variability* ☒ | *Probably no important uncertainty or variability* ☐ | *No important uncertainty or variability* ☐ | *No known undesirable outcomes* ☐	The majority of severe disease occurs in older individuals. Available scientific evidence suggests that the target population probably considers the desirable effects, i.e. the protection conferred by the vaccine, more important than the undesirable effects, i.e. the currently reported safety signals related to COVID-19 vaccination. There may also be variability around acceptance of novel product platforms for mRNA vaccines, which may represent a source of uncertainty/variability. Different population groups may have different opinions regarding the weights assigned to desirable and undesirable outcomes.	
	Values and preferences of the target	*No* | *Probably No* | *Uncertain* | *Probably Yes* | *Yes* | *Varies*	Available scientific evidence suggests that the target population probably assigns more weight to the desirable effects than the undesirable effects related to COVID-19 vaccination.	

	population: Are the desirable effects large relative to undesirable effects?	☐	☐	☐	☒	☐	☐	Targeted information campaigns should assess this aspect.	
RESOURCE USE	Are the resources required small?	*No* ☒	*Un-certain* ☐	*Yes* ☐	*Varies* ☐			Considerable resources will be needed to ensure the implementation of a COVID-19 vaccination programme, especially given: (i) that COVID-19 vaccination is likely to be prioritized for populations (e.g. health care workers, older adults) without pre-existing robust immunization programmes in many settings, and (ii) the urgency of vaccination roll-out worldwide, which may necessitate additional surge resources to accelerate implementation with adequate infection prevention and control procedures in the context of COVID-19. Resources required include, but are not restricted to human resources, vaccine costs, logistics, cold-chain capacity, planning and coordination, training, social mobilization and communications, and immunization safety surveillance.	An estimated US$15.9 billion is needed for the vaccines pillar (COVAX) of the Access to COVID-19 Tools Accelerator (ACT-A) for 2020–21, in order to deliver 2 billion doses by the end of 2021. This does not include all delivery costs in all countries participating in COVAX, bilateral procurement deals, or research and development investments outside of COVAX (6). The World Bank has approved a financing window of up to US $12 billion to support low- and middle-income countries in purchasing and distributing vaccine (7).
	Cost-effectiveness	*No* ☐	*Un-certain* ☐	*Yes* ☐	*Varies* ☒			Formal global cost-effectiveness analyses have not been conducted, but the emerging evidence indicates that the benefits, including the impact on recovery of the global economy are likely to outweigh the cost of COVID-19 vaccination in general. Cost-effectiveness analyses should be conducted at country level; cost-effectiveness of COVID-19 vaccination may vary by country depending on COVID-19 burden, comparator interventions assessed, analysis perspective, and local cost-effectiveness thresholds used.	The global economy is estimated to be losing US$375 billion per month due to the coronavirus pandemic. G20 countries have invested approximately US$10 trillion in domestic economic stimulus to mitigate the economic consequences of reduced business activity and unemployment due to the pandemic. Initial estimates suggest that COVID-19 vaccination will provide substantial economic value in terms of averted morbidity and mortality costs and averted GDP losses (6;8-13).
EQUITY		*Increa-sed*	*Un-certain*	*Reduced*	*Varies*			Equity and ethical considerations are critical. SAGE has produced a Values Framework (14),	Vaccine nationalism is seen as a threat to reducing health inequity, in

	What would be the impact on health inequities?	☒	☐	☐	☐		which offers guidance on the fair allocation of COVID-19 vaccines based on six core ethical principles that should guide distribution. If distributed fairly, COVID-19 vaccines may have considerable impact on reducing health inequities. Storage and distribution of mRNA-1273 vaccines lies at -20°C. This requirement is not shared by many other vaccine platforms. Once thawed, it can be kept in a refrigerator for up to 30 days. This cold chain capacity is not currently available in many low- and middle-income-countries, and in some regions of high-income countries, particularly in hard-to-reach or otherwise already disadvantaged communities. If other vaccines with less demanding storage requirements are not made available, or if vaccines that are feasible and available to deliver are less efficacious or less safe, health inequities will result and existing health inequities may be exacerbated.	particular as high-income countries have arranged bilateral contracts with manufacturers. This has led to the establishment of the Access to COVID-19 Tools (ACT) Accelerator and, within this, the COVAX facility, which aims to ensure equitable access to vaccines for its participating member states most of whom do not have bilateral contracts (15).
ACCEPTABILITY	Which option is acceptable to key stakeholders (e.g. ministries of health, immunization managers)?	*Inter-vention* ☒	*Com pari son* ☐	*Both* ☐	*Neit her* ☐	*Un-clear* ☐	No scientific evidence is available. As vaccination is an eagerly awaited tool to combat the COVID-19 pandemic, it is assumed that key stakeholders, in particular ministries of health and immunization managers are strongly in favour of COVID-19 vaccination.	The fact that 190 economies are participating in COVAX suggests a very high acceptability of COVID-19 vaccination in general, though not necessarily of this vaccine in particular.
	Which option is acceptable to target group?	*Inter-vention*	*Com pari son*	*Both*	*Neit her*	*Un-clear*	Vaccine acceptability varies between (sub-) population groups, and may be correlated with the perceived risk posed by the disease. In a global survey (19 countries) of acceptance rates in the general population of any COVID-19 vaccine	WHO has worked with an external expert group to develop tools to understand public intentions to get a COVID-19 vaccine. The survey and interview guides are targeted

		☒ ☐ ☐ ☐ ☐	product, 71.5% of participants reported that they would be very or somewhat likely to take a COVID-19 vaccine. Acceptance rates ranged from almost 55% to 87% (16). Acceptability of COVID-19 vaccination is currently being assessed by international polls (www.yougov.co.uk and www.ipsos.com).	towards populations prioritized for COVID-19 vaccines: adults and health workers. Gathering and using quality data on the behavioural and social drivers of vaccination will enable programmes to design, target and evaluate interventions to achieve greater impact with more efficiency, and to examine trends over time. The tools measure four domains that influence vaccine uptake: what people think and feel about vaccines; social processes that drive or inhibit vaccination; individual motivations (or hesitancy) to seek vaccination; and practical factors involved in seeking and receiving vaccination. Assessing all domains will enable more comprehensive planning and evaluation. Publication is expected imminently.
FEASIBILITY	Is the intervention feasible to implement?	*No* *Probably No* *Uncertain* *Probably Yes* *Yes* *Varies* ☐ ☐ ☐ ☐ ☐ ☒	Cold chain requirements and logistics may not be available in all settings, in particular in low- and middle-income-countries, and is expensive and time-consuming to establish.	
Balance of consequences		Undesirable consequences *clearly outweigh* desirable consequences in most settings	Undesirable consequences *probably outweigh* desirable consequences in most settings	The balance between desirable and undesirable consequences *is closely balanced or uncertain*	Desirable consequences *probably outweigh* undesirable consequences in most settings	Desirable consequences *clearly outweigh* undesirable consequences in most settings

	☐	☐	☐	☐	☒
Type of recommendation	We recommend the intervention ☐	We suggest considering recommendation of the intervention ☐ Only in the context of rigorous research ☒ Only with targeted monitoring and evaluation ☐ Only in specific contexts or specific (sub)populations		We recommend the comparison ☐	We recommend against the intervention and the comparison ☐
Recommendation (text)	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 above the age of 95 years and very frail older persons 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.				
Implementation considerations	Before implementation, countries should consider whether they have adequate logistic and cold-chain capacity in place to ensure vaccine distribution and administration under the mentioned requirements. In the countries where various immunization stakeholders have a crucial role in vaccine distribution, information and open discussion will be required before the vaccine is deployed.				
Monitoring and evaluation	WHO recommends the following post-authorization monitoring activities: • vaccine effectiveness over time; • ongoing collection of safety data in vaccine recipients; • surveillance for COVID-19 among vaccinated individuals, looking for vaccine-induced enhanced disease (possibly as vaccine-induced antibody levels decline); • safety data from inadvertently vaccinated pregnant women during trials and post-authorization; • safety data from pregnant women who receive vaccine because they are members of prioritized groups, e.g. health workers; • prospective studies on the safety of mRNA-1273 in pregnant women; • impact on infants of vaccination of breastfeeding mothers;				

	• safety data on vaccination in immunocompromised persons, including persons living with HIV and persons with autoimmune disease; • impact of delayed second dose as currently implemented by certain countries.
Research priorities	WHO recommends the following research activities: • immunogenicity and safety studies of co-administration with other vaccines, including influenza and pneumococcal vaccines, to adults and older persons; • studies to demonstrate whether this vaccine reduces SARS-CoV-2 transmission and viral shedding; • clinical trials on the efficacy and safety of vaccination of children below the age of 18 years; • 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; • global surveillance of virus evolution and the impact of virus mutants on vaccine effectiveness to support possible update of vaccines if needed; • head-to-head studies with other vaccines on extent and duration of immunity using standardized neutralization assays and mucosal immunity assays.

Annex 9: SAGE evidence-to-recommendation framework: MRNA-1273 mRNA vaccine use in individuals with comorbidities

Question: Should mRNA-1273 mRNA vaccine be administered to individuals with comorbidities or health states that increase risk for severe COVID-19[16] to prevent COVID-19?
Population: Individuals with comorbidities or health states that increase risk for severe COVID-19
Intervention: Two doses of mRNA-1273 vaccine
Comparison(s): No vaccination/Placebo
Outcome: COVID-19 (PCR-confirmed)

Background: On 31 December 2019, WHO was alerted to several cases of pneumonia of unknown origin in Wuhan City, Hubei Province, China. The cause was found to be a novel coronavirus, SARS-CoV-2. The disease caused by this novel virus has been named COVID-19. The outbreak of COVID-19 was declared a public health emergency of international concern in January 2020. The disease has since spread, with an enormous impact on the health and well-being of individuals and populations worldwide. It has further caused major disruptions to various sectors of society and the economy across the globe.

	CRITERIA	JUDGEMENTS				RESEARCH EVIDENCE	ADDITIONAL INFORMATION
PROBLEM	Is the problem a public health priority?	*No*	*Un-certain*	*Yes*	*Varies by setting*	The cumulative number of COVID-19 cases globally has surpassed 88 828 387 with more than 1 926 635 deaths. Cases have been found in 190 different countries or territories throughout the world (status 11 January 2021). There has been collateral damage to other public health programmes. Individuals with certain comorbidities are particularly affected by COVID-19 and bear a higher risk of severe COVID-19 outcomes and death. Identified risk factors include comorbidities such as hypertension, chronic cardiac disease, non-asthmatic chronic pulmonary disease, chronic kidney disease, liver disease and obesity (particularly a body mass index (BMI) >40). People	The COVID-19 situation is evolving rapidly; the most recent epidemiological situation can be found on the following website: https://covid19.who.int/table
		☐	☐	☒	☐		

[16] Medical and health conditions in individuals of any age, including the following: Chronic lung disease (e.g., emphysema and chronic bronchitis), idiopathic pulmonary fibrosis and cystic fibrosis) or moderate to severe asthma, significant cardiac disease (e.g., heart failure, coronary artery disease, congenital heart disease, cardiomyopathies, and pulmonary hypertension), severe obesity (body mass index ≥40 kg/m2), diabetes (Type 1, Type 2 or gestational), liver disease or chronic infection with human immunodeficiency virus (HIV).

						with multiple comorbidities are at a higher risk of COVID-19-related adverse outcomes (19). Although the relative risk may be high for some conditions, the absolute risk for younger adults with comorbidities is typically lower than for healthy older adults (>75 years).	
BENEFITS & HARMS OF THE OPTIONS	<u>Benefits of the intervention</u> Are the desirable anticipated effects large?	*No* ☐	*Un-certain* ☐	*Yes* ☒	*Varies* ☐	At least one protocol-defined high-risk condition for severe COVID-19 was present in 22.3% of participants, and 4% of participants had two or more high risk conditions. Approximately 41.4% of the study population was considered at risk for progression to severe COVID-19 due to underlying comorbidities such as diabetes, chronic lung disease, severe obesity, significant cardiovascular disease, liver disease, or infection with HIV and/or aged ≥65 years.(1;2) Primary efficacy analysis shows that mRNA-1273 vaccine is 94.4% efficacious (95%CI: 76.9–98.7%) beginning 14 days after the second dose in individuals aged 18–64 years at risk of severe COVID-19 due to underlying conditions. Efficacy %) in individuals aged 65 years and older with and without underlying conditions shows that mRNA-1273 is 86.4% efficacious (95%CI: 61.4–95.2). Point estimates were provided by subgroup of risk factor (chronic lung disease, cardiac disease, severe obesity, diabetes, liver disease and HIV). Vaccine efficacy was consistent across subgroups and comparable with the efficacy observed for the overall study population, though interpretation of the results is limited by small numbers of participants and cases.	Phase 1 trial data showed seroconversion of all participants by day 15, independent of dosage used. The study showed immunogenicity of the mRNA-1273 vaccine, binding antibody IgG concentrations and SARS-CoV-2 neutralizing titres in sera increased with dose level (25, 100 and 250 µg) and after a second dose. Further, two doses of either 25 or 100 µg of mRNA-1273 vaccine elicited robust CD4+ T-cell response. CD8+ T-cell responses were elicited at low levels after the second dose in the 100 µg group. (3) A phase 2a trial showed that the immune response as assessed by binding antibody IgG and neutralizing antibodies after 2 doses were comparable in the two groups assessed (50-µg and 100-µg).(1)

	Harms of the intervention Are the undesirable anticipated effects small?	*No* ☐	*Un-certain* ☒	*Yes* ☐	*Varies* ☐	Data from over 30 420 participants demonstrate that mRNA-1273 vaccine was well tolerated across all populations. Solicited systemic adverse events occurred more often in the mRNA-1273 group than in the placebo group after both the first dose (8320/15168 (54.9%), vs. 6399/15155 (42.2%)) and the second dose (11652/14677 (79.4%), vs. 5323/14566 (36.5%)), with severity increasing after the second dose. Both solicited injection-site and systemic adverse events were more common among younger participants (18 to 64 years of age) than among older participants (⩾65 years of age). The frequency of grade 3 adverse events in the placebo group (202/15166 (1.3%)) was similar to that in the vaccine group (234/15185 (1.5%)), as were the frequencies of medically attended adverse events (1465/15166 (9.7%) vs. 1372/15185 (9.0%)) and serious adverse events (89/15166 and 93/15185 (0.6% in both groups)). There were no specific safety concerns identified in subgroup analyses by medical comorbidities and occurrence of solicited, unsolicited, and serious adverse events in these subgroups were generally consistent with the overall study population. There are no long-term safety data available yet and follow-up time remains limited. After country implementation of vaccination programmes using mRNA vaccines in the United	

			Kingdom and the USA, cases of anaphylactic reactions to the vaccine were observed in people with and without a history of severe anaphylactic reactions to other antigens (5).	
	Balance between benefits and harms	*Favours inter-vention* ☒ | *Favours com-parison* ☐ | *Favours both* ☐ | *Favours neither* ☐ | Unclear ☐	Efficacy data suggest benefit, and the short-term safety data suggest minimal harms. Further studies are being undertaken as part of post-marketing surveillance.	
	What is the overall quality of this evidence for the critical outcomes?	Effectiveness of the intervention *No included studies* ☐ | *Very low* ☐ | *Low* ☐ | *Mod-erate* ☒ | *High* ☐ Safety of the intervention *No included studies* ☐ | *Very low* ☐ | *Low* ☒ | *Mod-erate* ☐ | *High* ☐	Please see the related GRADE tables.	
VALUES & PREFERENCES	How certain is the relative importance of the desirable and undesirable outcomes?	*Import ant uncerta inty or variabi lity* ☐ | *Possibl y import ant uncerta inty or variabi lity* ☒ | *Probab ly no import ant uncerta inty or variabi lity* ☐ | *No import ant uncerta inty or variabil ity* ☐ | *No known undesir able outcom es* ☐	There is possibly important uncertainty related to the target population weighing of desirable and undesirable effects (i.e. the protection conferred by the vaccine weighed against the currently reported safety signals, related to COVID-19 vaccination. There may also be variability around acceptance of novel product platforms for mRNA vaccines, which may represent a source of uncertainty/variability. Different population groups may have different opinions regarding the relative weights attributed to desirable and undesirable outcomes	

	Values and preferences of the target population: Are the desirable effects large relative to undesirable effects?	*No* ☐ / *Probably No* ☐ / *Uncertain* ☐ / *Probably Yes* ☒ / *Yes* ☐ / *Varies* ☐	Available scientific evidence suggests that the target population probably attached more weight to the desirable effects than the undesirable effects related to COVID-19 vaccination in general. Targeted information campaigns should assess this aspect.	
RESOURCE USE	Are the resources required small?	*No* ☒ / *Uncertain* ☐ / *Yes* ☐ / *Varies* ☐	Considerable resources will be needed to ensure the implementation of a COVID-19 vaccination programme, especially given: (i) that COVID-19 vaccination is likely to be prioritized for populations (e.g. health care workers, older adults) without pre-existing robust immunization programmes in many settings, and (ii) the urgency of vaccination roll-out worldwide, which may necessitate additional surge resources to accelerate implementation with adequate infection prevention and control procedures in the context of COVID-19. Resources required include, but are not restricted to: human resources, vaccine costs, logistics, cold-chain capacity, planning and coordination, training, social mobilization and communications, and immunization safety surveillance.	An estimated US$15.9 billion is needed for the vaccines pillar (COVAX) of the Access to COVID-19 Tools Accelerator (ACT-A) for 2020–21, in order to deliver 2 billion vaccine doses by the end of 2021. This does not include all delivery costs in all countries participating in COVAX, bilateral procurement deals, or research and development investments outside of COVAX (6). The World Bank has approved a financing window of up to US$12 billion to support low- and middle-income countries in purchasing and distributing vaccine (7).
	Cost-effectiveness	*No* ☐ / *Uncertain* ☐ / *Yes* ☐ / *Varies* ☒	Formal global cost-effectiveness analyses have not been conducted, but the emerging evidence indicates that the benefits, including the impact on recovery of the global economy, are likely to outweigh the cost of COVID-19 vaccination in general. Cost-effectiveness analyses should be conducted at country level; cost-effectiveness of COVID-19 vaccination may vary by country depending on COVID-19 burden, comparator interventions assessed, analysis perspective, and local cost-effectiveness thresholds used.	The global economy is estimated to be losing US$375 billion per month due to the coronavirus pandemic. G20 countries have invested approximately US$10 trillion in domestic economic stimulus to mitigate the economic consequences of reduced business activity and unemployment due to the pandemic. Initial estimates suggest that COVID-19 vaccination will provide substantial economic value in terms of averted morbidity and mortality costs and averted GDP losses (6;8-13)

EQUITY	What would be the impact on health inequities?	*Increa-sed* ☒	*Un-certain* ☐	*Reduced* ☐	*Varies* ☐	Equity and ethical considerations are critical. SAGE has produced a Values Framework (14), which offers guidance on the fair allocation of COVID-19 vaccines based on six core ethical principles that should guide distribution. If distributed fairly, COVID-19 vaccines may have considerable impact on reducing health inequities. Storage and distribution of mRNA-1273 vaccines lies at -20°C. This requirement is not shared by many other vaccine platforms. Once thawed, it can be kept in a refrigerator for up to 30 days. This cold chain capacity is not currently available in many low- and middle-income-countries, and in some regions of high-income countries, particularly in hard-to-reach or otherwise already disadvantaged communities. If other vaccines with less demanding storage requirements are not made available, or if vaccines that are feasible and available to deliver are less efficacious or less safe, health inequities will result and existing health inequities may be exacerbated.	Vaccine nationalism is seen as a threat to reducing health inequity, in particular as high-income countries have arranged bilateral contracts with manufacturers. This has led to the establishment of the Access to COVID-19 Tools (ACT) Accelerator and, within this, the COVAX facility, which aims to ensure equitable access to vaccines for its participating member states most of whom do not have bilateral contracts (15).
ACCEPTABILITY	Which option is acceptable to key stakeholders (e.g. ministries of	*Inter-vention*	*Com-parison*	*Both*	*Neither*	*Un-clear*	No scientific evidence is available. As vaccination is an eagerly awaited tool to combat the COVID-19 pandemic, it is assumed that key stakeholders, in particular ministries of health and immunization managers are strongly in favour of COVID-19 vaccination. But they may need to convince other partners or stakeholders to support COVID-19 immunization.	The fact that 190 economies are participating in COVAX suggests a very high acceptability of COVID-19 vaccination in general, though not necessarily of this vaccine in particular.

	health, immunization managers)?	☒	☐	☐	☐	☐		
	Which option is acceptable to target group?	*Inter-vention*	*Com-parison*	*Both*	*Neither*	*Un-clear*	Vaccine acceptability varies between (sub-) population groups, and may be correlated with the perceived risk posed by the disease. In a global survey (19 countries) on acceptance rates in the general population of any COVID-19 vaccine product, 71.5% of participants reported that they would be very or somewhat likely to take a COVID-19 vaccine. Acceptance rates ranged from almost 55% to 87% (16). Acceptability of COVID-19 vaccination is currently being assessed by international polls (www.yougov.co.uk and www.ipsos.com).	WHO has worked with an external expert group to develop tools to understand public intentions to get a COVID-19 vaccine. The survey and interview guides are targeted towards populations prioritized for COVID-19 vaccines: adults and health workers. Gathering and using quality data on the behavioural and social drivers of vaccination will enable programmes to design, target and evaluate interventions to achieve greater impact with more efficiency, and to examine trends over time. The tools measure four domains that influence vaccine uptake: what people think and feel about vaccines; social processes that drive or inhibit vaccination; individual motivations (or hesitancy) to seek vaccination; and practical factors involved in seeking and receiving vaccination. Assessing all domains will enable more comprehensive planning and evaluation. Publication is expected imminently.
		☒	☐	☐	☐	☐		
FEASIBILITY	Is the intervention feasible to implement?	*No*	*Probably No*	*Uncertain*	*Probably Yes*	*Yes*	*<u>Varies</u>*	Cold chain requirements and logistics may not be available in all settings, in particular in low- and middle-income-countries, and is expensive and time-consuming to establish.	
		☐	☐	☐	☐	☐	☒		

Balance of consequences	Undesirable consequences *clearly outweigh* desirable consequences in most settings ☐	Undesirable consequences *probably outweigh* desirable consequences in most settings ☐	The balance between desirable and undesirable consequences *is closely balanced or uncertain* ☐	Desirable consequences *probably outweigh* undesirable consequences in most settings ☒	Desirable consequences *clearly outweigh* undesirable consequences in most settings ☐
Type of recommendation	We recommend the intervention ☐	We suggest considering recommendation of the intervention ☐ Only in the context of rigorous research ☒ Only with targeted monitoring and evaluation ☒ Only in specific contexts or specific (sub)populations		We recommend the comparison ☐	We recommend against the intervention and the comparison ☐
Recommendation (text)	**Persons with comorbidities** Certain comorbidities have been identified as increasing the risk of severe COVID-19 disease and death. Phase 2/3 clinical trials have demonstrated that the vaccine has similar safety and efficacy profiles in persons with various underlying medical conditions, including those that place them at increased risk for severe COVID-19. The comorbidities studied in phase 2/3 clinical trials include hypertension; diabetes; asthma; and pulmonary, liver and kidney disease; as well as chronic (stable and controlled) infection with human immunodeficiency virus (HIV), hepatitis C virus (HCV) and hepatitis B virus (HBV). Vaccination is recommended for persons with comorbidities that have been identified as increasing the risk of severe COVID-19. **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.

Pregnant women

Pregnant women are at higher risk of severe COVID-19 compared to women of child-bearing age who are not pregnant, and COVID19 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, 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.

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

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.

Implementation considerations	Before implementation, countries should consider whether they have adequate logistic and cold-chain capacity in place to ensure vaccine distribution and administration under the mentioned requirements. In the countries where various immunization stakeholders have a crucial role in the vaccine distribution, information and open discussion will be required before the vaccine is deployed.
Monitoring and evaluation	WHO recommends the following post-authorization monitoring activities: • vaccine effectiveness over time; • ongoing collection of safety data in vaccine recipients; • surveillance for COVID-19 among vaccinated individuals, looking for vaccine-induced enhanced disease (possibly as vaccine-induced antibody levels decline); • safety data from inadvertently vaccinated pregnant women during trials and post-authorization; • safety data from pregnant women who receive vaccine because they are members of prioritized groups, e.g. health workers; • prospective studies on the safety of mRNA-1273 in pregnant women; • impact on infants of vaccination of breastfeeding mothers; • safety data on vaccination in immunocompromised persons, including persons living with HIV and persons with autoimmune disease; impact of delayed second dose as currently implemented by certain countries.
Research priorities	WHO recommends the following research activities: • immunogenicity and safety studies of co-administration with other vaccines, including influenza and pneumococcal vaccines, to adults and older persons; • studies to demonstrate whether this vaccine reduces SARS-CoV-2 transmission and viral shedding; • clinical trials on the efficacy and safety of vaccination of children below the age of 18 years; • 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; • global surveillance of virus evolution and the impact of virus mutants on vaccine effectiveness to support possible update of vaccines if needed; • head-to-head studies with other vaccines on extent and duration of immunity using standardized neutralization assays and mucosal immunity assays.

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