2024-2025 COVID-19 Vaccine Formula: Pfizer/BioNTech Clinical and Preclinical Supportive Data

Vaccines and Related Biological Products Advisory Committee

June 5, 2024
Real-World Evidence & Variant Epidemiology

Omicron XBB.1.5-Adapted Vaccine Clinical Humoral Immune Responses

Preclinical Evaluation of Omicron JN.1 Lineage-Adapted Vaccines
Seasonal COVID-19 Burden is Comparable to or Higher than Influenza

**U.S. Hospitalizations**¹-³

<table>
<thead>
<tr>
<th>Season</th>
<th>Influenza</th>
<th>COVID-19</th>
</tr>
</thead>
<tbody>
<tr>
<td>2017/18</td>
<td>553,000</td>
<td>1,921,000</td>
</tr>
<tr>
<td>2018/19</td>
<td>517,000</td>
<td>1,617,000</td>
</tr>
<tr>
<td>2019/20</td>
<td>784,000</td>
<td>553,000</td>
</tr>
<tr>
<td>2020/21</td>
<td>370,000</td>
<td>272,000</td>
</tr>
<tr>
<td>2021/22</td>
<td>70,000</td>
<td>42,000</td>
</tr>
<tr>
<td>2022/23</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>2023/24</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

**U.S. Deaths**²-⁴

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* Error bars represent 95% uncertainty intervals for influenza and are not listed for COVID-19 data.
† 2020-2021 season estimates are not available due to minimal influenza activity.


XBB.1.5 Vaccine Effectiveness Initially Robust, Decreased Over Course of 2023/2024 Season

VE, vaccine effectiveness
*Historical data from: https://cov-spectrum.org. Accessed 2024 March 14. † Includes outcomes such as symptomatic infections, outpatient visits, and infections that were almost all symptomatic.

Vaccine Effectiveness Lower Against JN.1 Compared to XBB, When Controlling for Time Since Vaccination

### HOSPITALIZATION

<table>
<thead>
<tr>
<th>VETERANS AFFAIRS HEALTHCARE SYSTEM†‡</th>
<th>KAISER PERMANENTE SOUTHERN CA‡</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sep 25, 2023 - Jan 31, 2024</td>
<td>Oct 10, 2023 - Feb 29, 2024</td>
</tr>
<tr>
<td>No. of cases = 20,523 (18% of total ARI episodes)</td>
<td>No. of cases = 7,572 (15% of total ARI episodes)</td>
</tr>
</tbody>
</table>

#### Adjusted VE*, % (95% CI)

<table>
<thead>
<tr>
<th>Time since BNT162b2 XBB.1.5 Dose:</th>
<th>≤60 days</th>
<th>&lt;60 days</th>
</tr>
</thead>
<tbody>
<tr>
<td>XBB</td>
<td>62</td>
<td>74</td>
</tr>
<tr>
<td>JN.1</td>
<td>32</td>
<td>50</td>
</tr>
</tbody>
</table>

ARI, acute respiratory infection; CA, California; CI, confidence interval; No., number; PCR, polymerase chain reaction; VE, vaccine effectiveness

* Compared to no receipt of any XBB vaccine.

† Strain predominance periods defined as >80% prevalence of sequenced strains in the United States. The XBB period was defined as Sep 25 – Nov 30, 2023, and the JN.1 period was defined as Jan 1 – Jan 31, 2024.

‡ Strain determined using a hierarchical approach depending on available information: (i) whole genome sequencing (WGS), (ii) spike gene target failure, or (iii) periods of >80% sublineage predominance based on WGS data from US Health and Human Services Region 9. For (iii), cases were classified as XBB from Oct 10 – Dec 9, 2023, and as JN.1 from Jan 20 – Feb 29, 2024.

1. Caffrey et al. medRxiv. https://www.medrxiv.org/content/10.1101/2024.04.05.24305063v1
2. Tartof et al. medRxiv. https://www.medrxiv.org/content/10.1101/2024.05.04.24306875v1
XBB.1.5 Dominance Declining and XBB.1.16 Peaking at Time of June 2023 VRBPAC

Source: GISAID - gisaid.org; data accessed/analysed/plotted within Pfizer, as of June 2, 2024. Each individual labelled lineage includes all sublineages with the same Spike protein amino acid sequence.
JN.1 Transitioning to Rise of Expanding Set of Closely Related Sublineages

- JN.1 and KP.2 differ at 3 Spike residues
- Major JN.1 sublineages differ from JN.1 by 1 to 5 Spike residues
- Major XBB lineages differed from XBB.1.5 by 2 to 4 Spike residues

Source: GISAID - gisaid.org; data accessed/analysed/plotted within Pfizer, as of June 2, 2024. Each individual labelled lineage includes all sublineages with the same Spike protein amino acid sequence, except JN.1+"FLiRT" curve does not contain KP.2. JN.1+"FLiRT" includes all JN.1 sublineages that contain S: R346T, F456L; KP.2 contains S: R346T, F456L, V1104L; KP.3 contains F456L, Q493E, V1104L.
XBB.1.5 Omicron-Adapted Vaccine
Clinical Humoral Immune Response
Clinical Study: XBB.1.5 Vaccine Neutralizing Titers Maintain Against Variant Drift Until Emergence of Omicron JN.1

Evaluable Immunogenicity Population* – FFRNT Assay

XBB.1.5  EG.5.1  BA.2.86  JN.1

<table>
<thead>
<tr>
<th></th>
<th>Pre n=36</th>
<th>1MPD n=36</th>
<th>Pre n=36</th>
<th>1MPD n=36</th>
<th>Pre n=36</th>
<th>1MPD n=36</th>
<th>Pre n=36</th>
<th>1MPD n=36</th>
</tr>
</thead>
<tbody>
<tr>
<td>FFRNT50 (titer)</td>
<td>73</td>
<td>543</td>
<td>49</td>
<td>448</td>
<td>119</td>
<td>559</td>
<td>67</td>
<td>264</td>
</tr>
</tbody>
</table>

All participants were 18-55 years old; baseline seropositive for prior SARS-CoV-2 infection and had ≥ 3 mRNA COVID-19 vaccines with last vaccine being a bivalent (Original + Omicron BA.4/5) COVID-19 vaccine 150-365 days prior to enrolment. GMFR = Geometric Mean Neutralizing Titer Fold Rise; Pre = Pre vaccination; 1MPD = 1 month post dose; FFRNT = fluorescent focus reduction neutralization test XBB.1.5, BA.2.86 and EG.5.1 assays (grey, blue and purple bars) were run at a different time to JN.1 (green bars), which was also run with XBB.1.5, BA.2.86 (Neutralization titers and GMFRs were similar to those presented here).
Preclinical Evaluation of an Omicron JN.1 Adapted Vaccine
Vaccine-Experienced: 1 Month Post 5th Dose Neutralizing Responses Elicited by JN.1 and XBB.1.5 Vaccines

Pseudovirus neutralization assay; LOD = Limit of detection; the lowest serum dilution of 1:20.
N = 10 mice per vaccine group. Vaccine dose 0.5 µg.

"FLiRT" contains S: F456L, R346T; "deFLiRT" contains S: S31del, F456L, R346T; "FluQE" contains S: F456L, Q493E
Vaccine-Experienced: Geometric Mean Ratios of JN.1 to XBB.1.5 Vaccine Neutralizing Titers at 1 Month Post 5th Dose

Pseudovirus neutralization assay.
N = 10 mice per vaccine group. Vaccine dose 0.5 µg.
Vaccine Naïve: 1 Month Post 2\textsuperscript{nd} Dose Neutralizing Responses Elicited by JN.1 and XBB.1.5 Vaccines

Pseudovirus neutralization assay; LOD = Limit of detection; the lowest serum dilution of 1:20.
N = 10 mice per vaccine group. Vaccine dose 0.5 µg.

“FLiRT” contains S: F456L, R346T; “deFLiRT” contains S: S31del, F456L, R346T; “FLuQE” contains S: F456L, Q493E
Preclinical Evaluation of an Omicron KP.2-Adapted Vaccine
Vaccine- Experienced: 2 Weeks Post 4th Dose Neutralizing Responses Elicited by XBB.1.5, JN.1 and KP.2 Vaccines

- XBB.1.5 Vaccine
- JN.1 Vaccine
- KP.2 Vaccine

50% Neutralization Titer

Pseudovirus neutralization assay; LOD = Limit of detection; the lowest serum dilution of 1:20.
N = 10 mice per vaccine group. Vaccine dose 0.5 µg

“FLiRT” = S: F456L, R346T; “deFLiRT” = S: S31del, F456L, R346T; “FLuQE” = S: F456L, Q483E
Vaccine-Experienced: Geometric Mean Ratio of JN.1 and KP.2 Vaccine Responses Compared to XBB.1.5 Vaccine Responses, 2 Weeks Post 4th Dose

Pseudovirus neutralization assay; LOD = Limit of detection; the lowest serum dilution of 1:20.
N = 10 mice per vaccine group. Vaccine dose 0.5 µg
“FLiRT” = S: F456L, R346T; “deFLiRT” = S: S31del, F456L, R346T; “FLuQE” = S: F456L, Q493E
Conclusions

Summary Evidence Supports a JN.1 Lineage Vaccine Update for the 2024/2025 Season

- XBB.1.5 vaccine had robust effectiveness against XBB lineages that declined against JN.1
- JN.1 sublineages are dominant, with minimal antigenic differences within family, mirroring observations for XBB lineages relative to XBB.1.5
- JN.1- and KP.2-adapted vaccines confer improved neutralizing responses over XBB.1.5 vaccine against broad panel of emerging variants
- Prepared to initiate supply of either JN.1 vaccine or KP.2 vaccine immediately upon approval
2024-2025 COVID-19 Vaccine Formula: Pfizer/BioNTech Preclinical Supportive Data

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