Updates to the Evidence to Recommendation Framework:
2nd COVID-19 booster dose in adults ages 50 years and older and immunocompromised individuals

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ACIP Meeting
April 20, 2022
Do the **balance** of **benefits** and **risks** warrant an update to COVID-19 vaccine policy, allowing adults ages ≥50 years and persons with moderate to severe immunocompromise ages ≥12 years to receive a second booster of an mRNA COVID-19 vaccine?
## Timeline of recommendations for COVID-19 vaccine booster doses

<table>
<thead>
<tr>
<th>Date</th>
<th>Events</th>
</tr>
</thead>
<tbody>
<tr>
<td>September 2021</td>
<td>Booster doses of Pfizer-BioNTech COVID-19 vaccine</td>
</tr>
<tr>
<td>October 2021</td>
<td>Booster doses of Moderna and Janssen COVID-19 vaccines (including heterologous boosting)</td>
</tr>
<tr>
<td>November 2021</td>
<td>Broadening recommendations for COVID-19 vaccine booster doses to all persons ages ≥18 years</td>
</tr>
<tr>
<td>December 2021</td>
<td>Booster doses of Pfizer-BioNTech COVID-19 vaccine for those ages 16–17 years</td>
</tr>
<tr>
<td>January 2022</td>
<td>Booster doses of Pfizer-BioNTech COVID-19 vaccine for those ages 12–15 years; Shorten interval between primary series and booster from 6 to 5 months</td>
</tr>
</tbody>
</table>

1. ACIP Meeting, September 23rd [https://www.cdc.gov/vaccines/acip/meetings/slides-2021-09-22-23.html](https://www.cdc.gov/vaccines/acip/meetings/slides-2021-09-22-23.html)
4. CDC’s Director’s Memo: [https://www.cdc.gov/media/releases/2021/s1208-16-17-booster.html](https://www.cdc.gov/media/releases/2021/s1208-16-17-booster.html)
5. CDC’s Director’s Memo: [https://www.cdc.gov/media/releases/2022/s0104-Pfizer-Booster.html](https://www.cdc.gov/media/releases/2022/s0104-Pfizer-Booster.html)
Recent updates to COVID-19 vaccine booster policy

- Following FDA’s regulatory action on March 29, 2022, CDC updated its COVID-19 vaccination guidance to give some individuals the option to receive a second booster dose using an mRNA COVID-19 vaccine. These individuals include:
  - People ages 50 years and older who received an initial COVID-19 booster dose (regardless of which vaccine was used) at least 4 months ago
  - People ages 12 years and older who are moderately or severely immunocompromised who received an initial COVID-19 booster dose (regardless of which vaccine was used) at least 4 months ago
  - People ages 18 years and older who received both a primary dose and a booster dose of J&J/Janssen COVID-19 vaccine at least 4 months ago
Summary of recommendations by primary series product and age

People who are **not** moderate to severely immunocompromised

- **Everyone** in the age group **SHOULD** receive the dose
- **Some people** in the age group **MAY** receive the dose

### Pfizer-BioNTech
- **(ages 5–11 years)**
  - Dose 1 (primary) → Dose 2 (primary) → Dose 3 (booster) → Dose 4 (2nd booster)
  - Timing: 3 weeks → At least 5 months → At least 4 months

### Pfizer-BioNTech
- **(ages 12 years and older)**
  - Dose 1 (primary) → Dose 2 (primary) → Dose 3 (booster) → Dose 4 (2nd booster)
  - Timing: 3-8 weeks → At least 5 months → At least 4 months

### Moderna
- **(ages 18 years and older)**
  - Dose 1 (primary) → Dose 2 (primary) → Dose 3 (booster)
  - Timing: 4-8 weeks → At least 5 months → At least 4 months

### Janssen (J&J)
- **(ages 18 years and older)**
  - Dose 1 (primary) → Dose 2 (booster) → Dose 3 (2nd booster)
  - Timing: At least 2 months → At least 4 months

#### Additional Notes
- People ages **50 years and older**
- People ages 18 years and older who received 2 Janssen doses
Timeline of recommendations for COVID-19 vaccine doses
Moderate to severely immunocompromised individuals

Additional doses of mRNA COVID-19 vaccines as a component of a 3-dose primary series

- Booster doses of Pfizer-BioNTech COVID-19 vaccine
- Booster doses of Moderna and Janssen COVID-19 vaccines
- Shorten interval to booster from 6 to 5 months
- Shorten interval to booster from 5 to 3 months

August 2021 | September 2021 | October 2021 | January 2022 | February 2022

1. ACIP Meeting, August 13th [https://www.cdc.gov/vaccines/acip/meetings/slides-2021-08-13.html](https://www.cdc.gov/vaccines/acip/meetings/slides-2021-08-13.html)
2. ACIP Meeting September 23rd [https://www.cdc.gov/vaccines/acip/meetings/slides-2021-09-22-23.html](https://www.cdc.gov/vaccines/acip/meetings/slides-2021-09-22-23.html)
4. CDC’s Director’s Memo: [https://www.cdc.gov/media/releases/2022/s0104-Pfizer-Booster.html](https://www.cdc.gov/media/releases/2022/s0104-Pfizer-Booster.html)
5. Interim Clinical Considerations: [https://www.cdc.gov/vaccines/covid-19/clinical-considerations/interim-considerations-us.html#recommendations](https://www.cdc.gov/vaccines/covid-19/clinical-considerations/interim-considerations-us.html#recommendations)
Summary of recommendations by primary series product and age

Persons who are moderate to severely immunocompromised

- **Everyone** in the age group **SHOULD** receive the dose
- **Some people** in the age group **MAY** receive the dose

**Pfizer-BioNTech** (ages 5–11 years)
- Dose 1 (primary): 3 weeks
- Dose 2 (primary): At least 4 weeks
- Dose 3 (primary): At least 3 months

**Pfizer-BioNTech** (ages 12 years and older)
- Dose 1 (primary): 3 weeks
- Dose 2 (primary): At least 4 weeks
- Dose 3 (primary): At least 3 months
- Dose 4 (booster): At least 4 months
- Dose 5 (2nd booster): At least 4 months

**Moderna** (ages 18 years and older)
- Dose 1 (primary): 4 weeks
- Dose 2 (primary): At least 4 weeks
- Dose 3 (primary): At least 3 months
- Dose 4 (booster): At least 4 months
- Dose 5 (2nd booster): At least 4 months

**Janssen (J&J)** (ages 18 years and older)
- Dose 1 (primary): 4 weeks
- Dose 2 (addl. dose): At least 2 months
- Dose 3 (booster): At least 4 months
- Dose 4 (2nd booster): At least 4 months
Evidence to Recommendations (EtR) Framework

- Public Health Problem
- Benefits and Harms
- Feasibility
- Equity
- Values and Acceptability
Evidence to Recommendations Framework
Booster doses of COVID-19 vaccines
Daily trends in number of COVID-19 cases, United States
January 23, 2020 – April 17, 2022

80,476,479 total cases

7-day average: 35,212 cases
Changing landscape of circulating variants


https://www.cdc.gov/mmwr/volumes/71/wr/mm7106a4.htm
Recent trends in weighted variant proportion estimates & Nowcast

http://covid.cdc.gov/covid-data-tracker/#variant-proportions
Accessed April 19, 2022
Daily trends in number of COVID-19 cases, United States
January 23, 2020 – April 17, 2022

Percentage of people with antibodies (anti-nucleocapsid) indicating resolving or past infection with SARS-CoV-2, United States
August 30, 2020 – January 29, 2022

Does not indicate:
- Antibodies from vaccination (anti-spike)
- Amount of antibodies or protection from reinfection

Data Source: CDC COVID Data Tracker: https://covid.cdc.gov/covid-data-tracker/#national-lab
Data Visualization: Dan Keating, Washington Post: https://www.washingtonpost.com/health/2022/02/28/covid-cases-nationwide/
Weekly trends in COVID-19-associated hospitalization rates by age group, United States, July 4, 2020 – April 9, 2022

Daily trends in number of COVID-19 deaths, United States
January 23, 2020 – April 17, 2022

COVID-19 vaccinations in the United States, As of April 18, 2022

218.9M
People fully vaccinated

70.1% Population
≥5 Years of Age

99.5M
People received a booster dose*

47.2% Population
≥12 Years of Age

*This includes people who received booster doses and people who received additional doses.
Percentage of people vaccinated with at least a primary series or booster dose by age group and date administered, United States

Primary Series

Booster Dose

- 29 jurisdictions that routinely link surveillance and immunization data*
  - 67% of total U.S. population
- Report COVID-19 cases and COVID-19 associated deaths by vaccination status
- Weekly rates and incidence rate ratios
  - Unvaccinated vs. fully vaccinated (overall, with or without a booster dose)

*AL, AR, AZ, CA, CO, CT, DC, FL, GA, ID, IN, KS, LA, MA, MI, MN, NC, NE, NM, NY, NY City, Philadelphia, RI, Seattle/King County, TN, TX, UT, WI, WV
Age-adjusted rates of COVID-19 cases & deaths by vaccination status and receipt of booster dose,*

**Cases**

- Unvaccinated
- Vaccinated with a primary series only
- Vaccinated with a primary series and booster dose*

**Deaths**

Unvaccinated people aged 12 years and older had:

- **3.1X** Risk of Testing Positive for COVID-19
- **2.0X** Risk of Testing Positive for COVID-19

AND

- **20X** Risk of Dying from COVID-19 in February, and
- **35X** in March, compared to people vaccinated with a primary series and a booster dose.

*This includes people who received booster doses and people who received additional doses.

** Data from September 19, 2021 – March 19, 2022 (24 U.S. jurisdictions)

+ Data from September 19, 2021 – February 26, 2022 (23 U.S. jurisdictions)

Age-adjusted rates of COVID-19 cases & deaths by vaccination status and receipt of booster dose among adults 50-64 years.*

*This includes people who received booster doses and people who received additional doses.

** Data from September 19, 2021 – March 19, 2022 (24 U.S. jurisdictions)
+ Data from September 19, 2021 – February 26, 2022 (23 U.S. jurisdictions)

Age-adjusted rates of COVID-19 cases & deaths by vaccination status and receipt of booster dose among adults ≥65 years.

*This includes people who received booster doses and people who received additional doses.

** Data from September 19, 2021 – March 19, 2022 (24 U.S. jurisdictions)
+ Data from September 19, 2021 – February 26, 2022 (23 U.S. jurisdictions)

COVID-19-associated hospitalization surveillance network (COVID-NET)

- **Population-based** surveillance for laboratory-confirmed COVID-19-associated hospitalizations
- Catchment area: >250 acute care hospitals in 99 counties in 14 states, representing 10% of U.S. population
- **Case definition**: Resident of the surveillance area and positive SARS-CoV-2 test within 14 days prior to or during hospitalization
- **Rates by vaccination status**
  - Linkage to immunization information systems
  - Representative sample of hospitalized cases (>37,000 to date)

*California, Colorado, Connecticut, Georgia, Maryland, Michigan, Minnesota, New Mexico, New York, Ohio, Oregon, Tennessee, and Utah are included in these analyses.*
COVID-19-associated hospitalizations among vaccinated adults ≥18 years with COVID-19 as primary reason for admission — COVID-NET
January 1, 2021–January 31, 2022

- Fully vaccinated persons with COVID-19-associated hospitalizations differ from unvaccinated persons with COVID-19-associated hospitalizations

- Fully vaccinated cases more likely to be:
  - Older
  - Long-term care facility resident
  - DNR/DNI/CMO code

- More underlying medical conditions in fully vaccinated cases

<table>
<thead>
<tr>
<th>Category</th>
<th>Unvaccinated weighted % N=8,013</th>
<th>Fully vaccinated weighted % N=1,768</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age group (median, IQR)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>18-49 years</td>
<td>31</td>
<td>11</td>
</tr>
<tr>
<td>50-64 years</td>
<td>33</td>
<td>16</td>
</tr>
<tr>
<td>≥65 years</td>
<td>37</td>
<td>72</td>
</tr>
<tr>
<td>LTCF residence</td>
<td>4</td>
<td>12</td>
</tr>
<tr>
<td>DNR/DNI/CMO</td>
<td>6</td>
<td>14</td>
</tr>
<tr>
<td>≥3 Underlying medical conditions</td>
<td>50</td>
<td>76</td>
</tr>
</tbody>
</table>

LTCF = long-term care facility; DNR = do not resuscitate; DNI = do not intubate; CMO=comfort measure only
Summary: mRNA VE during Omicron
Persons with moderate to severe immunocompromise

VISION platform

<table>
<thead>
<tr>
<th>Status</th>
<th>Immunocompromised</th>
<th>Immunocompetent</th>
</tr>
</thead>
<tbody>
<tr>
<td>3 doses</td>
<td></td>
<td></td>
</tr>
<tr>
<td>14-59 days</td>
<td>81 (75-85)</td>
<td>93 (91-94)</td>
</tr>
<tr>
<td>60-119 days</td>
<td>74 (68-78)</td>
<td>91 (90-92)</td>
</tr>
<tr>
<td>120-179 days</td>
<td>49 (37-58)</td>
<td>84 (81-87)</td>
</tr>
</tbody>
</table>

- More rapid waning for 3\(^{rd}\) dose with immunocompromised population
- Note that in immunocompromised population, 3\(^{rd}\) dose is considered part of primary series, and a booster (4\(^{th}\) dose) currently recommended

IVY platform

<table>
<thead>
<tr>
<th>Group</th>
<th>No. of vaccinated case-patients/total case-patients (%)</th>
<th>No. of vaccinated control-patients/total control-patients (%)</th>
<th>Adjusted* vaccine effectiveness % (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>3 doses overall</td>
<td>288/909 (32)</td>
<td>508/776 (65)</td>
<td>78 (73–83)</td>
</tr>
<tr>
<td>Immunocompromised</td>
<td>153/250 (61)</td>
<td>191/238 (80)</td>
<td>65 (44–78)</td>
</tr>
<tr>
<td>7–120 days</td>
<td>89/186 (48)</td>
<td>134/181 (74)</td>
<td>73 (55–84)</td>
</tr>
<tr>
<td>&gt;120 days</td>
<td>64/161 (40)</td>
<td>57/104 (55)</td>
<td>54 (16–75)</td>
</tr>
</tbody>
</table>
Summary: VE of 2 doses of mRNA vaccine increases with increasing severity of outcome during Omicron in adults ≥18 years; 3rd dose increases VE

- **Emergency department/urgent care**
  - Last dose <2m ago, VISION: 69 (62-75) vs 85 (84-86)
  - Last dose 4-<6m ago, VISION: 37 (34-40) vs 65 (60-69)

- **Hospitalization**
  - Last dose <2m ago, VISION: 71 (51-83) vs 84 (78-89)*
  - Last dose 4-<6m ago, VISION: 54 (48-59) vs 88 (81-92)*
  - 3rd dose 7-120 days ago, IVY: Not estimated vs 87 (80-92)*
  - 3rd dose >120 days ago, IVY: Not estimated vs 88 (69-95)*

- **Critical illness/death**
  - 2nd dose median 256 days/3rd dose median 60 days ago, IVY: 79 (66-87) vs 94 (88-97)

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*Among immunocompetent individuals ≥65 years of age.

**Booster receipt increases protection across all outcomes.**

Booster dose VE remains high among immunocompetent individuals 4-6 months after dose.
## Summary: mRNA VE during Omicron

**Persons with moderate to severe immunocompromise**

<table>
<thead>
<tr>
<th></th>
<th>Immunocompetent</th>
<th>Immunocompromised</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>2-dose VE against:</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Infection (+/- symptoms)</td>
<td>Limited protection, fast waning</td>
<td>Not estimated</td>
</tr>
<tr>
<td>ED/UC</td>
<td>Higher protection, some waning</td>
<td>Not estimated</td>
</tr>
<tr>
<td>Hospitalization</td>
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<td>Not estimated</td>
</tr>
<tr>
<td><strong>3-dose VE against:</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Infection (+/- symptoms)</td>
<td>Some protection, evidence of waning</td>
<td>Not estimated</td>
</tr>
<tr>
<td>ED/UC</td>
<td>Some protection, limited waning</td>
<td>Some protection, clear waning</td>
</tr>
<tr>
<td>Hospitalization</td>
<td>Highest protection, limited waning</td>
<td>Highest protection, clear waning</td>
</tr>
</tbody>
</table>

- **2-dose primary series + 1st booster**
- **3-dose primary series**
Summary
Public Health Problem

- Current 7-day average of COVID-19 cases ~4% of peak seen during Omicron surge
- COVID-19 related hospitalization admissions and deaths also continuing to decline from recent winter Omicron surge
- COVID-19 cases, hospitalizations, and deaths 2–20 times higher in unvaccinated individuals in recent months, compared to vaccinated individuals
- Vaccine effectiveness for 3 doses (primary series + booster) in immunocompetent older adults remains high, especially for more severe outcomes
Evidence to Recommendations Framework
Booster doses of COVID-19 vaccines
Efficacy of a fourth dose of COVID-19 mRNA vaccine against Omicron among healthcare workers – Israel

- Open-label non-randomized study among healthcare workers
- 4th doses administered 4 months after 3rd dose (Pfizer-BioNTech)
  - 154 received 4th dose of Pfizer-BioNTech
  - 120 received 4th dose of Moderna
  - Two age-matched controls selected for each participant
- After the fourth dose, both vaccines induced IgG antibodies to SARS-CoV-2 receptor-binding domain and increased neutralizing antibody titers to titers that were slightly higher than those achieved after the third dose
- Mild systemic and local reactogenicity reported by majority of recipients

Effectiveness of a fourth dose of COVID-19 mRNA vaccine against Omicron among healthcare workers – Israel

- Vaccine efficacy against infection of 4 vs. 3 doses
  - Pfizer-BioNTech: 30% (-9%, 55%); Moderna: 11% (-43%, 44%)

Effectiveness of a fourth dose of COVID-19 mRNA vaccine against Omicron among persons ages ≥60 years – Israel

- On January 2, 2022, began administering a 4th dose of Pfizer-BioNTech COVID-19 vaccine to people ages ≥60 years, who had received a 3rd dose of vaccine at least 4 months earlier
- Follow-up from January 10-March 2 for confirmed infection and February 18 for severe illness

<table>
<thead>
<tr>
<th></th>
<th>Cases (person-days at risk)</th>
<th>Rate Ratio (95% CI)</th>
<th>Adjusted rate difference per 100,000 person-days at risk (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>3rd dose only</td>
<td>Week 4 after 4th dose</td>
<td>3rd dose only vs week 4 after 4th dose</td>
</tr>
<tr>
<td>Confirmed infections</td>
<td>111,780 (31,000,299)</td>
<td>7,225 (3,883,824)</td>
<td>2.0 (1.9, 2.1)</td>
</tr>
<tr>
<td>Severe illness</td>
<td>1210 (24,857,976)</td>
<td>66 (3,639,393)</td>
<td>3.5 (2.7, 4.6)</td>
</tr>
</tbody>
</table>

4th dose estimated to prevent additional **3-4 cases** of severe disease per 100,000 person-days compared to 3 doses

Effectiveness of a fourth dose of COVID-19 mRNA vaccine against Omicron among persons ages ≥60 years – Israel

- Rapid waning of additional protection against infection

Effectiveness of a fourth dose of COVID-19 mRNA vaccine against Omicron among persons ages ≥60 in a large healthcare organization – Israel

• Included healthcare organization members ages ≥60 years, eligible to receive the fourth vaccine dose, with no previous PCR confirmed SARS-CoV-2 infection
• Matched to eligible persons who had not yet received a fourth dose according to a set of potential confounders
• 182,122 were recruited and matched to controls after receiving dose 4 and were followed for a median of 26 days (interquartile range: 7 to 30)

Effectiveness of a fourth dose of COVID-19 mRNA vaccine against Omicron among persons ages ≥60 in a large healthcare organization – Israel

**COVID-19-Related Hospitalization**

Day 14 to 30 Relative VE: 72% (95% CI: 63% – 79%)

**Death from COVID-19**

Day 14 to 30 Relative VE: 76% (95% CI: 48% – 91%)

Methods for assessment of benefits

Calculated per 1 million persons with a primary series vaccination, primary series and 1 booster dose, or primary series and 2 booster doses

- Age group: 50+ years
- VE against hospitalization estimates
  - Primary series VE estimate of 55%\(^1\)
  - Primary series and one booster dose VE estimate of 88%\(^1\)
  - Primary series and two booster doses VE estimate of 95\(^2\)
- Age-specific hospitalization rates: COVID-NET rates from the week ending on February 26\(^{th}\), 2022
- Time horizon: 120 days

VE: Vaccine Effectiveness
\(^1\) VE estimate from IVY and VISION: [https://covid.cdc.gov/covid-data-tracker/#vaccine-effectiveness](https://covid.cdc.gov/covid-data-tracker/#vaccine-effectiveness)
Weekly hospitalization rates by vaccination status among persons ages ≥50 years, COVID-NET

September 2021 – February 2022

Source: COVID-NET
Benefits after mRNA COVID-19 booster dose among persons ages ≥50 years

**Scenario:**
- 55% VE for primary series
- Boost to 88% VE for single booster
- Assumed boost to 95% VE for second booster

<table>
<thead>
<tr>
<th>Vaccine series</th>
<th>VE for hospitalization</th>
</tr>
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<tbody>
<tr>
<td>Primary series</td>
<td>55%</td>
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<tr>
<td>Primary series + one booster dose</td>
<td>88%</td>
</tr>
<tr>
<td>Primary series + two booster doses</td>
<td>95%</td>
</tr>
</tbody>
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COVID-19-Associated Hospitalizations Prevented per Million Series Completed

- Primary series: 3715
- First booster dose: 1483
- Second booster dose: 830

Benefits after mRNA COVID-19 booster dose among persons ages ≥50 years

**Scenario:**
- 55% VE for primary series
- Boost to 88% VE for single booster
- Assumed boost to 95% VE for second booster

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**For every million series completed**

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<tr>
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<td>Primary series + booster dose</td>
<td>88%</td>
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<tr>
<td>Primary series + second booster dose</td>
<td>95%</td>
</tr>
</tbody>
</table>

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**COVID-19-Associated Hospitalizations, ICU Admissions, Deaths**

Prevented per Million Series Completed

- **Primary series:**
  - VE: 55%
  - Hospitalizations: 401
  - ICU Admissions: 806
  - Deaths: 1483

- **First booster dose**
  - VE: 88%
  - Hospitalizations: 237
  - ICU Admissions: 122
  - Deaths: 183

- **Second booster dose**
  - VE: 95%
  - Hospitalizations: 183
  - ICU Admissions: 85
  - Deaths: 85

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To prevent one hospitalization:
Need to vaccinate **5 – 9 times** as many persons with booster doses compared to primary series.

Note: Number needed to vaccinate was calculated using the marginal benefit of each additional dose, therefore the number needed to vaccinate for each booster dose considers only the added benefit received from that booster dose.
Limitations

- The model assumes static hospitalization rate over 120 days
  - As rates increase, anticipated benefits also increase. Hospitalization rates among unvaccinated persons tend to have larger increases during times of increased transmission than those seen among vaccinated persons. Therefore, relative benefits of primary series compared to boosters will likely be larger during times of higher transmission.

- Model does not account for prior infection

- Unable to calculate benefits for persons with immunocompromise, however we anticipate that benefits would be greater and risks would be smaller in this population
Other considerations:
Myocarditis and pericarditis

- Risk of myocarditis/pericarditis identified after COVID-19 vaccine booster doses in individuals ages ≥12 years
  - Among those ages 12–39 years: mostly myocarditis and myopericarditis with onset <7 days after 1st booster; the risk is not as high as after the 2nd dose in primary series
  - Among those ages ≥40 years: mostly pericarditis, and the small elevated risk is more spread out in the 3 weeks after 1st booster

- Next steps:
  - Evaluate severity and clinical course for pericarditis cases in individuals ages ≥40 years

- Continue to review COVID-19 vaccine booster dose safety data with VaST
Other considerations:

Immune tolerance

- Concern that giving additional doses of COVID-19 vaccine would lead to lower antibody levels (failure to restore antibody levels to what was seen after a previous dose) or T-cell exhaustion

- Data do not suggest this is a concern with COVID-19 vaccines currently
  - Antibody levels (IgG binding antibodies) after a 4th dose in Israel returned to similar levels seen shortly after a 3rd dose

- **Timing** between doses likely an important factor as well
  - When attempting to induce immune tolerance (e.g. allergy shots), must have very frequent (weekly/monthly) exposure

- Continue to closely monitor
Concern that initial exposure to one virus strain primes B-cell memory and limits the development of memory B cells and neutralizing antibodies against new strains.

Data suggest a diverse response obtained after priming with current vaccines.

In animal study, majority of memory B-cell responses after a booster were cross-reactive to multiple variants (dark grey) after both ancestral vaccine and Omicron-specific vaccine.

After being primed with ancestral SARS-CoV-2 containing vaccine, boost with ancestral or Beta-variant vaccine elicited neutralizing antibody titers to variety of variants.

1. https://www.biorxiv.org/content/10.1101/2022.02.03.479037v1.full.pdf
Benefit and risk balance for COVID-19 vaccine booster doses

**Benefits**

- **Known**
  - Prevention of COVID-19 associated hospitalization, ICU and death

- **Possible**
  - Prevention of post-COVID conditions
  - Prevention of COVID-19 transmission

**Risks**

- **Known**
  - Rare vaccine-associated myo-pericarditis

- **Theoretical**
  - Immune tolerance
  - Imprinting
Summary

Benefits and Harms

- Data from Israel demonstrate increased immune response after fourth dose
  - Higher rates of infection and severe illness seen in 3-dose recipients compared to 4-dose recipients

- Greatest benefit from vaccination is achieved from receipt of primary series and first booster dose
  - Additional benefits may be achieved through receipt of a second booster dose

- Known and possible benefits outweigh risks (including theoretical risks)
  - Individual factors that influence magnitude of benefits for second booster
  - Monitor additional data to inform theoretical risks
Evidence to Recommendations Framework
Booster doses of COVID-19 vaccines
Survey on attitudes toward receiving a second booster shot among US adults, March 25 – 27, 2022 (N=2,028)

- I will in general receive a second booster shot if it becomes available to me (60%)
- I will only receive a second booster shot if a new variant arises or my area has a COVID surge in cases (22%)
- I have no plans to receive a second booster even if it becomes recommended (18%)

Additionally, 73% of Baby Boomers – those 57 years and older – plan to get a booster, if recommended, compared with 48% of Gen Z’ers, who are between 18 and 24 years old.

Among those polled, 54% of Black, non-Hispanic respondents and 43% of Hispanic individuals would get another booster, compared with 73% of Asian, non-Hispanic individuals and 65% of White, non-Hispanic respondents.
Attitudes and intentions for additional COVID-19 vaccine doses among “boosted” U.S. adults aged 50 years and older (N=1,412)

PURPOSES OF CONDUCTING THIS SURVEY

1) Assess vaccination intentions for a 2\textsuperscript{nd} COVID booster in the next 4 months among boosted, U.S. adults aged $\geq50$ years
2) Assess barriers towards receiving a 2nd booster
3) Assess vaccination intentions for receiving another COVID vaccine dose now and again in the Fall

CDC and University of Iowa/RAND survey, unpublished
SECOND COVID-19 VACCINE BOOSTER DOSE
82% of respondents “definitely” or “probably” will get a 2nd booster dose in the next 4 months

CDC and University of Iowa/RAND survey, unpublished
68% of respondents intending to get a 2nd booster reported they would get the currently available booster

Plan on getting the current booster
Waiting for a new booster that protects against variants
Unsure

CDC and University of Iowa/RAND survey, unpublished
19% of respondents intending to get a 2nd booster reported they would wait for a new booster that protects against variants.
Beliefs related to another dose of the currently available vaccines not providing additional protection were the top reasons given for not wanting a 2nd COVID-19 booster.

- Have enough protection from previous doses: 31.0%
- Waiting for new booster: 24.1%
- Booster not effective: 18.4%
- Worried about side effects: 15.7%
- Don’t know: 12.3%
- Other: 11.9%
- Have enough protection from COVID-19 infection: 9.6%
- Side effects after previous dose: 9.2%
- Booster not safe: 8.1%
- Fear of needles: 4.2%
- Can’t miss work if sick: 0.8%
- Refuse to answer: 0.4%
- No time to get booster: 0.0%

CDC and University of Iowa/RAND survey, unpublished
86% of respondents “definitely” or “probably” would get a 2nd booster dose if a new COVID vaccine that protects against variants became available.

CDC and University of Iowa/RAND survey, unpublished
COVID-19 BOOSTERS NOW + FALL
70% of respondents said they would get a COVID booster now and again in the Fall

CDC and University of Iowa/RAND survey, unpublished
10% of respondents said they would get a COVID booster either now or in the Fall

CDC and University of Iowa/RAND survey, unpublished
The emergence of new variants, preventing spread, and increased severity were top reasons given for getting boosted again now and in the Fall...

<table>
<thead>
<tr>
<th>Reason</th>
<th>% of Respondents Who Selected Response Option</th>
</tr>
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<tbody>
<tr>
<td>New variants</td>
<td>47.2%</td>
</tr>
<tr>
<td>Prevent me from spreading to others</td>
<td>40.8%</td>
</tr>
<tr>
<td>HCP recommendation</td>
<td>40.0%</td>
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<tr>
<td>Cases became more severe</td>
<td>39.9%</td>
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<tr>
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<tr>
<td>More information showing vaccine works</td>
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<td>Allow me to travel</td>
<td>28.8%</td>
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<tr>
<td>More COVID-19 vaccines get full FDA approval</td>
<td>27.6%</td>
</tr>
<tr>
<td>New type of vaccine available</td>
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<td>More information showing vaccine is safe</td>
<td>24.9%</td>
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<tr>
<td>It would allow me to do social activities</td>
<td>20.9%</td>
</tr>
<tr>
<td>Someone I knew became ill or died</td>
<td>14.9%</td>
</tr>
<tr>
<td>Community mandate</td>
<td>13.0%</td>
</tr>
<tr>
<td>Friend or family recommendation</td>
<td>9.4%</td>
</tr>
<tr>
<td>Mandate from work</td>
<td>8.9%</td>
</tr>
<tr>
<td>Community getting vaccinated</td>
<td>6.0%</td>
</tr>
<tr>
<td>None of these</td>
<td>5.2%</td>
</tr>
<tr>
<td>It would allow me to get to work</td>
<td>3.6%</td>
</tr>
<tr>
<td>Faith leader recommendation</td>
<td>3.1%</td>
</tr>
<tr>
<td>Other</td>
<td>2.6%</td>
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CDC and University of Iowa/RAND survey, unpublished
...so was a strong health care provider recommendation

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CDC and University of Iowa/RAND survey, unpublished
Summary
Values and Acceptability

- Majority of adults (60-80%) state they may get a second booster dose
  - Varies by age and race/ethnicity

- ~20% of boosted adults ages 50 and over would prefer a vaccine focused on new variants, and 10% state they would either get a vaccine now + fall, but not both

- Strong healthcare provider recommendation influential in decision to receive additional COVID-19 vaccine doses
Evidence to Recommendations Framework
Booster doses of COVID-19 vaccines
Weekly trends in completed COVID-19 primary series and booster doses among persons ages ≥50 years, United States

December 19, 2020 – April 24, 2022

Source: CDC IZ Data Lake. 3/28/2022
Eligible population for second COVID-19 vaccine booster doses

- Among people who are fully vaccinated, approximately 52% of people ages 50-64 years and 67% of people ages ≥65 years have received a COVID-19 vaccine booster dose.

- At the time of authorization, ~30 million people eligible (at least 4 months after their previous dose)
  - ~10 million eligible individuals ages 50-64 years
  - ~20 million eligible individuals ages ≥65 years

- Based on the timing of recommendations, people with immunocompromised conditions would not be eligible for second booster (5th total dose) until May 13th at the earliest.
Uptake of second COVID-19 vaccine booster doses

- The number of people reportedly getting vaccinated has nearly tripled since authorization of second booster doses, to an average of 447,000 per day in the week ending April 8\textsuperscript{th}, compared with 160,000 per day in the week ending March 29\textsuperscript{th}.\textsuperscript{1,2}

- As of April 19, 2022, approximately \textbf{1.1 million} second COVID-19 vaccine booster doses given in adults ages 50–64 years and \textbf{3.2 million} second booster doses given in adults ages ≥65 years since authorization

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3. Data Source: IZDL All Admin
Evidence to Recommendations Framework
Booster doses of COVID-19 vaccines
Booster vaccination trends by race or ethnicity among fully vaccinated people in the United States

August 13, 2021 – April 19, 2022

Percent Receiving Booster Dose

- AI/AN: 45.1%
- Asian: 68.5%
- Black: 44.4%
- Hispanic or Latino: 41.8%
- Multiracial: 72.3%
- NHOP: 47.0%
- White: 39.0%

### Population ages ≥65 years, by race and ethnicity

<table>
<thead>
<tr>
<th>Race or Ethnicity</th>
<th>Total Population</th>
<th>65 yrs and older</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hispanic or Latino</td>
<td>17.8%</td>
<td>8.0%</td>
</tr>
<tr>
<td>Not Hispanic or Latino</td>
<td>82.2%</td>
<td>92.0%</td>
</tr>
<tr>
<td>White</td>
<td>61.1%</td>
<td>77.3%</td>
</tr>
<tr>
<td>Black</td>
<td>12.3%</td>
<td>8.9%</td>
</tr>
<tr>
<td>AI/AN</td>
<td>0.7%</td>
<td>0.5%</td>
</tr>
<tr>
<td>Asian</td>
<td>5.4%</td>
<td>4.2%</td>
</tr>
<tr>
<td>NH/PI</td>
<td>0.2%</td>
<td>0.1%</td>
</tr>
<tr>
<td>Two or more races</td>
<td>2.4%</td>
<td>0.9%</td>
</tr>
</tbody>
</table>

Prevalence of selected underlying conditions that increase risk for severe COVID-19 disease, by race and ethnicity

Source: National Center for Health Statistics, National Health Interview Survey, 2018

Estimates were not available for Hawaiian/other Pacific Islanders or for chronic kidney disease among American Indian/Alaska Native.

Presented to ACIP September 22, 2020
COVID-19-associated hospitalizations among adults ages 50 years and older by race and ethnicity

Ages 50-64 Years

- **Primary series + booster**: 58% White
- **Primary series only**: Unvaccinated
- **Unvaccinated**: Primary series only + booster

Ages ≥65 Years

- **Primary series + booster**: 74% White
- **Primary series only**: Unvaccinated
- **Unvaccinated**: Primary series only + booster

Source: COVID-NET
Summary

Equity

- Racial and ethnic minority groups are under-represented in the population ages ≥65 years, both overall and among COVID-19-associated hospitalizations.
  - COVID-19-associated hospitalizations among adults ages 50-64 years are more consistent with underlying population.

- Underlying medical conditions more prevalent in racial and ethnic minority groups.

- A second booster recommendation for adults ages ≥50 years may prevent COVID-19 among persons from racial and ethnic minority groups and persons with underlying medical conditions.
Summary
Summary

- Top priority remains **vaccination** of **unvaccinated individuals**
  - **Benefits** of COVID-19 vaccine primary series **largest** across all sex and age groups
  - Additional benefits to receiving first COVID-19 booster dose

Current policy question focused on the population with COVID-19 vaccine primary series and booster, with lowest rates of severe disease currently

Work Group Interpretation

Goals of COVID-19 vaccines:

- Primary goal: Prevention of severe disease
- Secondary goals:
  - Maintaining workforce and healthcare capacity
  - Reduce infection rates and risk of transmission
  - Improved mental health with more social interactions
  - Prevention of post-COVID conditions
**Goals of COVID-19 vaccines:**

- **Primary goal:** Prevention of **severe disease**
- **Secondary goals:**
  - Maintaining workforce and healthcare capacity
  - Reduce infection rates and risk of transmission
  - Improved mental health with more social interactions
  - Prevention of post-COVID conditions

- COVID-19 vaccines continue to offer **high levels** of protection against severe disease—especially for individuals who have received a booster dose
- Vaccines are a critical aspect of protection against severe COVID-19; monoclonal antibodies and antivirals are also essential
- Continued research into vaccines that may also have prolonged protection against SARS-CoV-2 infection (e.g. mucosal vaccines) important
Work Group Interpretation
Adults ages 50 years and older

- The risk of COVID-19 increase with age; a 2\textsuperscript{nd} booster (4\textsuperscript{th} total dose) for older adults can help ensure those at risk are protected from severe disease
- Current VE data shows limited waning for immunocompetent adults after a 3\textsuperscript{rd} dose
- Lower COVID-19 case counts and hospitalization rates currently
- May have recommendations for additional COVID-19 vaccines in the future
- Work Group supported recommendation that adults ages 50 and over may receive a 2\textsuperscript{nd} COVID-19 vaccine booster dose
Work Group Interpretation

Immunocompromised individuals ages 12 years and older

- Earliest eligibility for this 2\textsuperscript{nd} booster (5\textsuperscript{th} dose) would be mid-May, based on timing of previous recommendations

- Currently available VE data from 3\textsuperscript{rd} dose in primary series; no VE data from the currently recommended 1\textsuperscript{st} booster (4\textsuperscript{th} dose)

- Lower COVID-19 case counts and hospitalization rates currently; however, immunocompromised individuals likely remain at higher risk for severe outcomes

- Important that immunocompromised individuals receive all doses of primary series (including additional doses) and 1\textsuperscript{st} booster dose

- Work Group supported recommendation that immunocompromised individuals ages 12 and over may receive a 2\textsuperscript{nd} COVID-19 vaccine booster dose
Recommendations that individuals may receive a COVID-19 vaccine 2nd booster reflect current conditions in the pandemic:

- Wide availability of COVID-19 vaccines
- High protection against severe disease from primary series and first booster dose
- Low rates of COVID-19 cases and hospitalizations
- Use of antivirals and monoclonal antibodies for SARS-CoV-2

As the 2nd booster is already authorized and available, can rapidly adjust recommendations if COVID-19 epi changes in the future

Current recommendation allows for flexibility, giving patients and providers access to this vaccine dose and the ability to decide based on individual factors and timing
Work Group Interpretation

- BREAK FOR CLINICAL CONSIDERATIONS PRESENTATION
Summary

- Additional booster doses of COVID-19 vaccines likely be needed in the future
- Important to optimize vaccine recommendations based on current conditions, while maintaining flexibility to update recommendations as needed if epidemiology changes
What are the factors that would influence the benefit/risk discussion for patients and providers regarding second booster doses of COVID-19 vaccines?
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- Valerie Morelli
- JoEllen Wolicki
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- Ruth Link-Gelles
- Heather Scobie
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- ACIP COVID-19 Vaccines Work Group
- Vaccine Task Force
- Epi Task Force
- Data Analytics and Visualization Task Force
- Respiratory Viruses Branch