Grading of Recommendations, Assessment, Development, and Evaluation (GRADE): Pfizer-BioNTech COVID-19 Vaccine for Children Aged 6 Months–4 Years

Overview

A Grading of Recommendations, Assessment, Development and Evaluation (GRADE) review of the evidence for benefits and harms for Pfizer-BioNTech coronavirus disease 2019 (COVID-19) vaccine for children aged 6 months–4 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 Pfizer-BioNTech COVID-19 vaccine (3 doses, 3 µg) be recommended for children 6 months–4 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 ≥3 (important).

A systematic review of evidence on the efficacy and safety of a three-dose regimen of Pfizer-BioNTech COVID-19 vaccine among children aged 6 months–4 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, but certainty in the estimate was very low (relative risk [RR]: 0.20; 95% confidence interval [CI]: 0.05, 0.77, evidence type 4). Immunobridging was also assessed in support of efficacy. In both age groups, 6–23 months and 2–4 years, the immune response to vaccine was non-inferior to that observed in young adults ages 16-25 years (6–23 months: GMR: 1.19; 95% CI: 1.00, 1.43; 2–4 years: GMR: 1.30; 95% CI: 1.13, 1.50; evidence type 2). The available data indicated that SAEs were balanced comparing vaccine and placebo recipients, but certainty in the estimate was low (RR 0.66; 95% CI: 0.38, 1.15; evidence type 4). One vaccine recipient had two SAEs which were considered potentially related by the investigator and FDA. FDA noted that the events were also consistent with viral myositis. Reactogenicity grade ≥3 was slightly higher in the vaccine group, but the confidence interval crossed the null (RR 1.20; 95% CI: 0.88, 1.64); evidence type 2). About 4.3% of vaccine recipients and 3.6% of placebo recipients reported any grade ≥3 local or systemic reactions following dose 1, dose 2, or dose 3.

Introduction

On June 17, 2022, the FDA updated the Emergency Use Authorization (EUA) for Pfizer-BioNTech (BNT162b2) vaccine for prevention of symptomatic COVID-19 to include children aged 6 months–4 years [*3*]. As part of the process employed by the ACIP, a systematic review and GRADE evaluation of the evidence for Pfizer-BioNTech 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 Pfizer-BioNTech COVID-19 vaccine (3 doses, 3 µg) be recommended for persons 6 months-4 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 three-dose regimen (3 µg per dose) of Pfizer-BioNTech 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 benefits 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 ≥3 was deemed an important harm. Hospitalization, MIS-C, and asymptomatic SARS-CoV-2 infection 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–4 years vaccinated with BNT162b2; 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) [4]. 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 June 3, 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% x (1-RR). Immunobridging data comparing geometric mean neutralizing antibody titers (GMTs) in 6–23 months and 2–4-year-olds to those in 18-25-year-olds in whom clinical efficacy was previously established was used in support of efficacy.

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: 0.20; 95% CI: 0.05, 0.77), but certainty in the estimate was very low. Serious concern for indirectness was noted due to the short duration of follow-up of 1.3 months in the available body of evidence, and very serious concern for imprecision was noted due to failure to meet minimum information requirements (Table 3a, Table 4). The immune response to the Pfizer-BioNTech COVID-19 vaccine among children aged 6 months–4 years was evaluated separately, 6–23 months and 2–4 years. The immune response for both age groups were non-inferior (6–23 months: GMR: 1.19; 95% CI: 1.00, 1.43; 2–4 years: GMR: 1.30; 95% CI: 1.13, 1.50) to the immune response among adults aged 18–25 years receiving the Pfizer-BioNTech COVID-19 vaccine primary series in whom clinical efficacy had been established (Table 3b).

For evaluation of potential harms, data were reviewed from the Phase II/III randomized controlled trial. Serious adverse events were comparable in vaccine and placebo recipients, but certainty in the estimate was very low (RR: 0.66; 95% CI: 0.38, 1.15). There was very serious concern of indirectness because of the short duration of follow up (1.3 months after dose 3) in the available body of evidence and because only 31% of trial participants received dose 3, limiting the ability to detect serious adverse events that occur specifically after dose 3. There was also serious concern for imprecision due to failure to meet minimum information requirements. Two SAEs (fever and pain in extremity requiring hospitalization) among one participant were considered potentially related by the investigator and FDA. FDA noted that the events were also consistent with viral myositis (Table 3c). There were no cases of vaccine-associated enhanced disease or deaths. Grade ≥3, or severe, local or systemic reactions within 7 days following any dose, were reported by 4.3% of vaccine recipients and 3.6% of placebo recipients (RR 1.20; 95% CI: 0.88, 1.64) (Table 3d). Serious concern for indirectness was noted because only 31% of trail participants received dose 3, limiting the ability to detect severe reactogenicity that occurs specifically after dose 3.

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, but certainty in the estimate was very low. The certainty in the estimate of the effect for preventing symptomatic COVID-19 was downgraded one point for serious concern of indirectness and two points for imprecision (type 4, very low). The certainty assessment for symptomatic, laboratory-confirmed COVID-19 assessed using immunobridging was downgraded once for indirectness (type 2, moderate). The certainty in the estimate of the effect for serious adverse events was downgraded two points due to very serious concern of indirectness and one point for imprecision (type 4, very low certainty). The certainty in the estimate of reactogenicity was downgraded one point due for indirectness (type 2, moderate certainty) (Table 4).

References

1. Ahmed F. U.S. Advisory Committee on Immunization Practices (ACIP) Handbook for Developing Evidence-based Recommendations.
2. Pfizer-BioNTech, 2022. personal communication, March 22 – June 08, 2022.
3. Food and Drug Administration. Pfizer-BioNTech COVID-19 Vaccine Emergency Use Authorization. https://www.fda.gov/media/150386/download . Accessed June 17, 2022.
4. International Vaccine Access Center (IVAC), Johns Hopkins Bloomberg School of Public Health. VIEW-hub. www.view-hub.org. Accessed: April 29, 2022.

Table 1: Policy Question and PICO

Policy question:	Should vaccination with Pfizer-BioNTech COVID-19 vaccine (3-doses, 3 µg) be recommended for children aged 6 months-4 years?
Population	Children aged 6 months-4 years
Intervention	Pfizer-BioNTech COVID-19 vaccine BNT162b2 (3 µg, 3 doses IM, the initial 2 doses 21 days apart, followed by a third dose at least 8 weeks after the second dose)
Comparison	No Pfizer-BioNTech COVID-19 vaccine
Outcomes	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 ≥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[a]
Multisystem inflammatory syndrome in children (MIS-C)	Important	No[a]
Asymptomatic SARS-CoV-2 infection	Important	No[b]

Outcome	Importance	Included in evidence profile
Serious adverse events	Critical	Yes
Reactogenicity grade ≥3	Important	Yes

[a]No events were observed in study identified in the review of evidence.

[b]Data on outcome not available in studies 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-IRR)]	Study limitations (Risk of Bias)
Pfizer-BioNTech, 2022 [*2*][a]	SARS-CoV-2 RT-PCR-positive symptomatic illness[b], in seronegative persons aged 6 months-4 years, ≥7 days post third dose	3/992	7/464	Placebo	80.0% (22.8%, 94.8%)	Not serious

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

[a]Based on data cutoff April 29, 2022; participants had a median 1.3 months of follow-up.

[b]RT-PCR symptomatic illness defined as: a positive post-baseline PCR result, and at least 1 systemic symptom: fever (temperature > 38°C/≥ 100.4°F) or chills (of any duration, including ≤ 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 ≤ 48 hours), shortness of breath or difficulty breathing (of any duration, including ≤ 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-23 Months	n 18-25 Years	GMRc (95%CI)	Met Noninferiority Objective[d]	Study limitations (Risk of Bias)
Pfizer-BioNTech, 2022 [*2*][a]	SARS-CoV-2 neutralization assay – NT50[a,b]	82	170	1.19 (1.00, 1.43)	Yes	Not serious

Authors last name, pub year	Age or other characteristic of importance	n 2-4 Years	n 18-25 Years	GMRc (95%CI)	Met Noninferiority Objective[d]	Study limitations (Risk of Bias)
Pfizer-BioNTech, 2022 [*2*][a]	SARS-CoV-2 neutralization assay – NT50[a,b]	143	170	1.30 (1.13, 1.50)	Yes	Not serious

Abbreviations: NT50 = 50% neutralizing titer; GMR= geometric mean ratio; CI = confidence interval; LLOQ = lower limit of quantitation

[a]Among participants who had no serological or virological evidence (1-month post-Dose 2 [16-25 years] or 1-month post-Dose 3 [6 mo – 4 years]) of past SARS-CoV-2 infection and had negative nucleic acid amplification test (NAAT) at any unscheduled visit up to one month after dose two.

[b]Sampling time point was one month after dose two.

[c]GMRs and 2-sided 95% CIs were calculated by exponentiating the mean difference of the logarithms of the titers (Group 1 [6 months-23 months or 2-4 years] – Group 2 [18-25 years]) and the corresponding CI (using t-distribution).

[d]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 Serious Adverse Events[a,b]

Authors last name, pub year	Age or other characteristic of importance	n[b]/N[c] (%) intervention	n[b]/N (%) comparison	Comparator	RR (95% CI)	Study limitations (Risk of Bias)
Pfizer-BioNTech, 2022 [*2*]	Persons aged 6 months-4 years	29/3013 (1.0%)[c]	22/1504 (1.5%)	Placebo	0.66 (0.38, 1.15)	Not serious

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

[a]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

[b]Included all randomized participants who received at least 1 dose of vaccine.

[c]Number of participants experiencing SAEs (participants may experience more than one SAE), data cutoff April 29, 2022

Table 3d: 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)
Pfizer-BioNTech, 2022 [*2*][b]	Persons aged 6 months-4 years	129/3010 (4.3%)	54/1510 (3.6%)	Placebo	1.20 (0.88, 1.64)	Not serious

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

[a]Reactogenicity outcome includes local and systemic events, grade ≥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	№ of patients	Effect	Certainty	Importance

			Certainty assessment				Pfizer-BioNTech COVID-19 vaccine, 50 mcg, 2 doses 28 days apart	No vaccine	Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Pfizer-BioNTech COVID-19 vaccine, 50 mcg, 2 doses 28 days apart	No vaccine	Relative (95% CI)	Absolute (95% CI)		
Symptomatic laboratory-confirmed COVID-19												
1	RCT	not serious[a,b]	not serious	serious[c,d,e,f]	very serious[g]	none	3/992 (0.3%)	7/464 (1.5%)	**RR 0.20** (0.05 to 0.77)	**1,207 fewer per 100,000** (from 1,433 fewer to 347 fewer)[h]	**Type 4** Very Low	CRITICAL
Symptomatic COVID-19 (assessed with: immunobridging)												
1	RCT	not serious	not serious	serious[d,i,j]	not serious	none	–	–	Not estimable[k]	[l]	**Type 3** Moderate	CRITICAL
Serious adverse events												
1	RCT	not serious[a]	not serious	serious[d,e,m]	serious[n]	none	29/3013 (1.0%)	22/1513 (1.5%)	**RR 0.66** (0.38 to 1.15)	**494 fewer per 100,000** (from 902 fewer to 218 more)[d]	**Type 4** Very low	CRITICAL
Reactogenicity, grade ≥3												
1	RCT	not serious	not serious	serious[d,e,o]	not serious	none	129/3010 (4.3%)	54/1510 (3.6%)	**RR 1.19** (0.88 to 1.64)	**679 more per 100,000** (from 429 fewer to 2,289 more)[e]	**Type 2** Moderate	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 or underestimate risk of serious adverse events, therefore the risk of bias was rated as not serious.

b. Risk of bias related to selective outcome reporting was considered. The efficacy data are preliminary and descriptive, as the protocol specified 21 cases for the symptomatic COVID-19 efficacy outcome have not yet been achieved. The small number of events in the available body of evidence are further considered in imprecision.

c. Serious concern for indirectness was noted due to the short duration of follow-up of 1.3 months in the available body of evidence.

d. The RCT excluded persons with prior or current MIS-C, individuals with known immunodeficiency, and diagnosis or a medical or psychiatric condition that, according to the investigator's judgment, may increase the risk of study participation or make the participant inappropriate for the study. The population included in the RCT may not represent all persons aged 6 months to 4 years.
e. The median interval between dose 2 and dose 3 in the trial was longer than the >8 weeks interval under consideration in the policy question. The median interval between dose 2 and dose 3 among trail participants was 16 weeks among children ages 6-23 months and 11 weeks among children ages 2 – 4 years.
f. The estimate of symptomatic COVID-19 included participants that were seropositive and seronegative at baseline. Approximately 5% of the population ages 6 – 23 months and 11% of the population ages 2-4 years were seropositive at baseline.
g. Very serious concern for imprecision was noted due to failure to meet minimum information criteria with only 10 events from a single RCT.
h. 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.
i. Indirectness noted because immunogenicity is a surrogate measure of efficacy.
j. The median interval between dose 2 and dose 3 among trail participants in the immunogenicity subset was 11 weeks which is longer than the >8 weeks interval between dose 2 and 3 under consideration in the policy question.
k. 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: 1406.5 [1211.3, 1633.1]) and ages 2-<5 years (GMT: 1535.2 [1388.2, 1697.8]) was noninferior to that observed in young adults aged 16-25 years (GMT: 1180.0 [1066.6, 1305.4]), with a geometric mean ratio of 1.19 (1.00, 1.43) in children ages 6 months -<2 years and a geometric mean ratio of 1.30 (1.13, 1.50), in children ages 6 months to <5, based on SARS-CoV-2 neutralization titers at 1 month after dose 3, in participants without prior evidence of SARS-CoV-2 infection.
l. Absolute effect not applicable for immunobridging outcome.
m. Serious concern for indirectness was noted due to the short duration of follow-up of 1 month post dose 3 in the available body of evidence and because only 31% of trial participants received dose 3, limiting the ability to detect serious adverse events that occur specifically after dose 3.
n. Serious concern for imprecision due to failure to meet minimum information criteria.
o. Serious concern for indirectness was noted because only 31% of trial participants received dose 3 limiting the ability to detect severe reactogenicity that occurs specifically after dose 3.

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
Pfizer-BioNTech, 2022 [*2*]	Phase II/III RCT	USA	Persons aged 6 months-4 years	4526	3013	1513	• Symptomatic laboratory-confirmed COVID-19 • Serious adverse events • Reactogenicity	Industry funded

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

Appendix 2. Databases and strategies used for systematic review

Database	Strategy

Database	Strategy
Clinicaltrails.gov	**Inclusion:** Relevant Phase 1, 2, or 3 randomized controlled trials of COVID-19 vaccine Search criteria: • Condition or disease: “COVID-19” • Other terms: “BNT162b2” “Pfizer-BioNTech” • Age group (advance search): Child (birth-17) • Phase (advanced search): Phase 1, Phase 2, Phase 3 **Additional resources:** Unpublished and other relevant data by consulting with vaccine manufacturers and subject matter experts
International Vaccine Access Center (IVAC)	**Inclusion criteria for IVAC systematic review:** • Published or preprint study with adequate scientific details • Includes groups with and without infection or disease outcome • Laboratory confirmed outcome • Vaccination status confirmed in ≥90% • Studies assess one vaccine or pooled mRNA vaccines • Includes participants who did or did not receive a COVID-19 vaccine • Vaccine effectiveness estimate calculated comparing vaccinated to unvaccinated** **Additional criteria for GRADE review:** • Restricted to PICO-defined population, intervention, comparison, and outcomes • Outcomes assessed 7 to 14 days after 3rd dose • Only Pfizer-BioNTech vaccine (not mRNA vaccines as a group) • Included studies of persons aged 6 months-4 years

a. Most recent search conducted June 3, 2022.

Page last reviewed: June 27, 2022