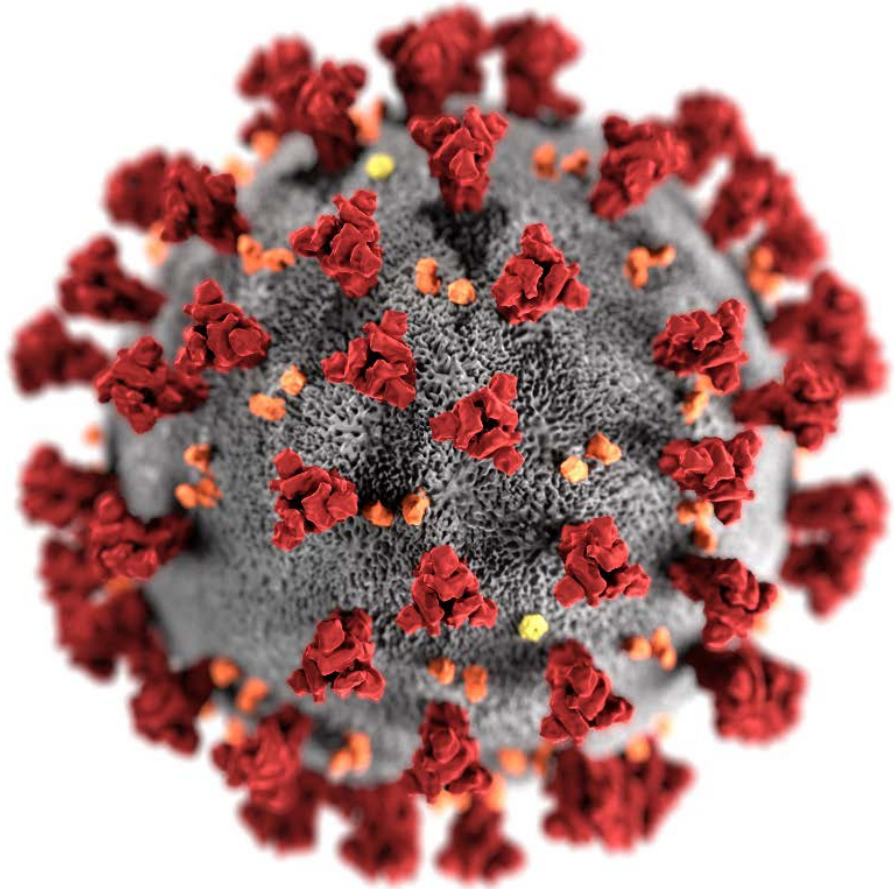
Grading of Recommendations, Assessment, Development, and Evaluation (GRADE): Pfizer-BioNTech COVID-19 Vaccine



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12 May 2021

Policy Question

- Should vaccination with Pfizer BioNTech COVID-19 vaccine (2-doses, IM) be recommended for persons 12-15 years of age under an Emergency Use Authorization?

PICO Question

Population	Persons aged 12-15 years
Intervention	Pfizer-BioNTech COVID-19 vaccine BNT162b2 (30 µg, 2 doses IM, 21 days apart)
Comparison	No vaccine
Outcomes	Symptomatic lab-confirmed COVID-19 Hospitalization due to COVID-19 Multisystem inflammatory syndrome in children (MIS-C) SARS-CoV-2 seroconversion to a non-spike protein Asymptomatic SARS-CoV-2 infection Serious Adverse Events Reactogenicity

Outcomes – Pediatric vs. Adult Vaccines

Pediatric COVID-19 Vaccines		Adult COVID-19 Vaccines	
Outcome	**Importance[a]**	**Outcome**	**Importance[a]**
Benefits			
Symptomatic lab-confirmed COVID-19 (direct efficacy and immunobridging)	Critical	Symptomatic lab-confirmed COVID-19	Critical
Hospitalization due to COVID-19	Important	Hospitalization due to COVID-19	Critical
Multisystem inflammatory syndrome in children (MIS-C)	Important	All-cause death	Important
SARS-CoV-2 seroconversion	Important	SARS-CoV-2 seroconversion	Important
Asymptomatic SARS-CoV-2 infection	Important	Asymptomatic SARS-CoV-2 infection	Important
Harms			
Serious adverse events (note: includes deaths)	Critical	Serious adverse events	Critical
Reactogenicity	Important	Reactogenicity	Important

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

Outcomes

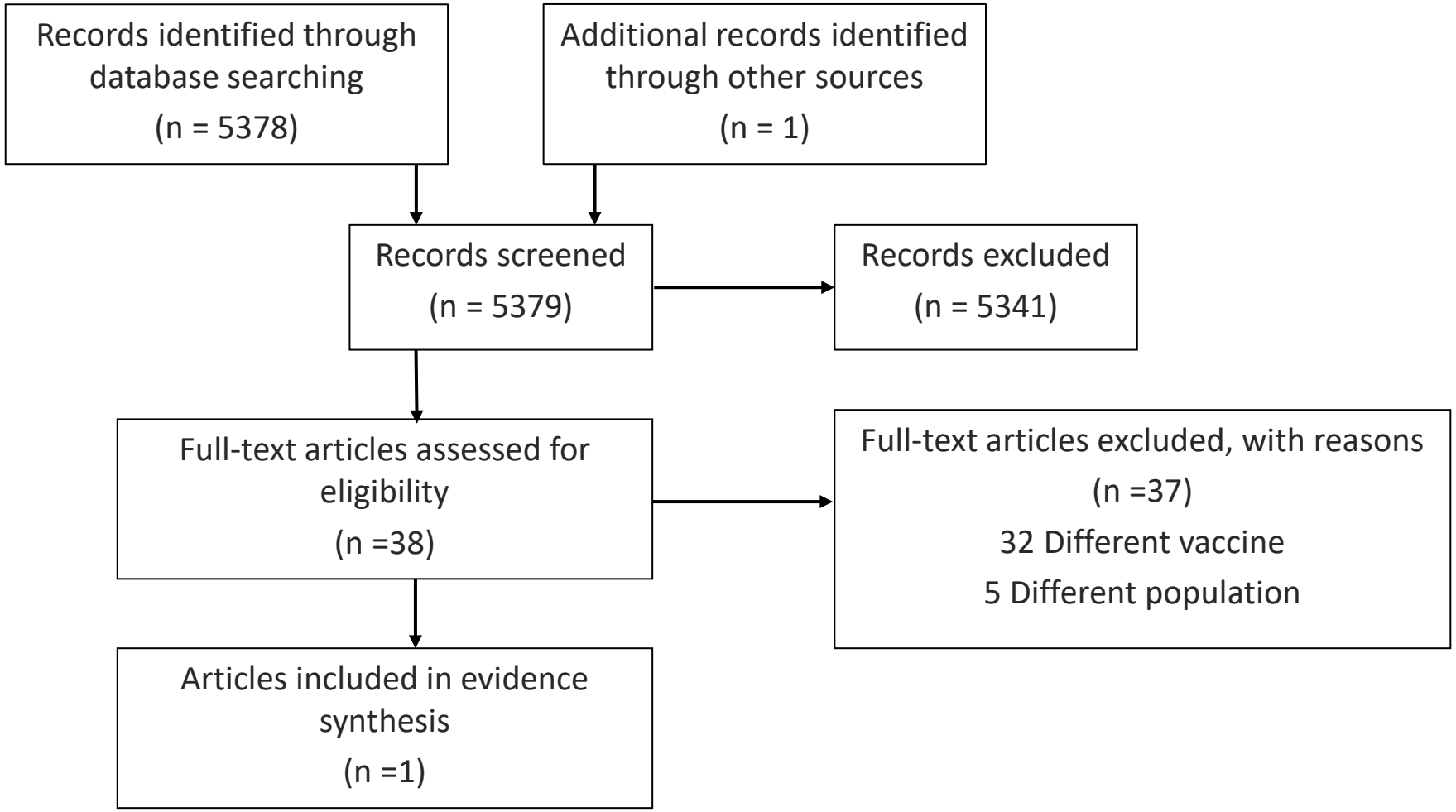
Outcome	Importance[a]	Description
Benefits		
Symptomatic lab-confirmed COVID-19	Critical	Current studies use PCR + specific symptoms; immunobridging
Hospitalization due to COVID-19	Important	Phase 3 trials not designed to detect statistical differences between treatment groups for this outcome
Multisystem inflammatory syndrome in children (MIS-C)	Important	Phase 3 trials not designed to detect statistical differences between treatment groups for this outcome
SARS-CoV-2 seroconversion	Important	Measured using antibodies to non-spike protein to differentiate seroconversion due to natural infection from immunogenicity to vaccine; no data available
Asymptomatic SARS-CoV-2 infection	Important	Measured using serial PCR; no data available
Harms		
Serious adverse events	Critical	Evaluating balance of events between arms; also reporting on number deemed vaccine-related
Reactogenicity	Important	Evaluating grade ≥3 severity of systemic events and local reactions

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

Evidence Retrieval

- **Databases**: Medline, Embase, and Cochrane Library, written in English, restricted to 2020
- **Search terms**: coronavirus, COVID-19, SARS-CoV-2, respiratory (symptom, disease, illness, condition), vaccine, immunization, trial, double blind, single blind, placebo, comparative study, phase 3, immunogenicity, efficacy, effective, adverse, evidence, and variations on these terms
- **Inclusion:** provided data on vaccination with BNT162b2 and 1) involved human subjects; 2) reported primary data; 3) included persons at risk for SARS-CoV-2 infection; 4) included data relevant to the efficacy and safety outcomes being measured; and 5) included data for the dosage and timing being recommended (30 µg, 2 doses at 0 and 21 days)
- **Additional resources:** unpublished and other relevant data by hand-searching reference lists, and consulting with vaccine manufacturers and subject matter experts
- Title and abstracts were screened independently by two separate reviewers.

Evidence Retrieval



GRADE Evidence Type

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

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

GRADE Criteria

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

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

Benefits

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

- Pfizer-BioNTech phase 2/3 randomized controlled trial (RCT) (unpublished, data obtained from sponsor)
- Persons aged 12-15 years in United States
- Data evaluated: all eligible randomized participants who received all vaccinations as randomized within the predefined window and no other important protocol deviations (data cut-off: March 13, 2021)

Pfizer/BioNTech phase 2/3 RCT Analysis Populations

Population	Description	N	Person-years
Evaluable efficacy	All eligible randomized participants who received all vaccination(s) as randomized within the predefined window and had no other important protocol deviations as determined by the investigator, and who did not have evidence of prior SARS-CoV-2 infection	**1,983**	**301**
	Including persons with prior infection	2,229	333
All-available efficacy	All randomized participants who received at least 1 vaccination.	2,260	507

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

Population	Events/Vaccine (n/N)	Events/Placebo (n/N)	Vaccine efficacy (95% confidence interval)
Primary outcome			
No evidence of prior infection, ≥7 d post dose 2	0/1001[a]	16/972[a]	100.0%[b]
Secondary outcomes			
± evidence of prior infection, ≥7 d post dose 2	0/1109[a]	18/1094[a]	100.0%[c]
All available efficacy (± evidence of prior infection, post dose 1)	3/1120[a]	35/1119[a]	91.4% (72.2%, 97.4%)

a. Number of subjects at risk for the endpoint
b. With a standard continuity correction of 0.5 applied, the estimated VE (95% CI) is 97.1% (51.0%, 99.8%)
c. With a standard continuity correction of 0.5 applied, the estimated VE (95% CI) is 97.3% (55.8%, 99.8%)

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Pfizer-BioNTech phase 2/3 RCT Immunogenicity Population

Population	Description	N
12-15 years	Random sample of vaccine arm of the evaluable efficacy population[a,b]	209
16-25 years	Random sample of vaccine arm of the evaluable efficacy population[a,b]	186

a. A random sample of 280 participants in each age group were selected, however 69 participants in the 12-15 year group and 89 participants in the 16-25 year group were excluded due to participants not having at least 1 valid and determinate immunogenicity result after Dose 2, mostly as the result of testing laboratory supply limitation of the qualified viral lot.
b. Some placebo participants were also randomly selected to maintain blinding of laboratory personnel.

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

Immunobridging: Summary of Geometric Mean Ratio

	12-15 Years		16-25 Years			
	n[c]	GMT[d] (95% CI)	n[c]	GMT[d] (95% CI)	GMR[e] (95% CI)	Met Noninferiority Objective[f]
SARS-CoV-2 neutralization assay – NT50[a,b]	190	1239.5 (1095.5, 1402.5)	170	705.1 (621.4, 800.2)	1.76 (1.47, 2.10)	Yes

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

[a]Among participants who had no serological or virological evidence (up to 1 month after receipt of the last dose) of past SARS-CoV-2 infection and had negative NAAT at any unscheduled visit up to one month after dose two.

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

[c]Number of subjects with valid and determinate assay results for the specified assay at the given dose and sampling time point.

[d]GMTs and 2-sided 95% CIs were calculated by exponentiating the mean logarithm of the titers and the corresponding CIs (based on the Student t distribution). Assay results below the LLOQ were set to 0.5 LLOQ

[e]GMRs and 2-sided 95% CIs were calculated by exponentiating the mean difference of the logarithms of the titers (Group 1 [12-15 years] – Group 2 [16-25 years]) and the corresponding CI (based on the Student t distribution)

[f]Noninferiority is declared if the lower bound of the 2-sided 95% CI for the GMR is greater than 0.67

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

Immunogenicity: Summary of Seroresponse (≥4-Fold Rise in Antibody Titer)

	12-15 Years		16-25 Years		
	N[c]	n[d] (%) (95% CI[e])	N[c]	n[d] (%) (95% CI[e])	Difference[f] (%) (95% CI[g])
SARS-CoV-2 neutralization assay – NT_{50}[a,b]	143	140 (97.9) (94.0, 99.6)	124	124 (100.0) (97.1, 100.0)	-2.1 (-6.0, 0.9)

Abbreviations: NT_{50} = 50% neutralizing titer; LLOQ = lower limit of quantitation

[a]Among participants who had no serological or virological evidence (up to 1 month after receipt of the last dose) of past SARS-CoV-2 infection and had negative NAAT at any unscheduled visit up to one month after dose two.

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

[c]Number of subjects with valid and determinate assay results for the specified assay both before vaccination and at the given dose and sampling time point. These values are the denominator for the percentage calculations.

[d]Number of subjects with a ≥4-fold rise in titer from before vaccination for the given assay at the given dose and sampling time point.

[e]Exact 2-sided CI based on the Clopper and Pearson method

[f]Difference in proportions, expressed as a percentage (12-15 years – 16-25 years).

[g]2-sided CI, based on the Miettinen and Nurminen method for the difference in proportions, expressed as a percentage.

Evidence Table: Symptomatic Lab-confirmed COVID-19

Certainty assessment							№ of patients		Effect		
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Pfizer BioNTech COVID-19 vaccine, 30 mcg, 2 doses 21 days apart	No vaccine	Relative (95% CI)	Certainty	Importance
Vaccine efficacy against symptomatic COVID-19											
1	RCT	Not serious a	Not serious	Not serious b,c,d	Not serious	None	0/1001 (0.0%)	16/972 (1.6%)	**RR 0.03** (0.00 to 0.49) e	Type 1	CRITICAL

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

b. The effects noted are from an analysis of the evaluable efficacy population with outcomes assessed at least 7 days post dose 2 among persons who received two doses and had no evidence of prior SARS-CoV-2 infection. In the all-available efficacy population (persons who received at least 1 dose, with or without evidence of prior SARS-CoV-2 infection), there were 3 cases reported among 1,131 persons who received the vaccine, and 35 cases among 1,129 persons who received the placebo, for a relative risk of 0.09 (95% CI: 0.03 to 0.28).

c. The RCT excluded persons with prior COVID-19 diagnosis, pregnant or breastfeeding women, and persons who were immunocompromised. The population included in the RCT may not represent all persons aged 12-15 years.

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

e. Relative risk calculated using the standard continuity correction of 0.5.

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

Harms

Outcome 6: Serious Adverse Events
Studies with Unvaccinated Comparator (n=1)

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

Outcome 6: Serious Adverse Events[a]
Studies with Unvaccinated Comparator (n=1)

Study/population[b]	Events/Vaccine (n/N)[c]	% SAE Vaccine	Events/Placebo (n/N)	% SAE Placebo	Associated with vaccination
Pfizer/BioNTech, unpublished	5/1131	0.4	2/1129	0.2	0

a. Serious adverse event (SAE) is defined as any untoward medical occurrence that, results in death, is life threatening, requires inpatient hospitalization or prolongation of existing hospitalization, results in persistent disability/incapacity, or is a congenital anomaly/birth defect
b. Included all randomized participants who received at least 1 dose of vaccine
c. Data cutoff of March 13, 2021

Evidence Table: Serious Adverse Events

№ of studies	Study design	Certainty assessment: Risk of bias	Certainty assessment: Inconsistency	Certainty assessment: Indirectness	Certainty assessment: Imprecision	Certainty assessment: Other considerations	№ of patients: Intervention	№ of patients: Comparison	Effect: Relative (95% CI)	Certainty	Importance
Serious adverse events											
2	RCT	Not serious [a]	Not serious	Serious [b,c]	Very Serious[d]	None	5/1131 (0.4%)	2/1129 (0.2%)	RR 2.50 (0.49 to 12.84)	**Type 4**	CRITICAL

a. Risk of bias related to blinding of participants was present. Although participants and study staff were blinded to intervention assignments, they may have inferred receipt of vaccine or placebo based on reactogenicity. Some reactogenicity outcomes may also have been reported as serious adverse events, and experiences of reactions immediately after vaccination could have influenced recall or reporting of subsequent serious adverse events. This was rated as not serious.

b. The RCT excluded persons with prior COVID-19 diagnosis, pregnant or breastfeeding women, and persons who were immunocompromised. The population included in the RCT may not represent all persons aged 12-15 years.

c. Serious concern of indirectness was noted. The body of evidence does not provide certainty that rare serious adverse events were captured due to the short duration of follow-up and the sample size.

d. Very serious concern for imprecision was noted based on the 95% confidence interval crossing the line of no effect. The width of the confidence interval contains estimates for which different policy decisions might be considered. This outcome may be imprecise due to the small number of events during the observation period.

Outcome 7: Reactogenicity, Severe (Grade ≥3)
Studies with Unvaccinated Comparator (n=1)

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

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

- Phase 2/3 trial solicited events through electronic diaries for 7 days following each dose
- Local reactions (pain at injection site, redness, swelling)
  - Grade 3: pain at injection site 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, necrosis (redness and swelling categories) or exfoliative dermatitis (redness category only).
- Systemic events (fever, vomiting, diarrhea, headache, fatigue, chills, new or worsened muscle pain, new or worsened joint pain)
  - Grade 3: fever >38.9°C to 40.0°C , vomiting that requires IV hydration; diarrhea of ≥6 loose stools in 24 hours; severe fatigue, severe headache, severe muscle pain, or severe joint pain that prevents daily activity.
  - Grade 4: fever >40.0°C, fatigue, headache, muscle pain, joint pain, diarrhea, or vomiting that require emergency room visit or hospitalization.

Outcome 7: Reactogenicity[a], Severe (Grade ≥3)
Studies with Unvaccinated Comparator (n=1)

Study/population	Events/Vaccine (n/N)	% Vaccine	Events/Placebo (n/N)	% Placebo
Pfizer/BioNTech, unpublished	121/1131	10.7	22/1129	1.9

a. Reactogenicity outcome includes local and systemic events, grade ≥3. Grade 3: prevents daily routine activity. Grade 4: requires emergency room visit or hospitalization. One participant in the vaccine group reported grade 4 pyrexia (40.4 °C).

Evidence Table: Reactogenicity, Severe (Grade ≥3)

Certainty assessment							№ of patients		Effect	Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Intervention	Comparison	Relative (95% CI)		
Reactogenicity, severe (grade ≥3)											
2	RCT	Not serious	Not serious	Not serious[a]	Not serious	None	121/1131 (10.7%)	22/1129 (1.9%)	**RR 5.49** (3.51 to 8.58)	**Type 1**	IMPORT-ANT

a. The RCT excluded persons with prior COVID-19 diagnosis, pregnant or breastfeeding women, and persons who were immunocompromised. The population included in the RCT may not represent all persons aged 12-15 years.

Summary of GRADE

Outcome	Importance	Design (# of studies)	Findings	Evidence type
Benefits				
Symptomatic lab-confirmed COVID-19	Critical	RCT (1)	Pfizer-BioNTech COVID-19 vaccine is effective in preventing symptomatic COVID-19	**1**
Hospitalization due to COVID-19	Important	No studies	Data not available from any studies	**ND**
Multisystem inflammatory syndrome in children (MIS-C)	Important	No studies	Data not available from any studies	**ND**
SARS-CoV-2 seroconversion	Important	No studies	Data not available from any studies	**ND**
Asymptomatic SARS-CoV-2 infection	Important	No studies	Data not available from any studies	**ND**
Harms				
Serious adverse events	Critical	RCT (1)	5 SAEs among vaccinated and 2 among unvaccinated; certainty in the estimate was very low. No SAEs were judged to be related to vaccination.	**4**
Reactogenicity	Important	RCT (1)	Severe reactions were more common in vaccinated; any grade ≥3 reaction was reported by 10.7% of vaccinated vs. 1.9% of placebo group	**1**

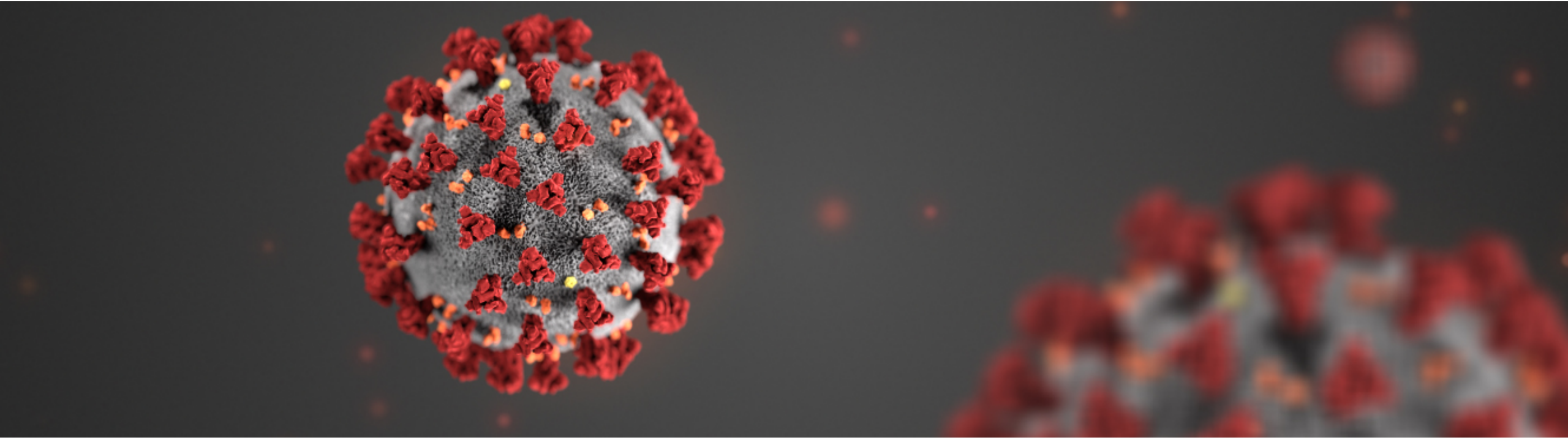
Evidence type: 1=high; 2=moderate; 3=low; 4=very low; ND, no data

Conclusion – GRADE for Pfizer-BioNTech COVID-19 vaccine in adolescents

- Phase 2/3 RCT conducted among persons aged 12-15 years in the United States.
- Vaccine efficacy estimate of **100%** for symptomatic laboratory-confirmed COVID-19.
- Serious adverse events were more common among vaccine than placebo participants (**0.4% vs 0.2%**), but our certainty in the estimate was very low. No SAEs were judged to be related to vaccination.
- Grade ≥3 local or systemic reactions more common among vaccine than placebo recipients and were reported by **~11%** of vaccine participants.
- Certainty for **critical** benefits was **type 1** (high).
- Certainty for **critical** harms was **type 4** (very low).

Acknowledgements

- **CDC Data team**
  - Julia Gargano
  - Amy Blain
  - Danielle Moulia
- Sara Oliver
- Heather Scobie
- Steven Hadler
- Jack Gersten
- Eddie Shanley
- Mary Chamberland
- Megan Lindley
- Nicole Reisman
- Karen Broder
- Naomi Tepper
- Rebecca Morgan
- Doug Campos-Outcalt



For more information, contact CDC
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Thank you

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