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2023-2024 COVID-19 Vaccine Formula: Pfizer/BioNTech
Clinical and Preclinical Supportive Data

Vaccines and Related Biological Products Advisory Committee

June 15, 2023
Kena A. Swanson, Ph.D.
Vice President, Viral Vaccines
Vaccine Research and Development, Pfizer Inc.

Epidemiology & Real-World Evidence

Omicron-Adapted Vaccine Booster Dose Humoral and Cell-Mediated Immune Responses

Preclinical Evaluation Against Contemporary Variant Vaccines

Supply of 2023-2024 Formula
The Current COVID-19 Epidemiologic Landscape in the US is Dominated by XBB.1.5 and Related Sublineages

Weekly Proportions from 1-Apr to 20-May

Circulating XBB Sublineages are Similar

- **XBB.1.9.1 and XBB.1.9.2**: same spike amino acid sequence as XBB.1.5
- **XBB.1.16**: differs from XBB.1.5 at two spike amino acid residues
- **XBB.2.3**: differs from XBB.1.5 at three spike amino acid residues

GISAID, data accessed as of June 4, 2023

XBB.1.5, XBB.1.16, XBB.2.3, XBB.1.9.1, XBB.1.9.2 sublineage categories include descendants that have no amino acid differences in spike protein from parental sublineage.

a. Others include: XBB.1.16.1, EU.1.1.1, FL.4, FD.2, XBB.1.5.1 (sublineages that exceed a threshold of 1.8% in any week).
### Rationale for Fall Vaccine Update

- **XBB sublineages dominant globally and antigenically distant from prior Omicron strains**\(^1,2\)
- **Current bivalent vaccines maintain effectiveness**\(^3-11\) but show signs of waning, including against severe COVID-19\(^3,9-11\)
- Immunity likely further reduced by fall
- **Better-matched vaccines improve protection**\(^3\)

#### Absolute VE Against Hospitalization, CDC\(^{11}\)
**Immunocompetent Adults, VISION Network, Sep 2022 – Apr 2023**

<table>
<thead>
<tr>
<th>Time Since mRNA Vaccination</th>
<th>Adjusted VE (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age 18–64y</strong></td>
<td></td>
</tr>
<tr>
<td>Monovalent only, ≥7 days*</td>
<td>17 (7–26)</td>
</tr>
<tr>
<td>Bivalent booster, 7–59 days</td>
<td>61 (44–72)</td>
</tr>
<tr>
<td>Bivalent booster, 60–119 days</td>
<td>25 (1–43)</td>
</tr>
<tr>
<td>Bivalent booster, 120–179 days</td>
<td>16 (-24–43)†</td>
</tr>
</tbody>
</table>

- Median (IQR) time since last dose: 403 (306-534) days
- These estimates are imprecise and should be interpreted with caution.

<table>
<thead>
<tr>
<th>Time Since mRNA Vaccination</th>
<th>Adjusted VE (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age ≥65y</strong></td>
<td></td>
</tr>
<tr>
<td>Monovalent only, ≥7 days*</td>
<td>24 (18–29)</td>
</tr>
<tr>
<td>Bivalent booster, 7–59 days</td>
<td>64 (58–68)</td>
</tr>
<tr>
<td>Bivalent booster, 60–119 days</td>
<td>51 (45–57)</td>
</tr>
<tr>
<td>Bivalent booster, 120–179 days</td>
<td>27 (15–37)</td>
</tr>
</tbody>
</table>

- Median (IQR) time since last dose: 362 (245-484) days

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2. covSPECTRUM dashboard. Available at: https://cov-spectrum.org/explore/World/AllSamples/Past6M
5. Surie et al. MMWR Morb Mortal Wkly Rep 2022;71:1625–1630. DOI: 10.15585/mmwr.mm715152e2
6. Tenforde et al. MMWR Morb Mortal Wkly Rep 2023;71:1637–1646. DOI: 10.15585/mmwr.mm7153a1
10. Link-Gelles R. CDC. Data presented at the ACIP meeting (April 19, 2023). Available at: ACIP meeting (CDC.gov)
SARS-CoV-2 Activity is Expected to Increase this Autumn/Winter

- Disease activity has peaked between November and April\(^1\)
  - Similar to patterns seen for influenza, RSV, and other coronaviruses\(^2\)

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Heatmap of Monthly Median COVID-19-Related Hospitalizations Per Million Population, Northern Hemisphere, Mar 2020 – Dec 2022\(^1\)

Weekly Seasonality of Confirmed Viral Infections, England and Wales, 1989 – 2019\(^2\)

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CC-5
Omicron-Adapted Vaccine Booster Dose Humoral and Cell-mediated Immune Responses
Immunogenicity Data From Omicron BA.1 and BA.4/5-adapted Vaccine Clinical Studies Support Real World Evidence Observations

- **Omicron-adapted boosters:**
  - Result in superior variant neutralization titers (NTs) compared to the original vaccine
  - Recall spike-specific memory B cells that recognize shared epitopes; Omicron-specific B cells are also induced
  - Expand spike-specific CD4 and CD8 T cell responses
<table>
<thead>
<tr>
<th>Modified Vaccine</th>
<th>Age Group</th>
<th>Vaccine Regimen</th>
<th>Clinical Data</th>
<th>Preclinical Data</th>
</tr>
</thead>
<tbody>
<tr>
<td>Beta</td>
<td>18 to 55 years</td>
<td>![Injection]</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>monovalent</td>
<td></td>
<td>![Injection]</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Omicron BA.1</td>
<td>18 to 55 years</td>
<td>![Injection]</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>monovalent</td>
<td></td>
<td>![Injection]</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Omicron BA.1</td>
<td>18 to 55 years</td>
<td>![Injection]</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>bivalent</td>
<td>&gt;55 years</td>
<td>![Injection]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Omicron BA.4/5</td>
<td>6 months to 11 years</td>
<td>![Injection]</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>bivalent</td>
<td>12 to 55 years</td>
<td>![Injection]</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>&gt;55 years</td>
<td>![Injection]</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Original Vaccine ![Injection]  
Variant Vaccine ![Injection]  

Clinical and Preclinical Experience with Variant-modified Vaccines – Supported Bivalent BA.4/5 Vaccine Authorization
Bivalent BA.4/5 Boosts Neutralization Activity Against XBB.1.5 and XBB.1.16

Participants >55 years With or Without Prior SARS-CoV-2 Infection at Baseline

<table>
<thead>
<tr>
<th></th>
<th>BA.4/5</th>
<th>XBB.1.5</th>
<th></th>
<th>BA.4/5</th>
<th>XBB.1.16</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>11.5</td>
<td>2.3</td>
<td>11.3</td>
<td>2.2</td>
<td>5.0</td>
</tr>
<tr>
<td></td>
<td>6.1</td>
<td>1.5</td>
<td>1.5</td>
<td></td>
<td>1.5</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Pre</th>
<th>Post</th>
<th>Pre</th>
<th>Post</th>
<th>Pre</th>
<th>Post</th>
</tr>
</thead>
<tbody>
<tr>
<td>n=36</td>
<td></td>
<td>n=40</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FFRNT50</td>
<td></td>
<td>FFRNT50</td>
<td></td>
<td>FFRNT50</td>
<td></td>
</tr>
<tr>
<td>106</td>
<td></td>
<td>1197</td>
<td></td>
<td>93</td>
<td></td>
</tr>
<tr>
<td>18</td>
<td></td>
<td>111</td>
<td></td>
<td>28</td>
<td></td>
</tr>
<tr>
<td>33</td>
<td></td>
<td>48</td>
<td></td>
<td>42</td>
<td></td>
</tr>
</tbody>
</table>

Pre = Pre-dose 4; Post = 1-month post dose 4; FFRNT50 = 50% fluorescent focus reduction neutralization titers; GMFR = geometric mean fold rises; GMT = geometric means of neutralization titers

The whiskers indicate 95% CI.

Omicron XBB.1.16 and concurrent Omicron BA.4/5 analyses shown on the right of this slide run after Omicron XBB.1.5 and concurrent Omicron BA.4/5 analyses on the left.
Spike-Specific Memory B cell ($B_{\text{mem}}$) Assessment After Bivalent Omicron BA.1 Booster Vaccination

Assessment of Spike-specific Memory B cells

Wild-type strain and Omicron BA.1 Spike protein are used to measure memory B cells recognizing wild-type or Omicron BA.1 exclusive and wild-type/Omicron BA.1 shared epitopes.

Memory B cells ($B_{\text{mem}}$) defined as CD3−CD19+CD20+IgD−CD38int/low.

- **BNT162b2** (3 prior doses)
  - 5-12 months

- **Bivalent BA.1**
  - 1-dose booster

- **WT+Omicron BA.1**
  - >55 years of age

**Wild-Type-Specific Stain**

**BA.1-Specific Stain**

- Fluorochrome-labeled BA.1-Spike tetramer
- Fluorochrome-labeled Wild-type-Spike tetramer
Bivalent Omicron BA.1 Booster Increases the Frequencies of Memory B Cells Recognizing Shared and BA.1-Specific Epitopes

Omicron BA.1 Booster in BNT162b2-experienced Individuals >55 years of Age

Similar trends were observed with a monovalent Omicron BA.1 booster

N=13; Memory B cells (Bmem) defined as CD3−CD19+CD20+IgD−CD38int/low.
Clinical Study Evaluated CD4 and CD8 T Cell Responses Elicited by Bivalent Omicron BA.4/5-Adapted Booster

Spike peptide pools included those:
- Covering both WT and BA.4/5
- Unique to BA.4/5
Bivalent WT+BA.4/5 Vaccine Boosts CD4 and CD8 T cell Responses

**Omicron BA.4/5 Booster in BNT162b2-experienced Individuals 18-55 Years of Age**

**CD4 T cells**

<table>
<thead>
<tr>
<th>Spike Pool</th>
<th>WT/BA.4/5</th>
<th>BA.4/5 Unique</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>D0</td>
<td>D7</td>
</tr>
<tr>
<td>GMFR (n=20)</td>
<td>1.8</td>
<td>1.3</td>
</tr>
<tr>
<td>Pos (n=14)</td>
<td>1.8</td>
<td>1.1</td>
</tr>
<tr>
<td>Neg (n=6)</td>
<td>1.9</td>
<td>1.7</td>
</tr>
</tbody>
</table>

**CD8 T cells**

<table>
<thead>
<tr>
<th>Spike Pool</th>
<th>WT/BA.4/5</th>
<th>BA.4/5 Unique</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>D0</td>
<td>D7</td>
</tr>
<tr>
<td>GMFR (n=20)</td>
<td>1.9</td>
<td>1.4</td>
</tr>
<tr>
<td>Pos (n=14)</td>
<td>1.7</td>
<td>1.2</td>
</tr>
<tr>
<td>Neg (n=6)</td>
<td>2.6</td>
<td>1.9</td>
</tr>
</tbody>
</table>

**WT/BA.4/5 Spike pool 1**: Pool of peptides representing aa 1-643 of WT and BA.4/5

**BA.4/5 Unique**: Pool of peptides representing mutations unique to BA.4/5
Preclinical Evaluation of Contemporary Variant Vaccines
Monovalent XBB.1.5 Booster Elicits Highest XBB Sublineage Neutralization Response

Pseudovirus neutralization assay; Reference strain, Wuhan-Hu-1
LOD = Limit of detection; the lowest serum dilution of 1:20. N = 10 mice per vaccine group
Monovalent XBB.1.5 Vaccine, as a Primary Series, Elicits Highest XBB Sublineage Neutralization Response

Pseudovirus neutralization assay; Reference strain, Wuhan-Hu-1
LOD = Limit of detection; the lowest serum dilution of 1:20. N = 10 mice per vaccine group
Supply Readiness
Readiness to Supply Updated COVID-19 Vaccine

• Dose distribution can begin as follows, subject to regulatory approval
  – XBB.1.5 monovalent: end July
  – XBB.1.16 monovalent: August
  – Any other formulation: October

• Note: ~60% of flu doses are distributed by end of September
  – Above timelines for both XBB monovalent formulations enable parallel distribution of flu and COVID-19 vaccines

• Primary presentation will be single dose units – enabling greater access and efficiency

Should the need arise Pfizer/BioNTech can support an off-cycle strain selection at a later date
Conclusions

• XBB.1.5 and XBB.1.16 are most predominant in the US
• Improved humoral and cell-mediated immunity with Omicron-adapted vaccines
• Preclinical data show XBB-adapted vaccines offer improved responses against circulating strains
  – Higher responses with monovalent than bivalent vaccines

Preclinical and Clinical Data Support a Monovalent XBB-adapted Vaccine for the 2023-2024 Formula
2023-2024 COVID-19 Vaccine Formula: Pfizer/BioNTech
Clinical and Preclinical Supportive Data

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