Benefit and risk assessment for COVID-19 vaccines

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Benefit-risk assessment

- Benefits of COVID-19 vaccine by age for **primary series**
- Incremental benefits of COVID-19 vaccine by age and time since last dose for **bivalent booster dose**
  - Sensitivity analyses model high and low points in the pandemic
- Benefit-risk assessment for bivalent booster dose
  - Focused on ages 12-17 years and 18-49 years
Methods for benefit assessment

Benefits – Calculated per 1 million primary series or bivalent booster doses

- **Hospitalization rates**: December 2022 COVID-19-associated hospitalization rate among persons aged 5–11, 12–17, 18–49, 50–65, 65+ years, by vaccination status, from COVID-NET
  - Sensitivity analyses model high and low points in the pandemic
- **Time horizon**: 6 months
- **Vaccine Effectiveness**: VE estimates from VISION with assumption of waning of effectiveness by 10% each month starting after month 2
  - VE of primary series based on absolute VE for bivalent dose
  - VE of bivalent booster dose based on relative VE by interval from last monovalent dose to bivalent

2. Period over which benefits of bivalent vaccination accrue
3. https://www.cdc.gov/mmwr/volumes/71/wr/mm715152e1.htm?s_cid=mm715152e1_w
4. Absolute VE of bivalent booster dose (57%) used as the estimated primary series VE. Absolute VE from the bivalent booster was used as an estimate of primary series VE because current VE of monovalent primary series is unknown.
5. Relative VE of bivalent booster dose used in booster dose assessment (5-7 month interval: 38%; 8-10 month interval: 42%; 11+ month interval 45%). Relative VE for ED/UC visit was used for 2-4 month interval (31%) because VE against hospitalization was not available
Monthly age-adjusted rates of COVID-19-associated hospitalization by vaccination status in patients ≥ 18 years, COVID-NET

December 2022 hospitalization rates per 100,000 vaccinated persons with no bivalent booster by age group, COVID-NET

<table>
<thead>
<tr>
<th>Age group</th>
<th>Rate per 100,000 persons</th>
</tr>
</thead>
<tbody>
<tr>
<td>5-11 Years</td>
<td>2.13</td>
</tr>
<tr>
<td>12-17 Years</td>
<td>2.66</td>
</tr>
<tr>
<td>18-49 Years</td>
<td>12.89</td>
</tr>
<tr>
<td>50-64 Years</td>
<td>27.48</td>
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<tr>
<td>≥ 65 Years</td>
<td>121.10</td>
</tr>
</tbody>
</table>

https://covid.cdc.gov/covid-data-tracker/#covidnet-hospitalizations-vaccination
Estimated COVID-19-associated hospitalizations prevented over 6 months for every million mRNA COVID-19 primary series given

![Bar chart showing COVID-19-associated hospitalizations prevented over 6 months per million doses by age group based on hospitalization rates from December 2022.]

- 5 – 11 years: 248
- 12 – 17 years: 944
- 18 – 49 years: 2465
- 50 – 64 years: 5033
- ≥ 65 years: 15978
Estimated COVID-19 hospitalizations prevented over 6 months for every million mRNA COVID-19 primary series and bivalent booster doses\(^1\)

<table>
<thead>
<tr>
<th>Age Group</th>
<th>Hospitalizations Prevented</th>
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</thead>
<tbody>
<tr>
<td>12 – 17 years</td>
<td>53 944</td>
</tr>
<tr>
<td>18 – 49 years</td>
<td>257 2465</td>
</tr>
<tr>
<td>50 – 64 years</td>
<td>549 5033</td>
</tr>
<tr>
<td>≥ 65 years</td>
<td>2419 15978</td>
</tr>
</tbody>
</table>

Based on hospitalization rates from December 2022

1. Calculated assuming booster dose given ≥11 months from last monovalent vaccine dose
Estimated COVID-19 hospitalizations prevented over 6 months for every million **bivalent mRNA COVID-19 booster doses**, by age group and dose interval

<table>
<thead>
<tr>
<th>Age Group</th>
<th>2 – 4 month interval</th>
<th>5 – 7 month interval</th>
<th>8 – 10 month interval</th>
<th>≥11 month interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>12 – 17 years</td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>18 – 49 years</td>
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<tr>
<td>50 – 64 years</td>
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</tr>
<tr>
<td>≥ 65 years</td>
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</tbody>
</table>

Based on hospitalization rates from December 2022

1 Interval refers to the time between the most recent monovalent dose and a bivalent dose.
Monthly age-adjusted rates of COVID-19-associated hospitalization by vaccination status in patients 12 – 17 years, COVID-NET

https://covid.cdc.gov/covid-data-tracker/#covidnet-hospitalizations-vaccination
Estimated COVID-19 hospitalizations prevented over 6 months for every million bivalent mRNA COVID-19 booster doses, 12 – 17-year-olds

COVID-19-associated hospitalizations prevented over 6 months per million doses by low, recent, and high incidence¹

2-5 month interval²

5-7 month interval²

8-10 month interval²

11+ month interval²

¹Low incidence scenario uses hospitalization rate from March 2022, recent incidence scenario uses hospitalization rate from December 2022, and high incidence scenario uses hospitalization rate from July 2022

²Interval refers to the time between the most recent monovalent dose and a bivalent dose.
Dosing intervals for monovalent booster and bivalent booster, by age group

- Among adolescents who received a monovalent booster, nearly **half** received the monovalent booster at an interval <8 months after their primary series.
- Over **90%** of adolescents received a bivalent booster ≥8 months after their previous dose.

**Interval between completion of the primary series and monovalent booster**

- 12-17 year olds:
  - 2-4 month interval: 0%
  - 5-7 month interval: 0%
  - 8-10 month interval: 0%
  - 11+ month interval: 100%

- 18-49 year olds:
  - 2-4 month interval: 0%
  - 5-7 month interval: 0%
  - 8-10 month interval: 40%
  - 11+ month interval: 60%

**Interval between completion of the most recent monovalent dose* and bivalent booster**

- 12-17 year olds:
  - 2-4 month interval: 0%
  - 5-7 month interval: 0%
  - 8-10 month interval: 0%
  - 11+ month interval: 100%

- 18-49 year olds:
  - 2-4 month interval: 0%
  - 5-7 month interval: 0%
  - 8-10 month interval: 40%
  - 11+ month interval: 60%

* Primary series or monovalent booster
Myocarditis and COVID-19 vaccines

- Limited data to inform myocarditis risk after bivalent COVID-19 vaccine booster dose
  - Preliminary VSD myocarditis rates following bivalent booster dose in adolescent and young adult males lower than first monovalent boosters, but limited by small numbers of doses administered

- Myocarditis risk lower with longer time between doses
  - Rates of myocarditis lower with extended interval between dose 1 and dose 2 for primary series
  - Longer interval between doses for bivalent boosters, compared to monovalent boosters, may also impact myocarditis rates

- Most individuals with myocarditis/pericarditis have fully recovered at follow-up

- The risk of adverse cardiac outcomes were 1.8 – 5.6 times higher after SARS-CoV-2 infection than after mRNA COVID-19 vaccination among males ages 12-17 years

3 https://www.cdc.gov/mmwr/volumes/71/wr/mm7114e1.htm?s_cid=mm7114e1_w
VSD incidence rates of verified myocarditis or pericarditis in the 0-7 days after Pfizer-BioNTech vaccination in people 12 – 39 years

<table>
<thead>
<tr>
<th>Age &amp; Sex</th>
<th>Cases</th>
<th>Dose 2 Total</th>
<th>Incidence rate/ million doses (95% CI)</th>
<th>Cases</th>
<th>1st Booster Total</th>
<th>Incidence rate/ million doses (95% CI)</th>
<th>Cases</th>
<th>Bivalent Booster Total</th>
<th>Incidence rate/ million doses (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>12-17 Years</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Males</td>
<td>45</td>
<td>308,046</td>
<td>146.1 (106.6 – 195.5) 19.3 (7.1 – 42.0)</td>
<td>14</td>
<td>129,487</td>
<td>108.1 (59.1 – 181.4) 14.4 (1.7 – 51.9)</td>
<td>0</td>
<td>48,066</td>
<td>0.0 (0.0 – 62.3)</td>
</tr>
<tr>
<td>Females</td>
<td>6</td>
<td>311,247</td>
<td></td>
<td>2</td>
<td>139,118</td>
<td></td>
<td>0</td>
<td>49,725</td>
<td>0.0 (0.0 – 60.2)</td>
</tr>
<tr>
<td>18-29 Years</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Males</td>
<td>27</td>
<td>331,889</td>
<td>81.4 (53.6 – 118.4) 5.0 (0.6 – 18.0)</td>
<td>7</td>
<td>166,973</td>
<td>41.9 (16.9 – 86.4) 4.2 (0.1 – 23.2)</td>
<td>1</td>
<td>50,687</td>
<td>19.7 (0.5 – 53.1)</td>
</tr>
<tr>
<td>Females</td>
<td>2</td>
<td>400,321</td>
<td></td>
<td>1</td>
<td>240,226</td>
<td></td>
<td>0</td>
<td>80,211</td>
<td>0.0 (0.0 – 37.3)</td>
</tr>
<tr>
<td>30-39 Years</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Males</td>
<td>5</td>
<td>341,527</td>
<td>14.6 (4.8 – 34.2) 7.3 (1.5 – 21.3)</td>
<td>3</td>
<td>197,554</td>
<td>15.2 (3.1 – 44.4) 3.7 (0.1 – 20.8)</td>
<td>0</td>
<td>82,191</td>
<td>0.0 (0.0 – 36.4)</td>
</tr>
<tr>
<td>Females</td>
<td>3</td>
<td>410,713</td>
<td></td>
<td>1</td>
<td>268,412</td>
<td></td>
<td>0</td>
<td>115,014</td>
<td>0.0 (0.0 – 26.0)</td>
</tr>
</tbody>
</table>

### VSD incidence rates of verified myocarditis or pericarditis in the 0–7 days after Moderna vaccination in people ages 18–39 years

<table>
<thead>
<tr>
<th>Age/sex</th>
<th>Dose 2 primary series Moderna</th>
<th>1st monovalent booster dose Moderna</th>
<th>Bivalent booster dose Moderna</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Cases</td>
<td>Dose 2 total</td>
<td>Incidence rate/ million doses (95% CI)</td>
</tr>
<tr>
<td>18–29 years</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Males</td>
<td>19</td>
<td>195,809</td>
<td>97.0 (58.4 – 151.5) 0.0 (0.0 – 12.3)</td>
</tr>
<tr>
<td>Females</td>
<td>0</td>
<td>243,560</td>
<td></td>
</tr>
<tr>
<td>30–39 years</td>
<td>8</td>
<td>216,583</td>
<td>36.9 (15.9 – 72.8) 3.9 (0.1 – 21.4)</td>
</tr>
<tr>
<td>Males</td>
<td></td>
<td>259,780</td>
<td></td>
</tr>
<tr>
<td>Females</td>
<td>1</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Estimated COVID-19 hospitalizations prevented vs. potential myocarditis cases for every million bivalent mRNA COVID-19 booster doses: 12 – 17-year-olds

Per million doses in 12 – 17-year-olds over 6 months¹

- 31 – 136 hospitalizations prevented
- 9 – 40 ICU admissions prevented
- 0 – 1 death prevented

0 myocarditis² cases in 48,066 males with a bivalent booster
0 myocarditis² cases in 49,725 females with a bivalent booster

¹Ranges presented for benefits are based on the high and low incidence scenarios presented on slides 7 and 8
²Based on preliminary Pfizer-BioNTech bivalent booster safety data from VSD (incident rate/million doses): 0 (95% CI: 0-62) in males and 0 (95% CI: 0-60) in females
Estimated COVID-19 hospitalizations prevented vs. potential myocarditis cases for every million bivalent mRNA COVID-19 booster doses: 12 – 17-year-olds
Accounting for potential incidental SARS-CoV-2 infections among hospitalized patients

Per million doses in 12 – 17-year-olds over 6 months

- \(17 – 75\) hospitalizations prevented
- \(5 – 22\) ICU admissions prevented
- \(0 – 1\) death prevented

0 myocarditis cases in 48,066 males with a bivalent booster
0 myocarditis cases in 49,725 females with a bivalent booster

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1 Results were adjusted to account for potential incidental findings of SARS-CoV-2 infection by multiplying the estimated hospitalizations, ICU admissions, and deaths prevented by the estimated percent of COVID-NET hospitalizations that are likely due to COVID-19 among 12 – 17-year-olds during Omicron BA.5 predominant period (55%)  
2 Ranges presented for benefits are based on the high and low incidence scenarios presented on slides 7 and 8  
3 Based on preliminary Pfizer-BioNTech bivalent booster safety data from VSD (incident rate/million doses): 0 (95% CI: 0-62) in males and 0 (95% CI: 0-60) in females
Estimated COVID-19 hospitalizations prevented vs. potential myocarditis cases for every million bivalent mRNA COVID-19 booster doses: 18 – 49-year-olds

Per million doses in 18 – 49-year-olds over 6 months\(^1\)

- 117 – 376 hospitalizations prevented
- 21 – 69 ICU admissions prevented
- 4 – 11 deaths prevented

1 myocarditis\(^2\) case in 186,695 males with a bivalent booster
0 myocarditis\(^2\) cases in 272,406 females with a bivalent booster

\(^1\)Ranges presented for benefits are based on the high and low incidence scenarios presented on slide 7

\(^2\)Based on preliminary bivalent booster safety data from VSD among persons ages 18-39 years. Among Pfizer-BioNTech recipients, rates per million doses were: 20 (95% CI: 1–53) in males ages 18–29 years; 0 (95% CI: 0–37) in females ages 18–29 years; 0 (95% CI: 0–36) in males ages 30–39 years and 0 (95% CI: 0–26) in females ages 30–39 years. Among Moderna recipients, rates per million doses were: 0 (95% CI: 0–162) in males ages 18–29 years; 0 (95% CI: 0–101) in females ages 18–29 years; 0 (95% CI: 0–101) in females ages 18–29 years; 0 (95% CI: 0–85) in males ages 30–39 years and 0 (95% CI: 0–63) in females ages 30–39 years.
Estimated COVID-19 hospitalizations prevented vs. potential myocarditis cases for every million bivalent mRNA COVID-19 booster doses: 18 – 49-year-olds
Accounting for potential incidental SARS-CoV-2 infections among hospitalized patients

Per million doses in 18 – 49-year-olds over 6 months

- 81 – 259 hospitalizations prevented
- 15 – 48 ICU admissions prevented
- 3 – 8 deaths prevented

1 myocarditis case in 186,695 males with a bivalent booster
0 myocarditis cases in 272,406 females with a bivalent booster

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1 Results were adjusted to account for potential incidental findings of SARS-CoV-2 infection by multiplying the estimated hospitalizations, ICU admissions, and deaths prevented by the estimated percent of COVID-NET hospitalizations that are likely due to COVID-19 among 18 – 49-year-olds during on Omicron BA.5 predominant period (69%)

2 Ranges presented for benefits are based on the high and low incidence scenarios presented on slides 7 and 8

3 Based on preliminary bivalent booster safety data from VSD among persons ages 18–39 years. Among Pfizer-BioNTech recipients, rates per million doses were: 20 (95% CI: 1–53) in males ages 18–29 years; 0 (95% CI: 0–37) in females ages 18–29 years; 0 (95% CI: 0–36) in males ages 30–39 years and 0 (95% CI: 0–26) in females ages 30–39 years. Among Moderna recipients, rates per million doses were: 0 (95% CI: 0–162) in males ages 18–29 years; 0 (95% CI: 0–101) in females ages 18–29 years; 0 (95% CI: 0–85) in males ages 30–39 years and 0 (95% CI: 0–63) in females ages 30–39 years.
Limitations

- Benefits of vaccination may continue to accrue beyond time horizon used
- Stable hospitalization rates were assumed for the duration of the time horizon
- Underlying complexity of vaccine histories and previous infections could not be accounted for
- COVID-NET hospitalization rates include hospitalizations for which COVID-19 was not a primary reason for admission
- Current COVID-19 epidemiology, including hospitalization rates used in assessment, reflects impact of both prior vaccination and prior infection
  - Cannot account for possible future increases in COVID-19 hospitalization rates or new variant
- Myocarditis rates following bivalent booster dose are uncertain. Studies are underway to assess the long-term impact of vaccine-associated myocarditis
Summary of benefit-risk balance for bivalent mRNA COVID-19 vaccination

- **Benefits** continue to **outweigh risks** for primary series vaccination in all age groups
- Benefits of bivalent booster dose vary by **age, time since last dose**, and COVID-19 **incidence**
- Risk of myocarditis after COVID-19 vaccines likely **reduced** by **longer interval** since last dose
  - Additional data can better define risk after bivalent vaccines, but current data encouraging
- Changes in COVID-19 hospitalization rates would impact the benefit assessment
- Additional **benefits** of COVID-19 vaccines unable to be quantified in benefit-risk assessment
  - Likely prevention of post-COVID conditions, possible reduction in transmission, increased confidence in social interactions
- Benefit risk assessment will continue to be monitored as new data are available
- **Receipt of primary series** continues to be important in all ages
- **Boosters** remain an **important option** to improve protection against severe COVID-19, especially for **higher-risk populations**
Acknowledgements

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