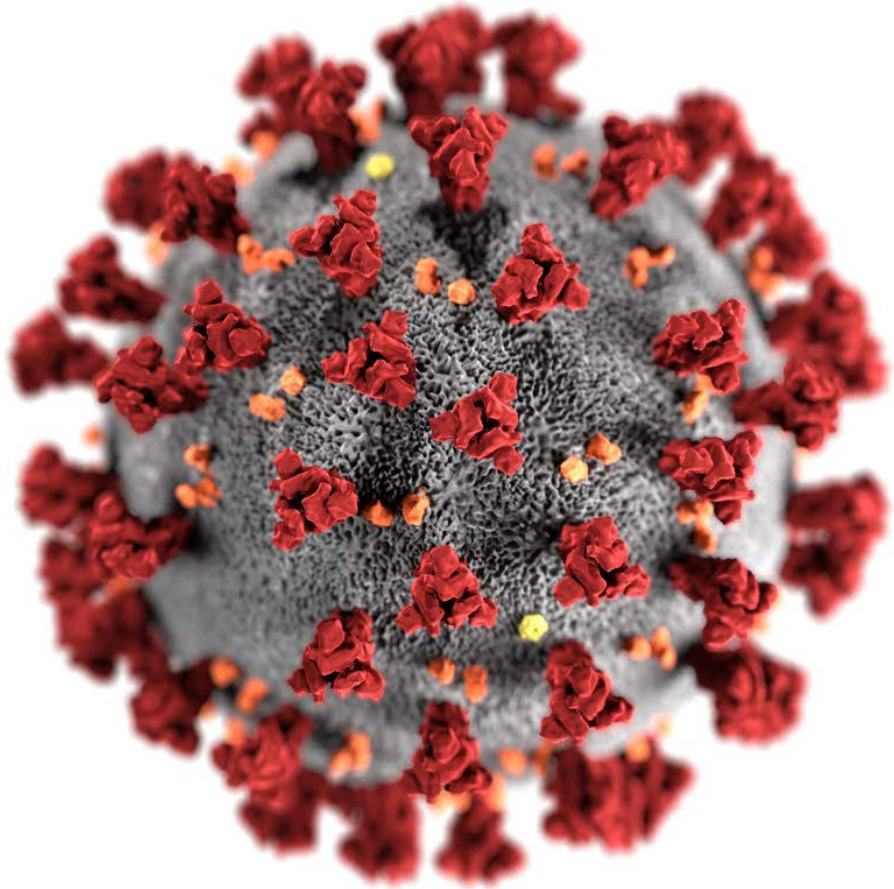
Grading of Recommendations, Assessment, Development, and Evaluation (GRADE): Moderna COVID-19 Vaccine



Dr. Julia Gargano
ACIP Meeting
19 December 2020

Policy Question

- Should vaccination with Moderna COVID-19 vaccine (2-doses, IM) be recommended for persons 18 years of age and older under an emergency use authorization?

PICO Question

Population	Persons aged ≥18 years
Intervention	Moderna COVID-19 vaccine mRNA-1273 (100 µg, 2 doses IM, 28 days apart)
Comparison	No COVID-19 vaccine
Outcomes	Symptomatic laboratory-confirmed COVID-19 Hospitalization due to COVID-19 All-cause death SARS-CoV-2 seroconversion to a non-spike protein Asymptomatic SARS-CoV-2 infection Serious adverse events Reactogenicity grade ≥3

Outcomes

Outcome	Importance[a]	Description
Benefits		
Symptomatic laboratory-confirmed COVID-19	Critical	Primary outcome; current studies use PCR + specific symptoms
Hospitalization due to COVID-19	Critical	Phase 3 trials not designed to detect statistical differences between treatment groups for this outcome
All-cause death	Important	Death from all causes; phase 3 trials not designed to detect statistical differences between treatment groups for this outcome
SARS-CoV-2 seroconversion	Important	Measured using antibodies to non-spike protein to differentiate seroconversion due to natural infection from immunogenicity to vaccine; no data available
Asymptomatic SARS-CoV-2 infection	Important	Measured using serial PCR; data available from single time point
Harms		
Serious adverse events	Critical	Evaluating balance of events between arms; also reporting on number deemed vaccine-related
Reactogenicity	Important	Evaluating grade ≥3 severity of systemic events and local reactions

[a]Three options: Critical; Important but not critical; Not important for decision making

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Phase 3 trials not powered to evaluate differences in hospitalizations and deaths; interpret in light of findings for symptomatic COVID-19

[a]Three options: Critical; Important but not critical; Not important for decision making

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Harms		
Serious adverse events	Critical	Evaluating balance of events between arms; also reporting on number deemed vaccine-related
Reactogenicity	Important	Evaluating grade ≥3 severity of systemic events and local reactions

Preliminary data

[a]Three options: Critical; Important but not critical; Not important for decision making

Outcomes

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Reactogenicity	Important	Evaluating grade ≥3 severity of systemic events and local reactions

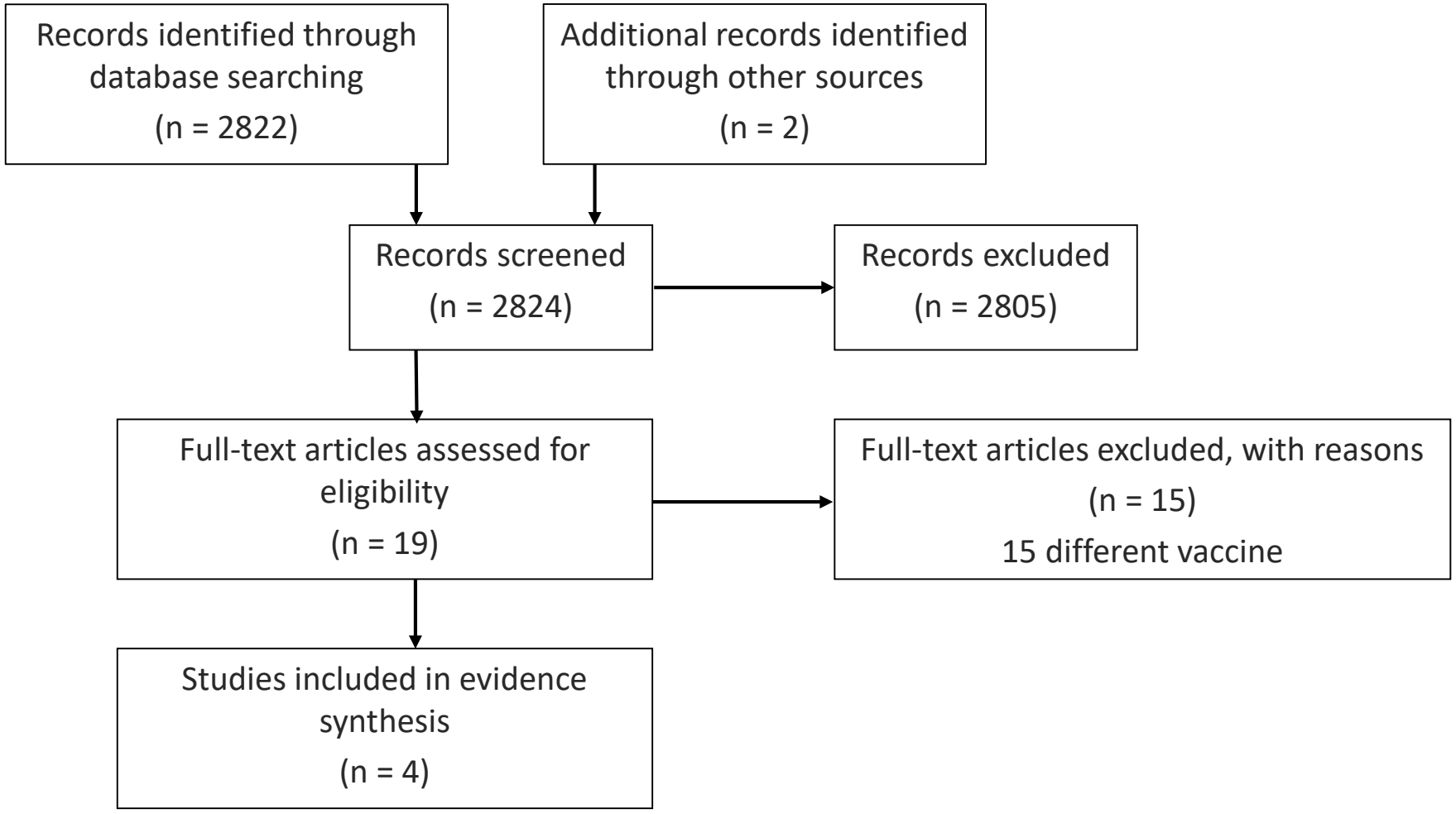
No data available to evaluate antibodies; not included in evidence profile

[a]Three options: Critical; Important but not critical; Not important for decision making

Evidence Retrieval

- **Databases**: Medline, Embase, and Cochrane Library, written in English, restricted to 2020
- **Search terms**: coronavirus, COVID-19, SARS-CoV-2, respiratory (symptom, disease, illness, condition), vaccine, immunization, trial, double blind, single blind, placebo, comparative study, phase 3, immunogenicity, efficacy, effective, adverse, evidence, and variations on these terms
- **Inclusion:** provided data on vaccination with mRNA-1273 and 1) involved human subjects; 2) reported primary data; 3) included adults (ages 18 and older) at risk for SARS-CoV-2 infection; 4) included data relevant to the efficacy and safety outcomes being measured; and 5) included data for the dosage and timing being recommended (100 µg, 2 doses at 0 and 28 days)
- **Additional resources:** unpublished and other relevant data by hand-searching reference lists, and consulting with vaccine manufacturers, and subject matter experts
- Title and abstracts were screened independently by two separate reviewers.

Evidence Retrieval



GRADE Evidence Type

- **Type 1 (high certainty):** We are very confident that the true effect lies close to that of the estimate of the effect.
- **Type 2 (moderate certainty):** We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
- **Type 3 (low certainty):** Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect.
- **Type 4 (very low certainty):** We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect.

NOTE: Evidence type is not measuring the quality of individual studies, but how much certainty we have in the estimates of effect across each outcome.

GRADE Criteria

- **Initial evidence type** (certainty level) determined by study design
  - Initial evidence type 1 (high certainty): A body of evidence from randomized controlled trials
  - Initial evidence type 3 (low certainty): A body of evidence from observational studies
- **Risk of bias:** Can include failure to conceal allocation, failure to blind, loss to follow-up. Risk of bias may vary across outcomes.
- **Inconsistency:** Criteria for evaluating include similarity of point estimates, extent of overlap of confidence intervals, and statistical criteria including tests of heterogeneity and I^2.
- **Indirectness:** Considers the generalizability of the evidence to the original PICO components (e.g., patients, intervention, comparison, or outcomes differ from those of interest[1]).
- **Imprecision:** Considers the fragility of the relative and absolute effect measures based on the interpretation of the 95% CIs and the optimal information size.
- **Other considerations:** Includes publication bias or indications of dose-response gradient, large or very large magnitude of effect, and opposing residual confounding.

Guyatt GH, Oxman AD, Kunz R et al. GRADE guidelines: 8. Rating the quality of evidence--indirectness. *J Clin Epidemiol.* 2011. DOI:10.1016/j.jclinepi.2011.04.014

Benefits

Outcome 1: Symptomatic Laboratory-confirmed COVID-19 Studies with Unvaccinated Comparator (n=1)

- Moderna phase 3 randomized controlled trial (RCT) (unpublished, data obtained from sponsor and FDA briefing documents)
- Persons aged ≥18 years in United States
- Data evaluated: primary scheduled analysis, data cut-off Nov 25, 2020
  - Interim analyses cut-off Nov 11, 2020

NOTE: denominators shown for some analyses may differ from the totals shown here due to censoring or other exclusions applied.

Outcome 1: Symptomatic Laboratory-confirmed COVID-19 Studies with Unvaccinated Comparator (n=1)

- Full analysis set: 15,181 vaccine; 15,170 placebo
- Modified intention to treat (mITT) set: 14,550 vaccine, 14,559 placebo
  - No immunologic or virologic evidence of prior SARS-CoV-2 infection
- Per-protocol set: 14,134 vaccine, 14,073 placebo
  - Subset of mITT who received planned doses per schedule, no major protocol deviations

NOTE: denominators shown for some analyses may differ from the totals shown here due to censoring or other exclusions applied.

Outcome 1: Symptomatic Laboratory-confirmed COVID-19 Studies with Unvaccinated Comparator (n=1)

Population	Events/Vaccine[a] (n/N)	Events/Placebo[a] (n/N)	Vaccine efficacy (95% CI)
Primary Outcome[b]			
Aged ≥18 years	11/14134[c]	185/14073[c]	94.1% (89.3%, 96.8%)
Aged 18–64 years	7/10551	156/10521	95.6% (90.6%, 97.9%)
Aged ≥65 years	4/3583	29/3552	86.4% (61.4%, 95.5%)
Aged ≥75 years	0/630	7/688	100% (CI not calculated)
At risk[d]	4/3206	43/3167	90.9% (74.7%, 96.7%)

[a]15,208 and 15,210 persons were randomized to vaccine and placebo.

[b]Cases diagnosed ≥14 days post dose 2 among persons without evidence of prior SARS-CoV-2 infection.

[c] Primary efficacy population (per protocol); includes a total of 3304.9 person-years of observation in vaccine group and 3273.7 person-years in placebo group.

[d] Symptomatic illness defined as at least one nasopharyngeal swab, nasal swab, or saliva sample (or respiratory sample, if hospitalized) positive for SARS-CoV-2 by RT-PCR; and at least two symptoms: fever (≥ 38ºC), chills, myalgia, headache, sore throat, new olfactory and taste disorder; or at least one symptom: cough, shortness of breath or difficulty breathing, or clinical or radiographical evidence of pneumonia.

[e]Participants were considered to be at risk for severe COVID-19 illness if they had at least 1 of the following risk factors at screening: chronic lung disease, significant cardiac disease, body mass index ≥ 40 kg/m2, diabetes, liver disease, or controlled HIV infection.

CI: confidence interval

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Outcome 1: Symptomatic Laboratory-confirmed COVID-19 Studies with Unvaccinated Comparator (n=1)

Population	Events/Vaccine (n/N)	Events/Placebo (n/N)	Vaccine efficacy (95% CI)
Primary outcome			
No evidence of prior infection, ≥14 days after dose 2	11/14134	185/14073	94.1% (89.3%, 96.8%)
Secondary outcomes			
± evidence of prior infection, ≥14 days after dose 2	12/15181	187/15170	93.6% (88.6%, 96.5%)
CDC definition of COVID-19, no evidence of prior infection, ≥14 days after dose 2	11/14134	221/14073	95.1% (91.1%, 97.3%)

CI: confidence interval

Outcome 1: Symptomatic Laboratory-confirmed COVID-19 Studies with Unvaccinated Comparator (n=1)

Population	Events/Vaccine (n/N)	Events/Placebo (n/N)	Vaccine efficacy (95% CI)
Secondary outcomes			
Modified intention-to-treat set, dose 1 efficacy, post dose 1[a]	7/996	39/1079	80.2% (55.2%, 92.5%)
Full analysis set, post dose 1, ≥1 dose[b]	21/15180	173/15170	87.9% (81.0%, 92.7%)
Full analysis set, post dose 1 and before dose 2[b]	14/15180	46/15170	69.5% (43.5%, 84.5%)

a. Modified intention to treat analysis excludes persons with evidence of prior infection. Interim analysis with Nov 11 cutoff to assess efficacy after one dose. Participants had a median of 28 days follow-up.
b. Full analysis set; interim analysis with Nov 11 cutoff.

CI: confidence interval

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b. Full analysis set; interim analysis with Nov 11 cutoff.

CI: confidence interval

Evidence Table: Symptomatic Laboratory-confirmed COVID-19

Certainty assessment							№ of patients		Effect	Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Moderna COVID-19 vaccine	No vaccine	Relative (95% CI)		
Vaccine efficacy against symptomatic COVID-19											
1	RCT	Not serious a	Not serious	Not serious b,c,d	Not serious	None	11/14134 (0.1%)	185/14073 (1.3%)	**RR 0.06** (0.03 to 0.11)	Type 1	CRITICAL

a. Risk of bias related to blinding of participants and personnel was present. Although participants and study staff were blinded to intervention assignments, they may have inferred receipt of vaccine or placebo based on reactogenicity. This was deemed unlikely to overestimate efficacy or underestimate risk of serious adverse events, therefore the risk of bias was rated as not serious.

b. The effects noted are from a per-protocol analysis with outcomes assessed at least 14 days post dose 2 among persons who received two doses, and had no evidence of prior SARS-CoV-2 infection. In an interim analysis using the full analysis set (persons who received at least 1 dose, with or without evidence of prior SARS-CoV-2 infection), there were 21 cases among 15180 persons in the vaccine arm and 173 cases among 15170 persons in the placebo arm (RR = 0.12 (0.07 to 0.19)).

c. The RCT excluded persons with prior COVID-19 diagnosis, pregnant or breastfeeding women, and persons who were in an immunosuppressive or immunodeficient state, had asplenia or recurrent severe infections (HIV-positive participants on stable antiretroviral therapy were not excluded). The population included in the RCT may not represent all persons aged ≥18 years.

d. Concern for indirectness was noted due to the short duration of observation in the available body of evidence. The vaccine efficacy observed at a median 2-month follow-up may differ from the efficacy observed with ongoing follow-up. However, in consideration of the strength of association and precision observed, it is unlikely that the efficacy estimate for symptomatic COVID-19 would change substantially enough to fall below the FDA-defined efficacy threshold for an Emergency Use Authorization authorization (e.g. to <50% efficacy).

CI: confidence interval; **RR:** relative risk

Outcome 2: Hospitalization for COVID-19
Studies with Unvaccinated Comparator (n=1)

- Moderna Phase 3 randomized controlled trial (RCT) (unpublished, data obtained from sponsor)
- Data on **severe COVID-19** per FDA guidance: COVID-19 case with ≥1 of following:
  - Clinical signs at rest indicative of severe systemic illness [a]
  - Respiratory failure [a]
  - Evidence of shock [a]
  - Significant acute renal, hepatic, or neurologic dysfunction
  - Admission to an intensive care unit
  - Death
- Hospitalizations among severe COVID-19 cases obtained [b]
  - One additional case, in vaccine recipient, adjudicated after data cutoff date, included

a. Severe systemic illness: respiratory rate ≥30, heart rate ≥125, SpO_2 ≤93% on room air at sea level or PaO_2/FiO_2<300 mm Hg; respiratory failure: needing high-flow oxygen, noninvasive ventilation, mechanical ventilation, ECMO; evidence of shock: SBP <90 mm Hg, DBP <60 mm Hg, requiring vasopressors.
b. Source: FDA VRBPAC briefing document, FDA VRBPAC presentation slides

Outcome 2: Hospitalization for COVID-19
Studies with Unvaccinated Comparator (n=1)

Outcome	Study/population	Events/Vaccine (n/N)	Events/Placebo (n/N)	Vaccine efficacy (95% CI)
Secondary endpoint: Severe COVID-19, protocol definition [a, b]	No evidence of prior infection, ≥14 d post dose 2	1/14134	30/14073	97% (76%, 100%)
Severe COVID-19 & hospitalized [b]	**No evidence of prior infection, ≥14 d post dose 2**	1/14134	9/14073	**89% (13%, 99%)**

a. Severe COVID-19, defined by FDA guidance: clinical signs at rest indicative of severe systemic illness; respiratory failure; evidence of shock; significant acute renal, hepatic, or neurologic dysfunction; admission to an intensive care unit; or death

b. There was one severe COVID-19 case in a vaccine recipient which occurred 2 months after dose 2, requiring hospitalization, that was not adjudicated by the data cutoff date.

CI: Confidence interval

Evidence Table: Hospitalization for COVID-19

Certainty assessment							№ of patients		Effect		
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Moderna COVID-19 vaccine	No vaccine	Relative (95% CI)	Certainty	Importance
Vaccine efficacy against hospitalization due to COVID-19											
1	RCT	Not serious a	Not serious	Serious b,c,d	Not serious	None	1/14134 (0.0%) e	9/14073 (0.2%)	**0.11 (0.01, 0.87)**	**Type 2**	CRITICAL

a. Risk of bias related to blinding of participants and personnel was present. Although participants and study staff were blinded to intervention assignments, they may have inferred receipt of vaccine or placebo based on reactogenicity. This was deemed unlikely to overestimate efficacy or underestimate risk of serious adverse events, therefore the risk of bias was rated as not serious.

b. The RCT excluded persons with prior COVID-19 diagnosis, pregnant or breastfeeding women, and persons who were in an immunosuppressive or immunodeficient state, had asplenia or recurrent severe infections (HIV-positive participants on stable antiretroviral therapy were not excluded). The population included in the RCT may not represent all persons aged ≥18 years.

c. The effects noted are from a per protocol analysis with outcomes assessed at least 14 days post dose 2, among persons who received 2 doses, and had no evidence of prior SARS-CoV-2 infection.

d. Serious concern for indirectness was noted due to the short duration of follow-up in the available body of evidence. Severe COVID-19 cases leading to hospitalization may not have had time to occur in a median 2-month follow-up. Additionally, hospitalization was ascertained on a subset of cases meeting a protocol-specified definition of severe COVID-19; hospitalization due to COVID-19 was not ascertained for all COVID-19 cases, and it is possible that hospitalizations for COVID-19 occurred in cases not meeting the specific severe COVID-19 criteria.

e. Includes one hospitalized case in the vaccine arm that had not yet been adjudicated by the data cutoff date.

CI: confidence interval; **RR:** relative risk

Outcome 3: All-cause Death
Studies with Unvaccinated Comparator (n=1)

- Moderna Phase 3 randomized controlled trial (RCT) (unpublished, data obtained from sponsor)

Outcome 3: All-cause Death
Studies with Unvaccinated Comparator (n=1)

Outcome[a]	Study/population	Events/Vaccine (n/N)[b]	Events/Placebo (n/N)	Relative Risk[c] (95% CI)
All-cause death	Persons aged ≥18 years	6/15184	7/15165	0.86 (0.29, 2.55)
COVID-19 related deaths	Persons aged ≥18 years	0/14134	1/14073	

a. Deaths in study participants as of December 3, 2020.

b. Six participants in mRNA-1273 group:

- 78 yo: cardio-respiratory arrest 21 days after dose 1
- 62 yo: completed suicide 21 days after dose 1
- 77 yo: myocardial infarction 45 days after dose 2
- 72 yo: multisystem organ failure 59 days after dose 2
- 70 yo: death not otherwise specified; found deceased at home 57 day after dose 2
- 56 yo: head injury; found deceased at home 37 days after dose 1

c. Estimate and confidence interval were calculated based on number of participants.

CI: Confidence interval; **YO**: Year old

Evidence Table: All-cause Death

Certainty assessment							№ of patients		Effect	Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Moderna COVID-19 vaccine	No vaccine	Relative (95% CI)		
Vaccine efficacy against death, all cause											
1	RCT	Not serious	Not serious	Serious [a,b, c]	Very serious [d,e]	None	6/15184 (0.0%)	7/15165 (0.0%)	**RR 0.86** (0.29 to 2.55)	**Type 4**	IMPORT-ANT

a. Serious concern for indirectness was noted due to the short duration of follow-up in the randomized trial data. The vaccine efficacy over a practical time frame for a vaccination program may differ from the short-term efficacy observed in the clinical trial data.
b. Deaths due to COVID-19 may not have had time to occur during the follow-up period.
c. The RCT excluded persons with prior COVID-19 diagnosis, pregnant or breastfeeding women, and persons who were in an immunosuppressive or immunodeficient state, had asplenia or recurrent severe infections (HIV-positive participants on stable antiretroviral therapy were not excluded). The population included in the RCT may not represent all persons aged ≥18 years.
d. Imprecision assessed based on the width of the 95% confidence interval. This outcome may be imprecise due to small number of events reported during the observation period.
e. Death from all causes was considered a descriptive outcome in the clinical trial data. The sponsor provided counts of total deaths but appropriate denominators for analysis to evaluate benefits for this outcome are not clear. While the number of events is accurate, lack of an agreed upon denominator may introduce some fragility in the estimate.

CI: confidence interval; **RR:** relative risk

Outcome 4: Asymptomatic SARS-CoV-2 Infection Studies with Unvaccinated Comparator (n=1)

- Moderna Phase 3 randomized controlled trial (RCT) (unpublished, data obtained from sponsor)
- Data evaluated: descriptive results of asymptomatic infections between dose 1 & dose 2 among participants without evidence of prior infection
  - Nasopharyngeal swab for PCR testing day of dose 1 & dose 2
  - No documented COVID-19 symptoms between dose 1 & dose 2
- Use of PCR at time of dose 2 to assess asymptomatic infection was not a pre-defined protocol objective

Outcome 4: Asymptomatic SARS-CoV-2 Infection Studies with Unvaccinated Comparator (n=1)

Outcome	Study/population	Events/Vaccine (n/N)	Events/Placebo (n/N)	Relative Risk (95% CI)
PCR-positive for SARS-CoV-2 at dose 2, no COVID-19 symptoms between doses 1 and 2	Persons aged ≥18 years, no evidence of prior SARS-CoV-2 infection at dose 1	14/14134	38/14073	0.37 (0.20, 0.68) a

a. FDA presentation on December 17, 2020 based on interim analysis included asymptomatic infection detected among 12/13934 in vaccination arm and 37/13883 in placebo arm based on interim analysis; RR 0.32 (0.17, 0.62).

CI: Confidence interval

Evidence Table: Asymptomatic SARS-CoV-2 Infection

Certainty assessment							№ of patients		Effect	Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Moderna COVID-19 vaccine	No vaccine	Relative (95% CI)		
Vaccine efficacy against death, all cause											
1	RCT	serious [a]	not serious	very serious [n]	not serious	none	14/14134 (0.1%)	38/14073 (0.3%)	**RR 0.37** (0.20 to 0.68)	**Type 4**	IMPORT-ANT

a.Serious concern for risk of bias due to selective outcome reporting was present. Evaluation of asymptomatic infection from SARS-CoV-2 PCR testing done at dose 2 was not a pre-defined protocol objective. Due to the limited COVID-19 symptom data provided, it is unknown whether persons classified as asymptomatic experienced COVID-19 symptoms after dose 2 and were truly presymptomatic.

b.Very serious concern for indirectness was present. The intended outcome was asymptomatic infection assessed with serial PCR testing for SARS-CoV-2, to include follow-up after completion of the full vaccination schedule. Data are presented from an analysis of participants with SARS-CoV-2 positive PCR test results from nasopharyngeal swabs collected on the day of the second vaccine dose, among persons who were seronegative at baseline and did not report COVID-19 symptoms after dose 1. The available evidence are indirect because they represent 1) SARS-CoV-2 testing at a single point in time, 2) assessment after one dose, and 3) short follow-up period.

CI: confidence interval; **RR:** relative risk

Harms

Outcome 6: Serious Adverse Events

Studies with Unvaccinated Comparator (n=2)

- Moderna phase 3 randomized controlled trial (RCT) (unpublished, data obtained from sponsor)
- Moderna phase 2 randomized controlled trial (RCT) (unpublished, data obtained from sponsor)

Studies without Unvaccinated Comparator (n=2)

- Moderna Phase 1 dose-escalation, open-label trial (Jackson, 2020)
- Moderna Phase 1 dose-escalation, open-label trial (Anderson, 2020)

Moderna Phase 3 Randomized Controlled Trial

- Unpublished, data obtained from sponsor and FDA briefing documents
- Persons aged ≥18 years in United States
- Data evaluated: final scheduled analysis, data cut-off Nov 25, 2020
  - Interim analyses cut-off Nov 11, 2020
- Safety set: 15,185 vaccine; 15,166 placebo
  - All randomized participants who received at least one dose
  - Contributed any solicited adverse reaction data
  - Analyzed according to intervention actually received

NOTE: denominators shown for some analyses may differ from the totals shown here due to censoring or other exclusions applied

Moderna Phase 2 Randomized Controlled Trial

- Moderna phase 2 dose-confirmation randomized controlled trial (RCT) (unpublished, data obtained from sponsor)
- Population: healthy adults aged ≥18 years, United States
- Data evaluated:
  - 200 persons received 2 doses of 100 µg of mRNA-1273
  - 200 persons received 2 doses of placebo
- Primary outcomes: Safety
  - Local and systemic reactions: collected using memory aid 7 days following each dose
  - Adverse events (AE): unsolicited AEs during 28 day follow up period
  - Serious AEs for duration of study period

Moderna Phase 1 Open Label Trial (Jackson, 2020)

- Population: healthy adults aged 18-55 years, United States
- Data evaluated:
  - 15 received 2 doses of 100 µg of mRNA-1273
- Primary outcomes: Safety
  - Local and systemic reactions: collected using memory aid 7 days following each dose
  - Adverse events (AE): unsolicited AEs during 28 day follow up period
  - Serious AEs for duration of study period

Jackson LA, Anderson EJ, Rouphael NG et al. An mRNA Vaccine against SARS-CoV-2. *NEJM*. 2020. DOI: 10.1056/NEJMoa2022483.

Moderna Phase 1 Open Label Trial (Anderson, 2020)

- Population: healthy adults aged >55 years, United States
- Data evaluated:
  - Aged 56-70 years: 10 received 2 doses of 100 µg of mRNA-1273
  - Aged ≥71 years: 10 received 2 doses of 100 µg of mRNA-1273
- Primary outcomes: Safety
  - Local and systemic reactions: collected using memory aid 7 days following each dose
  - Adverse events (AE): unsolicited AEs during 28 day follow up period
  - Serious AEs for duration of study period

Anderson EJ, Rouphael NG, Widge AT et al. Safety and Immunogenicity of SARS-CoV-2 mRNA-1273 Vaccine in Older Adults. *NEJM*. 2020. DOI: 10.1056/NEJMoa2028436.

Outcome 6: Serious Adverse Events (SAE)
Studies with Unvaccinated Comparator (n=2)

Study/population[a]	Events/Vaccine (n/N)	% SAE Vaccine	Events/Placebo (n/N)	% SAE Placebo	Associated with vaccination
Anderson, 2020	0/20	0	-	-	0
Jackson, 2020	0/15	0	-	-	0
Moderna, phase 2, unpublished	0/200	0	0/200	0	0
Moderna, phase 3, unpublished[b]	147/15185	1.0	153/15166	1.0	3[c]

a. Included all participants who received at least 1 dose of vaccine.
b. Proportion of participants who reported at least one SAE from dose 1 to primary analysis cutoff date (Nov 25).
c. Seven serious adverse events were deemed by blinded investigators to be related to vaccination. These included: intractable nausea/vomiting; facial swelling (two reports); rheumatoid arthritis; dyspnea with exertion and peripheral edema; autonomic dysfunction; and B-cell lymphocytic lymphoma. Through further investigation by the FDA, only three were classified as related to vaccination: one report of intractable nausea/vomiting and two reports of facial swelling. The FDA concluded that the possibility that the vaccine contributed to the SAE reports of rheumatoid arthritis, dyspnea and peripheral edema, and autonomic dysfunction cannot be excluded. The FDA concluded that B-cell lymphocytic lymphoma was not related to vaccination.

Evidence Table: Serious Adverse Events

Certainty assessment							№ of patients		Effect	Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Moderna COVID-19 vaccine	No vaccine	Relative (95% CI)		
Serious adverse events											
2	RCT	Not serious a	Not serious	Serious b,c	Not serious	None	147/15385 (1.0%)	153/15366 (1.0%)	**RR 0.96** (0.77 to 1.20)	**Type 2**	CRITICAL

a. Risk of bias related to blinding of participants was present. Although participants and study staff were blinded to intervention assignments, they may have inferred receipt of vaccine or placebo based on reactogenicity. Some reactogenicity outcomes may also have been reported as serious adverse events, and experiences of reactions immediately after vaccination could have influenced recall or reporting of subsequent serious adverse events. This was rated as not serious.
b. The RCT excluded persons with prior COVID-19 diagnosis, pregnant or breastfeeding women, and persons who were in an immunosuppressive or immunodeficient state, had asplenia or recurrent severe infections (HIV-positive participants on stable antiretroviral therapy were not excluded). The population included in the RCT may not represent all persons aged ≥18 years.
c. Serious concern of indirectness was noted. The body of evidence does not provide certainty that rare serious adverse events were captured due to the short duration of follow-up and the sample size.

CI: confidence interval; **RR:** relative risk

Outcome 7: Reactogenicity, Severe (Grade ≥3)[a]

Studies with Unvaccinated Comparator (n=2)

- Moderna phase 3 randomized controlled trial (RCT) (unpublished, data obtained from sponsor)
- Moderna phase 2 randomized controlled trial (RCT) (unpublished, data obtained from sponsor)

Studies without Unvaccinated Comparator (n=2)

- Moderna Phase 1 dose-escalation, open-label trial (Jackson, 2020)
- Moderna Phase 1 dose-escalation, open-label trial (Anderson, 2020)

[a]Grade 3: prevents daily routine activity. Grade 4: requires emergency room visit or hospitalization.

Outcome 7: Reactogenicity, Severe (Grade ≥3) Definitions

- Both trials solicited events through electronic diaries for 7 days following each dose
- Local reactions (pain at injection site, redness, swelling, axillary swelling/tenderness)
  - Grade 3: pain at injection site or axillary swelling/tenderness that prevents daily activity or use of prescription pain reliever; redness > 10 cm; and swelling > 10 cm
  - Grade 4: emergency room visit or hospitalization for severe pain at the injection site or axillary swelling/tenderness, necrosis (redness and swelling categories) or exfoliative dermatitis (redness category only).
- Systemic events (fever, nausea/vomiting, headache, fatigue, chills, muscle pain, joint pain)
  - Grade 3: fever >38.9°C to 40.0°C , vomiting that requires IV hydration; fatigue, headache, chills muscle pain, or joint pain that prevents daily activity.
  - Grade 4: fever >40.0°C, fatigue, headache, muscle pain, joint pain, diarrhea, or vomiting that require emergency room visit or hospitalization.

Outcome 7: Reactogenicity, Severe (Grade ≥3)[a,b]
Studies with and without unvaccinated comparator (n=4)

Study/population	Events/Vaccine (n/N)	% Vaccine	Events/Placebo (n/N)	% Placebo
Anderson, 2020	1/20	5.0	-	-
Jackson, 2020	1/15	6.7	-	-
Moderna, phase 2, unpublished	32/200	16.0	6/200	3.0
Moderna, phase 3, unpublished [c]	3276/15176	21.6	665/15162	4.4

a. Grade 3: prevents daily routine activity or requires use of a pain reliever. Grade 4: requires emergency room visit or hospitalization. There were 26 grade 4 systemic adverse reactions, 17 in vaccine group and 7 in placebo group.
b. Includes local and systemic events, grade ≥3.
c. Based on interim analysis, data cutoff Nov. 11, 2020.
Note: GRADE was conducted considering pooled phase 2 and 3 data.

Evidence Table: Reactogenicity, Severe (Grade ≥3)

Certainty assessment							№ of patients		Effect	Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Moderna COVID-19 vaccine	No vaccine	Relative (95% CI)		
Reactogenicity, severe (grade ≥3)											
2	RCT	not serious	not serious	not serious [a]	not serious	none	3308/15376 (21.5%)	671/15362 (4.4%)	**RR 4.93** (4.55 to 5.34)	**Type 1**	IMPORT-ANT

a. The RCT excluded persons with prior COVID-19 diagnosis, pregnant or breastfeeding women, and persons who were in an immunosuppressive or immunodeficient state, had asplenia or recurrent severe infections (HIV-positive participants on stable antiretroviral therapy were not excluded). The population included in the RCT may not represent all persons aged ≥18 years.

CI: confidence interval; **RR:** relative risk

Summary of GRADE

Outcome	Importance	Design (# of studies)	Findings	Evidence type
Benefits				
Symptomatic laboratory-confirmed COVID-19	Critical	RCT (1)	Moderna COVID-19 vaccine prevents symptomatic COVID-19	**1**
Hospitalization due to COVID-19	Critical	RCT (1)	Moderna COVID-19 vaccine prevents COVID-19-resulting in hospitalization	**2**
All-cause death	Important	RCT (1)	Moderna COVID-19 vaccine may or may not prevent death; certainty is very low because this is a rare outcome	**4**
SARS-CoV-2 seroconversion	Important	No studies	Data not yet available from any studies	**ND**
Asymptomatic SARS-CoV-2 infection	Important	RCT (1)	Preliminary data consistent with a lower incidence of asymptomatic SARS-CoV-2 infection among vaccinated compared with placebo	**4**
Harms				
Serious adverse events	Critical	RCT (2)	SAEs were balanced between vaccine and placebo arms. 3 SAEs were judged by FDA to be related to vaccination	**2**
Reactogenicity	Important	RCT (2)	Severe reactions were almost 5 times more common in vaccinated vs. placebo; any grade ≥3 reaction was reported by 21.5% of vaccinated	**1**

Evidence type: 1=high; 2=moderate; 3=low; 4=very low; ND, no data

Conclusion

- **Policy question:** focuses on recommendation during an EUA
- **Benefits**: Phase 3 trial is ongoing, and effect estimates may change with additional follow-up
  - Unlikely that efficacy estimate for symptomatic COVID-19 would change substantially enough in the months following vaccination to fall below the FDA-defined efficacy threshold for EUA (i.e., to <50% efficacy)
  - Direct evidence of efficacy for hospitalization and deaths limited; from efficacy against disease, we infer that vaccination would reduce hospitalizations and deaths
  - No data were available to assess prevention of asymptomatic infection
- **Harms**: Grade 3 reactions not uncommon in vaccinated persons; serious adverse events occurred at a similar frequency in vaccine and placebo groups

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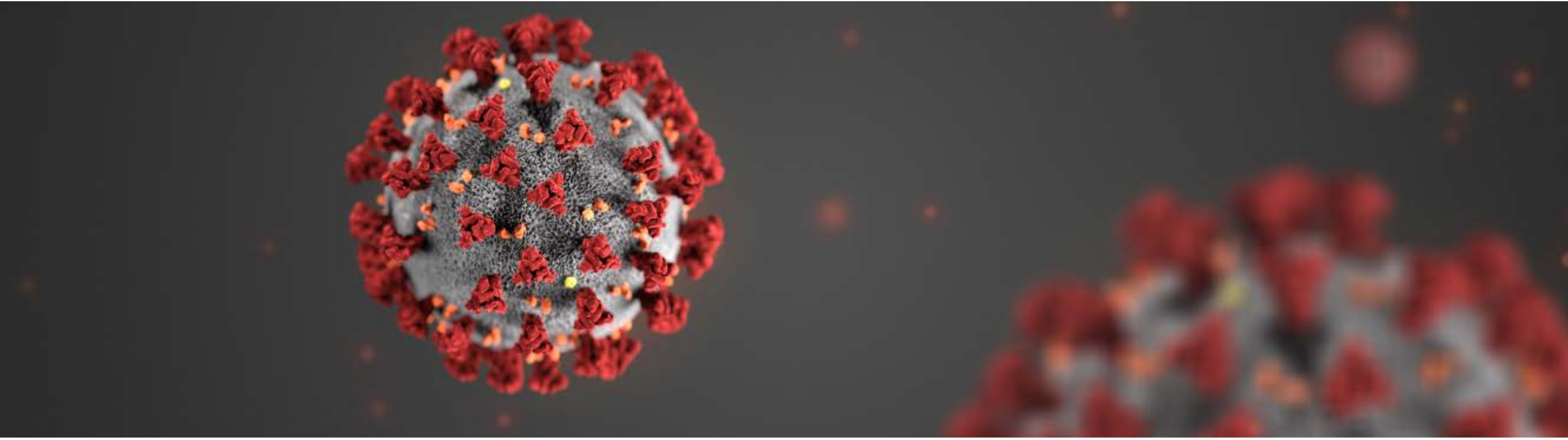

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Thank you

The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention.

Summary of GRADE

Outcome	Importance	Design (# of studies)	Findings	Evidence type
Benefits				
Symptomatic lab-confirmed COVID-19	Critical	RCT (1)	Moderna COVID-19 vaccine is effective in preventing symptomatic COVID-19	**2**
Hospitalization due to COVID-19	Critical	RCT (1)	Moderna COVID-19 vaccine may prevent COVID-19-resulting in hospitalization	**2**
Death	Important	RCT (1)	Moderna COVID-19 vaccine may or may not prevent death; uncertainty is high because this is a rare outcome	**4**
SARS-CoV-2 seroconversion	Important	No studies	Data not available from any studies	**ND**
Asymptomatic SARS-CoV-2 infection	Important	No studies	Data not available from any studies	**ND**
Harms				
Serious adverse events	Critical	RCT (2)	SAEs were balanced between vaccine and placebo arms. It is currently unknown how many SAEs were judged to be related to vaccination.	**2**
Reactogenicity	Important	RCT (2)	Reactogenicity grade ≥ 3 was five times more common in vaccinated than placebo, and grade 3 reactions occurred in over 1/5 of vaccinated	**1**

Evidence type: 1=high, 2=moderate, 3=low, 4=very low. ND, no data

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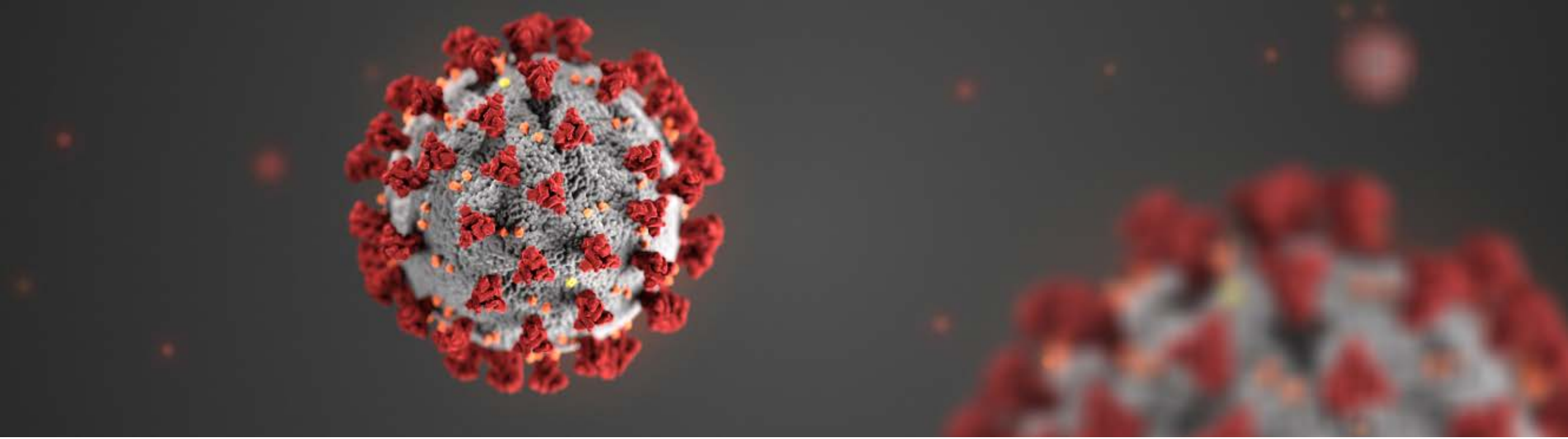

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Moderna: Demographics

Characteristics	Vaccine (N=15180)	Placebo (N=15170)	Total[a] (N=30350)
Sex - Female	7252 (47.8)	7103 (46.8)	14355 (47.3)
Race			
White	12029 (79.2)	11994 (79.1)	24023 (79.2)
Black or African American	1562 (10.3)	1528 (10.1)	3090 (10.2)
American Indian or Alaska Native	110 (0.7)	120 (0.8)	230 (0.8)
Asian	653 (4.3)	732 (4.8)	1385 (4.6)
Native Hawaiian or other Pacific Islander	314 (2.1)	32 (0.2)	66 (0.2)
Multiracial	314 (2.1)	320 (2.1)	634 (2.1)
Hispanic/Latino Ethnicity	3120 (20.6)	3114 (20.5)	6234 (20.5)
Age ≥65 Years	3763 (24.8)	3749 (24.7)	7512 (24.8)
Body mass index (BMI), mean (SD)	29.3 (6.9)	29.3 (6.7)	29.3 (6.8)
Aged 18-64 years and at risk[b]	2530 (16.7)	2535 (16.7)	5065 (16.7)
SARS-CoV-2 positive, baseline	341 (2.2)	334 (2.2)	675 (2.2)

[a]Race other (636), not reported (174), or unknown (112); Ethnicity not reported (188) or unknown (94); BMI missing for 451 persons.
[e]Participants aged < 65 years at risk if: chronic lung disease or moderate to severe asthma; significant cardiac disease, severe obesity (BMI≥ 40 kg/m2), diabetes, liver disease or HIV.

Moderna: Unsolicited Adverse Events

Adverse Event Category	Events/Vaccine (N=15184)	% AE Vaccine	Events/Placebo (N=15165)	% AE Placebo
TEAE	3325	21.9%	2949	19.4%
TEAE related to study vaccination	1127	7.4%	609	4.0%
Medically attended	122	0.8%	73	0.5%
Severe	70	0.5%	29	0.2%

TEAE: any event occurring during study and not present before or any event already present that worsened after exposure to IP; unsolicited, occurring up to 28 days after any injection.

Risk of Bias: Blinding - Moderna

Blinded	Unblinded
▪ Investigator, study staff, study participants, site monitors, and sponsor personnel are blinded to study intervention assignments. In particular, staff who perform post-vaccination assessments and interact with participants are blinded. ▪ An opaque sleeve over the syringe will maintain blinding at injection.	▪ Study staff responsible for study vaccine management, documentation, accountability, preparation, and administration are unblinded. ▪ Statistical and programming team conducting interim analysis will be unblinded. DSMB will review unblinded outputs. ▪ Reactogenicity may have resulted in unblinding of participants and any study personnel with access to reactogenicity data.

Moderna Eligibility Criteria

Inclusion Criteria	Exclusion Criteria
1. Adults, ≥ 18 years of age at time of consent, who are at high risk of SARS-CoV-2 infection, defined as adults whose locations or circumstances put them at appreciable risk of exposure to SARS-CoV-2 and COVID-19. 2. Understands and agrees to comply with the study procedures and provides written informed consent. 3. Able to comply with study procedures based on the assessment of the Investigator. 4. Female participants of nonchildbearing potential may be enrolled in the study. Nonchildbearing potential is defined as surgically sterile (history of bilateral tubal ligation, bilateral oophorectomy, hysterectomy) or post-menopausal (defined as amenorrhea for ≥ 12 consecutive months prior to Screening without an alternative medical cause). A follicle-stimulating hormone (FSH) level may be measured at the discretion of the investigator to confirm post-menopausal status. 5. Female participants of childbearing potential may be enrolled in the study if the participant fulfills all the following criteria: • Has a negative pregnancy test at Screening and on the day of the first injection (Day 1). • Has practiced adequate contraception or has abstained from all activities that could result in pregnancy for at least 28 days prior to the first injection (Day 1). • Has agreed to continue adequate contraception through 3 months following the second injection (Day 29). • Is not currently breastfeeding. 6. Adequate female contraception is defined as consistent and correct use of an FDA approved contraceptive method in accordance with the product label. 7. Healthy adults or adults with pre-existing medical conditions who are in stable condition. A stable medical condition is defined as disease not requiring significant change in therapy or hospitalization for worsening disease during the 3 months before enrollment.	1. Is acutely ill or febrile 72 hours prior to or at Screening. Fever is defined as a body temperature ≥ 38.0°C/100.4°F. Participants meeting this criterion may be rescheduled within the relevant window periods. Afebrile participants with minor illnesses can be enrolled at the discretion of the investigator. 2. Is pregnant or breastfeeding. 3. Known history of SARS-CoV-2 infection. 4. Prior administration of an investigational coronavirus (SARS-CoV, MERS-CoV) vaccine or current/planned simultaneous participation in another interventional study to prevent or treat COVID-19. 5. Demonstrated inability to comply with the study procedures. 6. An immediate family member or household member of this study's personnel. 7. Known or suspected allergy or history of anaphylaxis, urticaria, or other significant AR to the vaccine or its excipients. 8. Bleeding disorder considered a contraindication to intramuscular injection or phlebotomy. 9. Has received or plans to receive a non-study vaccine within 28 days prior to or after any injection of IP (except for seasonal influenza vaccine which is not permitted within 14 days before or after any injection of IP). 10. Has participated in an interventional clinical study within 28 days prior to the day of enrollment. 11. Immunosuppressive or immunodeficient state, asplenia, recurrent severe infections (HIV-positive participants on stable antiretroviral therapy are not excluded). 12. Has received systemic immunosuppressants or immune-modifying drugs for > 14 days in total within 6 months prior to Screening (for corticosteroids ≥ 20 mg/day of prednisone equivalent). Topical tacrolimus is allowed if not used within 14 days prior to Screening. 13. Has received systemic immunoglobulins or blood products within 3 months prior to the day of screening. 14. Has donated ≥ 450 mL of blood products within 28 days prior to Screening.

COVID-19 Case Definitions & Assessment - Moderna

Outcome	Definition
COVID-19 case	At least one NP swab, nasal swab, or saliva sample (or respiratory sample, if hospitalized) positive for SARS-CoV-2 by RT-PCR; AND At least two symptoms: fever (≥ 38ºC), chills, myalgia, headache, sore throat, new olfactory and taste disorder; OR At least one symptom: cough, shortness of breath or difficulty breathing, OR clinical or radiographical evidence of pneumonia
CDC criteria-defined COVID-19 cases	Above, including symptoms: fatigue, headache, nasal congestion or runny nose, nausea
Severe COVID-19 (FDA guidance)	COVID-19 case with at least 1 of following: • Clinical signs at rest indicative of severe systemic illness[1] • Respiratory failure[1] • Evidence of shock[1] • Significant acute renal, hepatic, or neurologic dysfunction • Admission to an intensive care unit Death

* Acceptable test: a RT-PCR test (Cepheid; FDA approved under EUA), or other equivalent nucleic acid amplification–based test (i.e., NAAT), to detect SARS-CoV-2.

[1]Severe systemic illness: respiratory rate ≥30, heart rate ≥125, SpO_2 ≤93% on room air at sea level or PaO_2/FiO_2<300 mm Hg; respiratory failure: needing high-flow oxygen, noninvasive ventilation, mechanical ventilation, ECMO; evidence of shock: SBP <90 mm Hg, DBP <60 mm Hg, requiring vasopressors.

Outcome 2: Hospitalization for COVID-19
Studies with Unvaccinated Comparator (n=1)

Outcome	Study/population	Events/Vaccine (n/N)	Events/Placebo (n/N)	Vaccine efficacy (95% CI)
Secondary endpoint: Severe COVID-19, protocol definition [a]	No evidence of prior infection, ≥14 d post dose 2	0/13934	30/13883	100%
Severe COVID-19 (CDC) & hospitalized	**No evidence of prior infection, ≥14 d post dose 2**	0/13934	9/13883	**100%**
Alternative analyses – intention to treat population				
Severe COVID-19, protocol definition	After dose 1	1/21314	9/21259	88.9% (20.1, 99.7%)
Severe COVID-19 (CDC) & hospitalized [b]	**After dose 1**	**1/21299**	**14/21238**	**92.9% (53.2%, 99.8%)**

a. FDA definition of severe COVID-19: clinical signs at rest indicative of severe systemic illness; respiratory failure; evidence of shock; significant acute renal, hepatic, or neurologic dysfunction; admission to an intensive care unit; or death

b. CDC definition of severe COVID-19: hospitalization, admission to the ICU, intubation or mechanical ventilation, or death

Moderna phase 3 RCT Analysis Populations*

Population	Description	N*	Person-years
Per protocol	All eligible randomized participants who receive all vaccination(s) as randomized within the predefined window and have no other important protocol deviations as determined by the clinician, who did not have evidence of prior SARS-CoV-2 infection	**28,207**	**4,436**
	Including persons with prior infection	40,137	4,677
Modified Intention to treat (ITT)	All participants who received at least 1 dose, no evidence of prior/current SARS-CoV-2 infection at dose 1	43,355	7,997

*Includes participants meeting population definition through Nov 14 data cutoff date, including persons randomized on or after Oct 10. Persons aged 16-17 years, and those with stable chronic infections (i.e., HIV, Hepatitis) were enrolled later in the trial.
NOTE: for some analyses, numbers vary due to number of persons at risk for outcome