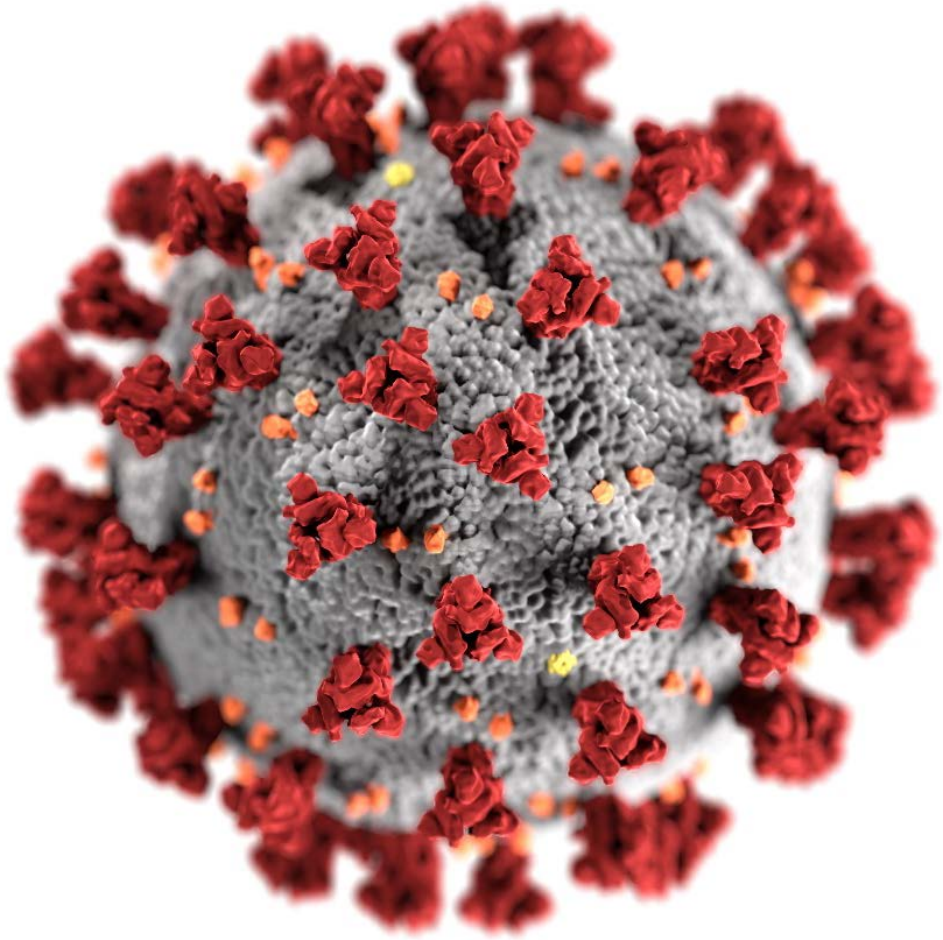
Grading of Recommendations, Assessment, Development, and Evaluation (GRADE): Pfizer-BioNTech COVID-19 Vaccine



Dr. Julia Gargano
ACIP Meeting
August 30, 2021

cdc.gov/coronavirus

Policy Question

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

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 laboratory-confirmed COVID-19 Hospitalization due to COVID-19 Death due to COVID-19 Asymptomatic SARS-CoV-2 infection Serious Adverse Events Reactogenicity

PICO: Population, intervention, comparison, outcomes

Outcomes, Importance, and Data Sources

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

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

RCT: randomized controlled trial

Evidence Retrieval for Randomized Controlled Trials (RCTs)

- **Data source:** clinicaltrials.gov
- **Inclusion:** Relevant Phase 1, 2, or 3 randomized controlled trials of COVID-19 vaccine
  - 1) involved human subjects
  - 2) reported primary data
  - 3) included adults (age ≥16 years) at risk for SARS-CoV-2 infection
  - 4) included data relevant to the efficacy and safety outcomes being measured
  - 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- **Additional resources:** unpublished and other relevant data by consulting with vaccine manufacturers and subject matter experts

Evidence Retrieval for Vaccine Effectiveness (VE) Data

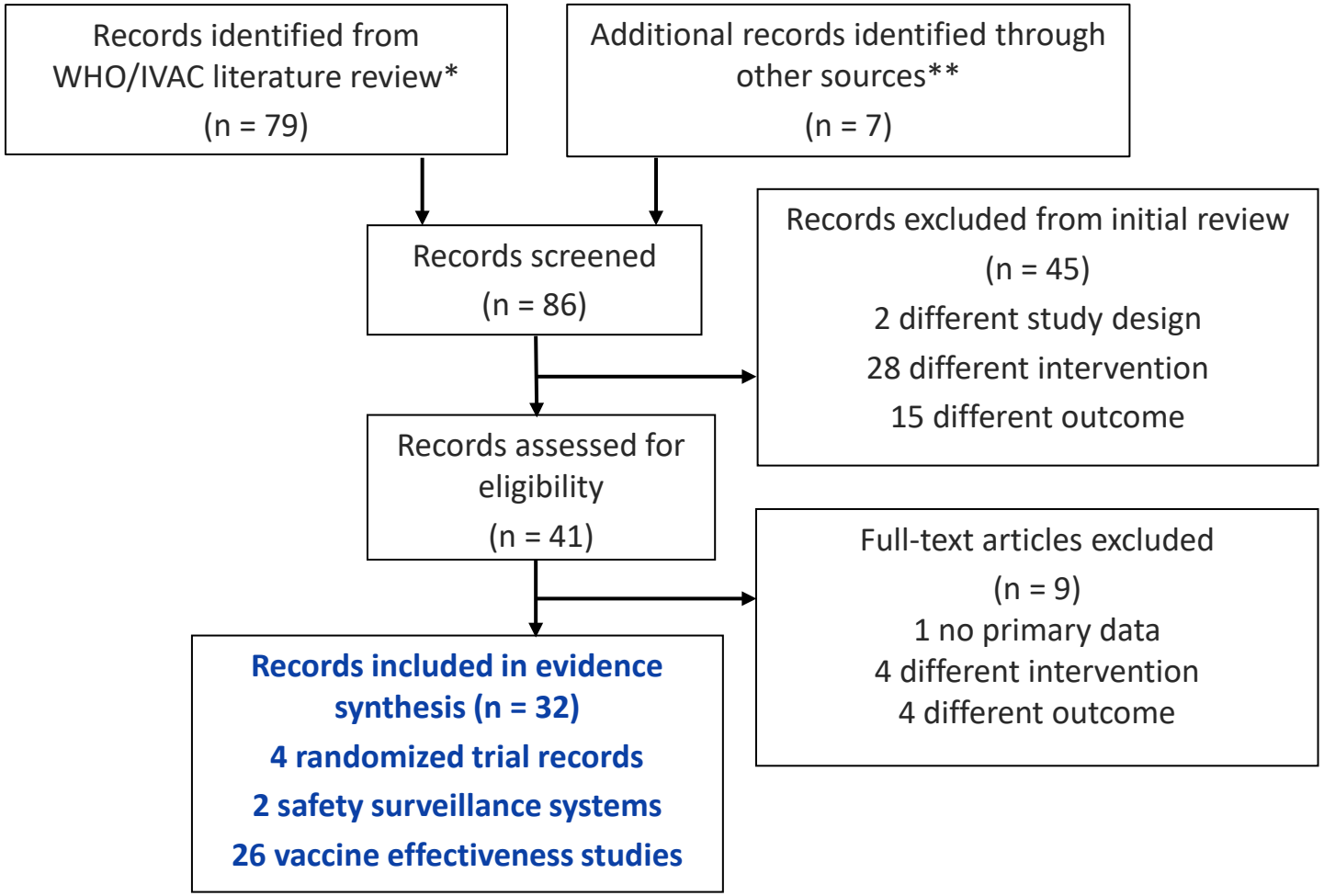
- **Inclusion Criteria for IVAC systematic review***
  - Published or preprint study with adequate scientific details
  - Includes group with and without infection or disease outcome
  - Laboratory confirmed outcome†
  - Vaccination status confirmed in ≥90%§
  - Studies assess one vaccine or pooled mRNA 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 or 14 days after 2nd dose
  - Only Pfizer-BioNTech vaccine (not mRNA vaccines as a group)
  - Included studies of general population and special populations (e.g. elderly, pregnant persons, healthcare workers)

Articles were eligible for inclusion if published before 8/20/21. *Criteria included in the ongoing systematic review conducted by the International Vaccine Access Center and the World Health Organization (see https://view-hub.org/resources). † Estimates of effectiveness against progression from infection disease are excluded §Studies were included with a lower proportion with confirmed vaccination status if there was sufficient cross-validation of vaccination status against confirmed information. ¶ Comparison group is not modelled or historical ** Vaccine effectiveness estimate includes confidence intervals if possible. Estimate accounts for confounding or statement that adjustment had no effect on estimate

Evidence Retrieval for Observational Safety Studies

- Based on input from ACIP's COVID-19 Vaccines Safety Technical (VaST) Work Group
- Data on safety signals identified by vaccine safety surveillance systems
- Data have been presented to ACIP

Evidence Retrieval



*See https://view-hub.org/resources

** clinicaltrials.gov, CDC vaccine safety surveillance systems, and other

Observational Data (n = 28)

- 28 records identified (one or more PICO outcomes)
- Assessed risk of bias using Newcastle-Ottawa Scale (9-point scale)
  - For cohort studies: **Selection** of cohorts, **Comparability** of cohorts, **Assessment** of outcome
  - For case-control or test-negative design studies: **Selection** of cases and controls, **Comparability** of cases and controls, **Ascertainment** of exposure
- Two reviewers assessed each study for each outcome
- Serious limitations identified by score <7

Pooling of VE Estimates

- For each outcome, assessed body of evidence for suitability for pooling
  - Estimates subject to serious limitations excluded
  - Most representative study selected if multiple studies in same population
- Meta-analyses conducted
- Estimates evaluated for heterogeneity
  - Examined I^2
  - Sensitivity analyses conducted to assess influence of study characteristics (e.g., special population vs. full population, preprint vs. peer-reviewed, standard/extended dosing interval, study design, circulating variants)
- Resulting pooled estimates summarize real-world data available at time of GRADE analysis

GRADE Evidence Type

- **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 can 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% confidence intervals 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 Laboratory-confirmed COVID-19 Randomized Studies with Unvaccinated Comparator (n=1)

- Pfizer-BioNTech phase 2/3 randomized controlled trial (RCT)[a,b]
- Persons aged ≥16 years in United States, Brazil, Argentina, South Africa, Turkey, Germany
- Enrolled over 40,000 participants for approximately 12,000 person years of follow-up
- Data evaluated: all eligible randomized participants who received all vaccinations as randomized within the predefined window and no other important protocol deviations, up through unblinding date (data cut-off: March 13, 2021)

[a]Polack et al., New England Journal of Medicine; additional unpublished data obtained from authors
[b]Thomas et al., preprint; additional unpublished data obtained from authors

Outcome 1: Symptomatic Laboratory-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	77/19711	833/19741	91.1% (88.8%, 93.1%)
Aged 16–64 years	70/15519	709/15515	90.5% (87.9%, 92.7%)
Aged ≥65 years	7/4192	124/4226	94.5% (88.3%, 97.8%)
Aged ≥75 years[c]	1/842	26/847	96.2% (76.9%, 99.9%)
At risk[d]	35/8954	395/8933	91.5% (88.0%, 94.2%)
Aged ≥65 years and at risk[d]	6/2322	71/2304	91.8% (81.4%, 97.1%)

[a]22,085 and 22080 persons were randomized to vaccine and placebo, respectively; 20,064 and 20,197 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 Laboratory-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	77/19711	833/19741	91.1% (88.8%, 93.1%)
Aged 16–64 years	70/15519	709/15515	90.5% (87.9%, 92.7%)
Aged ≥65 years	7/4192	124/4226	94.5% (88.3%, 97.8%)
Aged ≥75 years[c]	1/842	26/847	96.2% (76.9%, 99.9%)
At risk[d]	35/8954	395/8933	91.5% (88.0%, 94.2%)
Aged ≥65 years and at risk[d]	6/2322	71/2304	91.8% (81.4%, 97.1%)

[a]22,085 and 22080 persons were randomized to vaccine and placebo, respectively; 20,064 and 20,197 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 Laboratory-confirmed COVID-19 Studies with Unvaccinated Comparator (n=1)

Population	Events/Vaccine (n/N)	Events/Placebo (n/N)	Vaccine efficacy (95% confidence interval)
Vaccine efficacy by timing[a]			
≥7 days after dose 2[b]	77/19711	833/19741	91.1% (88.8%, 93.1%)
1 to <11 days after dose 1	38/21385	46/21315	17.6% (-29.4%, 47.9%)
≥11 days after dose 1 to before dose 2	5/21282	52/21254	90.5% (76.3%, 97.0%)
≥7 days post dose 2 to <2 months after dose 2	11/19711	285/19741	96.2% (93.0%, 98.1%)
≥2 months post dose 2 to <4 months after dose 2	43/18908	425/18620	90.2% (86.6%, 93.0%)
≥4 months after dose 2 to unblinding	23/11951	123/11099	83.9% (74.7%, 90.1%)

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

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

Population	Events/Vaccine (n/N)	Events/Placebo (n/N)	Vaccine efficacy (95% confidence interval)
Vaccine efficacy by timing[a]			
≥7 days after dose 2[b]	77/19711	833/19741	91.1% (88.8%, 93.1%)
1 to <11 days after dose 1	38/21385	46/21315	17.6% (-29.4%, 47.9%)
≥11 days after dose 1 to before dose 2	5/21282	52/21254	90.5% (76.3%, 97.0%)
≥7 days post dose 2 to <2 months after dose 2	11/19711	285/19741	96.2% (93.0%, 98.1%)
≥2 months post dose 2 to <4 months after dose 2	43/18908	425/18620	90.2% (86.6%, 93.0%)
≥4 months after dose 2 to unblinding	23/11951	123/11099	83.9% (74.7%, 90.1%)

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

Outcome 1: Symptomatic Laboratory-confirmed COVID-19 Observational Studies with Unvaccinated Comparator (n=17)

	Overall n=17	Peer-reviewed n=10	Pre-print n=7
Design			
- Case-control	1	0	1
- Cohort, prospective	4	2	2
- Cohort, retrospective	5	4	1
- Test-negative	6	4	2
- Other	1	0	1
Location			
- Europe	7	5	2
- Middle East	7	4	3
- North America	3	1	2
Most recent study period (2021)	August	May	August

Outcome 1: Symptomatic Laboratory-confirmed COVID-19

Observational Studies with Unvaccinated Comparator, Peer-reviewed (n=10)

Location	Study	Population	Method	Time period (predominant variant)	Days after dose 2	n/N Vaccinated (or person-time)	n/N Unvaccinated (or person-time)	VE*	95% CI	Included in pooled estimate? (reason if no)
Canada (Ontario)	Chung, August 2021	General population ≥16 years	Test-negative	12/14/20–4/19/21; (Alpha)	≥7	51/51,271	3,275/254,816	91	88–93	Yes
England	Lopez Bernal, April 2021	Adults >80 years	Test-negative	12/8/2020–2/19/2021	7–13	28/8,988	201/15,718	79	68–86	No (same population as Whitaker preprint)
					≥14	41/8,988	634/15,718	85	79–89	
	Lopez Bernal August 2021	general population ≥16 years	Test-negative	10/26/20 –5/16/21 (Alpha and Delta)	≥14	Alpha: 143/23,993 Delta: 122/23,993	Alpha: 7,313/96,371 Delta: 4,043/96,371	Alpha: 93.7 Delta: 88.0	91.6–95.3 85.3–90.1	
Europe (8 countries)	Kissling, July 2021	Symptomatic adults ≥65 years	Test-negative	12/10/20–5/31/21 (Alpha)	≥14	14/519	512/2,857	87	74–93	Yes
Israel	Haas, May 2021	General population ≥16 years	Retrospective cohort	1/24–4/3/21; (Alpha)	≥7	1,692/201,882,183 p-d	39,065/120,076,136 p-d	97.0	96.7–97.2	Yes
	Angel, May 2021	Healthcare workers	Retrospective cohort	12/20/20–2/25/21 (Alpha)	>7	8/5,372	38/696	97	94–99	No (population subgroups of Haas)
	Dagan, April 2021	General population ≥16 years	Retrospective cohort	12/20/20–2/1/21	>7	2,389/596,618	3,607/596,618	94	87–98	
	Regev-Yochay, August 2021	Healthcare worders	Prospective cohort	12/19/20 – 3/14/21 (Alpha)	≥11	19/329,071 p-d	115/119,12 p-d	90	84–94	
Italy	Fabiani, April 2021**	Healthcare worker	Retrospective cohort	12/27/21–3/24/21	≥7	2/ 216,098 p-d	13 / 77,073 p-d	93.7	50.8–99.2	Yes
Spain	Martínez-Baz, May 2021	Close contacts ≥18 years	Prospective cohort	Jan–April 2021 (Alpha)	≥14	1/491	548/19,580	82	73–88	Yes

VE: vaccine effectiveness. CI: confidence intervals *Adjusted VE estimates used when available. See references for covariates. **Excluded from general population sensitivity analysis

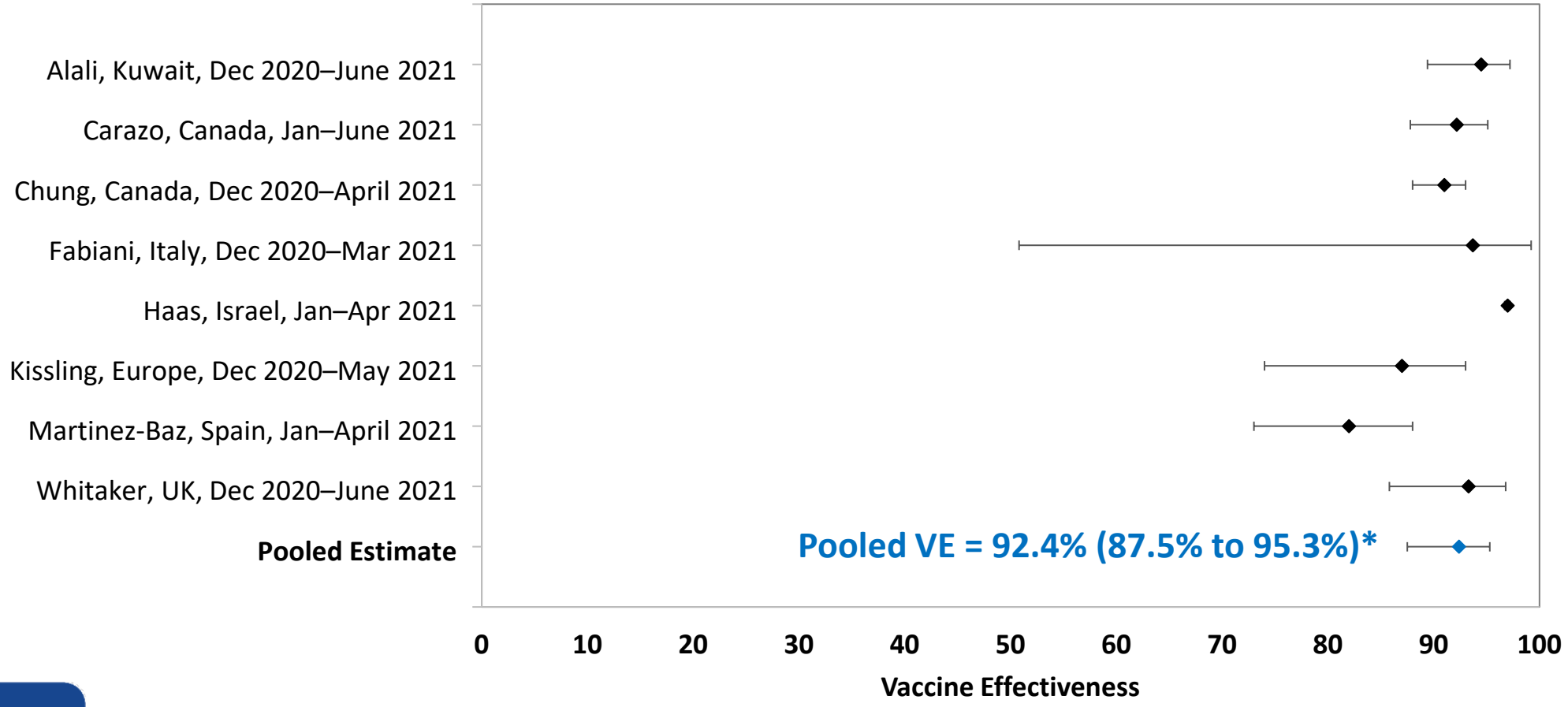
Outcome 1: Symptomatic Laboratory-confirmed COVID-19

Observational Studies with Unvaccinated Comparator, Pre-print (n=7)

Location	Study	Population	Method	Time period (predominant variant)	Days after dose 2	n/N Vaccinated (or person-time)	n/N Unvaccinated (or person-time)	VE*	95% CI	Included in pooled estimate? (reason if no)
Canada (Ontario)	Nasreen	General population ≥16 years (symptomatic)	Test-negative	12/14/20–5/2/21 (Multiple)	≥7	Non-VOC: 18/28,705 Alpha: 92/36,832 Beta/gamma: 9/3,005 Delta: 6/991	6,914/351,540	Non-VOC: 93 Alpha: 89 Beta/gamma: 84 Delta: 87	88–96 86–91 69–92 64–95	No (same population as Chung)
Canada (Quebec)	Carazo**	Healthcare workers	Test-negative	1/17–6/5/21 (Alpha)	≥7	20/2,813	1,954/18,663	92.2	87.8–95.1	Yes
England	Whitaker	General population with medically-attended COVID-19	Prospective cohort	12/7/20–6/13/21 (Original, Alpha)	≥14	8/12,273.3 p-y	4,228/1,460,81 1.4 p-y	93.3	85.8–96.8	Yes
Israel	Balicer	Pregnant women	Prospective cohort	12/20/21–6/3/21 (Original, Alpha)	≥7	67/10,861	144/10,861	97	91–100	No (population subgroup of Haas)
Kuwait	Alali**	Health care workers	Retrospective cohort	12/24/20–6/15/21	≥7	12 /90,015 p-d	114/ 90,367 p-d	94.5	89.4–97.2	Yes
Qatar	Tang	General population (any age)	Matched case control	12/21/20–7/21/21 (Delta only)	≥14	98/571	183/571	56.1	41.4–67.2	No (study limitations)
United Kingdom	Pouwels	General population ≥18 years	Longitudinal household survey	12/1/20–8/1/21 (Alpha, Delta)	≥14	Not reported	Not reported	Alpha-dominant period: 97 Delta-dominant period: 84	96–98 82–86	No (same population as Whitaker)

VE: vaccine effectiveness. CI: confidence intervals *Adjusted VE estimates used when available. See references for covariates. **Excluded from general population sensitivity analysis

Outcome 1: Symptomatic Laboratory-confirmed COVID-19 Observational Studies with Unvaccinated Comparator (n=8)



*Sensitivity analyses resulted in pooled estimates ranging from 90.4% to 93.5%

Evidence Table: Symptomatic Laboratory-confirmed COVID-19

Certainty assessment							№ of patients		Effect	Certainty	Importance
№ 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)		
1	RCT	not serious[a]	not serious	not serious[b]	not serious	none	77/19711 (0.4%)	833/19741 (4.2%)	RR 0.09 (0.07 to 0.12)	Type 1	CRITICAL
8[c]	Observational[d]	not serious	not serious[e]	not serious	not serious	strong association	85 cases 54603 controls 1715/ exposed 43968/ unexposed [d,f]		RR 0.10 (0.05 to 0.16) [g]	Type 2	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. 17 studies were available in the body of evidence. 8 were excluded because the study population was already represented, and 1 was excluded due to serious study limitations.
d. The body of evidence includes preprints.
e. Although I2 value was high (95.0%), no serious concern for inconsistency was judged because all studies showed a high degree of vaccine effectiveness, with point estimates ranging from 87% to 97%. In a sensitivity analysis including results from one study with study limitations identified that had a vaccine effectiveness estimate of 56%, the pooled RR was .10 (95% CI .05, .18), and I2 was 98.1%.
f. Data on numerators and denominators were not consistently reported in the available body of evidence. The n shown excludes events from studies that did not report the number of cases. The N is not included because studies variously provided person-time or number of persons.
g. Pooled RR based on a random effects meta-analysis, using adjusted vaccine effectiveness estimates on a log scale.

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

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

- Pfizer/BioNTech phase 2/3 RCT[a,b]
- Severe COVID-19[c]: COVID-19 case with at least 1 of following:
  - Clinical signs at rest indicative of severe systemic illness;[d]
  - Respiratory failure;[c]
  - Evidence of shock;[c]
  - 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. Polack et al., New England Journal of Medicine; additional unpublished data obtained from authors
b. Thomas et al., preprint; additional unpublished data obtained from authors
c. Severe COVID-19 as defined in protocol using guidance from FDA.
d. **Severe systemic illness**: respiratory rate ≥30, heart rate ≥125, SpO_2 ≤93% on room air at sea level or PaO_2/FiO_2<300 mm Hg; **respiratory failure**: needing high-flow oxygen, noninvasive ventilation, mechanical ventilation, ECMO; **evidence of shock**: SBP <90 mm Hg, DBP <60 mm Hg, requiring vasopressors.

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

Outcome	Study/population	Events/Vaccine (n/N)	Events/Placebo (n/N)	Vaccine efficacy (95% CI)
Secondary endpoint: Severe COVID-19, protocol definition [a]	No evidence of prior infection, ≥7 d post dose 2	1/19,711	21/19,741	95.3% (71.0%, 99.9%)
Severe COVID-19 (CDC) & hospitalized	**No evidence of prior infection, ≥7 d post dose 2**	**0/19,687**	**31/19,708**	**100% (87.6%, 100%)**
Severe COVID-19 (CDC) & hospitalized, includes confirmed and non-confirmed COVID-19	No evidence of prior infection, after dose 1	2/21,909	59/21,908	96.6% (87.2%, 99.6%)

a. FDA definition of severe COVID-19: clinical signs at rest indicative of severe systemic illness; respiratory failure; evidence of shock; significant acute renal, hepatic, or neurologic dysfunction; admission to an intensive care unit; or death
b. CDC definition of severe COVID-19: hospitalization, admission to the ICU, intubation or mechanical ventilation, or death

Outcome 2: Hospitalization for COVID-19
Observational Studies with Unvaccinated Comparator (n=13)

	Overall n=13	Peer-reviewed n=6	Pre-print n=7
Design			
- Case-control	1	1	0
- Cohort, prospective	3	1	2
- Cohort, retrospective	7	4	3
- Test-negative	2	0	2
Location			
- Europe	4	2	2
- Middle East	5	2	3
- North America	4	2	2
Most recent study period (2021)	July	July	July

Outcome 2: Hospitalization for COVID-19

Observational Studies with Unvaccinated Comparator, Peer-reviewed (n=6)

Location	Study	Population	Method	Time period (predominant variant)	Days after dose 2	n/N vaccinated	n/N unvaccinated	VE*	95% CI	Included in pooled estimate? (reason if no)
Israel	Haas, May 2021	general population ≥16 years	Retrospective cohort	1/24–4/3/21 (Alpha)	≥7	596/201882183 p-d	5526/120076136 p-d	97.2	96.8– 97.5	Yes
	Dagan, April 2021	General population ≥16 years	Retrospective cohort	12/20/20– 2/1/21	>7	110/596,618 p-d	259/596,618 p-d	87	55–100	No (population subgroup of Haas)
Italy	Flacco, June 2021	General population ≥18 years	Retrospective cohort	1/2–5/21/21 (Original, Alpha)	≥14	NR/30,817	NR/174,023	99	96–100	Yes
Spain	Martínez-Baz, May 2021	Close contacts ≥18 years	Prospective cohort	Jan–April 2021 (Alpha)	≥14	1/491	548/19,580	94	60–99	Yes
United States	Pawlowski, August 2021	Mayo Health system patients	Retrospective cohort	2/15– 4/20/21 (Original, Alpha)	≥7	7 cases/1,915,615 person-days	60 cases /1,837,276	88.8	75.5–95.7	No (overlapping population with Puranik preprint)
					≥14	6 /1,671,628 p-d	49/1,599,076 p-d	88.3	72.6–95. 9	
	Tenforde, August 2021	Hospitalized adults ≥18 years	Case-control	3/11–5/5/21 (Alpha)	≥14	95 /1,194	571/1,895	84.3	74.6– 90.3	Yes

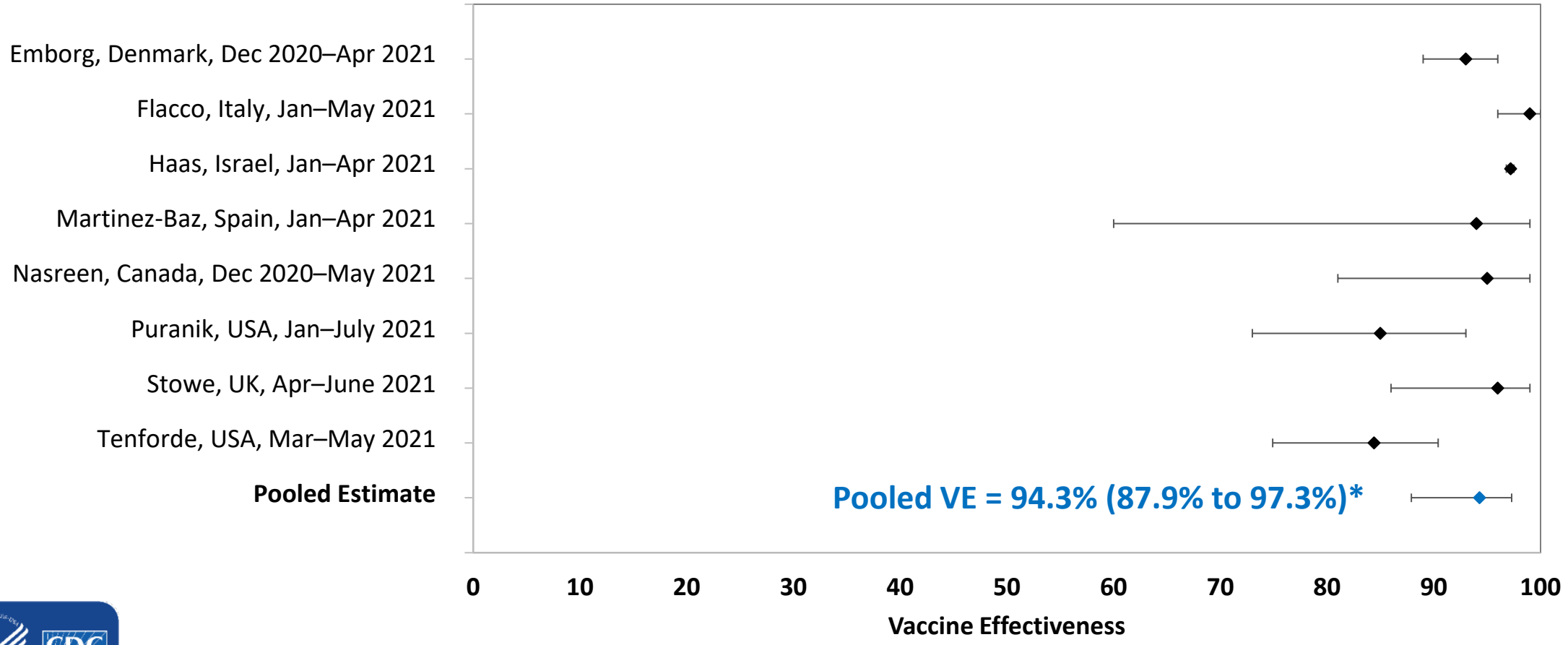
VE: vaccine effectiveness. CI: confidence intervals *Adjusted VE estimates used when available. See references for covariates. **Excluded from general population sensitivity analysis

Outcome 2: Hospitalization for COVID-19
Observational Studies with Unvaccinated Comparator, Pre-print (n=7)

Location	Study	Population	Method	Time period (predominant variant)	Days after dose 2	n/N vaccinated	n/N unvaccinated	VE*	95% CI	Included in pooled estimate? (reason if no)
Canada (Ontario)	Nasreen	General population ≥16 years (symptomatic)	Test-negative	12/14/20–5/2/21 (Multiple)	≥7	Non-VOC: ≤5/6,327 Alpha: 26/6,896 Beta/gamma: ≤5/780 Delta: ≤5/165	6,910/ 351,240	nonVOC: 96 Alpha: 95 Beta/Gamma: 95** Delta: -	82–99 92–97 81–99** -	Yes
Denmark	Emborg	Groups prioritized for vaccination	Retrospective cohort	12/27/20–4/11/21 (Original, Alpha)	>7	24/37,429.7 p-y	1,014/152,171.4 p-y	93	89–96	Yes
England	Stowe	General population	Test-negative	4/12–6/4/21	≥14	Not reported	Not reported	Alpha: 95 Delta: 96**	78–99 86–99**	Yes
Israel	Balicer	Pregnant women	Prospective cohort	12/20/21–6/3/21 (Original, Alpha)	≥7	11/10,861	25/10,861	89	43–100	No (population subgroups of Haas)
	Goldberg	General population ≥16 years	Prospective cohort	12/20/20–3/20/21	≥7	493/136.8M p-d	10057/288.5M p-d	94.2	93.6–94.7	
	Saciuk	active members of a large HMO ≥16 years	Retrospective cohort	1/18–4/25/21	≥7	105/1,353,847	942/ 1,162,033	94.4	93.2–95.5	
United States	Puranik	Adults ≥18 years with access to Mayo Health System (MN)	Matched retrospective cohort	Jan–July 2021 (Alpha, Delta)	≥14	11 /2,333,145 p-d	82/ 2,532,948 p-d	85	73–93	Yes

VE: vaccine effectiveness. CI: confidence intervals *Adjusted VE estimates used when available. See references for covariates. **Used for pooled analysis

Outcome 2: Hospitalization for COVID-19
Observational Studies with Unvaccinated Comparator (n=8)



*Sensitivity analyses resulted in pooled estimates ranging from 89.4% to 95.7%

Evidence Table: Hospitalization for 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 hospitalization due to COVID-19											
1	RCT	not serious[a,b]	not serious	not serious[c]	serious[d]	none	0/19,687 (0.0%)	31/19,708 (0.2%)	**RR 0.02** (0.00–0.26)[e]	**Type 2**	CRITICAL
8[f]	Obs[g]	not serious	not serious[h]	not serious[i]	not serious	strong association	95 cases 1359 controls 632/ exposed 7170/ unexposed[g,j]		**RR 0.06** (0.03–0.12) [k]	**Type 2**	CRITICAL
							_	0.2%			

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 was considered due to concern about misclassification of outcome. Hospitalization due to COVID-19 is not specified in the study protocol, and the data shown include only persons who met the protocol definition of COVID-19 using an approved assay or confirmation in a central laboratory; it was unclear if constructing a non-protocol measure may have resulted in bias. Data on all hospitalizations due to COVID-19 diagnosed by any assay after dose 1 were also obtained and reviewed. Two hospitalizations due to COVID-19 occurred among 21909 persons in the vaccine arm and 59 occurred among 21908 persons in the placebo arm (RR = 0.03, 95% CI 0.01, 0.10); the similar efficacy diminished concerns regarding risk of bias.
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. Serious concerns of imprecision due to fragility in the estimate was present because there were only 31 events observed from a single RCT.
e. RR calculated using a standard continuity correction of 0.5.
f. 13 studies were available in the body of evidence. 5 were excluded because the study population was already represented.
g. The body of evidence includes preprints.
h. Although I2 value was high (91.7%), no serious concern for inconsistency was judged because all studies showed a high degree of vaccine effectiveness, with point estimates ranging from 84% to 99%.
i. Definitions varied by study. Indirectness was considered given COVID-19 was not necessarily confirmed as the cause of hospitalizations, but this was deemed not serious.
j. Data on numerators and denominators were not consistently reported in the available body of evidence. The n shown excludes events from studies that did not report the number of cases. The N is not included because studies variously provided person-time or number of persons.
k. Pooled RR based on a random effects meta-analysis, using adjusted vaccine effectiveness estimates on a log scale.

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

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

- Pfizer/BioNTech phase 2/3 randomized controlled trial (RCT)[a]
- Data evaluated: any COVID-19 death in eligible randomized trial participants, irrespective of the confirmation of the COVID-19 diagnosis by trial protocol (data cut-off: March 13, 2021)

a. Polack et al., New England Journal of Medicine; additional unpublished data obtained from authors
b. Thomas et al., preprint; additional unpublished data obtained from authors

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

Study/population	Events/Vaccine (n/N)	Events/Placebo (n/N)	VE (95% confidence interval)
Persons aged ≥16 years	1/19687	6/19708	83% (-39%, 98%)
Persons aged ≥16 years, COVID-19 case confirmed using a protocol-approved assay or centrally confirmed	0/19687	3/19708	100%

Outcome 3: Death due to COVID-19
Observational Studies with Unvaccinated Comparator (n=6)

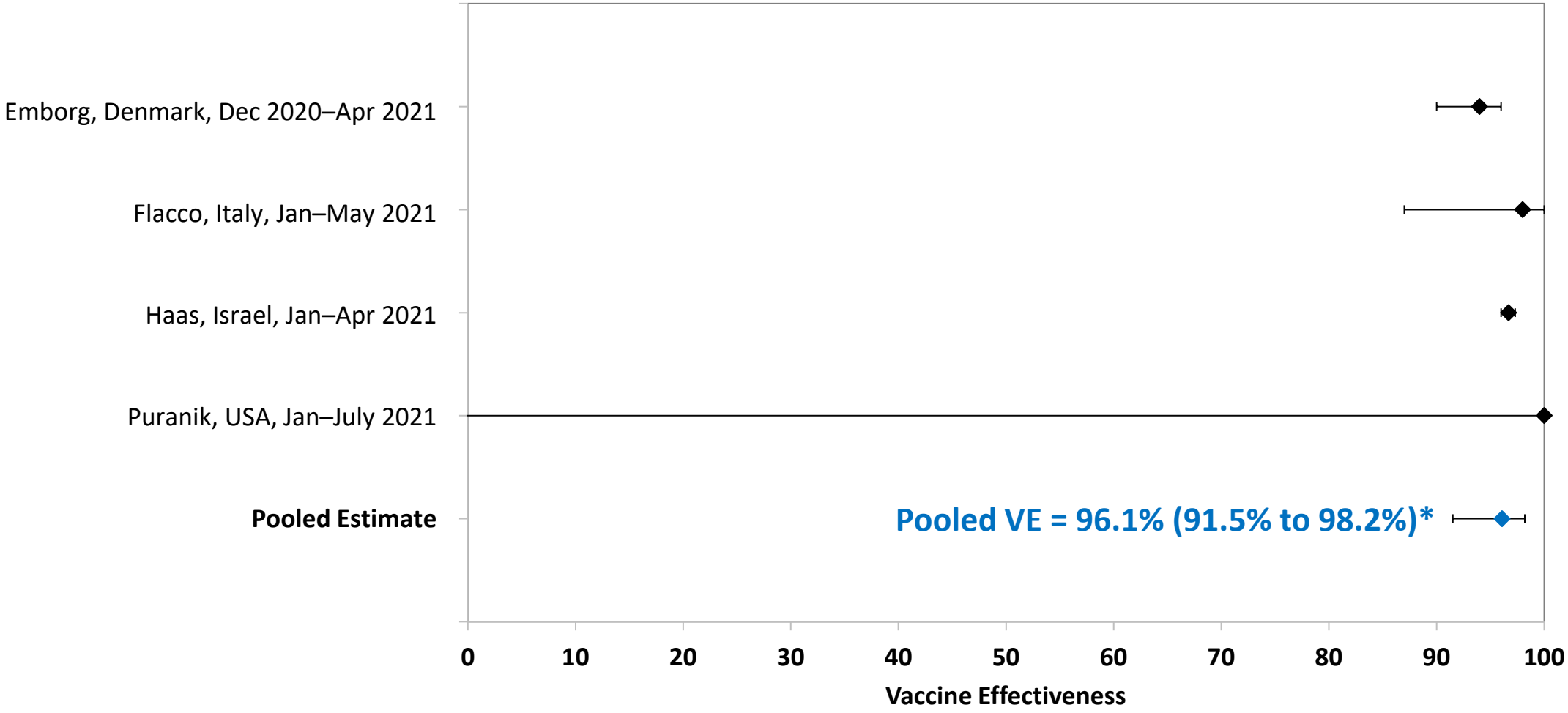
	Overall n=6	Peer-reviewed n=2	Pre-print n=4
Design			
- Case-control	0	0	0
- Cohort, prospective	1	0	1
- Cohort, retrospective	5	2	3
- Test-negative	0	0	0
Location			
- Europe	2	1	1
- Middle East	3	1	2
- North America	1	0	1
Most recent study period (2021)	July	May	July

Outcome 3: Death due to COVID-19
Observational Studies with Unvaccinated Comparator (n=6)

Locationc	Study	Population	Method	Time period (predominant variant)	Days after dose 2	n/N vaccinated	n/N unvaccinated	VE*	95% CI	Included in pooled estimate? (reason if no)
Peer-reviewed										
Israel	Haas, May 2021	General population ≥16 years	Retrospective cohort	1/24 –4/3/21 (Alpha)	≥7	138/201882183 p-d	715/120076136 p-d	96.7	96.0–97.3	Yes
Italy	Flacco, June 2021	General population ≥18 years	Retrospective cohort	1/2–5/21/21 (Original, Alpha)	≥14	NR/30,817	NR/174,023	98	87–100	Yes
Pre-print										
Denmark	Emborg	Groups prioritized for vaccination	Retrospective cohort	12/27/20–4/11/21 (Original, Alpha)	>7	25/ 37631.7 p-y	445/ 153,179.6 p-y	Overall: 94	90–96	Yes
Israel	Goldberg	General population ≥16 years	Prospective cohort	12/20/20–3/20/21	≥7	136/136.8M p-d	1749/288.5 p-d	93.7	92.5–94.7	No (population subgroups of Haas)
	Saciuk	active members of a large HMO ≥16 years	Retrospective cohort	1/18–4/25/21	≥7	33/1,354,444	131/1,166,487	84.0	76.6–89.1	
United States	Puranik	Adults ≥18 years with access to Mayo Health System (MN)	Matched retrospective cohort	Jan–July 2021 (Alpha, Delta)	≥14	0 /2,333,860 p-d	4 /2,537,030 p-d	100	-60–100	Yes

VE: vaccine effectiveness. CI: confidence intervals *Adjusted VE estimates used when available. See references for covariates.

Outcome 3: Death due to COVID-19
Observational Studies with Unvaccinated Comparator (n=4)



*Sensitivity analyses resulted in pooled estimates ranging from 95.6% to 96.8%

Evidence Table: Death Due to 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)		
1	RCT	not serious[a]	not serious	not serious[b]	serious[c]	none	1/19687 (0.0%)	6/19708 (0.0%)[d]	**RR 0.17** (0.02 to 1.39)	**Type 2**	IMPORTANT
4[e]	observational[f]	not serious	not serious[g]	not serious[h]	not serious	strong association	163/ exposed 1164/ unexposed[i]	0.0%	**RR 0.03** (0.02 to .07)[j]	**Type 2**	IMPORTANT

a. Risk of bias was considered due to possible misclassification of outcomes. One death in a vaccine recipient and 3 deaths among placebo recipients were in persons who had been diagnosed with COVID-19 based on local clinical nucleic acid amplification tests that were not protocol approved; these diagnoses were not confirmed by the central study laboratory and were not counted in the efficacy estimates for symptomatic laboratory-confirmed COVID-19 or hospitalization due to COVID-19. In an analysis using only protocol approved or central laboratory confirmed cases resulting in death, with a standard continuity correction applied, the relative risk was 0.14 (95% CI 0.01, 2.77).
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 for imprecision was present due to the small number of events that were observed. In addition to a 95% confidence interval crossing the line of no effect, there was concern for fragility in the estimate due to the small number of events.
d. Calculated risk among placebo arm in available body of evidence from RCT was 0.03%, but it appears lower here due to rounding.
e. 6 studies were available in the body of evidence. 2 were excluded because the study population was already represented.
f. The body of evidence includes preprints.
g. The relative risk shown is from a pooled analysis of 4 cohort studies conducted in different populations. I^2 was 48.8%.
h. Definitions varied by study. Indirectness was considered given COVID-19 was not necessarily confirmed as the cause of deaths, but this was not deemed not serious.
i. Data on numerators and denominators were not consistently reported in the available body of evidence. The n shown excludes events from studies that did not report the number of cases. The N is not included because the type of denominator varied across studies (e.g., person-time or number of persons).
j. Pooled RR based on a random effects meta-analysis, using adjusted vaccine effectiveness estimates on a log scale.

Outcome 4: Asymptomatic SARS-CoV-2 Infection Randomized Studies with Unvaccinated Comparator (n=0)

- No RCT studies provided data on this outcome

Outcome 4: Asymptomatic SARS-CoV-2 Infection Studies with Unvaccinated Comparator (n=5)

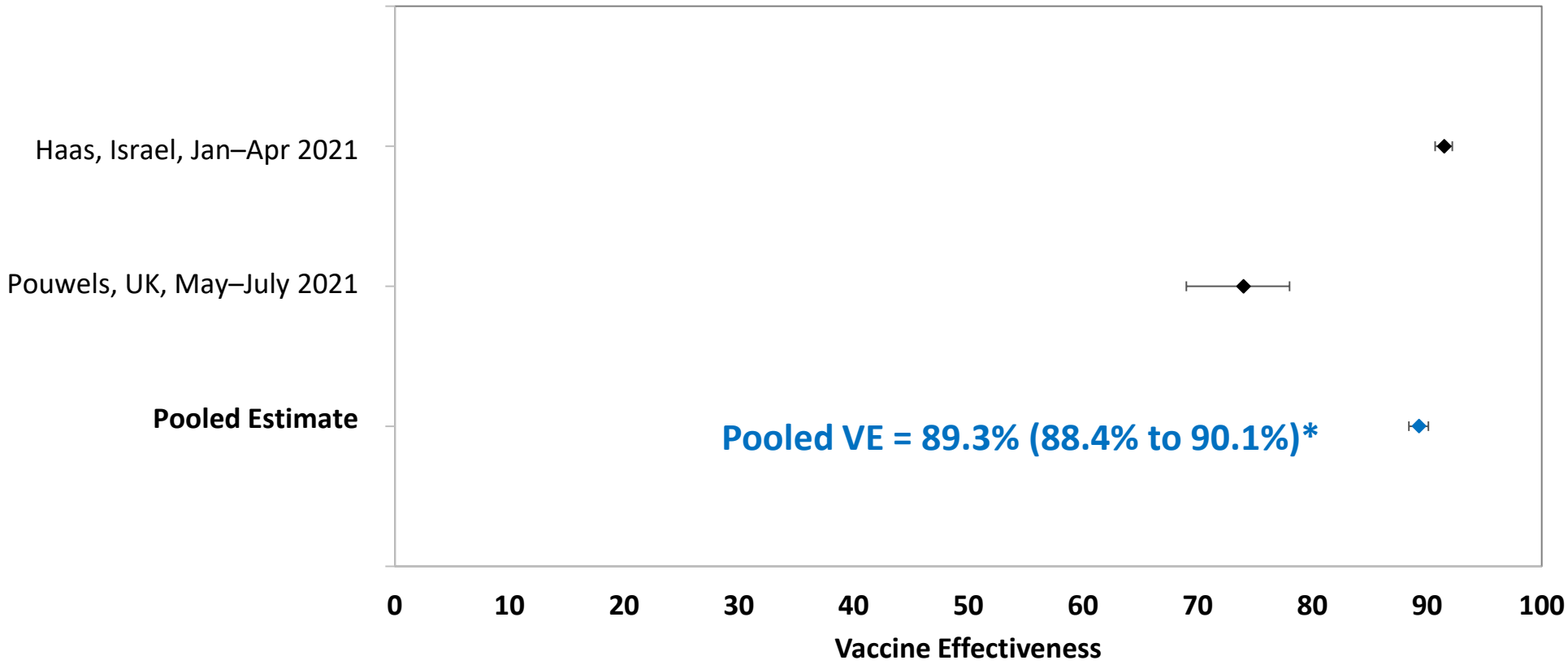
	Overall n=5	Peer-reviewed n=3	Pre-print n=2
Design			
- Case-control	1	0	1
- Cohort, prospective	1	1	0
- Cohort, retrospective	2	2	0
- Test-negative	0	0	0
- Other	1	0	1
Location			
- Europe	1	0	1
- Middle East	4	3	1
- North America	0	0	0
Most recent study period (2021)	August	April	August

Outcome 4: Asymptomatic SARS-CoV-2 Infection Studies with Unvaccinated Comparator (n=5)

Location	Study	Population	Method	Time period (predominant variant)	Days after dose 2	n/N Vaccinated (or person-time)	n/N Unvaccinated (or person-time)	VE*	95% CI	Included in pooled estimate? (reason if no)
Peer-reviewed										
Israel	Haas, May 2021	general population ≥16 years	Retrospective cohort	1/24–4/3/21 (Alpha)	≥7	3632/201882183 p-d	49138/120076136 p-d	91.5	90.7–92.2	Yes
	Angel, May 2021	Healthcare workers	Retrospective cohort	12/20/20–2/25/21 (Alpha)	>7	19/5372	17/696	86	69–93	No (population subgroups of Haas)
	Regev-Yochay, August 2021	Healthcare worders	Prospective cohort	12/19/20 – 3/14/21 (Alpha)	≥11	12/1300 exposure events	48/1441 exposure events	72	48–86	
Pre-print										
Qatar	Tang	General population (any age)	Matched case control	12/21/20–7/21/21 (Delta only)	≥14	73 vaccinated/757 cases	108 vaccinated/757 controls	35.9	11.1–53.9	No (study limitations)
United Kingdom	Pouwels	General population 18–64 years	Longitudinal household survey	12/1/20–8/1/21 (Delta)	≥14	NR	NR	Delta-dominant period: 74	69–78	Yes

VE: vaccine effectiveness. CI: confidence intervals *Adjusted VE estimates used when available. See references for covariates.

Outcome 5: Asymptomatic SARS-CoV-2 infection Observational Studies with Unvaccinated Comparator (n=2)



*Including a 3rd study that did not meet inclusion criteria, the pooled VE was 88.1% (87.2%, 89.0%)

Evidence Table: Asymptomatic SARS-CoV-2 Infection

Certainty assessment							№ of patients		Effect	Certainty	Importance
№ 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)		
2[a]	observational studies[b]	not serious	serious[c]	not serious	not serious	none	3,632/ exposed 49138/ unexposed	4.2%	**RR 0.11** (0.10–0.12) [d]	**Type 4**	IMPORTANT

a. 5 studies were available in the body of evidence. 2 were excluded because the study population was already represented, and one study was excluded due to study limitations.
b. The body of evidence includes preprints.
c. Serious concern for inconsistency was present (I^2 = 98.1%). The magnitude of the relative risks from the two studies in the body of evidence varied widely, possibly reflecting different prevalence of circulating SARS-CoV-2 variants at the time of data collection or differences in study design. In a sensitivity analysis including results from one study with study limitations identified that had a vaccine effectiveness estimate of 35.9%, the pooled RR was 0.12 (95% CI 0.11, 0.13), and I^2 was 99.1%.
d. Pooled RR based on a fixed effects meta-analysis, using adjusted vaccine effectiveness estimates on a log scale. Fixed effects model was used for this analysis due to imprecise estimates of the between-studies variance.

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

Harms

Outcome 5: Serious Adverse Events
Studies with Unvaccinated Comparator (n=2)

- Pfizer-BioNTech phase 2/3 RCT[a,b]
- Pfizer-BioNTech phase 1 RCT[c]

a. Polack et al., New England Journal of Medicine; additional unpublished data obtained from authors
b. Thomas et al., preprint; additional unpublished data obtained from authors
c. Walsh et al., New England Journal of Medicine; additional unpublished data obtained from authors

Pfizer-BioNTech Phase 1 RCT*

- 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, 3 placebo
  - 65–85 years: 12 received 2 doses of 30 µg of BNT162b2, 3 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

*Unpublished data and 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 5: Serious Adverse Events
Studies with Unvaccinated Comparator, Randomized (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	0/6	0	0
Polack, 2020, Thomas, 2021	268/21926	1.2	268/21921	1.2	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. One report of pericarditis was identified in the vaccine group, 28 days after dose 2. This SAE was deemed unassociated with vaccination.
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.

Serious Adverse Events (Myocarditis)

- A rapid cycle analysis from Vaccine Safety Datalink (VSD) evaluated chart-reviewed cases of myocarditis occurring among persons aged 18–39 years following dose 2

	n/N	Rate per 1 million person-years	Adjusted rate ratio (95% CI)
7-day risk interval after BNT-162b2 dose 2, persons 18–39 years	9/24,432	368	9.1 (2.1–48.6)
Comparison interval in vaccinated individuals	3/62,481	48	REF

Serious Adverse Events (Myocarditis)

- Data from the national Vaccine Adverse Event Reporting System (VAERS)[a] showed an elevated ratio of observed to expected myocarditis cases[b] in the 7-day interval following vaccination among females in age groups 16–24 years, and among males in age groups 16–49 years, with higher observed/expected ratios in males than females.
- Although VAERS data are subject to the limitations of a passive surveillance system, the elevated risk of myocarditis following Pfizer vaccination is consistent with that observed in VSD.

[a] As of August 18, 2021

[b] Counts among persons aged 16–29 years were verified by provider interview or medical record review to meet the case definition; counts in older age groups were identified by computer search for standardized codes assigned to reports and have not been verified to meet case definition.

Serious Adverse Events (Anaphalaxis)

- A rapid cycle analysis of data from VSD evaluated chart-reviewed cases of anaphalaxis among all vaccinated persons aged 12 years and older. Based on events occurring in a 0–1 day risk interval after vaccination, the estimated incidence of confirmed anaphalaxis was 5.0 (95% CI 3.5–6.9) per million doses.
- The absolute reporting rate to VAERS was 4.7 per million doses administered.

Evidence Table: Serious Adverse Events

Certainty assessment							№ of patients		Effect	Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Intervention	Comparison	Relative (95% CI)		
2	RCT	not serious[a]	not serious	not serious[b]	serious[c]	None	269/21950 (1.2%)	268/21927 (1.2%)	**RR 1.00** (0.85 to 1.18) [d]	**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 for imprecision was present. The confidence interval indicates that both reduced and increased risk of serious adverse events are possible.
d. Pooled RR based on a fixed effects meta-analysis. Fixed effects model was used for this analysis due to imprecise estimates of the between-studies variance.

Evidence Table: Serious Adverse Events (Myocarditis and Anaphalaxis)

Certainty assessment							№ of patients		Effect	Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Intervention	Comparison	Relative (95% CI)		
2	Obs	not serious	not serious	not serious [a]	not serious	None	• A rapid cycle analysis from Vaccine Safety Datalink (VSD) evaluated chart-reviewed cases of myocarditis occurring among persons aged 18–39 years following dose 2. Based on events occurring in a 7-day risk interval after vaccination vs. a comparison interval in vaccinated individuals, the adjusted rate ratio was 9.1 (95% CI 2.1–48.6). The rates of myocarditis were 368 per 1 million person-years (9/24432) in the 0–7 day risk interval and 48 per 1 million person-years (3/62481) in vaccinated comparators. • Data from the national Vaccine Adverse Event Reporting System (VAERS) showed an elevated ratio of observed to expected myocarditis cases[b] in the 7-day interval following vaccination among females in age groups 16-24 years, and among males in age groups 16-49 years, with higher observed/expected ratios in males than females. Although VAERS data are subject to the limitations of a passive surveillance system, the elevated risk of myocarditis following Pfizer vaccination is consistent with that observed in VSD. • A rapid cycle analysis of data from VSD evaluated chart-reviewed cases of anaphalaxis among all vaccinated persons aged 12 years and older. Based on events occurring in a 0–1 day risk interval after vaccination, the estimated incidence of confirmed anaphalaxis was 5.0 (95% CI 3.5–6.9) per million doses. The absolute reporting rate to VAERS was 4.7 per million doses administered.			**Type 3**	CRITICAL

a. For the outcomes of myocarditis and anaphalaxis evaluated in Vaccine Safety Datalink, data are shown for the age groups 18-39 and ≥12 years, respectively, therefore these were not completely generalizable to the age groups of all persons aged >=16 years as defined in the PICO question. This was deemed not serious.

b. Counts among persons aged 16–29 years were verified by provider interview or medical record review to meet the case definition; counts in older age groups were identified by computer search for standardized codes assigned to reports and have not been verified to meet the case definition.

Outcome 6: Reactogenicity, Severe (Grade ≥3) Studies with Unvaccinated Comparator (n=2)

- Pfizer-BioNTech phase 2/3 RCT[a,b]
- Pfizer-BioNTech phase 1 randomized RCT[c]

a. Polack et al., New England Journal of Medicine; additional unpublished data obtained from authors
b. Thomas et al., preprint; additional unpublished data obtained from authors
c. Walsh et al., New England Journal of Medicine; additional unpublished data obtained from authors

Outcome 6: 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 6: 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]	3/24	8.3	0/6	0.0
Polack, 2020, Thomas, 2021[a]	520/4924	10.6	111/4915	2.3

a. Additional data provided by 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]	not serious	none	531/4,948 (10.7%)	111/4,921 (2.3%)	**RR 4.69** (3.83–5.73) [b]	**Type 1**	IMPORTANT

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. Pooled RR based on a fixed effects meta-analysis. Fixed effects model was used for this analysis due to imprecise estimates of the between-studies variance.

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

Summary of GRADE

Outcome	Importance	Design (# of studies)	Findings	Evidence type
Benefits				
Symptomatic laboratory-confirmed COVID-19	Critical	RCT (1) OBS (9)	Pfizer-BioNTech COVID-19 vaccine is effective in preventing symptomatic COVID-19	**1**
Hospitalization due to COVID-19	Critical	RCT (1) OBS (8)	Pfizer-BioNTech COVID-19 vaccine prevents COVID-19-resulting in hospitalization	**2**
Death due to COVID-19	Important	RCT (1) OBS (4)	Pfizer-BioNTech COVID-19 vaccine prevents death due to COVID-19	**2**
Asymptomatic SARS-CoV-2 infection	Important	OBS (2)	Two cohort studies show benefit of vaccination for preventing asymptomatic infections, but magnitude inconsistent	**4**
Harms				
Serious adverse events	Critical	RCT (2)	In the RCT, SAEs were balanced between vaccine and placebo arms. In post-authorization safety monitoring, myocarditis and anaphylaxis were rare but more common following vaccination	**2**
Reactogenicity	Important	RCT (2)	Severe reactions within 7 days were more common in vaccinated; any grade ≥3 reaction was reported by 10.7% of vaccinated vs. 2.3% of placebo group	**1**

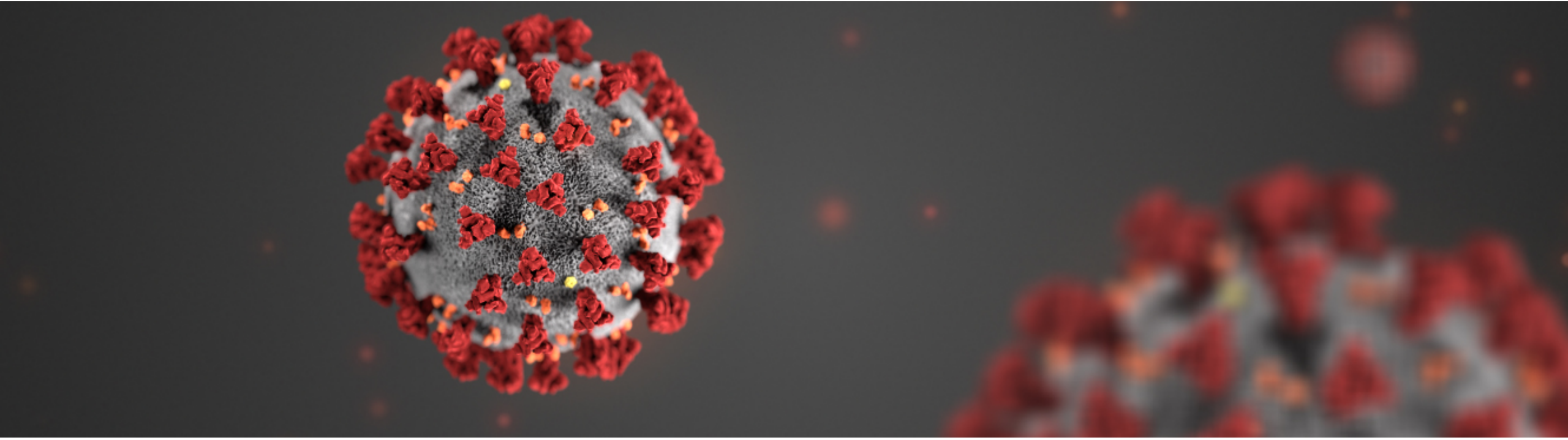
Evidence type: 1=high; 2=moderate; 3=low; 4=very low; ND, no data

Conclusion

- **Policy question:** focuses on recommendation following licensure of Pfizer-BioNTech COVID-19 vaccine that has been in use for several months under an emergency use authorization
- **Benefits**: Supported by body of evidence from RCTs and observational studies
  - RCT evidence demonstrated efficacy against the 2 critical outcomes: symptomatic disease and hospitalization
  - Direct evidence of efficacy for hospitalization and deaths limited from RCTs; body of evidence from observational studies demonstrates effectiveness
  - Few data from observational studies available to assess prevention of asymptomatic infection
- **Harms**:
  - Grade 3 reactions were more common in vaccine than placebo recipients
  - Serious adverse events occurred at a similar frequency in vaccine and placebo groups
  - Two specific, rare SAEs have been associated with vaccination through safety surveillance

Acknowledgements

- Megan Wallace
- Jennifer Collins
- Heidi Moline
- Monica Godfrey
- Ian Plumb
- Hannah Rosenblum
- Kathleen Dooling
- Sara Oliver
- Karen Broder
- Naomi Tepper
- Rebecca Morgan
- Doug Campos-Outcalt
- VTF ACIP WG Team
- ACIP COVID-19 Vaccines Work Group



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.