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

Grading of evidence –
Evidence to recommendation tables

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(included in the background document)

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World Health Organization

Background

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).

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

Population:	Adults (18–64 years)
Intervention:	Two doses of mRNA-1273 vaccine
Comparison:	Placebo/active control
Outcome:	COVID-19 (PCR-confirmed)

What is the efficacy of two doses of mRNA-1273 vaccine compared with placebo/active control 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	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 the estimate of the effect on the health outcome (level 4).**
	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.

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

Population:	Adults (18–64 years)			
Intervention:	Two doses of mRNA-1273 vaccine			
Comparison:	Placebo/active control			
Outcome:	Serious adverse events following immunization			
What is the risk of serious adverse events following mRNA-1273 vaccination compared with placebo/active control 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]	Not serious	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 the estimate of the effect on the health outcome (level 4).**
	Conclusion			We are 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 https://www.covid-nma.com/vaccines/.

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

Population:	Older adults (≥65 years)			
Intervention:	Two doses of mRNA-1273 vaccine			
Comparison:	Placebo/active control			
Outcome:	COVID-19 (PCR-confirmed)			
What is the efficacy of two doses of mRNA-1273 vaccine compared with placebo/active control 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 the estimate of the effect on the health outcome (level 4).**
	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 https://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 vaccine in older adults

Population:	Older adults (≥65 years)
Intervention:	Two doses of mRNA-1273 vaccine
Comparison:	Placebo/active control
Outcome:	Serious adverse events following immunization

What is the risk of serious adverse events following mRNA-1273 vaccination compared with placebo/active control in older adults (≥65 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]	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 the estimate of the effect on the health outcome (level 4).**
	Conclusion			We are 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 https://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 5. GRADE table: Efficacy of mRNA-1273 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/active control
Outcome:	COVID-19 (PCR-confirmed)

What is the efficacy of two doses of mRNA-1273 vaccine compared with placebo/active control 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 the estimate of the effect on the health outcome (level 3).**
	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 https://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 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/active control
Outcome:	Serious adverse events following immunization

What is the risk of serious adverse events following mRNA-1273 vaccination compared with placebo/active control 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 the estimate of the effect on the health outcome (level 2).**
	Conclusion			We have low confidence in the quality of evidence that the risk of serious adverse events in individuals with comorbidities or health states that increase risk for severe COVID-19 following one or two doses of mRNA-1273 vaccine is low.

[a] For the risk of bias assessments using the revised Cochrane risk-of-bias tool for randomized trials (RoB 2), please see https://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 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):	Placebo/active control
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.

Vaccines are a critical tool in combating the pandemic. In the rapidly evolving field of COVID-19 vaccines, WHO has issued to date interim recommendations on the use of a number of COVID-19 vaccines (4).

	CRITERIA	JUDGEMENTS				RESEARCH EVIDENCE	ADDITIONAL INFORMATION
PROBLEM	Is the problem a public health priority?	*No* ☐	*Uncertain* ☐	*Yes* ☒	*Varies by setting* ☐	The cumulative number of COVID-19 cases globally has surpassed 157 897 763 with more than 3 287 082 deaths. Cases have been found in 190 different countries or territories throughout the world (status 10 May 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 &		*No*	*Uncertain*	*Yes*	*Varies*	Primary efficacy analysis shows that mRNA-1273 vaccine is 95.6% efficacious (95%CI: 90.6–97.9%) in	Phase 1 trial data showed seroconversion of all participants by day 15,

	Benefits of the intervention Are the desirable anticipated effects large?	☐	☐	☒	☐	individuals aged 18–64 years against COVID-19 beginning 14 days after the second dose.(1, 2)	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* ☐	*Uncertain* ☐	*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)).	
	Balance between benefits and harms	*Favours intervention* ☒	*Favours comparison* ☐	*Favours both* ☐	*Favours neither* ☐	Unclear ☐	Efficacy data suggest benefit, and safety data suggest minimal harms. Further ongoing studies will need to be 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* ☒	Please see the related GRADE tables.	
		Safety of the intervention *No included studies* ☐	*Very low* ☐	*Low* ☐	*Moderate* ☐	*High* ☒		

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 outcomes (i.e. protection conferred by the vaccine) and the undesirable outcomes (i.e. the currently reported safety signals), varies. 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 undesirable effects?	*No* ☐	*Probably No* ☐	*Uncertain* ☐	*Probably Yes* ☒	*Yes* ☐	*Varies* ☐		Available scientific evidence suggests that the target population assigns more weight to the desirable effects than to the undesirable effects related to COVID-19 vaccination. Targeted studies 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 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	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. This does not include all delivery costs in all countries participating in COVAX, bilateral procurement deals, or research and development investments outside of COVAX. (5) The World Bank has approved a

						are not restricted to, human resources, vaccine costs, logistics, planning and coordination, training, social mobilization and communications, and immunization safety surveillance.	financing window of up to US$12 billion to support low- and middle-income countries in purchasing and distributing vaccine (6).
	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 at global level. No formal cost-effectiveness analyses of mRNA-1273 compared with other vaccines have been conducted. The ability to use mRNA-1273 in existing cold-chain infrastructure in all country settings may allow higher population-level coverage. 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 because of 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 losses in gross domestic product (GDP).(5, 7-12)
EQUITY	What would be the impact on health inequities?	*Increased* ☒	*Uncertain* ☐	*Reduced* ☐	*Varies* ☐	Equity and ethical considerations are critical. SAGE has produced a Values Framework (13), which offers guidance on the fair allocation of COVID-19 vaccines based on six core ethical principles that should guide distribution. If distributed	Vaccine nationalism is seen as a threat to reducing health inequity, in particular as high-income countries have arranged bilateral contracts with

							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.	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.(14)
ACCEPTABILITY	Which option is acceptable to key stakeholders (e.g. ministries of health, immunization managers)?	*Intervention*	*Comparison*	*Both*	*Neither*	*Un-clear*	As vaccination is an eagerly awaited tool to combat COVID-19, 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.
		☒	☐	☐	☐	☐		
	Which option is acceptable to target group?	*Intervention*	*Comparison*	*Both*	*Neither*	*Un-clear*	COVID-19 vaccine acceptability in general 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 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%. (15) Additionally, representative multi-country surveys are carried out periodically to assess the percentage of those willing to receive (or of those who have already received) COVID-19 vaccination (non-product specific). While these polls are limited to selected countries, they provide a certain degree of insight into vaccine acceptance and trends over time. (16, 17)	
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. Administration of the vaccine to novel target groups currently not reached by national immunization programmes may pose a challenge in certain settings	
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)	Please see the interim recommendations.			
IMPLEMENTATION CONSIDERATIONS	Please see the interim recommendations.			
MONITORING, EVALUATION AND RESEARCH PRIORITIES	Please see the interim recommendations.			

Annex 8. SAGE evidence-to-recommendation framework: mRNA-1273 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):	Active control/ 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.

Vaccines are a critical tool in combating the pandemic. In the rapidly evolving field of COVID-19 vaccines, WHO has issued to date interim recommendations on the use of a number of COVID-19 vaccines (4).

	CRITERIA	JUDGEMENTS				RESEARCH EVIDENCE	ADDITIONAL INFORMATION
PROBLEM	Is the problem a public health priority?	*No* ☐	*Uncertain* ☐	*Yes* ☒	*Varies by setting* ☐	The cumulative number of COVID-19 cases globally has surpassed 157 897 763 with more than 3 287 082 deaths. Cases have been found in 190 different countries or territories throughout the world (status 10 May 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 &		*No*	*Uncertain*	*Yes*	*Varies*	Of the trial participants, approximately 24% were aged 65 years or older.	Phase 1 trial data showed seroconversion of all participants by day

	Benefits of the intervention Are the desirable anticipated effects large?	☐	☐	☒	☐	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)	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 1, dose-escalation, open-label trial suggests that the 100-µg dose induced higher binding- and neutralizing-antibody titers than the 25-µg dose in older adults, which supports the use of the 100-µg dose in a phase 3 vaccine trial.(18) 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* ☐	*Uncertain* ☐	*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%).	In older adults (⩾ 56 years), solicited adverse events were predominantly mild or moderate in severity and most frequently included fatigue, chills, headache, myalgia, and pain at the injection site. Such adverse events were dose-dependent and were more common after the second immunization.(18)
	Balance between benefits and harms	*Favours intervention* ☒	*Favours comparison* ☐	*Favours both* ☐	*Favours neither* ☐	Unclear ☐	Efficacy data suggest benefit, and safety data suggest minimal harm. Further ongoing studies are being undertaken as part of post-marketing surveillance.	
	What is the overall quality of this	**Effectiveness of the intervention** *No included studies*	*Very low*	*Low*	*Moderate*	*High*	Please see the related GRADE tables.	

	evidence for the critical outcomes?	☐	☐	☐	☒	☐		
		Safety of the intervention						
		No included studies	*Very low*	*Low*	*Moderate*	*High*		
		☐	☐	☐	☒	☐		
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 potential protection conferred by the vaccine, more important than the undesirable effects, i.e. the currently reported safety signals related to COVID-19 vaccination. 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 undesirable effects?	*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. Targeted studies should assess this aspect. As more data on vaccine efficacy in older adults are generated, the uncertainty around the importance of the desirable effects of the intervention will probably be reduced.	
		☐	☐	☐	☒	☐	☐	

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, 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. This does not include all delivery costs in all countries participating in COVAX, bilateral procurement deals, or research and development investments outside of COVAX. (5) 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 (6).
	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 at global level. No formal cost-effectiveness analyses of mRNA-1273 vaccine compared with other vaccines have been conducted. Cost-effectiveness analyses should be conducted at country level; cost-effectiveness of COVID-19 vaccination may vary by country depending on COVID-19 burden,	The global economy is estimated to be losing US$375 billion per month because of 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

						comparator interventions assessed, analysis perspective, and local cost-effectiveness thresholds used.	of averted morbidity and mortality costs and averted losses in gross domestic product (GDP).(5, 7-12)
EQUITY	What would be the impact on health inequities?	*Increased*	*Uncertain*	*Reduced*	*Varies*	Equity and ethical considerations are critical. SAGE has produced a Values Framework (13), 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.	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.(14)
		☒	☐	☐	☐		

ACCEPTABILITY	Which option is acceptable to key stakeholders (e.g. ministries of health, immunization managers)?	*Intervention* ☒	*Comparison* ☐	*Both* ☐	*Neither* ☐	*Un-clear* ☐			No scientific evidence is available. As vaccination is an eagerly awaited tool to combat COVID-19, 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?	*Intervention* ☒	*Comparison* ☐	*Both* ☐	*Neither* ☐	*Un-clear* ☐			COVID-19 vaccine acceptability in general 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 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%. (15) Additionally, representative multi-country surveys are carried out periodically to assess the percentage of those willing to receive (or of those who have already received) COVID-19 vaccination (non-product specific). While these polls are limited to selected countries, they provide a certain degree of insight into vaccine acceptance and trends over time. (16, 17)	
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. Administration of the vaccine to novel target groups currently not reached by national immunization programmes may pose a challenge in certain settings	
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)	Please see the interim recommendations.				
IMPLEMENTATION CONSIDERATIONS	Please see the interim recommendations.				
MONITORING, EVALUATION AND RESEARCH PRIORITIES	Please see the interim recommendations.				

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

Question:	Should mRNA-1273 vaccine be administered to individuals with comorbidities[a] or health states that increase risk for severe COVID-19 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):	Active control/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.

Vaccines are a critical tool in combating the pandemic. In the rapidly evolving field of COVID-19 vaccines, WHO has issued to date interim recommendations on the use of a number of COVID-19 vaccines (4).

	CRITERIA	JUDGEMENTS				RESEARCH EVIDENCE	ADDITIONAL INFORMATION
PROBLEM	Is the problem a public health priority?	*No* ☐	*Uncertain* ☐	*Yes* ☒	*Varies by setting* ☐	The cumulative number of COVID-19 cases globally has surpassed 157 897 763 with more than 3 287 082 deaths. Cases have been found in 190 different countries or territories throughout the world (status 10 May 2021). There has been collateral damage to other public health programmes. There	The COVID-19 situation is evolving rapidly; the most recent epidemiological situation can be found on the following website: https://covid19.who.int/table

[a] Comorbidities included were cardiovascular disease, hypertension, obesity and type 2 diabetes. Comorbidities for which there were too few data to evaluate were asthma, cancer, chronic kidney disease, chronic obstructive pulmonary disorder (COPD), HIV infection, immunocompromised, liver disease, and neurological conditions.

				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 with multiple comorbidities are at a higher risk of COVID-19-related adverse outcomes. 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* ☐ *Uncertain* ☐ *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.	
	<u>Harms of the intervention</u> Are the undesirable anticipated effects small?	*No* ☐	*Uncertain* ☐	*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.	
	Balance between benefits and harms	*Favours intervention* ☒	*Favours comparison* ☐	*Favours both* ☐	*Favours neither* ☐	Unclear ☐	Efficacy data suggest benefit, and the safety data suggest minimal harms. Further studies will need to be 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* ☐	Please see the related GRADE tables.	
		Safety of the intervention *No included studies* ☐	*Very low* ☐	*Low* ☒	*Moderate* ☐	*High* ☐		

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* ☐		There is possibly important uncertainty regarding how the target population weighs the desirable and undesirable effects (i.e. the protection conferred by the vaccine weighed against the currently reported safety signals), related to COVID-19 vaccination. 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 attaches more weight to the desirable effects than the undesirable effects related to COVID-19 vaccination. 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-	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. This does not include all delivery costs in all countries participating in COVAX, bilateral procurement deals, or research and development investments outside of COVAX. (5) The World Bank has approved a

						19. Resources required include, but are not restricted to, human resources, vaccine costs, logistics, planning and coordination, training, social mobilization and communications, and immunization safety surveillance.	financing window of up to US$12 billion to support low- and middle-income countries in purchasing and distributing vaccine. (6)
	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 at global level. No formal cost-effectiveness analyses of mRNA-1273 vaccine compared with other vaccines have been conducted. 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 because of 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 losses in gross domestic product (GDP).(5, 7-12)
EQUITY	What would be the impact on health inequities?	*Increased* ☒	*Uncertain* ☐	*Reduced* ☐	*Varies* ☐	Equity and ethical considerations are critical. SAGE has produced a Values Framework (13), 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.	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

							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.	this, the COVAX facility, which aims to ensure equitable access to vaccines for its participating member states.(14)
ACCEPTABILITY	Which option is acceptable to key stakeholders (e.g. ministries of health, immunization managers)?	*Intervention*	*Comparison*	*Both*	*Neither*	*Un-clear*	No scientific evidence is available. As vaccination is an eagerly awaited tool to combat COVID-19, 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?	*Intervention*	*Comparison*	*Both*	*Neither*	*Un-clear*	COVID-19 vaccine acceptability in general 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 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%. (15) Additionally, representative multi-country surveys are carried out periodically to assess the percentage of those willing to receive (or of those who have already received) COVID-19 vaccination (non-product specific). While these polls are limited to selected countries, they provide a certain degree of insight into vaccine acceptance and trends over time. (16, 17)	
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. Administration of the vaccine to novel target groups currently not reached by national immunization programmes may pose a challenge in certain settings
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				We recommend the comparison		We recommend against the intervention and the comparison

	☐	☐ Only in the context of rigorous research ☒ Only with targeted monitoring and evaluation ☐ Only in specific contexts or specific (sub)populations	☐	☐
RECOMMENDATION (TEXT)	Please see the interim recommendations.			
IMPLEMENTATION CONSIDERATIONS	Please see the interim recommendations.			
MONITORING, EVALUATION AND RESEARCH PRIORITIES	Please see the interim recommendations.			

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