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

These are the annexes to the Interim recommendations for use of the Moderna mRNA-1273 vaccine against COVID-19. Annexes 1–8 contain tables that summarize the grading of recommendations, assessment, development and evaluations (GRADE). Annexes 9–12 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 15 February 2022).

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

Population:	Adults (aged 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 (aged 18–64 years)?

			Rating	Adjustment to rating
Quality Assessment	No. of studies/starting rating[a]		1/ RCT *(1)*	4
	Factors decreasing confidence	Limitation in study design[b]	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) up to approx. 2 months following immunization in the context of wild-type and pre-Omicron variants of concern.

[a] High vaccine effectiveness of mRNA-1273 against severe disease and death has been confirmed in post-introduction observational studies, including in settings where Omicron is present.

[b] 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 (aged 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 (aged 18–64 years)?

			Rating	Adjustment to rating
Quality Assessment	No. of studies/starting rating		2/ RCT *(1, 2)*[a]	4
	Factors decreasing confidence	Limitation in study design[b]	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 (aged 18–64 years) is low. A very rare, but significantly elevated risk of myocarditis and pericarditis has been reported after mRNA COVID-19 vaccine use. These cases occurred more often in younger men (aged 16–24 years) and after the second dose of the vaccine, typically within a few days after vaccination.

[a] Post-licensure data have identified a very rare but increased risk of myocarditis and pericarditis, mainly in male individuals (aged 18–24 years) who received COVID-19 mRNA vaccines.

[b] 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 3. GRADE table: Efficacy of mRNA-1273 vaccine in older adults

Population:	Older adults (aged ≥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 (aged ≥65 years)?

			Rating	Adjustment to rating
Quality Assessment	No. of studies/starting rating		1/ RCT *(1)* [a]	4
	Factors decreasing confidence	Limitation in study design[b]	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 2 doses of mRNA-1273 vaccine are efficacious in preventing PCR-confirmed COVID-19 in older adults (aged ≥65 years) up to approx. 2 months following immunization in the context of wild-type and pre-Omicron variants of concern.

[a] Observational studies have confirmed the high vaccine effectiveness against COVID-19 and especially against hospitalization and severe disease in older adults.

[b] 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 4. GRADE table: Safety of mRNA-1273 vaccine in older adults

Population:	Older adults (aged ≥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 (aged ≥65 years)?

			Rating	Adjustment to rating
Quality Assessment	No. of studies/starting rating		2/ RCT *(1, 2)*[a]	4
	Factors decreasing confidence	Limitation in study design[b]	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 older adults (aged ≥65 years) is low.

[a] Observational data supports the low risk of serious adverse events in older adults following mRNA-1273 vaccine.

[b] 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 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[a]		1/ RCT *(1)*	4
	Factors decreasing confidence	Limitation in study design[b]	Not serious	0
		Inconsistency	Not serious	0
		Indirectness	Serious[c,d]	-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 up to approx. 2 months following immunization in the context of wild-type and pre-Omicron variants of concerns. Data suggest that individuals with moderately to severely compromised immune systems; or people living with organ or stem cell transplants, blood cancer, certain autoimmune disease and treatment with specific immunosuppressive medications, may not mount the same level of immunity following a regular 2-dose vaccination schedule compared to people who are not immunocompromised.

[a] High vaccine effectiveness in specific subpopulations of mRNA-1273 has been confirmed in post-introduction observational studies.

[b] 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.

[c] 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 comorbidities. SAGE will continue to review any emerging data and adjust its quality assessment as required.

[d] 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	4
	Factors decreasing confidence	Limitation in study design[a]	Not serious	0
		Inconsistency	Not serious	0
		Indirectness	Not serious[b]	0
		Imprecision	Serious[c]	-1
		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 have moderate 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: www.covid-nma.com/vaccines.

[b] The phase 3 trial excluded pregnant and breastfeeding women, and persons who were immunocompromised. Additional studies in pregnant and lactating women with regard to the COVID-19 mRNA vaccines (BNT162b2 or mRNA-1273) were conducted and data generated demonstrating a good safety profile in these populations.

[c] Missing safety data in certain subpopulations and data in immunocompromised individuals were considered as limitations that led to downgrading of the evidence.

Annex 7. GRADE table: Efficacy of mRNA-1273 vaccine in children (12–17 years)

Population:	Children (aged 12–17 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 children (aged 12–17 years)?

			Rating	Adjustment to rating
Quality Assessment	No. of studies/starting rating		1/ RCT *(1)*	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 2 doses of mRNA-1273 vaccine are efficacious in preventing PCR-confirmed COVID-19 in children (aged 12–17 years) up to approx. 2 months following immunization in the context of wild-type and pre-Omicron variants of concerns.