Information For The Vaccine And Related Biological Products Advisory Committee
CBER, FDA

Global Influenza Virus Surveillance and Characterization
March 3, 2022

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Atlanta, GA 30333

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.
WHO-VCM Recommendations for the Northern Hemisphere (NH) 2022-2023 Season

- Continuous surveillance conducted by Global Influenza Surveillance and Response System (GISRS)
  - WHOCCs, NICs, WHO ERLs, WHO H5 Reference Laboratories
  - Supported by countries and partners including GISAID
- A WHO Consultation held from February 21 – 24, 2022
  - A hybrid of in-person and virtual meeting
  - Chaired by Dr John McCauley
  - 10 Advisers: Directors of WHOCCs and ERLs
    - 8 advise on seasonal influenza (2 focus on zoonotic)
    - In their capacity as a representative of their corresponding WHO CCs and ERLs
    - Disclosure of interests at the start of meeting
- 39 observers from WHO CCs, WHO ERLs, other GISRS laboratories and academia
- Experts from WHO Regional offices and Head Quarters
WHO Collaborating Center for Surveillance, Epidemiology and Control of Influenza, Influenza Division, National Center for Immunization and Respiratory Diseases

Number of Specimens Positive for Influenza By Subtype

Virus type name
- A(H1N1)pdm09
- A(H3)
- A (Not subtyped)
- B (Victoria lineage)
- B (Yamagata lineage)
- B (Lineage not determined)
- A(H1)
- A(H5)

Data source: FluNet, [www.who.int/flu](http://www.who.int/flu), Global Influenza Surveillance and Response System (GISRS)
Global Circulation of Influenza Viruses

Number of specimens positive for influenza by subtype

Data source: FluNet (https://www.who.int/tools/flunet), GISRS

Data from: All sites
Percentage of Influenza A Viruses By Subtypes (Sep 2021 – Jan 2022)

Data source: FluNet, (www.who.int/flu), Global Influenza Surveillance and Response System (GISRS)
Influenza Activity – (1 Sep 21 – 31 Jan 22)

Percentage of respiratory specimens that tested positive for influenza
By influenza transmission zone

Status as of 11 February 2022

The available country data were joined in larger geographical areas with similar influenza transmission patterns to be able to give an overview (www.who.int/influenza/surveillance_monitoring/updates/EN_GIP_Influenza_transmission_zones.pdf). The displayed data reflect reports of the week from 01 September 2021 to 31 January 2022.

Note: The boundaries and names shown and the designations used on this map do not imply the expression of any opinion whatsoever on the part of the World Health Organization concerning the legal status of any country, territory, city or area or of its authorities, or concerning the delimitation of its frontiers or boundaries. Dotted and dashed lines on maps represent approximate border lines for which there may not yet be full agreement.

WHO Collaborating Center for Surveillance, Epidemiology and Control of Influenza, Influenza Division, National Center for Immunization and Respiratory Diseases
Countries, Areas and Territories That Shared Viruses With WHO-CCs (Sep 2021 – Jan 2022)
A(H1N1)pdm09 Viruses
September 2021 – February 2022
Number of A(H1N1)pdm09 Viruses Detected By GISRS

Data source: FluNet, [www.who.int/flu](http://www.who.int/flu), Global Influenza Surveillance and Response System (GISRS)
Influenza A(H1N1)pdm09 Activity

Influenza A(H1N1)pdm09, September 2021 to January 2022, percent of all samples tested

Colour intensity shows the percent of positive influenza A(H1N1) among all samples tested during this period per country.

A(H1N1)pdm09 HA Phylogeography

- Two major 6B.1.5A subclades emerging from the COVID-19 bottleneck
  - 5A1 (e.g., HI/70)
    - Recent viruses from West Africa and Europe
  - 5A2 HA (e.g., WI/588)
    - Recent viruses from Asia, Mideast, Europe

Source: Cambridge Univ., S. James and D. Smith
Recent A(H1N1)pdm09 HA Phylogeography

Two major 6B.1.5A subclades

- **5A1** (e.g., HI/70)
  - NH 2020-21 vaccine antigen
  - Often share D187A, Q189E
  - Few with G155E (NC/01) or P137S and G155E
  - Recent viruses from West Africa and Europe

- **5A2 HA** (e.g., WI/588)
  - NH 2021-2022 vaccine virus
  - Often share N156K
  - Recent viruses, primarily in India (e.g., IND/PUN–..) have acquired more changes
    - K54Q, A186T, Q189E, E224A, R259K, and K308R
The viruses with HA from 6B.1A subclades 5a.1 (187A) and 5a.2 (156K) form two antigenically distinct groups:

- Virus of each subclade cluster with respective vaccine reference viruses
- Few 5a.1 viruses with G155E are antigenically distinguishable
### Human Post-vaccination Sera Analysis of A(H1N1)pdm09 Viruses

<table>
<thead>
<tr>
<th>Vaccine (5a.2)</th>
<th>+N156K +N156K +A186T +A186T +G189E +G189E +E224A +E224A</th>
<th>+D187A +D187A +G181E +G181E +A187S +A187S</th>
<th>+I166T +I166T</th>
<th>Sera Type</th>
<th>NH 2021-2022</th>
<th>5a.2</th>
<th>5a.1</th>
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<tbody>
<tr>
<td>Pediatric (6-35M)</td>
<td>USA</td>
<td>IRV4</td>
<td>43</td>
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<td>11</td>
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<tr>
<td>Pediatric (3-8Y)</td>
<td>USA</td>
<td>IrIV4</td>
<td>83</td>
<td>83</td>
<td>46</td>
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<tr>
<td>Pediatric (9-17Y)</td>
<td>USA</td>
<td>cciIV4 (Flucelvax)</td>
<td>331</td>
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<td>171</td>
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<td>Pediatric (9-17Y)</td>
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<td>cciIV4 (Flucelvax)</td>
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<td>166</td>
<td>166</td>
<td>166</td>
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<td>Adult</td>
<td>USA</td>
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<td>USA</td>
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<td>874</td>
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<tr>
<td>Adult</td>
<td>USA</td>
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<td>874</td>
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<tr>
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<td>USA</td>
<td>IRV4</td>
<td>19</td>
<td>19</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Elderly</td>
<td>USA</td>
<td>IRV4</td>
<td>10</td>
<td>10</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
</tbody>
</table>

Geometric Mean Titer (GMT) ratios between reference and test antigens are calculated with 90% (CI) confidence intervals for each cohort and panel location. Unadjusted model results are shown. If the CI lower bound is greater than 50%, it is statistically non-inferior (50% confidence level), otherwise it is possibly inferior. Heat map cells are colored using the GMT ratio lower bound. Blue indicates statistical non-inferiority and orange denotes possible inferiority. Numbers shown are post-vaccination GMTs for the unadjusted model. They are shown for reference antigens and possibly inferior test antigens. Marks, √ or X denote statistically significant non-inferiority when the reference virus GMT is ≥40 or <40 respectively. Strain abbreviations: A/HAWAII/70/2019 (H7/0); A/INDIA/PUN-NIV/323546/2021 (IND/PUN-NIV/323546); A/NORTH CAROLINA/01/2021 (NC/01); A/TOGO/881/2020 (TGO/881); AVICTORIA/2570/2019 (VIC/2570); A/WISCONSIN/588/2019 (WI/588).

WHO Collaborating Center for Surveillance, Epidemiology and Control of Influenza, Influenza Division, National Center for Immunization and Respiratory Diseases
- Inhibits both 5a.2 and most 5a.1 viruses
  - Exceptions
    - Very young pediatric (6-35 Month old)
    - G155E viruses (e.g., NC/01), which were less frequently detected

<table>
<thead>
<tr>
<th>NH 2021-2022 Vaccine (5a.2) Sera</th>
<th>5a.2</th>
<th>5a.1</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pediatric (6-35M) USA IV4</td>
<td>40</td>
<td>11</td>
</tr>
<tr>
<td>Pediatric (3-8Y) USA IV4</td>
<td>85</td>
<td>101</td>
</tr>
<tr>
<td>Pediatric (9-17Y) USA IV4</td>
<td>402</td>
<td>402</td>
</tr>
<tr>
<td>Adult USA IV4</td>
<td>243</td>
<td>146</td>
</tr>
<tr>
<td>Japan IV4</td>
<td>650</td>
<td>178</td>
</tr>
<tr>
<td>UK IV4</td>
<td>114</td>
<td>178</td>
</tr>
<tr>
<td>Older Adult (60-64Y) USA IV4</td>
<td>160</td>
<td>384</td>
</tr>
<tr>
<td>Elderly USA IV4</td>
<td>48</td>
<td>98</td>
</tr>
<tr>
<td>USA IV4</td>
<td>40</td>
<td>32</td>
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<tr>
<td>Japan IV4</td>
<td>149</td>
<td>149</td>
</tr>
<tr>
<td>USA IV4</td>
<td>136</td>
<td>75</td>
</tr>
</tbody>
</table>
Pediatric Human Post-vaccination Sera Analysis of A(H1N1)pdm09 Viruses (Individual Responses)

- 6-35 month panel
  - ~60% have HI titer increase >40 to 5a.2 viruses
    - Including IND/PUN (5a.2+186T..)
  - Poor reactivity with 5a.1 viruses
  - Similar pattern as naive ferrets
- Older pediatric panels (3-17 y)
  - Increase titers to both 5a.2 and 5a.1 viruses
    - Back boost (HI/70 (5a.1))
    - Forward boost (Ind/Pun (5a.2+186T..) and NC/01 (5a.1+155E.. and TGO/881 5a.1+166T..)
Adult Human Post-vaccination Sera Analysis of A(H1N1)pdm09 Viruses (Individual Responses)

Adults and ≥ 65 years of age

• Increase titers to both 5a.2 and 5a.1 viruses
  • 75-100% of individuals have post vaccination titers ≥ 40
  • Back boost, HI/70 (5a.1)
  • Forward boost, Ind/Pun (5a.2+186T..), NC/01 (5a.1 + 155E.. and TGO/881 5a.1 + 166T..)
A(H1N1)pdm09 Summary (1)

• A(H1N1)pdm09 viruses have been detected in Africa, Europe, the Middle East, southern Asia, Oceania and sporadically in a few other regions

• The great majority of HA gene sequences belonged to clade 6B.1A5a, subclades;
  • 5a.1 (D187A, Q189E) HA proteins predominant in Africa and Europe
    • Some HA's share with additional substitutions P137S and G155E
  • 5a.2 (K130N, N156K, L161I, V250A) HA proteins were predominant in the Middle East, southern Asia and Oceania
    • Many recent virus have additional HA substitutions K54Q, **A186T**, Q189E, E224A, R259K and K308R (e.g., IND/PUN-...)

• Ferret antisera show that HA clade 5a.1 viruses are antigenically distinct from HA clade 5a.2 viruses
Post vaccination sera collected from humans vaccinated with NH 2021-2022 vaccines (Immunized with HA subclade 5a.2 antigens)

- GMTs against viruses representing HA subclade 5a.2 (N156K) were generally recognized well, as were most of those in subclade 5a.1 (D187A, Q198E).
  - Vaccine induced antibodies that cross react with 5a.1
    - Likely because of B-cell memory response, since 5a.1 viruses circulated previously and were a component of 2020-2021 vaccine
  - Exception were the 6-35 month old sera panels
    - Only react with 5a.2 viruses

- None of the viruses tested showed evidence of reduced inhibition by neuraminidase inhibitors (n=190) or reduced susceptibility to the endonuclease inhibitor baloxavir (n=158).
A(H3N2) Viruses
September 2021 - February 2022
Number of A(H3N2) Viruses Detected by GISRS

Data source: FluNet, (www.who.int/flunet), Global Influenza Surveillance and Response System (GISRS)
Influenza A(H3N2) Activity

Influenza A(H3N2), September 2021 to January 2022, percent of all samples tested

Colour intensity shows the percent of influenza A(H3N2) positive among all samples tested during this period per country.

A(H3N2) HA Phylogeography

- Two major clades survived the COVID-19 bottleneck
  - 2a1b.1
    - 1a and 1b subclades in Africa and Europe
  - 2a1b.2a
    - 2a.1 in Asia, decreased in 2021
    - 2a.2 in Europe, Russia, North and South America increased in 2021-22
Phylogenetics of A(H3N2) HA Gene (time tree)

- HA clade 2a.2 predominate
  - Continue to diversify into genetic subgroups typically encoding D53G, H156S, L157I or D53N, N96S, H156S, I192F
- Small proportion of 1a (yellow) and 1b (green) clades circulating

Source: Nextflu (J. Huddleston, T. Bedford, J. Lee & R. Neher). Based on HA sequences available as of 02/12/2022
Global Circulation of A(H3N2) HA Clades

- HA clade 2a.2 predominate and show global distribution
  - Predominance of subclades differ regionally (e.g., D53G, H156S, L157I in North America (e.g., U.S.) vs D53N, D96N, H156S, I192F in Western Europe (e.g., Netherlands and Sweden) and South America (e.g., Brazil)

- HA clade 1a viruses circulating in Africa (e.g., Côte d’Ivoire, Ghana, Niger, Nigeria, Ethiopia, Togo)

- HA clade 1b viruses sporadically identified (i.e., Armenia, France, Kenya, Madagascar, South Africa)

Source: Nextflu Based on HA sequence available as of 02/12/2022
Location of Substitutions on H3 HA Monomer

- HA Clade 2a1b.2a.2 (e.g., Darwin/6) have additional substitutions (i.e., H156S, Y159N, T160I, L164Q, S186D, D190N) compared to A/Cambodia/e0826360/2020
### Analysis of A(H3N2) Viruses By Antisera to Antigens Recommended for NH 2021-2022

#### A/Cambodia/e0826360/2020-like (cell)*

<table>
<thead>
<tr>
<th>WHO CC</th>
<th>Like (2-4 fold)</th>
<th>Low (≥ 8 fold)</th>
</tr>
</thead>
<tbody>
<tr>
<td>FCI</td>
<td>50 (17%)</td>
<td>246 (83%)</td>
</tr>
<tr>
<td>VIDRL</td>
<td>10 (25%)</td>
<td>30 (75%)</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>60 (18%)</strong></td>
<td><strong>276 (82%)</strong></td>
</tr>
</tbody>
</table>

#### WHO CC Like (2-4 fold) | Low (≥ 8 fold)
---|---
FCI | 20 (7%) | 276 (93%)
VIDRL | 0 (0%) | 40 (100%)
**Total** | **20 (6%)** | **316 (94%)**

**Showing data from viruses isolated from swabs collected from September to January 2022**

*Reference viruses are in HA clade 3C.2a1b.2a1

#### HI Assay

#### VN Assay

**CDC**

<table>
<thead>
<tr>
<th>WHO CC</th>
<th>Like (2-4 fold)</th>
<th>Low (≥ 8 fold)</th>
</tr>
</thead>
<tbody>
<tr>
<td>4 (6%)</td>
<td>63 (94%)</td>
<td></td>
</tr>
<tr>
<td>0 (0%)</td>
<td>5 (100%)</td>
<td></td>
</tr>
<tr>
<td>16 (18%)</td>
<td>75 (82%)</td>
<td></td>
</tr>
<tr>
<td>13 (52%)</td>
<td>12 (48%)</td>
<td></td>
</tr>
<tr>
<td><strong>TOTAL</strong></td>
<td><strong>33 (18%)</strong></td>
<td><strong>155 (82%)</strong></td>
</tr>
</tbody>
</table>

**NIID**

<table>
<thead>
<tr>
<th>WHO CC</th>
<th>Like (2-4 fold)</th>
<th>Low (≥ 8 fold)</th>
</tr>
</thead>
<tbody>
<tr>
<td>22 (33%)</td>
<td>45 (67%)</td>
<td></td>
</tr>
<tr>
<td>0 (0%)</td>
<td>5 (100%)</td>
<td></td>
</tr>
<tr>
<td><strong>TOTAL</strong></td>
<td><strong>22 (31%)</strong></td>
<td><strong>50 (69%)</strong></td>
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</table>

*Reference viruses are in HA clade 3C.2a1b.2a1

**Showing data from viruses isolated from swabs collected from September to January 2022**
## Analysis of A(H3N2) Viruses By Antisera to Antigens Recommended for SH 2022

### HI Assay

<table>
<thead>
<tr>
<th>WHO CC</th>
<th>Like (2-4 fold)</th>
<th>Low (≥ 8 fold)</th>
</tr>
</thead>
<tbody>
<tr>
<td>FCI</td>
<td>259 (88%)</td>
<td>37 (13%)</td>
</tr>
<tr>
<td>VIDRL</td>
<td>25 (63%)</td>
<td>15 (38%)</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>284 (85%)</td>
<td>52 (15%)</td>
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### VN Assay

<table>
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<tr>
<th>WHO CC</th>
<th>Like (2-4 fold)</th>
<th>Low (≥ 8 fold)</th>
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<tbody>
<tr>
<td>CDC</td>
<td>66(99%)</td>
<td>1(1%)</td>
</tr>
<tr>
<td>FCI</td>
<td>259(88%)</td>
<td>37(13%)</td>
</tr>
<tr>
<td>NIID</td>
<td>5 (100%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>VIDRL</td>
<td>19 (73%)</td>
<td>7 (27%)</td>
</tr>
<tr>
<td><strong>TOTAL</strong></td>
<td>349(89%)</td>
<td>45 (11%)</td>
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### A/Darwin/09/2021-like (egg)

<table>
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<tr>
<th>WHO CC</th>
<th>Like (2-4 fold)</th>
<th>Low (≥ 8 fold)</th>
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</thead>
<tbody>
<tr>
<td>FCI</td>
<td>207 (70%)</td>
<td>89 (30%)</td>
</tr>
<tr>
<td>VIDRL</td>
<td>7 (18%)</td>
<td>33 (83%)</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>214 (64%)</td>
<td>122 (36%)</td>
</tr>
</tbody>
</table>

### Reference viruses are in HA clade 3a.I2a1b.2a.2r.

*Shewing data from viruses isolated from swabs collected from September to January 2022.*
WHO Collaborating Center for Surveillance, Epidemiology and Control of Influenza, Influenza Division, National Center for Immunization and Respiratory Diseases

A(H3N2) Antigenic Cartography

- 2a.2 viruses are antigenically distinct from 2a.1 and 1b
  - Various subgroups are antigenically closely related (i.e., form overlapping clusters)
  - A/Darwin/6/2021 (SH 22: Cell 3c2a1b.2a.2)
    - Well recognized 2a.2 viruses in multiple subclades (e.g., D53G, H156S, L157I and D53N, N96S, H156S, I192F)
      - Poorly reacted 1a, 1b, and 2a.1 HA clade viruses
  - A/Cambodia/e0826360/2020 (NH 21-22: Cell 3C.2a1b.2a.1)
    - Reacted well with 1a, 1b and 2a.1 viruses but 2a.2 viruses were reduced
  - A/Hong Kong/45/2019-like viruses (SH 21: Cell 3C.2a1b.1b)
    - Reacted with 1a, 1b viruses well, 2a.1 viruses less well, and 2a.2 viruses poorly
A(H3N2) Antigenic Cartography

A(H3N2) HINT
CC Atlanta

A/Darwin/6/21-cell
A/Darwin/9/21-egg
A/Cambodia/E0826360/20-cell
A/Hong Kong/2671/19-egg

Source: Cambridge Univ., S. James and D. Smith

Last 6 months, 2021-08 to 2022-02, older viruses in grey

A(H3N2) HI
CC London

A/Stockholm/5/21-cell
(A/Darwin/6/21-cell like)
A/Darwin/9/21-egg
A/Hong Kong/2671/19-egg

WHO Collaborating Center for Surveillance, Epidemiology and Control of Influenza, Influenza Division, National Center for Immunization and Respiratory Diseases

Source: Cambridge Univ., S. James and D. Smith

Last 6 months, 2021-08 to 2022-02, older viruses in grey
Human Post-vaccination Sera Analysis of A(H3N2) Viruses

- Multiple serum panels show reduced reactivity with the representative 2a.2 test viruses
  - Various 2a.2 subgroups were not differentiated

### NH 2021-2022 Vaccine (2a.1)

<table>
<thead>
<tr>
<th>Vaccine Type</th>
<th>USA</th>
<th>IV4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pediatric (6-35M)</td>
<td>21</td>
<td>X</td>
</tr>
<tr>
<td>Pediatric (3-8Y)</td>
<td>171</td>
<td>√</td>
</tr>
<tr>
<td>Pediatric (9-17Y)</td>
<td>368</td>
<td>√</td>
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<tr>
<td>Adult</td>
<td>294</td>
<td>√</td>
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<tr>
<td>Japan</td>
<td>11</td>
<td>X</td>
</tr>
<tr>
<td>UK</td>
<td>29</td>
<td>X</td>
</tr>
<tr>
<td>Older Adult (60-64Y)</td>
<td>70</td>
<td>√</td>
</tr>
<tr>
<td>&gt;64 Y</td>
<td>89</td>
<td>√</td>
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### NH 2021-2022 Vaccine (2a.2)

<table>
<thead>
<tr>
<th>Vaccine Type</th>
<th>USA</th>
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</tr>
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<tbody>
<tr>
<td>Pediatric (6-35M)</td>
<td>+CAM/E0826360</td>
<td>+T160K(CHO-)</td>
</tr>
<tr>
<td>Pediatric (3-8Y)</td>
<td>+CAM/E0826360</td>
<td>+5196R</td>
</tr>
<tr>
<td>Pediatric (9-17Y)</td>
<td>+CAM/E0826360</td>
<td>+G185D-+D190N</td>
</tr>
<tr>
<td>Adult</td>
<td>TGO/771</td>
<td>+192F</td>
</tr>
<tr>
<td>Japan</td>
<td>HK/45</td>
<td>-</td>
</tr>
<tr>
<td>UK</td>
<td>DAR/06</td>
<td>D56G</td>
</tr>
<tr>
<td>Older Adult (60-64Y)</td>
<td>MD/02</td>
<td>+H156S</td>
</tr>
<tr>
<td>&gt;64 Y</td>
<td>AK/01</td>
<td>+D53G</td>
</tr>
</tbody>
</table>

### Geometric Mean Titers (GMT)

Strain abbreviations: A/ALASKA/01/2021 (AK/01); A/CAMBODIA/E0826360/2020 (CAM/E0826360); A/DAVOS/06/2021 (DAR/06); A/HONG KONG/45/2019 (HK/45); A/MARYLAND/02/2021 (MD/02); A/TOGO/771/2020 (TGO/771).

Source: U.S. CDC
Pediatric Human Post-vaccination Sera Analysis of A(H3N2) \n
NH 2021-2022 Vaccine (2a.1), Individual Responses

- 6-35 M panel
  - Limited response
    - Only 25% have titers ≥ 40
- Older pediatric panels
  - Vaccination increased titers to HA clade 1a, 1b, 2a.1 and 2a.2 viruses
  - Back boost (HK/45 (1b)
  - Forward boost
    - Recent 1a (TGO/771)
    - Multiple 2a.2 variants
      - DAR/06 (D53G, H156S)
      - MD/02 (D53G, H156S, L157I)
      - AK/01 (D53N...I192F)

(Chart showing vaccine responses with orange icons for titers ≥ 40)
NH 2021-2022 Vaccine (2a.1), Individual Responses

- Adults: vaccination increased titers to HA clade 1a, 1b, and 2a.2 viruses
  - Back boost (HK/45 (1b))
  - Forward boost
    - Recent 1a (TGO/771)
    - Multiple 2a.2 variants
      - DAR/06 (D53G, H156S)
      - MD/02 (D53G, H156S, L157I)
      - AK/01 (D53N...I192F)
  - Titer and forward boost reduced in older adults and elderly
A(H3N2) Summary (1): Global Circulation and Phylogeny

• In many countries, areas and territories reporting influenza A viruses, A(H3N2) subtype predominated
  • Most countries in Europe, North America, the Middle East, South America and some countries in Africa (e.g., Côte d'Ivoire, Ethiopia, Kenya, Uganda and Togo)

• HA phylogenetics: circulating A(H3N2) viruses in this period belonged to 3C.2a1b subclades including:
  • 1a, 1b, 2a.1 and 2a.2
  • 2a.2 HA clade viruses predominated in this period and continue to diversify into genetic groups that typically encode:
    • D53G, H156S, L157I
    or
    • D53N, N96S, H156S, I192F
A(H3N2) Summary (2): Antigenic Characteristics

• 2a.2 viruses are antigenically distinct from 2a.1, 1a and 1b

• Ferret antisera to:
  • A/Hong Kong/45/2019-like viruses (SH 21: Cell 3C.2a1b.1b)
    • Reacted with 1a, 1b viruses well, 2a.1 viruses less well, and 2a.2 viruses poorly
  • A/Cambodia/e0826360/2020 (NH 21-22: Cell 3C.2a1b.2a.1)
    • Reacted well with 1a, 1b and 2a.1 viruses but 2a.2 viruses were reduced
  • A/Darwin/6/2021 (SH 22: Cell 3c2a1b.2a.2)
    • Well recognized 2a.2 viruses in multiple subclades (e.g., D53G, H156S, L157I and D53N, N96S, H156S, I192F)
    • Poorly reacted 1a, 1b, and 2a.1 HA clade viruses
A(H3N2) Summary (3)

• Human serology studies with serum panels from individuals vaccinated with A/Cambodia/e0826360/2020-like (2a.1) viruses:
  • Post-vaccination GMTs were significantly reduced against cell culture-propagated 2a.2 viruses
    • Viruses with HA in 2a.2 subclades (e.g., D53N or D53G) all showed very similar reactivity patterns
    • Nevertheless, the 2a.1 vaccine provided forward boost against 1a and 2a.2 viruses and often majority of individuals had neutralizing titers > 40

• Antiviral Susceptibility
  • Genetic and/or phenotypic testing showed 1 of the 1023 A(H3N2) viruses collected after September 2021 showed reduced inhibition to neuraminidase inhibitors.
  • Of 962 A(H3N2) viruses collected and analyzed after September 2021, none showed genetic or phenotypic evidence of reduced susceptibility to baloxavir.
Influenza B Viruses
September 2021 - February 2022
Number of B Viruses Detected By GISRS

Data source: FluNet, (www.who.int/flu), Global Influenza Surveillance and Response System (GISRS)
Influenza B Viruses Ascribed to Lineages: Numbers and Percentage (Sep 2021 – Jan 2022)

Influenza B Viruses Activity

Influenza B, September 2021 to January 2022, percentage positive of all samples tested

Colour intensity shows the percent of influenza B positive among all samples tested during this period per country.

B/Victoria Lineage Viruses
Influenza B/Victoria HA Phylogeography

- Two subclades emerged from the COVID-19 bottleneck
  - 1A.3a.1, primarily in China
  - 1A.3a.2, geographically diverse (Africa, Europe, Asia)

V1A.1 (Double deletion, Δ162 − 163)
V1A.3a
1A.3a.1
1A.3a.2
V1A.3 (Triple deletion, Δ162 − 164)

Source: Cambridge Univ.
WHO Collaborating Center for Surveillance, Epidemiology and Control of Influenza,
Influenza Division, National Center for Immunization and Respiratory Diseases

B/Victoria HA Phylogenetics

Recommended 2022-23 prototypes

1A.3a.2 (A127T, P144L, K203R)

1A.3a.1 (V220M, P241Q)

NH 2021-22 cell prototype

1A.3
Influenza B Viruses Antigenically Characterized During The Last 3 Reporting Periods
### Analysis of B/Victoria Viruses By Antisera to Antigens
Recommended for NH 2021-2022

**B/Washington/02/2019-like (cell)**

<table>
<thead>
<tr>
<th>WHO CC</th>
<th>Like (2-4 fold)</th>
<th>Low (≥ 8 fold)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CDC</td>
<td>15 (68%)</td>
<td>7 (32%)</td>
</tr>
<tr>
<td>CNIC</td>
<td>629 (38%)</td>
<td>1028 (62%)</td>
</tr>
<tr>
<td>FCI</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>NIID</td>
<td>1 (20%)</td>
<td>4 (80%)</td>
</tr>
<tr>
<td>VIDRL</td>
<td>14 (47%)</td>
<td>16 (53%)</td>
</tr>
<tr>
<td>TOTAL</td>
<td>659 (38%)</td>
<td>1055 (62%)</td>
</tr>
</tbody>
</table>

**B/Washington/02/2019-like (egg)**

<table>
<thead>
<tr>
<th>WHO CC</th>
<th>Like (2-4 fold)</th>
<th>Low (≥ 8 fold)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CDC</td>
<td>17 (77%)</td>
<td>5 (23%)</td>
</tr>
<tr>
<td>CNIC</td>
<td>550 (33%)</td>
<td>1107 (67%)</td>
</tr>
<tr>
<td>FCI</td>
<td>5 (11%)</td>
<td>39 (89%)</td>
</tr>
<tr>
<td>NIID</td>
<td>5 (100%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>VIDRL</td>
<td>2 (14%)</td>
<td>12 (86%)</td>
</tr>
<tr>
<td>TOTAL</td>
<td>579 (33%)</td>
<td>1163 (67%)</td>
</tr>
</tbody>
</table>
### Analysis of B/Victoria Viruses By Antisera to Antigens Recommended for SH 2022

#### B/Austria/1359417/2021-like (cell)

<table>
<thead>
<tr>
<th>WHO CC</th>
<th>Like (2-4 fold)</th>
<th>Low (≥ 8 fold)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CDC</td>
<td>5 (45%)</td>
<td>6 (55%)</td>
</tr>
<tr>
<td>CNIC</td>
<td>1315 (88%)</td>
<td>180 (12%)</td>
</tr>
<tr>
<td>FCI</td>
<td>39 (89%)</td>
<td>5 (11%)</td>
</tr>
<tr>
<td>NIID</td>
<td>5 (100%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>VIDRL</td>
<td>25 (83%)</td>
<td>5 (17%)</td>
</tr>
<tr>
<td><strong>TOTAL</strong></td>
<td><strong>1389 (88%)</strong></td>
<td><strong>196 (12%)</strong></td>
</tr>
</tbody>
</table>

#### B/Austria/1359417/2021-like (egg)

<table>
<thead>
<tr>
<th>WHO CC</th>
<th>Like (2-4 fold)</th>
<th>Low (≥ 8 fold)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CDC</td>
<td>6 (55%)</td>
<td>5 (45%)</td>
</tr>
<tr>
<td>CNIC</td>
<td>1329 (89%)</td>
<td>166 (11%)</td>
</tr>
<tr>
<td>FCI</td>
<td>39 (89%)</td>
<td>5 (11%)</td>
</tr>
<tr>
<td>NIID</td>
<td>5 (100%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>VIDRL</td>
<td>30 (100%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td><strong>TOTAL</strong></td>
<td><strong>1409 (89%)</strong></td>
<td><strong>176 (11%)</strong></td>
</tr>
</tbody>
</table>
Antigenic Cartography

- HA subclade V1A.3a2 and 3a1 viruses are antigenically distinct from clade 3 viruses (WA/02).
  - Various subgroups are antigenically closely related (i.e., form overlapping clusters)
    - i.e., 3a2, 3a2+ 122Q, 3a2 +197E
  - HA subclade 3a2 (lighter greens) and 3a1 (dark green) viruses are antigenically related but distinguishable from each other.

Source: Cambridge Univ., S. James and D. Smith
Human Post-vaccination Serum Analysis

- Multiple serum panels show cross reactivity with the representative 3a.1 and 3a.2 test viruses
  - Various 3a.2 subgroups were not differentiated

<table>
<thead>
<tr>
<th>Vaccine (V1A.3)</th>
<th>V1A.3</th>
<th>V1A.3a.1</th>
<th>V1A.3a.2</th>
</tr>
</thead>
<tbody>
<tr>
<td>NH 2021-2022</td>
<td>+WA02</td>
<td>+V220M</td>
<td>+H1220</td>
</tr>
<tr>
<td>Pediatric (6-35M)</td>
<td>-N1973(CHO)</td>
<td>+P241Q</td>
<td>+A127T</td>
</tr>
<tr>
<td>Pediatric (3-8Y)</td>
<td>MDCK</td>
<td>MDCK</td>
<td>MDCK</td>
</tr>
<tr>
<td>Pediatric (5-17Y)</td>
<td>USA/IV4</td>
<td>USA/IV4</td>
<td>USA/IV4</td>
</tr>
<tr>
<td>Adult</td>
<td>V1A</td>
<td>V1A.3a</td>
<td>V1A.3a.2</td>
</tr>
<tr>
<td>Japan</td>
<td>IV4</td>
<td>IV4</td>
<td>IV4</td>
</tr>
<tr>
<td>UK</td>
<td>IV4</td>
<td>IV4</td>
<td>IV4</td>
</tr>
<tr>
<td>Older Adult (50-64Y)</td>
<td>USA/IV4</td>
<td>USA/IV4</td>
<td>USA/IV4</td>
</tr>
<tr>
<td>Elderly</td>
<td>USA</td>
<td>IV4/IV4-HD</td>
<td>USA/IV4</td>
</tr>
</tbody>
</table>

Geometric Mean Titer (GMT) ratios between reference and test antigens are calculated with 90% (CI) confidence intervals for each cohort and panel location. Unadjusted model results are shown. If the CI lower bound is greater than 50%, it is statistically non-inferior (50% confidence level), otherwise it is possibly inferior. Heat map cells are colored using the GMT ratio lower bound. Blue indicates statistically non-inferiority and orange denotes possible inferiority. Numbers shown are post-vaccination GMTs for the unadjusted model. They are shown for reference antigens and possibly inferior test antigens. Marks ‘x’ or X denote statistically significant non-inferiority when the reference virus GMT is >40 or <40 respectively.

Strain abbreviations: A/AUSTRIA/135941/2021 (A/135941); B/HENAN-XIGONG/1118/2021 (HEN/1118); B/MARYLAND/1102/2021 (MD/01); B/SICHUAN-JINGYANG/12048/2019 (SIC/12048); B/WASHINGTON/02/2019 (WA/02).
B/Yamagata Lineage Viruses
B/Yamagata Lineage Virus Detections

• Occasional B/Yamagata/16/88 lineage viruses have been reported in FluNet during this reporting period (13 specimens), but none have been confirmed by WHO Collaborating Centres

• No viruses of B/Yamagata/16/88 lineage have been available for analysis during this period
B/Yamagata: Future Considerations

- No B/Yamagata/16/88 viruses have been detected and confirmed by WHO CCs since March 2020
- It is unclear at this point if B-viruses of this lineage are truly extinct
- Hence for the 2022-23 NH quadrivalent influenza vaccines, a B/Yamagata lineage virus is still recommended
- WHO GISRS in consultation with other parties will re-consider the situation in approximately 12 months as to the necessity for including a B/Yamagata lineage virus in influenza vaccines
Summary of Influenza B Viruses (1)

• Only influenza B/Victoria lineage viruses were detected and available for analysis

• HA phylogenetics of B/Victoria lineage viruses
  • Nearly all HA genes belonged to subclade 1A.3, that has a deletion of residues 162-164 and a K136E substitution in HA
  • 1A.3a HA genes encoding further substitutions of N150K, G184E, N197D (resulting in the loss of a glycosylation site) and R279K have predominated
    • Two subgroups have emerged:
      • 1A.3a.1 has additional HA substitutions V220M and P241Q, seen exclusively in China,
      • 1A.3a.2 with A127T, P144L and K203R seen in Asia, Africa, Oceania, Europe and North America
    • 1A.3a.2 viruses have shown further genetic divergence, with additional HA amino acid substitutions encoded in viruses from different geographic locations
Summary of Influenza B Viruses (2)

• Occasional B/Yamagata/16/88 lineage viruses have been reported in FluNet during this reporting period (13 specimens) but none have been confirmed by WHO Collaborating Centres.

• No viruses of B/Yamagata/16/88 lineage have been available for analysis during this period.
Acknowledgements

• WHO Collaborating Centers in Beijing, Melbourne, London and Tokyo and WHO Geneva staff
  • GISRS; National Influenza Centers
  • University of Cambridge partners

• Essential Regulatory Laboratories

• US partners:
  • Association of Public Health Laboratories
  • United States Air Force School of Aerospace Medicine (USAFSAM)
  • Naval Health Research Center (NHRC)

• Fitness forecasting partners in Europe and US
  • M. Lässig, M. Łuksza
  • T. Bedford, R. Neher

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