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

Megan Wallace, DrPH, MPH
ACIP Meeting
February 4, 2022
Should vaccination with Moderna COVID-19 vaccine (Spikevax, 2-dose primary series) be recommended for persons 18 years of age and older?
## PICO Question

<table>
<thead>
<tr>
<th><strong>Population</strong></th>
<th>Persons ages 18 years and older</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Intervention</strong></td>
<td>Moderna COVID-19 vaccine mRNA-1273 (100 μg, 2 doses IM, 28 days apart)</td>
</tr>
<tr>
<td><strong>Comparison</strong></td>
<td>No vaccine</td>
</tr>
<tr>
<td><strong>Outcomes</strong></td>
<td>Symptomatic laboratory-confirmed COVID-19 Hospitalization due to COVID-19 Death due to COVID-19 Asymptomatic SARS-CoV-2 infection Serious Adverse Events Reactogenicity</td>
</tr>
</tbody>
</table>

*PICO: Population, intervention, comparison, outcomes*
# Outcomes, Importance, and Data Sources

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Importance</th>
<th>Data sources</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Benefits</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Symptomatic laboratory-confirmed COVID-19</td>
<td>Critical</td>
<td>RCTs, observational studies of vaccine effectiveness</td>
</tr>
<tr>
<td>Hospitalization due to COVID-19</td>
<td>Critical</td>
<td>RCTs, observational studies of vaccine effectiveness</td>
</tr>
<tr>
<td>Death due to COVID-19</td>
<td>Important</td>
<td>RCTs, observational studies of vaccine effectiveness</td>
</tr>
<tr>
<td>Asymptomatic SARS-CoV-2 infection</td>
<td>Important</td>
<td>RCTs, observational studies of vaccine effectiveness</td>
</tr>
<tr>
<td><strong>Harms</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Serious adverse events (SAE) (including myocarditis and anaphylaxis)</td>
<td>Critical</td>
<td>RCTs for all SAEs, safety surveillance for specific SAEs</td>
</tr>
<tr>
<td>Reactogenicity</td>
<td>Important</td>
<td>RCTs</td>
</tr>
</tbody>
</table>

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

RCT: randomized controlled trial
Evidence Retrieval for Randomized Controlled Trials (RCTs)

- **Randomized Controlled Trials (RCTs)**
  - Relevant phase 1, 2, or 3 RCTs from clinicaltrials.gov
  - Unpublished data from vaccine manufacturers
  - Restricted to PICO defined population, intervention, comparison, and outcome

- **Observational Studies**
  - Peer reviewed and preprint articles from IVAC systematic review\(^a\)
  - Restricted to PICO defined population, intervention, comparison, and outcome

- **Safety Surveillance**
  - Data on safety signals identified by vaccine safety surveillance systems
  - Based on input from ACIP’s COVID-19 Vaccines Safety Technical (VaST) Work Group

\(^a\)Articles were eligible for inclusion if published before 12/10/21
Evidence Retrieval

Records identified from WHO/IVAC literature review* (n = 127)

Additional records identified through other sources** (n = 7)

Records excluded from initial review (n = 96)
72 different intervention
23 different study design
1 different outcome

Records screened (n = 134)

Records assessed for eligibility (n = 38)

Full-text articles excluded (n = 5)
4 different intervention
1 different outcome

Records included in evidence synthesis (n = 33)
5 randomized trial records
2 safety surveillance systems
26 vaccine effectiveness studies

*See https://view-hub.org/resources
** Includes 5 records from clinicaltrials.gov and 2 CDC vaccine safety surveillance systems
Observational Data (n = 26)

- 26 records identified (one or more PICO outcomes)
- Assessed risk of bias using Newcastle-Ottawa Scale (9-point scale)
  - For cohort studies: Selection of cohorts, Comparability of cohorts, Assessment of outcome
  - For case-control or test-negative design studies: Selection of cases and controls, Comparability of cases and controls, Ascertainment of exposure
- Two reviewers assessed each study for each outcome
- Serious limitations identified by score <7
Pool of Vaccine Effectiveness (VE) Estimates

- For each outcome, assessed body of evidence for suitability for pooling
  - Estimates subject to serious limitations excluded
  - Most representative study selected if multiple studies in same population
- Meta-analyses conducted
- Estimates evaluated for heterogeneity
  - Examined \( I^2 \)
  - Sensitivity analyses conducted to assess influence of study characteristics
    (e.g., special population vs. full population, preprint vs. peer-reviewed, standard/extended dosing interval, study design, circulating variants)
- Resulting pooled estimates summarize real-world data available at time of GRADE analysis
GRADE Evidence Type

- **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

- Evidence type may be downgraded due to risk of bias, inconsistency, indirectness, and imprecision. Evidence type may be upgraded or downgraded due to other considerations including publication bias or indications of dose-response gradient, large or very large magnitude of effect, and opposing residual confounding.

- **Final evidence type** may range from type 1 (high certainty) to type 4 (very low certainty)

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

- Moderna phase 3 randomized controlled trial (RCT)\textsuperscript{a,b}
- Persons ages 18 years and older in United States
- Enrolled over 30,000 participants for approximately 11,000 person years of follow-up
- Data evaluated: all eligible randomized participants who received all vaccinations as randomized within the predefined window and no other important protocol deviations, up through unblinding date (data cut-off: May 04, 2021)
  - Unblinded safety follow-up continues
- To consistently apply GRADE in a rapidly evolving pandemic, we considered the data for benefits in the context of the pandemic during the study time

\textsuperscript{a}Baden et al., New England Journal of Medicine; additional unpublished data obtained from authors
\textsuperscript{b}El Sahly et al., New England Journal of Medicine; additional unpublished data obtained from authors
# Outcome 1: Symptomatic Laboratory-confirmed COVID-19 Studies with Unvaccinated Comparator (n=1)

<table>
<thead>
<tr>
<th>Population</th>
<th>Events/Vaccine&lt;sup&gt;b&lt;/sup&gt; (n/N)</th>
<th>Events/Placebo&lt;sup&gt;b&lt;/sup&gt; (n/N)</th>
<th>Vaccine efficacy (95% confidence interval)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ages 18 years and older</td>
<td>55/14287</td>
<td>744/14164</td>
<td>92.7 (90.4, 94.4)</td>
</tr>
<tr>
<td>Ages 16–64 years</td>
<td>46/10661</td>
<td>644/10569</td>
<td>92.9 (90.5, 94.7)</td>
</tr>
<tr>
<td>Ages 65 years and older</td>
<td>9/3626</td>
<td>100/3595</td>
<td>91.1 (82.4, 95.5)</td>
</tr>
<tr>
<td>Ages 75 years and older</td>
<td>0/636</td>
<td>19/697</td>
<td>97.1 (52.3, 99.8)</td>
</tr>
<tr>
<td>At risk&lt;sup&gt;c&lt;/sup&gt;</td>
<td>16/3283</td>
<td>177/3212</td>
<td>91.2 (85.3, 94.7)</td>
</tr>
<tr>
<td>Ages 65 years and older and at risk&lt;sup&gt;d&lt;/sup&gt;</td>
<td>9/3626</td>
<td>100/3595</td>
<td>91.1 (82.4, 95.5)</td>
</tr>
<tr>
<td>Ages 18 years and older, including prior infection</td>
<td>58/15180</td>
<td>754/15166</td>
<td>92.3 (90.0, 94.1)</td>
</tr>
</tbody>
</table>

<sup>a</sup>Cases diagnosed ≥14 days post dose 2 among persons without evidence of prior SARS-CoV-2 infection  
<sup>b</sup>15180 and 15166 persons were randomized to vaccine and placebo, respectively; 14746 and 14745 in each arm had no evidence of prior infection.  
<sup>c</sup>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.
Outcome 1: Symptomatic Laboratory-confirmed COVID-19 Studies with Unvaccinated Comparator (n=1)

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*aCases diagnosed ≥14 days post dose 2 among persons without evidence of prior SARS-CoV-2 infection.

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

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<tr>
<th>Population</th>
<th>Events/Vaccine (n/N)</th>
<th>Events/Placebo (n/N)</th>
<th>Vaccine efficacy (95% confidence interval)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vaccine efficacy by timing&lt;sup&gt;a&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥14 days after dose 2&lt;sup&gt;b&lt;/sup&gt;</td>
<td>55/14287</td>
<td>744/14164</td>
<td>92.7 (90.4, 94.4)</td>
</tr>
<tr>
<td>≥14 days post dose 2 to &lt;2 months after dose 2</td>
<td>19/14278</td>
<td>227/14125</td>
<td>91.7 (86.8, 94.8)</td>
</tr>
<tr>
<td>≥2 months post dose 2 to &lt;4 months after dose 2</td>
<td>28/13984</td>
<td>434/13540</td>
<td>93.8 (90.9, 97.7)</td>
</tr>
<tr>
<td>≥4 months after dose 2 to unblinding</td>
<td>8/8424</td>
<td>83/7197</td>
<td>91.8 (83.0, 96.0)</td>
</tr>
</tbody>
</table>

<sup>a</sup>All analyses shown among persons without evidence of prior infection.

<sup>b</sup>Primary efficacy endpoint, for comparison.
Outcome 1: Symptomatic Laboratory-confirmed COVID-19
Observational Studies with Unvaccinated Comparator (n=14)\(^a\)

<table>
<thead>
<tr>
<th></th>
<th>Overall n=14</th>
<th>Peer-reviewed n=11</th>
<th>Pre-print n=3</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Design</strong></td>
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<td></td>
</tr>
<tr>
<td>- Case-control</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>- Cohort, prospective</td>
<td>2</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>- Cohort, retrospective</td>
<td>3</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>- Test-negative</td>
<td>9</td>
<td>7</td>
<td>2</td>
</tr>
<tr>
<td>- Other</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td><strong>Location</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Europe</td>
<td>4</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>- Middle East</td>
<td>2</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>- North America</td>
<td>8</td>
<td>7</td>
<td>1</td>
</tr>
<tr>
<td><strong>Most recent study period (2021)</strong></td>
<td>October</td>
<td>September</td>
<td>October</td>
</tr>
</tbody>
</table>

\(^a\) Among the 14 observational studies, 11 were included in the final pooled analysis. Reasons for exclusion from the pooled analysis were: overlapping population with included study (2) and confidence intervals for effect estimate not included in manuscript (1)
Outcome 1: Symptomatic Laboratory-confirmed COVID-19 Observational Studies with Unvaccinated Comparator (n=11)

Bruxvoort, USA, Dec 2020-March 2021
Chemaitelly, QTAR, Dec 2020-May 2021
Pilishvili, USA, Dec 2020-May 2021
Thompson, USA, Jan-June 2021
Nasreen, CAN, Dec 2020-Aug 2021
Andrews, ENG, Dec 2020-Sept 2021
Martinez-Baz, SPN, Apr-Aug 2021
Grannis, USA, June-Aug 2021
Chin, USA, July-Aug 2021
Tang, QTAR, March-Sept 2021
Nordstrom, SWE, Jan-Oct 2021

Pooled VE = 89.2% (95% CI: 82.0% to 93.6%)*

Sensitivity analyses resulted in pooled estimates ranging from 79.4% to 91.9%

Note: Studies are listed on the y-axis by study period

* Sensitivity analyses resulted in pooled estimates ranging from 79.4% to 91.9%
GRADE: Symptomatic Laboratory-confirmed COVID-19

- **RCTs (n=1)**
  - RR 0.07 (95% CI: 0.05 to 0.09)
  - No serious concerns in certainty assessment
  - Evidence type: High certainty (type 1)

- **Observational Studies (n=11)**
  - Pooled RR 0.11 (95% CI: 0.06 to 0.18)
  - No serious concerns in certainty assessment. Certainty increased due to strong association
  - Evidence type: Moderate certainty (type 2)
Outcome 2: Hospitalization due to COVID-19
Randomized Studies with Unvaccinated Comparator (n=1)

- Moderna phase 3 RCT\textsuperscript{a,b}
- **Severe COVID-19\textsuperscript{c}:** COVID-19 case with at least 1 of following:
  - Clinical signs at rest indicative of severe systemic illness;\textsuperscript{d}
  - Respiratory failure;\textsuperscript{d}
  - Evidence of shock;\textsuperscript{d}
  - Significant acute renal, hepatic, or neurologic dysfunction;
  - Admission to an intensive care unit; or
  - Death
- **Severe COVID-19 per CDC definition:** hospitalization, admission to the ICU, intubation or mechanical ventilation, or death

\textsuperscript{a} Baden et al., New England Journal of Medicine; additional unpublished data obtained from authors
\textsuperscript{b} El Sahly et al., New England Journal of Medicine; additional unpublished data obtained from authors
\textsuperscript{c} Severe COVID-19 as defined in protocol using guidance from FDA.
\textsuperscript{d} **Severe systemic illness:** respiratory rate $\geq$30, heart rate $\geq$125, $\text{SpO}_2 \leq 93\%$ on room air, or $\text{PaO}_2/\text{FiO}_2 < 300$ 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 due to COVID-19
Studies with Unvaccinated Comparator, RCT (n=1)

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Study/population</th>
<th>Events/Vaccine (n/N)</th>
<th>Events/Placebo (n/N)</th>
<th>Vaccine efficacy (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Secondary endpoint: Severe COVID-19, protocol definition(^a)</td>
<td>No evidence of prior infection, ≥14 d post dose 2</td>
<td>2/14287</td>
<td>106/14164</td>
<td>98.1 (92.4, 99.5)</td>
</tr>
<tr>
<td>Severe COVID-19 (CDC(^b)) &amp; hospitalized</td>
<td>No evidence of prior infection, ≥7 d post dose 2</td>
<td>1/14287</td>
<td>24/14164</td>
<td>95.9 (69.5, 99.4)</td>
</tr>
</tbody>
</table>

\(^a\) 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
Outcome 2: Hospitalization due to COVID-19
Observational Studies with Unvaccinated Comparator (n=19)\(^1\)

<table>
<thead>
<tr>
<th></th>
<th>Overall n=19</th>
<th>Peer-reviewed n=14</th>
<th>Pre-print n=5</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Design</strong></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Case-control</td>
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<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Cohort, prospective</td>
<td>2</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Cohort, retrospective</td>
<td>4</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Test-negative</td>
<td>13</td>
<td>10</td>
<td>3</td>
</tr>
<tr>
<td><strong>Location</strong></td>
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</tr>
<tr>
<td>Europe</td>
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</tr>
<tr>
<td>Middle East</td>
<td>2</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>North America</td>
<td>15</td>
<td>11</td>
<td>4</td>
</tr>
<tr>
<td><strong>Most recent study period (2021)</strong></td>
<td>October</td>
<td>September</td>
<td>October</td>
</tr>
</tbody>
</table>

1. Among the 19 observational studies which provided 20 VE estimates, 14 studies providing 15 estimates were included in the final pooled analysis. Reasons for exclusion from the pooled analysis were: overlapping population with included study (4) and confidence intervals for effect estimate not included in manuscript (1)
Outcome 2: Hospitalization due to COVID-19
Observational Studies with Unvaccinated Comparator (n=15)

Vaccine Effectiveness

Pooled VE = 94.8% (95% CI: 93.1% to 96.1%)*

*Sensitivity analyses resulted in pooled estimates ranging from 93.4% to 97.1%

Note: Studies are listed on the y-axis by study period
GRADE: Hospitalization due to COVID-19

- **RCTs (n=1)**
  - RR 0.04 (95% CI: 0.01–0.31)
  - Serious concerns of imprecision due to the small number of events observed from a single RCT
  - Evidence type: *Moderate certainty (type 2)*

- **Observational Studies (n=15)**
  - Pooled RR 0.05 (95% CI: 0.04–0.07)
  - No serious concerns in certainty assessment. Certainty increased due to strong association
  - Evidence type: *Moderate certainty (type 2)*
Outcome 3: Death due to COVID-19
Randomized studies with Unvaccinated Comparator (n=1)

- Moderna phase 3 randomized controlled trial (RCT)\textsuperscript{a,b}
- Death due to COVID-19 starting 14 days after second injection
  - Defined as any participant who died during the study with a cause directly attributed to a complication of COVID-19 (data cut-off: May 4, 2021)

\textsuperscript{a} Baden et al., New England Journal of Medicine; additional unpublished data obtained from authors
\textsuperscript{b} El Sahly et al., New England Journal of Medicine; additional unpublished data obtained from authors
## Outcome 3: Death due to COVID-19
Studies with Unvaccinated Comparator, RCT (n=1)

<table>
<thead>
<tr>
<th>Study/population</th>
<th>Events/Vaccine (n/N)</th>
<th>Events/Placebo (n/N)</th>
<th>VE (95% confidence interval)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Persons ages 18 years and older</td>
<td>0/14287</td>
<td>3/14164</td>
<td>100%</td>
</tr>
</tbody>
</table>
## Outcome 3: Death due to COVID-19
### Observational Studies with Unvaccinated Comparator (n=5)

<table>
<thead>
<tr>
<th></th>
<th>Overall n=5</th>
<th>Peer-reviewed n=3</th>
<th>Pre-print n=2</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Design</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Case-control</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Cohort, prospective</td>
<td>1</td>
<td>1</td>
<td>0</td>
</tr>
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<td>4</td>
<td>2</td>
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</tr>
<tr>
<td>Test-negative</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td><strong>Location</strong></td>
<td></td>
<td></td>
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<tr>
<td>Europe</td>
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<td>1</td>
<td>0</td>
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<tr>
<td>Middle East</td>
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</tr>
<tr>
<td>North America</td>
<td>4</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td><strong>Most recent study period (2021)</strong></td>
<td>October</td>
<td>September</td>
<td>October</td>
</tr>
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Outcome 3: Death due to COVID-19
Observational Studies with Unvaccinated Comparator (n=5)

Pooled VE = 93.8% (95% CI: 91.5% to 95.4%)*

*Sensitivity analyses resulted in pooled estimates ranging from 93.7% to 94.3%

Note: Studies are listed on the y-axis by study period
GRADE: Death due to COVID-19

- RCTs (n=1)
  - RR 0.14 (95% CI: 0.01 to 2.79)$^1$
  - Very serious concern of imprecision due to the small number of events observed from a single RCT
  - Evidence type: Low certainty (type 3)

- Observational Studies (n=5)
  - Pooled RR 0.06 (95% CI: 0.05 to 0.08)
  - No serious concerns in certainty assessment. Certainty increased due to strong association
  - Evidence type: Moderate certainty (type 2)

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1. RR calculated using a standard continuity correction of 0.5
Outcome 4: Asymptomatic SARS-CoV-2 Infection
Randomized Studies with Unvaccinated Comparator (n=1)

- Moderna phase 3 randomized controlled trial (RCT)a,b
- Asymptomatic SARS-CoV-2 infection
  - Negative SARS-CoV-2 status with both negative RT-PCR and negative binding antibody levels against SARS-CoV-2 at baseline (prior to dose 1)
  - AND positive RT-PCR at the participant-decision visit; OR seroconversion due to infection assessed by binding antibody levels against SARS-CoV-2 at Day 57 (28 days after dose 2)
  - AND absence of COVID-19 symptoms, including both symptoms for the primary endpoint of COVID-19 and CDC-definition of COVID-19.

a. Baden et al., New England Journal of Medicine; additional unpublished data obtained from authors
b. El Sahly et al., New England Journal of Medicine; additional unpublished data obtained from authors
### Outcome 4: Asymptomatic SARS-CoV-2 Infection
Randomized Studies with Unvaccinated Comparator (n=1)

<table>
<thead>
<tr>
<th>Population</th>
<th>Events/Vaccine (n/N)</th>
<th>Events/Placebo(^a) (n/N)</th>
<th>Vaccine efficacy (95% confidence interval)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Persons ages 18 years and older(^a)</td>
<td>214/14287</td>
<td>498/14164</td>
<td>57.4 (50.1, 63.6)</td>
</tr>
</tbody>
</table>

\(^a\)Cases diagnosed $\geq$14 days post dose 2 among persons without evidence of prior SARS-CoV-2 infection
### Outcome 4: Asymptomatic SARS-CoV-2 Infection Studies with Unvaccinated Comparator (n=3)

<table>
<thead>
<tr>
<th>Design</th>
<th>Overall n=3</th>
<th>Peer-reviewed n=3</th>
<th>Pre-print n=0</th>
</tr>
</thead>
<tbody>
<tr>
<td>Case-control</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Cohort, prospective</td>
<td>1</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Cohort, retrospective</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Test-negative</td>
<td>2</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Other</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Location</th>
<th>Overall n=3</th>
<th>Peer-reviewed n=3</th>
<th>Pre-print n=0</th>
</tr>
</thead>
<tbody>
<tr>
<td>Europe</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Middle East</td>
<td>2</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>North America</td>
<td>1</td>
<td>1</td>
<td>0</td>
</tr>
</tbody>
</table>

**Most recent study period (2021)**

- September
- September
Outcome 5: Asymptomatic SARS-CoV-2 infection
Observational Studies with Unvaccinated Comparator (n=3)

Pooled VE = 69.8% (95% CI: 60.9% to 76.7%)

Bruxvoort, USA, Dec 2020-Mar 2021
Chemaitelly, QTAR, Dec 2020-May 2021
Tang, QTAR, March-Sept 2021

Note: Studies are listed on the y-axis by study period
GRADE: Asymptomatic SARS-CoV-2 Infection

- **RCTs (n=1)**
  - RR 0.43 (95% CI: 0.36–0.50)
  - No serious concerns in certainty assessment
  - Evidence type: **High certainty (type 1)**

- **Observational Studies (n=3)**
  - Pooled RR 0.30 (95% CI: 0.23–0.39)
  - Serious concern for inconsistency because the magnitude of the relative risks from the three studies in the body of evidence varied widely
  - Evidence type: **Very low certainty (type 4)**

CI: Confidence interval; RR: Risk ratio
Harms
Outcome 5: Serious Adverse Events
Studies with Unvaccinated Comparator

Studies with Unvaccinated Comparator (n=2)
- Moderna phase 3 randomized controlled trial (RCT) (Baden 2021, El Sahly 2021)
- Moderna phase 2 randomized controlled trial (RCT) (Chu 2021)

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)
Moderná Phase 3 Randomized Controlled Trial\textsuperscript{a,b}

- Persons ages 18 years and older in United States
- Data evaluated:
  - Final analysis cut-off May 4, 2021\textsuperscript{c}
- Safety set: 15,184 vaccine; 15,162
  - All randomized participants who received at least one dose
  - Contributed any solicited adverse reaction data
  - Analyzed according to intervention actually received

\textsuperscript{a.} Baden et al., New England Journal of Medicine; additional unpublished data obtained from authors
\textsuperscript{b.} El Sahly et al., New England Journal of Medicine; additional unpublished data obtained from authors
\textsuperscript{c.} Additional follow up continues in the unblinded phase of the study
Moderna Phase 2 Randomized Controlled Trial

- Moderna phase 2 dose-confirmation randomized controlled trial (RCT)\(^a\)
- Population: healthy adults ages 18 years and older, 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

\(^a\) Chu et al., Vaccine; additional unpublished data obtained from authors
### Outcome 5: Serious Adverse Events

Studies with Unvaccinated Comparator, Randomized (n=2)

<table>
<thead>
<tr>
<th>Study/population&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Events/Vaccine (n/N)</th>
<th>% SAE Vaccine</th>
<th>Events/Placebo (n/N)</th>
<th>% SAE Placebo</th>
<th>Associated with vaccination&lt;sup&gt;b&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chu 2021</td>
<td>0/200</td>
<td>0</td>
<td>0/200</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Baden 2021, El Sahly 2021</td>
<td>268/15184&lt;sup&gt;c&lt;/sup&gt;</td>
<td>1.8</td>
<td>292/15164&lt;sup&gt;c&lt;/sup&gt;</td>
<td>1.9</td>
<td>12</td>
</tr>
</tbody>
</table>

<sup>a</sup> Included all randomized participants who received at least 1 dose of vaccine
<sup>b</sup> 15 serious adverse events reported in 12 participants were deemed by blinded investigators to be related to vaccination. These included: B-cell small lymphocytic lymphoma, Basedow’s disease, autonomic nervous system imbalance, cerebrovascular accident, multiple sclerosis, pericardial effusion, pericarditis, pleural effusion, nausea, vomiting, alopecia areata, angioedema, rheumatoid arthritis, and two reports of facial swelling.
<sup>c</sup> 32 deaths were reported the Phase 3 trial: 16 participants (0.1%) in each group. None of the deaths were considered by the investigator to be related to the intervention
Serious Adverse Events (Myocarditis)

- A rapid cycle analysis from Vaccine Safety Datalink (VSD) evaluated confirmed myocarditis and pericarditis in the 0–7-day risk interval among 18–39-year-olds compared with outcome events in vaccinated comparators on the same calendar days for Moderna COVID-19 vaccination (thru Jan 15, 2022)

<table>
<thead>
<tr>
<th>Dose</th>
<th>Events in risk interval (per million doses)</th>
<th>Events in comparison interval</th>
<th>Adjusted rate ratio (^2) (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Both doses</td>
<td>38 (21.1)</td>
<td>7</td>
<td>9.18 (4.12–22.89)</td>
</tr>
<tr>
<td>Dose 1</td>
<td>9 (9.7)</td>
<td>7</td>
<td>3.46 (1.12–11.07)</td>
</tr>
<tr>
<td>Dose 2</td>
<td>29 (33.0)</td>
<td>4</td>
<td>18.75 (6.73–64.94)</td>
</tr>
</tbody>
</table>

\(^1\) Comparison interval is 22–42 days after either dose.
\(^2\) Adjusted for VSD site, 5-year age group, sex, race/ethnicity, and calendar date.
Serious Adverse Events (Myocarditis)

- Data from the national Vaccine Adverse Event Reporting System (VAERS)\(^a\) showed an elevated ratio of observed to expected myocarditis cases in the 7-day interval following vaccination among females ages 18–29 years, and among males ages 18–49 years, with higher observed/expected ratios in males than females.

- Although VAERS data are subject to the limitations of a passive surveillance system, the elevated risk of myocarditis following Moderna vaccination is consistent with that observed in VSD.

\(^a\) Counts among persons aged 16–29 years were verified by provider interview or medical record review to meet the case definition; counts in older age groups were identified by computer search for standardized codes assigned to reports and have not been verified to meet case definition.
Serious Adverse Events (Anaphylaxis)

- A rapid cycle analysis of data from VSD evaluated chart-reviewed cases of anaphylaxis among all vaccinated persons aged 18 years and older. Based on events occurring in a 0–1 day risk interval after vaccination, the estimated incidence of confirmed anaphylaxis was 5.1 (95% CI 3.3–7.6) per million doses.¹

GRADE: Serious Adverse Events

- **RCTs (n=2)**
  - Pooled RR 0.92 (95% CI: 0.78–1.08)
  - Serious concern for imprecision because the CI indicates that both reduced and increased risk of serious adverse events are possible
  - Evidence type: **Moderate certainty (type 2)**

- **Observational Studies (n=2)**
  - Two specific, rare SAEs have been associated with vaccination through safety surveillance
  - No serious concerns in certainty assessment
  - Evidence type: **Low certainty (type 3)**
Outcome 6: Reactogenicity, Severe (Grade ≥3) Definitions

- The phase 2 and 3 RCTs 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; 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, muscle pain, or joint pain that prevents daily activity
  - **Grade 4**: fever >40.0°C, fatigue, headache, muscle pain, joint pain, or vomiting that require emergency room visit or hospitalization
Outcome 6: Reactogenicity, Severe (Grade ≥3) Studies with Unvaccinated Comparator (n=2)

<table>
<thead>
<tr>
<th>Study/population</th>
<th>Events/Vaccine (n/N)</th>
<th>% Vaccine</th>
<th>Events/Placebo (n/N)</th>
<th>% Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chu 2021</td>
<td>32/200</td>
<td>16.0</td>
<td>6/200</td>
<td>3.0</td>
</tr>
<tr>
<td>Baden 2021, El Sahly 2021</td>
<td>3243/15179</td>
<td>22.6</td>
<td>679/15159</td>
<td>4.5</td>
</tr>
</tbody>
</table>
GRADE: Reactogenicity, Severe (Grade ≥3)

- RCTs (n=2)
  - Pooled RR 5.03 (95% CI: 4.65–5.45)
  - No serious concerns in certainty assessment
  - Evidence type: **High certainty (type 1)**
# Summary of GRADE

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Importance</th>
<th>Design (# of studies)</th>
<th>Findings</th>
<th>Evidence type</th>
</tr>
</thead>
<tbody>
<tr>
<td>Symptomatic laboratory-confirmed COVID-19</td>
<td>Critical</td>
<td>RCT (1) OBS (11)</td>
<td>Moderna COVID-19 vaccine is effective in preventing symptomatic COVID-19</td>
<td>High</td>
</tr>
<tr>
<td>Hospitalization due to COVID-19</td>
<td>Critical</td>
<td>RCT (1) OBS (15)</td>
<td>Moderna COVID-19 vaccine prevents hospitalization due to COVID-19</td>
<td>Moderate</td>
</tr>
<tr>
<td>Death due to COVID-19</td>
<td>Important</td>
<td>RCT (1) OBS (5)</td>
<td>Moderna COVID-19 vaccine prevents death due to COVID-19</td>
<td>Moderate</td>
</tr>
<tr>
<td>Asymptomatic SARS-CoV-2 infection</td>
<td>Important</td>
<td>RCT (1) OBS (3)</td>
<td>Moderna COVID-19 vaccine is effective in preventing asymptomatic SARS-CoV-2 infection</td>
<td>High</td>
</tr>
<tr>
<td>Serious adverse events</td>
<td>Critical</td>
<td>RCT (2)</td>
<td>In the RCT, SAEs were balanced between vaccine and placebo arms. In post-authorization safety monitoring, myocarditis and anaphylaxis were rare but more common following vaccination</td>
<td>Moderate</td>
</tr>
<tr>
<td>Reactogenicity</td>
<td>Important</td>
<td>RCT (2)</td>
<td>Severe reactions within 7 days were more common in vaccinated; any grade ≥3 reaction was reported by 21.3% of vaccinated vs. 4.5% of placebo group</td>
<td>High</td>
</tr>
</tbody>
</table>
Limitations

- In this rapidly evolving pandemic, the available body of evidence often does not represent the most recent epidemiology, including the impact of a new dominant variant on VE.
  - The evidence available for inclusion in this GRADE does not capture the impact of the Omicron variant on vaccine effectiveness

- The VE estimates presented represent the best estimates within the context of the pandemic during the time of the studies but may not be representative of VE in different phases of the pandemic or with different circulating variants.
  - The evidence available for inclusion in this GRADE is predominantly from time periods in which Alpha and Delta were the dominant circulating variants
Conclusion

- Policy question focuses on recommendation following licensure of Moderna COVID-19 vaccine primary series that has been in use for a year under an emergency use authorization

- **Benefits**: Supported by body of evidence from RCTs and observational studies
  - RCT evidence demonstrated efficacy for all beneficial outcomes, including the 2 critical outcomes: symptomatic disease and hospitalization. Efficacy data were further supported by body of evidence from observational studies.

- **Harms**:
  - Grade 3 reactions were more common in vaccine than placebo recipients
  - Serious adverse events occurred at a similar frequency in vaccine and placebo groups
  - Two specific, rare SAEs have been associated with vaccination through safety surveillance
Acknowledgements

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- VTF ACIP WG Team
- ACIP COVID-19 Vaccines Work Group
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1-800-CDC-INFO (232-4636)

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.

Thank you