Global Influenza Virus Surveillance and Characterization
March 5, 2021

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Chief, Virology Surveillance and Diagnosis Branch
Influenza Division, National Center for Immunization and Respiratory Diseases
Centers for Disease Control and Prevention
Atlanta, GA 30333
Outline

- Overview of the WHO-VCM and Recommendations
- Influenza Virus Activity
- A(H1N1)pdm09, describe major highlights
  - Was covered in depth at Sept. 2020 VRBPAC
  - While recommendation is an update for the NH 2021-2022 season, it is the same as the SH 2021 recommendation.
- A(H3N2), will be discussed in detail
  - Update to the recommendation
- B/Victoria lineage viruses
  - Vaccine recommendation remains same as NH 2021-2022 and SH 2021
    - Expansion of previously small group
- B/Yamagata lineage, will be brief as there has been very little circulation of this lineage
WHO Influenza Vaccine Consultation Meeting

- **Year around surveillance conducted by GISRS**
  - WHO Collaborating Centers (WHO CC), National Influenza Centers, WHO Essential Regulatory Laboratories, WHO H5 Reference Laboratories
  - Supported by many countries and partners including GISAID

- **WHO consultation meeting held from Feb 17 – 25, 2021**
  - A virtual meeting – 17 hours’ time difference among participants
  - Chaired by Drs David Wentworth and John McCauley
  - 8 Advisers: Directors of WHOCCs and ERLs
    - In their capacity as representative of their corresponding WHO CCs and ERLs
  - 57 observers from WHO CCs, WHO ERLs, academia, H5 Reference laboratories and veterinary sector OFFLU
  - Experts from WHO Regional Offices and Head Quarters
WHO Influenza Vaccine Recommendation

It is recommended vaccines for use in the 2021-2022 northern hemisphere influenza season contain the following:

**Quadrivalent:** Egg-based Vaccines

- an A/Victoria/2570/2019 (H1N1)pdm09-like virus*;
- an A/Cambodia/e0826360/2020 (H3N2)-like virus*;
- a B/Washington/02/2019 (B/Victoria lineage)-like virus; and
- a B/Phuket/3073/2013 (B/Yamagata lineage)-like virus

**Quadrivalent:** Cell- or recombinant-based Vaccines

- an A/Wisconsin/588/2019 (H1N1)pdm09-like virus*;
- an A/Cambodia/e0826360/2020 (H3N2)-like virus*;
- a B/Washington/02/2019 (B/Victoria lineage)-like virus; and
- a B/Phuket/3073/2013 (B/Yamagata lineage)-like virus.

* Different from that recommended for the northern hemisphere 2020-2021 season
Number of Specimens Processed by GISRS

Data source: FluNet, (www.who.int/flunet), Global Influenza Surveillance and Response System (10 February 2021)
Percent Influenza Positive by Calendar Week and Year
Global Circulation of Influenza Viruses

2019 - 2020

Number of specimens positive for influenza by subtype

2020 - 2021

Number of specimens positive for influenza by subtype

Influenza Laboratory Surveillance Information by the Global Influenza Surveillance and Response System (GISRS)
Influenza Activity – Sep 2020 to Jan 2021

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

Status as of 05 February 2021

Note: 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 2020 to 4 February 2021.

Data Source:
Global Influenza Surveillance and Response System (GISRS), FlurNet (www.who.int/influenza)
Countries, Areas And Territories That Shared Viruses With WHO CCs (Sep 2020 – Jan 2021)

Specimens shared with WHO CCs
No specimens shared or data not available
Not applicable

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. United and dashed lines on maps represent approximate border lines for which there may not yet be full agreement.

Data Source: WHO CC reports for the WHO influenza vaccine composition consultation in February 2021
Map Production: WHO Global Influenza Programme
World Health Organization
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Percentage of Influenza Viruses by Type/Subtype (Sep 2020– Jan 2021)

- A(H3N2) 20%
- A(not subtyped) 20%
- B/Victoria 22%
- B/Yamagata 0%
- B (not determined) 33%
- A(H1N1)pdm09 5%

Data source: FluNet (www.who.int/flunet), Global Influenza Surveillance and Response System (14 February 2021)
A(H1N1)pdm09 Viruses
September 2020 – February 2021
Influenza A(H1N1)pdm09 Virus Activity Geographic Distribution

Influenza A(H1N1)pdm09, September 2020 to January 2021, percent of all samples tested
Number of A(H1N1)pdm09 Viruses Detected By GISRS

Data source: FluNet, [www.who.int/flunet](http://www.who.int/flunet), Global Influenza Surveillance and Response System (10 February 2021)
Phylogenetics of A(H1N1)pdm09 HA Gene
A(H1N1)pdm09 HA 6B.1A Clade Distribution
September 2020 - February 2021*

*Based on HA Sequence Availability

WHO Collaborating Center for Surveillance, Epidemiology and Control of Influenza, Influenza Division, National Center for Immunization and Respiratory Diseases
Reactivity of A(H1N1)pdm09 Viruses With Ferret Antisera To Antigens Recommended For NH 2020-21

Ferret antisera to vaccine reference viruses in clade 6B.1A 5A1

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Like (2-4 fold)</td>
<td>Low (≥ 8 fold)</td>
</tr>
<tr>
<td>CDC</td>
<td>8 (100%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>CNIC</td>
<td>0 (0%)</td>
<td>1 (100%)</td>
</tr>
<tr>
<td>FCI</td>
<td>2 (100%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>NIID</td>
<td>1 (100%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>TOTAL</td>
<td>11 (92%)</td>
<td>1 (8%)</td>
</tr>
</tbody>
</table>

Data from hemagglutination inhibition assays using viruses isolated from specimens with collection dates from September 1, 2020 to January 31, 2021.
A(H1N1)pdm09 Antigenic Cartography

WHO Collaborating Center for Surveillance, Epidemiology and Control of Influenza, Influenza Division, National Center for Immunization and Respiratory Diseases
### Human Post-vaccination Sera Analysis With H1N1 Viruses (1)

**Clade or Subclade (+ additional substitutions)**

<table>
<thead>
<tr>
<th></th>
<th>5A1 (H1N1)</th>
<th>5A1 + A187Y</th>
<th>5A2 (N156K)</th>
<th>5A2 (N156K) + K205M</th>
<th>5B (K132N + K160M)</th>
<th>3</th>
<th>7</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>H1/70 Slat</em></td>
<td><em>GUAN/1536 Egg</em></td>
<td><em>W1/588 Slat</em></td>
<td><em>AR/08 Slat</em></td>
<td><em>MD/42 Slat</em></td>
<td><em>ID/07 Slat</em></td>
<td><em>LA/01 Slat</em></td>
<td></td>
</tr>
<tr>
<td>6-35mo Pediatric</td>
<td>80</td>
<td>51</td>
<td>10</td>
<td>11</td>
<td>16</td>
<td>16</td>
<td>18</td>
</tr>
<tr>
<td>3-8yr Pediatric</td>
<td>788</td>
<td>331</td>
<td>166</td>
<td>381</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>9-17yr Pediatric</td>
<td>485</td>
<td>150</td>
<td>83</td>
<td>190</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Adult</td>
<td>422</td>
<td>219</td>
<td>83</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Japon</td>
<td>618</td>
<td>309</td>
<td>86</td>
<td>251</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>UK/NIBSC</td>
<td>422</td>
<td>219</td>
<td>83</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>50-64yr Older Adult</td>
<td>816</td>
<td>453</td>
<td>166</td>
<td>355</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Elderly</td>
<td>381</td>
<td>184</td>
<td>43</td>
<td>166</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>≥85yr Elderly</td>
<td>394</td>
<td>✓</td>
<td>49</td>
<td>106</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
</tbody>
</table>

**Geometric Mean Titers (GMTs)**

- GMTs relative to **CELL-propagated** A/Haw/1/1918:
  - 5A1: H1/70 Slat
  - 5A1 + A187Y
  - 5A2 (N156K)
  - 5A2 (N156K) + K205M
  - 5B (K132N + K160M)

**A/HAWAII/70/2019 Slat**

- 6-35mo Pediatric
- 3-8yr Pediatric
- 9-17yr Pediatric
- Adult
- Japon
- UK/NIBSC
- 50-64yr Older Adult
- Elderly
- ≥85yr Elderly

**Countries and Regions:**

- USA
- China
- Japan
- UK/NIBSC

**Strain Abbreviations:**

- A/Arkansas/08/2020 (AR/08)
- A/Guangdong/Madon/1536/2019 (GUAN/1536)
- A/Hawaii/70/2019 (H1/70)
- A/Idaho/07/2018 (ID/07)
- A/Louisiana/01/2020 (LA/01)
- A/Maryland/4/2019 (MD/42)
- A/Wisconsin/588/2019 (W1/588)

**Statistical Comparisons:**

- Green indicates statistical non-inferiority.
- Red 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 ✓ denote statistically significant non-inferiority when the reference virus GMT is >40 or <40 respectively.

**Legend:**

- GMT ratio lower bound (90% CI)
Human post-vaccination sera analysis with H1N1 viruses (2)

Clade or Subclade (+ additional substitutions)

<table>
<thead>
<tr>
<th>Clade or Subclade</th>
<th>5A1</th>
<th>5A1 +A187V</th>
<th>5A2 (N156K)</th>
<th>5A2 (N156K)+K209M</th>
<th>5B (K130N+K160M)</th>
<th>3</th>
<th>7</th>
</tr>
</thead>
<tbody>
<tr>
<td>*HI/70 Siat</td>
<td>*GUAN/1536 Egg</td>
<td>WI/588 Siat</td>
<td>AR/08 Siat</td>
<td>MD/42 Siat</td>
<td>ID/07 Siat</td>
<td>LA/01 Siat</td>
<td></td>
</tr>
<tr>
<td>6-35mo Pediatric</td>
<td>USA</td>
<td>IIIV4</td>
<td>51%</td>
<td>35%</td>
<td>20%</td>
<td>20%</td>
<td>20%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>9</td>
<td>6</td>
<td>8</td>
<td>8</td>
<td>8</td>
</tr>
<tr>
<td>50-64yr Older Adult</td>
<td>USA</td>
<td>IIIV4</td>
<td>65%</td>
<td>45%</td>
<td>25%</td>
<td>75%</td>
<td>75%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>70%</td>
<td>40%</td>
<td>35%</td>
<td>60%</td>
<td>60%</td>
</tr>
<tr>
<td>≥65yr Elderly</td>
<td>USA</td>
<td>IIIV4-HD</td>
<td>75%</td>
<td>70%</td>
<td>90%</td>
<td>85%</td>
<td>85%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>94%</td>
<td>90%</td>
<td>90%</td>
<td>184</td>
<td>94</td>
</tr>
</tbody>
</table>

Arrow (↑) represents percent (%) seroconversion: ≥4-fold rise from pre- to post-vaccination with post-vaccination titer ≥ 40

Pre (Bl.) (Or.) Vac Tite

WHO Collaborating Center for Surveillance, Epidemiology and Control of Influenza, Influenza Division, National Center for Immunization and Respiratory Diseases
Summary of A(H1N1)pdm09 Viruses (1)

- A(H1N1)pdm09 viruses predominated in some countries in northern hemisphere
  - Africa (Egypt, Niger and Togo), Asia (the Democratic People’s Republic of Korea) and Europe (Ukraine).

- HA gene sequences belong to clade 6B.1A, with subclades 5A, 5B co-circulating
  - Majority belong to subclade 5A, which has further diversified
    - 5A1 HA proteins have D187A and Q189E substitutions (site Sb)
    - 5A2 HA proteins have N156K and L161I, K130N, V250A in HA1, as well as E179D in HA2

- Ferret antisera to reference A(H1N1)pdm09 viruses (e.g., A/Guangdong-Maonan/SWL1536/2019-like (5A1) well recognized many circulating viruses, except HA subclade 5A2 (156K) viruses
Summary of A(H1N1)pdm09 Viruses (2)

• Post vaccination sera collected from humans vaccinated with NH 2020-2021 vaccines
  • GMTs against viruses representing HA group 5A2 (156K) were significantly reduced
• Of 20 viruses analyzed, none showed reduced susceptibility to one or more of the neuraminidase inhibitors.
• Genetic analysis of 20 viruses indicated that all should be susceptible to baloxavir.
Influenza A(H3N2) viruses
September 2020 - February 2021
Number of A(H3N2) viruses detected by GISRS

Data source: FluNet, (www.who.int/flunet), Global Influenza Surveillance and Response System (10 February 2021)
Influenza A(H3N2) Virus Activity Global Distribution

Influenza A(H3N2), September 2020 to January 2021, percent of all samples tested

WHO Collaborating Center for Surveillance, Epidemiology and Control of Influenza, Influenza Division, National Center for Immunization and Respiratory Diseases
Phylogeography of A(H3N2) HA and Integrated Antigenic Data

2021-22 vaccine recommendation in this subclade

Current cell prototype
A(H3N2)HA 3C clade distribution
February 2020 to September 2020*

*Based on HA Sequence Availability

Source: US CDC
A(H3N2)HA 3C clade distribution
September - February 2021*

*Based on HA Sequence Availability

Source: US CDC
Reactivity of Recent A(H3N2) Viruses with Antisera to Antigens Recommended for NH 2020-21 and SH 2021

Ferret antisera to vaccine reference viruses in subclade 3C.2a1b.1b

<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>12 (38%)</td>
<td>20 (63%)</td>
</tr>
<tr>
<td>FCI</td>
<td>10 (67%)</td>
<td>5 (33%)</td>
</tr>
<tr>
<td>VIDRL</td>
<td>0</td>
<td>3 (100%)</td>
</tr>
<tr>
<td>TOTAL</td>
<td>22 (44%)</td>
<td>28 (56%)</td>
</tr>
</tbody>
</table>

<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>0 (0%)</td>
<td>32 (100%)</td>
</tr>
<tr>
<td>FCI</td>
<td>0 (0%)</td>
<td>15 (100%)</td>
</tr>
<tr>
<td>VIDRL</td>
<td>0 (0%)</td>
<td>3 (100%)</td>
</tr>
<tr>
<td>TOTAL</td>
<td>0 (0%)</td>
<td>50 (100%)</td>
</tr>
</tbody>
</table>

Data from virus neutralization assays using viruses isolated from specimens with collection dates from September 1, 2020 to January 31, 2021.
A(H3N2) Antigenic Cartography of VN Data

Since January 2020 (older viruses in grey)

A/HK/2671/19-egg
A/HK/2671/19-cell
A/Tasmania/503/20-cell
A/HK/45/19-cell
A/HK/45/19-cell like
A/Cambodia/e0826360/20-egg
A/Cambodia/e0826360/20-cell

University of Cambridge
### Antigenic analysis of Recently Circulating A(H3N2) Viruses

<table>
<thead>
<tr>
<th>Reference viruses for:</th>
<th>Current Vaccine</th>
<th>Recommended Vaccine</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>S3 EG</td>
<td>Cell</td>
</tr>
<tr>
<td></td>
<td>A8/69</td>
<td>DAR726</td>
</tr>
<tr>
<td></td>
<td>A1b/131K</td>
<td>A1b/137F</td>
</tr>
</tbody>
</table>

#### REFERENCE ANTIGENS

<table>
<thead>
<tr>
<th>Virus</th>
<th>Fold Difference</th>
<th>Hemagglutination Inhibition Assay</th>
</tr>
</thead>
<tbody>
<tr>
<td>A/South Australia/34/2019</td>
<td>320 160 40</td>
<td>80 640 640 160 320 80</td>
</tr>
<tr>
<td>A/Darwin/728/2019</td>
<td>40 1280 80</td>
<td>40 640 640 160 320 80</td>
</tr>
<tr>
<td>A/Hong Kong/2871/2019</td>
<td>60 1280 1280</td>
<td>80 640 640 160 320 80</td>
</tr>
<tr>
<td>A/Bangladesh/10006/2020</td>
<td>60 80 40</td>
<td>320 320 160 160 80 20</td>
</tr>
<tr>
<td>A/Bangladesh/10009/2020</td>
<td>60 80 40</td>
<td>320 320 160 160 80 20</td>
</tr>
<tr>
<td>A/Cambodia/E0826360/2020</td>
<td>80 40 20</td>
<td>160 160 80 320 80 10</td>
</tr>
<tr>
<td>A/Cambodia/E0826360/2020.1</td>
<td>80 40 20</td>
<td>160 160 80 320 80 10</td>
</tr>
<tr>
<td>A/Taiwan/5032/2020</td>
<td>40 40 20</td>
<td>80 80 320 40 160 10</td>
</tr>
</tbody>
</table>

#### TEST ANTIGENS

<table>
<thead>
<tr>
<th>Virus</th>
<th>Fold Difference</th>
<th>Hemagglutination Inhibition Assay</th>
</tr>
</thead>
<tbody>
<tr>
<td>A/Bangladesh/30112020</td>
<td>80 160 80</td>
<td>640 640 160 320 80 40</td>
</tr>
<tr>
<td>A/Bangladesh/40022020</td>
<td>80 160 80</td>
<td>640 640 160 320 80 40</td>
</tr>
<tr>
<td>A/Bangladesh/30052020</td>
<td>80 80 80</td>
<td>640 640 160 320 80 40</td>
</tr>
<tr>
<td>A/Bangladesh/9110092020</td>
<td>40 80 40</td>
<td>640 640 160 320 80 40</td>
</tr>
<tr>
<td>A/Timor-Leste/172020</td>
<td>160 160 40</td>
<td>320 320 640 160 640 20</td>
</tr>
<tr>
<td>A/Cambodia/E0826361/2020</td>
<td>80 80 40</td>
<td>160 160 640 80 320 20</td>
</tr>
<tr>
<td>A/Cambodia/E0903837/2020</td>
<td>80 80 40</td>
<td>160 160 640 80 320 20</td>
</tr>
<tr>
<td>A/Cambodia/E0826362/2020</td>
<td>80 40 40</td>
<td>160 320 640 80 320 20</td>
</tr>
<tr>
<td>A/Cambodia/E0826363/2020</td>
<td>160 80 20</td>
<td>160 160 640 160 320 20</td>
</tr>
<tr>
<td>A/Timor-Leste/22020</td>
<td>80 80 20</td>
<td>160 160 640 80 320 20</td>
</tr>
<tr>
<td>A/Cambodia/E0826363/2020</td>
<td>80 40 20</td>
<td>160 160 640 80 320 20</td>
</tr>
<tr>
<td>A/Cambodia/E0903836/2020</td>
<td>80 40 20</td>
<td>160 160 640 80 320 20</td>
</tr>
<tr>
<td>A/Cambodia/E09025253/2020</td>
<td>80 40 20</td>
<td>160 160 640 80 320 20</td>
</tr>
<tr>
<td>A/Cambodia/E09025256/2020</td>
<td>80 40 20</td>
<td>160 160 640 80 320 20</td>
</tr>
<tr>
<td>A/California/65/2020</td>
<td>40 20 20</td>
<td>320 80 160 10</td>
</tr>
</tbody>
</table>

Hemagglutination Inhibition Assay Source: VIDRL

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

CDC
### Human Post-vaccination Sera Analysis With A(H3N2) Viruses (1)

#### GMTs relative to CELL-propagated A/Hong Kong/45/2019 (2a1b.1b)

<table>
<thead>
<tr>
<th>Region</th>
<th>Age Group</th>
<th>Vaccine</th>
<th>HK/45/19 EGG</th>
<th>PA/1028/19</th>
<th>NY/21/19</th>
<th>TAS/503/19</th>
<th>MA/006/19</th>
<th>KS/14/19</th>
</tr>
</thead>
<tbody>
<tr>
<td>USA</td>
<td>6-35mo Pediatric</td>
<td>IIIV4</td>
<td>23</td>
<td>X</td>
<td>10</td>
<td>X</td>
<td></td>
<td>9</td>
</tr>
<tr>
<td>USA</td>
<td>3-8yr Pediatric</td>
<td>IIIV4</td>
<td>640</td>
<td>171</td>
<td>331</td>
<td>260</td>
<td>155</td>
<td>320</td>
</tr>
<tr>
<td>USA</td>
<td>6yr or older</td>
<td>IIIV4</td>
<td>597</td>
<td>149</td>
<td>160</td>
<td>166</td>
<td>83</td>
<td>309</td>
</tr>
<tr>
<td>USA</td>
<td>50-64yr Older Adult</td>
<td>IIIV4</td>
<td>485</td>
<td>126</td>
<td>126</td>
<td>92</td>
<td>57</td>
<td>279</td>
</tr>
<tr>
<td>USA</td>
<td>50-64yr Older Adult</td>
<td>IIIV-AD</td>
<td>44</td>
<td>18</td>
<td>17</td>
<td>15</td>
<td>13</td>
<td></td>
</tr>
</tbody>
</table>

**Recent 2a subclade viruses:**

- H5N1, H7N9
- H5N2
- H9N2

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**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 considered non-inferior. *p* values are shown for GMTs for the unadjusted model. They are shown for reference antigens and possibly inferior test antigens. Marks ‘\( \sqrt \)' or ‘X’ denote statistically significant non-inferiority when the GMT ratio lower bound is between 0.40 and 0.40 respectively. Strain abbreviations: A/BANGLADESH/10008/2020 (BGD/10008); A/CA/55/2020 (CA/55); A/HONG KONG/2671/2019 (HK/2671); A/HONG KONG/45/2019 (HK/45); A/KANSAS/14/2017 (KS/14); A/NEW YORK/21/2020 (NY/21); A/MISSOURI/1029/2016 (PA/1029); A/TASMANIA/903/2020 (TAS/903).
Human post-vaccination sera analysis with A(H3N2) viruses (2)

Arrow (↑) represents percent (%) seroconversion: ≥4-fold rise from pre- to post-vaccination with post-vaccination titer ≥ 40
Summary of A(H3N2) Viruses (1)

- In most countries, areas and territories reporting influenza A viruses, both A(H1N1)pdm09 and A(H3N2) subtypes were detected.
- HA phylogenetics: Circulating A(H3N2) viruses in this period belonged to 3C.2a1b subclades with the following shared HA1 substitutions
  - 1a (also called T135K-A), with T135K, A138S, G186D, D190N, F193S & S198P
  - 1b (also called T135K-B) with T135K, S137F, A138S & F193S
    - 2020-21 vaccine virus in this group
  - 2a (also called T131K-A) with K83E, Y94N & T131K
    - New vaccine virus recommendations are in this group
    - Two subgroups that share F193S and Y195F formed these have:
      - K171N, G186S & S198P
      - Y159N, T160I (resulting in the loss of a glycosylation site), L164Q, G186D & D190N
    - Both groups shared D463N and N465S substitutions in the NA, which creates a potential N-linked glycosylation motif.
  - Viruses with HA genes belonging to 3C.2a1b subclade 2b (also called T131K-B) with T131K, Q197R and S219F, or clade 3C.3a were not detected in this period.
Summary of A(H3N2) Viruses (2)

- Ferret antisera raised against cell culture-propagated A/Hong Kong/45/2019-like viruses (3C.2a1b.1b) recognized
  - subclade 3C.2a1b.1a viruses well
  - the group within subclade 3C.2a1b.2a with HA1 substitutions K171N, G186S and S198P less well
  - the group within subclade 3C.2a1b.2a with HA1 substitutions Y159N, T160I, L164Q, G186D and D190N poorly
- Ferret antisera raised against egg-propagated A/Hong Kong/2671/2019-like viruses (3C.2a1b.1b) recognized all recent viruses poorly.
Summary of A(H3N2) Viruses (3)

• Ferret antisera to cell culture-propagated A/Cambodia/e0826360/2020 and A/Tasmania/503/2020 (3C.2a1b.2a) recognized viruses from
  • Subclade 3C.2a1b.1a and subclade 3C.2a1b.2a with additional HA1 substitutions K171N, G186S and S198P well
  • Subclade 3C.2a1b.2a with additional HA1 substitutions Y159N, T160I, L164Q, G186D and D190N less well
• Neither group of 3C.2a1b.2a viruses was recognized as well by antisera to egg-propagated A/Cambodia/e0826360/2020-like viruses in HI and VN assays.
Summary of A(H3N2) Viruses (4)

Human serology studies with serum panels from individuals vaccinated with A/Hong Kong/2671/2019-like or A/Hong Kong/45/2019-like (3C.2a1b.1b) viruses:

- Post-vaccination GMTs were significantly reduced against cell culture-propagated subclade 3C.2a1b.1b and 3C.2a1b.2a viruses but not against either 3C.2a1b.1a or 3C.2a1b.2b subclades or the 3C.3a HA clade.

- When compared to titres against egg-propagated A/Hong Kong/2671/2019-like reference viruses, significant reductions in GMTs were observed against cell culture-propagated viruses from all HA subclades.

Antiviral Susceptibility

- Of 140 A(H3N2) viruses collected and tested after August 2020, none showed reduced inhibition to neuraminidase inhibitors.

- Of 147 A(H3N2) viruses collected and tested after August 2020, none showed genetic or phenotypic evidence of reduced susceptibility to baloxavir.
Influenza B viruses
September 2020 - February 2021
Influenza B Virus Activity Geographic Distribution

Influenza B, September 2020 to January 2021, percent of all samples tested

- Not applicable
- No detections or no data
- 0-5% Positive
- 5-10% Positive
- 10-20% Positive
Number of B viruses detected by GISRS

Data source: FluNet, (www.who.int/flunet), Global Influenza Surveillance and Response System (10 February 2021)
Influenza B virus lineages %
(Sep 2020 – Jan 2021)

Data source: FluNet, (www.who.int/flunet), Global Influenza Surveillance and Response System (10 February 2021)
Influenza B/Victoria lineage viruses
B/Victoria HA clade distribution
September 2020-January 2021*

*Based on HA Sequence Availability

Source: CDC, USA
B/Victoria lineage phylogenetic and antigenic integration
### Reactivity of B/Victoria viruses with ferret antisera to antigens recommended for NH 2020-21 and SH 2021 by HI Assay

<table>
<thead>
<tr>
<th>B/Washington/02/2019-like (cell)</th>
<th>B/Washington/02/2019-like (egg)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>WHO CC</strong></td>
<td><strong>Like (2-4 fold)</strong></td>
</tr>
<tr>
<td>CDC</td>
<td>144 (95%)</td>
</tr>
<tr>
<td>CNIC</td>
<td>93 (38%)</td>
</tr>
<tr>
<td>FCI</td>
<td>176 (81%)</td>
</tr>
<tr>
<td>NIID</td>
<td>59 (98%)</td>
</tr>
<tr>
<td>VIDRL</td>
<td>32 (100%)</td>
</tr>
<tr>
<td><strong>TOTAL</strong></td>
<td>504 (72%)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>WHO CC</strong></th>
<th><strong>Like (2-4 fold)</strong></th>
<th><strong>Low (≥ 8 fold)</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>CDC</td>
<td>2 (100%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>CNIC</td>
<td>32 (18%)</td>
<td>149 (82%)</td>
</tr>
<tr>
<td>FCI</td>
<td>1 (20%)</td>
<td>4 (80%)</td>
</tr>
<tr>
<td><strong>TOTAL</strong></td>
<td>35 (19%)</td>
<td>153 (81%)</td>
</tr>
</tbody>
</table>

**WHO Collaborating Center for Surveillance, Epidemiology and Control of Influenza, Influenza Division, National Center for Immunization and Respiratory Diseases**
B/Victoria Antigenic Cartography

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

University of Cambridge
Reactivity patterns of various antisera
Antisera circles (within 4-fold of homologous titer) using antisera to:

B/Victoria/705/2018-cell

B/Sichuan Jingyang/12048/2019-cell

University of Cambridge

Influenza Division, National Center for Immunization and Respiratory Diseases
## Human post-vaccination sera analysis with B/Victoria Viruses (1)

<table>
<thead>
<tr>
<th>Age Group</th>
<th>Serum Type</th>
<th>MD/24 MDCK</th>
<th>WA/02 MDCK</th>
<th>WA/02 Egg</th>
<th>LBN/16 MDCK</th>
<th>FL/09 MDCK</th>
<th>IAV/06 MDCK</th>
</tr>
</thead>
<tbody>
<tr>
<td>6-35mo Pediatric</td>
<td>USA</td>
<td>IIV4</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
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<tr>
<td>3-8yr Pediatric</td>
<td>USA</td>
<td>ccIIV4 (Flucelvax)</td>
<td>92</td>
<td>√</td>
<td>√</td>
<td>√</td>
<td>51</td>
</tr>
<tr>
<td>9-17yr Pediatric</td>
<td>USA</td>
<td>ccIIV4 (Flucelvax)</td>
<td>70</td>
<td>√</td>
<td>√</td>
<td>√</td>
<td>57</td>
</tr>
<tr>
<td>Adult</td>
<td>USA</td>
<td>ccIIV4 (Flucelvax)</td>
<td>106</td>
<td>√</td>
<td>√</td>
<td>63</td>
<td>√</td>
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<tr>
<td>Japan</td>
<td>IIV4</td>
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<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>UK/NIBSC</td>
<td>IIV4</td>
<td>46</td>
<td>√</td>
<td>25</td>
<td>√</td>
<td>29</td>
<td></td>
</tr>
<tr>
<td>50-64yr Older Adult</td>
<td>USA</td>
<td>IIV4</td>
<td>X</td>
<td>17</td>
<td>X</td>
<td>20</td>
<td>X</td>
</tr>
<tr>
<td>Elderly</td>
<td>USA</td>
<td>IIV4-HD</td>
<td>46</td>
<td>√</td>
<td>√</td>
<td>√</td>
<td>31</td>
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<tr>
<td>Japan</td>
<td>IIV4</td>
<td>27</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>24</td>
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</tr>
</tbody>
</table>

**Note:** HI GMTs relative to CELL-propagated B/Washington/02/2019 (V1A.3)

**Source:** CDC, USA
Human post-vaccination sera analysis with B/Victoria Viruses (2)

<table>
<thead>
<tr>
<th></th>
<th>V1A.3</th>
<th>V1A.3 +E128K</th>
<th>V1A.3 +N150K</th>
<th>V1A.3 +D129G +N23355 (CHO-)</th>
<th>V1A.3 +N128K</th>
<th>V1A.1</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>WA/02 MDCK</td>
<td>WA/02 Egg</td>
<td>MD/24 MDCK</td>
<td>RII/01 MDCK</td>
<td>LBN/16 MDCK</td>
<td>FL/09 MDCK</td>
</tr>
<tr>
<td>6-35mo Pediatric</td>
<td>USA</td>
<td>IV4</td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
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<td></td>
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</tr>
<tr>
<td>3-4yr Pediatric</td>
<td>USA</td>
<td>IV4</td>
<td></td>
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</tr>
<tr>
<td>Elderly</td>
<td>USA</td>
<td>IV4-HD</td>
<td></td>
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<td></td>
<td></td>
</tr>
</tbody>
</table>

Arrow (↑) represents percent (%) seroconversion: ≥4-fold rise from pre- to post-vaccination with post-vaccination titer ≥ 40
Summary of B/Victoria Lineage Viruses (1)

• Influenza B Victoria lineage viruses greatly predominated over those of the B/Yamagata lineage
  • Majority of viruses from this period were identified in China

• HA phylogenetics
  • All HA genes belonged to subclade 1A.3. These have a deletion of residues 162-164 and a K136E substitution in HA1.
    • Many also share G133R
  • The HA of most recently collected viruses are in subclade 1A.3 and form a subgroup sharing N150K, G184E, N197D (CHO loss) and R279K, but lack G133R (1A.3-150K)
    • Two recent subgroups that have either V220M and P241Q (China and West Africa), or A127T, P144L and K203R (Europe, West Africa and Oman)
Summary of B/Victoria Lineage Viruses (2)

• Antigenic characteristics
  • Most viruses tested since February 2020 were recognized well by ferret antisera raised against cell-propagated or egg-propagated B/Washington/02/2019
  • 1A.3-150K HA subgroup of viruses predominated since September 2020
    • Showed reduced inhibition by ferret antisera to cell- or egg-propagated B/Washington/02/2019-like viruses
  • Ferret antisera to cell-propagated HA subgroup 1A.3-150K reference viruses
    • well inhibited closely related 1A.3-150K HA subgroup viruses
    • poorly inhibited most other viruses that have 1A.3 HA genes
  • Post vaccination human sera generally well inhibited all test viruses including 1A.3-150K HA subgroup viruses

• Antiviral susceptibility
  • Of 144 viruses analyzed, all were susceptible to oseltamivir, 1 showed reduced inhibition by zanamivir
  • All 16 viruses tested were susceptible to laninamivir and peramivir
  • None of the 41 viruses analyzed showed evidence of reduced susceptibility to baloxavir
B/Yamagata lineage viruses
B/Yamagata phylogenetic tree

North America
South America
Europe
Africa
Middle East
Russia
E SE Asia
Oceania

Clade 3
A/Phuket/3073/2013
Reactivity of recent B/Yamagata viruses with antisera to antigens recommended for NH 2020-21 and SH 2021

• No B/Yamagata lineage viruses with collection dates after August 2020 were available for antigenic analysis

• The few viruses available with collection dates earlier in 2020 were antigenically similar to B/Phuket/3073/2013
B/Yamagata Antigenic Cartography

University of Cambridge

Past 12 months (older viruses in grey)

B/Yamagata
CC Atlanta

B/Phuket/3073/2013-egg

B/Phuket/3073/2013-cell

(HI data)

Y3
Summary of B/Yamagata Lineage Viruses

• Influenza B viruses of the B/Yamagata lineage were rarely detected
  • No viruses were available with collection dates after August 2020
• All viruses from 2020 had HA genes in clade 3 (e.g. B/Phuket/3073/2013)
• Most recent viruses were well recognized by ferret antisera to cell culture-propagated or egg-propagated B/Phuket/3073/2019
• Post vaccination human sera well recognized viruses representative of those most recently circulating
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
• CDC Influenza Division staff
  • Special thanks to Rebecca Kondor, Min Levine, Larisa Gubareva and John Steel
Candidate vaccine viruses

• The WHO recommended candidate viruses for vaccine development and production for NH 2021-2022 available:  http://www.who.int/influenza/vaccines/virus/en/

• Guidance to tropical and subtropical countries: which formulation (northern hemisphere vs. southern hemisphere) and when to start vaccination:
  • http://www.who.int/influenza/vaccines/tropics/en/

• FAQ – vaccine composition recommendation:  http://www.who.int/influenza/

• Candidate vaccine viruses and reagents
  • http://www.who.int/influenza/vaccines/virus/candidates_reagents/home/en/

• Zoonotic influenza summary reports and candidate vaccine viruses on H5/H7/H9 vaccine viruses:
  • WHO GISRS website:  http://www.who.int/influenza/gisrs_laboratory/en/
    • http://www.who.int/influenza/vaccines/virus/en/
Publications

- Guidance to tropical and subtropical countries: which formulation (northern hemisphere vs. southern hemisphere) and when to start vaccination:

- Vaccine composition recommendation report and summary report on H5/H7/H9 vaccine viruses:


- Candidate vaccine viruses and reagents

Global Influenza Programme (GIP): GISRS-whohq@who.int