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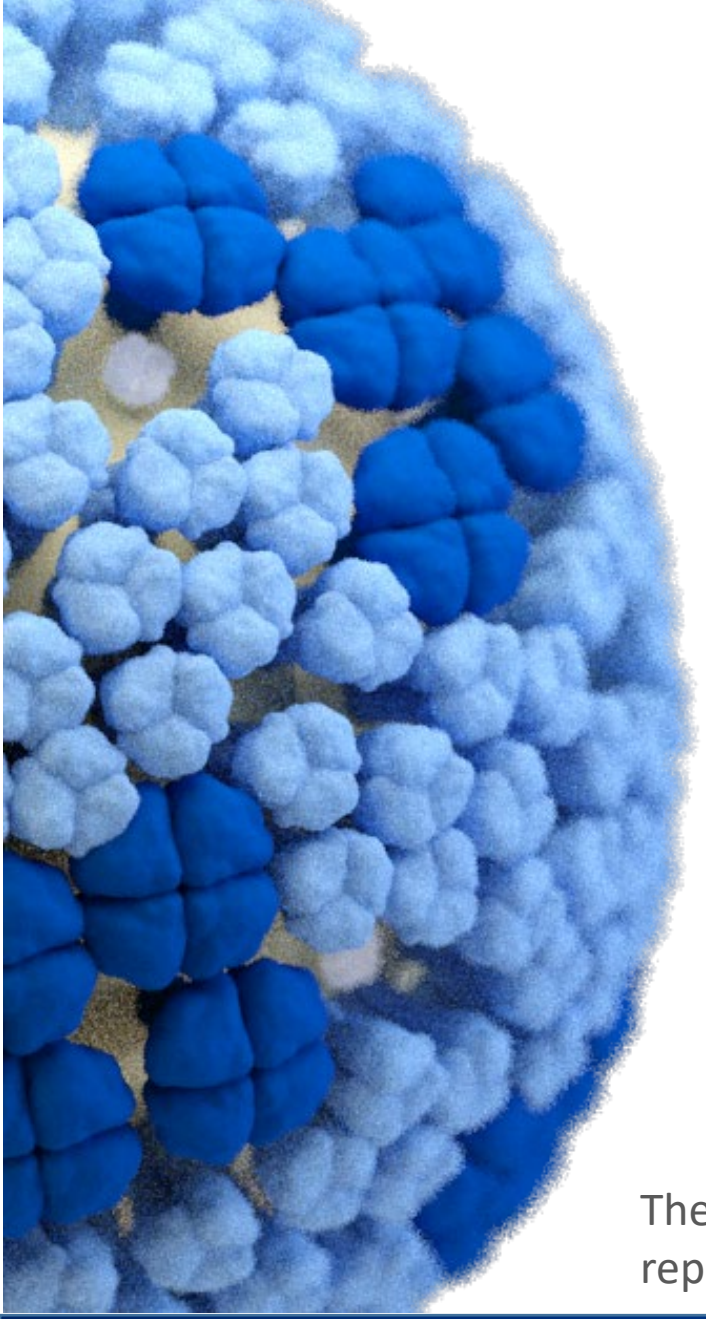


Information For The Vaccine And Related Biological Products Advisory Committee CBER, FDA

Global Influenza Virus Surveillance and Characterization March 7, 2023

David E. Wentworth, Ph.D.

Director, WHO Collaborating Center for Surveillance, Epidemiology and Control of Influenza

Chief, Virology Surveillance and Diagnosis Branch

Influenza Division, National Center for Immunization and Respiratory Diseases

Centers for Disease Control and Prevention

Atlanta, GA 30333

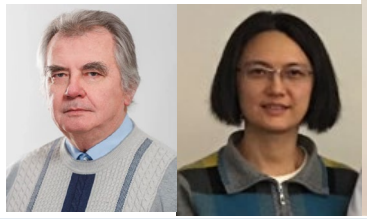
Outline

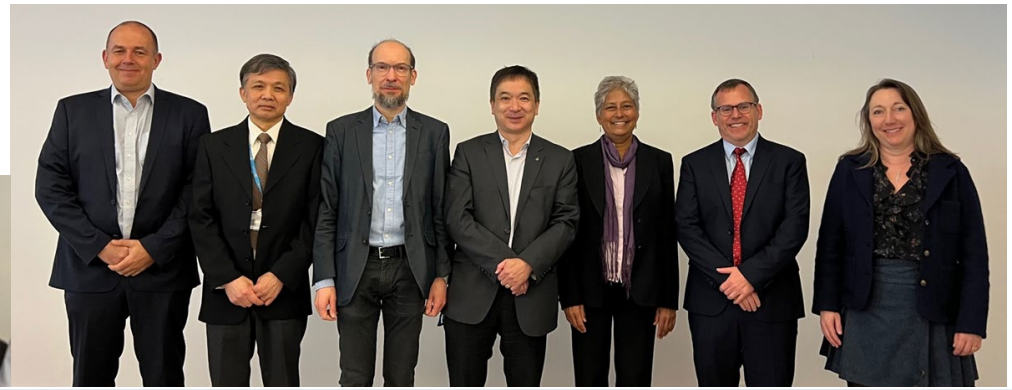
- Cover WHO-Vaccine Consultation Meeting, NH-2023-24 recommendations and influenza virus activity
- Influenza A(H1N1)pdm09 Viruses
  - Described to detail key information leading to the recommendation to update the vaccine antigen for NH-2023-24.
- Influenza A(H3N2) viruses and influenza B viruses
  - Vaccine antigens remain unchanged, will limit to key data

WHO-Vaccine consultation meeting for the northern hemisphere 2023-24 influenza vaccine

- **Continuous surveillance conducted by Global Influenza Surveillance and Response System (GISRS)**
  - WHO CCs, NICs, WHO ERLs, WHO H5 Reference Laboratories
  - Supported by countries and partners including GISAID
- **WHO Consultation Meeting held 20 – 23 Feb 2023:** review, analysis and conclusion
  - A hybrid of in-person and virtual meeting
    - Chaired by Dr Kanta Subbarao
  - 9 Advisers: Directors of WHOCCs and ERLs
    - Disclosure of interests at the start of meeting
  - 39 observers from NICs, WHO CCs, WHO ERLs, other GISRS laboratories and academia; WOAH, FAO and OFFLU
  - Experts from WHO ROs and HQ
- **WHO Information Meeting held 24 Feb 2023**

GISRS
GLOBAL INFLUENZA SURVEILLANCE & RESPONSE SYSTEM
Uniting the world in the fight against influenza
1952 - - -





WHO vaccine recommendations for the northern hemisphere 2023-24

It is recommended that vaccines for use in the 2023-24 northern hemisphere influenza season contain the following:

Trivalent: Egg-based Vaccines
- an A/Victoria/4897/2022 (H1N1)pdm09-like virus*;
- an A/Darwin/9/2021 (H3N2)-like virus; and
- a B/Austria/1359417/2021 (B/Victoria lineage)-like virus.

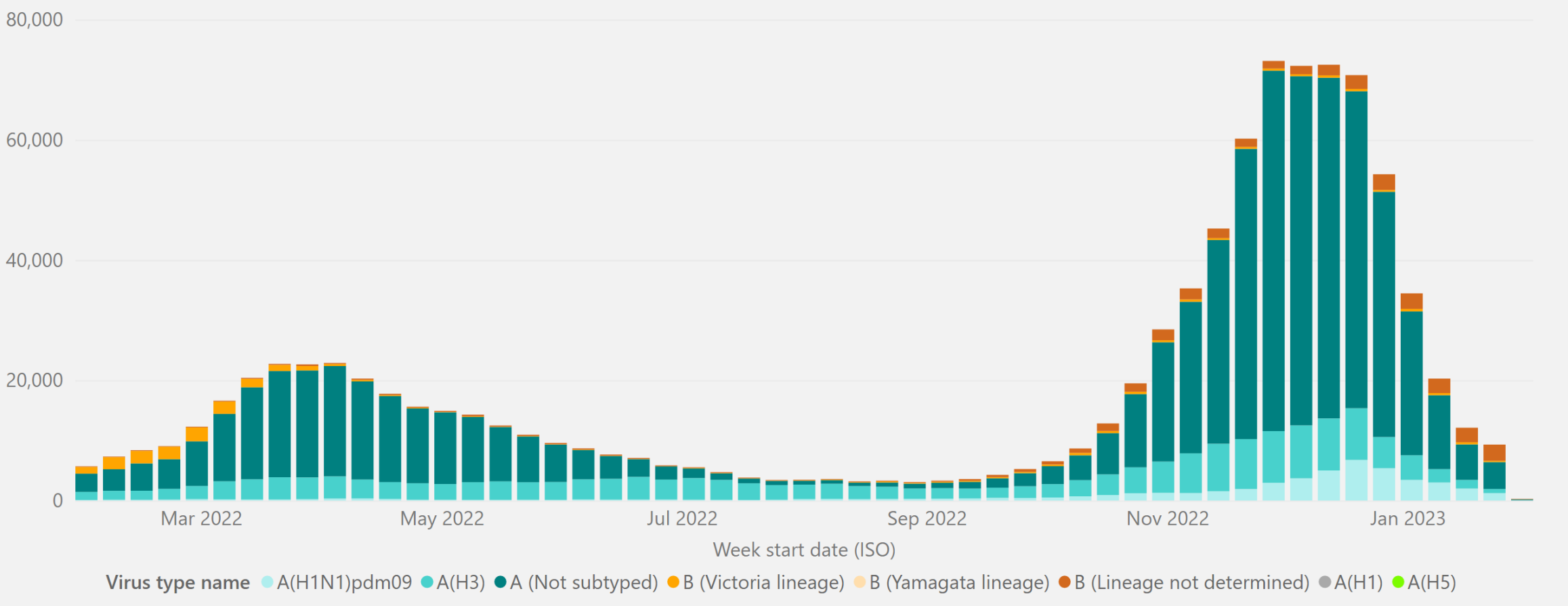
Trivalent: Cell- or recombinant-based Vaccines
- an A/Wisconsin/67/2022 (H1N1)pdm09-like virus*;
- an A/Darwin/6/2021 (H3N2)-like virus; and
- a B/Austria/1359417/2021 (B/Victoria lineage)-like virus.

Quadrivalent: egg- or cell culture- or recombinant-based vaccines
- Above 3 components; and
- a B/Phuket/3073/2013 (B/Yamagata lineage)-like virus.

* Different from that recommended for the 2022-23 northern hemisphere season

WHO recommendation and technical reports available on the WHO web site: https://www.who.int/teams/global-influenza-programme/vaccines/who-recommendations

Number of specimens positive for influenza by subtype/lineage



Select week start date (ISO)

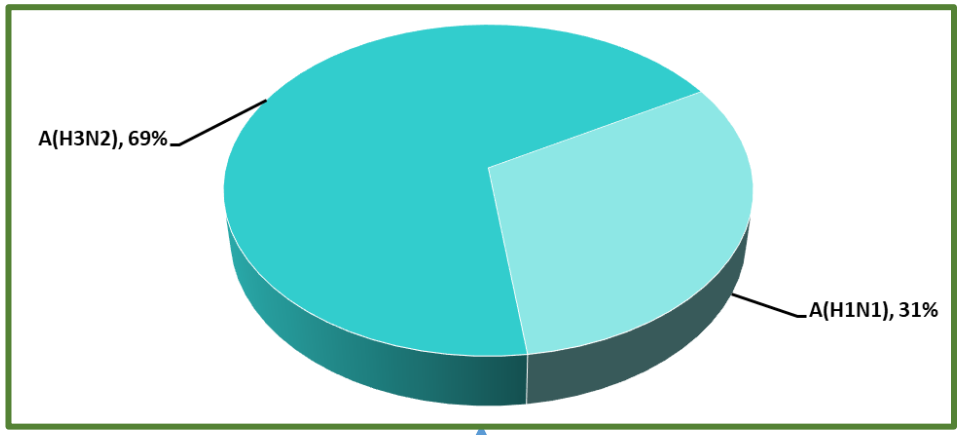
1/31/2022 1/30/2023

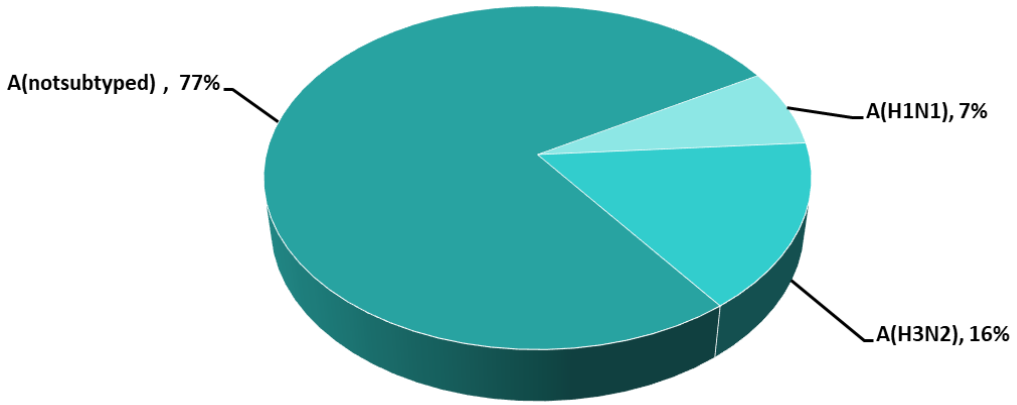
Data source: FluNet, (https://www.who.int/tools/flunet), Global Influenza Surveillance and Response System (GISRS)

Percentage of influenza A viruses by subtypes

Specimens characterized from Sept. 2022 – Feb 2023

- Of those subtyped (23%)
  - 69% A(H3N2)
  - 31% A(H1N1)pdm09
- 77% not subtyped

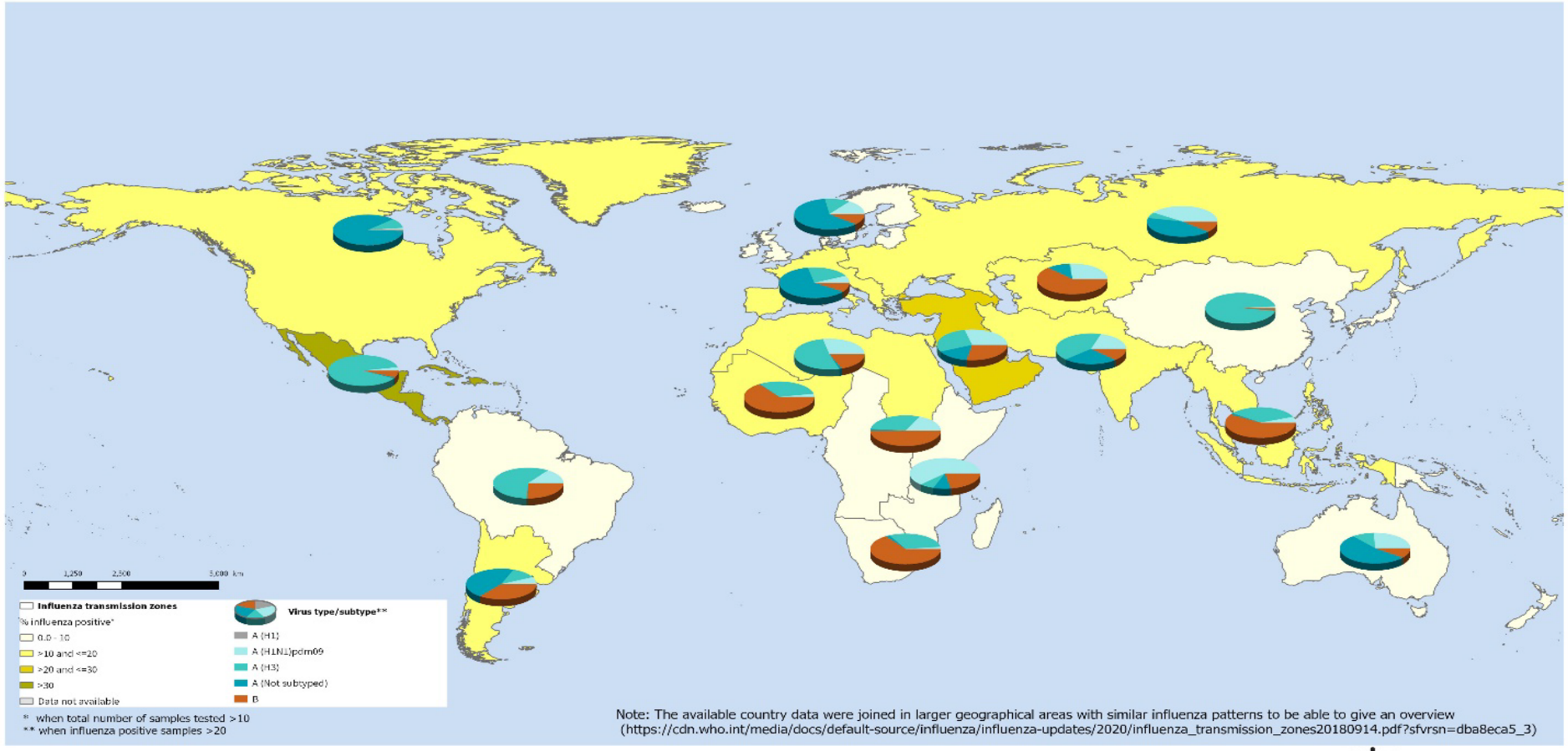




Source: Global Influenza Programme (who.int)

Global distribution of influenza viruses

Distribution of influenza virus type/subtype by influenza transmission zone, between September 2022 and January 2023



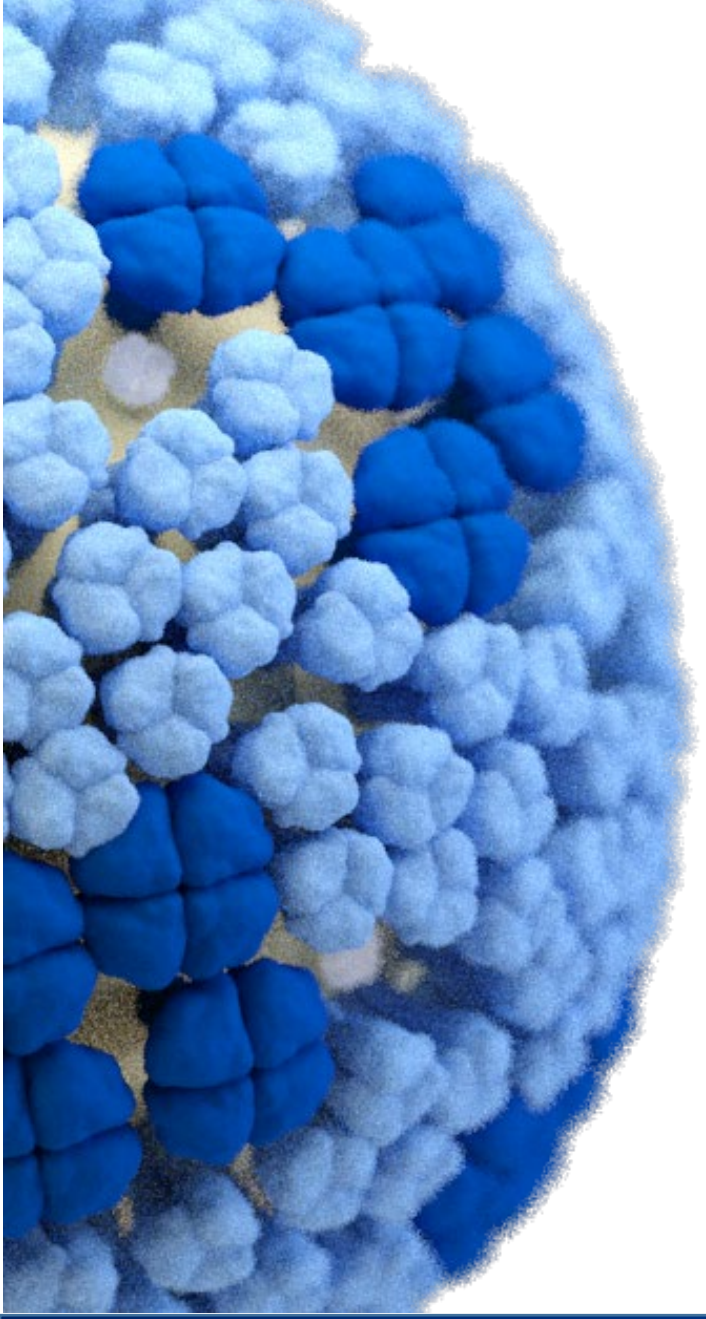
Note: The available country data were joined in larger geographical areas with similar influenza patterns to be able to give an overview (https://cdn.who.int/media/docs/default-source/influenza/influenza-updates/2020/influenza_transmission_zones20180914.pdf?sfvrsn=dba8eca5_3)

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 of of its authorities, of 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.

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

Source: Global Influenza Programme (who.int)

World Health Organization



A(H1N1)pdm09 Viruses

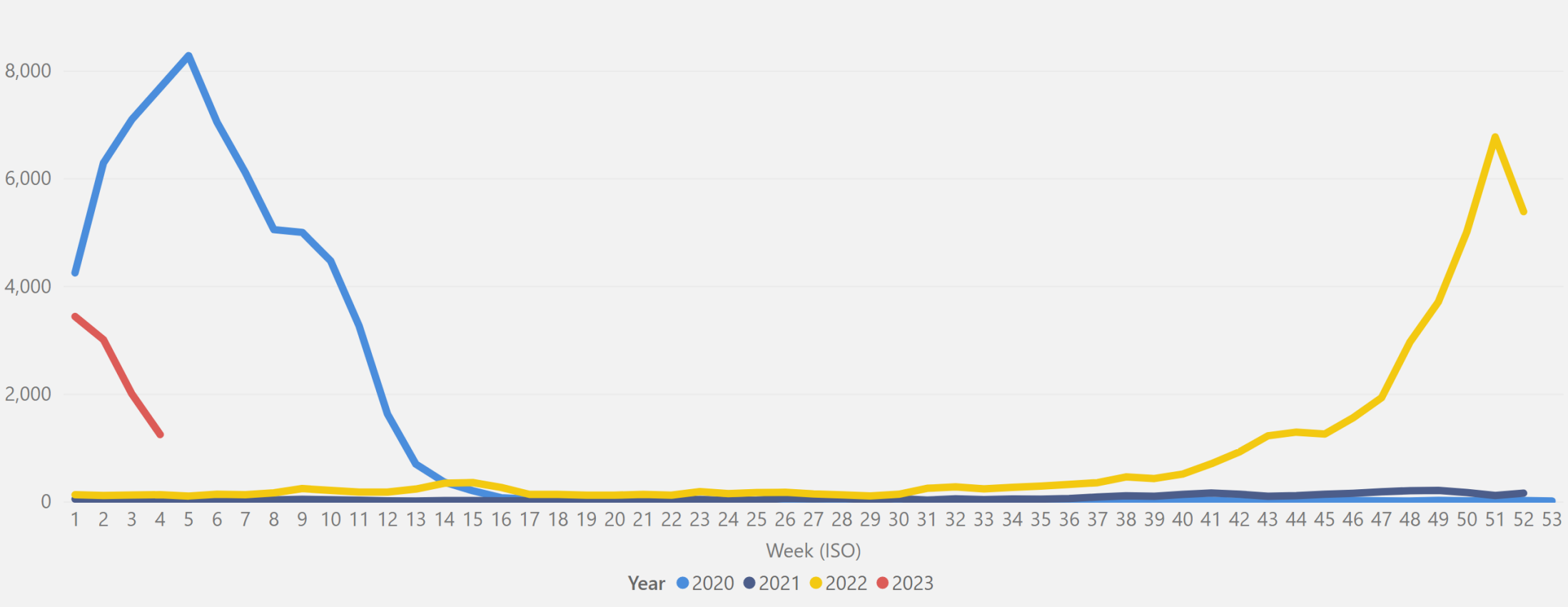
Number of A(H1N1)pdm09 viruses detected by GISRS

World Health Organization

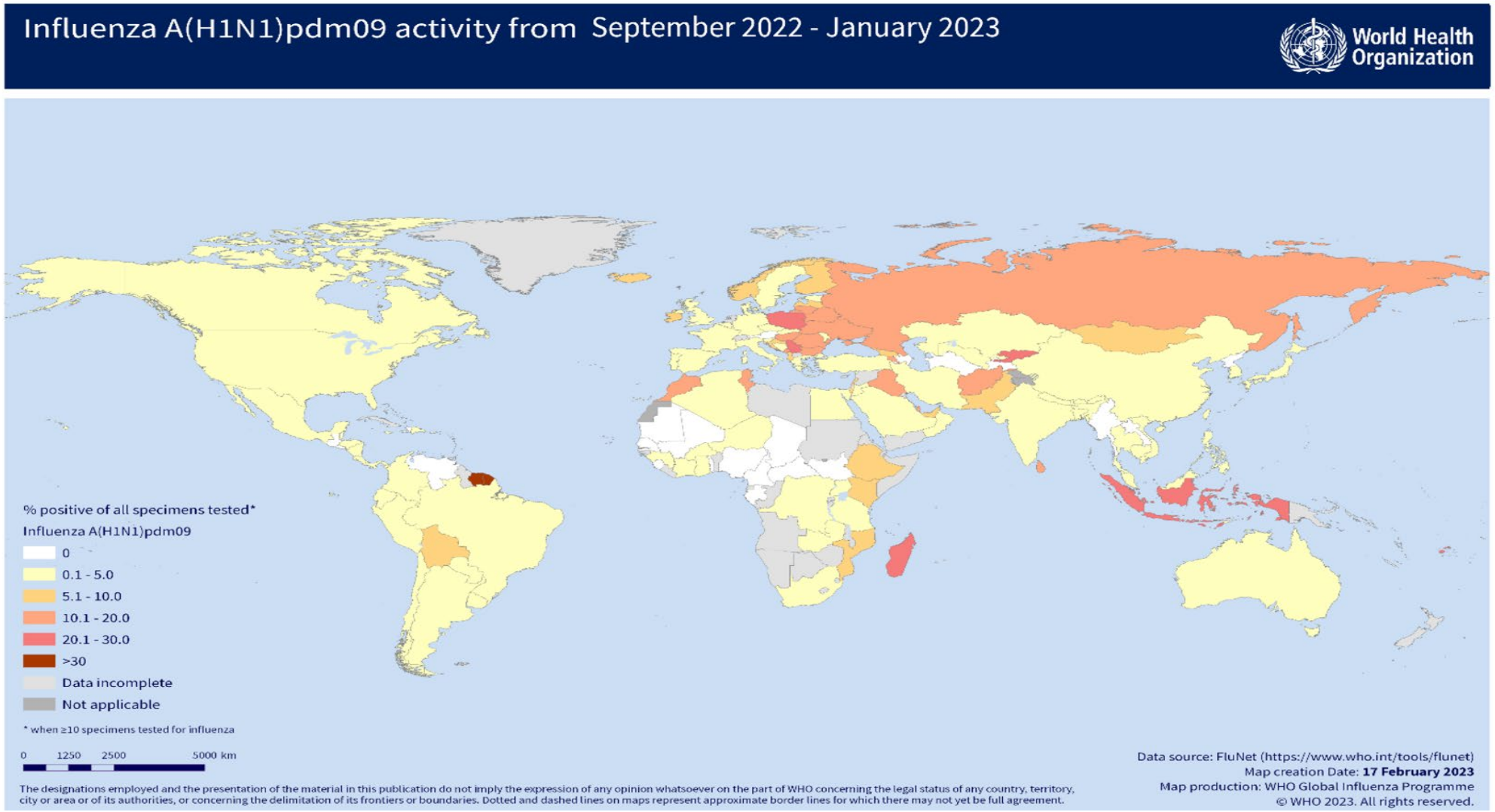
GISRS GLOBAL INFLUENZA SURVEILLANCE & RESPONSE SYSTEM

Last data refresh (UTC date)
2/7/2023 3:45:09 PM

Number of A(H1N1)pdm09 viruses detected by GISRS



Influenza A(H1N1)pdm09 activity

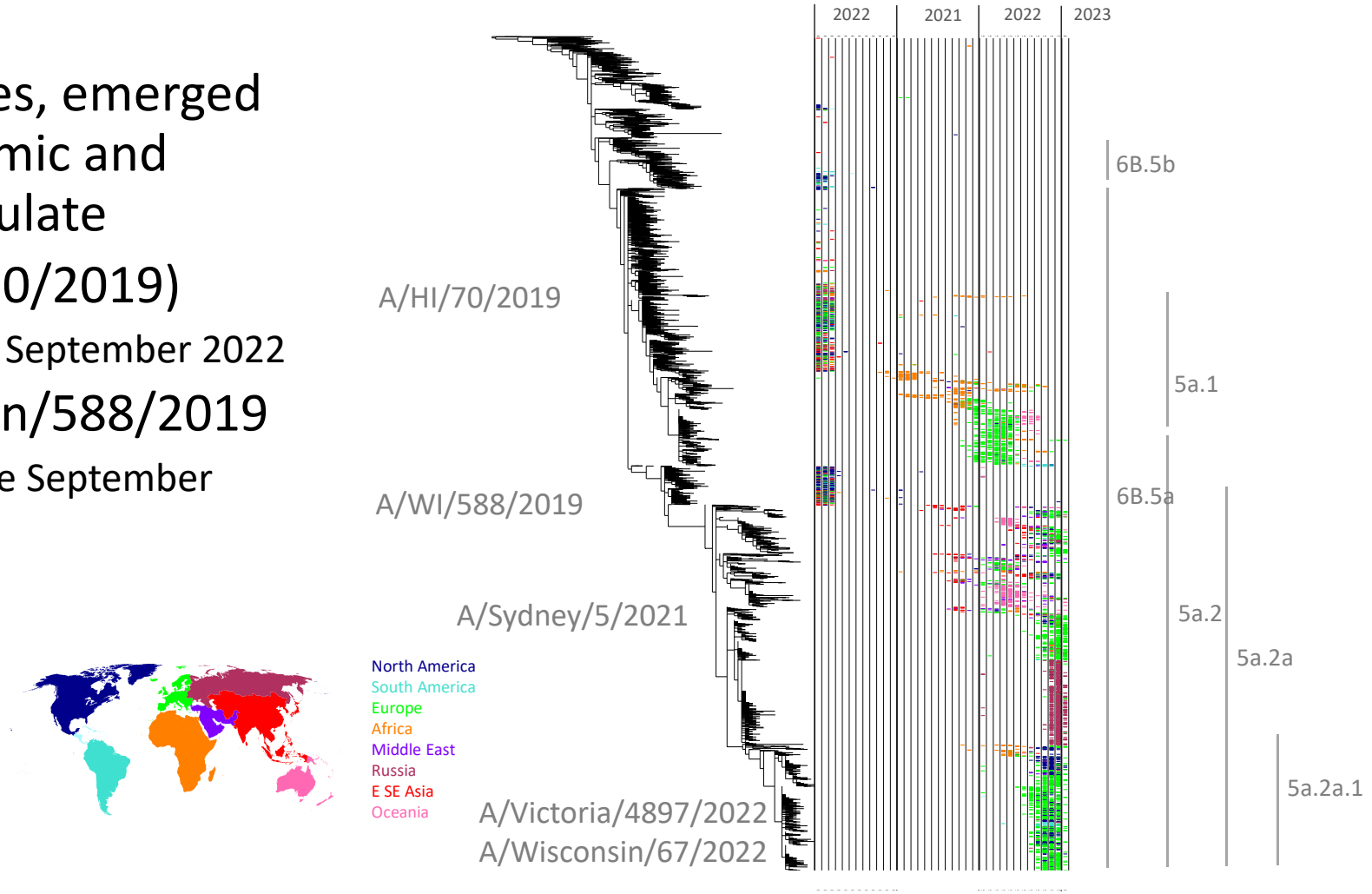


Colour intensity shows the percent of positive influenza A(H1N1) among all samples tested during this period per country

Source: Global Influenza Programme (who.int)

Overall A(H1N1)pdm09 HA phylogeography

- Two major 6B.1A.**5a** subclades, emerged prior to the COVID-19 pandemic and descendants continue to circulate
  - **5a.1** HA (e.g., A/Hawaii/70/2019)
    - 2% of viruses collected since September 2022
  - **5a.2** HA (e.g., A/Wisconsin/588/2019
    - 98% of viruses collected since September 2022

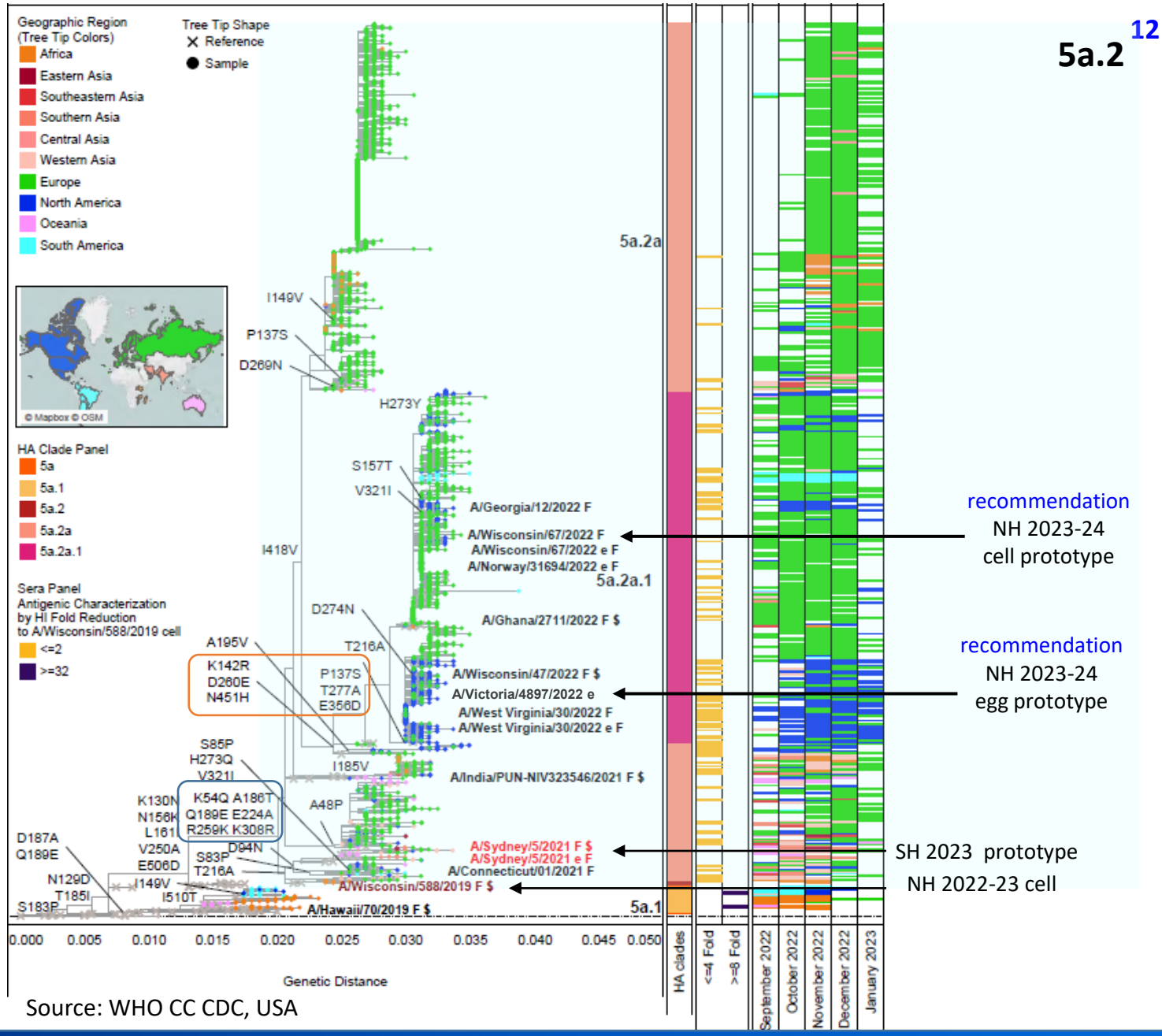


Source: Cambridge Univ., S. James and D. Smith

Recent A(H1N1)pdm09 HA phylogeography

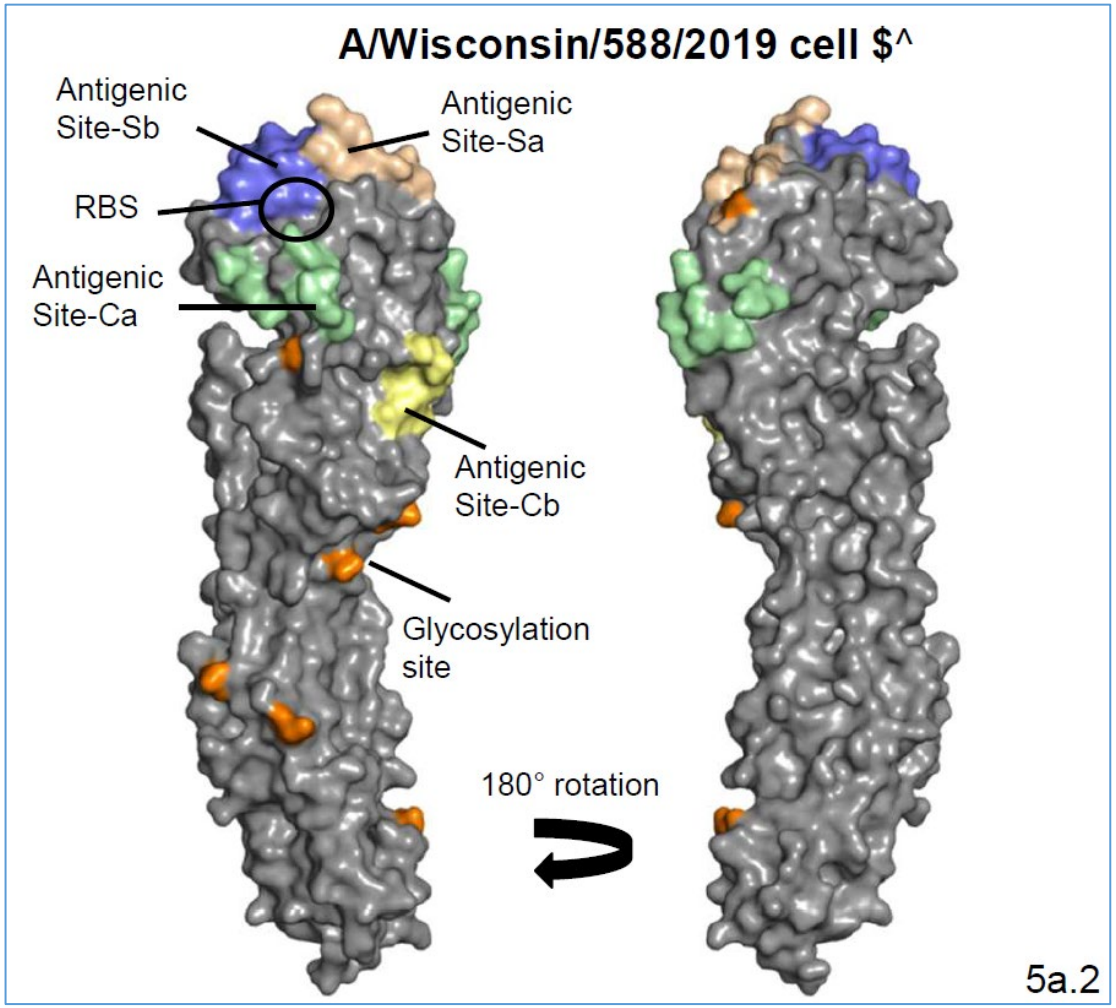
Two major 6B.1.5a subclades

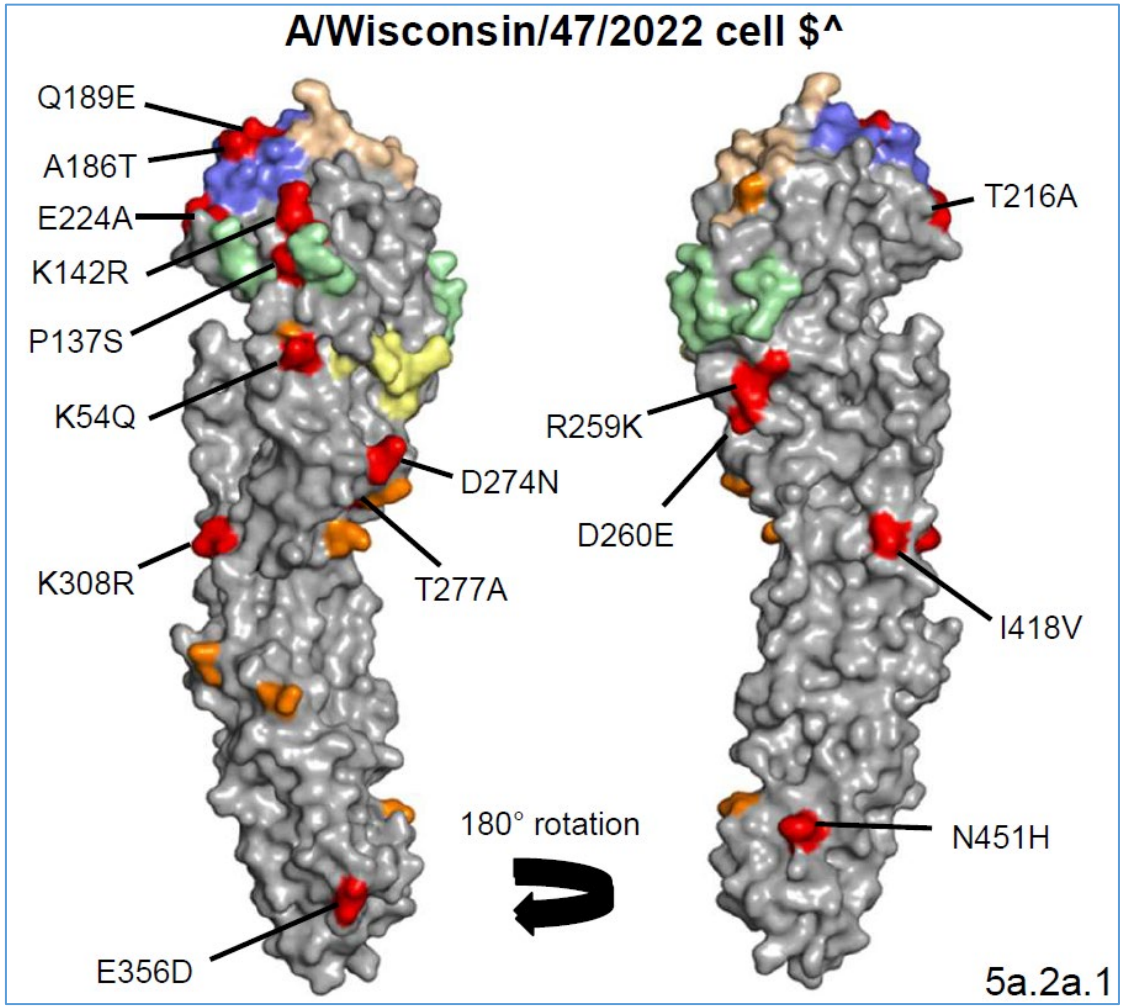
- 5a.1 HA (e.g., A/HI/70/2019)
  - Decreasing in proportion
  - Africa, South America, Oceania
- 5a.2 HA (e.g., A/WI/588/2019)
  - 59% belong to 5a.**2a**:
    - Typically have K54Q, A186T , Q189E, E224A, R259K, and K308R
      - A/Sydney/5/2021
      - A/India/PUN-NIV323546/2021
    - Recent viruses primarily from Africa, Asia, Europe, Oceania
  - 41% belong to 5a.**2a.1**:
    - Typically have additional P137S, K142R, D260E, T277A, E356D and N451H
      - A/Victoria/4897/2022
      - A/Wisconsin/67/2022
    - North America, Central/South America, Europe



Source: WHO CC CDC, USA

Location of changes in advanced serology antigen





Source: WHO CC CDC, USA

Antigenic analysis of A(H1N1)pdm09 viruses

Antisera to northern hemisphere 2022-23 antigens (5a.2)

A/Wisconsin/588/2019-like (cell)

WHO CC	Like (2-4 fold)	Low (≥ 8 fold)
CDC	138 (94%)	9 (6%)
CNIC	1 (100%)	0 (0%)
FCI	126 (81%)	30 (19%)
NIID	5 (100%)	0 (0%)
VIDRL	175 (94%)	12 (6%)
TOTAL	445 (90%)	51 (10%)

A/Victoria/2570/2019-like (egg)

WHO CC	Like (2-4 fold)	Low (≥ 8 fold)
CDC	138 (94%)	9 (6%)
CNIC	1 (100%)	0 (0%)
FCI	147 (94%)	9 (6%)
NIID	5 (100%)	0 (0%)
VIDRL	173 (93%)	14 (7%)
TOTAL	464 (94%)	32 (6%)

Low titers ≥ 8-fold lower than homologous titer of reference vaccine virus

HI analysis of recent H1N1pdm09 viruses

- HA clade 5a.1 and 5a.2 viruses show distinct recognition patterns
- Ferret antisera does not detect large antigenic differences between the viruses with 5a.2, .2a, .2a.1 HA genes
- **5a.2a.1 HA clade virus antisera inhibited recently circulating viruses very well.**
  - Both 5a.2a, and 5a.2a.1

Ferret antisera to:

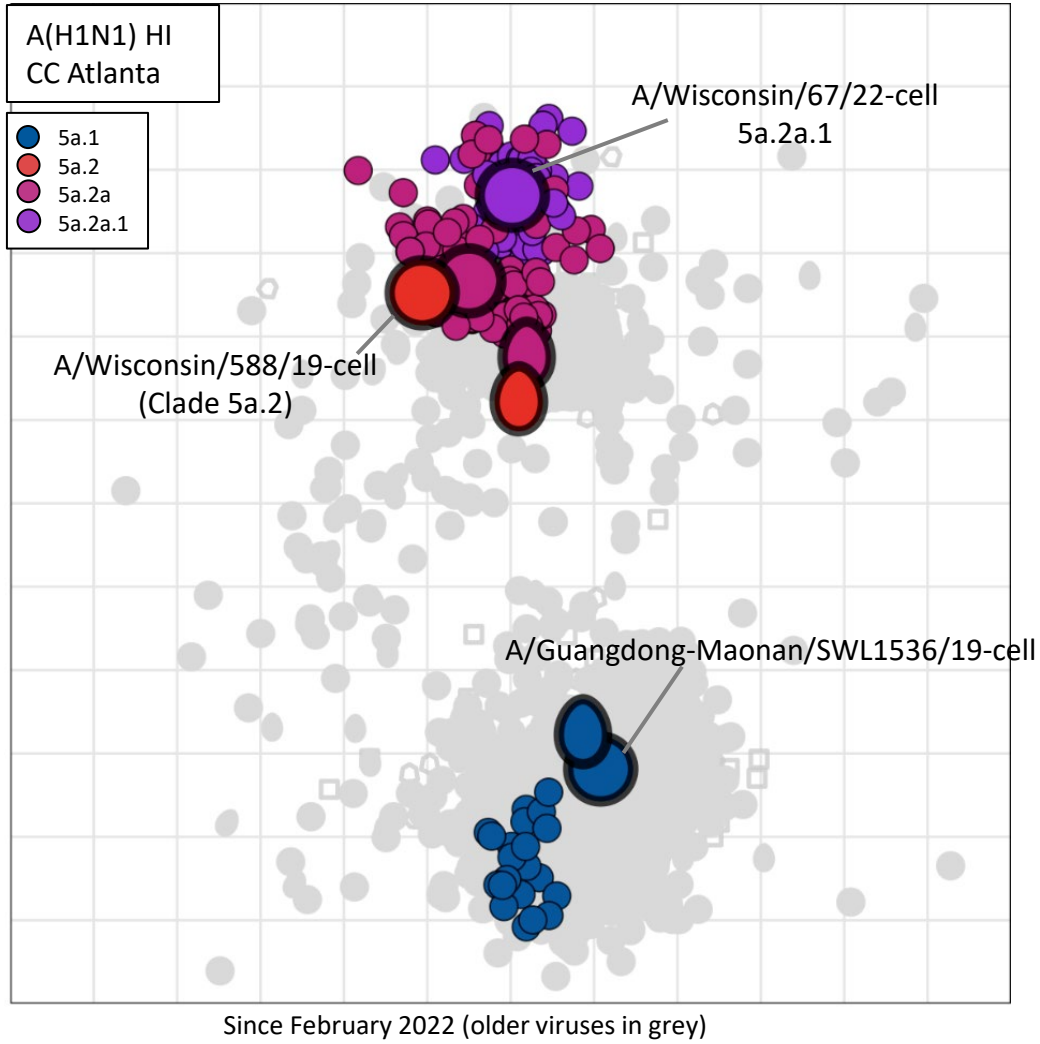
		Clade	1 Cell Bris/50 5a.1	2 Egg G.M./SWL1536 5a.1	3 Cell Vic2570 5a.2	4 Egg Vic2570 5a.2	5 Cell Syd/5 5a.2a	6 Egg Syd/5 5a.2a	7 Cell Vic/4897 5a.2a.1	8 Egg Vic/4897 5a.2a.1
Ref. virus										
1	A/Brisbane/50/2022	5a.1	**2560**	1280	<80	<80	<80	<80	<80	<80
2	A/G. Maonan/SWL1536/2019	5a.1	5120	**2560**	<80	80	<80	<80	80	<80
3	A/Victoria/2570/2019	5a.2	160	<80	**1280**	640	640	2560	5120	640
4	A/Victoria/2570/2019	5a.2	80	<80	1280	**640**	320	640	2560	640
5	A/Sydney/5/2021	5a.2a	<80	<80	320	640	**320**	640	2560	320
6	A/Sydney/5/2021	5a.2a	80	<80	2560	1280	1280	**2560**	>10240	1280
7	A/Victoria/4897/2022	5a.2a.1	<80	<80	1280	1280	640	1280	**>10240**	2560
8	A/Victoria/4897/2022	5a.2a.1	<80	<80	1280	1280	640	1280	>10240	**2560**
Test virus										
1	A/Tasmania/340/2022	5a.2a	80	<80	2560	2560	1280	2560	>10240	1280
2	A/Cambodia/g1207361/2022	5a.2a	80	<80	2560	2560	1280	2560	>10240	1280
3	A/Canberra/538/2022	5a.2a	80	<80	2560	640	1280	2560	5120	1280
4	A/Victoria/34/2023	5a.2a	<80	<80	1280	1280	640	2560	5120	1280
5	A/Philippines/29/2022	5a.2a	80	<80	1280	1280	320	1280	>10240	640
6	A/Darwin/7/2023	5a.2a	<80	<80	2560	1280	1280	2560	>10240	1280
7	A/Brisbane/1/2023	5a.2a	<80	<80	640	640	320	1280	5120	1280
8	A/Fiji/68/2023	5a.2a	80	80	5120	2560	2560	5120	>10240	2560
9	A/Victoria/19/2023	5a.2a.1	<80	<80	640	1280	640	1280	5120	1280
10	A/Victoria/21/2023	5a.2a.1	<80	<80	1280	1280	640	2560	>10240	2560
11	A/Philippines/36/2022	5a.2a.1	<80	<80	1280	1280	320	1280	5120	1280
12	A/Tasmania/2/2023	5a.2a.1	<80	<80	1280	1280	640	1280	>10240	1280
13	A/Victoria/52/2023	5a.2a.1	<80	<80	1280	1280	640	2560	>10240	2560
14	A/Victoria/14A/2023	5a.2a.1	<80	<80	1280	1280	640	1280	>10240	1280

Fold reduction
< 4-fold
4-fold
8-fold
8-fold <

NH 22-23

Prop. NH 23-24

A(H1N1)pdm09 antigenic cartography

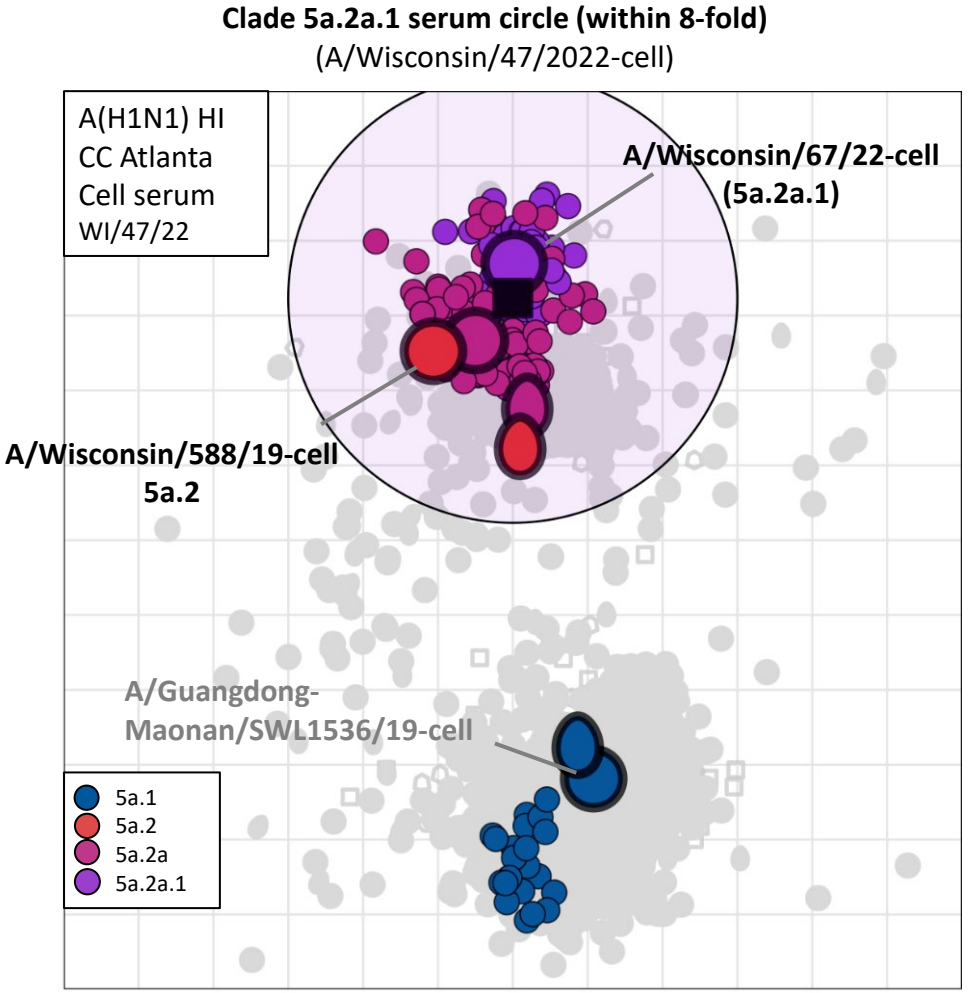


Since February 2022 (older viruses in grey)

Source of visualization: S. James D. Smith Univ. of Cambridge

- The viruses with HA from 6B.1A subclades **5a.1** and **5a.2** form two antigenically distinct groups
  - Viruses of each clade cluster with respective vaccine reference viruses
    - 5a.2a and 5a.2a.1 cluster close together

A(H1N1)pdm09 cartography illustrating serum reactivity



Recently circulating 5a.2a and 5a.2a.1 viruses were well recognized by ferret antisera 5a.2a.1 reference viruses (e.g, A/Wisconsin/47/2022-cell).

Source: S. James D. Smith Univ. of Cambridge

NH-2022-23 Post-Vaccination (5a.2 HA) Human Serology

Inhibition by vaccine induced antibodies decreased as changes in 5a.2 HA proteins have evolved.

- Excepting the youngest pediatric group, reduced geometric mean titers (GMTs) found in:
  - A 5a.**2a** HA clade reference (A/Sydney/5/2021) and both 5a.**2a.1** references
- GMTs to clade 5a.1 HA reference (A/Hawaii/70/2019)
  - Reduced among age 8 years and under
  - Ages 9-64 years showed good reactivity
    - Likely boost memory response

GMTs compared to A/Wisconsin/588/2019-cell

A/WISCONSIN/588/2019 SIAT				5a.2 - *WI/588 SIAT	5a.2a - IND/PUN-NIV323546 SIAT	5a.2a +D94N +T216A SYD/5 SIAT	5a.2a.1 - GHA/2711 SIAT	5a.2a.1 +T216A WI/47 SIAT	5a.1 - HI/70 SIAT
	Pediatric (6-35M)	USA	IIV4	70	√	√	√	√	8
	Pediatric (3-8Y)	USA	ccIIV4 (Flucelvax)	190	√	√	109	109	109
			IIV4	197	√	92	106	92	86
	Pediatric (9-17Y)	USA	ccIIV4 (Flucelvax)	288	√	160	95	83	√
			IIV4	368	√	184	135	144	√
	Adult	USA	ccIIV4 (Flucelvax)	618	368	299	171	190	√
			RIV4 (Flublok)	437	√	190	135	121	√
			IIV4	343	√	149	171	144	√
	Older Adult (50-64Y)	USA	IIV4	204	109	98	70	98	√
	Elderly (≥65Y)	USA	IIV4-HD	166	√	95	31	44	117

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 (95% 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.

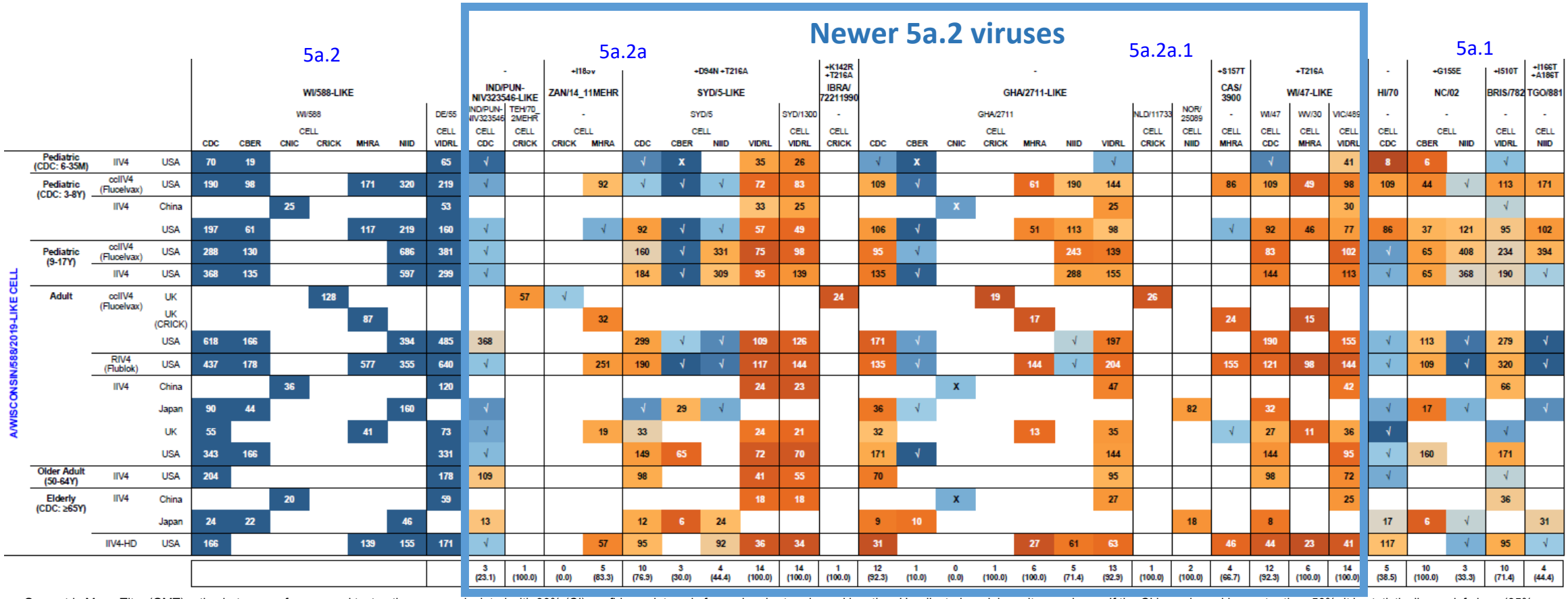
Strain abbreviations: A/GHANA/2711/2022 (GHA/2711); A/HAWAII/70/2019 (HI/70); A/INDIA/PUN-NIV323546/2021 (IND/PUN-NIV323546); A/SYDNEY/5/2021 (SYD/5); A/WISCONSIN/47/2022 (WI/47); A/WISCONSIN/588/2019 (WI/588).

Source: WHO CC CDC, USA

Statistically non-inferior = √
Statistically non-inferior but reference virus GMT < 40 = X

GMT ratio lowerbound (90% CI)
0.0 — 1.0

Post vaccination human serology – summary of GMT reductions



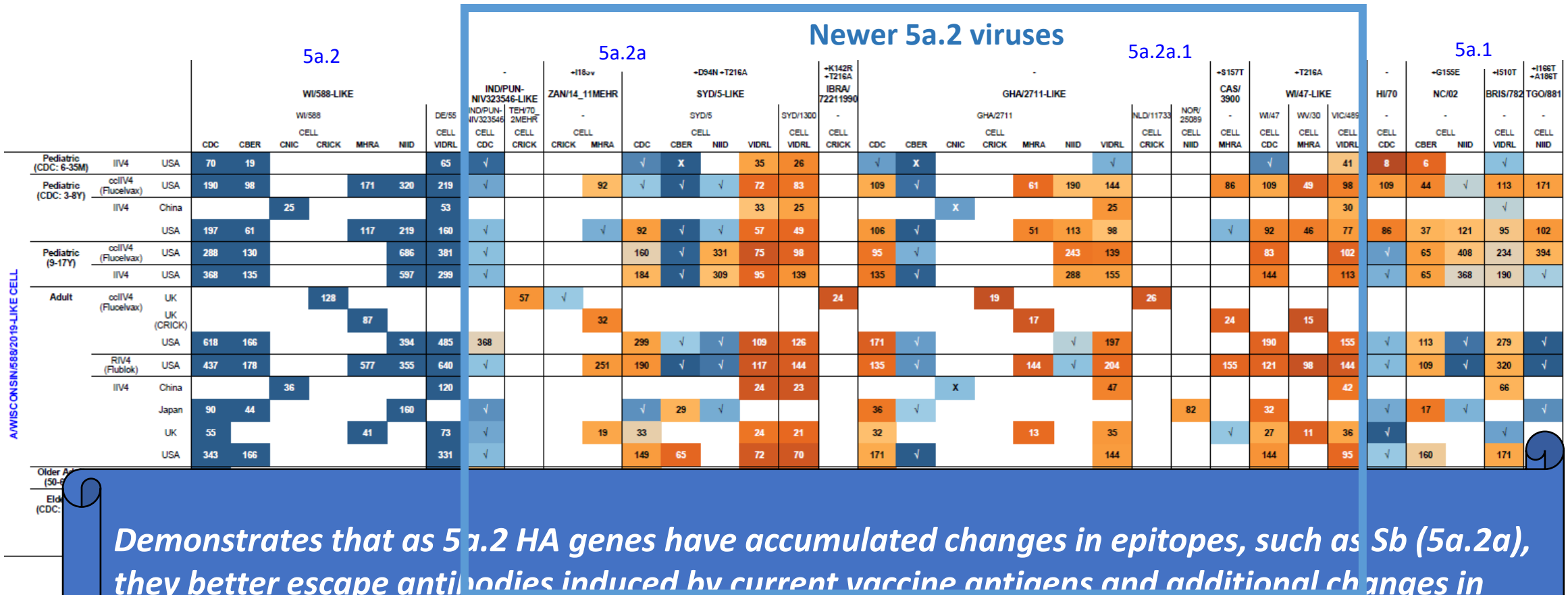
Geometric Mean Titer (GMT) ratios between reference and test antigens are calculated with 90% (CI) confidence intervals for each cohort and panel location. Unadjusted model results are shown. If the CI lower bound is greater than 50%, it is statistically non-inferior (95% confidence level), otherwise 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 common *reference antigens* and possibly inferior test antigens (consolidated by passage-type). Marks √ or X denote statistically significant non-inferiority when the reference virus GMT is ≥40 or <40, respectively. **Number** and **percent** (in parentheses) of *possibly* inferior responses are summarized below the heat map.

Included Strains: A/BRISBANE/782/2022 (BRIS/782); A/CASTILLALAMANCHA/3900/2022 (CAS/3900); A/DELAWARE/55/2019 (DE/55); A/GHANA/2711/2022 (GHA/2711); A/HAWAII/70/2019 (HI/70); A/IBRA/72211990/2022 (IBRA/72211990); A/INDIA/PUN-NIV323546/2021 (IND/PUN-NIV323546); A/NETHERLANDS/11733/2022 (NLD/11733); A/NORTH CAROLINA/02/2021 (NC/02); A/NORWAY/25089/2022 (NOR/25089); A/SYDNEY/1300/2022 (SYD/1300); A/SYDNEY/5/2021 (SYD/5); A/TEHRAN.IRAN/70_2MEHR/2022 (TEH/70_2MEHR); A/TOGO/881/2020 (TGO/881); A/VICTORIA/4897/2022 (VIC/4897); A/WEST VIRGINIA/30/2022 (WV/30); A/WISCONSIN/47/2022 (WI/47); A/WISCONSIN/588/2019 (WI/588); A/ZANJAN.IRAN/14_11MEHR/2022 (ZAN/14_11MEHR).

Statistically non-inferior = √
Statistically non-inferior but reference virus GMT < 40 = X
GMT Ratio Lower-Bound (90% CI) 0.000 – 1.000

Multiple sources: compiled by WHO CC CDC, USA

Post vaccination human serology – summary of GMT reductions



Demonstrates that as 5a.2 HA genes have accumulated changes in epitopes, such as Sb (5a.2a), they better escape antibodies induced by current vaccine antigens and additional changes in site Ca (i.e., P137S and K142R in 5a.2a.1 genes) further reduce <u>human</u> antibody recognition.

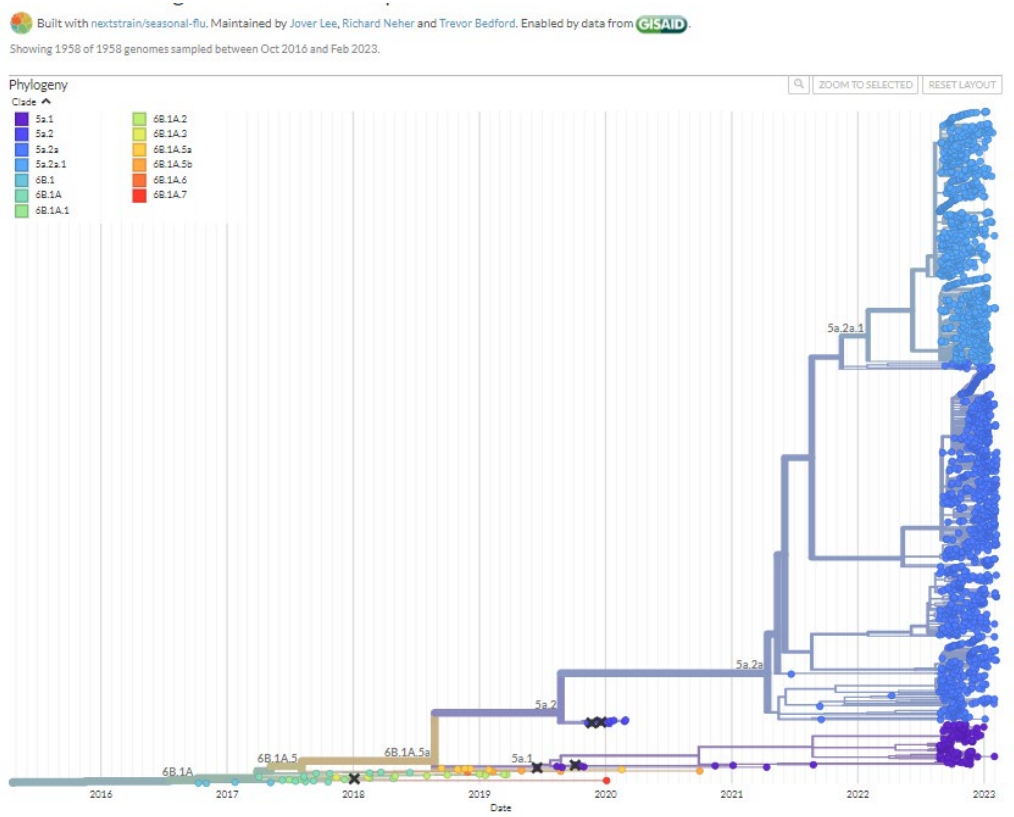
Geome
confide
shown
inferior

Include
NIV323
(TEH/70_2MEHR); A/TOGO/881/2020 (TGO/881); A/VICTORIA/4897/2022 (VIC/4897); A/WEST VIRGINIA/30/2022 (WV/30); A/WISCONSIN/47/2022 (WI/47); A/WISCONSIN/588/2019 (WI/588); A/ZANJAN.IRAN/14_11MEHR/2022 (ZAN/14_11MEHR).

Multiple sources: compiled by WHO CC CDC, USA

A(H1N1)pdm09 – Summary (1): global circulation and phylogeny

- A(H1N1)pdm09 viruses have been detected in all geographic regions
- Most viruses circulating in this period expressed HA genes in major clades 5a.1 or 5a.2, new 5a.2 subclades predominating:
  - 5a.2a (K54Q, A186T, Q189E, E224A, R259K and K308R)
    - Predominating in Asia and some countries in Europe and Africa.
  - 5a.2a.1 (P137S, K142R, D260E and T277A)
    - Predominating in North America and some countries in South America and Europe.



https://nextstrain.org/flu/seasonal/h1n1pdm/ha/6m

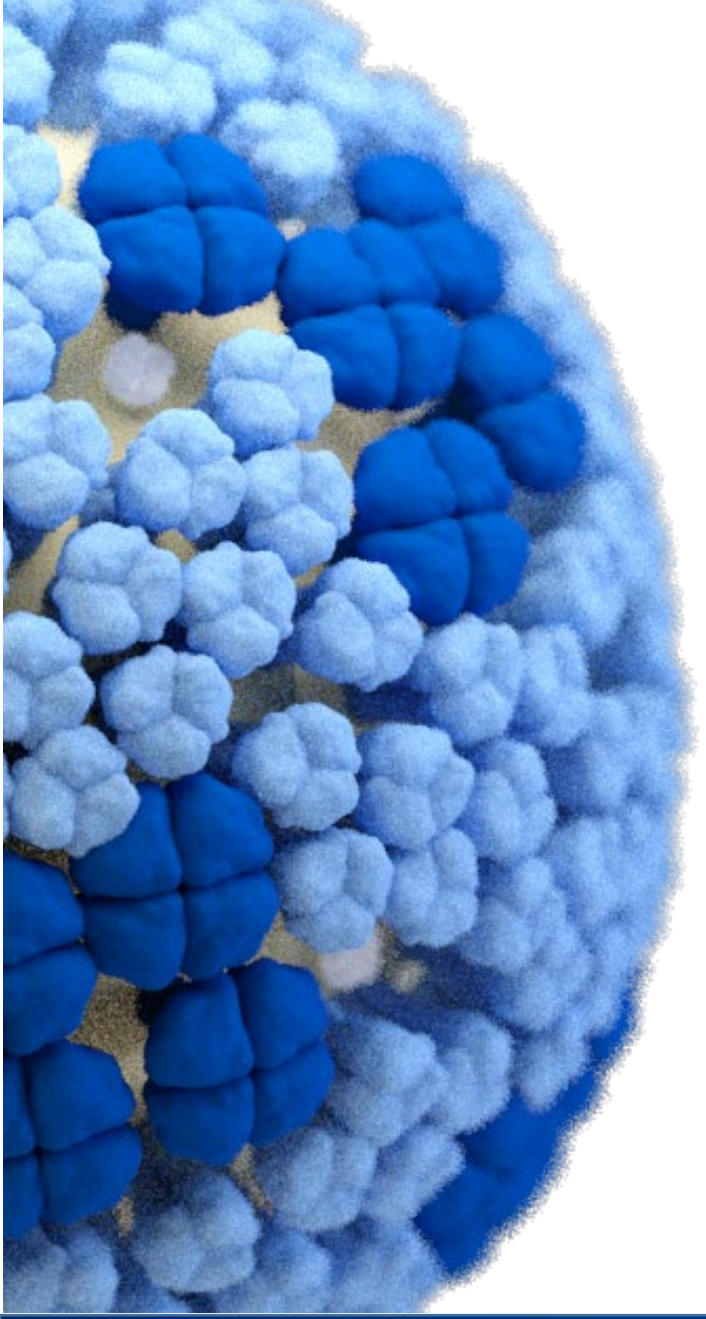
A(H1N1)pdm09 – Summary (2): antigenicity, and human serology

Ferret antisera showed clear antigenic difference between clade 5a.1 and 5a.2 viruses.

- Ferret antisera to:
  - HA clade 5a.2 viruses (e.g., A/Wisconsin/588/2019-cell) recognized recently circulating subclade 5a.2a and 5a.2a.1 viruses, but poorly recognized 5a.1 viruses
  - HA clade 5a.2a.1 viruses (e.g., A/Wisconsin/67/22-cell and /Victoria/4897/22-egg), recognized recently circulating subclade 5a.2a and 5a.2a.1 viruses well
- Post vaccination sera collected from humans vaccinated with NH 2022-2023 vaccines:
  - GMTs were reduced significantly in most serum panels against most recent A(H1N1)pdm09 viruses expressing 5a.2a and 5a.2a.1 HA genes
  - Showed that majority of recent viruses, particularly HA clade 5a.2a.1 were escaping some of the antibodies induced by vaccination

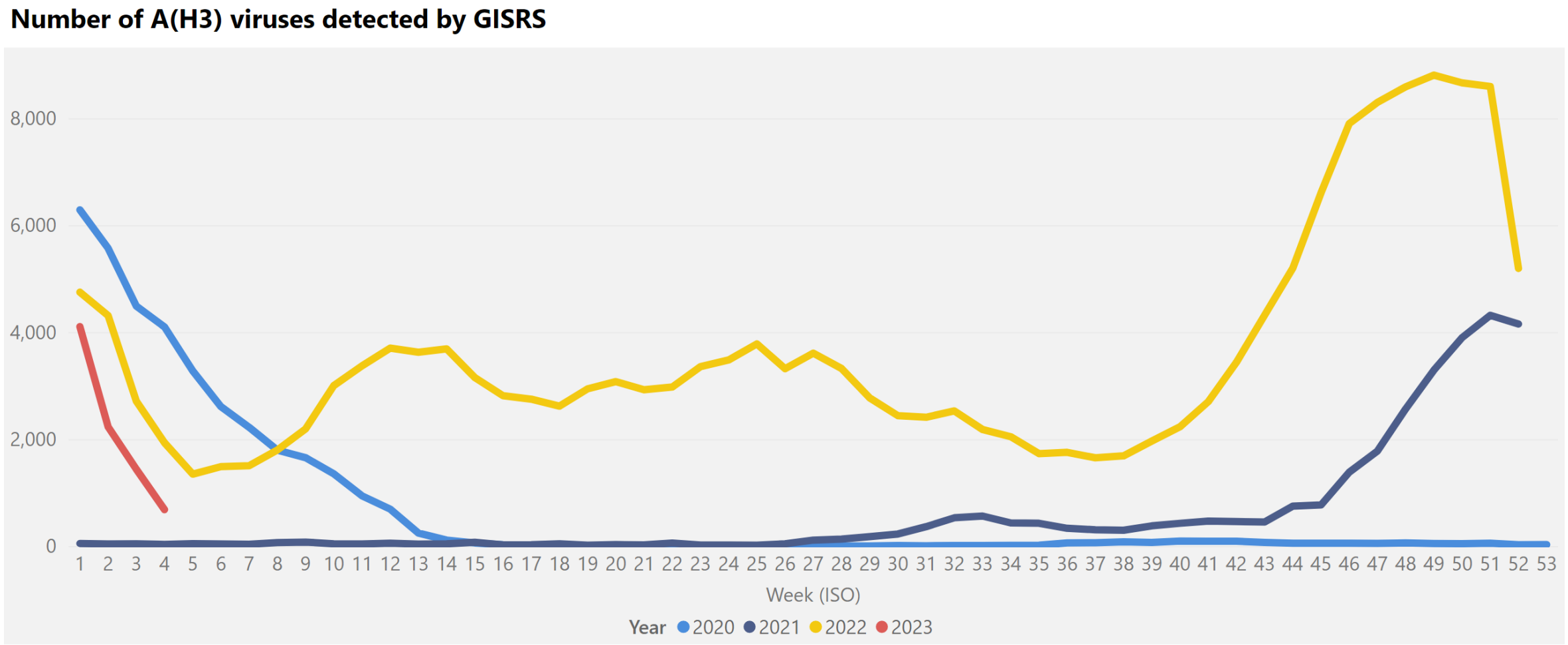
A(H1N1)pdm09 – Summary (3): antiviral susceptibility

- NA inhibitors
  - Of 1,361 viruses tested – 4 showed resistance in genetic and/or phenotype analyses
- Endonuclease inhibitor (baloxavir marboxil)
  - Of 1,107 viruses tested – none showed resistance in genetic and/or phenotype analyses

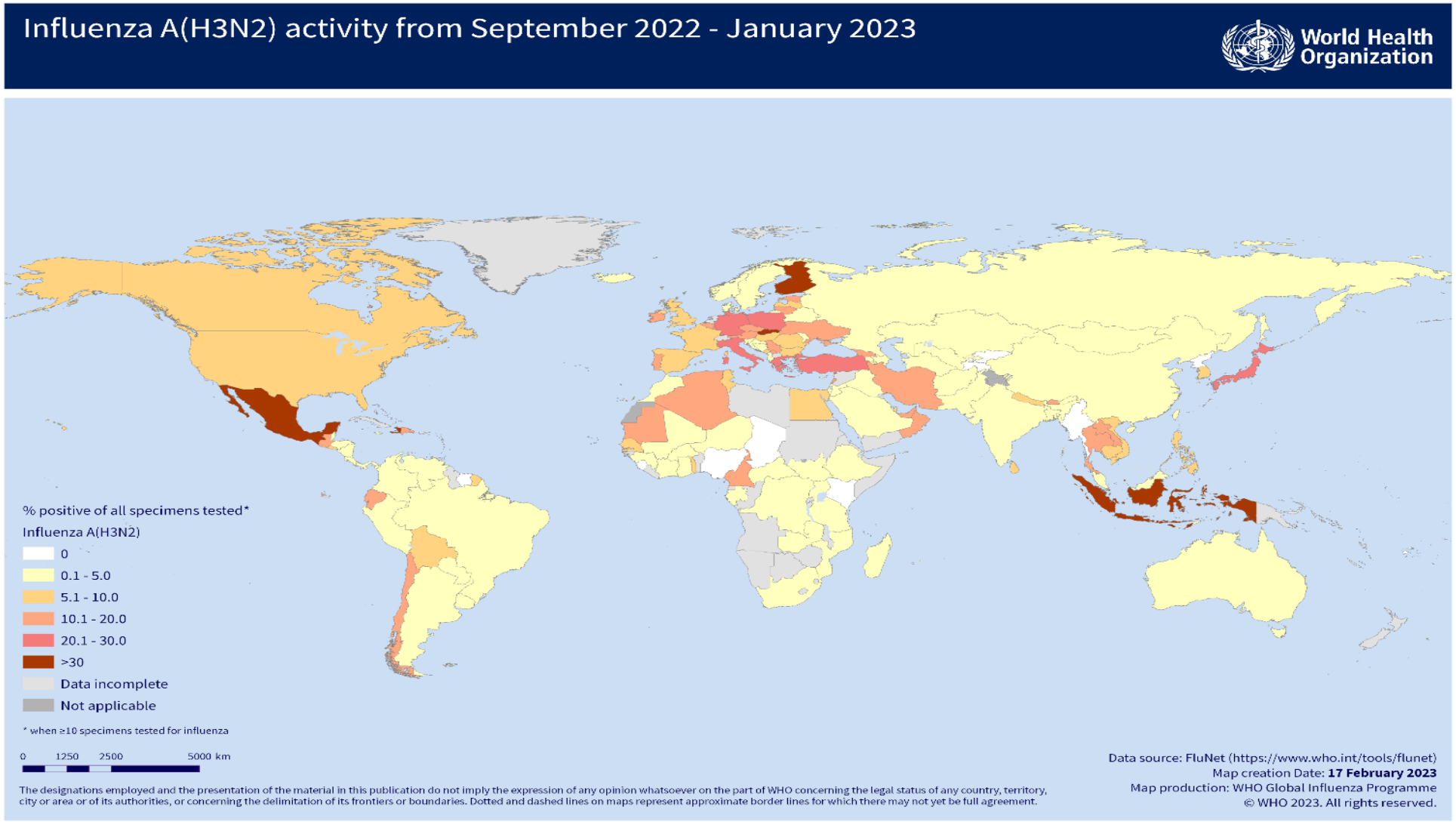


A(H3N2) Viruses

Number of A(H3N2) viruses detected by GISRS



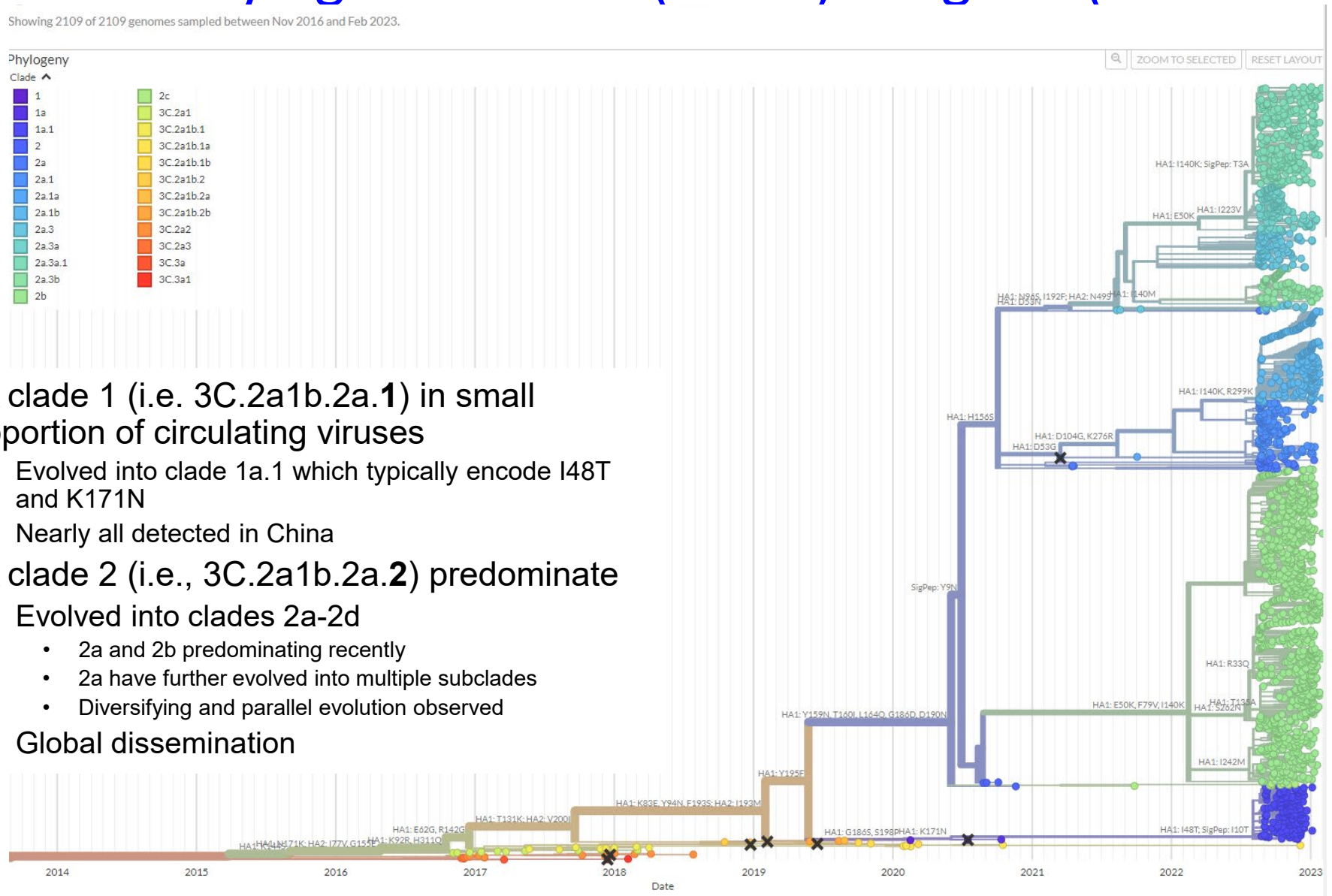
Influenza A(H3N2) activity



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

Source: Global Influenza Programme (who.int)

Phylogenetics of A(H3N2) HA gene (time tree)



2a.3a.1 **A/Massachusetts /18/2022**

2a.3a

2a.3 **A/Alaska/01/2021**

2a.3b

2a.1b **A/Michigan/60/2022**

2a.1 **A/Maryland/02/2021**

A/Florida/57/2022 (2b)

1a.1 **A/Hainan-Baotinglizumiaozuzizhi/ 35/2022**

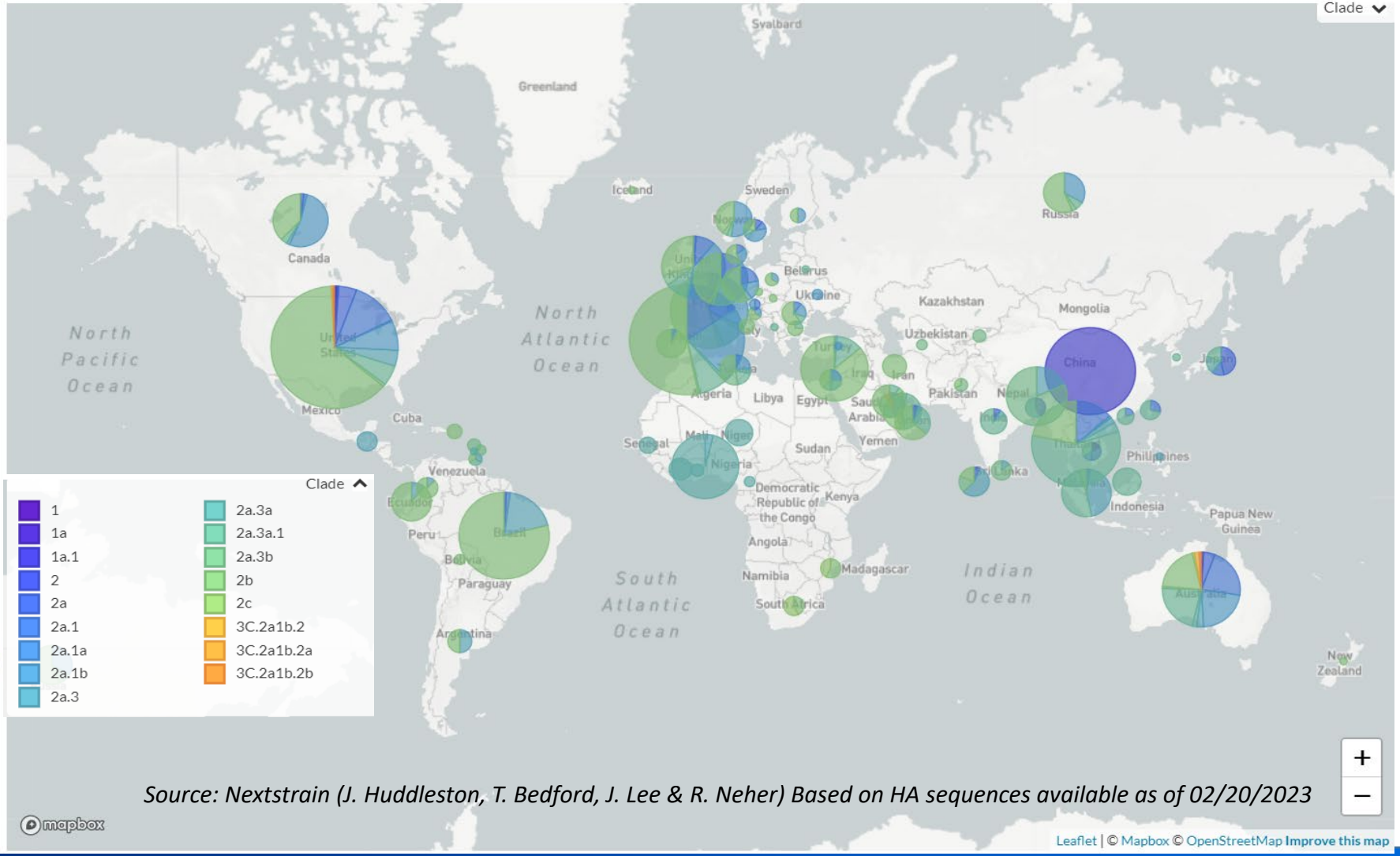
- ❑ HA clade 1 (i.e. 3C.2a1b.2a.**1**) in small proportion of circulating viruses
  - Evolved into clade 1a.1 which typically encode I48T and K171N
  - Nearly all detected in China
- ❑ HA clade 2 (i.e., 3C.2a1b.2a.**2**) predominate
  - Evolved into clades 2a-2d
    - 2a and 2b predominating recently
    - 2a have further evolved into multiple subclades
    - Diversifying and parallel evolution observed
  - Global dissemination

Source: Nextstrain (J. Huddleston, T. Bedford, J. Lee & R. Neher) Based on HA sequences available as of 02/20/2023 02/20/2023

Global circulation of A(H3N2) HA clades

September 2022 to February 2023

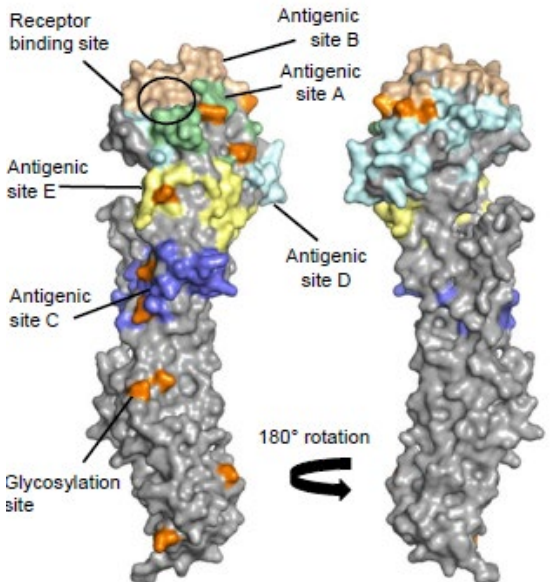
- HA clade 1a.1 found in viruses circulating in China
- HA clade 2 subclades predominate and show global distribution
  - Viruses with subclades 2a.1b, 2a.3a.1 and 2b HA genes circulating in many countries
    - 2b predominated in this period



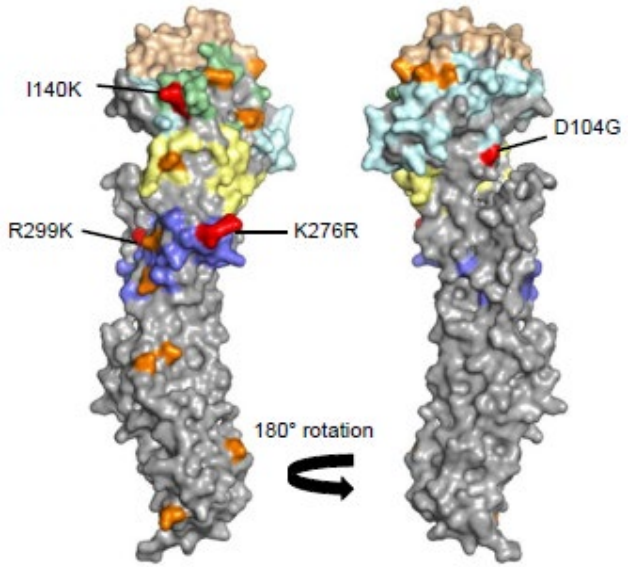
Source: Nextstrain (J. Huddleston, T. Bedford, J. Lee & R. Neher) Based on HA sequences available as of 02/20/2023

Location of key substitutions on H3 HA protein monomer

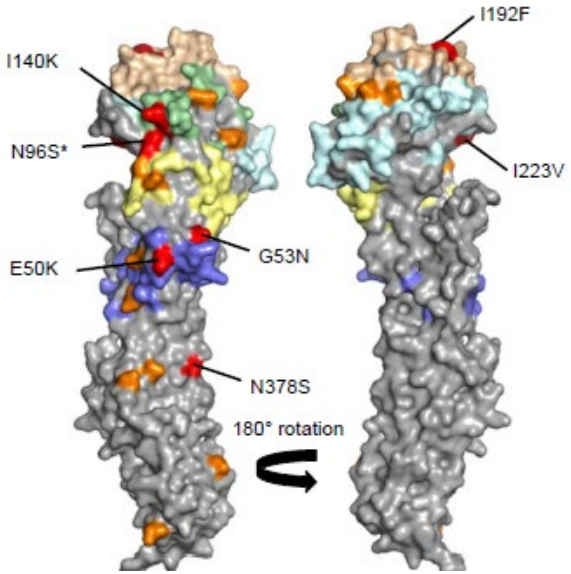
A/Darwin/6/2021 cell (2a)



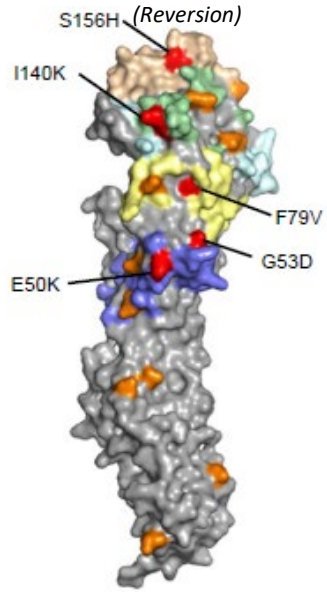
A/Michigan/60/2022 cell (2a.1b)



A/Massachusetts/18/2022 cell (2a.3a.1)



A/Florida/57/2022 cell (2b)



- Positions where amino acids differ from A/Darwin/6/2021 HA are indicated
- Parallel evolution observed (e.g., I140K, E50K)

Analysis of A(H3N2) viruses by antisera to antigens recommended for NH 2022-23

VN Assay

Antisera to northern hemisphere 2022-23 antigens (2a)

A/Darwin/6/2021-like (cell)*

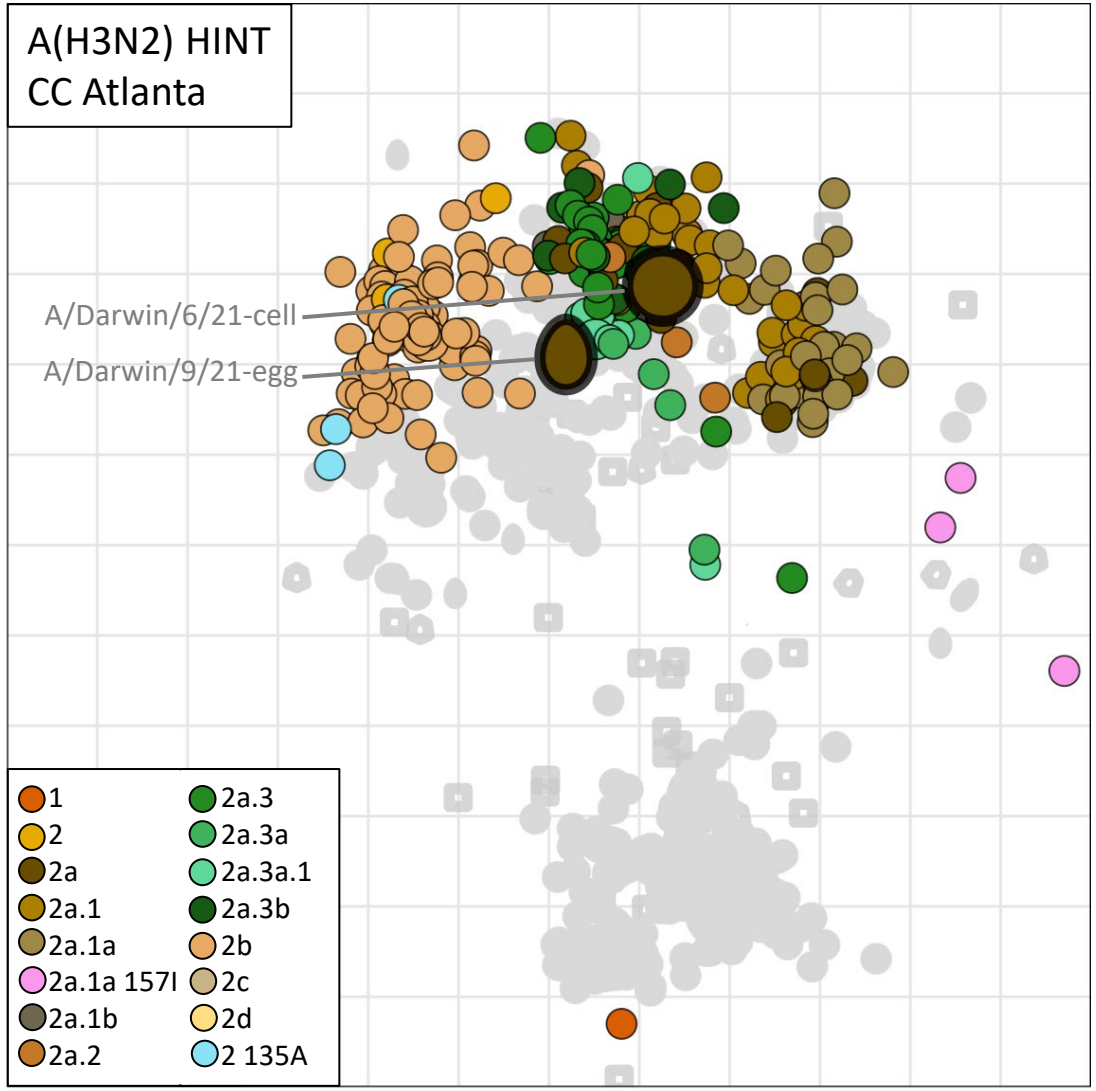
WHO CC	Like (2-4 fold)	Low (≥ 8 fold)
CDC	186 (94%)	11 (6%)
CNIC	110 (100%)	0 (0%)
FCI	121 (100%)	0 (0%)
NIID	40 (98%)	1 (2%)
VIDRL	19 (95%)	1 (5%)
Total	476 (97%)	13 (3%)

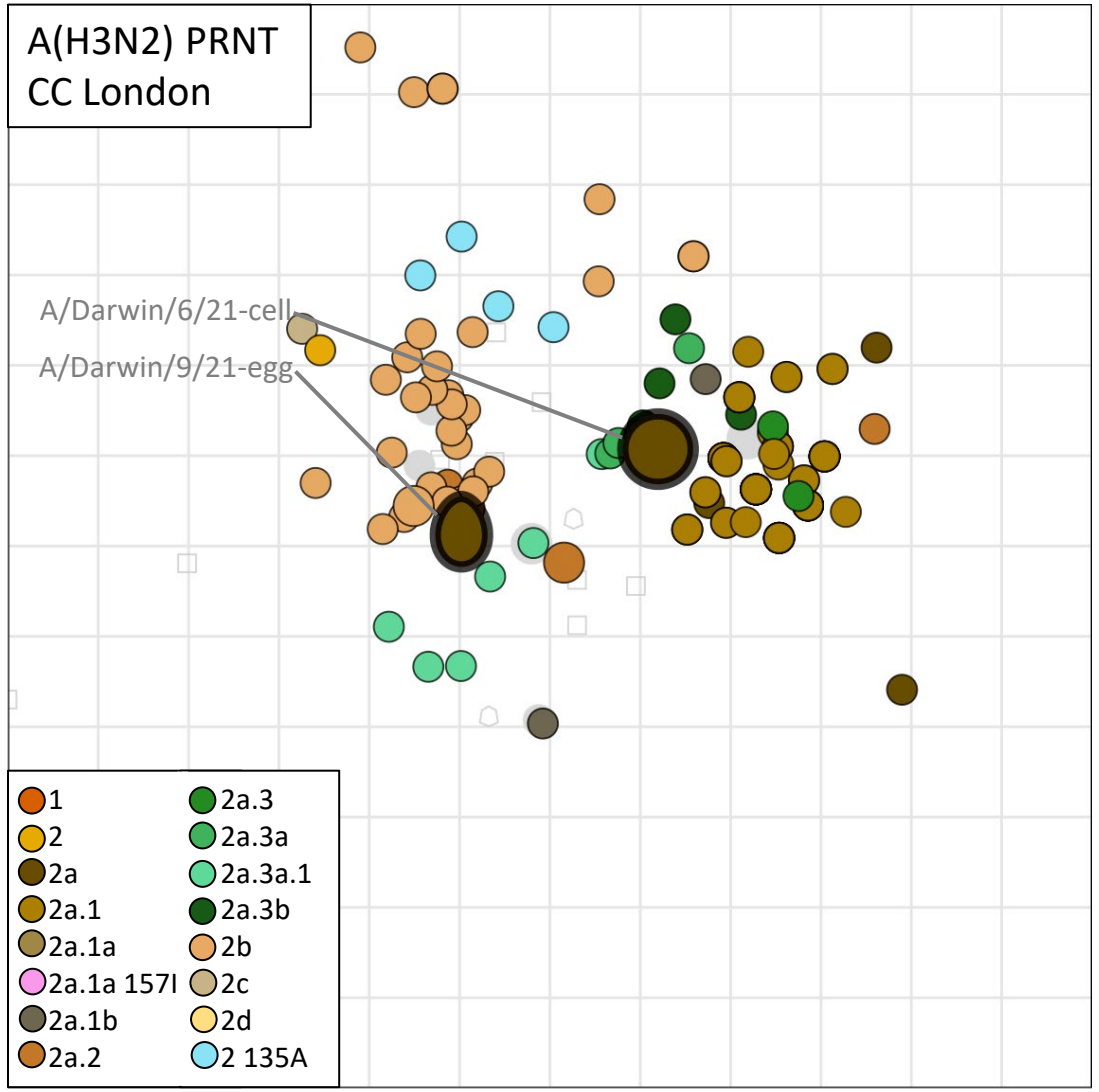
A/Darwin/09/2021-like (egg)

WHO CC	Like (2-4 fold)	Low (≥ 8 fold)
CDC	87 (51%)	85 (49%)
CNIC	8 (7%)	102 (93%)
FCI	---	---
NIID	39 (95%)	2 (5%)
VIDRL	17 (85%)	3 (15%)
Total	151 (44%)	192 (56%)

Reference viruses are in HA clade 3C.2a1b.**2a.2a.** Showing data from viruses isolated from swabs collected from September to January 2023

A(H3N2) antigenic cartography

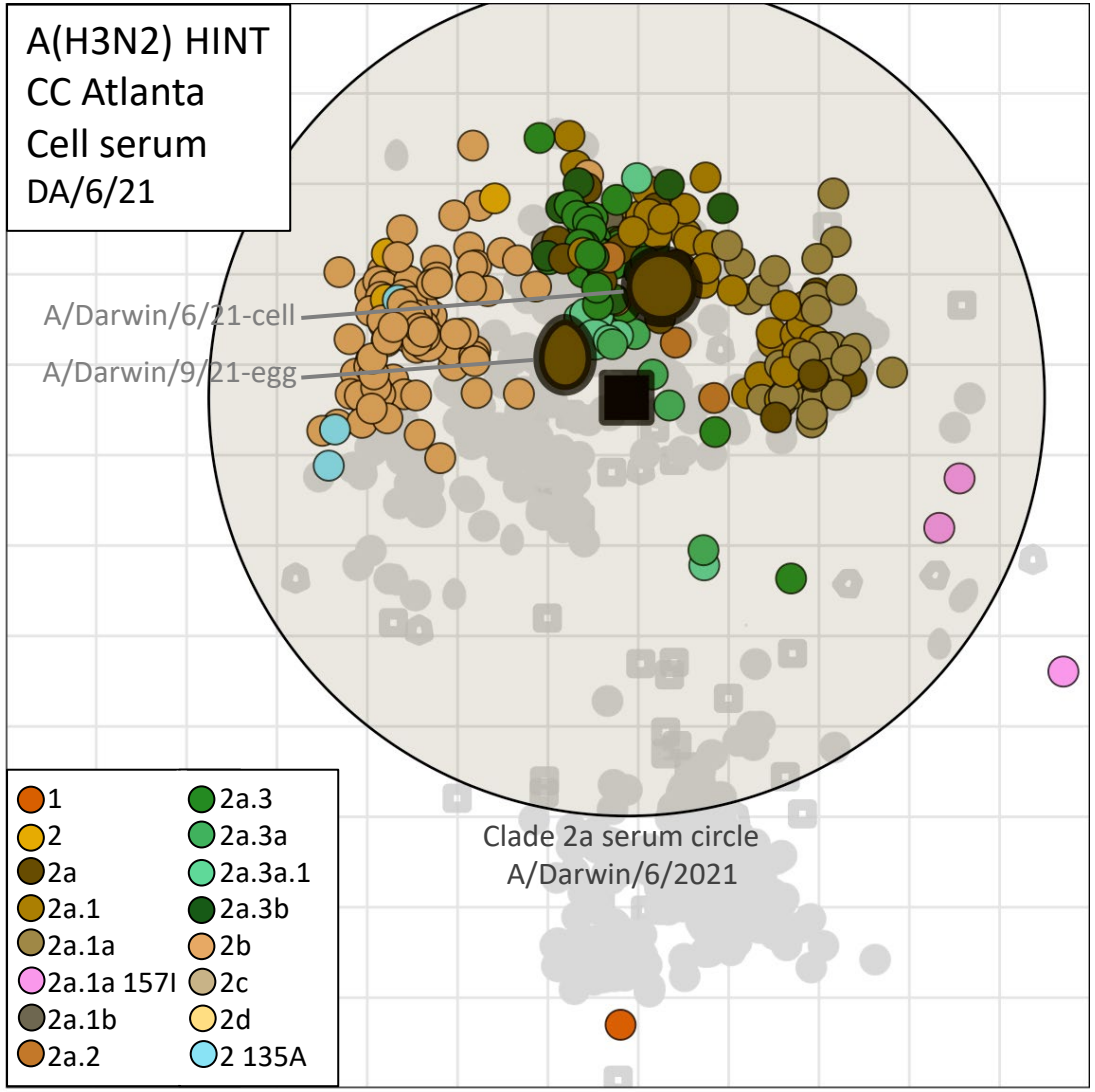


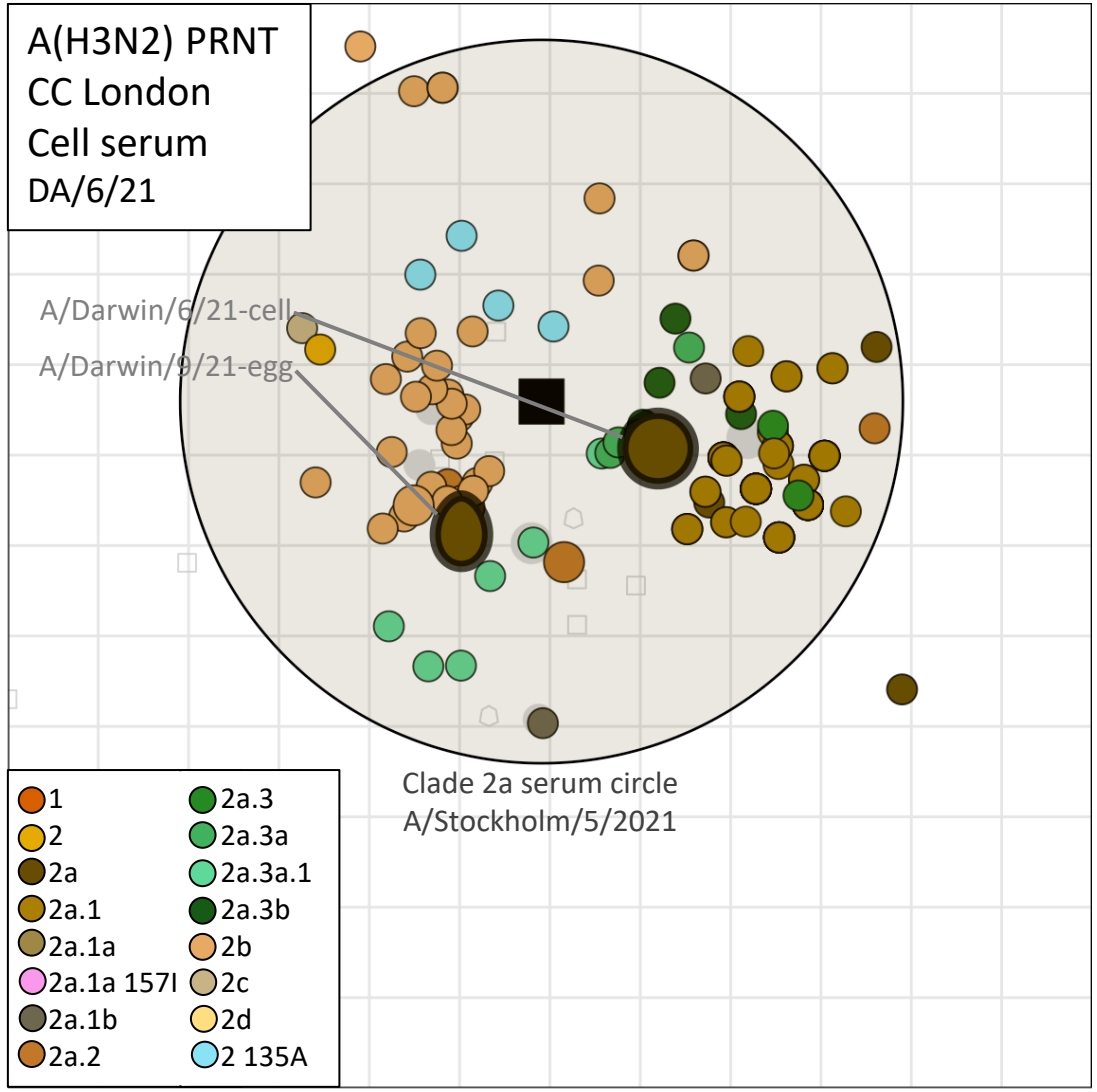


Source: Cambridge Univ., S. James and D. Smith

Since February 2022 (older viruses in grey)

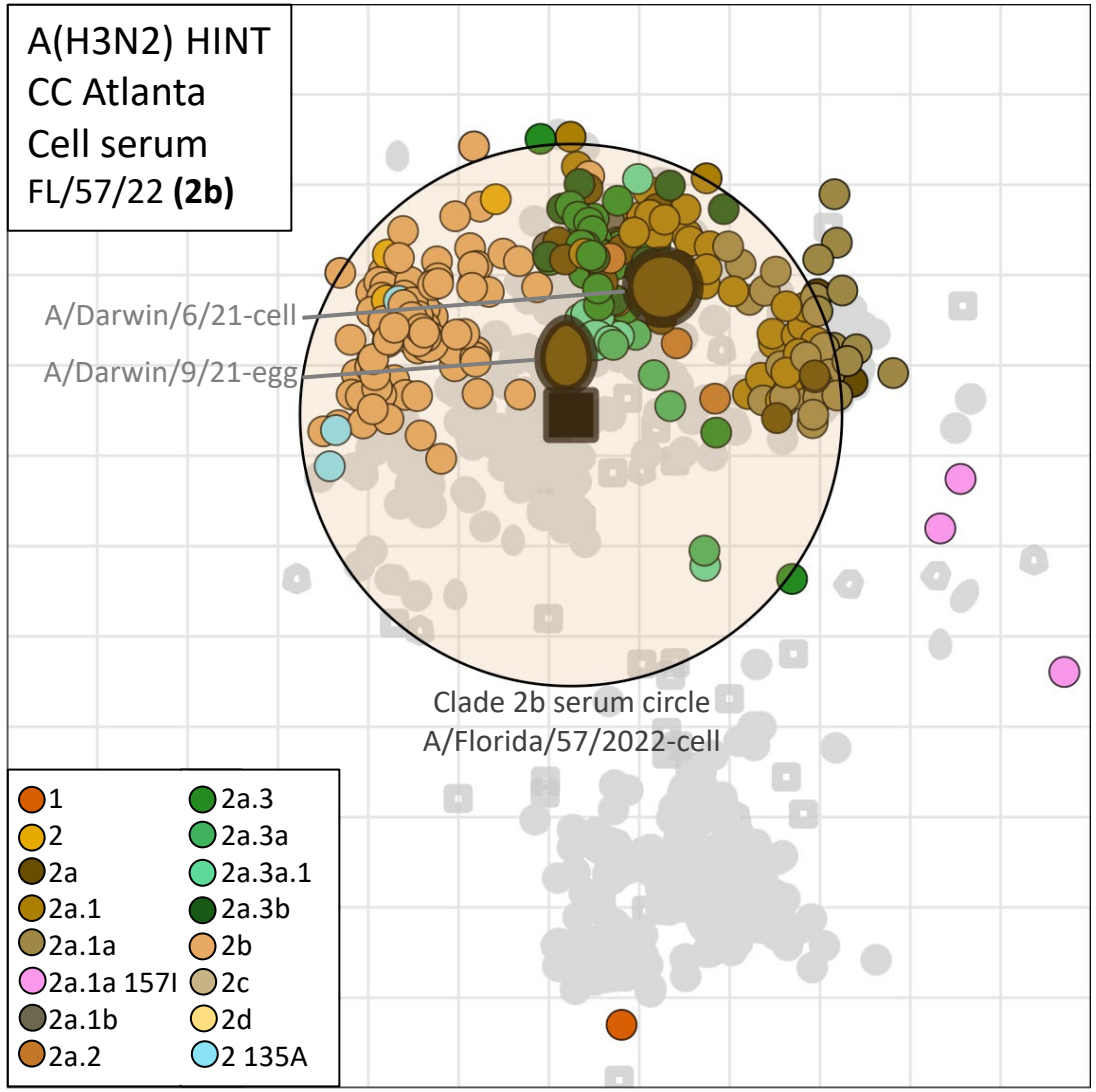
Cartography illustrating ferret antisera reactivity (A/Darwin/6/21 cell-like)

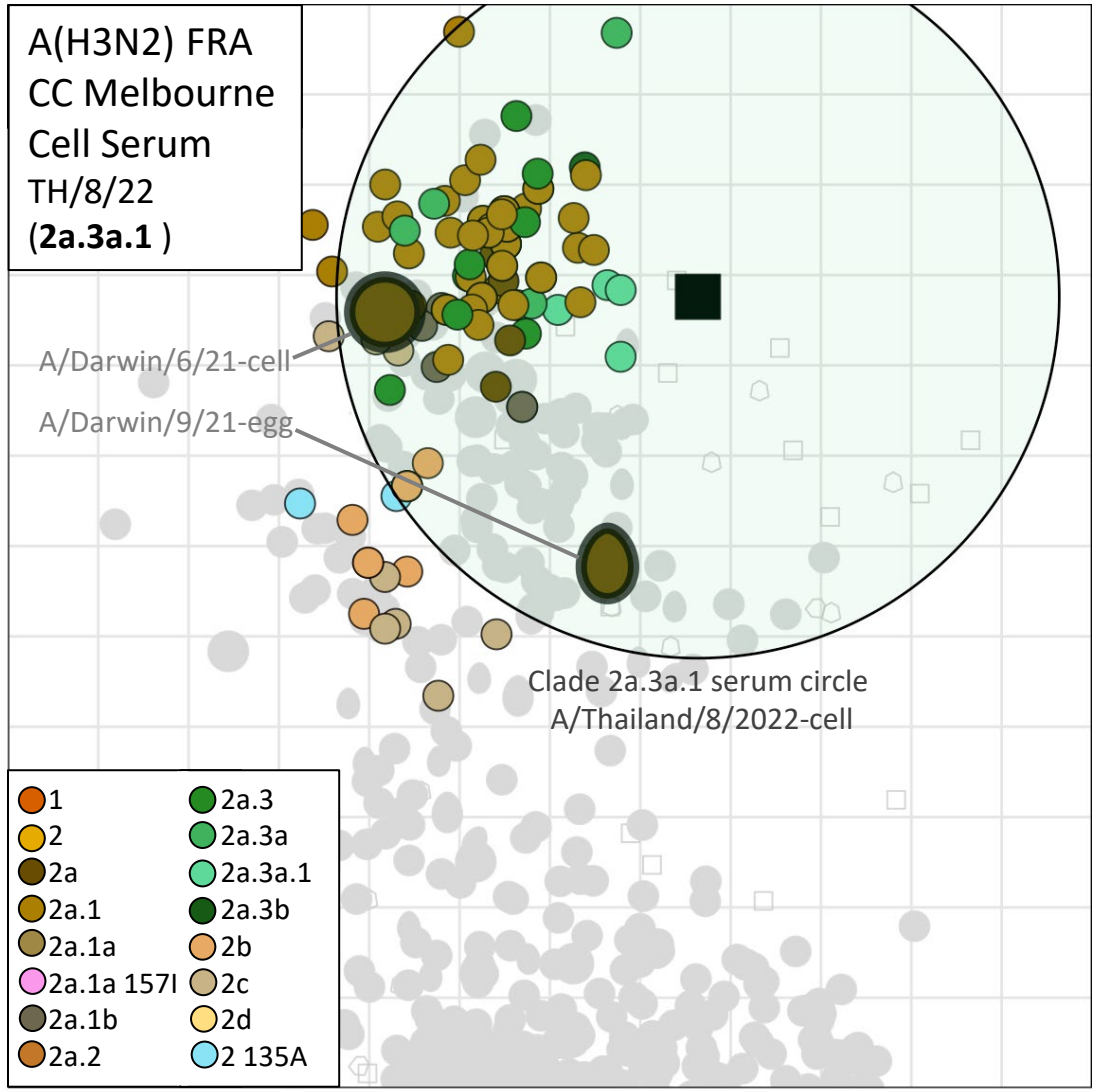




Source: Cambridge Univ., S. James and D. Smith

Cartography illustrating ferret antisera reactivity





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

Human post-vaccination sera analysis of A(H3N2) viruses

Multiple serum panels from subjects vaccinated with A/Darwin/6/2021-like viruses showed good neutralization against viruses expressing various emerging 2a subclade HA genes.

A/Darwin/6/2021-like (2a) vaccines				2a *DAR/6 SIAT	2a.1a MD/02 SIAT	2a.1b MI/60 SIAT	2a.3 AK/01 SIAT	2a.3a.1 MA/18 SIAT	2b FL/57 SIAT	1a.1 HAI/35 SIAT
A/DARWIN/6/2021 SIAT	Pediatric (6-35M)	USA	IIV4	144	√	√	√	√	√	70
	Pediatric (3-8Y)	USA	ccIIV4 (Flucelvax)	408	√	√	√	√	√	√
			IIV4	538	√	√	√	√	355	355
	Pediatric (9-17Y)	USA	ccIIV4 (Flucelvax)	437	√	243	√	√	320	299
			IIV4	320	√	190	√	√	√	√
	Adult	USA	ccIIV4 (Flucelvax)	279	√	√	√	√	171	197
			RIV4 (Flublok)	618	√	√	√	√	√	√
			IIV4	269	√	√	√	√	184	√
	Older Adult (50-64Y)	USA	IIV4	204	√	√	√	√	√	√
	Elderly (≥65Y)	USA	IIV4-HD	160	√	√	√	√	√	√

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 (95% 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/ALASKA/01/2021 (AK/01); A/DARWIN/6/2021 (DAR/6); A/FLORIDA/57/2022 (FL/57); A/HAINAN-BAOTINGLIZUMIAOZUZIZHI/35/2022 (HAI/35); A/MARYLAND/02/2021 (MD/02); A/MASSACHUSETTS/18/2022 (MA/18); A/MICHIGAN/60/2022 (MI/60).

Statistically non-inferior = √
Statistically non-inferior but reference virus GMT < 40 = X

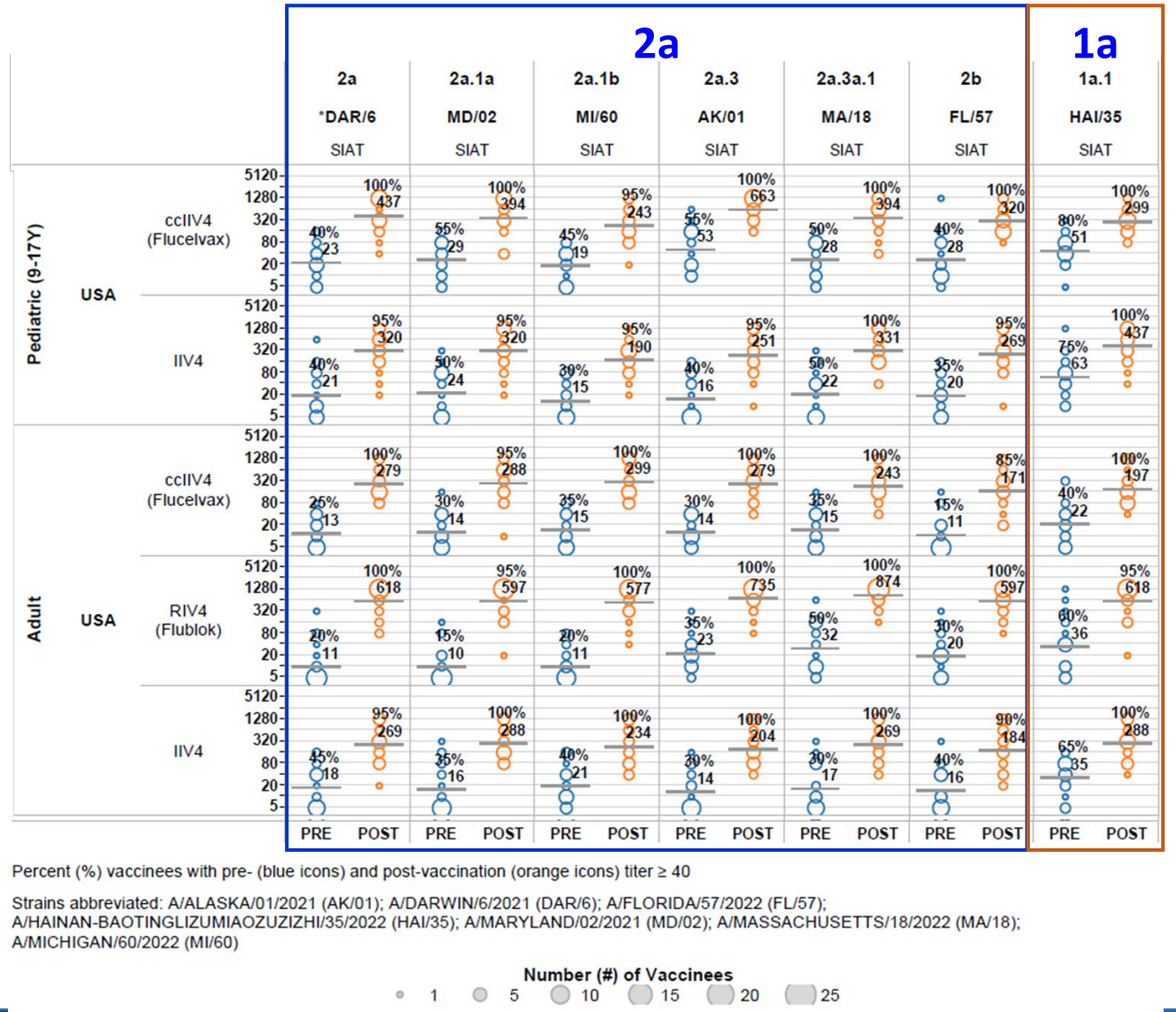
GMT ratio lowerbound (90% CI)
0.0 — 1.0

Source: U.S. CDC

Adult human post-vaccination sera: individual responses (NH-2022-23)

Vaccinated with A/Darwin/6 or 9/2021-like antigen (clade 2a)

- Increased antibody titers to all clades tested
  - Importantly emerging HA clades were well neutralized
    - 2a.1a, 2a.1b, 2a.3a.1
    - Good but smaller increase in HA clade 2b (e.g., FL/57) viruses
- Boosts to titers against 1a.1 representative (HAI/35)
  - A/Hainan-Baotinglizumiaozuzizhi/35/2022
- Likely immune memory response
  - sometimes called “Back boost”



Percent (%) vaccinees with pre- (blue icons) and post-vaccination (orange icons) titer ≥ 40

Strains abbreviated: A/ALASKA/01/2021 (AK/01); A/DARWIN/6/2021 (DAR/6); A/FLORIDA/57/2022 (FL/57); A/HAINAN-BAOTINGLIZUMIAOZUZIZHI/35/2022 (HAI/35); A/MARYLAND/02/2021 (MD/02); A/MASSACHUSETTS/18/2022 (MA/18); A/MICHIGAN/60/2022 (MI/60)

A(H3N2) summary (1): global circulation and phylogeny

- In many countries, areas and territories reporting influenza A viruses, A(H3N2) subtype predominated
  - Significant H3 activity was observed in North America, northwest Africa, Europe and some countries in Asia
- HA phylogenetics: HA of circulating A(H3N2) viruses in this period belonged to two major clades:
  - Clade 1 (complete classification 3C.2a1b.2a.**1**)
    - Evolved into subclade 1a.1 (typically encoding I48T and K171N substitutions) and were detected primarily in viruses circulating in China.
  - Clade 2 (complete classification 3C.2a1b.2a.**2**)
    - Global dissemination
    - Evolved into clades 2a-2d
      - 2a have further evolved into multiple subclades
      - 2a.1b, 2a.3a and 2b have predominated in this period

A(H3N2) summary (2): antigenic characteristics

- Viruses expressing clade 2 HA genes including subclades are antigenically closely related and are antigenically distinct from 1a.1 viruses
- Ferret antisera to:
  - A/Darwin/6/2021 (2a)
    - HA clade 2 viruses from multiple subclades were well recognized
      - Viruses expressing clade 2b HA showed subtle reductions in reactivity
    - Had reduced to poor reactivity with viruses expressing clade 1a.1
  - A/Florida/57/2022 (2b)
    - HA clade 2b viruses were well recognized, but showed reduced recognition of other clade 2 subclades
  - A/Thailand/8/2022 or A/Massachusetts/18/2022 (2a.3a.1)
    - HA clade 2a.3a.1 viruses were well recognized, but showed reduced recognition of other clade 2 subclades

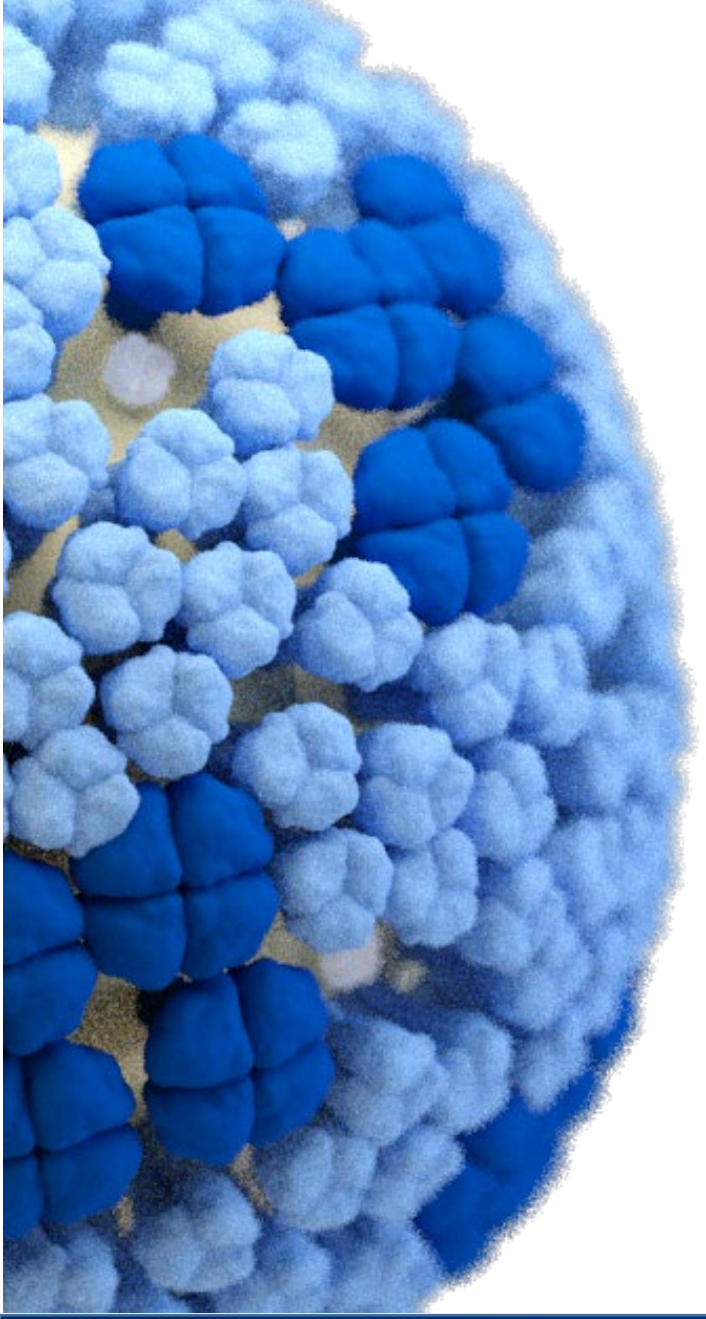
A(H3N2) summary (3): human serology and antiviral susceptibility

Human serology studies with serum panels from individuals vaccinated with A/Darwin/6/2021-like or A/Darwin/9/2021-like(2a) viruses:

- Most post-vaccination human serum panels reacted well with recent A(H3N2) viruses expressing clade 2a, 2a.1b, 2a.3a.1, or 2b HA genes.
  - Panels from some of the younger age groups showed reduced reactivity with viruses expressing 2b or 1a.1 HA genes

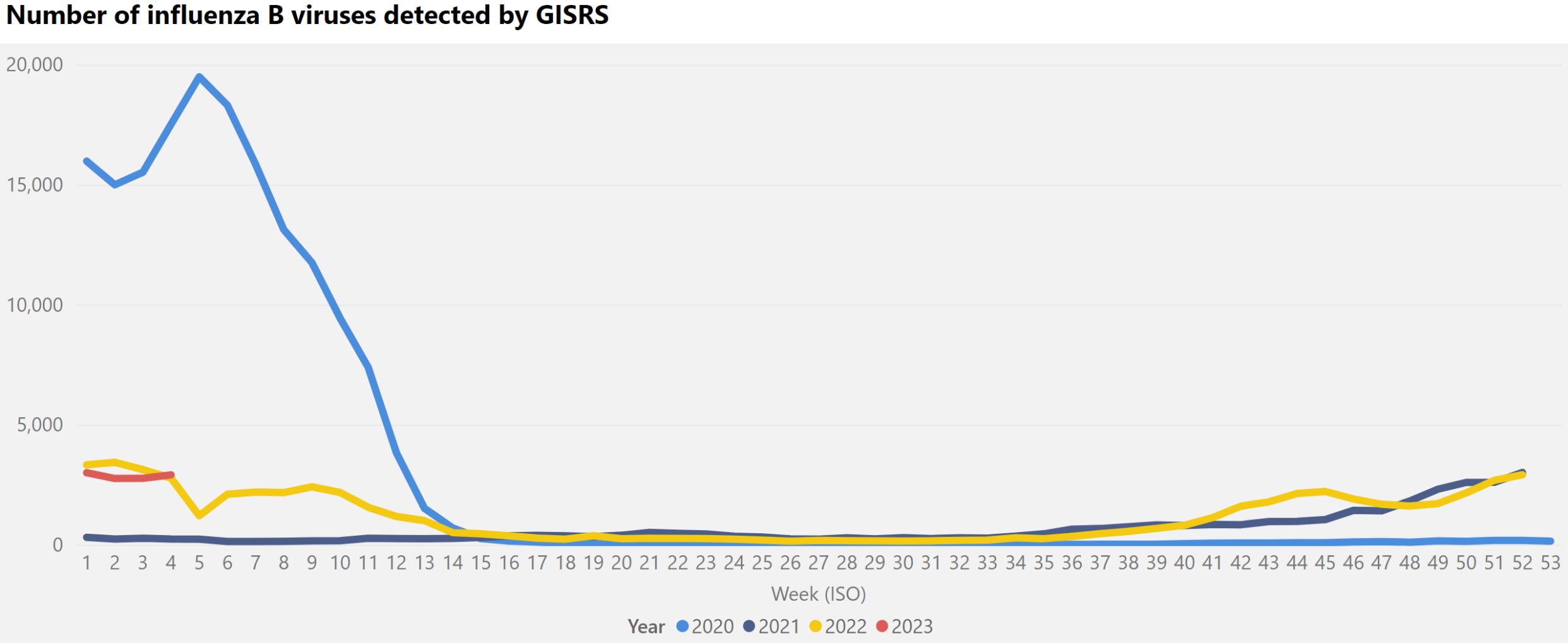
Antiviral Susceptibility viruses collected and analyzed since 1 September 2022

- Of 2,686 A(H3N2) viruses analyzed, none showed genetic or phenotypic evidence of reduced inhibition to neuraminidase inhibitors.
- Of 2,429 A(H3N2) viruses analyzed, none showed genetic or phenotypic evidence of reduced susceptibility to endonuclease inhibitor (baloxavir marboxil).

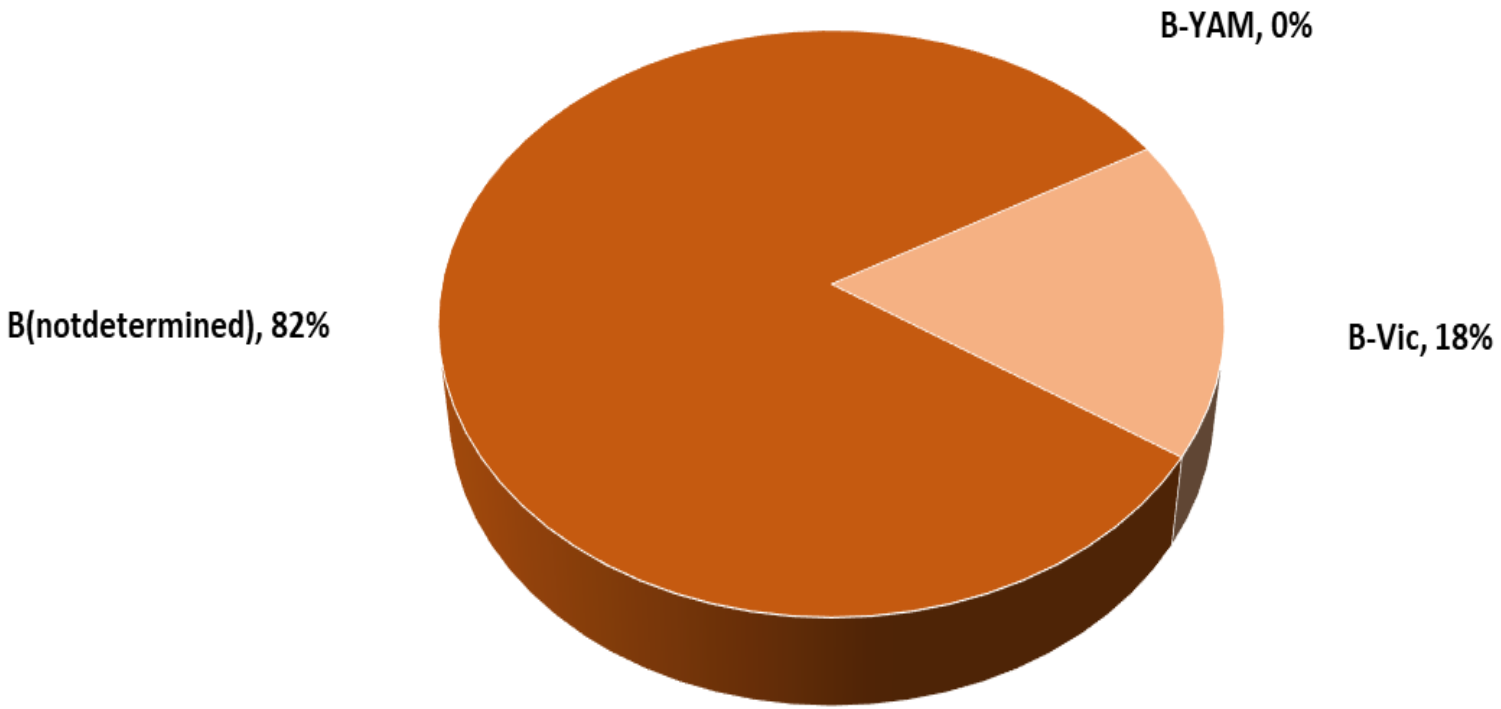


Influenza B Viruses

Number of influenza B viruses detected by GISRS



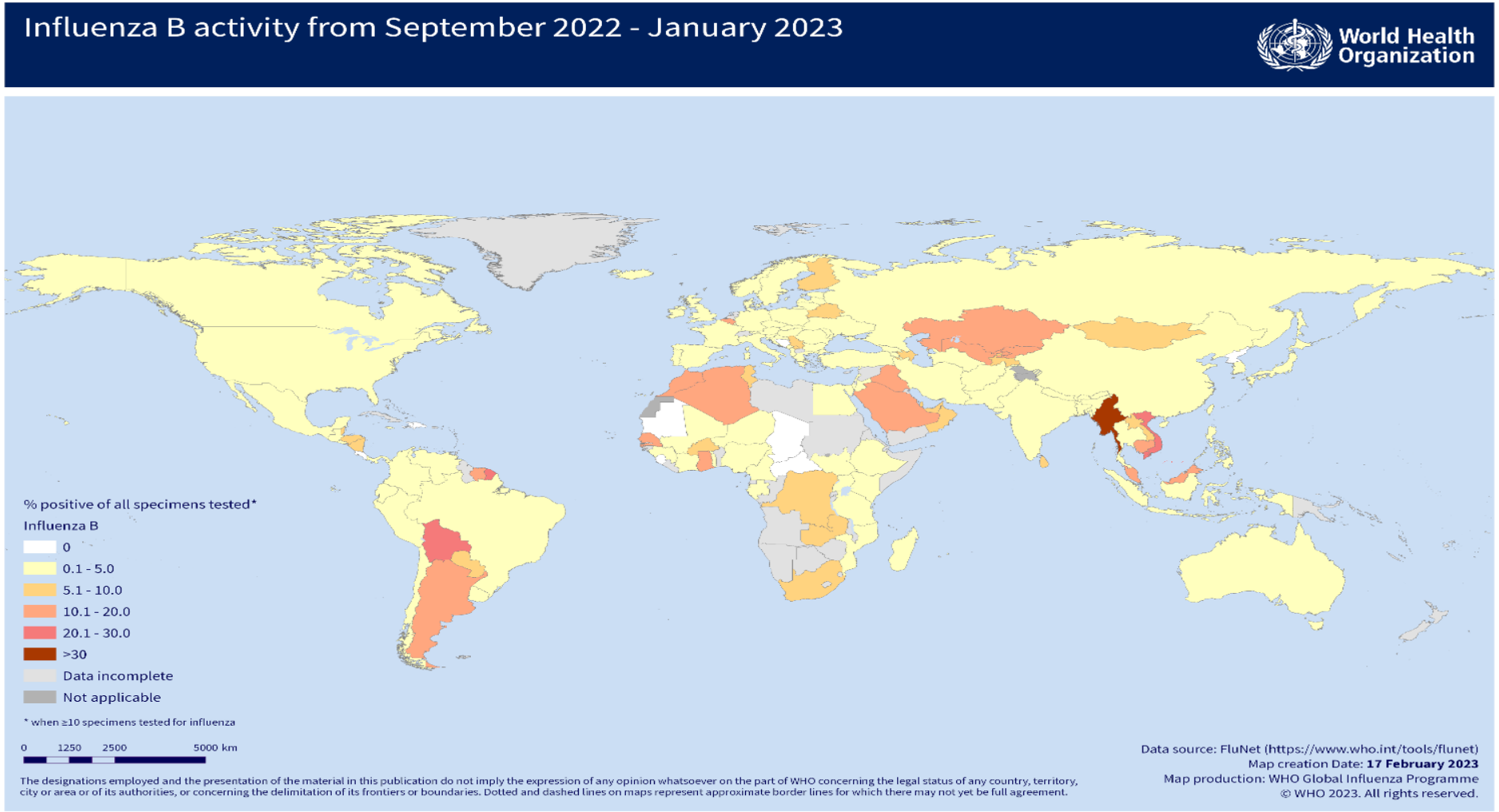
Circulating influenza B virus lineages (Sept. 2022-Jan. 2023)



- B lineage summary
  - 18% B/Victoria
  - 0% B/Yamagata
  - 82% not determined

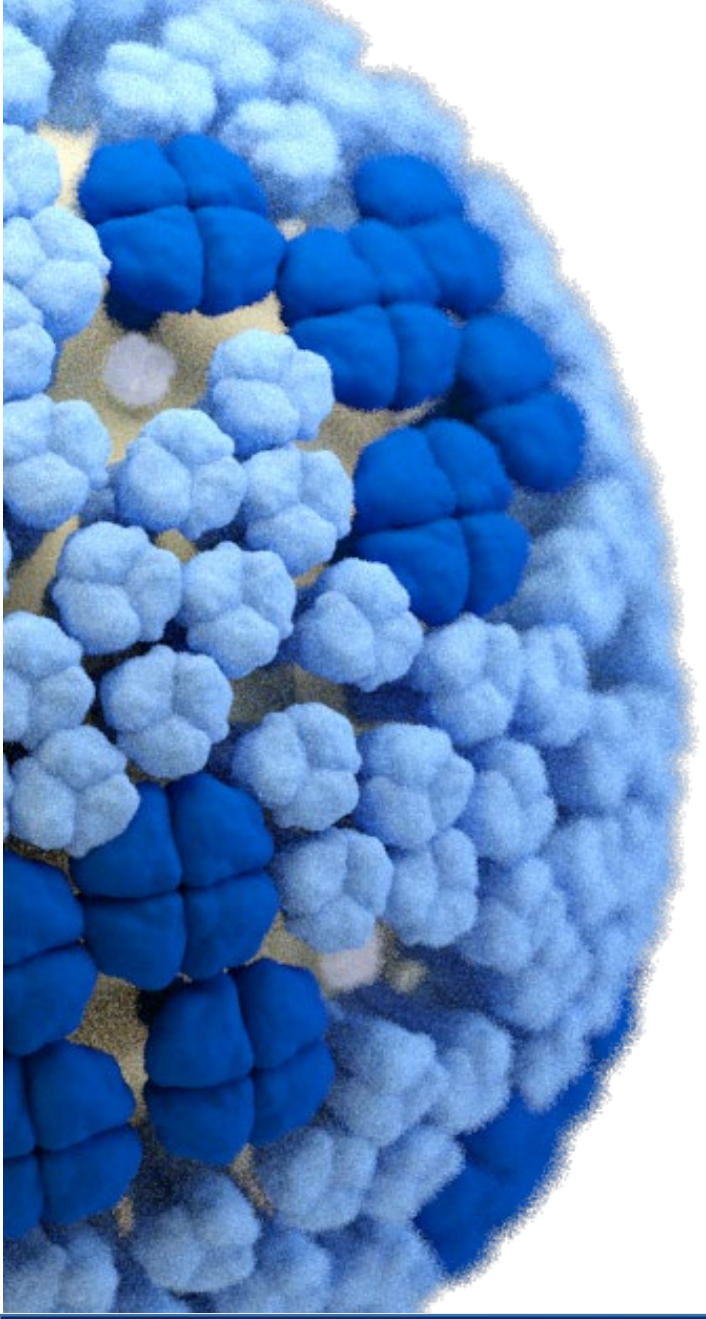
Data source: FluNet, (https://www.who.int/tools/flunet), Global Influenza Surveillance and Response System

Influenza B virus activity



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

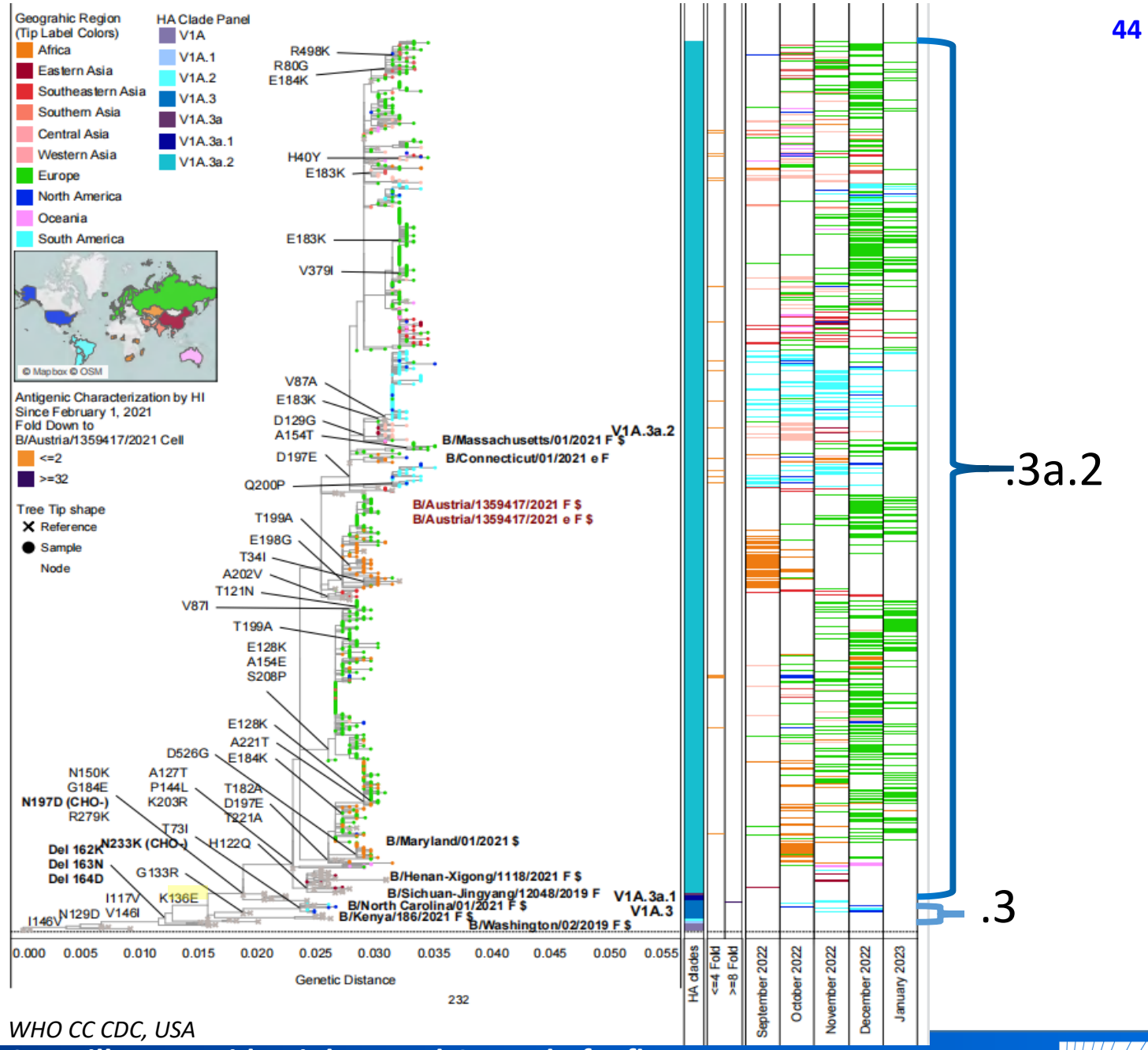
Data source: FluNet, (https://www.who.int/tools/flunet), Global Influenza Surveillance and Response System (17 Feb 2023)



Influenza B/Victoria Viruses

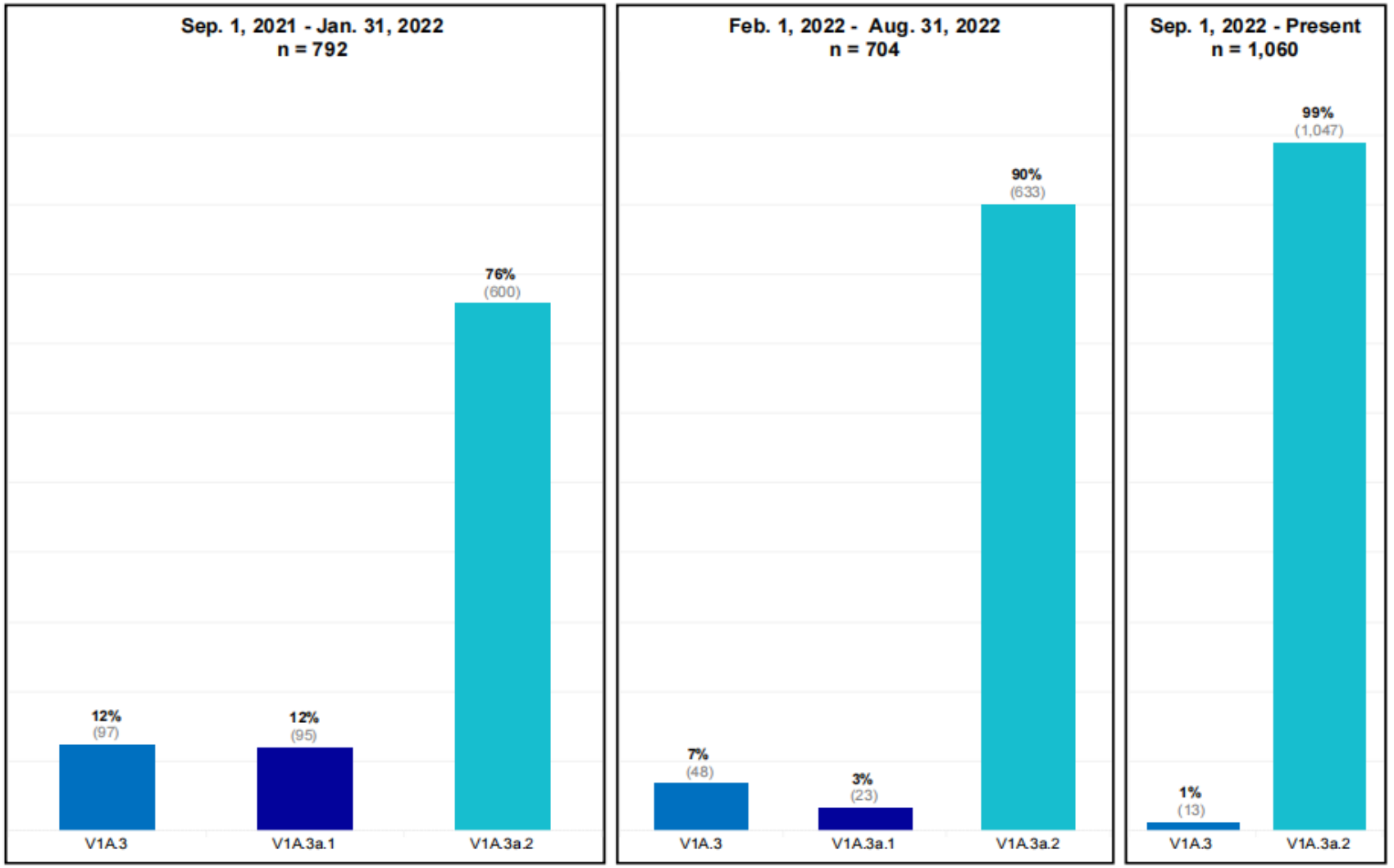
Recent B/Victoria HA phylogeography

- 1A.**3** descendants in North and Central America
  - 1% of viruses collected since September 2022
  - B/Kenya/186/2021
- 1A.**3a.2**, global distribution
  - Share A127T, P144L, K203R
    - B/Austria/1359417/2021-like
  - Continue to diversify
    - H122Q in China
    - T182A, D197E and T221A in Africa, Europe and North America
    - D197E in Asia and the Americas



WHO CC CDC, USA

Global B/Victoria HA clade diversity



Based on HA sequence availability

Source: WHO CC CDC, USA

Antigenic analysis of B/Victoria viruses

Antisera to northern hemisphere 2022-23 antigens

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

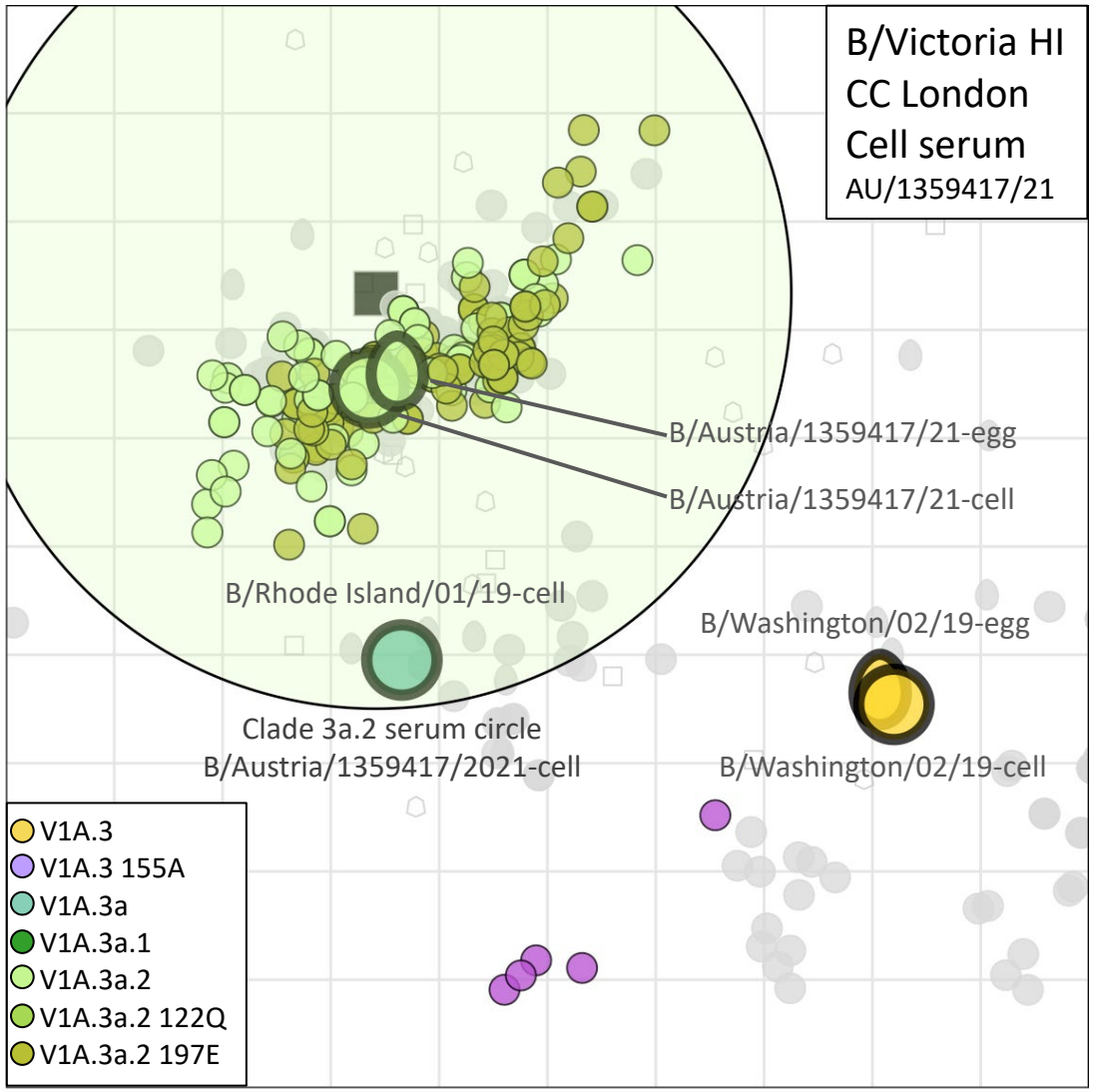
WHO CC	Like (2-4 fold)	Low (≥ 8-fold)
CDC	22 (96%)	1 (4%)
CNIC	7 (88%)	1 (13%)
FCI	100 (100%)	0 (0%)
NIID	19 (100%)	0 (0%)
VIDRL	128 (100%)	0 (0%)
TOTAL	276 (99%)	2 (1%)

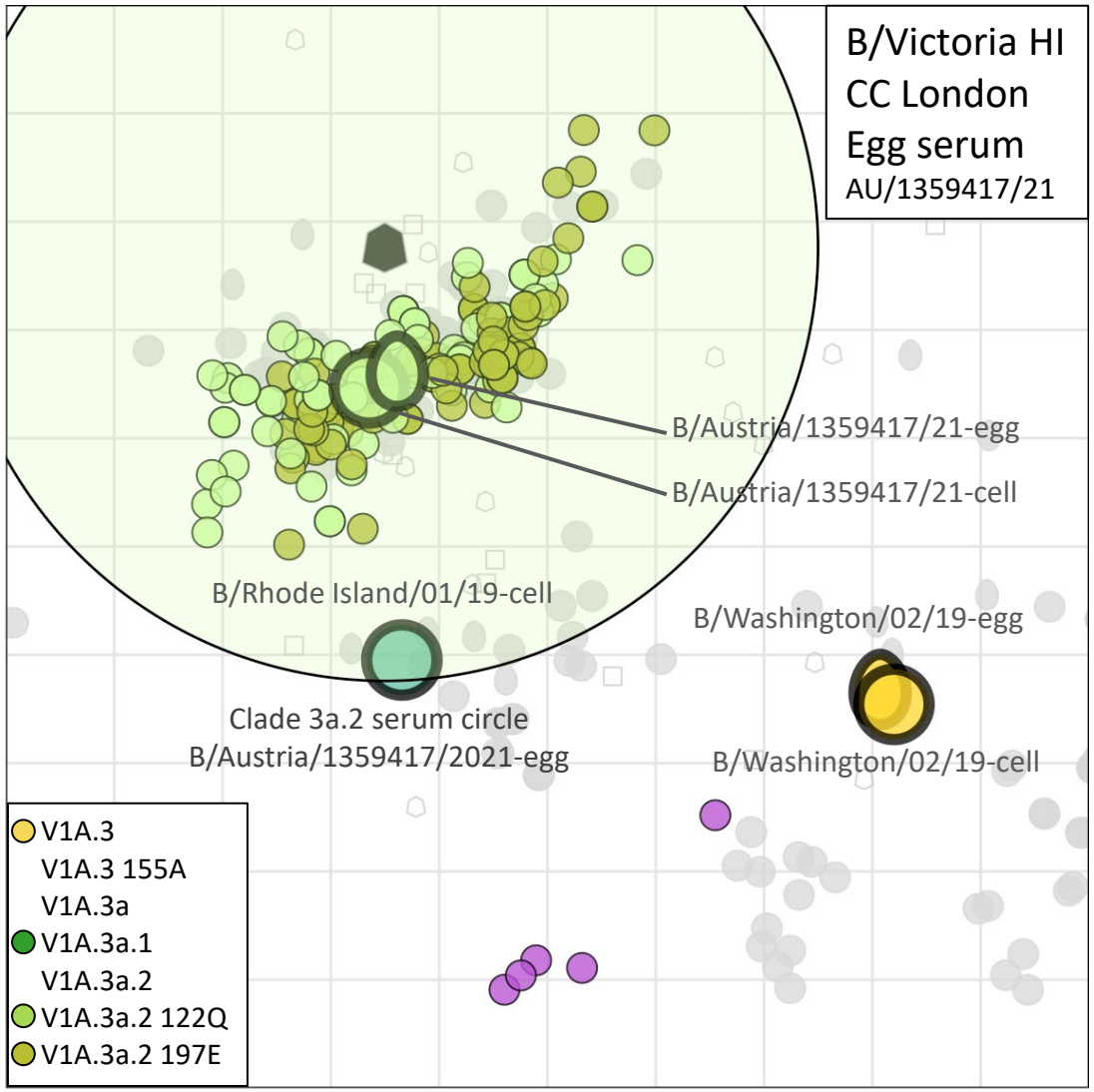
B/Austria/1359417/2021-like (egg)

WHO CC	Like (< 8-fold)	Low (≥ 8-fold)
CDC	22 (96%)	1 (4%)
CNIC	7 (88%)	1 (13%)
FCI	100 (100%)	0 (0%)
NIID	19 (100%)	0 (0%)
VIDRL	127 (99%)	1 (1%)
TOTAL	275 (99%)	3 (1%)

"Low" represented titers ≥ 8-fold lower than vaccine strain homologous titer

B/Victoria antigenic cartography showing serum reactivity



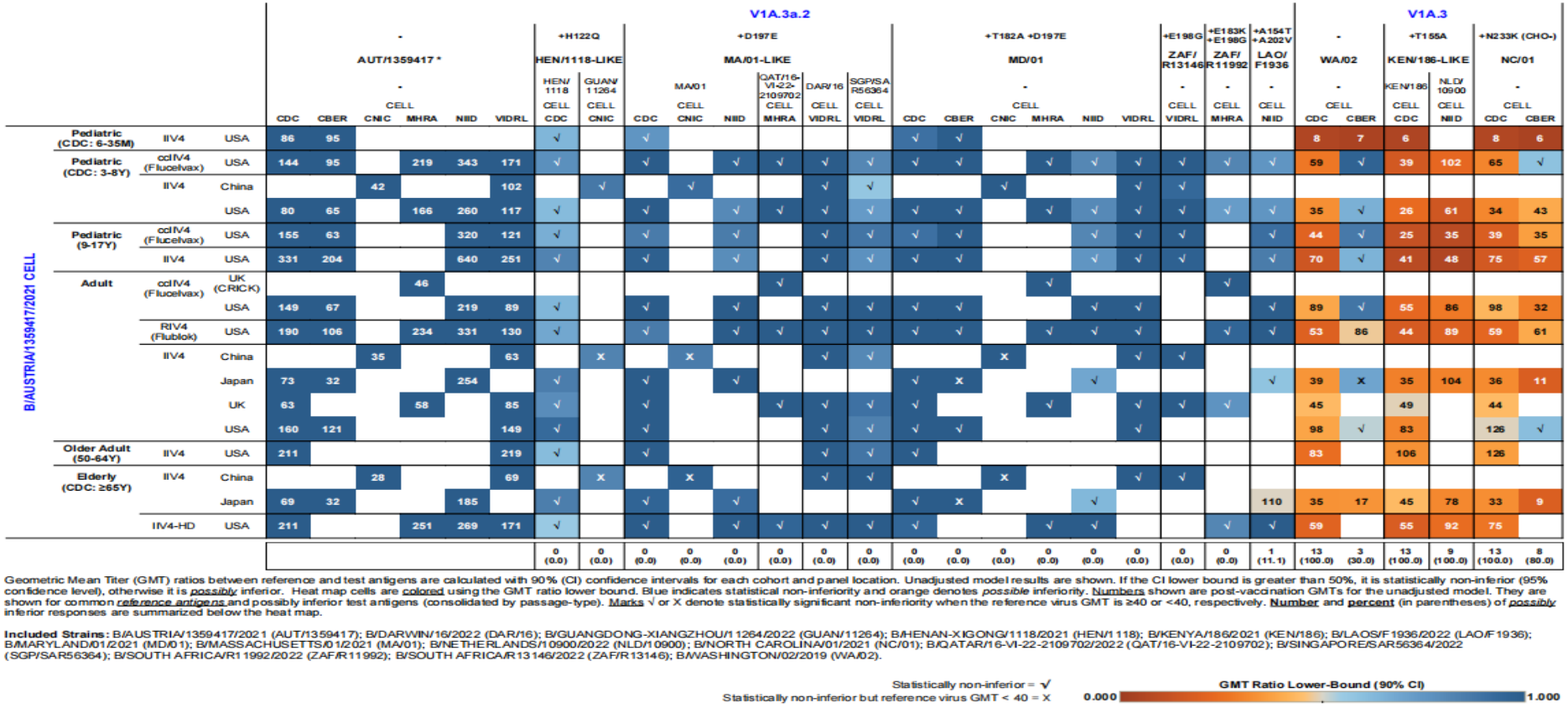


Source: Cambridge Univ., S. James and D. Smith

Human post-vaccination serum analysis of B/Victoria viruses

2022-2023 northern hemisphere panels

WHO Collaborating Center (CC): Human Serological Panels
B/Victoria -- HI Protocol [CELL]



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 (95% 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 common *reference antigens* and possibly inferior test antigens (consolidated by passage-type). Marks √ or X denote statistically significant non-inferiority when the reference virus GMT is ≥40 or <40, respectively. Number and percent (in parentheses) of *possibly* inferior responses are summarized below the heat map.

Included Strains: B/AUSTRIA/1359417/2021 (AUT/1359417); B/DARWIN/16/2022 (DAR/16); B/GUANGDONG-XIANGZHOU/11264/2022 (GUAN/11264); B/HENAN-XIGONG/1118/2021 (HEN/1118); B/KENYA/186/2021 (KEN/186); B/LAOS/F1936/2022 (LAO/F1936); B/MARYLAND/01/2021 (MD/01); B/MASSACHUSETTS/01/2021 (MA/01); B/NETHERLANDS/10900/2022 (NLD/10900); B/NORTH CAROLINA/01/2021 (NC/01); B/QATAR/16-VI-22-2109702/2022 (QAT/16-VI-22-2109702); B/SINGAPORE/SAR56364/2022 (SGP/SAR56364); B/SOUTH AFRICA/R11992/2022 (ZAF/R11992); B/SOUTH AFRICA/R13146/2022 (ZAF/R13146); B/WASHINGTON/02/2019 (WA/02).

Multiple sources: compiled by WHO CC CDC, USA

Shows that current vaccine antigens elicit antibodies that well inhibit inhibited the majority of recent representative B/Victoria lineage viruses from the 1A.3a.2 subclade

Influenza B/Yamagata Lineage Viruses September 2022-February 2023

- There have been no confirmed detections of circulating, naturally occurring B/Yamagata/16/88 lineage viruses after March 2020, including in this period.
- Recent reports of B/Yamagata detections could not be confirmed as naturally occurring B/Yamagata-lineage viruses or were identified as the B/Yamagata lineage component of live attenuated vaccines.
- We cannot yet be confident that B/Yamagata-lineage influenza viruses are extinct.
- GISRS will continue to actively conduct targeted surveillance for influenza B/Yamagata lineage viruses.

Influenza B virus summary (1): global circulation, phylogeny and antigenic characteristics

- Only influenza B/Victoria lineage viruses were available for analysis
- HA phylogenetics of B/Victoria lineage viruses
  - 1A.**3** descendants in North and Central America
    - 1% of viruses collected since September 2022
    - B/Kenya/186/2021
  - 1A.**3a.2**, predominated and have global distribution
    - Share A127T, P144L, K203R
    - B/Austria/1359417/2021-like
    - Continue to diversify
- Post-infection ferret antisera raised against B/Austria/1359417/2021-like viruses (1A.3a.2):
  - Well inhibited HA clade 1A.3a.2 viruses, which predominate
  - Poorly inhibited HA clade 1A.3 viruses, which continue to decrease

Influenza B virus summary (3): human serology and antiviral susceptibility

- Human serology studies, using the serum panels from recipients of the NH 2022-2023 vaccines that contained B/Austria/1359417/2021-like viruses
  - The recent representative B/Victoria lineage viruses from the 1A.3a.2 subgroup were well inhibited by all serum panels
  - Significant reductions in GMTs were detected with most serum panels for viruses from clade 1A.3
- Antiviral susceptibility
  - None of the viruses analysed showed reduced susceptibility to neuraminidase or endonuclease inhibitors.

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