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

Global Influenza Virus Surveillance and Characterization
September 30, 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

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.
Outline

• Overview of the WHO-VCM and Recommendations for the Southern Hemisphere 2022
• Influenza virus activity
• A(H1N1)pdm09, describe major highlights
  • Recommendation is same as the NH 2021-2022 season and SH 2021 recommendation
• A(H3N2), provide details central to the recommendation
  • Update from previous SH 2021 recommendation
  • Similarities and differences from NH 2021-22 recommendation
• B/Victoria lineage viruses, provide details central to the recommendation
  • Update from previous SH 2021 recommendation
• B/Yamagata lineage, will not cover
  • Recommendation remains the same and no circulation of this lineage during this period
WHO Influenza Vaccine Consultation Meeting

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

- WHO consultation meeting held from Sep 13 – 24, 2021
  - A virtual meeting – 17 hours’ time difference among participants
  - Chaired by Dr Kanta Subbarao (pictured right)
  - 10 Advisers: Directors of WHOCCs and ERLs
    - 8 for seasonal influenza and represent their corresponding WHO CCs and ERLs

- 42 observers from WHO CCs, WHO ERLs, academia, H5 Reference laboratories and veterinary sector OFFLU
- Experts from WHO Regional Offices and Head Quarters
It is recommended that vaccines for use in the 2022 southern hemisphere influenza season contain the following:

**Quadrivalent: Egg-based Vaccines**

- an A/Victoria/2570/2019 (H1N1)pdm09-like virus*;
- an A/Darwin/9/2021 (H3N2)-like virus*;
- a B/Austria/1359417/2021 (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/Darwin/6/2021 (H3N2)-like virus*;
- a B/Austria/1359417/2021 (B/Victoria lineage)-like virus*; and
- a B/Phuket/3073/2013 (B/Yamagata lineage)-like virus.

* Different from that recommended for the southern hemisphere 2021 season
Number of Specimens Processed by GISRS
Number of Specimens Positive for Influenza by Subtype

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

Data source: FluNet, (www.who.int/flu)
Percentage of Influenza A and B Viruses (Feb – Aug 2021)

- Type A, 40%
  - H1 -> 20%
  - H3 -> 80%
- Type B, 60%
  - B/Victoria greater than 99%
  - B/Yamagata less than 0.5%

Data source: FluNet, (www.who.int/flunet), Global Influenza Surveillance and Response System (GISRS)
Influenza Activity – (Feb – Aug 2021)

Distribution of influenza virus type/subtype by influenza transmission zone, between February and September 2021

Note: The available country data were joined in larger geographical areas with similar influenza transmission patterns to be able to give an overview (https://cdn.who.int/media/docs/default-source/influenza/influenza-updates/2020/influenza_transmission_zones20180914.pdf?sfvrsn=8dbade6c_3).

Data Source: WHO/GIP. FLNet (www.who.int/flu) as of 13 September 2021, 07:15 UTC

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Influenza Viruses Genetically Characterized By WHO-CCs

- **A(H1N1)pdm09**: 987 (February to August 2020), 144 (February to August 2021)
- **A(H3N2)**: 444 (February to August 2020), 151 (February to August 2021)
- **B-Victoria**: 572 (February to August 2020), 544 (February to August 2021)
- **B-Yamagata**: 45 (February to August 2020), 0 (February to August 2021)

WHO Collaborating Center for Surveillance, Epidemiology and Control of Influenza, Influenza Division, National Center for Immunization and Respiratory Diseases
A(H1N1)pdm09 Viruses
Number of A(H1N1)pdm09 Viruses Detected by GISRS

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

Influenza A(H1N1)pdm09, February 2021 to August 2021, percent of positive samples

Colour intensity shows the proportion of influenza A(H1N1) among all influenza positives during this period per country

Data source: FluNet, (www.who.int/flunet), Global Influenza Surveillance and Response System (9 Sep 2021)
A(H1N1)pdm09 HA Phylogenetics

- Two major 6B.1.5A subclades
  - 5A1 (e.g., HI/70)
    - Often share D187A, Q189E
    - 2020-21 vaccine antigen
    - Recent viruses from West Africa
    - Few with G155E (NC/01)
  - 5A2 HA (e.g., WI/588)
    - Often share N156K
    - NH 2021-2022 vaccine virus
    - SH 2022 recommendation
    - Recent viruses from India
A(H1N1)pdm09 Antigenic Maps

- The viruses with HA from 6B.1A subclades **5A1** (187A) and **5A2** (156K) form two antigenically distinct groups
  - Virus of each subclade cluster with respective vaccine reference viruses
  - Few 5A viruses with G155E are antigenically distinguishable
Human Post-vaccination Sera Analysis of A(H1N1)pdm09 Viruses (NH 2020-21 Vaccine (5A1))

- Post vaccination sera from NH 2020-21 (5A1), inhibits 5A1 viruses
  - Except G155E viruses (e.g., NC/01), which were infrequently detected
  - GMTs to HA subclade 5A2 (N156K) viruses were low in all serum panels
Human Post-vaccination Sera Analysis of A(H1N1)pdm09 Viruses (SH 2021 Vaccine (5A2))

• Post vaccination sera from SH 2021 (5A2), inhibits 5A2 and most 5A1 viruses
  • Exception G155E virus (e.g., NC/01), which were infrequently detected
A(H1N1)pdm09 Summary (I)

- Low circulation but, A(H1N1)pdm09 viruses were detected in West Africa and India, and sporadically in a few other regions.

- The great majority of HA gene sequences belonged to clade 6B.1A5A, subclades;
  - **5A1** (HA1 D187A, Q189E) HA proteins predominant in West Africa with additional HA1 substitutions I166T and A186T;
  - **5A2** (HA1 K130N, N156K, L161I, V250A and HA2 E179D) HA proteins were seen in recent viruses from India with additional HA1 substitutions K54Q, A186T, Q189E and E224A in HA1 and N43S in HA2;

- Characterization with ferret antisera showed **5A1 and 5A2 viruses were antigenically distinct**
  - Antisera 5A1 viruses (e.g., A/Hawaii/70/2019) well recognized most recent 5A1 viruses, but not 5A2 viruses
  - Antisera to 5A2 viruses (e.g. A/Wisconsin/588/2019) well recognized recently circulating 5A2 viruses, but not HA subclade 5A1 viruses
A(H1N1)pdm09 Summary (II)

Post vaccination sera collected from humans vaccinated with:

• NH 2020-21 vaccines (5A1 antigens) inhibited reference viruses representing most 5A1 viruses, but not 5A2 viruses
• SH 2021 vaccines (5A2 antigens) had sera that inhibited 5A2 viruses and well recognized viruses representing most 5A1 viruses

Antiviral susceptibility

• All A(H1N1)pdm09 viruses analyzed showed normal susceptibility to the neuraminidase inhibitors.
• Genetic analysis revealed a single virus with reduced susceptibility to baloxavir.
Influenza A(H3N2) Viruses
Number of A(H3N2) Viruses Detected by GISRS (2018-2021)

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

Colour intensity shows the proportion of influenza A(H3N2) among all influenza positives during this period per country.

Data source: FluNet, (www.who.int/flunet), Global Influenza Surveillance and Response System (9 Sep 2021)
Phylogenetics of A(H3N2) HA Gene

- Many clades co-circulate
- Major clades
  - 3C.3a
  - 3C.2a
    - Many 2a1b subclades
- 2a1b1a subclades 1a and 2a represent most recent circulating viruses

Source: University of Cambridge
Nearly all viruses have clade 3C.2a1b HA gene which continues to diversify

- **2a1b.1b** (e.g., A/Hong Kong/45/2019)
  - Often share T135K, S137F
- **2a1b.1a** (e.g., A/New York/21/2020)
  - Typically share T135K, G186D, S198P
  - Further diversified
    - I192F (e.g., A/Togo/771/2020)
    - T131I & I192F (e.g., A/Niger/8749/2021)
- **2a1b.2a** (most of the recent viruses)
  - Usually share T131K, Y94N, F193S, Y195F
  - Evolved into two subclades
    - **2a1** (e.g., A/Cambodia/E0826360/2020)
      - Often have K171N,G186S, S198P
    - **2a2** (e.g., A/Bangladesh/10006/2020)
      - Often have Y159N, T160I, L164Q, G186D, D190N

Source: U.S. CDC: Based on HA Sequence Availability on 09/13/2021
Global Circulation of A(H3N2) Viruses

September 2020 – January 2021

February 2021 – August 2021

Source: U.S. CDC: Based on HA Sequence Availability on 09/13/2021

- Phylogeography of the HA gene shows transition of 2a1b subclades
  - Global distribution of 1a and 1b decreased (yellow/aqua)
  - Global distribution of 2a2 (forest green) increased and 2a1 continued to circulate
Location of Substitutions on H3 HA Monomer

- HA Clade 2a1b.2A viruses have mutations in many epitopes compared to SH 2021 vaccine prototype (2a1b.1b)
  - 2a1 and 2a2 share many changes (e.g., Y94N, S138A, F137S, G186S/D, K135T, T131K, A128T)
  - Compared to 2a1, emerging 2a2 have a few additional substitutions (e.g., Y159N, D190N)

Source: U.S. CDC
# Neutralization of A(H3N2) Viruses By Antisera To Antigens Recommended For The 2021 Southern Hemisphere

## A/Hong Kong/45/2019-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>0 (0%)</td>
<td>20 (100%)</td>
</tr>
<tr>
<td>FCI</td>
<td>6 (21%)</td>
<td>22 (79%)</td>
</tr>
<tr>
<td>NIID</td>
<td>0 (0%)</td>
<td>14 (100%)</td>
</tr>
<tr>
<td>VIDRL</td>
<td>1 (4%)</td>
<td>26 (96%)</td>
</tr>
<tr>
<td>TOTAL</td>
<td>7 (8%)</td>
<td>82 (92%)</td>
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## A/Hong Kong/2671/2019-like (egg)*

<table>
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<th>WHO CC</th>
<th>Like (2-4 fold)</th>
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<tr>
<td>CDC</td>
<td>0 (0%)</td>
<td>20 (100%)</td>
</tr>
<tr>
<td>NIID</td>
<td>0 (0%)</td>
<td>14 (100%)</td>
</tr>
<tr>
<td>VIDRL</td>
<td>0 (0%)</td>
<td>12 (100%)</td>
</tr>
<tr>
<td>TOTAL</td>
<td>0 (0%)</td>
<td>46 (100%)</td>
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</table>

*Reference viruses are in HA clade 3C.2a1b.1b

Showing data from viruses isolated from swabs collected from February through August 2021
Neutralization of A(H3N2) Viruses By Antisera To Antigens Recommended for Northern Hemisphere 2021-2022

<table>
<thead>
<tr>
<th>WHO CC</th>
<th>Like (2-4 fold)</th>
<th>Low (≥ 8 fold)</th>
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</thead>
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<tr>
<td>CDC</td>
<td>8 (40%)</td>
<td>12 (60%)</td>
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<tr>
<td>FCI</td>
<td>14 (50%)</td>
<td>14 (50%)</td>
</tr>
<tr>
<td>NIID</td>
<td>13 (80%)</td>
<td>1 (20%)</td>
</tr>
<tr>
<td>VIDRL</td>
<td>22 (81%)</td>
<td>5 (19%)</td>
</tr>
<tr>
<td>TOTAL</td>
<td>57 (64%)</td>
<td>32 (36%)</td>
</tr>
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</table>

<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>9 (32%)</td>
<td>19 (68%)</td>
</tr>
<tr>
<td>NIID</td>
<td>0 (0%)</td>
<td>14 (100%)</td>
</tr>
<tr>
<td>VIDRL</td>
<td>0 (0%)</td>
<td>12 (100%)</td>
</tr>
<tr>
<td>TOTAL</td>
<td>9 (17%)</td>
<td>45 (83%)</td>
</tr>
</tbody>
</table>

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

Showing data from viruses isolated from swabs collected from February through August 2021
A(H3N2) Antigenic Cartography

Source: University of Cambridge

Since September 2020 (older viruses in grey)
### Human Post-vaccination Sera Analysis of A(H3N2) Viruses

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

<table>
<thead>
<tr>
<th>Major clades</th>
<th>2a1b1b</th>
<th>2a1b1a</th>
<th>2a1b2a1</th>
<th>2a1b2a2</th>
<th>3a</th>
</tr>
</thead>
<tbody>
<tr>
<td>-</td>
<td>+TI60 (CHO-O) +G156V +D223N +N312S</td>
<td>-</td>
<td>+</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>HK/45</td>
<td>HK/2671</td>
<td>TGO/771</td>
<td>NER/87/49</td>
<td>KHM/E0826360</td>
<td>DE/01</td>
</tr>
<tr>
<td>Siat</td>
<td>Egg</td>
<td>Siat</td>
<td>Siat</td>
<td>Siat</td>
<td>Siat</td>
</tr>
<tr>
<td>22</td>
<td>14</td>
<td>11</td>
<td>11</td>
<td>11</td>
<td>10</td>
</tr>
</tbody>
</table>

- **6-35mo Pediatric**
  - USA IV4: 22, X, 11, 11, 10
  - cell/IV (Pleulavax) IV4: 018, 102, 155, 90, 279
  - Australia IV4: 166, 64, 46, 24, 39

- **Adult**
  - USA IV4: 018, 102, 155, 90, 279
  - USA IV4-HD: 166, 64, 46, 24, 39
  - Australia IV4-Adjuvant: 47, 18, 26, 22, 18

- **65yr or older**
  - USA IV4: 83, 43, 22, 46, 25
  - Australia IV4-Adjuvant: 36, 14, 19, 15, 9

**Source:** U.S. CDC

- Multiple serum panels show the clade 2a1b.2a viruses escaped neutralization
  - GMTs to 2a2 viruses were typically the lowest
Antigenic Analysis of Reference Viruses & Candidate Vaccine Viruses (CVVs)

Ferret antisera to:

- **SH 2021 reference viruses**
  - Inhibit clade 1a and 1b
  - Poorly inhibited clade 2a1 and 2a2 viruses

- **NH 2021-22 reference viruses**
  - Inhibited 1a, 1b and 2a1 viruses
  - Reduced inhibition of clade 2a2 viruses

- **2a2 reference viruses**
  - SH 2022 recommendation
  - Well inhibited 2a2
  - Reduced inhibition of 2a1
  - Poor inhibition of 1a and 1b viruses

<table>
<thead>
<tr>
<th>Reference Antigens</th>
<th>Passage</th>
<th>Clade</th>
<th>SH 21</th>
<th>NH 21-22</th>
<th>SH 22</th>
</tr>
</thead>
<tbody>
<tr>
<td>A/Perth/20/2020</td>
<td>MDCK-1, SIAT2</td>
<td>3C.2a1b.1a</td>
<td>320</td>
<td>80</td>
<td>160</td>
</tr>
<tr>
<td>A/Darwin/7/2021</td>
<td>SIAT2</td>
<td>3C.2a1b.1b</td>
<td>640</td>
<td>40</td>
<td>160</td>
</tr>
<tr>
<td>A/Hong Kong/2671/2019</td>
<td>E9</td>
<td>3C.2a1b.1b</td>
<td>1280</td>
<td>640</td>
<td>80</td>
</tr>
<tr>
<td>A/Cambodia/e0826360/2020</td>
<td>SIAT2</td>
<td>3C.2a1b.2a1</td>
<td>40</td>
<td>&lt;40</td>
<td>320</td>
</tr>
<tr>
<td>A/Cambodia/e0826360/2020</td>
<td>E5</td>
<td>3C.2a1b.2a1</td>
<td>40</td>
<td>40</td>
<td>160</td>
</tr>
<tr>
<td>A/Bangladesh/10006/2020</td>
<td>S3, SIAT1</td>
<td>3C.2a1b.2a2</td>
<td>80</td>
<td>40</td>
<td>320</td>
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<tr>
<td>A/Darwin/6/2021</td>
<td>SIAT2</td>
<td>3C.2a1b.2a2</td>
<td>&lt;40</td>
<td>40</td>
<td>160</td>
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<tr>
<td>A/Darwin/11/2021</td>
<td>QMC2</td>
<td>3C.2a1b.2a2</td>
<td>40</td>
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<tr>
<td>A/Darwin/9/2021</td>
<td>E4</td>
<td>3C.2a1b.2a2</td>
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<table>
<thead>
<tr>
<th>Test Antigens</th>
<th>Passage</th>
<th>Clade</th>
<th>Collection Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>A/Philippines/1/2021</td>
<td>MDCK2, SIAT1</td>
<td>3C.2a1b.1a</td>
<td>320</td>
</tr>
<tr>
<td>A/Philippines/8/2021</td>
<td>SIAT1</td>
<td>3C.2a1b.1a</td>
<td>320</td>
</tr>
<tr>
<td>A/Yamagata/1/2021</td>
<td>hCK2, SIAT1</td>
<td>3C.2a1b.2a1</td>
<td>80</td>
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<tr>
<td>A/Darwin/17/2021</td>
<td>SIAT1</td>
<td>3C.2a1b.2a2</td>
<td>&lt;40</td>
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<tr>
<td>A/Darwin/18/2021</td>
<td>SIAT1</td>
<td>3C.2a1b.2a2</td>
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<tr>
<td>A/Darwin/19/2021</td>
<td>SIAT1</td>
<td>3C.2a1b.2a2</td>
<td>&lt;40</td>
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<tr>
<td>A/Darwin/23/2021</td>
<td>SIAT1</td>
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<td>&lt;40</td>
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<tr>
<td>A/Darwin/24/2021</td>
<td>SIAT1</td>
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<tr>
<td>A/Nepal/NPWR-05637/2021</td>
<td>hCK2, SIAT1</td>
<td>3C.2a1b.2a2</td>
<td>80</td>
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<tr>
<td>A/Philippines/4/2021</td>
<td>MDCK2, SIAT1</td>
<td>3C.3a</td>
<td>&lt;40</td>
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</table>

Source: VIDRL HI test
Antigenic Analysis of Reference Viruses & Candidate Vaccine Viruses (CVVs)

Ferret antisera to:
- **SH 2021 reference viruses**
  - Inhibit clade 1a and 1b
  - Poorly inhibited clade 2a1 and 2a2 viruses
- **NH 2021-22 reference viruses**
  - Inhibited 1a, 1b and 2a1 viruses
  - Reduced inhibition of clade 2a2 viruses
- **2a2 reference viruses**
  - SH 2022 recommendation
  - Well inhibited 2a2
  - Reduced inhibition of 2a1
  - Poor inhibition of 1a and 1b viruses

<table>
<thead>
<tr>
<th>Reference Antigens</th>
<th>Passage</th>
<th>Clade</th>
<th>3C.2a1b.1b</th>
<th>3C.2a1b.1b</th>
<th>3C.2a1b.1b</th>
<th>3C.2a1b.1b</th>
<th>3C.2a1b.2a</th>
<th>3C.2a1b.2a</th>
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<tbody>
<tr>
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<td>SIAT2</td>
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<td>40</td>
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</tr>
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</table>

Source: VIDRL HI test
A(H3N2) Cartography: Antisera Reactivity

Source: University of Cambridge

Since September 2020 (older viruses in grey)
A(H3N2) Summary (I): Global Circulation

- In many countries, areas and territories reporting influenza A viruses, A(H3N2) subtypes were detected.
  - Included countries in Southeast Asia, South Asia, Middle East, Africa, Oceania, North America and Europe
- HA phylogenetics: circulating A(H3N2) viruses in this period belonged to 3C.2a1b subclades that typically have HA1 substitutions indicated:
  - 1a (T135K (-CHO), A138S, G186D, D190N, F193S and S198P)
  - 1b (T135K (-CHO), S137F, A138S and F193S)
  - 2a (K83E, Y94N and T131K)
    - 2a1 (G186S, F193S, Y195F and S198P)
    - 2a2 (Y159N, T160I (-CHO), L164Q, G186D, D190N, F193S and Y195F)
  - Viruses in the 2a2 group represented increasing proportion
    - 2a2>2a1>1a>1b
A(H3N2) Summary (II): Antigenic Characteristics

• 2a2 viruses are antigenically distinct
  • Ferret antisera to:
    • A/Hong Kong/45/2019-like viruses (SH 21: Cell, 3C.2a1b.1b)
      • Neutralized 1a, 1b viruses well, 2a1 viruses less well, and 2a2 viruses poorly
    • A/Cambodia/e0826360/2020 (NH 21-22: Cell 3C.2a1b.2a1)
      • Reacted well with 1a, 1b and 2a1 viruses but 2a2 viruses were reduced
    • A/Darwin/6/2021 (SH 22 rec: Cell 3c2a1b.2a2)
      • Well recognized 2a2 viruses, showed reduced recognition of 2a1 and poorly reacted 1a, and 1b viruses
A(H3N2) Summary (III)

**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 3C.2a1b.2a1 and 3C.2a1b.2a2

**Antiviral Susceptibility**

- Of 105 A(H3N2) viruses collected and tested after January 2021, none showed reduced inhibition to neuraminidase inhibitors.
- Of 125 A(H3N2) viruses collected and tested after January 2021, none showed genetic or phenotypic evidence of reduced susceptibility to baloxavir.
Influenza B Viruses
Number of B Viruses Detected by GISRS

Data source: FluNet, (www.who.int/flu-net), Global Influenza Surveillance and Response System (GISRS)
Influenza B Virus Activity

Influenza B, February 2021 to August 2021, percent of positive samples

Colour intensity shows the proportion of influenza B among all influenza positives during this period per country

Data source: FluNet, [www.who.int/flunet](http://www.who.int/flunet), Global Influenza Surveillance and Response System (9 Sep 2021)
Influenza B/Victoria Lineage Viruses
B/Victoria HA Phylogenetic Tree

- Clade 1A.3
  - Predominated prior to COVID-19

- Clade 1A.3a (N150K)
  - re-emerged & diversified
    - 1A.3a1
    - 1A.3a2

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

University of Cambridge

WHO Collaborating Center for Surveillance, Epidemiology and Control of Influenza, Influenza Division, National Center for Immunization and Respiratory Diseases
Integrated B/Victoria HA Phylogenetics

• Clade 1A.3
  • Predominated prior to COVID-19
  • SH 2021 vaccine virus (e.g., B/Washington/02/2019)
• Clade 1A.3a (N150K) evolved further
  • Represent most recent viruses
  • 3a1 (V220M, P241Q)
    • Predominated in China early in 2021
    • B/Sichuan-Jingyang/12048/2019
  • 3a2 (A127T, P144L, K203R)
    • Increased steadily in recent months
    • B/Austria/1359417/2021
    • B/MI/01/2021
Neutralization of B/Victoria Viruses By Antisera To Antigens Recommended For The 2021 Southern Hemisphere

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

<table>
<thead>
<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>12 (60%)</td>
<td>8 (40%)</td>
</tr>
<tr>
<td>CNIC</td>
<td>251 (17%)</td>
<td>1224 (83%)</td>
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<tr>
<td>FCI</td>
<td>0 (0%)</td>
<td>10 (100%)</td>
</tr>
<tr>
<td>VIDRL</td>
<td>15 (50%)</td>
<td>15 (50%)</td>
</tr>
<tr>
<td>TOTAL</td>
<td>278 (18%)</td>
<td>1257 (82%)</td>
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</table>

### B/Washington/02/2019-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>CDC</td>
<td>15 (75%)</td>
<td>5 (25%)</td>
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<tr>
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<td>FCI</td>
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<tr>
<td>VIDRL</td>
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<td>25 (100%)</td>
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<tr>
<td>TOTAL</td>
<td>563 (37%)</td>
<td>967 (63%)</td>
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</table>

*Reference viruses are in HA clade 1A.3

Showing data from viruses isolated from swabs collected from February through August 2021
Reactivity Patterns of Various Antisera

Antiserum circles (within 4-fold of homologous titers) using antisera raised against:

1A. 3
B/Washington/02/2019-cell

1A. 3
B/Washington/02/2019-egg

1A. 3a2
B/Austria/1359417/2021-egg
### Human Post-vaccination Sera Analysis of B/Victoria Viruses

#### GMTs Relative to B/Washington/02/2019 (Cell, 1A.3)

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</table>

|                   | V1A.3 | V1A.3a | V1A.3a1 | V1A.3a2 |
|                   |       |        |         |         |
| B/WASHINGTON/02/2019 MDCK |       |        |         |         |
| V/1A.3            |       |        |         |         |
| Pediatric (6-35M) | USA   | BV4    |         |         |
| Pediatric (3-8Y) | USA   | cllBV4 (Flucelvax) |        |         |
| Pediatric (9-17Y) | USA   | cllBV4 (Flucelvax) |        |         |
| Adult             | USA   | BV4    |         |         |
| Australia         | USA   | BV4    |         |         |
| Older Adult (50-64Y) | USA   | BV4    |         |         |
| Elderly           | Australia | BV4-Adjuvant |        |         |
| Elderly (25-65Y)  | USA   | BV4-HD |         |         |

Geometric Mean Titers (GMTs) relative to 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 (90% confidence level), otherwise it is possibly inferior. Heat map cells are colored using the GMT ratio lower bound. Green indicates statistical non-inferiority and 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 0 denote statistically significant non-inferiority when the reference virus GMT is >40 or <40 respectively. Strain abbreviations: B/MARYLAND/01/2021 (MD/01), B/MICHIGAN/01/2021 (MI/01), B/ROYOE ISLAND/01/2019 (RI/01), B/SICHUAN-JINDUYAN/01/2019 (CHN/12048), B/WASHINGTON/02/2019 (WA/02).

1. This virus stock has amino acid polymorphisms K289K/R, W141GW and G241GK.

- Geometric mean titers of some serum panels were reduced to the 1A.3a1 and 1A.3a2 viruses
## Antigenic Analysis of Reference Viruses & Candidate Vaccine Viruses (CVVs)

### Reference Ferret Antisera

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### Test Antigens

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<th>1A.3a1</th>
<th>1A.3a2</th>
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<td>1280</td>
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Source: WHO CC VIDRL, Australia
B/Yamagata Lineage Viruses

Sporadic B/Yamagata/16/88 lineage viruses have been reported in 2021 but none have been confirmed by WHO Collaborating Centres and no viruses with collection dates after March 2020 were available for characterization.
Summary of Influenza B Viruses (I)

• Influenza B/Victoria lineage viruses predominated by a huge margin and no B/Yamagata lineage viruses were available for analysis

• HA phylogenetics of B/Victoria lineage viruses
  • Nearly all HA genes belonged to subclade 1A.3
    • These have a deletion of residues 162-164 and a K136E substitution in HA1
  • Group 1A.3a viruses with HA genes encoding further substitutions of N150K, G184E, N197D and R279K in HA1 have predominated and two subgroups have emerged:
    • 1A.3a1 has additional HA1 substitutions V220M and P241Q, seen almost exclusively in China
    • 1A.3a2 with A127T, P144L and K203R seen in Asia, Africa, Oceania, Europe and North America
  • The number and the proportion of 1A.3a2 viruses have increased steadily over recent months, and they are geographically dispersed
Summary of Influenza B Viruses (II)

Antigenic characteristics of B/Victoria lineage viruses using ferret antisera

- Subgroup 1A.3a1 and 1A.3a2 viruses are antigenically drifted from B/Washington/02/2019-like (1A.3) viruses
  - 3a1 and 3a2 viruses are antigenically distinguishable from each other
- Antisera to B/Austria/1359417/2021-like viruses (1A.3a2) well inhibited circulating viruses from the 3a2 subclade

Human post vaccination sera

- GMTs of some serum panels were significantly reduced against 3a1 and 3a2 viruses

Antiviral susceptibility

- All viruses analyzed showed normal susceptibility to the neuraminidase inhibitors and endonuclease inhibitors
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
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