

# Grading of Recommendations, Assessment, Development, and Evaluation (GRADE): Moderna COVID-19 Vaccine for Children Aged 6 Months–5 Years

## Overview

A Grading of Recommendations, Assessment, Development and Evaluation (GRADE) review of the evidence for benefits and harms for Moderna coronavirus disease 2019 (COVID-19) vaccine for children aged 6 months–5 years was presented to the Advisory Committee for Immunization Practices (ACIP) on June 18, 2022. GRADE evidence type indicates the certainty in estimates from the available body of evidence. Evidence certainty ranges from type 1 (high certainty) to type 4 (very low certainty) [1].

The policy question was, “Should vaccination with Moderna COVID-19 vaccine (2 doses, 25 µg) be recommended for children 6 months–5 years of age during an Emergency Use Authorization?” The potential benefits pre-specified by the ACIP COVID-19 Vaccines Work Group included prevention of symptomatic laboratory-confirmed COVID-19 (critical), hospitalization due to COVID-19 (important), multisystem inflammatory syndrome in children (MIS-C) (important), and asymptomatic SARS-CoV-2 infection (important). The two pre-specified harms were serious adverse events (SAEs) (critical) and reactogenicity grade  $\geq 3$  (important).

A systematic review of evidence on the efficacy and safety of a two-dose regimen of Moderna COVID-19 vaccine among children aged 6 months–5 years was conducted. The quality of evidence from one Phase II/III randomized controlled trial was assessed using a modified GRADE approach [2].

A lower risk of symptomatic COVID-19 was observed with vaccination compared with placebo (relative risk [RR]: 0.62; 95% confidence interval [CI]: 0.49, 0.79, evidence type 1). Immunobridging was also assessed. In both age groups, 6–23 months and 2–5 years, the immune response to vaccine was non-inferior to that observed in adults ages 18–25 years (6–23 months GMR: 1.28; 95% CI: 1.12, 1.47; 2–5 years GMR: 1.01; 95% CI: 0.88, 1.17; evidence type 2). There was also a lower risk of asymptomatic SARS-CoV-2 infection seen in the vaccine group compared with the placebo group, however the confidence interval crossed the line of no effect (RR: 0.84; 95% CI: 0.60, 1.19; evidence type 3). The available data indicated that SAEs were more common in vaccine recipients, but certainty in the estimate was very low (RR 2.67; 95% CI: 0.80, 8.84; evidence type 4). Two serious adverse events in one participant were determined by the Food and Drug Administration (FDA) as potentially related to the vaccination. No specific safety concerns were identified among vaccine recipients aged 6 months–5 years. Reactogenicity grade  $\geq 3$  was associated with vaccination (RR 1.87; 95% CI: 1.44, 2.42); evidence type 1). About 7.7% of vaccine recipients and 4.4% of placebo recipients reported any grade  $\geq 3$  local or systemic reactions following either dose 1 or dose 2.

## Introduction

On June 17, 2022, the FDA updated the Emergency Use Authorization (EUA) for Moderna (mRNA-1273) vaccine for prevention of symptomatic COVID-19 to include children aged 6 months–5 years [3]. As part of the process employed by the ACIP, a systematic review and GRADE evaluation of the evidence for Moderna COVID-19 vaccine was conducted and presented to ACIP. The ACIP adopted a modified GRADE approach in 2010 as the framework for evaluating the scientific evidence that informs recommendations for vaccine use. Evidence of benefits and harms were reviewed based on the GRADE approach [1].

The policy question was, “Should vaccination with Moderna COVID-19 vaccine (2 doses, 25 µg) be recommended for persons 6 months–5 years of age during an Emergency Use Authorization?” (Table 1).

## Methods

We conducted a systematic review of evidence on the efficacy and safety of a two-dose regimen (25 µg per dose) of Moderna COVID-19 vaccine. We assessed outcomes and evaluated the quality of evidence using the GRADE approach.

During Work Group calls, members were asked to pre-specify and rate the importance of relevant patient-important outcomes (including benefits and harms) before the GRADE assessment. No conflicts of interest were reported by CDC and ACIP COVID-19 Vaccines Work Group members involved in the GRADE analysis. Outcomes of interest included individual benefits and harms ([Table 2](#)). The critical benefit of interest was prevention of symptomatic laboratory-confirmed COVID-19. Other important outcomes included prevention of hospitalization due to COVID-19, prevention of MIS-C, and prevention of asymptomatic SARS-CoV-2 infection. The critical harm of interest was serious adverse events, including death; reactogenicity grade  $\geq 3$  was deemed an important harm. Hospitalization and MIS-C were not included in the evidence profile because no data were available.

We identified clinical trials through [clinicaltrials.gov](#). Records of relevant Phase I, II, or III RCTs of COVID-19 vaccine were included if they 1) provided data on children aged 6 months–5 years vaccinated with mRNA-1273; 2) involved human subjects; 3) reported primary data; and 4) included data relevant to the efficacy and safety outcomes being measured. We identified relevant observational studies through an ongoing systematic review conducted by the International Vaccine Access Center (IVAC) and the World Health Organization (WHO). In addition, unpublished and other relevant data were obtained by hand-searching reference lists, and consulting with vaccine manufacturers and subject matter experts. The systematic review was limited to studies published from January 1, 2020 to April 29, 2022. Characteristics of all included studies are shown in [Appendix 1](#) and evidence retrieval methods are found in [Appendix 2](#).

Relative risks (RR) were calculated from numerators and denominators available in the body of evidence. Vaccine efficacy estimates were defined as  $100\% \times (1 - RR)$ . Immunobridging data comparing geometric mean neutralizing antibody titers (GMTs) in 6–23-month-olds and 2–5-year-olds to those in 18–25-year-olds in whom clinical efficacy was previously established.

The evidence certainty assessment addressed risk of bias, inconsistency, indirectness, imprecision, and other characteristics. The GRADE assessment across the body of evidence for each outcome was presented in an evidence profile; the evidence certainty of Type 1, 2, 3, or 4 corresponds to high, moderate, low, or very low certainty, respectively.

## Results

The results of the GRADE assessment were presented to ACIP on June 18, 2022. One study was reviewed that provided data on outcomes specified for GRADE ([Appendix 1](#)). Data were reviewed from one Phase II/III randomized controlled trial using data provided by the sponsor [2]. Symptomatic COVID-19 was less common among the vaccine group compared with the placebo group (RR: 0.62; 95% CI: 0.49, 0.79) ([Table 3a](#), [Table 4](#)). No serious concerns impacted the certainty of the estimate. The immune response to the Moderna COVID-19 vaccine among children aged 6 months–5 years was evaluated separately, 6–23 months and 2–5 years. The immune response for both age groups were non-inferior (6-23 months: GMR: 1.28; 95% CI: 1.12, 1.47; 2-5 years: GMR: 1.01; 95% CI: 0.088, 1.17) to the immune response among adults aged 18–25 years receiving the Moderna COVID-19 vaccine in whom clinical efficacy had been established ([Table 3b](#)). Serious concern for indirectness was noted because immunogenicity is a surrogate measure of efficacy. A lower risk of asymptomatic SARS-CoV-2 infection was also seen in the vaccine group compared with the placebo group, though the 95% CI crossed the null (RR: 0.84; 95% CI: 0.60, 1.19), based on an analysis of seronegative participants with SARS-CoV-2 positive PCR test results from nasopharyngeal swabs at scheduled or unscheduled visits ([Table 3c](#)). Serious concern for indirectness was noted because the outcome of interest was asymptomatic infection assessed with serial PCR testing for SARS-CoV-2 or seroconversion to a non-spike protein and the available evidence represent SARS-CoV-2 testing of the full cohort at a single point in time. Serious concern for imprecision was also noted due to the width of the confidence interval containing estimates for which different policy decisions might be considered.

For evaluation of potential harms, data were reviewed from the Phase II/III randomized controlled trial. Serious adverse events were more common in vaccine recipients, but certainty in the estimate was very low (RR: 2.67; 95% CI: 0.80, 8.84). There was serious concern of indirectness because the body of evidence does not provide certainty that rare serious adverse events were captured due to the follow-up of 70 days after dose 2. There was also very serious concern for imprecision, due to the 95% confidence interval crossing the line of no effect ([Table 3d](#)). One vaccine recipient experienced two SAEs (fever and febrile seizure) that the investigator and FDA determined to be potentially related to the vaccine. There were no cases of vaccine-associated enhanced disease or deaths. Severe (grade  $\geq 3$ ) local or systemic reactions within 7 days following either vaccination, were reported by 7.7% of vaccine recipients and occurred more frequently in the vaccine than placebo group ([Table 3e](#)). No serious concerns impacted the certainty of the estimate of reactogenicity.

# GRADE Summary

The initial GRADE evidence level was type 1 (high) for each outcome because the body of evidence was from a randomized controlled trial (Table 4). In terms of benefits, the available data indicated that the vaccine was efficacious for preventing symptomatic COVID-19 and no serious concerns impacting certainty in the estimate were identified for this outcome (type 1, high). Protection from symptomatic COVID-19, assessed through immunobridging, was downgraded due to indirectness (type 2, moderate). The outcome of asymptomatic COVID-19 was less certain, noting serious concern for indirectness and impression (type 3, low). The certainty in the estimate of the effect for serious adverse events was downgraded one point due to serious concern of indirectness and two points for imprecision (type 4, very low certainty). No serious concerns impacted the certainty in the estimate of reactogenicity (type 4, high certainty) (Table 4).

## References



1. Ahmed F. U.S. Advisory Committee on Immunization Practices (ACIP) [Handbook for Developing Evidence-based Recommendations.pdf icon](#) 
2. Moderna, 2022. personal communication, March 22 – June 3, 2022.
3. Food and Drug Administration. Moderna COVID-19 Vaccine Emergency Use Authorization. <https://www.fda.gov/media/144636/download>  . Accessed June 17, 2022.
4. International Vaccine Access Center (IVAC), Johns Hopkins Bloomberg School of Public Health. VIEW-hub. [www.view-hub.org](http://www.view-hub.org). Accessed: 4/29/2022.

Table 1: Policy Question and PICO

<b>Policy question:</b>	Should vaccination with Moderna COVID-19 vaccine (2-doses, 25 µg) be recommended for children aged 6 months-5 years?
<b>Population</b>	Children aged 6 months-5 years
<b>Intervention</b>	Moderna COVID-19 vaccine mRNA-1273 (25 µg, 2 doses IM, 28 days apart)
<b>Comparison</b>	No Moderna COVID-19 vaccine
<b>Outcomes</b>	Symptomatic laboratory-confirmed COVID-19 Hospitalization due to COVID-19 Multisystem inflammatory syndrome in children (MIS-C) Asymptomatic SARS-CoV-2 infection Serious adverse events Reactogenicity grade $\geq 3$

Abbreviations: IM = intramuscular.

Table 2: Outcomes and Rankings

Outcome	Importance	Included in evidence profile
Symptomatic laboratory-confirmed COVID-19	Critical	Yes
Hospitalization due to COVID-19	Important	No <sup>a</sup>
Multisystem inflammatory syndrome in children (MIS-C)	Important	No <sup>a</sup>
Asymptomatic SARS-CoV-2 infection	Important	Yes
Serious adverse events	Critical	Yes

Outcome	Importance	Included in evidence profile
Reactogenicity grade $\geq 3$	Important	Yes

<sup>a</sup>No events were observed in study identified in the review of evidence.

**Table 3a: Summary of Studies Reporting Symptomatic Laboratory-confirmed COVID-19**

Authors last name, pub year	Age or other characteristic of importance	n/N intervention	n/N comparison	Comparator	Vaccine Efficacy (95% CI) [100 x (1-RR)]	Study limitations (Risk of Bias)
Moderna, 2022 [2] <sup>a</sup>	SARS-CoV-2 RT-PCR-positive symptomatic illness <sup>b</sup> , in seronegative or seropositive persons aged 6 months-5 years, $\geq 14$ days post second dose	181/4791	97/1597	Placebo	37.8% (20.9%, 51.1%)	Not serious

**Abbreviations:** RT-PCR = real-time polymerase chain reaction; CI = confidence interval; RR = relative risk.

<sup>a</sup>Based on data cutoff February 21, 2021; participants had a median 70 days of follow-up.

<sup>b</sup>RT-PCR symptomatic illness defined as: a positive post-baseline PCR result, and at least 1 systemic symptom: fever (temperature  $> 38^{\circ}\text{C}/\geq 100.4^{\circ}\text{F}$ ) or chills (of any duration, including  $\leq 48$  hours), fatigue, headache, myalgia, nasal congestion or rhinorrhea, new loss of taste or smell, sore throat, abdominal pain, diarrhea, nausea/vomiting, poor appetite/poor feeding, OR respiratory signs/symptoms: cough (of any duration, including  $\leq 48$  hours), shortness of breath or difficulty breathing (of any duration, including  $\leq 48$  hours)

**Table 3b: Summary of Studies Reporting Symptomatic Laboratory-confirmed COVID-19 (assessed using immunobridging)**

Authors last name, pub year	Age or other characteristic of importance	n 6 Months- <2 Years	n 18-25 Years	GMR <sup>c</sup> (95%CI)	Met Noninferiority Objective <sup>d</sup>	Study limitations (Risk of Bias)
Moderna, 2022 [2] <sup>a</sup>	Pseudovirus neutralizing antibody level by pseudovirus neutralizing assay (ID50) Pseudovirus neutralizing antibody level by pseudovirus neutralizing assay (ID50) <sup>a</sup>	230	291	1.28 (1.12, 1.47)	Yes	Not serious

Authors last name, pub year	Age or other characteristic of importance	n 2-5 Years	n 18-25 Years	GMR <sup>c</sup> (95%CI)	Met Noninferiority Objective <sup>d</sup>	Study limitations (Risk of Bias)

Authors last name, pub year	Age or other characteristic of importance	n 2-5 Years	n 18-25 Years	GMR <sup>c</sup> (95%CI)	Met Noninferiority Objective <sup>d</sup>	Study limitations (Risk of Bias)
Moderna, 2022 [2] <sup>a</sup>	Pseudovirus neutralizing antibody level by pseudovirus neutralizing assay (ID50) Pseudovirus neutralizing antibody level by pseudovirus neutralizing assay (ID50) <sup>a</sup>	264	291	1.01 (0.9, 1.17)	Yes	Not serious

**Abbreviations:** GMR= geometric mean ratio; CI = confidence interval; LLOQ = lower limit of quantitation

<sup>a</sup>Immune response was measured at Day 57

<sup>b</sup>Among participants immunologic or virologic evidence of prior COVID-19 (ie, negative NP swab test at Day 1 and/or binding antibodies against SARS-CoV-2 nucleocapsid below limit of detection or lower limit of quantification) at Day 1 before the first dose of IP.

<sup>c</sup>GMRs and 2-sided 95% CIs were calculated by exponentiating the mean difference of the logarithms of the titers (Group 1 [6 months-2 years or 2-5 years] – Group 2 [18-25 years]) and the corresponding CI (using t-distribution).

<sup>d</sup>Noninferiority is declared if the lower bound of the 2-sided 95% CI for the GMR is greater than 0.67.

### Table 3c: Summary of Studies Reporting Asymptomatic SARS-CoV-2 Infection

Authors last name, pub year	Age or other characteristic of importance	n/N (%) intervention	n/N (%) comparison	Comparator	Vaccine Efficacy (95% CI) [100 x (1-RR)]	Study limitations (Risk of Bias)
Moderna, 2021 [2]	SARS-CoV-2 RT-PCR positive among asymptomatic persons 28 days after dose 2, or at unscheduled study visits, among participants with negative SARS-CoV-2 serology at baseline	111/4105 (2.7%)	44/1371 (3.2%)	Placebo	16.0% (-18.5%, 40.5%)	Not serious

**Abbreviations:** RT-PCR = real-time polymerase chain reaction; CI = confidence interval; RR = relative risk

### Table 3d: Summary of Studies Reporting Serious Adverse Events

Authors last name, pub year	Age or other characteristic of importance	n <sup>b</sup> /N <sup>c</sup> (%) intervention	n <sup>b</sup> /N (%) comparison	Comparator	RR (95% CI)	Study limitations (Risk of Bias)
Moderna, 2022 [2]	Persons aged 6 months-5 years	24/4792 (0.5%) <sup>c</sup>	3/1596 (0.2%) <sup>d</sup>	Placebo	2.67 (0.80, 8.84)	Not serious

**Abbreviations:** RR = relative risk; CI = confidence interval; RCT = randomized controlled trial.

<sup>a</sup>Death, life-threatening event, inpatient hospitalization or prolongation of existing hospitalization, persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, medically important event, or congenital anomaly/birth defect

<sup>b</sup>Serious adverse events through 70 days after dose 2

<sup>c</sup>Number of participants experiencing SAEs (participants may experience more than one SAE)

<sup>d</sup>Included all randomized participants who received at least 1 dose of vaccine.

**Table 3e: Summary of Studies Reporting Reactogenicity**

Authors last name, pub year	Age or other characteristic of importance	n/N (%) intervention	n/N (%) comparison	Comparator	RR (95% CI)	Study limitations (Risk of Bias)
Moderna, 2022 [2] <sup>b</sup>	Persons aged 6 months-5 years	366/4774 (7.7%)	65/1582 (4.1%)	Placebo	1.87 (1.44, 2.42)	Not serious

**Abbreviations:** RR = relative risk; CI = confidence interval; RCT = randomized controlled trial.

<sup>a</sup>Reactogenicity outcome includes local and systemic events, grade  $\geq 3$ . Grade 3: prevents daily routine activity or requires use of a pain reliever. Grade 4: requires emergency room visit or hospitalization.

**Table 4. Grade Summary of Findings Table**

Certainty assessment							N° of patients		Effect		Certainty	Importance
N° of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Moderna COVID-19 vaccine, 50 mcg, 2 doses 28 days apart	No vaccine	Relative (95% CI)	Absolute (95% CI)		
<b>Symptomatic laboratory-confirmed COVID-19</b>												
1	RCT	not serious <sup>a,b</sup>	not serious	not serious <sup>c,d</sup>	not serious	none	181/4791 (3.8%)	95/1597 (5.9%)	RR 0.62 (0.49 to 0.79)	2,260 fewer per 1,000 (from 3,034 fewer to 1,249 fewer) <sup>e</sup>	Type 1 High	CRITICAL
<b>Symptomatic laboratory-confirmed COVID-19 (assessed with immunobridging)</b>												
1	RCT	not serious	not serious	serious <sup>c,f</sup>	not serious	none			not estimable <sup>g</sup>		Type 2 Moderate	
<b>Asymptomatic SARS-CoV-2 infection</b>												
1	RCT	not serious <sup>a,h</sup>	not serious	serious <sup>c,i</sup>	serious <sup>j</sup>	none	111/4105 (2.7%)	44/1371 (3.2%)	RR 0.84 (0.60 to 1.18)	513 fewer per 100,000 (from 1,284 fewer to 578 fewer) <sup>d</sup>	Type 3 Low	IMPORTANT

Serious adverse events

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Certainty assessment							Nº of patients		Effect		Certainty	Importance
Nº of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Moderna COVID-19 vaccine, 50 mcg, 2 doses 28 days apart	No vaccine	Relative (95% CI)	Absolute (95% CI)		
1	RCT	not serious <sup>k</sup>	not serious	serious <sup>cl</sup>	very serious <sup>m</sup>	none	24/4792 (0.5%)	3/1596 (0.2%)	RR 2.67 (0.80 to 8.84)	314 fewer per 100,000 (from 38 fewer to 1,474 more) <sup>d</sup>	Type 4 Very Low	CRITICAL
<b>Reactogenicity, grade ≥3</b>												
1	RCT	not serious	not serious	not serious <sup>c</sup>	not serious	none	366/4774 (7.7%)	65/1582 (4.1%)	RR 1.87 (1.44 to 2.42)	3,575 more per 100,000 (from 1,808 more to 5,834 more) <sup>e</sup>	Type 1 High	IMPORTANT

**Abbreviations:** CI = confidence interval; RR = relative risk; COVID-19 = coronavirus disease 2019; RCT = randomized controlled trial.

- 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, therefore the risk of bias was rated as not serious.
- b. The estimate for symptomatic COVID-19 is from a per-protocol definition in which COVID-19 cases were laboratory confirmed by PCR. During the trial, increased case incidence resulted in COVID-19 diagnoses in trial participants through home antigen tests, which were never confirmed by PCR. Results from a sensitivity analysis including those diagnosed using home antigen tests (RR: 0.63; 95% CI: 0.52, 0.78) were consistent with the results from the per-protocol analysis.
- c. The RCT excluded persons with prior COVID-19 diagnosis or a medical or psychiatric condition that, according to the investigator's judgment, may pose additional risk as a result of participation, interfere with safety assessments, or interfere with interpretation of results. The population included in the RCT may not represent all persons aged 6 months to 5 years.
- d. The estimate of symptomatic COVID-19 included participants that were seropositive and seronegative at baseline. Approximately 10% of the population was seropositive at baseline.
- e. Absolute risk was calculated using the observed risk among placebo recipients in the available body of evidence. Absolute risk estimates should be interpreted in this context.
- f. Indirectness noted because immunogenicity is surrogate measure of efficacy.
- g. The immune response to vaccine was evaluated using the geometric mean titer ratio of children to young adults. Non-inferiority criteria are met when the lower bound of the 95% confidence interval for the ratio comparing the geometric mean neutralizing antibody titer for the two groups is not less than a pre-set value, which for this study was 0.67. The immune response to vaccine in children ages 6 months -<2 years (GMT: 1780.7 [1606.4, 1973.8]) and ages 2-5 years (GMT: 1410.0 [1260.1 1524.2]) was noninferior to that observed in young adults aged 18-25 years (GMT: 1390.8 [1066.6, 1305.4]), with a geometric mean ratio of 1.28 (1.12, 1.47) in children ages 6 months -<2 years and a geometric mean ratio of 1.01 (0.9, 1.17), in children ages 2 – 5 years based on SARS-CoV-2 neutralization titers at 1 month after dose 3, in participants without prior evidence of SARS-CoV-2 infection.
- h. The estimate for asymptomatic SARS-CoV-2 infection is from a per-protocol definition in which SARS-CoV-2 cases were laboratory confirmed by PCR or serology. During the trial, increased case incidence resulted in SARS-CoV-2 diagnoses in trial participants through home antigen tests, which were never confirmed by PCR. Results from a sensitivity analysis

including those diagnosed using home antigen tests (RR: 0.79; 95% CI: 0.65, 0.96) were consistent with the results from the per-protocol analysis.

- i. Serious concern for indirectness was noted. The intended outcome was asymptomatic infection assessed with serial PCR testing for SARS-CoV-2 or seroconversion to a non-spike protein. Data are presented from an analysis of participants with SARS-CoV-2 positive PCR test results from nasopharyngeal swabs collected 28 days after the second vaccine dose or at unscheduled visits, among persons who were seronegative at baseline and did not report COVID-19 symptoms after dose 1. Additionally, seroconversion data are included on a subset of participants enrolled in the immunogenicity portion of the trial (n=494). The available evidence are indirect because they represent SARS-CoV-2 testing of the full cohort at a single point in time.
- j. Serious concern for imprecision was noted due to the width of the confidence interval containing estimates for which different policy decisions might be considered.
- k. 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.
- l. Serious concern of indirectness was noted. The body of evidence does not provide certainty that rare serious adverse events were captured due to the 70-day follow-up after dose 2.
- m. Very serious concern for imprecision was noted based on the confidence interval containing estimates for which different policy decisions might be considered and failure to meet minimum information requirements.

## Appendix 1. Studies Included in the Review of Evidence

Last name first author, Publication year	Study design	Country (or more detail, if needed)	Population	Total population	N Intervention	N comparison	Outcomes	Funding source
Moderna, 2022 [2]	Phase II/III RCT	USA	Persons aged 6 months-5 years	6388	4791	1597	<ul style="list-style-type: none"> <li>• Symptomatic laboratory-confirmed COVID-19</li> <li>• Asymptomatic SARS-CoV-2 infection</li> <li>• Serious adverse events</li> <li>• Reactogenicity</li> </ul>	Industry funded

**Abbreviations:** RCT = randomized controlled trial; COVID-19 = coronavirus disease 2019.

## Appendix 2. Databases and strategies used for systematic review

Database	Strategy
Clinicaltrials.gov	<p><b>Inclusion:</b> Relevant Phase 1, 2, or 3 randomized controlled trials of COVID-19 vaccine</p> <p>Search criteria:</p> <ul style="list-style-type: none"> <li>• Condition or disease: "COVID-19"</li> <li>• Other terms: "mRNA-1273" "Moderna"</li> <li>• Age group (advance search): Child (birth-17)</li> <li>• Phase (advanced search): Phase 1, Phase 2, Phase 3</li> </ul> <p><b>Additional resources:</b> Unpublished and other relevant data by consulting with vaccine manufacturers and subject matter experts</p>



Database	Strategy
International Vaccine Access Center (IVAC)	<p><b>Inclusion criteria for IVAC systematic review:</b></p> <ul style="list-style-type: none"> <li>• Published or preprint study with adequate scientific details</li> <li>• Includes groups with and without infection or disease outcome</li> <li>• Laboratory confirmed outcome</li> <li>• Vaccination status confirmed in <math>\geq 90\%</math></li> <li>• Studies assess one vaccine or pooled mRNA vaccines</li> <li>• Includes participants who did or did not receive a COVID-19 vaccine</li> </ul> <p>Vaccine effectiveness estimate calculated comparing vaccinated to unvaccinated</p> <p><b>Additional criteria for GRADE review:</b></p> <ul style="list-style-type: none"> <li>• Restricted to PICO-defined population, intervention, comparison, and outcomes</li> <li>• Outcomes assessed 7 to 14 days after 2nd dose</li> <li>• Only Moderna vaccine (not mRNA vaccines as a group)</li> <li>• Included studies of persons aged 6 months-5 years</li> </ul>

a. Most recent search conducted April 29, 2022.