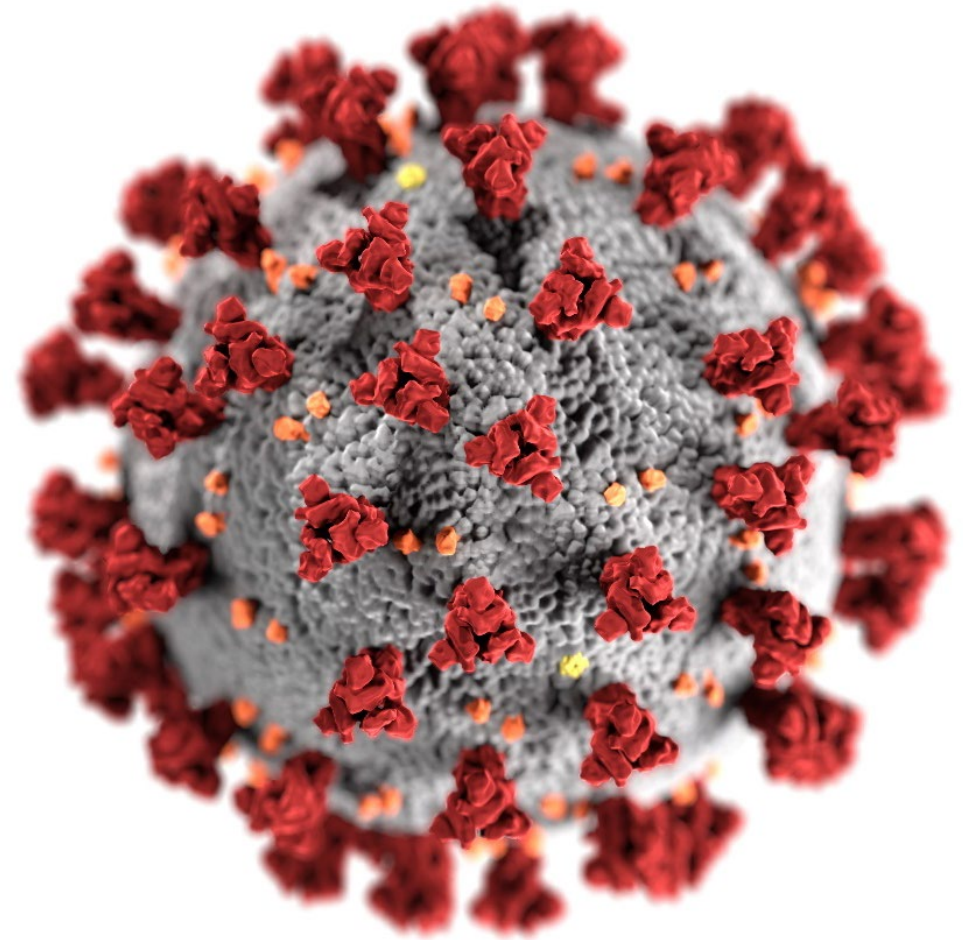# Grading of Recommendations, Assessment, Development, and Evaluation (GRADE): Moderna COVID-19 Vaccine

Megan Wallace, DrPH, MPH
ACIP Meeting
February 4, 2022

Policy Question

- Should vaccination with Moderna COVID-19 vaccine (Spikevax, 2-dose primary series) be recommended for persons 18 years of age and older?

PICO Question

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

PICO: Population, intervention, comparison, outcomes

Outcomes, Importance, and Data Sources

Outcome	Importance[a]	Data sources
Benefits		
Symptomatic laboratory-confirmed COVID-19	Critical	RCTs, observational studies of vaccine effectiveness
Hospitalization due to COVID-19	Critical	RCTs, observational studies of vaccine effectiveness
Death due to COVID-19	Important	RCTs, observational studies of vaccine effectiveness
Asymptomatic SARS-CoV-2 infection	Important	RCTs, observational studies of vaccine effectiveness
Harms		
Serious adverse events (SAE) (including myocarditis and anaphylaxis)	Critical	RCTs for all SAEs, safety surveillance for specific SAEs
Reactogenicity	Important	RCTs

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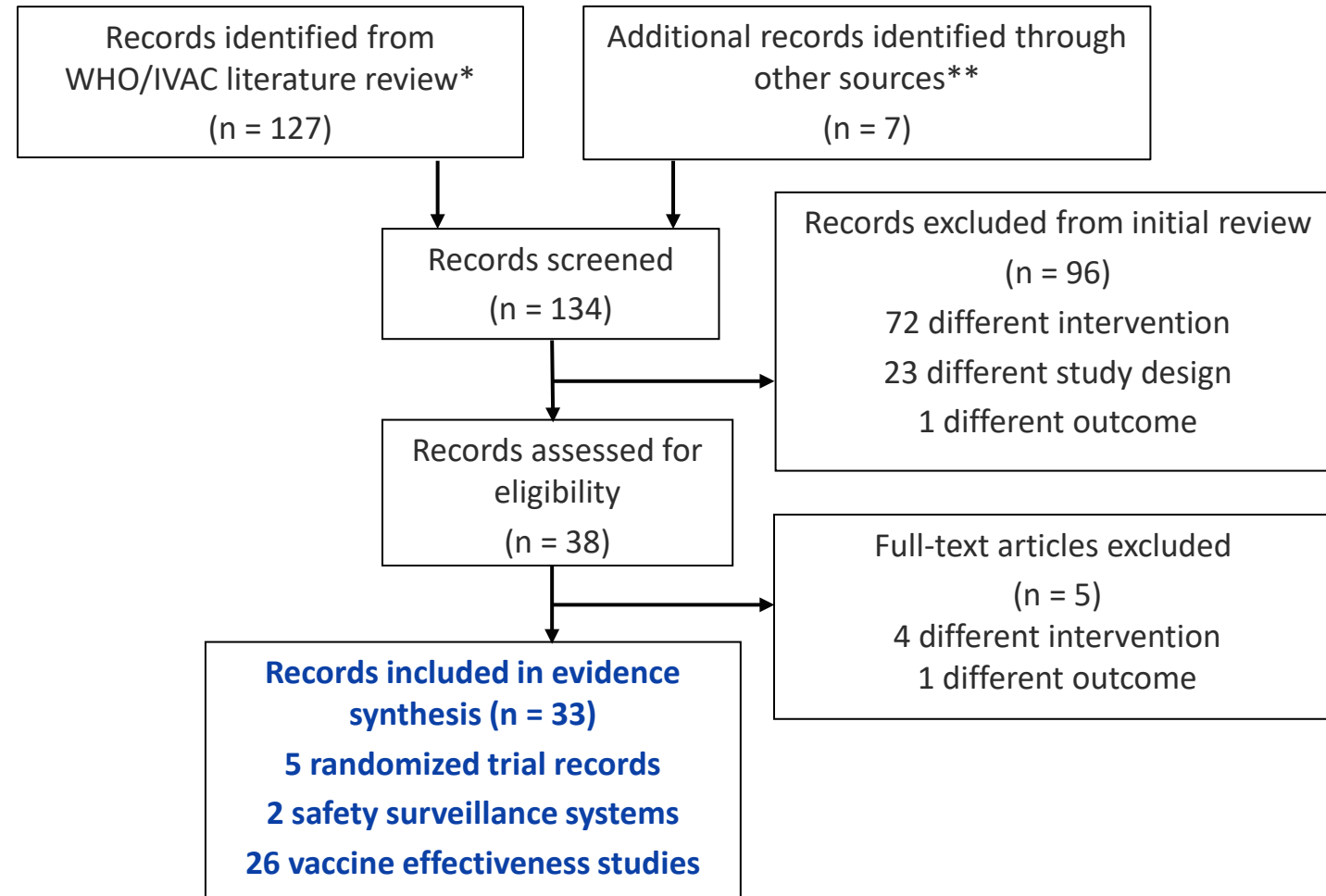
RCT: randomized controlled trial

Evidence Retrieval for Randomized Controlled Trials (RCTs)

- **Randomized Controlled Trials (RCTs)**
  - Relevant phase 1, 2, or 3 RCTs from clinicaltrails.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  - Unpublished data from vaccine manufacturers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

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┌─────────────────────────────┐        ┌─────────────────────────────────┐
│   Records identified from   │        │ Additional records identified    │
│  WHO/IVAC literature review*│        │      through other sources**     │
│          (n = 127)          │        │            (n = 7)               │
└─────────────────────────────┘        └─────────────────────────────────┘
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Records screened
(n = 134)

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

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

Pooling 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)[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

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

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

[a]Cases diagnosed ≥14 days post dose 2 among persons without evidence of prior SARS-CoV-2 infection
[b]15180 and 15166 persons were randomized to vaccine and placebo, respectively; 14746 and 14745 in each arm had no evidence of prior infection.
[c]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)

Population[a]	Events/Vaccine[b] (n/N)	Events/Placebo[b] (n/N)	Vaccine efficacy (95% confidence interval)
Ages 18 years and older	55/14287	744/14164	92.7 (90.4, 94.4)
Ages 16–64 years	46/10661	644/10569	92.9 (90.5, 94.7)
Ages 65 years and older	9/3626	100/3595	91.1 (82.4, 95.5)
Ages 75 years and older	0/636	19/697	97.1 (52.3, 99.8)
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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% confidence interval)
Vaccine efficacy by timing[a]			
≥14 days after dose 2[b]	55/14287	744/14164	92.7 (90.4, 94.4)
≥14 days post dose 2 to <2 months after dose 2	19/14278	227/14125	91.7 (86.8, 94.8)
≥2 months post dose 2 to <4 months after dose 2	28/13984	434/13540	93.8 (90.9, 97.7)
≥4 months after dose 2 to unblinding	8/8424	83/7197	91.8 (83.0, 96.0)

[a]All analyses shown among persons without evidence of prior infection.
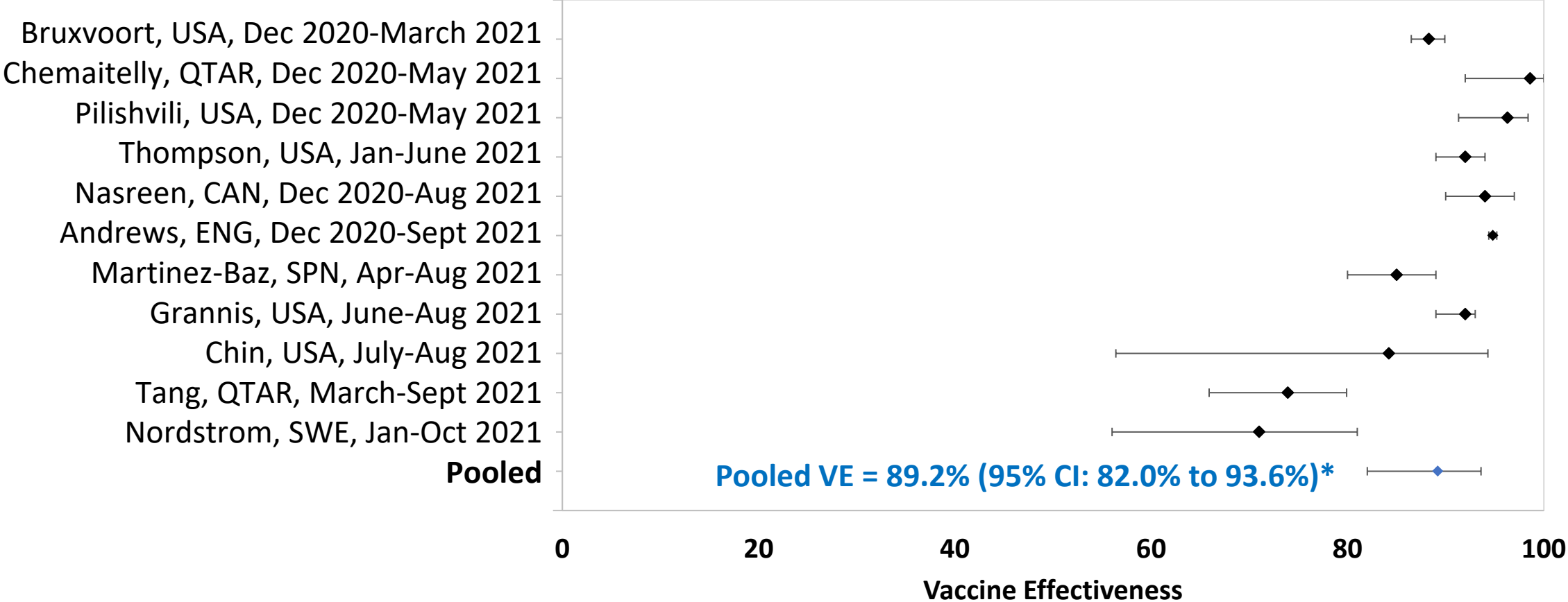[b]Primary efficacy endpoint, for comparison.

Outcome 1: Symptomatic Laboratory-confirmed COVID-19 Observational Studies with Unvaccinated Comparator (n=14)[a]

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

[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)

Forest plot of Vaccine Effectiveness (x-axis 0 to 100):

- 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**: 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

16

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)**

CI: Confidence interval; **RR:** Risk ratio

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

- Moderna phase 3 RCT[a,b]

- <u>Severe COVID-19[c]</u>: COVID-19 case with at least 1 of following:
  - Clinical signs at rest indicative of severe systemic illness;[d]
  - Respiratory failure;[d]
  - Evidence of shock;[d]
  - Significant acute renal, hepatic, or neurologic dysfunction;
  - Admission to an intensive care unit; or
  - Death

- <u>Severe COVID-19 per CDC definition</u>: hospitalization, admission to the ICU, intubation or mechanical ventilation, or death

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
c. Severe COVID-19 as defined in protocol using guidance from FDA.
d. **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 due to COVID-19 Studies with Unvaccinated Comparator, RCT (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	2/14287	106/14164	98.1 (92.4, 99.5)
Severe COVID-19 (CDC[b]) & hospitalized	**No evidence of prior infection, ≥7 d post dose 2**	**1/14287**	**24/14164**	**95.9 (69.5, 99.4)**

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

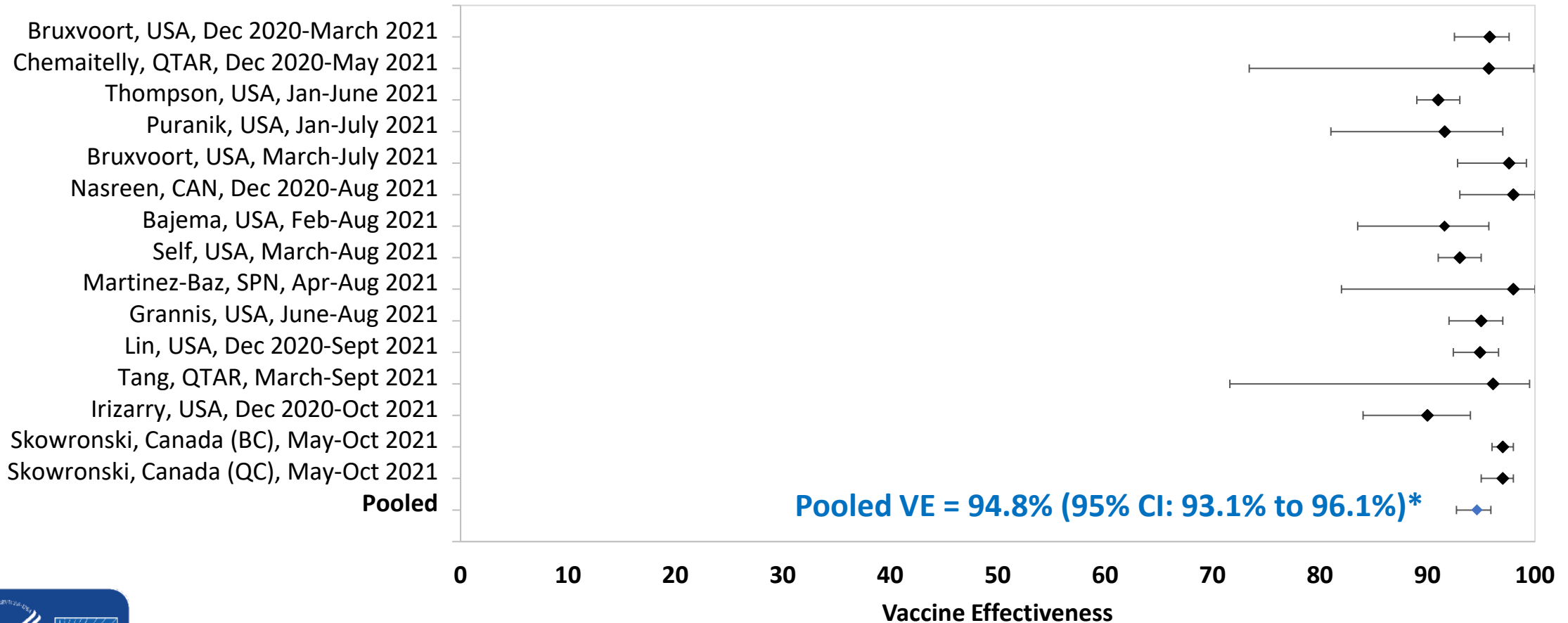# Outcome 2: Hospitalization due to COVID-19 Observational Studies with Unvaccinated Comparator (n=19)[1]

	Overall n=19	Peer-reviewed n=14	Pre-print n=5
Design			
- Case-control	0	0	0
- Cohort, prospective	2	2	0
- Cohort, retrospective	4	2	2
- Test-negative	13	10	3
Location			
- Europe	2	1	1
- Middle East	2	2	0
- North America	15	11	4
Most recent study period (2021)	October	September	October

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)

Forest plot showing Vaccine Effectiveness (x-axis: 0 to 100) for the following studies:
- Bruxvoort, USA, Dec 2020-March 2021
- Chemaitelly, QTAR, Dec 2020-May 2021
- Thompson, USA, Jan-June 2021
- Puranik, USA, Jan-July 2021
- Bruxvoort, USA, March-July 2021
- Nasreen, CAN, Dec 2020-Aug 2021
- Bajema, USA, Feb-Aug 2021
- Self, USA, March-Aug 2021
- Martinez-Baz, SPN, Apr-Aug 2021
- Grannis, USA, June-Aug 2021
- Lin, USA, Dec 2020-Sept 2021
- Tang, QTAR, March-Sept 2021
- Irizarry, USA, Dec 2020-Oct 2021
- Skowronski, Canada (BC), May-Oct 2021
- Skowronski, Canada (QC), May-Oct 2021
- Pooled

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)**

CI: Confidence interval; **RR:** Risk ratio

Outcome 3: Death due to COVID-19
Randomized studies with Unvaccinated Comparator (n=1)

- Moderna phase 3 randomized controlled trial (RCT)[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)

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 3: Death due to COVID-19
Studies with Unvaccinated Comparator, RCT (n=1)

Study/population	Events/Vaccine (n/N)	Events/Placebo (n/N)	VE (95% confidence interval)
Persons ages 18 years and older	0/14287	3/14164	100%

Outcome 3: Death due to COVID-19
Observational Studies with Unvaccinated Comparator (n=5)

	Overall n=5	Peer-reviewed n=3	Pre-print n=2
Design			
- Case-control	0	0	0
- Cohort, prospective	1	1	0
- Cohort, retrospective	4	2	2
- Test-negative	0	0	0
Location			
- Europe	1	1	0
- Middle East	0	0	0
- North America	4	2	2
Most recent study period (2021)	October	September	October

Outcome 3: Death due to COVID-19
Observational Studies with Unvaccinated Comparator (n=5)

*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)**

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)

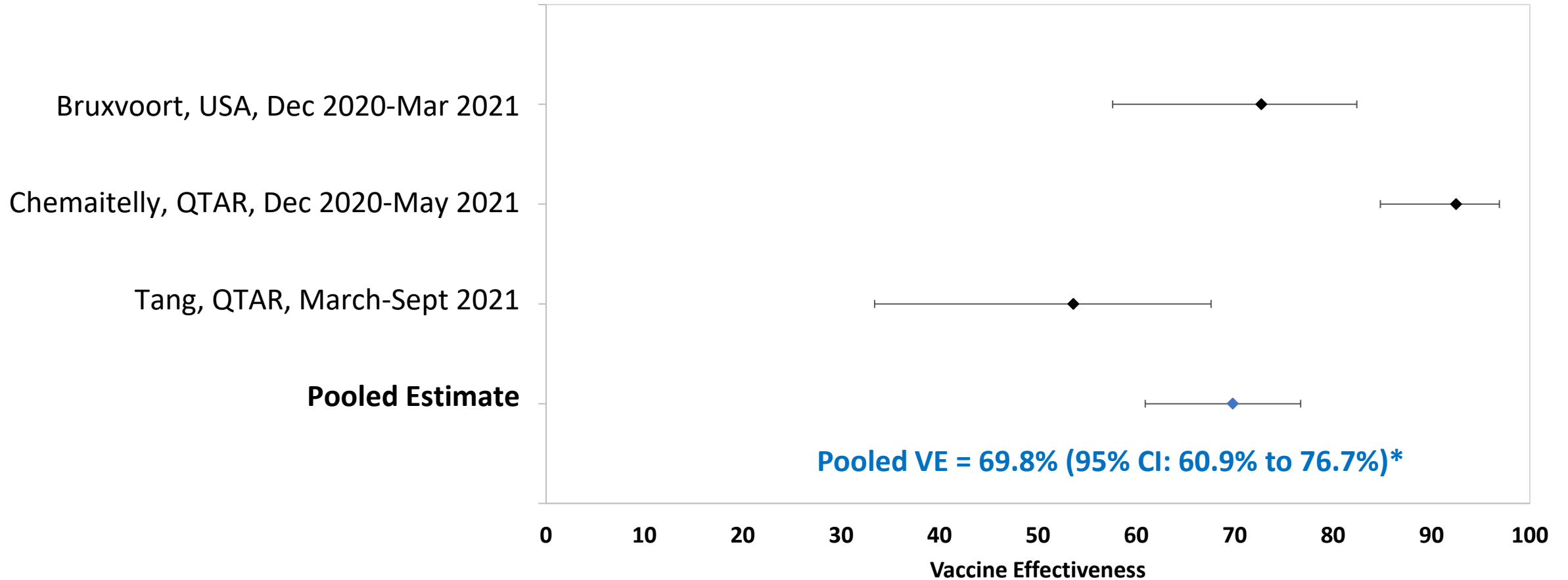| Population	Events/Vaccine (n/N)	Events/Placebo[a] (n/N)	Vaccine efficacy (95% confidence interval)
Persons ages 18 years and older[a]	214/14287	498/14164	57.4 (50.1, 63.6)

[a]Cases diagnosed ≥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)

	Overall n=3	Peer-reviewed n=3	Pre-print n=0
Design			
- Case-control	0	0	0
- Cohort, prospective	1	1	0
- Cohort, retrospective	0	0	0
- Test-negative	2	2	0
- Other	0	0	0
Location			
- Europe	0	0	0
- Middle East	2	2	0
- North America	1	1	0
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%)*

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)**

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)

Moderna Phase 3 Randomized Controlled Trial[a,b]

- Persons ages 18 years and older in United States
- Data evaluated:
  - Final analysis cut-off May 4, 2021[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

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
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)

Study/population[a]	Events/Vaccine (n/N)	% SAE Vaccine	Events/Placebo (n/N)	% SAE Placebo	Associated with vaccination[b]
Chu 2021	0/200	0	0/200	0	0
Baden 2021, El Sahly 2021	268/15184[c]	1.8	292/15164[c]	1.9	12

a. Included all randomized participants who received at least 1 dose of vaccine
b. 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.
c. 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)

Dose	Events in risk interval (per million doses)	Events in comparison interval [1]	Adjusted rate ratio [2] (95% CI)
Both doses	38 (21.1)	7	9.18 (4.12–22.89)
Dose 1	9 (9.7)	7	3.46 (1.12–11.07)
Dose 2	29 (33.0)	4	18.75 (6.73–64.94)

[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]

1. Klein et al. Surveillance for Adverse Events After COVID-19 mRNA Vaccination. JAMA. 2021;326(14):1390-1399

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)**

CI: Confidence interval; **RR:** Risk ratio

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)

Study/population	Events/Vaccine (n/N)	% Vaccine	Events/Placebo (n/N)	% Placebo
Chu 2021	32/200	16.0	6/200	3.0
Baden 2021, El Sahly 2021	3243/15179	22.6	679/15159	4.5

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)**

CI: Confidence interval; **RR:** Risk ratio

Summary of GRADE

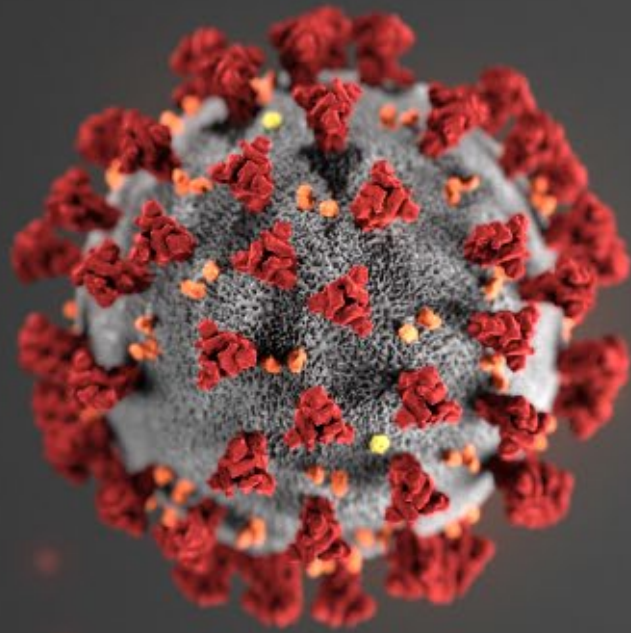| Outcome	Importance	Design (# of studies)	Findings	Evidence type
Benefits				
Symptomatic laboratory-confirmed COVID-19	Critical	RCT (1) OBS (11)	Moderna COVID-19 vaccine is effective in preventing symptomatic COVID-19	**High**
Hospitalization due to COVID-19	Critical	RCT (1) OBS (15)	Moderna COVID-19 vaccine prevents hospitalization due to COVID-19	**Moderate**
Death due to COVID-19	Important	RCT (1) OBS (5)	Moderna COVID-19 vaccine prevents death due to COVID-19	**Moderate**
Asymptomatic SARS-CoV-2 infection	Important	RCT (1) OBS (3)	Moderna COVID-19 vaccine is effective in preventing asymptomatic SARS-CoV-2 infection	**High**
Harms				
Serious adverse events	Critical	RCT (2)	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	**Moderate**
Reactogenicity	Important	RCT (2)	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	**High**

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

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- ACIP COVID-19 Vaccines Work Group

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Thank you