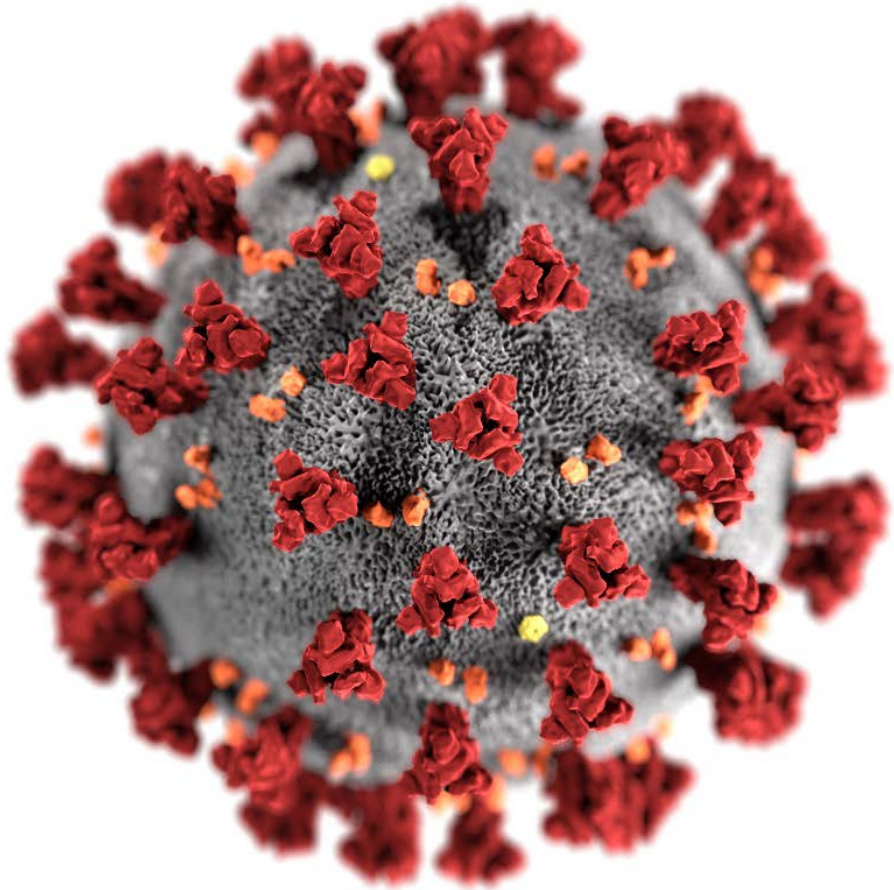
Grading of Recommendations, Assessment, Development, and Evaluation (GRADE): Pfizer BioNTech COVID-19 Vaccine



Dr. Julia Gargano
ACIP Meeting
11 December 2020

CONFIDENTIAL DRAFT

Policy Question

- Should vaccination with Pfizer BioNTech COVID-19 vaccine (2-doses, IM) be recommended for persons 16 years of age and older under an emergency use authorization?

PICO Question

Population	Persons aged ≥16 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 All-cause death SARS-CoV-2 seroconversion to a non-spike protein Asymptomatic SARS-CoV-2 infection Serious Adverse Events Reactogenicity

Outcomes

Outcome	Importance[a]	Description
Benefits		
Symptomatic lab-confirmed COVID-19	Critical	Primary outcome; current studies use PCR + specific symptoms
Hospitalization due to COVID-19	Critical	Phase 3 trials not designed to detect statistical differences between treatment groups for this outcome
All-cause death	Important	Death from all causes; 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

Outcomes

Outcome	Importance[a]	Description
Benefits		
Symptomatic lab-confirmed COVID-19	Critical	Primary outcome; current studies use PCR + specific symptoms
Hospitalization due to COVID-19	Critical	Phase 3 trials not designed to detect statistical differences between treatment groups for this outcome
All-cause death	Important	Death from all causes; 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

Outcomes

Outcome	Importance[a]	Description
Benefits		
Symptomatic lab-confirmed COVID-19	Critical	Primary outcome; current studies use PCR + specific symptoms
Hospitalization due to COVID-19	Critical	Phase 3 trials not designed to detect statistical differences between treatment groups for this outcome
All-cause death	Important	Death from all causes; 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 protei due to natural infection from immunogenicity t
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

Phase 3 trials not powered to evaluate differences in hospitalizations and deaths; interpret in light of findings for symptomatic COVID-19

[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	Primary outcome; current studies use PCR + specific symptoms
Hospitalization due to COVID-19	Critical	Phase 3 trials not designed to detect statistical differences between treatment groups for this outcome
All-cause death	Important	Death from all causes; 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 vaccine-related
Reactogenicity	Important	Evaluating grade ≥ 3 severity of systemic events and local reactions

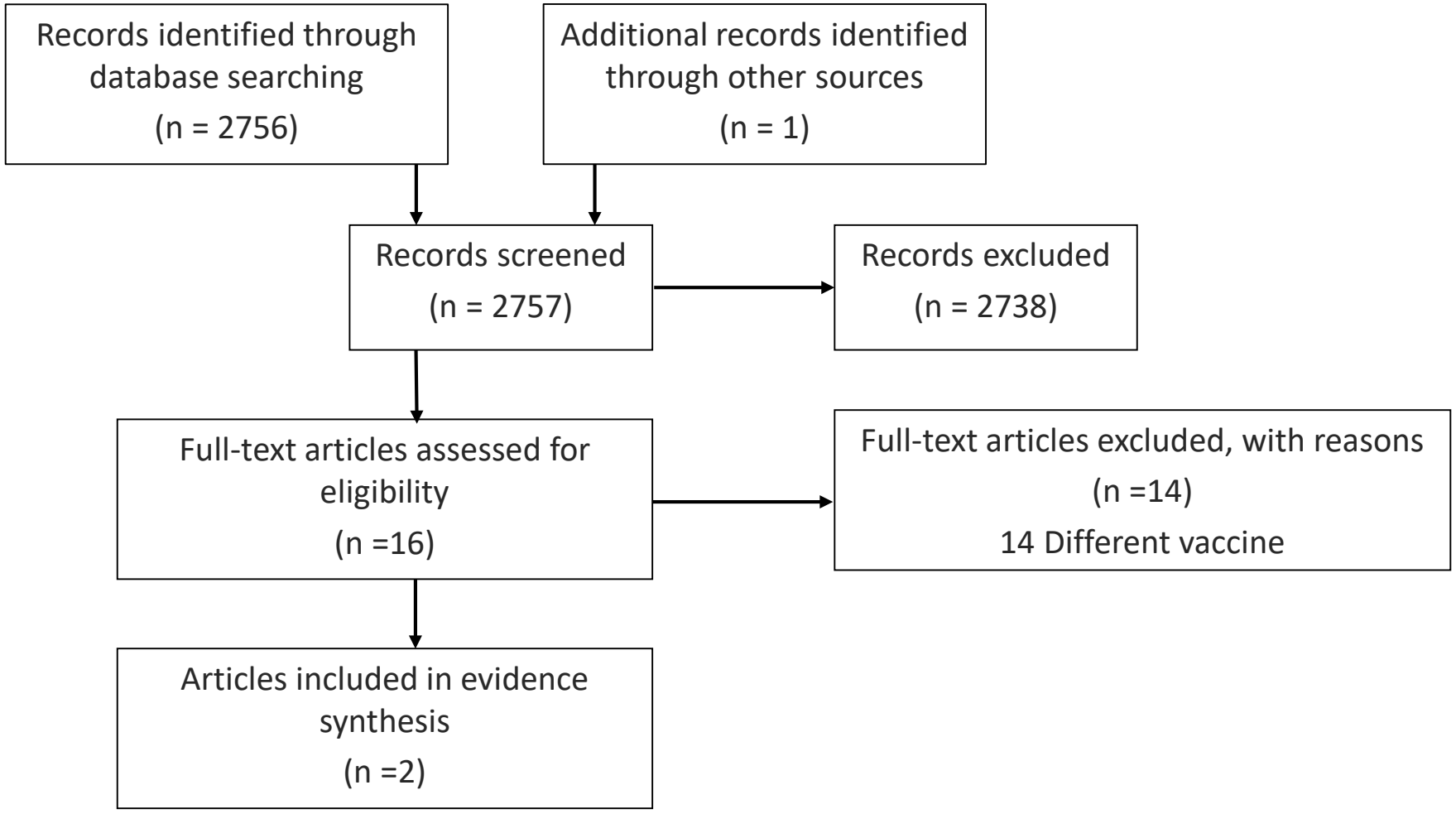
No data available to evaluate antibodies or asymptomatic infection; not included in evidence profile

[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 adults (ages 18 and older) 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 ≥16 years in United States, Brazil, Argentina, South Africa, Turkey, Germany
- 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: Nov 14, 2020)

Pfizer/BioNTech phase 2/3 RCT Analysis Populations*

Population	Description	N*	Person-years
Evaluable efficacy	All eligible randomized participants who receive all vaccination(s) as randomized within the predefined window and have no other important protocol deviations as determined by the clinician, who did not have evidence of prior SARS-CoV-2 infection	**36,523**	**4,436**
	Including persons with prior infection	40,137	4,677
All-available efficacy	All randomized participants who receive at least 1 vaccination.	43,355	7,997

*Includes participants meeting population definition through Nov 14 data cutoff date, including persons randomized on or after Oct 10. Persons aged 16-17 years, and those with stable chronic infections (i.e., HIV, Hepatitis) were enrolled later in the trial.
NOTE: for some analyses, numbers vary due to number of persons at risk for outcome

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

Population	Events/Vaccine[a] (n/N)	Events/Placebo[a] (n/N)	Vaccine efficacy (95% confidence interval)
Primary Outcome[b]			
Aged ≥16 years	8/17411	162/17511	95.0% (90.3%, 97.6%)
Aged 16–64	7/13563	143/13631	95.1% (89.6%, 98.1%)
Aged ≥65 years	1/3848	19/3880	94.7% (66.7%, 99.9%)
Aged ≥75 years[c]	0/774	5/785	100.0% (-13.1%, 100.0%)
At risk[d]	4/8030	86/8029	95.3% (87.7%, 98.8%)
Aged ≥65 years and at risk[d]	1/2147	12/2109	91.7% (44.2%, 99.8%)

[a]18,198 and 18,325 persons were randomized to vaccine and placebo, respectively; 17,411 and 17,511 in each arm had no evidence of prior infection.

[b]Cases diagnosed ≥7 days post dose 2 among persons without evidence of prior SARS-CoV-2 infection

[c]FDA requested subgroup analysis

[d]Includes persons with at least 1 comorbidity as assessed by Charlson Comorbidity Index, or obesity (BMI ≥ 30)

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

Population	Events/Vaccine[a] (n/N)	Events/Placebo[a] (n/N)	Vaccine efficacy (95% confidence interval)
Primary Outcome[b]			
Aged ≥16 years	8/17411	162/17511	95.0% (90.3%, 97.6%)
Aged 16–64	7/13563	143/13631	95.1% (89.6%, 98.1%)
Aged ≥65 years	1/3848	19/3880	94.7% (66.7%, 99.9%)
Aged ≥75 years[c]	0/774	5/785	100.0% (-13.1%, 100.0%)
At risk[d]	4/8030	86/8029	95.3% (87.7%, 98.8%)
Aged ≥65 years and at risk[d]	1/2147	12/2109	91.7% (44.2%, 99.8%)

[a]18,198 and 18,325 persons were randomized to vaccine and placebo, respectively; 17,411 and 17,511 in each arm had no evidence of prior infection.

[b]Cases diagnosed ≥7 days post dose 2 among persons without evidence of prior SARS-CoV-2 infection

[c]FDA requested subgroup analysis

[d]Includes persons with at least 1 comorbidity as assessed by Charlson Comorbidity Index, or obesity (BMI ≥ 30)

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	8/14711	162/17511	95.0% (90.3%, 97.6%)
Secondary outcomes			
± evidence of prior infection, ≥7 d post dose 2	9/18559	169/18708	94.6% (89.9%, 97.3%)
No evidence of prior infection, ≥14 d post dose 2	8/16612	139/16663	94.2% (88.7%, 97.2%)
± evidence of prior infection, ≥14 d post dose 2	8/17645	144/17746	94.4% (89.1%, 97.3%)
All available efficacy (± evidence of prior infection, post dose 1)	50/21314	275/21258	82.0% (75.6%, 86.9%)

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	8/14711	162/17511	95.0% (90.3%, 97.6%)
Secondary outcomes			
± evidence of prior infection, ≥7 d post dose 2	9/18559	169/18708	94.6% (89.9%, 97.3%)
No evidence of prior infection, ≥14 d post dose 2	8/16612	139/16663	94.2% (88.7%, 97.2%)
± evidence of prior infection, ≥14 d post dose 2	8/17645	144/17746	94.4% (89.1%, 97.3%)
All available efficacy (± evidence of prior infection, post dose 1)	50/21314	275/21258	82.0% (75.6%, 86.9%)

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	8/17411 (0.0%)	162/17511 (0.9%)	**RR 0.05** (0.02 to 0.10)	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 a modified intention to treat analysis 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 50 cases reported among 21,314 persons who received the vaccine, and 275 cases among 21,258 persons who received the placebo, for a relative risk of 0.18 (95% CI: 0.13 to 0.24).

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 >=16 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).

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

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

- Pfizer/BioNTech phase 2/3 randomized controlled trial (RCT) (unpublished, data obtained from sponsor)
- Severe COVID-19[a]: COVID-19 case with at least 1 of following:
  - Clinical signs at rest indicative of severe systemic illness;[b]
  - Respiratory failure;[b]
  - Evidence of shock;[b]
  - Significant acute renal, hepatic, or neurologic dysfunction;
  - Admission to an intensive care unit; or
  - Death
- Severe COVID-19 per CDC definition: hospitalization, admission to the ICU, intubation or mechanical ventilation, or death

a. Severe COVID-19 as defined in protocol using guidance from FDA.
b. **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 for COVID-19
Studies with Unvaccinated Comparator (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, ≥7 d post dose 2	1/17411	3/17511	66.4% (-124.8, 96.3%)
Severe COVID-19 (CDC) & hospitalized	**No evidence of prior infection, ≥7 d post dose 2**	**0/17399**	**5/17495**	**100% (-9.9%, 100%)**
Alternative analyses – all available efficacy population				
Severe COVID-19, protocol definition	After dose 1	1/21314	9/21259	88.9% (20.1, 99.7%)
Severe COVID-19 (CDC) & hospitalized [b]	**After dose 1**	**1/21299**	**14/21238**	**92.9% (53.2%, 99.8%)**

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

Evidence Table: Hospitalization for COVID-19

Certainty assessment							№ of patients		Effect	Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Intervention	comparison	Relative (95% CI)		
Vaccine efficacy against hospitalization due to COVID-19											
1	RCT	Not serious a	Not serious	Serious b,c,d	Serious e	None	0/17399 (0.0%)	5/17495 (0.0%)	**RR: 0.00** (0.00 to 1.10)	**Type 3**	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 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 ≥16 years.

c. The effects noted are from a modified intention to treat analysis with outcomes assessed at least 7 days post dose 2, among persons who received 2 doses, and had no evidence of prior SARS-CoV-2 infection. In the all available efficacy population (persons who received at least 1 dose, among those with or without evidence of prior infection), 1 hospitalized occurred among 21,299 persons who received the vaccine, and 14 hospitalized cases occurred among 21,238 persons (RR=0.07; 95% CI: 0.02 to 0.47).

d. Serious concern for indirectness was noted due to the short duration of follow-up in the available body of evidence. Severe COVID-19 cases leading to hospitalization may not have had time to occur in a median 2-month follow-up.

e. Serious concern for imprecision was present due to the small number of events that were observed.

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

Outcome 3: All-cause Death
Studies with Unvaccinated Comparator (n=1)

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

Outcome 3: All-cause Death
Studies with Unvaccinated Comparator (n=1)

Study/population	Events/Vaccine (n/N)[b,c]	Events/Placebo (n/N)[d]	Relative Risk[e] (95% confidence interval)
Persons aged ≥16 years [a]	2/21621	4/21631	0.50 (0.09, 2.73)

a. All participants enrolled as of Nov 14 data cutoff date, including persons randomized on or after Oct 10.
b. None of these 6 deaths were assessed by the investigator as related to study intervention.
c. Two participants in older vaccine group: one experienced an SAE of arteriosclerosis and died 3 days after Dose 1; one experienced an SAE of cardiac arrest 60 days after Dose 2 and died 3 days later.
d. Four participants in placebo group (two in younger, two in older):

- One in younger group experienced an SAE of unevaluable event (unknown of unknown origin; no additional information currently available at the time of this report) 8 days after Dose 1 and died the same day;
- One in older group experienced an SAE of hemorrhagic stroke 15 days after Dose 2 and died the next day;
- One in younger group experienced an SAE of death (cause unknown; no additional information currently available at the time of this report) 34 days after Dose 2;
- One in the older placebo experienced an SAE of myocardial infarction 16 days after Dose 1 and died the same day.

e. Estimate and confidence interval were calculated based on number of participants. Person-time was not provided for this outcome.

Evidence Table: All-cause Death

Certainty assessment							№ of patients		Effect	Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Intervention	comparison	Relative (95% CI)		
Vaccine efficacy against death, all cause											
1	RCT	Not serious	Not serious	Serious [a,b]	Very serious [c,d]	None	2/21621 (0.0%)	4/21631 (0.0%)	RR 0.50 (0.09 to 2.73)	**Type 4**	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 ≥16 years.
b. Serious concern for indirectness was noted due to the short duration of follow-up in the available body of evidence. Deaths due to COVID-19 may not have had time to occur during the follow-up period.
c. Serious concern for imprecision was present due to the small number of events that were observed.
d. Death from all causes was considered a descriptive outcome in the clinical trial data. The sponsor provided counts of total deaths but appropriate denominators for analysis to evaluate benefits for this outcome are not clear, further increasing concern for imprecision.

Harms

Outcome 6: Serious Adverse Events
Studies with Unvaccinated Comparator (n=2)

- Pfizer/BioNTech phase 2/3 randomized controlled trial (RCT) (unpublished, data obtained from sponsor)
- Pfizer/BioNTech Phase 1 randomized trial (Walsh, 2020)

Pfizer/BioNTech Phase 1 RCT (Walsh, 2020)

- Population: healthy adults aged 18-55 or 65-85 years, United States
- Data evaluated:
  - 18-55 years: 12 received 2 doses of 30 µg of BNT162b2, 9 placebo
  - 65-85 years: 12 received 2 doses of 30 µg of BNT162b2, 9 placebo
- Primary outcomes: safety
  - local and systemic reactions: active surveillance through prompted electronic diary for 7 days following each dose
  - adverse events: passive surveillance (unprompted reporting), clinical laboratory assessments 1-2 and 7 days after each dose

Walsh EE, Frenck RW, Falsey AR et al. Safety and Immunogenicity of Two RNA-Based Covid-19 Vaccine Candidates. *NEJM*. 2020. DOI: 10.1056/NEJMoa2027906.

Outcome 6: Serious Adverse Events
Studies with Unvaccinated Comparator (n=2)

Study/population[a]	Events/Vaccine (n/N)[b]	% SAE Vaccine	Events/Placebo (n/N)	% SAE Placebo	Associated with vaccination[c]
Walsh, 2020	1/24	4.2	0/18	0	0
Pfizer/BioNTech, unpublished	126/21621	0.6	111/21631	0.5	2

a. Included all randomized participants who received at least 1 dose of vaccine
b. One SAE of neuritis was reported from the phase 1 trial that had not been identified at the time of the Walsh publication. This SAE was deemed unassociated to vaccination. In the phase 3 trial, there was a potential clinical imbalance of appendicitis, with 8 events in the vaccine group and 4 in the placebo group
c. Four serious adverse events were deemed by blinded investigators to be related to vaccination. These included: shoulder injury related to vaccine administration, ventricular arrhythmia, lymphadenopathy, and lower back pain and bilateral lower extremity pain with radicular paresthesia. Through further investigation by the FDA, only two were classified as related to vaccination: shoulder injury and lymphadenopathy.

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]	Not serious	Not serious	127/21645 (0.6%)	111/21649 (0.5%)	RR 1.14 (0.89 to 1.47)	**Type 2**	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 ≥16 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.

Outcome 7: Reactogenicity, Severe (Grade ≥3)
Studies with Unvaccinated Comparator (n=2)

- Pfizer/BioNTech phase 2/3 randomized controlled trial (RCT) (unpublished, data obtained from sponsor)
  - Data collected on subset (N=8214)
- Pfizer/BioNTech Phase 1 randomized trial (Walsh, 2020)

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

- Both trials 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, Severe (Grade ≥3)
Studies with Unvaccinated Comparator (n=2)

Study/population	Events/Vaccine (n/N)	% Vaccine	Events/Placebo (n/N)	% Placebo
Walsh, 2020[a]	2/24	8.3	1/18	5.6
Pfizer/BioNTech, unpublished	362/4108	8.8	84/4106	2.1

a. Data are updated with additional information from sponsor.

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, b	not serious	none	364/4132 (8.8%)	85/4124 (2.1%)	**RR 4.27** (3.39 to 5.38)	**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 ≥16 years.
b. Reactogenicity data were not collected from persons aged 16-17 years, raising some concern of indirectness. However, there is no reason to expect their reactions to vaccination to be different from young adults who were included. In addition, reactogenicity data from adolescents aged 12-15 years were obtained and reviewed, and were similar to that from adults aged 18-55 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	Critical	RCT (1)	Pfizer-BioNTech COVID-19 vaccine may prevent COVID-19-resulting in hospitalization, but the uncertainty is high because this is a rare outcome	**3**
All-cause Death	Important	RCT (1)	Pfizer-BioNTech COVID-19 vaccine may prevent death, but the uncertainty is high because this is a rare outcome	**4**
SARS-CoV-2 seroconversion	Important	No studies	Data not yet 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 (2)	SAEs were balanced between vaccine and placebo arms. Two SAEs were judged to be related to vaccination.	**2**
Reactogenicity	Important	RCT (2)	Severe reactions were more common in vaccinated; any grade ≥3 reaction was reported by 8.8% of vaccinated vs. 2.1% of placebo group	**1**

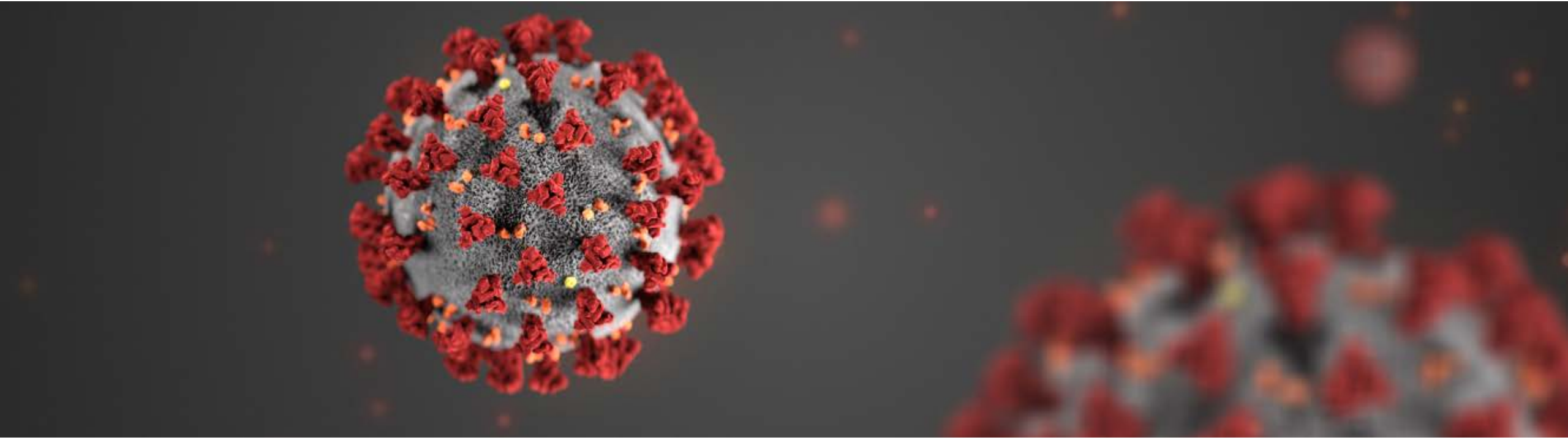
Evidence type: 1=high; 2=moderate; 3=low; 4=very low; ND, no data

Conclusion

- **Policy question:** focuses on recommendation during an EUA
- **Benefits**: Phase 3 trial is ongoing, and effect estimates may change with additional follow-up
  - Unlikely that efficacy estimate for symptomatic COVID-19 would change substantially enough in the months following vaccination to fall below the FDA-defined efficacy threshold for EUA (i.e., to <50% efficacy)
  - Direct evidence of efficacy for hospitalization and deaths limited; from efficacy against disease, we infer that vaccination would reduce hospitalizations and deaths
  - No data were available to assess prevention of asymptomatic infection
- **Harms**: Grade 3 reactions not uncommon in vaccinated persons; serious adverse events occurred at a similar frequency in vaccine and placebo groups

Acknowledgements

- Katie Curran
- Megan Wallace
- Kathleen Dooling
- Mona Marin
- Sara Oliver
- Karen Broder
- Rebecca Morgan
- Doug Campos-Outcalt
- VTF ACIP WG Team



For more information, contact CDC
1-800-CDC-INFO (232-4636)
TTY: 1-888-232-6348 www.cdc.gov

Thank you

The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention.

Demographics

Characteristics	Vaccine (N=18860)	Placebo (N=18846)	Total[a] (N=37706)
Sex - Female	9221 (48.9)	9410 (49.9)	18631 (49.4)
Race			
White	15636 (82.9)	15630 (82.9)	31266 (82.9)
Black or African American	1729 (9.2)	1763 (9.4)	3492 (9.3)
American Indian or Alaska Native	102 (0.5)	99 (0.5)	201 (0.5)
Asian	801 (4.2)	807 (4.3)	1608 (4.3)
Native Hawaiian or other Pacific Islander	50 (0.3)	26 (0.1)	76 (0.2)
Multiracial	449 (2.4)	406 (2.2)	855 (2.3)
Hispanic/Latino Ethnicity	5266 (27.9)	5277 (28.0)	10543 (28.0)
Age >55 Years	7971 (42.3)	7950 (42.2)	15921 (42.2)
Body mass index (BMI)			
Underweight (<18.5 kg/m^2)	201 (1.1)	235 (1.2)	436 (1.2)
Normal weight (≥18.5 – 24.9 kg/m^2)	5517 (29.3)	5460 (29.0)	10977 (29.1)
Overweight (≥25.0 – 29.9 kg/m2)	6578 (34.9)	6662 (35.3)	13059 (34.6)
Obese (≥30.0 kg/m2)	6556 (34.8)	6662 (35.3)	13218 (35.1)
At risk[b]	8030 (44.1)	8029 (43.8)	16059 (44.0)

[a]Race missing for 208 persons, Ethnicity missing for 222 persons, BMI missing for 16 persons

[e]At risk defined as persons with at least 1 comorbidity, as assessed by Charlson Comorbidity Index, or obesity (BMI ≥ 30). Evaluable efficacy population used as denominator.

Additional Vaccine Efficacy Estimates

Population	Events/Vaccine[a,b] (n/person-years)	Events/Placebo[a,b] (n/person-years)	Vaccine efficacy [c] (95% confidence interval)
First COVID-19 occurrence after Dose 1	50/4015	275/3982	82.0% (75.6, 86.9)
After Dose 1 to before Dose 2	39	82	52.4% (29.5%, 68.4%)
Dose 2 to 7 days after Dose 2	2	21	90.5% (61.0%, 98.9%)
≥7 Days after Dose 2	9	172	94.8% (89.8%, 97.6%)
Race			
White	7/1889	146/1903	95.2% (89.8%, 98.1%)
Black or African American	0/165	7/164	100.0% (31.2%, 100.0%)
All others	1/160	9/155	89.3% (22.6%, 99.8%)
Hispanic/Latino Ethnicity	3/605	53/600	94.4% (82.7%, 98.9%)

[a]21,669 and 21,686 persons were randomized to vaccine and placebo, respectively for dose estimates; 18,198 and 18,325 persons were randomized to vaccine and placebo, respectively for race/ethnicity estimates.
[b]Follow-up time not provided for dose sub-category estimates
[c] VE = (1-RR)*100%

Outcome 6: Serious Adverse Events by System Organ Class

System Organ Class	Events in Vaccine Group, n (%) (N=18801)	Events in Placebo Group, n (%) (N=18785)
Blood and Lymphatic System Disorders	1 (0.0)	1 (0.0)
Cardiac Disorders	14 (0.1)	12 (0.1)
Congenital, Familial, and Genetic Disorders	1 (0.0)	0 (0.0)
Ear and Labyrinth Disorders	1 (0.0)	0 (0.0)
Gastrointestinal Disorders	8 (0.0)	6 (0.0)
General Disorders and Administration Site Conditions	4 (0.0)	3 (0.0)
Hepatobiliary Disorders	4 (0.0)	2 (0.0)
Immune System Disorders	2 (0.0)	1 (0.0)
Infections and Infestations	25 (0.1)	14 (0.1)
Injury, Poisoning and Procedural Complications	6 (0.0)	11 (0.1)
Investigations	1 (0.0)	2 (0.0)
Metabolism and Nutrition Disorders	2 (0.0)	3 (0.0)
Musculoskeletal and Connective Tissue Disorders	3 (0.0)	1 (0.0)
Neoplasms Benign, Malignant and Unspecified	7 (0.0)	8 (0.0)
Nervous System Disorders	15 (0.1)	13 (0.1)
Pregnancy, Puerperium and Perinatal Conditions	0 (0.0)	1 (0.0)
Renal and Urinary Disorders	5 (0.0)	1 (0.0)
Reproductive System and Breast Disorders	2 (0.0)	1 (0.0)
Respiratory, Thoracic and Mediastinal Disorders	5 (0.0)	4 (0.0)
Uncoded Term (Jammed Right Inguinal Hernia)	1 (0.0)	0 (0.0)
Vascular Disorders	5 (0.0)	3 (0.0)

Adverse Events
Studies with unvaccinated comparator (n=2)[1]

Study/population	Events/Vaccine (n/N)	% AE Vaccine	Events/Placebo (n/N)	% AE Placebo	Associated with vaccination[2,3]
Pfizer/BioNTech, unpublished	5770/21621	26.7	2638/21631	12.2	4484

[1]Included all randomized participants who received at least 1 dose of vaccine
[2]AEs of lymphadenopathy were reported in 64 participants in the vaccine group and 6 participants in the placebo group, 47 of 67 were considered by the investigator as related to the intervention
[3]Imbalances were primarily accounted for by reactogenicity events: general disorders and administration site conditions (includes injection site pain, fatigue, pyrexia, chills; 18.6% vaccine vs 3.9% placebo), musculoskeletal and connective tissue disorders (includes myalgia and arthralgia; 7.3% vaccine vs 2.0% placebo), and nervous system disorders (includes headaches; 6.1% vaccine vs 2.4% placebo).

Eligibility Criteria

Inclusion Criteria	Exclusion Criteria
1. Aged ≥12 years. 2. Willing and able to comply with study procedures and lifestyle considerations (e.g., appropriate method of contraception). 3. Healthy determined by medical history, physical examination (if required), and clinical judgment of the investigator. Note: Healthy participants with preexisting stable disease (including HIV, HCV, HBV) can be included. 4. At higher risk of acquiring COVID-19 (i.e., use of mass transportation, demographics, frontline essential workers). 5. Signed informed consent.	<u>Medical conditions:</u> 1. Other medical or psychiatric condition including recent (within the past year) or active suicidal ideation/behavior or laboratory abnormality that may increase the risk of study participation. 2. History of severe adverse reaction associated with a vaccine. 3. Receipt of medications intended to prevent COVID-19. 4. Previous diagnosis of COVID-19 [clinical (based on COVID-19 symptoms/signs alone, if a SARS-CoV-2 NAAT result was not available) or microbiological (based on COVID-19 symptoms/signs and a positive SARS-CoV-2 NAAT result) diagnosis]. 5. Immunocompromised individuals with known or suspected immunodeficiency, as determined by history and/or laboratory/physical examination. 6. Bleeding diathesis or condition associated with prolonged bleeding that would contraindicate intramuscular injection. 7. Women who are pregnant or breastfeeding. <u>Prior/concomitant therapy:</u> 8. Previous vaccination with any coronavirus vaccine. 9. Individuals who receive treatment with immunosuppressive therapy. 10. Receipt of blood/plasma products or immunoglobulin, from 60 days before study intervention administration or planned receipt throughout the study. <u>Prior/concurrent clinical study experience:</u> 11. Participation in other studies involving study intervention within 28 days prior to study. 12. Previous participation in other studies involving intervention containing lipid nanoparticles. <u>Other exclusions:</u> 13. Investigator site staff or Pfizer/BioNTech employees directly involved in the conduct of the study, site staff otherwise supervised by the investigator, and their respective family members.

COVID-19 Case Definitions & Assessment

Outcome	Definition	Assessment

COVID-19 cases	SARS-CoV-2 positive test result per central laboratory or local testing facility (using an acceptable test* within 4 days of symptom onset) AND
	At least one symptom: fever, new/increased cough, new/increased shortness of breath, chills, new/increased muscle pain, new loss of taste or smell, sore throat, diarrhea, vomiting
		Participants:
		• Complete COVID-19 illness e-diary on personal or provided device
		• Instructed to contact site immediately if any potential COVID-19 symptoms
		• If confirmed, participate in an in-person or telehealth visit (≤4 days after onset)
		  ◦ In-person: site staff collect nasal (midturbinate) swab
		  ◦ Telehealth: self-collect nasal swab and ship to central lab
		• Encouraged to seek care, as appropriate, from usual provider
		• Participate in routine follow-up visits after dose 2: 1 week, 2 weeks, 1 month, 6 months, 12 months, 24 months
		
		Study staff:
		• Contact if COVID-19 illness e-diary is not completed
		• Contact to collect COVID-19 clinical and lab information, number and type of any healthcare contact, duration of hospitalization and ICU stay, death
		• Schedule potential COVID-19 convalescent visit (28-35 days after COVID-19 illness visit: collect/update clinical and lab information, collect blood for immunogenicity testing)
		
		Note: During 7 days following each dose, potential COVID-19 symptoms that overlap with specific systemic events should not trigger a potential COVID-19 illness visit unless the investigator believes clinical picture is more indicative of COVID-19 than vaccine reactogenicity.

CDC criteria-defined COVID-19 cases	Above, including symptoms: fatigue, headache, nasal congestion or runny nose, nausea	
Severe COVID-19 (FDA guidance)	COVID-19 case with at least 1 of following: • Clinical signs at rest indicative of severe systemic illness[1] • Respiratory failure[1] • Evidence of shock[1] • Significant acute renal, hepatic, or neurologic dysfunction • Admission to an intensive care unit Death	

*Acceptable test: a RT-PCR test (Cepheid; FDA approved under EUA), or other equivalent nucleic acid amplification–based test (i.e., NAAT), to detect SARS-CoV-2.

[1]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.

Adverse Event Definitions & Assessment

Outcome	Definition	Assessment
Adverse event	Any untoward medical occurrence in a patient or clinical study participant, temporally associated with the use of study intervention, whether or not considered related to the study intervention. *NOTE*: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of study intervention.	Recorded for up to 1 month after dose 2 Categorized by frequency, severity, seriousness, and relationship to study intervention using SOC and PT according to the MeDRA Proactively follow participant and obtain adequate information (for independent review) until resolution Supplemental evaluations done to elucidate nature and causality *NOTE*: For any Phase 3 participants that were not in the reactogenicity subset, local reactions and systemic events consistent with reactogenicity were detected and reported as AEs.
Adverse event of special interest	Not prespecified in protocol TME of clinical interest or specific AEs for a product or program's protocol(s) based on review of known pharmacology, toxicology, findings, possible class effects, published literature, and potential signs arising from safety data assessments (*Appendix 2*)	*See above* *NOTE*: Pfizer safety review highlights TME of clinical interest, specific AE terms reviewed on ongoing basis
Serious adverse event	Any untoward medical occurrence, at any dose: 1) results in death, 2) is life-threatening, 3) requires inpatient hospitalization or prolongation of existing hospitalization, 4) results in persistent disability/incapacity, 5) is a congenital anomaly/birth defect, or 6) other situations*	Recorded for up to 6 months after dose 2 Deaths and related SAEs will be recorded for up to 2 years after dose 2 (end of study)

SOC: System Organ Class; PT: Preferred Term; MeDRA: Medical Dictionary for Regulatory Activities; TME: Targeted Medical Event.
*Determined by medical or scientific judgment, important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition.

Risk of Bias: Blinding

Blinded	Unblinded
▪ All other study and site personnel, including the investigator, investigator staff, and participants, were blinded to study intervention assignments. In particular, the individuals who evaluated participant safety were blinded. ▪ The study intervention syringes were administered in a manner that prevented the study participants from identifying the study intervention type based on its appearance.	▪ Study staff receiving, storing, dispensing, preparing, and administering the study interventions were unblinded. ▪ Reactogenicity may have resulted in unblinding of participants and any study personnel with access to reactogenicity data.

Follow-up Time after Dose 2, Safety Population (n=37,706)

	Vaccine Group, as administered (N=18,860)	Placebo Group, as administered (N=18,846)	Total (N=37,706)
Participants (%) with length of follow-up of:			
<2 months	**9,329 (49.5)**	**9,310 (49.4)**	**18,639 (49.4)**
<2 weeks	363 (1.9)	388 (2.1)	751 (2.0)
≥2 to <4 weeks	1,223 (6.5)	1,200 (6.4)	2,423 (9.4)
≥4 to <6 weeks	3,239 (17.2)	3,235 (17.2)	6,474 (17.2)
≥6 to <8 weeks	4,504 (23.9)	4,487 (23.8)	8,991 (23.8)
≥2 months	**9,531 (50.5)**	**9,536 (50.6)**	**19,067 (50.6)**
≥8 to <10 weeks	6,296 (33.4)	6,329 (33.6)	12,625 (33.5)
≥10 to <12 weeks	2,853 (15.1)	2,809 (14.9)	5,662 (15.0)
≥12 to <14 weeks	382 (2.0)	398 (2.1)	780 (2.1)

Outcome 4: Seroconversion to Non-spike Protein

- No studies to date provided data on seroconversion to non-spike protein

Outcome 5: Asymptomatic SARS-CoV-2 Infection

- No studies to date provided data on asymptomatic infection

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

- Primary efficacy endpoint:
  - COVID-19, in participants without evidence of prior infection, ≥7 days after dose 2
- Secondary efficacy endpoints:
  - COVID-19, in participants with and without evidence of prior infection, ≥7 days after dose 2
  - COVID-19, in participants (1) without or (2) with and without evidence of prior infection, ≥14 days after dose 2
  - Severe COVID-19, in participants (1) without or (2) with and without evidence of prior infection, either (1) ≥7 days after dose 2 or (2) ≥14 days after dose 2
- CDC-defined COVID-19, in participants (1) without or (2) with and without evidence of prior infection, either (1) ≥7 days after dose 2 or (2) ≥14 days after dose 2
- All available efficacy:
  - COVID-19, in participants with and without evidence of prior infection, after dose 1

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

Outcome	Study/population	Events/Vaccine (n/N)	Events/Placebo (n/N)	Vaccine efficacy (95% CI)
Secondary endpoint: Severe COVID-19, FDA definition [a]	No evidence of prior infection, ≥7 d post dose 2	1/17411	3/17511	66.4% (-124.8, 96.3%)
Severe COVID-19 (FDA) & hospitalized	No evidence of prior infection, ≥7 d post dose 2	0/17411	2/17511	100% (Exact p= 0.16)
Severe COVID-19 (CDC) & hospitalized	**No evidence of prior infection, ≥7 d post dose 2**	**0/17399**	**5/17495**	**100% (-9.9%, 100%) (Exact p=0.03)**
Alternative analyses – all available efficacy population				
Severe COVID-19 (FDA)	After dose 1	1/21314	9/21259	88.9% (20.1, 99.7%)
Severe COVID-19 (FDA), hospitalized	After dose 1	0/21314	7/21259	100% (Exact p= 0.008)
First severe COVID-19, CDC definition (& hospitalized) [b]	**After dose 1**	**1/21314**	**14/21259**	**92.9% (53.2%, 99.8%)**

[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