Evidence to Recommendations (EtR) Framework

- Structure to describe information considered in moving from evidence to ACIP vaccine recommendations

- Provide transparency around the impact of additional factors on deliberations when considering a recommendation

- Questions around vaccine policy for booster doses are complex
  - Require some adaptation of our standard Evidence to Recommendation Framework
## Evidence to Recommendations (EtR) Framework

<table>
<thead>
<tr>
<th>Standard EtR Domains</th>
</tr>
</thead>
<tbody>
<tr>
<td>Public Health Problem</td>
</tr>
<tr>
<td>Benefits and Harms</td>
</tr>
<tr>
<td>Values</td>
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<tr>
<td>Acceptability</td>
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<tr>
<td>Feasibility</td>
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<tr>
<td>Resource Use</td>
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<tr>
<td>Equity</td>
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</table>
## Evidence to Recommendations (EtR) Framework

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</tr>
</tbody>
</table>

- **Public Health Problem**
  - Are booster doses needed?

- **Benefits and Harms**
  - What is the balance of benefits and harms for booster doses by age?

- **Values and Acceptability**
  - Do people want a booster dose?
Evidence to Recommendations (EtR) Framework

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</tr>
</tbody>
</table>

- **Public Health Problem**
- **Benefits and Harms**
- **Values and Acceptability**
- **Feasibility**
- **Resource Use**
- **Equity**

- How would booster doses be implemented?
- What are the costs associated with booster doses?
Evidence to Recommendations (EtR) Framework

Standard EtR Domains

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<td>Resource Use</td>
</tr>
<tr>
<td>Equity</td>
</tr>
</tbody>
</table>

What are equity considerations for booster doses?
Booster doses of COVID-19 vaccines

- Policy on booster doses will be coordinated with FDA for regulatory allowance, and ACIP for recommendations for use.
Evidence to Recommendations (EtR) Framework

Question

- Who should be recommended to receive a Pfizer-BioNTech COVID-19 booster dose under the current Emergency Use Authorization, based on the balance of benefits and risks?
Evidence to Recommendations Framework

Booster doses of COVID-19 vaccines

Are booster doses of COVID-19 vaccines needed?
Daily trends in number of COVID-19 cases in the United States

January 23, 2020 – September 20, 2021

42,234,211 total cases

Number of people fully vaccinated in the U.S. by COVID-19 vaccine series type

- Pfizer-BioNTech 2-dose: 99,477,041
- Moderna 2-dose: 67,779,695
- J&J/Janssen single dose: 14,651,137
- Unknown 2-dose: 104,470

Total: 182,012,343 Fully Vaccinated

Age-adjusted weekly COVID-19-associated hospitalization rates among adults by week of admission and age group*—COVID-NET, January 24–July 17, 2021

**18-49 years**

- **23x higher**

**50-64 years**

- **22x higher**

**≥65 years**

- **13x higher**

*Data are preliminary and case counts and rates for recent hospital admissions are subject to lag. As data are received each week, prior case counts and rates are updated accordingly.
†Cumulative rate ratio from January 24 – July 17, 2021. Shaded area indicates preliminary July data that does not include one site.

Havers et al. [https://medrxiv.org/cgi/content/short/2021.08.27.21262356v1](https://medrxiv.org/cgi/content/short/2021.08.27.21262356v1). COVID-19-associated hospitalizations among vaccinated and unvaccinated adults ≥18 years - COVID-NET, 13 states, January 1-July 24, 2021
Incidence among vaccinated people, for hospitalization by month in United States and for severe disease by time since 2nd dose in Israel

*Israel estimates were derived from rate of severe COVID-19 (per 1,000 persons) from July 11, 2021 to July 31, 2021. Each data point represents all person stratified by when second dose of COVID-19 vaccine received.
Public Health Problem:
Are booster doses of COVID-19 vaccines needed?

- Is vaccine effectiveness (VE) waning by age?
- Is VE waning for those with underlying medical conditions?
- Is VE waning for those with high-risk occupations?
- How do these data vary by vaccine?
Vaccine effectiveness against *infection* over time
Adults ≥18 years of age


Keehner J, Horton LE, Binkin NJ et al. Resurgence of SARS-CoV-2 Infection in a Highly Vaccinated Health System Workforce. NEJM, September 1, 2021. DOI: 10.1056/NEJMoa2112981
Vaccine effectiveness against **symptomatic infection**, by age and time since vaccination

Source: Unpublished ICATT data, 2021
Vaccine effectiveness against **hospitalization** by month
Adults ≥18 years of age

![Graph showing vaccine effectiveness against hospitalization by month](image)


Vaccine effectiveness against **hospitalization** over time

Adults ≥16 years of age


Summary

Vaccine effectiveness by age

- Significant declines in VE against *infection* in individuals ≥65 years of age for mRNA products in the Delta period
- Smaller declines in VE against *hospitalization* in individuals ≥65 years of age, but more substantial than younger populations
- Among adults <65 years of age: vaccines *remain effective* in preventing hospitalization and severe disease
- Vaccines may be less effective in preventing infection or symptomatic illness due to waning over time and the Delta variant
Public Health Problem:
Are booster doses of COVID-19 vaccines needed?

Is vaccine effectiveness (VE) waning by age?

Is VE waning for those with underlying medical conditions?

Is VE waning for those with high-risk occupations?

How do these data vary by vaccine?
Vaccine effectiveness against hospitalization among adults with underlying medical conditions

Estimates controlled for age. Excludes individuals with immunocompromising conditions.
Vaccine effectiveness against **infection** among US veterans with underlying conditions, pre-Delta period

![Bar chart showing vaccine effectiveness against infection among US veterans with different Charlson Comorbidity Index scores.](image)

Summary
Vaccine effectiveness by underlying medical condition

- **Limited data** currently to evaluate VE by a variety of underlying medical conditions
  - Current data with limited waning in those with at least 1 underlying medical condition
- These estimates exclude immunocompromised individuals
- Estimates may not represent effectiveness across **all** underlying medical conditions
  - Cannot produce estimates for rare (and possibly more severe) underlying conditions
  - Spectrum of underlying medical conditions with a range of severity; may have varying impact in effectiveness
Public Health Problem: Are booster doses of COVID-19 vaccines needed?

Is vaccine effectiveness (VE) waning by age?

Is VE waning for those with underlying medical conditions?

Is VE waning for those with high-risk occupations?

How do these data vary by vaccine?
Vaccine effectiveness against infection among healthcare providers, first responders and frontline workers


Keehner J, Horton LE, Binkin NJ et al. Resurgence of SARS-CoV-2 Infection in a Highly Vaccinated Health System Workforce. NEJM, September 1, 2021. DOI: 10.1056/NEJMc2112981
Summary

Vaccine effectiveness by high-risk occupation

- Effectiveness among healthcare and other frontline essential workers are similar to estimates for general population of the same age
- Severe disease among vaccinated essential workers is rare
- Vaccine effectiveness waning against infections in this population
  - Impact of lower VE against infections may be different among healthcare and other frontline essential workers
- Many prioritized for earlier doses of COVID-19 vaccines
  - Longer duration since primary series
Public Health Problem:
Are booster doses of COVID-19 vaccines needed?

Is vaccine effectiveness (VE) waning by age?

Is VE waning for those with underlying medical conditions?

Is VE waning for those with high-risk occupations?

How do these data vary by vaccine?
Summary of **VE estimates** since introduction of the **Delta** variant
Adults ≥18 years of age

See reference list in later slides
Summary
Vaccine effectiveness by vaccine

- Vaccine effectiveness varies by initial vaccine type
- Protection against hospitalization for mRNA vaccines high
- Protection against infection is lower for all vaccines
Summary

- Hospitalization rates are ~10X-22X higher in unvaccinated as compared to vaccinated adults
- Over 182 million people are fully vaccinated in the U.S.
- Although COVID-19 continues to be a public health problem, among persons who have received a primary series, data support continued protection against hospitalizations and deaths
  - Need to follow data around long-term outcomes among infections after vaccination
Evidence to Recommendations Framework
Booster doses of COVID-19 vaccines

What is the balance of benefits and harms for booster doses by age?
Benefits and Harms:
What is the balance of benefits and harms for booster doses by age?

Are booster doses of the COVID-19 vaccine safe and immunogenic (GRADE)?

What is the benefit/risk assessment by age?

What is the summary of benefits and harms by age and population?
# PICO Question

<table>
<thead>
<tr>
<th><strong>Population</strong></th>
<th>Persons aged ≥18 years who completed a COVID-19 vaccine primary series ≥6 months ago</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Intervention</strong></td>
<td>Pfizer-BioNTech COVID-19 Vaccine BNT162b2 <strong>booster dose</strong> (30 μg, IM)</td>
</tr>
<tr>
<td><strong>Comparison</strong></td>
<td>No booster dose</td>
</tr>
<tr>
<td><strong>Outcomes</strong></td>
<td>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</td>
</tr>
</tbody>
</table>
Evidence retrieval

Articles were eligible for inclusion if published or available on a pre-print server before 9/20/21. Criteria included in the ongoing systematic review conducted by the International Vaccine Access Center (IVAC) and the World Health Organization.

*See https://view-hub.org/resources
** Phase 1 and Phase 2/3 Clinical Trial results from clinicaltrials.gov and other
Observational studies from Israel (n=2)

- Delta variant became dominant in Israel in mid-June
- Israel authorized a 3rd dose for immunocompromised residents on July 12, 2021, and for all residents ≥60 years on July 30, 2021
- Two studies have assessed the effectiveness of a 3rd dose:
  - Large studies: Data extracted from Ministry of Health national database or large health system database
  - Time since 2nd dose: ≥5 months
  - Control population: individuals that completed the 2 dose series

Bar-O et al. BNT162b2 vaccine booster dose protection: A nationwide study from Israel. medRxiv preprint August 31, 2021. doi: https://doi.org/10.1101/2021.08.27.21262679
Patalon et al. Short Term Reduction in the Odds of Testing Positive for SARS-CoV-2; a Comparison Between Two Doses and Three doses of the BNT162b2 Vaccine. MedRxiv, August 31, 2021
Observational studies from Israel (n=2)

Bar-On et al.

Patalon et al.

Documented Infection

<table>
<thead>
<tr>
<th>July 25</th>
<th>26</th>
<th>27</th>
<th>28</th>
<th>29</th>
<th>30</th>
<th>31</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aug 1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
<td>6</td>
<td>7</td>
</tr>
<tr>
<td></td>
<td>8</td>
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<td>25</td>
<td>26</td>
<td>27</td>
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<tr>
<td></td>
<td>29</td>
<td>30</td>
<td>31</td>
<td>Sept 1</td>
<td>2</td>
<td>3</td>
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</tbody>
</table>

Severe Disease

<table>
<thead>
<tr>
<th>July 25</th>
<th>26</th>
<th>27</th>
<th>28</th>
<th>29</th>
<th>30</th>
<th>31</th>
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<tr>
<td>Aug 1</td>
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<td>27</td>
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<tr>
<td></td>
<td>29</td>
<td>30</td>
<td>31</td>
<td>Sept 1</td>
<td>2</td>
<td>3</td>
</tr>
</tbody>
</table>

Both 3rd dose studies have short follow up periods, with a maximum of 21 days for documented infection and 16 days for severe disease.

Patalon et al. Short Term Reduction in the Odds of Testing Positive for SARS-CoV-2; a Comparison Between Two Doses and Three doses of the BNT162b2 Vaccine. MedRxiv, August 31, 2021
# Outcome 1: Symptomatic laboratory-confirmed COVID-19 observational studies with dose 2 comparison group (n=2)

<table>
<thead>
<tr>
<th>Location</th>
<th>Study</th>
<th>Population</th>
<th>Methoda</th>
<th>Time period (dominant variant)</th>
<th>Days after booster dose</th>
<th>Control Group</th>
<th>Outcome</th>
<th>Booster vaccinees n/N (or person-time)</th>
<th>Dose 2 vaccinees n/N (or person-time)</th>
<th>Incremental VE (booster dose vs. dose 2)</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Israela</td>
<td>Bar-On, September 2021</td>
<td>General population ≥60 years</td>
<td>Retrospective Cohort</td>
<td>7/30–8/31/21 (Delta)</td>
<td>≥12</td>
<td>Dose 2</td>
<td>Any infection</td>
<td>934 infections / 10,603,410 person-days</td>
<td>4,439 infections / 5,193,825 person-days</td>
<td>91.2%b</td>
<td>90.4–91.9%</td>
</tr>
<tr>
<td>Israela</td>
<td>Patalon, August 2021 (preprint)</td>
<td>General population ≥40 years</td>
<td>Test Negative Design</td>
<td>8/1–8/21/21 (Delta)</td>
<td>14–20</td>
<td>Dose 2</td>
<td>Any infection</td>
<td>1,188 positive / 32,697 total tests</td>
<td>8.285 positive / 149,379 total tests</td>
<td>79%c</td>
<td>72–84%</td>
</tr>
</tbody>
</table>

a. A minimum interval of 5 months after the 2nd dose is required to be eligible for the BNT162b2 booster dose in Israel. Israeli authorities approved a booster dose for “high risk-populations” on 7/12/21 and for persons aged ≥60 years on 7/30/21.

b. VE was calculated from the rate ratio reported in the manuscript. Rate ratio calculated using a Poisson regression model, adjusted for age (60–69, 70–79, ≥80), gender, demographic group (General Jewish, Arab, ultra-Orthodox Jewish), date of second vaccine dose (in half-month intervals), and calendar date.

c. VE calculated from odds ratios (and 95% CI) from logistic regression models, adjusted for 10-year age category, sex, time since vaccination category, comorbidities, and log number of positive tests.

NR: Not reported  VE: vaccine effectiveness  CI: confidence intervals
### Evidence Table: Symptomatic laboratory-confirmed COVID-19

<table>
<thead>
<tr>
<th>Certainty assessment</th>
<th>Ne of patients</th>
<th>Effect</th>
<th>Ne of studies</th>
<th>Study design</th>
<th>Risk of bias</th>
<th>Inconsistency</th>
<th>Indirectness</th>
<th>Imprecision</th>
<th>Other considerations</th>
<th>Pfizer BioNTech COVID-19 Vaccine, 30 mcg, booster dose</th>
<th>Pfizer BioNTech COVID-19 Vaccine, 30 mcg, dose 2</th>
<th>Relative (95% CI)</th>
<th>Absolute (95% CI)</th>
<th>Certainty</th>
<th>Importance</th>
</tr>
</thead>
<tbody>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Number of participants not known</td>
<td>Number of participants not known</td>
<td>Number of participants not known</td>
<td>Number of participants not known</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>RCT</td>
<td>Very serious(^a)</td>
<td>Not serious</td>
<td>Very serious(^b)</td>
<td>Serious(^c)</td>
<td>None</td>
<td>Pfizer BioNTech COVID-19 Vaccine,</td>
<td>Pfizer BioNTech COVID-19 Vaccine,</td>
<td>Relative (95% CI)</td>
<td>Absolute (95% CI)</td>
<td>Type 4</td>
<td>CRITICAL</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Not serious</td>
<td>Not serious</td>
<td>Very serious(^d)</td>
<td>Not serious</td>
<td>None</td>
<td>30 mcg, booster dose</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1(^e)</td>
<td>Obs</td>
<td>Not serious</td>
<td>Not serious</td>
<td>Not serious</td>
<td>None</td>
<td>934/1,137,804 (0.0%)(^8)</td>
<td>4,439/1,137,804 (0.4%)(^h)</td>
<td>RR 0.09 (0.08 to 0.10)</td>
<td>277 fewer per 100,000 (from 290 to 275 fewer)</td>
<td>Type 4</td>
<td>CRITICAL</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

\(^a\) Concern for very 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 primarily for participants aged 18–55 years, which might not be representative of older participants.

\(^c\) Serious risk of imprecision was noted because number of study participants did not meet optimal information size.

\(^d\) Seroresponse was also assessed for noninferiority. 197/198 participants (99.5%) in the booster trial had a seroresponse at 1 month after booster dose, and 194/198 (98%) had a seroresponse at 1 month after dose 1, for a 1.5% difference (95% CI 0.8–3.7%). Noninferiority was declared because the lower bound of the 2-sided CI for the % difference is greater than -10. Seroresponse was not reported for Phase 1 trial participants.

\(^e\) 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 vaccine effectiveness of 79% (95% CI 72%-84%) for the booster dose compared to the primary series. This corresponds to a relative risk of 0.21 (95% CI 0.16–0.28).

\(^f\) 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.

\(^g\) The number of participants who received 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 (≥12 days after booster; ≥ 5 months after dose 2).

\(^h\) 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).

CI: Confidence interval; RR: Risk ratio
### Evidence Table: Hospitalization due to COVID-19

<table>
<thead>
<tr>
<th>Certainty assessment</th>
<th>No of patients</th>
<th>Effect</th>
<th>Ne of studies</th>
<th>Study design</th>
<th>Risk of bias</th>
<th>Inconsistency</th>
<th>Indirectness</th>
<th>Imprecision</th>
<th>Other considerations</th>
<th>Pfizer BioNTech COVID-19 Vaccine, 30 mcg, booster dose</th>
<th>Pfizer BioNTech COVID-19 Vaccine, 30 mcg, dose 2</th>
<th>Relative (95% CI)</th>
<th>Absolute (95% CI)</th>
<th>Certainty</th>
<th>Importance</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>1</td>
<td>Obs</td>
<td>not serious</td>
<td>not serious</td>
<td>very serious</td>
<td>not serious</td>
<td>none</td>
<td>29/1,137,804 (0.0%)(^a)</td>
<td>294/1,137,804 (0.0%)(^c)</td>
<td>RR 0.05 (0.03 to 0.08)</td>
<td>26 fewer per 100,000 (from 27 to 25 fewer)</td>
<td>Type 4</td>
<td>CRITICAL</td>
</tr>
</tbody>
</table>

**Vaccine efficacy against hospitalization due to COVID-19**

<table>
<thead>
<tr>
<th>No of patients</th>
<th>Effect</th>
<th>Ne of studies</th>
<th>Study design</th>
<th>Risk of bias</th>
<th>Inconsistency</th>
<th>Indirectness</th>
<th>Imprecision</th>
<th>Other considerations</th>
<th>Pfizer BioNTech COVID-19 Vaccine, 30 mcg, booster dose</th>
<th>Pfizer BioNTech COVID-19 Vaccine, 30 mcg, dose 2</th>
<th>Relative (95% CI)</th>
<th>Absolute (95% CI)</th>
<th>Certainty</th>
<th>Importance</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td></td>
<td>29/1,137,804</td>
<td>294/1,137,804</td>
<td>RR 0.05</td>
<td>26 fewer per</td>
<td>CRITICAL</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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\(^a\) 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.

\(^b\) The number of participants who received the booster dose was not known. The study population included 1,137,804 persons, who contributed 6,265,361 person-days to the booster cohort (≥12 days after booster; ≥ 5 months after dose 2).

\(^c\) The number of participants who did not receive the booster dose was not known. The study population included 1,137,804 persons, who contributed 4,574,439 person-days to the no booster cohort (2 vaccine doses).
**Evidence Table: Harms**

<table>
<thead>
<tr>
<th>Certainty assessment</th>
<th>№ of patients</th>
<th>Effect</th>
<th>Certainty</th>
<th>Importance</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Pfizer BioNTech COVID-19 vaccine, 30 mcg, booster</td>
<td>no booster</td>
<td>(95% CI)</td>
<td>(95% CI)</td>
</tr>
<tr>
<td></td>
<td>Relative</td>
<td>Absolute</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>(95% CI)</td>
<td>(from 353 fewer to 1,967 more)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>RR</td>
<td>RR</td>
<td>Type</td>
<td>CRITICAL</td>
</tr>
</tbody>
</table>

### Serious adverse events (follow up: median 2 months)

<table>
<thead>
<tr>
<th>No. of studies</th>
<th>Study design</th>
<th>Risk of bias</th>
<th>Inconsistency</th>
<th>Indirectness</th>
<th>Imprecision</th>
<th>Other considerations</th>
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<tbody>
<tr>
<td>1</td>
<td>randomized trials</td>
<td>very serious a,b</td>
<td>not serious</td>
<td>serious c</td>
<td>very serious d</td>
<td>none</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1/306 (0.3%)e</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>43/10841 (0.4%)b</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>RR 0.82 (0.11 to 5.96)</td>
</tr>
<tr>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td>71 fewer per 100,000</td>
</tr>
<tr>
<td></td>
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<td>(from 353 fewer to 1,967 more)</td>
</tr>
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</table>

**Type 4**

### Reactogenicity, grade >=3

<table>
<thead>
<tr>
<th>No. of studies</th>
<th>Study design</th>
<th>Risk of bias</th>
<th>Inconsistency</th>
<th>Indirectness</th>
<th>Imprecision</th>
<th>Other considerations</th>
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</thead>
<tbody>
<tr>
<td>1</td>
<td>randomized trials</td>
<td>very serious a,f</td>
<td>not serious</td>
<td>serious c</td>
<td>serious g</td>
<td>none</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>19/289 (6.6%)</td>
</tr>
<tr>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td>362/4108 (8.8%)f</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>RR 0.62 (0.40 to 0.97)</td>
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<td></td>
<td>3,349 fewer per 100,000</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(from 5,287 fewer to 264 fewer)</td>
</tr>
</tbody>
</table>

**Type 4**

---

a. 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.
b. 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.
c. Serious concern for indirectness was noted because participants were restricted to persons aged 18–55 years and might not be representative of older participants.
d. 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.
e. One serious adverse event, a myocardial infarction, occurred 62 days after dose 3. This was judged by investigators to be unrelated to the intervention.
f. 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).
g. Serious risk of imprecision was noted because number of study participants did not meet optimal information size.
Lymphadenopathy was more common after the 3rd dose than after the 2nd dose

- 16/306 participants (5.2%) in the Phase 3 trial (adults 18–55 years) reported lymphadenopathy
  - All 16 subjects had axillary lymphadenopathy
  - One subject also had lymphadenopathy reported in the neck
  - One severe event of lymphadenopathy was reported by 1 participant (onset of 2 days post-booster), recovered/resolved 5 days from onset

- Lymphadenopathy was observed more frequently following the booster dose than after primary series doses (5.2% compared to 0.4%)
Safety data regarding 3rd dose Pfizer-BioNTech COVID-19 vaccination, Israel

- 3rd doses became authorized for all adults ≥60 years on July 30, 2021
  - Expanded to ≥12 years at the end of August
- ~2.8 M 3rd doses administered to persons ≥12 years (through September 13)
  - Most to persons ≥60 years
- Rates of reported systemic, local, neurologic, allergic, and other reactions were substantially lower after dose 3 than after dose 1 or 2. Suspected under-reporting
- 1 case of myocarditis in individual ≥30 years of age
  - Due to limited follow up time, unable to determine rates of myocarditis in younger adults from Israeli data available to date

https://www.fda.gov/media/152205/download
### Summary of GRADE

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Importance</th>
<th>Design (# of studies)</th>
<th>Findings</th>
<th>Evidence type</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Benefits</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Symptomatic laboratory-confirmed COVID-19</td>
<td>Critical</td>
<td>RCT (2) OBS (1)</td>
<td>Pfizer-BioNTech COVID-19 booster dose induced immune responses (GMR, seroresponse) noninferior to those following dose 2. Observational data suggest increased protective effect against any SARS-CoV-2 infection.</td>
<td>4</td>
</tr>
<tr>
<td>Hospitalization due to COVID-19</td>
<td>Critical</td>
<td>RCT (0) OBS (1)</td>
<td>Observational data suggest increased protective effect against severe COVID-19.</td>
<td>4</td>
</tr>
<tr>
<td>Death due to COVID-19</td>
<td>Important</td>
<td>RCT (0) OBS (0)</td>
<td>No data available.</td>
<td>ND</td>
</tr>
<tr>
<td>Transmission of SARS-CoV-2 infection</td>
<td>Important</td>
<td>OBS (0)</td>
<td>No data available.</td>
<td>ND</td>
</tr>
<tr>
<td><strong>Harms</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Serious adverse events</td>
<td>Critical</td>
<td>RCT (1)</td>
<td>No SAEs were attributed to booster dose.</td>
<td>4</td>
</tr>
<tr>
<td>Reactogenicity</td>
<td>Important</td>
<td>RCT (1)</td>
<td>Grade ≥3 reactogenicity was reported by 6.6% of booster dose recipients.</td>
<td>4</td>
</tr>
</tbody>
</table>

Evidence type: 1=high; 2=moderate; 3=low; 4=very low; ND, no data
Benefits and Harms:
What is the balance of benefits and harms for booster doses by age?

Are booster doses of the COVID-19 vaccine safe and immunogenic (GRADE)?

What is the benefit/risk assessment by age?

What is the summary of benefits and harms by age and population?
Number needed to vaccinate with booster dose to prevent one hospitalization over 6 months

Number needed to vaccinate to prevent one hospitalization

**Age groups (years)**

- 18-29: 8738
- 30-49: 3361
- 50-64: 2051
- 65+: 481
Benefits and risks after Pfizer-BioNTech COVID-19 vaccination for persons aged 18 – 29 years, by sex

For every million doses of vaccine given

Benefit/risk balance among younger population varies by sex, VE after booster dose, rates of myocarditis, and incidence. As incidence declines, more uncertainty around the balance of benefits and risks

COVID-19-Associated Hospitalizations Among Males & Females Prevented per Million Doses

Pre-Booster VE

Cases of Myocarditis Among Males & Females Expected per Million Doses

1https://www.cdc.gov/mmwr/volumes/70/wr/mm7037e1.htm?s_cid=mm7037e1_w.
Summary
Benefit/risk assessment

- Risks of myocarditis after a 3rd dose of mRNA vaccines is unknown
  - After 2\textsuperscript{nd} dose, risk varies by age and sex

- Benefit/risk balance is the most favorable for adults $\geq 65$ years of age using current estimates of vaccine effectiveness

- Benefit/risk balance among younger population varies by sex, VE after booster dose, rates of myocarditis, and incidence. As incidence declines, more uncertainty around the balance of benefits and risks
Benefits and Harms:
What is the balance of benefits and harms for booster doses by age?

Are booster doses of the COVID-19 vaccine safe and immunogenic (GRADE)?

What is the benefit/risk assessment by age?

What is the summary of benefits and harms by age and population?
Summary-balance of benefits and harms for booster doses

- Data from clinical trial limited in size (n~300) and age (primarily 18-55 years)

- Booster dose of Pfizer-BioNTech COVID-19 vaccine increases immune response in those who have completed a primary series approximately 6 months previously

- Individual benefit/risk balance varies by age
  - Largest benefit from vaccination of individuals ≥65 years of age
  - Benefit to other ages incrementally smaller, given higher VE maintained from primary series
  - Even within age categories, likely variation within balance of benefits and risks given risk of exposure, medical condition and sex

- Unable to account for other benefits
  - Possible impact on rates of community transmission
Evidence to Recommendations Framework
Booster doses of COVID-19 vaccines

Values and Acceptability

Do people want a booster dose?
Values and Acceptability

- In published surveys completed in August (n=5), 76%-87% of vaccinated adults reported they would get a booster dose, if available\(^1-5\)
  - In one survey, this increased to 93% of surveyed adults if it was recommended by their primary care provider

Around 2/3 of vaccinated respondents said they would get a COVID-19 booster vaccine

% of vaccinated respondents

- Get booster ASAP: 63.8%
- Wait to see if booster works: 12.1%
- Wait to see if booster is safe: 10.0%
- Don’t know: 6.1%
- Only if required for work/school: 3.8%
- Definitely not: 2.1%
- Already received booster: 1.8%
- Refused to answer: 0.4%
Around 1/3 of unvaccinated respondents said that COVID-19 booster vaccines would make them less likely to get vaccinated at all.
At least 2/3 of respondents believed that healthcare workers, LTCF residents and adults ≥75 should be prioritized for booster doses

<table>
<thead>
<tr>
<th>Category</th>
<th>High</th>
<th>Medium</th>
<th>Low</th>
</tr>
</thead>
<tbody>
<tr>
<td>Healthcare workers</td>
<td>70.9%</td>
<td>18.3%</td>
<td>10.9%</td>
</tr>
<tr>
<td>Care facility residents</td>
<td>67.0%</td>
<td>24.5%</td>
<td>8.5%</td>
</tr>
<tr>
<td>Aged &gt;=75</td>
<td>65.8%</td>
<td>24.3%</td>
<td>9.8%</td>
</tr>
<tr>
<td>Essential workers</td>
<td>57.3%</td>
<td>30.0%</td>
<td>12.7%</td>
</tr>
<tr>
<td>Aged 65-74</td>
<td>56.4%</td>
<td>32.6%</td>
<td>11.0%</td>
</tr>
<tr>
<td>Other countries</td>
<td>56.4%</td>
<td>29.5%</td>
<td>14.1%</td>
</tr>
<tr>
<td>Aged 50-64</td>
<td>47.8%</td>
<td>35.3%</td>
<td>16.9%</td>
</tr>
<tr>
<td>Aged 12-17</td>
<td>39.1%</td>
<td>37.1%</td>
<td>23.7%</td>
</tr>
<tr>
<td>Aged 18-49</td>
<td>50.3%</td>
<td>28.1%</td>
<td>21.6%</td>
</tr>
</tbody>
</table>

CDC/University of Iowa unpublished data, August 2021
Over half felt that essential workers, adults aged 65–74 years of age and other countries should be recommended for booster doses

CDC/University of Iowa unpublished data, August 2021
Adults ≤64 years were the least prioritized groups for booster doses.

CDC/University of Iowa unpublished data, August 2021
Summary
Values and Acceptability

- At least \( \frac{2}{3} \) of vaccinated adults willing to receive a booster dose
- Survey respondents prioritized older adults and healthcare workers for booster doses; younger adults less prioritized
Evidence to Recommendations Framework
Booster doses of COVID-19 vaccines

How would booster doses be implemented?
Completed primary vaccination series by week
Completed primary vaccination series by week:
Adults ≥65 years of age
Completed primary vaccination series by week:
Adults ≥65 years of age

Completed primary series 6 months prior

- Pfizer
- Moderna
- J&J

Millions
Completed primary vaccination series by week and age

- **50-64 years**
- **30-49 years**
- **18-29 years**
Completed primary vaccination series by week and age

- **50-64 years**
- **30-49 years**
- **18-29 years**

Completed primary series 6 months prior
## Number of persons eligible (in millions) for a booster dose on September 27th, 2021

<table>
<thead>
<tr>
<th>Age group</th>
<th>≥6 months after primary series</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Pfizer-BioNTech</td>
<td>Moderna</td>
</tr>
<tr>
<td>18-29 years old</td>
<td>2.0</td>
<td>1.5</td>
</tr>
<tr>
<td>30-49 years old</td>
<td>5.5</td>
<td>4.4</td>
</tr>
<tr>
<td>50-64 years old</td>
<td>5.3</td>
<td>4.4</td>
</tr>
<tr>
<td>65+ years old</td>
<td>13.6</td>
<td>12.9</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>26.4</strong></td>
<td><strong>23.4</strong></td>
</tr>
</tbody>
</table>
Jurisdictional preparations

- Jurisdictions have begun preparing for implementation of booster doses

- Booster doses likely given in a variety of settings: pharmacies, providers offices, health departments, occupational clinics and federal programs (e.g., LTCF program)
  - Over 70% of current COVID-19 vaccine administration occurring in pharmacies

- Many jurisdictions experiencing surge in cases of COVID-19, outreach for unvaccinated individuals to receive primary series, fall/winter influenza campaigns
Implementation
Variation in primary series receipt

- 3 vaccines are currently being administered in the United States
- For additional doses of mRNA vaccines in immunocompromised persons, the current recommendations state that the additional dose should be the same product as the primary series.
  - If the product given for the first 2 doses is not available, the other vaccine product may be administered
- Evidence reviewed by FDA only evaluated a booster dose of Pfizer-BioNTech vaccine after completion of a Pfizer-BioNTech primary series
Implementation
Long-term care facility (LTCF) residents

- LTCFs can arrange for an on-site vaccination clinic or help residents access vaccine in local community
  - Federal LTCF program can help implement vaccination in long-term care settings
- 8.1 million doses administered during original LTCF program (December 2020-March 2021): 6.2M (76%) were Pfizer-BioNTech, 1.9M (24%) were Moderna
- LTCFs can have substantial turnover over time:
  - 30% per month for residents
  - 100% per year for staff
Current CDC clinical considerations state:
“For public health purposes, immunocompromised people who have completed a primary vaccine series (i.e. 2-dose mRNA vaccine series or a single dose of the Janssen vaccine) are considered fully vaccinated ≥2 weeks after completion of the primary series”

Based on current data, the definition of ‘fully vaccinated’ would remain the same after recommendations for booster dose
- Fully vaccinated ≥2 weeks after completion of the primary series

Summary - Feasibility and Implementation

- To date, >220 million doses of Pfizer-BioNTech Covid-19 vaccine have been administered in the U.S., demonstrating that the vaccine is feasible to implement
  - ~2.24 million individuals have received an additional dose

- Over 27 million adults ≥65 years of age completed their primary series ≥6 months ago
  - Over 50 million adults ≥18 years of age completed their primary series ≥6 months ago

- Pharmacies delivering majority of COVID-19 vaccines currently

- Recommendations that are **clear** and **simple** will facilitate implementation
Evidence to Recommendations Framework
Booster doses of COVID-19 vaccines

What is the cost associated with booster doses?
All COVID-19 vaccines, including booster doses, will be provided **free of charge** to the U.S. population. However, health systems or health departments could incur costs for vaccination program planning and implementation.

Fees for administration of COVID-19 vaccines recommended by ACIP are reimbursable by insurance or other federal programs.

Cost effectiveness analyses will be important in the future, when vaccine not purchased and distributed by the federal government.
Evidence to Recommendations Framework
Booster doses of COVID-19 vaccines

What are the equity considerations with booster doses?
Annual excess death incidence rates for persons aged 25-64 years by race/ethnicity – United States, 2020

- Al/AN: 221.1
- Black: 133.4
- NH/PI: 124.9
- Hispanic: 98.5
- White: 51.2
- Asian: 30.2

Excess death incidence rate per 100,000 person-years

Cumulative COVID-19 associated hospitalizations in the United States by race/ethnicity, March 7, 2020 – September 11, 2021

What percentage of people in each race or ethnic group received at least one dose of COVID-19 vaccine?

- AI/AN: 56.1%
- NH/PI: 46.2%
- Asian: 43.2%
- Hispanic/Latino: 41.8%
- White: 40.7%
- Black: 34.6%

Percentage of people who have received at least one dose of the COVID-19 vaccine by race/ethnicity over time

[Graph showing the percentage of people vaccinated by race/ethnicity from December 2020 to September 2021.]

Vaccine effectiveness by race and ethnicity

- Among VE platforms able to provide specific estimates for vaccine effectiveness by race or ethnicity, no differences noted

- VE against hospitalization among adults ≥50 years of age:
  - Overall: 89% (95% CI: 87-91%)
  - Black individuals: 86% (95% CI: 75-92%)
  - Hispanic individuals: 90% (95% CI: 85-93%)

- VE against hospitalization among VA centers:
  - Black individuals: 86% (95% CI: 77-93%)
  - White individuals: 88% (95% CI: 77-94%)

Summary - Equity

- COVID-19 disease and COVID-19 vaccination varies by socioeconomic and sociodemographic groups
  - However, vaccine effectiveness does not vary by race and ethnicity

- Equity gap in vaccines administered by race is closing
  - Disparities were more pronounced this spring (individuals who would be 6 months after 2\text{nd} dose)
Summary
Work Group Interpretation

- **Top priority** should be *continued vaccination* of unvaccinated individuals

- Jurisdictions have a variety of vaccination and disease control priorities
  - E.g. COVID-19 cases, delivery of primary COVID-19 vaccines series and influenza vaccines

- Balance of benefits and risks *varies by age*
  - Adults ≥65 years have the clearest benefit/risk
  - Benefit to other age groups incrementally smaller, given high effectiveness maintained from primary series

**Goals of booster program:**

- Prevention of *severe disease*

- Other considerations are important, such as maintaining workforce and healthcare capacity, prevention of transmission, individual benefit/risk balance
Clinical Considerations
## Evidence to Recommendations Framework

### Summary: Work Group Interpretations

<table>
<thead>
<tr>
<th>Type of recommendation</th>
<th>We do not recommend the intervention</th>
<th>We recommend the intervention for individuals based on assessment of <strong>benefits</strong> and <strong>risks</strong></th>
<th>We recommend the intervention</th>
</tr>
</thead>
</table>

- **Used when the risks clearly outweigh the benefits in a population**
- **Used when there is diversity of the benefits and risks in a population**
- **Used when the benefits clearly outweigh the risks in a population**

Can allow **flexibility** across a population
Policy Options

Policy question #1:
Should adults ≥65 years of age and LTCF residents receive a Pfizer-BioNTech COVID-19 vaccine booster dose?
Policy Options

Policy question #1:
Should adults $\geq 65$ years of age and LTCF residents receive a Pfizer-BioNTech COVID-19 vaccine booster dose?

Policy question #2:
Should adults 18–64 years of age at risk for severe COVID-19 due to underlying medical conditions or at risk of SARS-CoV-2 exposure due to occupation/setting receive a Pfizer-BioNTech COVID-19 vaccine booster dose?
# Policy Question #1

**Adults ≥65 years of age and LTCF residents**

<table>
<thead>
<tr>
<th>PROS</th>
<th>CONS</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Highest risk of severe disease</td>
<td>Age cut-off may not represent continuum of risk</td>
</tr>
<tr>
<td>• Largest impact in waning VE against severe disease</td>
<td></td>
</tr>
<tr>
<td>• Prioritized for early doses of COVID-19 vaccines (longer duration since primary series)</td>
<td></td>
</tr>
</tbody>
</table>
**Policy Question #2**

Adults 18–64 years of age at risk for severe COVID-19 due to **underlying medical conditions** or at risk of SARS-CoV-2 exposure due to **occupation/setting**

<table>
<thead>
<tr>
<th>Type of recommendation</th>
<th>PROS</th>
<th>CONS</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Standard recommendation</strong></td>
<td>• Simple</td>
<td>• Not strong evidence of increased risk of hospitalization or death in all individuals</td>
</tr>
<tr>
<td></td>
<td>• Reduces barriers for individuals who may have increased risk of disease</td>
<td>• Balance of benefits and risks likely varies</td>
</tr>
<tr>
<td></td>
<td>• Reduction in infection could reduce work absenteeism</td>
<td>• Large number of people initially eligible (&gt;50 million)</td>
</tr>
<tr>
<td><strong>Recommended for individuals based on assessment of benefits and risks</strong></td>
<td>• Reduces barriers for individuals who may have increased risk of disease</td>
<td>• Large number of people initially eligible (&gt;50 million)</td>
</tr>
<tr>
<td></td>
<td>• Reduction in infection could reduce work absenteeism</td>
<td>• More complicated to implement</td>
</tr>
<tr>
<td></td>
<td>• Reflects uncertainty in current balance of benefits and risks in this population</td>
<td></td>
</tr>
</tbody>
</table>
Acknowledgments

- Monica Godfrey
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- Ian Plumb
- Amy Blain
- Neela Goswami
- Mary Chamberland
- CDC/University of Iowa
- VTF ACIP WG Team
- ACIP COVID-19 Vaccines Work Group
- Vaccine Task Force
- Epi Task Force
- Respiratory Viruses Branch
For more information, contact CDC
1-800-CDC-INFO (232-4636)

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.