Grading of Recommendations, Assessment, Development, and Evaluation (GRADE): Pfizer-BioNTech, Moderna, and Janssen COVID-19 booster doses

Overview

A Grading of Recommendations, Assessment, Development and Evaluation (GRADE) review of the evidence for benefits and harms for booster doses of Pfizer-BioNTech, Moderna, and Janssen COVID-19 vaccines were presented to the Advisory Committee for Immunization Practices (ACIP) during September–October, 2021. GRADE evidence type indicates the certainty of estimates from the available body of evidence, ranging from type 1 (high certainty) to type 4 (very low certainty).[1]

The policy questions asked whether a booster dose of Pfizer-BioNTech BNT162b2 COVID-19 Vaccine (30 µg, IM), Moderna mRNA-1273 COVID-19 Vaccine (50 µg, IM), or Janssen COVID-19 Ad26.COV2.S Vaccine (5×10^{10} viral particles, IM) should be recommended for persons aged ≥18 years who completed a COVID-19 vaccine primary series ≥6 months ago (Pfizer-BioNTech, Moderna) or ≥2 months ago (Janssen) (Table 1).

The potential benefits pre-specified by the ACIP COVID-19 Vaccines Work Group included prevention of the following outcomes: symptomatic laboratory-confirmed COVID-19 (critical), hospitalization due to COVID-19 (critical), death due to COVID-19 (important), and transmission of SARS-CoV-2 infection (important). The two pre-specified harms were serious adverse events (SAEs) (critical) and reactogenicity (severe, grade ≥3) (important) (Tables 1 and 2).

For each vaccine booster product, a systematic review of evidence on the benefits and harms among persons ≥18 years was conducted. Studies identified were assessed using a modified GRADE approach.[1] The final level of certainty was type 4 (very low) for the evidence used to assess prevention of symptomatic laboratory-confirmed COVID-19 (all products), prevention of hospitalization due to COVID-19 (Pfizer-BioNTech, Janssen), prevention of death due to COVID-19 (Janssen), serious adverse events (all products), and reactogenicity (all products). No data were available to assess transmission of SARS-CoV-2 infection.

Introduction

During September–October, 2021, the U.S. Food and Drug Administration (FDA) amended the emergency use authorizations (EUAs) for Pfizer-BioNTech, Moderna, and Janssen COVID-19 vaccines to allow for a booster dose in persons at increased risk for serious complications of COVID-19, including severe disease.[2] As part of the process used by the Advisory Committee for Immunization Practices (ACIP), a systematic review and Grading of Recommendations, Assessment, Development and Evaluation (GRADE) assessment of the evidence for a Pfizer-BioNTech, Moderna, or Janssen COVID-19 vaccine booster dose among persons aged ≥18 years was conducted and presented to ACIP on September 24 and October 21, 2021.[1]

Methods

We conducted systematic reviews of evidence on the benefits and harms of a booster dose of Pfizer-BioNTech, Moderna, and Janssen COVID-19 vaccines using a modified GRADE approach.[1] The policy questions asked whether a booster dose of Pfizer-BioNTech BNT162b2 COVID-19 Vaccine (30 µg, IM), Moderna mRNA-1273 COVID-19 Vaccine (50 µg, IM), or Janssen COVID-19 Ad26.COV2.S Vaccine (5×10^{10} viral particles, IM) should be recommended for persons aged ≥18 years who completed a COVID-19 vaccine primary series ≥6 months ago (Pfizer-BioNTech, Moderna) or ≥2 months ago (Janssen) (Table 1).

During Work Group calls, members were asked to pre-specify and rate the importance of relevant patient-important outcomes (including benefits and harms) before the GRADE assessment. No conflicts of interest were reported by CDC and ACIP COVID-19 Vaccines Work Group members involved in the GRADE analysis. The pre-specified benefits (importance) were prevention of symptomatic laboratory-confirmed COVID-19 (critical), prevention of hospitalization due to COVID-19 (critical),

prevention of death due to COVID-19 (important), and prevention of transmission of SARS-CoV-2 infection (important). The two pre-specified harms were serious adverse events (SAEs) (critical) and reactogenicity (severe, grade ≥3) (important) (Table 2). Indirect effects of vaccination were not considered as part of GRADE.

We identified clinical trials through clinicaltrials.gov. Records of relevant Phase I, II, or III clinical trials of COVID-19 vaccine were included if they 1) provided data on booster vaccination with BNT162b2, mRNA-1273, or Ad26.COV2.S; 2) involved human subjects; 3) reported primary data; 4) included adults (aged ≥18 years) at risk for SARS-CoV-2 infection; and 5) included data relevant to the efficacy and safety outcomes being measured. We identified relevant observational studies through an ongoing systematic review conducted by the International Vaccine Access Center (IVAC) and the World Health Organization (WHO),[3] as previously described.[4] Relevant observational studies were restricted to the defined population, intervention, comparison, and outcome outlined in the policy question, or related outcomes if direct data were not available. In addition, unpublished and other relevant data were obtained by hand-searching reference lists and by consulting with vaccine manufacturers and subject matter experts. Characteristics of all included studies are shown in Appendix 1[5–16], and evidence retrieval methods are shown in Appendix 2.

If the available clinical trial data on booster doses did not include a comparator group appropriate to the PICO questions, comparator data were pulled from the most relevant available clinical trial data on the primary vaccination or series. When multiple observational studies provided estimates based on overlapping study populations, the study with the most comprehensive population and follow-up time was selected.

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

Results

The results of the GRADE assessments were presented to ACIP on September 24 (Pfizer-BioNTech) and October 21, 2021 (Moderna, Janssen).

Pfizer-BioNTech COVID-19 vaccine

For Pfizer-BioNTech BNT162b2 booster, five records screened and deemed eligible for full-text review were included in the GRADE evidence synthesis, and additional data was obtained from the study sponsor (Appendix 1).[5–10] Prevention of symptomatic laboratory-confirmed COVID-19 was assessed using observational vaccine effectiveness (VE) studies on the outcome any SARS-CoV-2 infection and Phase I and Phase II/III clinical trials assessing immunobridging in the same participants pre-and post-booster; immunogenicity data were not available according to randomization. Prevention of hospitalization due to COVID-19 was assessed using an observational VE study on the outcome severe COVID-19. No data were available to assess prevention of death due to COVID-19 or transmission of SARS-CoV-2 infection. SAEs and reactogenicity following a booster dose were assessed using Phase II/III clinical trial data; because data on a randomized comparison group was not provided by the sponsor, Phase II/III clinical trial data on the primary series at the time of the Biologics Licensure Application to the FDA (data cut-off March 13, 2021) were used as the comparator. GRADE results are summarized in tables 3–4.

Moderna COVID-19 vaccine

For the Moderna mRNA-1273 booster, two records screened and deemed eligible for full-text review were included in the GRADE evidence synthesis, and additional data was obtained from the study sponsor (Appendix 1).[11–13] Prevention of symptomatic laboratory-confirmed COVID-19 was assessed by immunobridging using open-label Phase II clinical trial data (booster dose) and Phase III randomized control trial (RCT) data on the 100 µg primary series (comparator). No data were available to assess prevention of hospitalization due to COVID-19, death due to COVID-19, or transmission of SARS-CoV-2 infection. SAEs and reactogenicity were assessed using data from two parts of a Phase II clinical trial: an open-label non-randomized booster study and a randomized dose confirmation study from which the booster study population was drawn (100 µg primary series recipients used as comparator). For reactogenicity, Phase III RCT data on the 100 µg primary series were also included in the comparator data. GRADE results are summarized in tables 3–4.

Janssen COVID-19 vaccine

For the Janssen booster, two records screened and deemed eligible for full-text review were included in the GRADE evidence synthesis, and additional data was obtained from the study sponsor (Appendix 1).[14–17] Prevention of symptomatic laboratory-confirmed COVID-19, hospitalization due to COVID-19, and death due to COVID-19 were assessed using Phase III RCT data comparing 2 doses of Ad26.COV2.S administered 56 days apart (i.e., booster) versus 2 doses of placebo. Given concerns that a 2-dose placebo comparison group may overestimate the benefit of the booster relative to the primary series, Phase III RCT data on the primary vaccination were used as the comparator for benefits. SAEs and reactogenicity were assessed using the Phase II RCT comparing 2-doses of Ad26.COV2.S administered 56 days apart (booster) versus 2 doses of placebo (comparator). The 2-dose placebo group was used as the comparator for harms to provide a conservative risk estimate and because of the randomized controlled study design. GRADE results are summarized in tables 3–4.

GRADE Summary

The final level of certainty was type 4 (very low) for prevention of symptomatic laboratory-confirmed COVID-19 (all products), prevention of hospitalization due to COVID-19 (Pfizer-BioNTech, Janssen), prevention of death due to COVID-19 (Janssen), serious adverse events (all products), and reactogenicity (all products). No data were available to assess effects on transmission of SARS-CoV-2 infection.

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Table 1: Policy Question and PICO

Population	Persons aged ≥18 years who completed a COVID-19 vaccine primary series ≥6 months ago		Persons aged ≥18 years who completed a COVID-19 vaccine primary series ≥2 months ago
Intervention	Pfizer-BioNTech COVID-19 Vaccine BNT162b2 booster dose (30 µg, IM)	Moderna COVID-19 Vaccine mRNA-1273 booster dose (50 µg, IM)	Janssen COVID-19 vaccine Ad26.COV2.S booster dose (5 x 1010 viral particles, IM)
Comparison	No booster dose		
Outcomes	Symptomatic laboratory-confirmed COVID-19 Hospitalization due to COVID-19 Death due to COVID-19 Transmission of SARS-CoV-2 infection Serious adverse events Reactogenicity		

Table 2: Outcomes and Rankings

Outcome	Importance[a]	Included in evidence profile
Benefits		
Symptomatic laboratory-confirmed COVID-19	Critical	Yes (all)
Hospitalization due to COVID-19	Critical	Yes (Pfizer-BioNTech, Janssen)
Death due to COVID-19	Important	Yes (Janssen)
Transmission of SARS-CoV-2 infection	Important	No data available
Harms		
Serious Adverse Events (SAEs)	Critical	Yes (all)
Reactogenicity	Important	Yes (all)

[a]Three options: 1. Critical; 2. Important but not critical; 3. Not important for decision making

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

Authors last name, pub year	Design, study population	No. of patients vaccinated with booster or No. of cases	No. of patients with no booster or No. of controls	Comparator	Estimated vaccine efficacy or incremental vaccine effectiveness (95% CI)	Study limitations (Risk of Bias)
Pfizer-BioNTech BNT162b2						

Authors last name, pub year	Design, study population	No. of patients vaccinated with booster or No. of cases	No. of patients with no booster or No. of controls	Comparator	Estimated vaccine efficacy or incremental vaccine effectiveness (95% CI)	Study limitations (Risk of Bias)
Bar-On, September 2021[5]	Observational (retrospective cohort); general population aged ≥60 years; Israel[a]	934 infections/ 10,603,410 person-days[b]	4,439 infections/ 5,193,825 person-days	Dose 2	91.2% (90.4–91.9%)[c]	Not serious
Patalon, August 2021[d,6]	Observational (test negative design); general population aged ≥40 years; Israel[a]	1,188 positive/32,697 total tests[e]	8,285 positive/149,379 total tests	Dose 2	79% (72–84%)[f]	Not serious
Patalon, August 2021[d,6]	Observational (matched case-control); general population aged ≥40 years; Israel[a]	Not reported/30,295 booster vaccines[e]	Not reported/238,018 dose 2 vaccines	Dose 2	70% (62–76%)[f]	Not serious
Janssen Ad26.COV2.S						
Janssen, 2021[14–16]	Observational[g]; adults ≥18 years	14/7,484 (0.2%)[h]	53/7,008 (0.8%)[h,i]	Placebo dose 2	75.6% (55.48%–87.52%)[j]	Not serious

a. Israeli authorities approved a booster dose at a minimum interval of 5 months after the primary series for "high risk-populations" on 7/12/21 and for persons aged ≥60 years on 7/30/21.

b. Assessed ≥12 days after booster dose administration.

c. VE was calculated from the adjusted rate ratio reported in the manuscript. This VE estimate was used for Pfizer-BioNTech GRADE because the study population was most comprehensive. Estimate shown is incremental VE of booster dose compared with 2-dose primary series.

d. Pre-print manuscript.

e. Assessed 14–20 days after booster dose.

f. Adjusted VE was reported in the manuscript based on odds ratios from multivariable logistic regression models. Estimate shown is incremental VE of booster dose compared with 2-dose primary series.

g. Data shown is from a Janssen Phase 3 RCT of 2-doses Ad26.COV.2S (5×10^{10} viral particles, IM) versus 2-doses placebo, ≥56 days apart. Data used for GRADE were considered observational because the control group was drawn from a separate Phase 3 study (see footnote i).

h. Assessed ≥14 days after the intervention.

i. Placebo dose 2 comparator data shown were not used for GRADE. Comparison used for GRADE was Phase 3 RCT seronegative participants aged ≥18 years without prior evidence of infection, ≥14 days post-vaccination with the primary dose, experiencing symptomatic SAR-CoV-2 RT-PCR-positive COVID-19 by the time of the EUA (data cutoff January 22, 2021): 173/19,514 (0.9%).[17]

j. Estimate shown is vaccine efficacy of 2 doses of Ad26.COV2.S compared with 2 doses of placebo. This was not used for GRADE.

Table 3b: Summary of Studies Relevant to Symptomatic Laboratory-confirmed COVID-19 (indirect evidence assessed using immunobridging)

Authors last name, pub year	Age or other characteristic of importance	n booster	n comparator	GMR	Met noninferiority objective	Study limitations (Risk of Bias)
Pfizer-BioNTech BNT162b2						
Pfizer-BioNTech, 2021[7,8]	Adults aged 18–55 years[a]; Phase II/III clinical trial; GMT to SARS-CoV-2 neutralization assay– NT50[b]	210[c]	210[c,d]	3.29 (97.5% CI: 2.76–3.91)[e]	Yes[f]	Very serious[g,h]
Pfizer-BioNTech, 2021[9]	Adults aged 65–85 years[a]; Phase 1 clinical trial; GMT to SARS-CoV-2 neutralization assay – NT50[b]	12[c]	12[c,d]	8.2[i]	NA	Very serious[h]
Moderna mRNA-1273						
Moderna, 2021[11–13]	Adults aged ≥18 years[j]; observational; GLSM to pseudotyped virus neutralizing antibodies – ID50[k]	149	1,053[l]	1.76 (95% CI: 1.496–2.060)[m]	Yes[n]	Not serious

Abbreviations: NT50 = 50% neutralizing titer; GMT = geometric mean titer; GMR= geometric mean ratio; CI = confidence interval; LLOQ = lower limit of quantitation NA=not applicable; ID50 = 50% inhibitory dilution; GLSM = geometric least squares mean

a. Without prior evidence of SARS-CoV-2 infection. Study participants were randomized 1:1 to booster BNT162b2 or another investigational vaccine a median of 6.8 months (range 4.8–8 months) after dose 2.
b. Sampling time point is 1 month after booster or dose 2.
c. Number of subjects with valid and determinate assay results for both the specified assays at the given dose/sampling time point within specified window.
d. Comparator is booster recipients 1 month after dose 2.
e. GMRs and 2-sided 97.5% CIs were calculated by exponentiating the mean differences in the logarithms of the assay and the corresponding CIs.
f. Noninferiority was declared because the lower bound of the 2-sided 97.5% CI for the GMR is >0.67 and the point estimate of the GMR is ≥0.8
g. Although a non-random subset of participants from the phase 3 trial were randomized to a booster dose or another investigational vaccine, none were randomized to a placebo.
h. The only data available for GRADE were from a pre-post booster analysis.
i. Data were not available to calculate 97.5% confidence intervals. 95% CIs for the point estimate do not overlap.
j. A 50 µg booster dose was administered ≥6 months after the 100 µg primary series.
k. Sampling time point is 28 days (1 month after booster or dose 2)
l. Comparator was 100 ug primary series recipients aged ≥18 years in a separate study (phase 3 RCT). Data provided by study sponsor.
m. Antibody values reported as below the lower limit of quantification (LLOQ) were replaced by 0.5 x LLOQ. GMR calculated based on an analysis of covariance model.
n. Based on prespecified criteria: point estimate of GMR ≥1 and lower bound of 95% CI ≥0.67, based on noninferiority margin of 1.5.

Table 3c: Summary of Studies Reporting Hospitalization due to COVID-19

Authors last name, pub year	Design, study population	No. of patients vaccinated with booster or No. of cases	No. of patients with no booster or No. of controls	Comparator	Vaccine efficacy or incremental vaccine effectiveness (95% CI)	Study limitations (Risk of Bias)
Pfizer-BioNTech BNT162b2 (assessed by severe COVID-19)						
Bar-On, September 2021[a,5]	Observational (retrospective cohort); general population aged ≥60 years; Israel[b]	29/6,265,361 person-days[c]	294/4,574,439 person-days	Dose 2	94.9% (92.3–96.1%)[d]	Not serious
Janssen Ad26.COV2.S (assessed by hospitalization due to COVID-19)						
Janssen, 2021[14–16]	Observational[e]; adults ≥18 years	0/6,024 (0%)[f]	5/5,615 (<0.1%)[f,g]	Placebo dose 2	Not evaluable	Not serious

a. Severe COVID-19 defined by study investigators as a resting respiratory rate of > 30 breaths per minute, an oxygen saturation of <94% while breathing ambient air, or a ratio of partial pressure of arterial oxygen to fraction of inspired oxygen of <300.

b. Israeli authorities approved a booster dose at a minimum interval of 5 months after the primary series for "high risk-populations" on 7/12/21 and for persons aged ≥60 years on 7/30/21.

c. Assessed ≥12 days after booster dose administration.

d. VE was calculated from the adjusted rate ratio reported in the manuscript. Estimate shown is incremental VE of booster dose compared with 2-dose primary series.

e. Data shown is from a Janssen Phase 3 RCT of 2-doses Ad26.COV.2S (5 x 10^{10} viral particles, IM) versus 2-doses placebo, ≥56 days apart. Data used for GRADE were considered observational because the control group was drawn from a separate Phase 3 study (see footnote g).

f. Assessed ≥14 days after the intervention.

g. Placebo dose 2 comparator data shown were not used for GRADE. Comparison used for GRADE was Phase 3 RCT seronegative participants aged ≥18 years without prior evidence of infection, ≥14 days post-vaccination with the primary dose, experiencing hospitalization due to COVID-19 by the time of the EUA (data cutoff January 22, 2021): 2/19,514 (0.01%).[17]

Table 3d: Summary of Studies Reporting Death due to COVID-19

Authors last name, pub year	Design, study population	No. of patients vaccinated with booster or No. of cases	No. of patients with no booster or No. of controls	Comparator	Vaccine Efficacy/Effectiveness (95% CI)	Study limitations (Risk of Bias)
Pfizer-BioNTech BNT162b2 (assessed by severe COVID-19)						
Janssen, 2021[14–16]	Observational[a]; adults ≥18 years	0/7,484 (0%)[b,c]	1/7,008 (0.01%)[b,c]	Placebo dose 2	Not evaluable	Not serious

a. Data shown is from a Janssen Phase 3 RCT of 2-doses Ad26.COV.2S (5 x 10^{10} viral particles, IM) versus 2-doses placebo, ≥56 days apart. Data used for GRADE were considered observational because the control group was drawn from a separate Phase 3 study (see footnote c).

b. Assessed ≥14 days after the intervention.

c. Placebo dose 2 comparator data shown were not used for GRADE. Comparison used for GRADE assessment was Phase 3 RCT seronegative participants aged ≥18 years without prior evidence of infection, ≥14 days post-vaccination with the

primary dose, with death from any cause by the time of the EUA (data cutoff February 5, 2021): 5/21,895 (0.02%).[17]

Table 3e: Summary of Studies Reporting Serious Adverse Events

Authors last name, pub year	Age or other characteristics of importance	n/N (%) booster	n/N (%) comparison	Comparator	RR (95% CI)	Study limitations (Risk of Bias)
Pfizer-BioNTech BNT162b2						
Pfizer-BioNTech, 2021[7,8]	Randomized[a]; adults 18–55 years	1/306 (0.3%)[b]	NR[c]	NR[c]	0.82 (0.11–5.96)	very serious[d]
Moderna mRNA-1273						
Moderna, 2021[11–13]	Observational[e]; adults ≥18 years	0/171 (0%)[f,g,h]	0/200 (0%)[g,i]	100 µg primary series	1.17 (0.02–59.59)	serious[j]
Janssen Ad26.COV2.S						
Janssen, 2021[14–16]	RCT[k]; adults ≥18 years	28/8,646 (0.3%)[l,m]	27/8,043 (0.3%)[n]	Dose 2 placebo	0.96 (0.57–1.64)	Serious[o]

Abbreviations: NR=not reported

a. A non-random subset of participants from the Pfizer-BioNTech phase 3 trial were randomized to a booster dose or another investigational vaccine a median of 6.8 months (range 4.8–8 months) after BNT162b2 dose 2.

b. 1 serious adverse event, a myocardial infarction, occurred 62 days after dose 3. This was judged by the investigators to be unrelated to the intervention. Median follow-up from booster vaccination to cut-off date was 2.6 months (range 1.1–2.8 months)

c. Data on a comparison group was not provided for the Pfizer-BioNTech booster RCT. The comparison group used for GRADE was the safety population, subgroup aged 16–55 years, with SAEs during blinded follow-up from dose 1 to 1 month after dose 2, at the time of the data cut-off for the Biologics Licensure Application to the FDA (March 13, 2021) (43/10,841 (0.4%)). Not all persons in the comparison group received 2 doses.[8]

d. The only booster trial data available for GRADE were not according to randomization.

e. Data are from two parts of a Phase II clinical trial: an open label non-randomized booster study (booster), and a randomized dose confirmation study from which the booster study population was drawn (comparison).

f. A 50 µg booster dose was administered ≥6 months after 100 µg primary series.

g. Follow-up duration 28 days.

h. Overall, 4/344 (1.2%) participants experienced 5 SAEs during a median follow-up of 5.7 months after booster dose (administered at least 6 months after a 50 mcg (n=173) or 100 mcg (n=171) 2-dose primary series); the sponsor deemed these unrelated to mRNA-1273. Data on an equivalent primary series comparison group was not available at the time of the GRADE assessment.

i. Comparator group is 100 µg primary series recipients in the Phase II randomized dose confirmation study.

j. Participants' ability to choose whether to receive a booster likely introduced selection bias (e.g., those with adverse events or reactions with the primary series may have been less likely to choose a booster).

k. Data shown is from a Janssen Phase 3 RCT of 2-doses Ad26.COV.2S (5×10^{10} viral particles, IM) versus 2-doses placebo, ≥56 days apart.

l. Median follow-up 38 days.

m. An additional 12/5,070 (0.2%) evaluable Janssen booster dose recipients and 7/4,681 (0.1%) evaluable 2-dose placebo recipients experienced 1 or more SAEs from 30 days to 6 months after the dose. Overall, 3 SAEs (facial paresis,

pulmonary embolism, and cerebrovascular accident in 1 participant each) were attributed to booster within 6 months of administration, among 5,070 booster recipients in the evaluable population.

n. Median follow-up 37 days.

o. Although the study was an RCT, marked loss of participants by the time of booster dose and placebo dose 2 administration may have introduced bias.

Table 3f: Summary of Studies Reporting Reactogenicity (≥Grade 3)[a]

Authors last name, pub year	Age or other characteristics of importance	n/N (%) booster	n/N (%) comparison	Comparator	RR (95% CI)	Study limitations (Risk of Bias)
Pfizer-BioNTech BNT162b2						
Pfizer-BioNTech, 2021[7,8]	Randomized[b]; adults 18–55 years	14/306 (4.6%)	NR[c]	NR[c]	0.62 (0.40–0.97)	Very serious[d]
Moderna mRNA-1273						
Moderna, 2021[11–13]	Observational study[e]; adults ≥18 years	18/167 (10.8%)[f]	2,940/14,889 (19.7%)[g,h]	100 µg primary series	0.55 (0.35 – 0.85)	Serious[i]
Janssen Ad26.COV2.S						
Janssen, 2021[14–16]	RCT[j]; adults ≥18 years	32/1,559 (2.1%)	8/1,425 (0.6%)	Dose 2 placebo	3.66 (1.69–7.91)	Serious[k]

a. Solicited for 7 days after dose administration. Symptoms collected and severity definitions varied by study sponsor.[7,11,14]

b. A non-random subset of participants from the Pfizer-BioNTech phase 3 trial were randomized to a booster dose or another investigational vaccine a median of 6.8 months (range 4.8–8 months) after BNT162b2 dose 2.

c. Data on a comparison group was not provided for the RCT. The comparison group was based on any grade ≥3 reaction reported among all participants post-dose 1 or 2, at the time of the data analysis before the Biologics Licensure Application to the FDA (March 13, 2021).[8,10]

d. The only booster trial data available for GRADE were not according to randomization.

e. Data are from two parts of a Phase II clinical trial: an open label non-randomized booster study (booster), and a randomized dose confirmation study from which the booster study population was drawn (comparison).

f. A 50 µg booster dose was administered ≥6 months after 100 µg primary series.

g. Comparator group is 100 µg primary series recipients in the Phase II randomized dose confirmation study.

h. In the Moderna Phase 3 RCT, 2,909/14,691 (19.8%) of participants aged ≥18 years who received the 100 ug primary series experienced Grade ≥3 reactogenicity within 7 days.[13]

i. Participants' ability to choose whether to receive a booster likely introduced selection bias (e.g., those with adverse events or reactions with the primary series may have been less likely to choose a booster).

j. Data shown is from a Janssen Phase 3 RCT of 2-doses Ad26.COV.2S (5 x 10^{10} viral particles, IM) versus 2-doses placebo, ≥56 days apart.

k. Although the study was an RCT, marked loss of participants by the time of booster dose and placebo dose 2 administration may have introduced bias.

Table 4a: Grade Summary of Findings Table for Pfizer-BioNTech BNT162b2 booster

Certainty assessment	№ of patients Vaccinated	№ of patients Unvaccinated	Effect Relative	Effect Absolute	Cert

№ of studies	Study design	Risk of bias	Certainty assessment Inconsistency	Indirectness	Imprecision	Other considerations	№ of patients Vaccinated	№ of patients Unvaccinated	(95% CI) Effect Relative	(95% CI) Effect Absolute	Cert
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**			**(95% CI)**	**(95% CI)**	
Symptomatic laboratory-confirmed COVID-19 (assessed with immunobridging to post-dose 2)											
2	randomised trials	very serious[a]	not serious	very serious[b]	serious[c]	none			See narrative[d,e]		Type
Symptomatic laboratory-confirmed COVID-19 (assessed with vaccine effectiveness against any SARS-CoV-2 infection ≥12 days after booster dose)											
1[f]	observational studies	not serious	not serious	very serious[g]	not serious	none	934/1,137,804 (0.1%)[h]	4,439/1,137,804 (0.4%)[i]	RR 0.09 (0.08 to 0.10)	355 fewer per 100,000 (from 359 fewer to 351 fewer)[j]	Type
Hospitalization due to COVID-19 (assessed with vaccine effectiveness against severe COVID-19 ≥12 days after booster dose)											
1	observational studies	not serious	not serious	very serious[k]	not serious	none	29/1,137,804 (0.0%)[h]	294/1,137,804 (0.0%)[i]	RR 0.05 (0.03 to 0.08)	25 fewer per 100,000 (from 25 fewer to 24 fewer)[j]	Type
Death due to COVID-19											
0	–	–	–	–	–	–	–	–	–	–	
Transmission of SARS-CoV-2 infection											
0	–	–	–	–	–	–	–	–	–	–	
Serious adverse events (follow-up: median 2 months)											
1	randomised trials	very serious[l,m]	not serious	serious[n]	very serious[o]	none	1/306 (0.3%)[p]	43/10,841 (0.4%)	RR 0.82 (0.11 to 5.96)	71 fewer per 100,000 (from 353 fewer to 1,967 more)	Type
Reactogenicity, grade ≥3											
1	randomised trials	very serious[l,q]	not serious	serious[n]	serious[c]	none	19/289 (6.6%)	362/4,108 (8.8%)	RR 0.62 (0.40 to 0.97)	3,349 fewer per 100,000 (from 5,287 fewer to 264 fewer)	Type

CI: confidence interval; **RR:** risk ratio

a. Serious risk of bias was present. Although a non-random subset of participants from the phase 3 trial were randomized to a booster dose or another investigational vaccine, none were randomized to a placebo, the only data available for GRADE were from a pre-post booster analysis.

b. Very serious concern for indirectness was noted because efficacy is inferred from immunobridging to the same participants after dose 2 of Pfizer-BioNTech COVID-19 vaccine, and because immunogenicity data were only obtained for participants aged 18–55 years, which might not be representative of older participants.

c. Serious concern for imprecision was noted because number of study participants did not meet optimal information size.

d. For Phase 2/3 trial participants aged 18-55 (n=210), the ratio of geometric mean titers (GMT) of neutralizing antibodies at 1 month after booster dose (2,476.4 [2210.1, 2,774.9]) was noninferior to the GMT detected at 1 month after dose 2

(753.7 [95% CI 658.2, 863.1]). The geometric mean ratio was 3.29 (95% CI 2.76-3.91). Noninferiority was declared because the lower bound of the 2-sided 97.5% CI for the GMR is > 0.67 and the point estimate of the GMR is >=0.8.d For Phase 1 trial participants aged 65-85, the ratio of geometric mean titers (GMT) of neutralizing antibodies at 1 month after booster dose (1612.7 [875.5,2970]) was higher than the GMT detected at 1 month after dose 2 (195.8 [95% CI 114.7, 334.4]). The geometric mean ratio was 8.2 (95% CI for the point estimates do not overlap).

e. Seroresponse was also assessed for noninferiority. In the booster trial, 197/198 participants (99.5%) had a seroresponse at 1 month after booster dose, and 194/198 (98%) had a seroresponse at 1 month after dose 2, for a 1.5% difference (95% CI -0.7-3.7%). Noninferiority was declared because the lower bound of the 2-sided CI for the % difference is greater than -10.

f. The results of one study are shown. A second study (preprint) provided results for any SARS-CoV-2 infection, with a study population that overlapped with the included study, therefore results were not pooled. The additional study used test-negative design, and indicated a marginal vaccine effectiveness of 79% (95% CI 72%–84%) for the booster dose compared with the primary series. This corresponds to a relative risk of 0.21 (95% CI 0.16–0.28).

g. Very serious concern for indirectness was noted. The outcome of the study was any SARS-CoV-2 infection, which was an indirect measure of the PICO outcome of symptomatic COVID-19. The short duration of follow-up likely limited assessment of VE.

h. The number of participants who received the booster dose was not known. The study population included 1,137,804 persons, who contributed 10,603,410 person-days to the booster cohort (≥12 days after booster; ≥ 5 months after dose 2) for any SARS-CoV-2 infection and 6,265,361 person-days for severe COVID-19.

i. The number of participants who did not receive the booster dose was not known. The study population included 1,137,804 persons, who contributed 5,193,825 person-days to the no booster cohort (2 vaccine doses) for any SARS-CoV-2 infection and 4,574,439 person-days for severe COVID-19.

j. Absolute risk was calculated using the observed risk attributed to the cohort who had received 2 doses but no booster, among all persons included in the study, which assumes that all persons contributed some person-time before receiving a booster. Absolute risk estimates should be interpreted in this context.

k. Very serious concern for indirectness was noted. The outcome of the study was severe COVID-19, which was an indirect measure of the PICO outcome of hospitalization for COVID-19. The short duration of follow-up likely limited an accurate assessment of VE.

l. Very serious risk of bias; although a non-random subset of participants from the phase 3 trial were randomized to a booster dose or another investigational vaccine, the only booster trial data available for GRADE were not according to randomization.

m. Comparison group is safety population, subgroup aged 16–55 years, with blinded follow-up from dose 1 to 1 month after dose 2, at the time of the data cut-off date for the Biologics Licensure Application to the FDA (March 13, 2021). Not all persons in the comparison group received two doses.

n. Serious concern for indirectness was noted because participants in the booster group were restricted to persons aged 18–55 years and might not be representative of older participants.

o. Very serious concern for imprecision was present because the number of study participants did not meet optimal information size, and the 95% CIs for the relative and absolute risks include both benefits and harms. One event was observed among persons who received a booster dose.

p. One serious adverse event, a myocardial infarction, occurred 62 days after dose 3. This was judged by investigators to be unrelated to the intervention.

q. Comparison group based on any grade 3 reaction reported in all participants post dose 1 or 2, at the time of the data analysis prior to the Biologics Licensure Application to the FDA (March 13, 2021).

Table 4b: Grade Summary of Findings Table for Moderna mRNA-1273 booster

Certainty assessment							№ of Patients Vaccinated	№ of Patients Unvaccinated	Effect Relative (95% CI)	Effect Absolute (95% CI)	Certainty
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations					
Symptomatic laboratory-confirmed COVID-19 (assessed with immunobridging to post-dose 2)											
2	observational studies	not serious	not serious	very serious[a]	not serious	none			See narrative[b,c]		Type 4
Hospitalization due to COVID-19											
0	–	–	–	–	–	–	–	–	–	–	–

Certainty assessment							№ of Patients Vaccinated	№ of Patients Unvaccinated	Effect Relative (95% CI)	Effect Absolute (95% CI)	Certainty
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations					
Death due to COVID-19											
0	–	–	–	–	–	–	–	–	–	–	–
Transmission of SARS-CoV-2 infection											
0	–	–	–	–	–	–	–	–	–	–	–
Serious adverse events (follow-up: 28 days)											
1	observational studies	serious[d]	not serious	serious[e]	serious[f]	none	0/171 (0.0%)[g]	0/200 (0.0%)[h]	**RR 1.17** (0.02 to 59.59)	**0 fewer per 100,000** (from 0 fewer to 0 fewer)	Type 4
Reactogenicity, grade ≥3											
2	observational studies	serious[d]	not serious	not serious	not serious	none	18/167 (10.8%)	2,940/14,889 (19.7%)	**RR 0.55** (0.35 to 0.85)	**8,886 fewer per 100,000** (from 12,835 fewer to 2,962 fewer)	Type 4

CI: confidence interval; **RR:** risk ratio

a. Very serious concern for indirectness was noted because efficacy is inferred from immunobridging to a different group of participants after the primary series of Moderna COVID-19 vaccine (100 mcg). Although immunogenicity was evaluated 28 days after booster or primary series, these evaluations occurred at different calendar times, and the VE that formed basis of immunobridging was based on a data cutoff of May 4, 2021.

b. For the open label non-randomized booster trial among 149 participants aged ≥18 years, the geometric least squares mean (GLSM) of pseudovirus neutralizing antibodies (ID50) 28 days after 50 µg booster dose was 1,802.426 (95% CI: 1,548.020–2,098.643). The GLSM of 1,053 participants in the primary series RCT 28 days after dose 2 of 100 µg primary series was 1,026.854 (95% CI: 967.880 – 1,089.420). The geometric mean ratio (GMR) was 1.76 (95% CI: 1.496–2.060) Noninferiority was declared based on prespecified criteria: point estimate of GMR ≥1 and lower bound of 95% CI ≥0.67 based on noninferiority margin of 1.5.

c. Seroresponse rate (SRR) was also assessed for non-inferiority as a co-primary endpoint. 275/294 (93.5%) participants in the open label booster trial had seroresponse (based on PsVNA ID50 assay-specific definition) 29 days after booster, and 1,038/1,050 (98.9%) had seroresponse 57 days after Moderna COVID-19 vaccine primary series (either 50 mcg or 100 mcg), for a -5.3% difference (95% CI: -8.8,-2.9%). Noninferiority was declared because the lower bound of the 95% CI of the difference in SRR is ≥-10%, based on the noninferiority margin of 10%.

d. Serious risk of bias because participants' ability to choose whether to receive a booster likely introduced selection bias (e.g., those with adverse events or reactions with the primary series may have been less likely to choose a booster).

e. Serious concern for indirectness because of the short duration of follow-up (28 days for both groups). The comparison group included participants in the blinded phase of the booster study who received a 100 mcg primary series.

f. Serious concern for imprecision because of the small sample size and number of events, and the wide 95% CI crosses the line of no effect. The body of evidence does not provide certainty that rare SAEs were captured.

g. In the open-label booster study, 4/344 (1.2%) participants experienced 5 SAEs during a median follow-up of 5.7 months after booster dose (administered at least 6 months after a 50 mcg (n=173) or 100 mcg (n=171) 2-dose primary series.) Data on an equivalent primary series comparison group was not available at the time of the GRADE assessment.

h. In the Moderna Phase I/II/III trial, 147/15,385 (1.0%) of participants aged ≥18 years experienced at least 1 SAE after dose 2 of the Moderna primary series at the time of the EUA (median follow-up 2 months).

Table 4c: Grade Summary of Findings Table for Janssen booster

Certainty assessment							№ of Patients Vaccinated	№ of Patients Unvaccinated	Effect Relative (95% CI)	Effect Absolute (95% CI)	Certainty	Imp
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations						
Symptomatic laboratory-confirmed COVID-19 (assessed with vaccine efficacy ≥14 days after dose 2)												
2[a]	observational studies	not serious	not serious	serious[b]	not serious	none	14/7,484 (0.2%)[c]	173/1,9514 (0.9%)[d]	**RR 0.21** (0.12 to 0.36)	**700 fewer per 100,000** (from 780 fewer to 567 fewer)	Type 4	Crit
Hospitalization due to COVID-19 (assessed with vaccine efficacy ≥14 days after dose 2)												
2[a]	observational studies	not serious	not serious	serious[e]	serious[f]	none	0/6,024 (0.0%)[c]	2/19,514 (0.0%)[g]	**RR 0.65** (0.03 to 13.49)	**4 fewer per 100,000** (from 10 fewer to 128 more)	Type 4	Crit
Death due to COVID-19 (assessed with vaccine efficacy ≥14 days after dose 2)												
2[a]	observational studies	not serious	not serious	serious[e,h]	serious[f]	none	0/7,484 (0.0%)[c]	5/21,895 (0.0%)[i]	**RR 0.27** (0.01 to 4.81)	**17 fewer per 100,000** (from 23 fewer to 87 more)	Type 4	Imp
Transmission of SARS-CoV-2 infection												
0	–	–	–	–	–	–	–	–	–	–	–	Imp
Serious adverse events (follow-up: median 38 days for booster, 37 days for placebo)												
1[a]	randomised trials	serious[j]	not serious	serious[k]	serious[l]	none	28/8,646 (0.3%)[m]	27/8,043 (0.3%)[n]	**RR 0.96** (0.57 to 1.64)	**13 fewer per 100,000** (from 144 fewer to 215 more)	Type 4	Crit
Reactogenicity, grade ≥3												
1[a]	randomised trials	serious[j]	not serious	serious[o]	serious[p]	none	32/1,559 (2.1%)[q]	8/1,425 (0.6%)[n]	**RR 3.66** (1.69 to 7.91)	**1,493 more per 100,000** (from 387 more to 3,879 more)	Type 4	Imp

CI: confidence interval; **RR:** risk ratio

a. Estimates provided are for a 56-day dosing interval between first and booster dose.

b. Serious concern for indirectness was noted because the available data did not allow for a comparison between booster and no booster at the same time point; booster and primary vaccination groups were from different studies. The short duration of follow-up for booster (median 45 days) and primary dose (median 28 days) likely limited an accurate assessment of VE.

c. Assessed at least 14 days after booster dose (median follow-up 45 days).

d. Comparison group is Phase III RCT seronegative participants aged ≥18 years ≥14 days post-vaccination with the primary dose experiencing symptomatic SARS-CoV-2 RT-PCR-positive symptomatic illness by the time of the EUA (data cutoff

January 22, 2021; median follow-up: 2 months).

e. Serious concern for indirectness was noted because the available data did not allow for a comparison between booster and no booster at the same time point; booster and primary vaccination groups were from different studies. The short duration of follow-up for booster (median 45 days) likely limited an accurate assessment of VE.

f. Serious concern for imprecision due to fragility in the estimate because few events were observed. The 95% CI for the relative risk includes both benefits and harms.

g. Comparison group is Phase III RCT seronegative participants aged ≥18 years without prior evidence of infection ≥14 days post-vaccination with the primary dose experiencing hospitalization due to COVID-19 by the time of the EUA (data cutoff January 22, 2021).

h. The booster study outcome was COVID-19-related deaths, whereas the comparison outcome was all-cause deaths, including COVID-related or SAEs.

i. Comparison group is Phase III RCT seronegative participants aged ≥18 years ≥14 days post-vaccination with the primary dose with death from any cause by the time of the EUA (data cutoff February 5, 2021).

j. Serious risk of bias; although the study was designed as an RCT, marked loss of participants by the time of booster dose and placebo dose 2 administration may have introduced bias.

k. Serious concern for indirectness based on the short duration of follow-up (median duration 38 days for booster and 37 days for placebo)) for the estimates shown, and comparison group (2-dose placebo) differs from PICO comparator (no booster).

l. Serious concern for imprecision; the small sample size does not provide certainty that rare serious adverse events were captured, and the wide confidence interval includes both benefits and harms.

m. An additional 12/5,070 (0.2%) evaluable Janssen booster dose recipients and 7/4,681 (0.1%) evaluable 2-dose placebo recipients experienced 1 or more SAEs from 30 days to 6 months after the dose. Overall, 3 SAEs (facial paresis, pulmonary embolism, and cerebrovascular accident in 1 participant each) were attributed to booster within 6 months of administration, among 5,070 booster recipients in the evaluable population.

n. Comparison group is 2-dose placebo recipients.

o. Serious concern for indirectness; comparison group (2-dose placebo) differs from PICO comparator (no booster).

p. Serious concern for imprecision was present based on wide 95% confidence intervals for the effect estimates.

q. In a Phase 1/2a, randomized, double-blind placebo controlled with a 6-month dosing interval between dose 1 and booster, 8/267 (3.0%) of booster dose and 2/481 (0.4%) dose 2 placebo recipients reported Grade ≥3 reactogenicity within 7 days.

Appendix 1. Studies Included in the Review of Evidence

Last name first author, publication year	Study design	Country (or more detail, if needed)	Population	Total population	N booster	N comparison	Outcomes	Fun sou
Pfizer-BioNTech BNT162b2								
Bar-On, 2021[5]	Observational (retrospective cohort)	Israel	General population aged ≥60 years	1,137,804	10,603,410 person-days[a]	5,193,825 person-days[b]	• Symptomatic laboratory-confirmed COVID-19 • Hospitalization due to COVID-19 (assessed by severe COVID-19[c])	Not
Patalon, 2021 [d 6]	Observational (test negative design; matched case control)	Israel	General population aged ≥40 years	Varied based on study design	32,697 total tests (test negative design) 30,295 booster vaccinees (matched case-control)	149,379 total tests (test negative design) 238,018 dose 2 vaccinees (matched case-control)	• Symptomatic laboratory-confirmed COVID-19	Not

Last name first author, publication year	Study design	Country (or more detail, if needed)	Population	Total population	N booster	N comparison	Outcomes	Fun sou
Pfizer-BioNTech, 2021[7,8]	Phase II/III clinical trial	United States	Adults aged 18–55 years	Varied based on outcome	• 210 (symptomatic laboratory-confirmed COVID-19 (immunobridging) • 306 (SAEs, reactogenicity)	• 210 (symptomatic laboratory-confirmed COVID-19 (immunobridging)[e]	• Symptomatic laboratory-confirmed COVID-19 (immunobridging) • Serious adverse events • Reactogenicity	Indu
Pfizer-BioNTech, 2021[9]	Phase I clinical trial	Not reported in record	Adults aged 65–85 years	12	• 12 (symptomatic laboratory-confirmed COVID-19 (immunobridging)	• 12 (symptomatic laboratory-confirmed COVID-19 (immunobridging)[e]	• Symptomatic laboratory-confirmed COVID-19 (immunobridging)	Indu
Pfizer-BioNTech, 2021[8,10]	Phase II/III RCT	United States Brazil Argentina South Africa Turkey Germany	Adults aged ≥18 years	Varied based on outcome	None	• 10,841 SAEs • 4,108 (reactogenicity)	• SAEs • Reactogenicity	Indu
Moderna mRNA-1273								
Moderna, 2021[11–13]	Phase II clinical trial • Part A: RCT (dose confirmation) • Part B: open-label non-randomized booster study	United States	Adults aged ≥18 years	Varied based on outcome	• 149 (symptomatic laboratory-confirmed COVID-19 (immunobridging) • 171 (SAEs) • 167 (reactogenicity)	• 200 (SAEs)[f] • 198 (reactogenicity)[f]	• Symptomatic laboratory-confirmed COVID-19 (immunobridging) • Serious adverse events • Reactogenicity	Gov Indu
Moderna, 2021[11–13]	Phase III RCT	United States	Adults aged ≥18 years	Varied based on outcome	NA	• 1,053 (symptomatic laboratory-confirmed COVID-19 (immunobridging)[f] • 14,691 (reactogenicity)[f]	• Symptomatic laboratory-confirmed COVID-19 (immunobridging) • Reactogenicity	Gov Indu
Janssen Ad26.COV2.S								
Janssen, 2021[14–16]	Phase III RCT (booster dose)	Belgium, Colombia, Germany, Spain, France, United Kingdom, Philippines, United States, South Africa	Adults aged ≥18 years	Varied based on outcome	• 7,484 (symptomatic laboratory-confirmed COVID-19, death due to COVID-19) • 6,024 (death due to COVID-19) • 8,646 (SAEs) • 1,559 (reactogenicity)	• 8,043 (SAEs)[g] • 1,425 (reactogenicity)[g]	• Symptomatic laboratory-confirmed COVID-19 • Hospitalization due to COVID-19 • Death due to COVID-19 • Serious adverse events • Reactogenicity	Indu

Last name first author, publication year	Study design	Country (or more detail, if needed)	Population	Total population	N booster	N comparison	Outcomes	Fun sou
Janssen, 2021[17]	Phase III RCT (primary dose)	United States	Adults aged ≥18 years	Varied based on outcome	NA	• 19,514 (symptomatic laboratory-confirmed COVID-19, hospitalization due to COVID-19)[h] • 21,895 (death due to COVID-19)[h]	• Symptomatic laboratory-confirmed COVID-19 • Hospitalization due to COVID-19 • Death due to COVID-19	Gov Indi

NA = Not applicable

a. The number of participants who received a booster is not known.

b. The number of participants who did not receive a booster is not known.

c. Severe COVID-19 defined by study investigators as a resting respiratory rate of > 30 breaths per minute, an oxygen saturation of <94% while breathing ambient air, or a ratio of partial pressure of arterial oxygen to fraction of inspired oxygen of <300.

d. Preprint manuscript.

e. The comparison group is the same participants, 1 month after BNT162b2 dose 2.

f. The comparison group is recipients of 100 µg mRNA-1273 primary series.

g. The comparison group is recipients of placebo dose 2.

h. The comparison group is recipients of Janssen Ad26.COV2.S primary vaccination.

Appendix 2. Databases and strategies used for systematic review:

Database	Strategy
Clinicaltrials.gov	**Inclusion:** Phase 1, 2, or 3 clinical trials that provided data on: 1. booster vaccination with Pfizer (dose 3), Moderna (dose 3), or Janssen (dose 2) 2. involved human subjects 3. reported primary data 4. included adults (aged ≥18 years) at risk for SARS-CoV-2 infection 5. included data relevant to the efficacy and safety outcomes specified in the PICO questions **Additional resources:** Unpublished and other relevant data by consulting with vaccine manufacturers and subject matter experts

Database	Strategy
International Vaccine Access Center (IVAC)	**IVAC inclusion criteria:** 1. published or preprint study with adequate scientific details 2. includes group with and without infection or disease outcome 3. laboratory-confirmed outcome† 4. vaccination status confirmed in ≥90%§ 5. studies assess one vaccine or pooled mRNA vaccines 6. includes participants who did or did not receive a COVID-19 vaccine¶ 7. vaccine effectiveness estimate calculated comparing vaccinated to unvaccinated** **Additional GRADE inclusion criteria:** 1. restricted to PICO-defined population, intervention, comparison, and outcomes (or related outcomes if no direct data available) 2. outcomes assessed after booster dose of Pfizer-BioNTech, Moderna, or Janssen COVID-19 vaccine

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