Vaccines and Related Biological Products Advisory Committee Meeting

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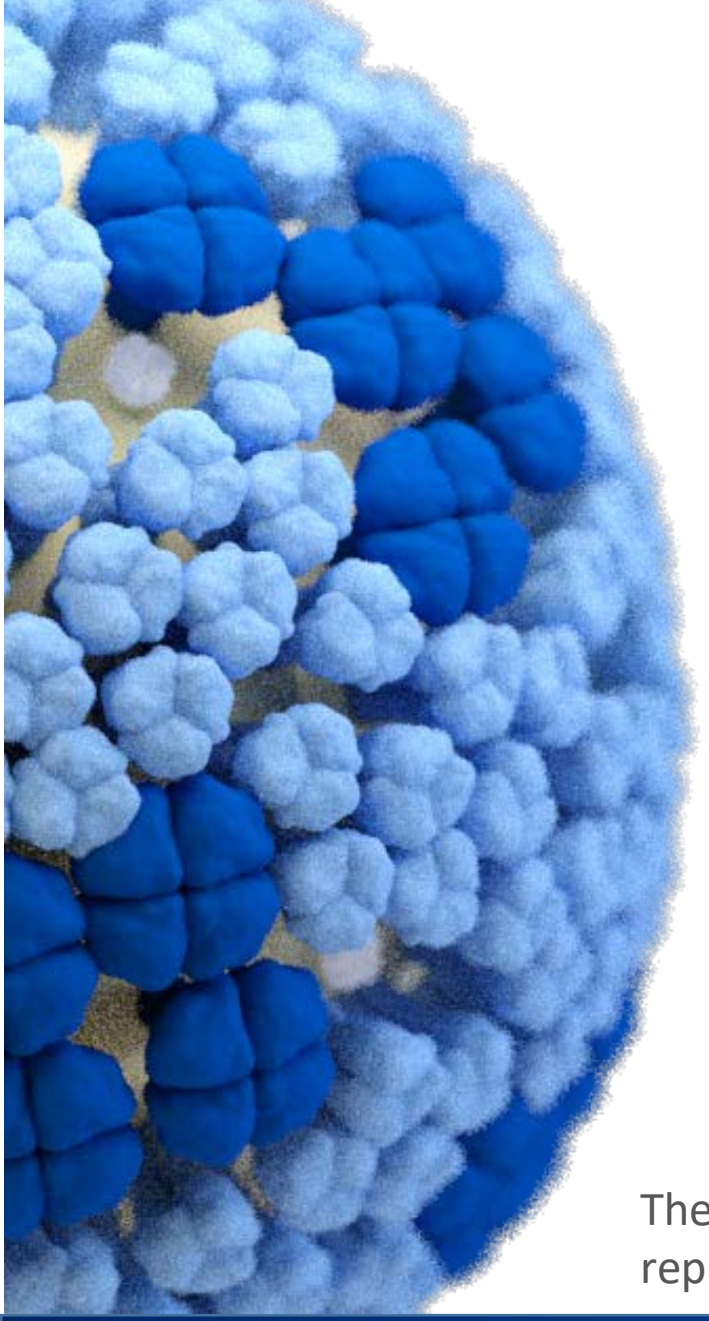


Information For The Vaccine And Related Biological Products Advisory Committee CBER, FDA

Global Influenza Virus Surveillance and Characterization March 3, 2022

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

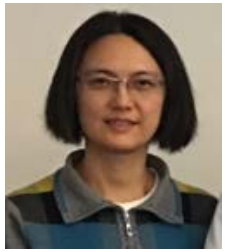
WHO-VCM Recommendations for the Northern Hemisphere (NH) 2022-2023 Season

- **Continuous surveillance conducted by Global Influenza Surveillance and Response System (GISRS)**
  - WHOCCs, NICs, WHO ERLs, WHO H5 Reference Laboratories
  - Supported by countries and partners including GISAID
- **A WHO Consultation held from February 21 – 24, 2022**
  - A hybrid of in-person and virtual meeting
  - Chaired by Dr John McCauley
  - 10 Advisers: Directors of WHOCCs and ERLs
    - 8 advise on seasonal influenza (2 focus on zoonotic)
    - In their capacity as a representative of their corresponding WHO CCs and ERLs
    - Disclosure of interests at the start of meeting

GISRS
GLOBAL INFLUENZA SURVEILLANCE & RESPONSE SYSTEM
Uniting the world in the fight against influenza
1952 - 2022







- 39 observers from WHO CCs, WHO ERLs, other GISRS laboratories and academia
- Experts from WHO Regional offices and Head Quarters

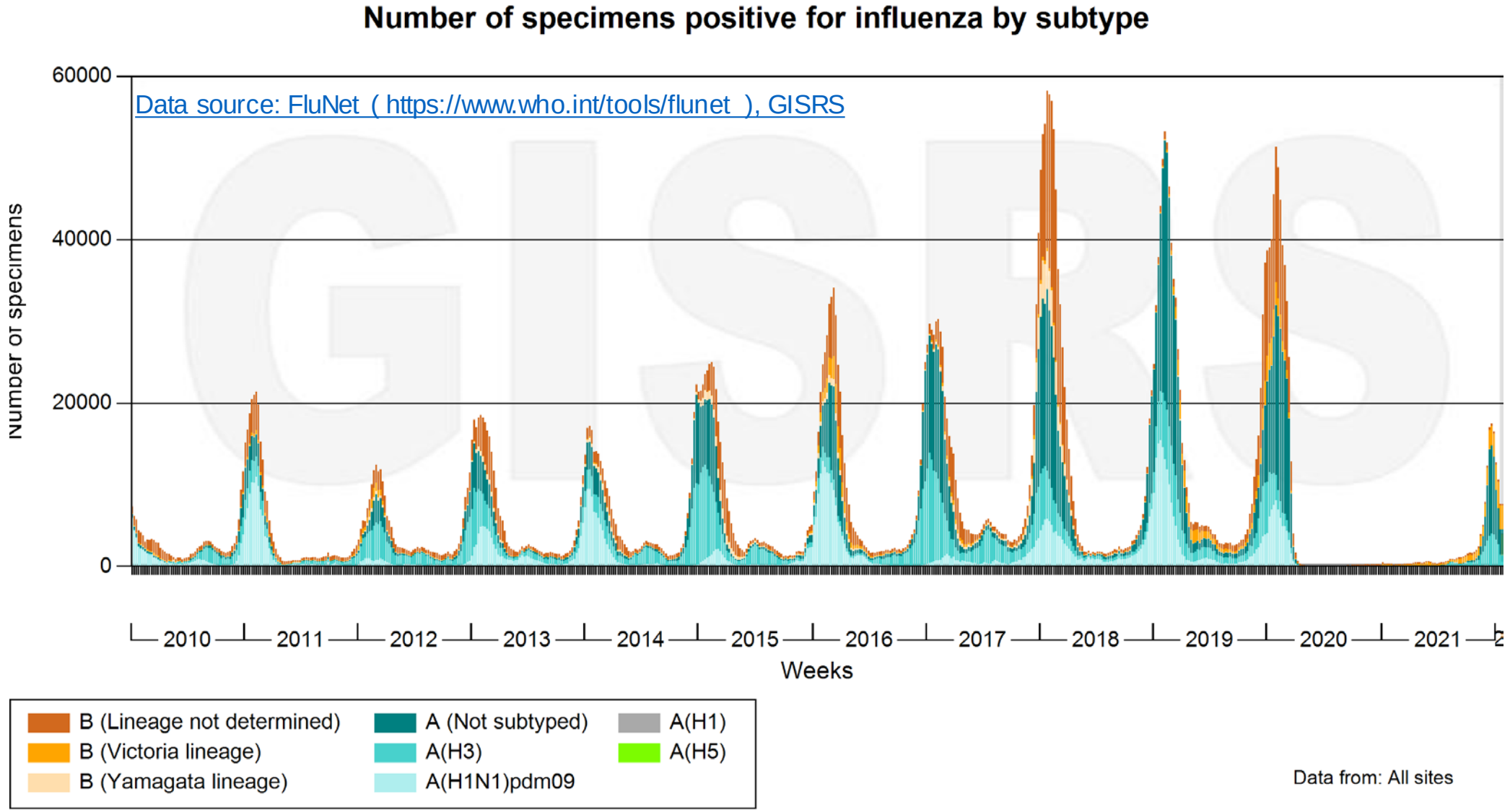
Number of Specimens Positive for Influenza By Subtype

Select week start date (ISO)

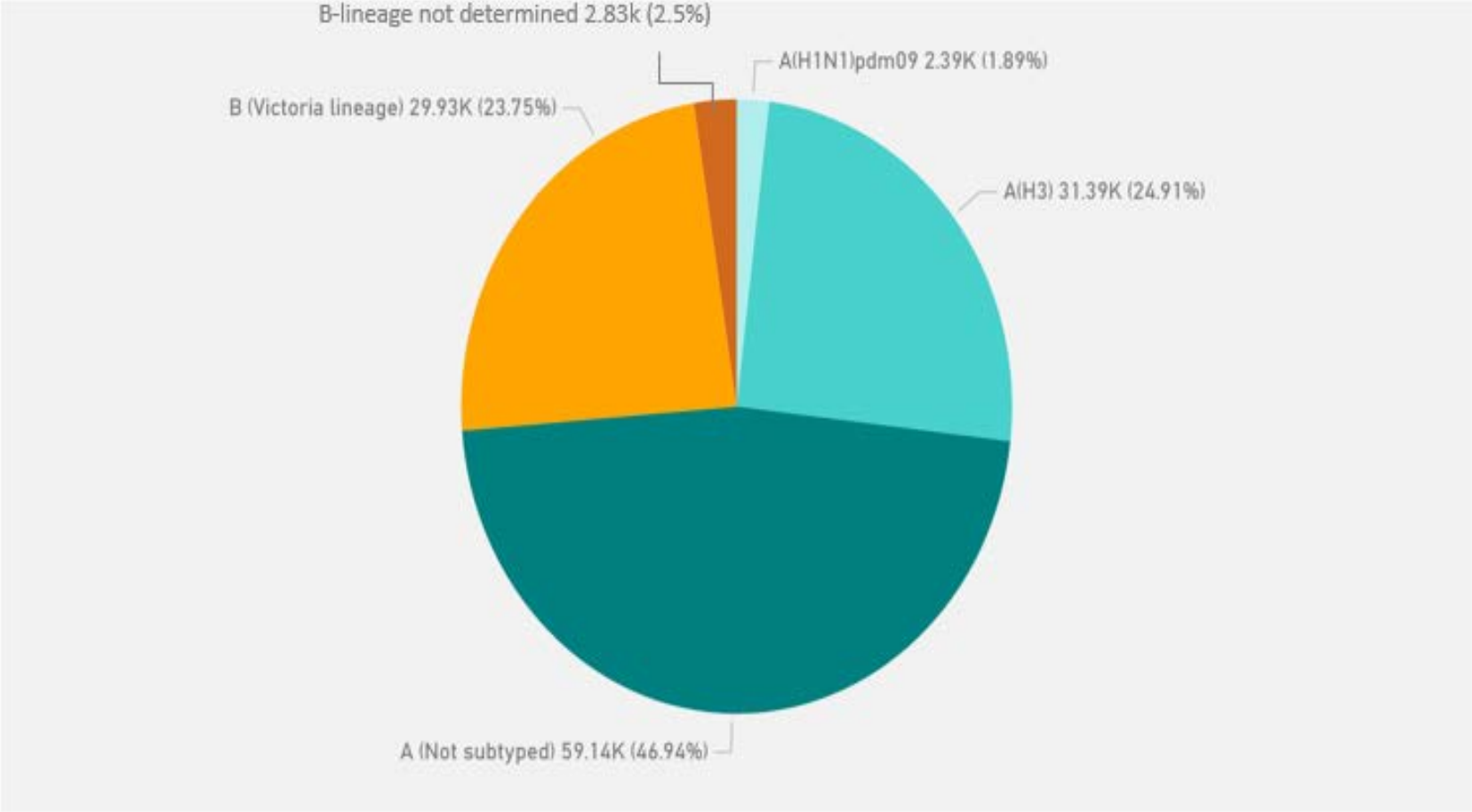
9/1/2019 1/24/2022

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

Global Circulation of Influenza Viruses



Percentage of Influenza A Viruses By Subtypes (Sep 2021 – Jan 2022)

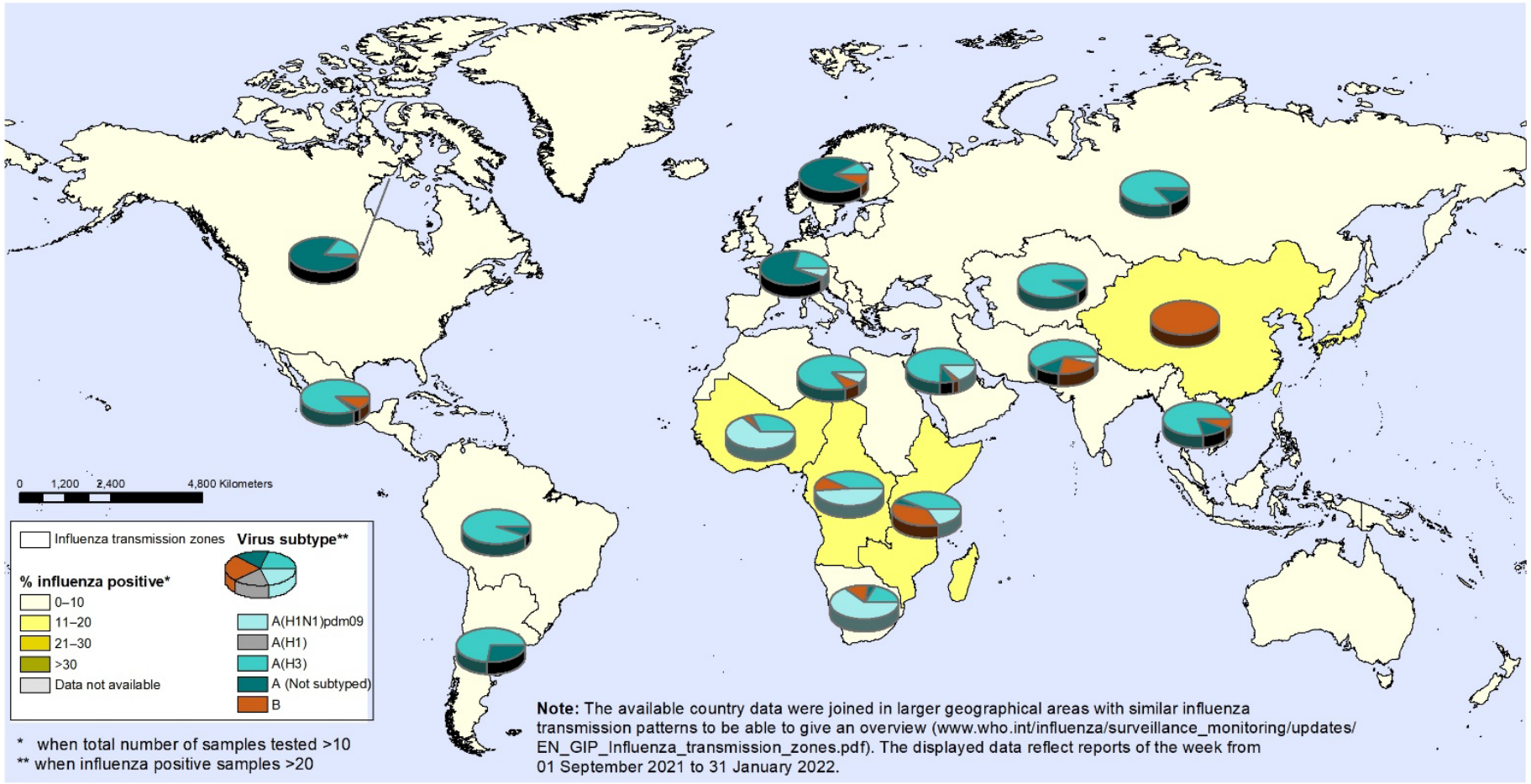


Data source: FluNet, (www.who.int/flunet), Global Influenza Surveillance and Response System (GISRS)

Influenza Activity – (1 Sep 21 – 31 Jan 22)

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

Status as of 11 February 2022



* when total number of samples tested >10
** when influenza positive samples >20

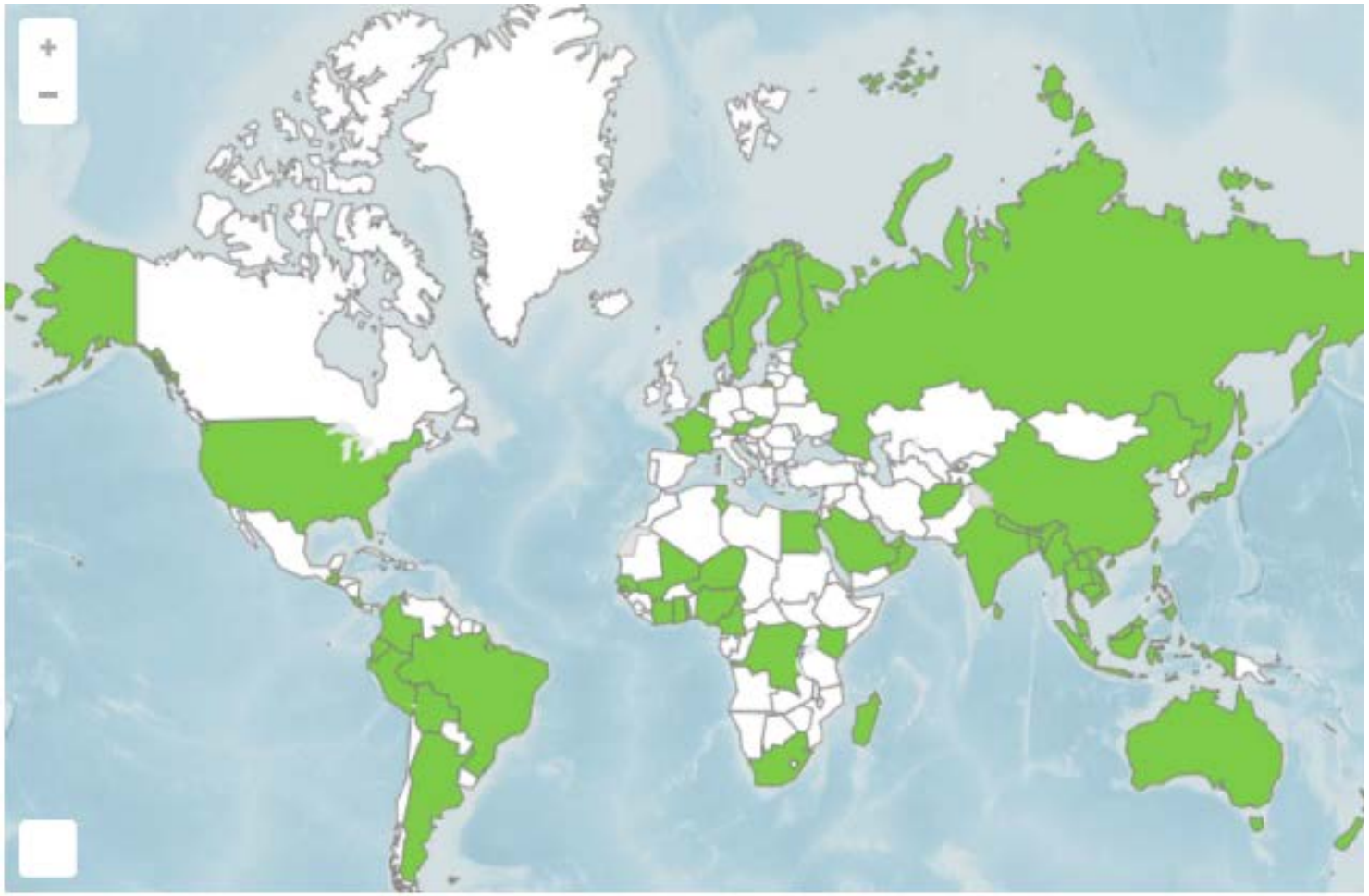
Note: The available country data were joined in larger geographical areas with similar influenza transmission patterns to be able to give an overview (www.who.int/influenza/surveillance_monitoring/updates/EN_GIP_Influenza_transmission_zones.pdf). The displayed data reflect reports of the week from 01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

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

World Health Organization

CDC

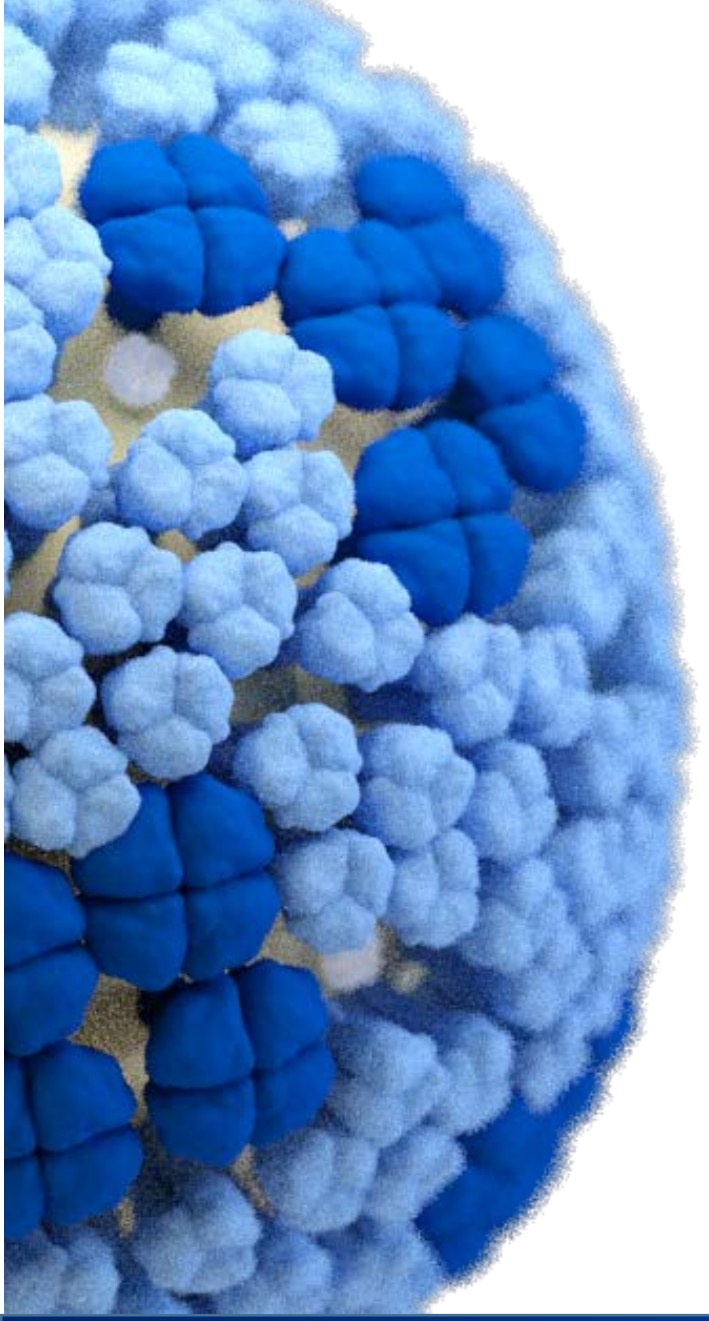
Countries, Areas and Territories That Shared Viruses With WHO-CCs (Sep 2021 – Jan 2022)



Disclaimer

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

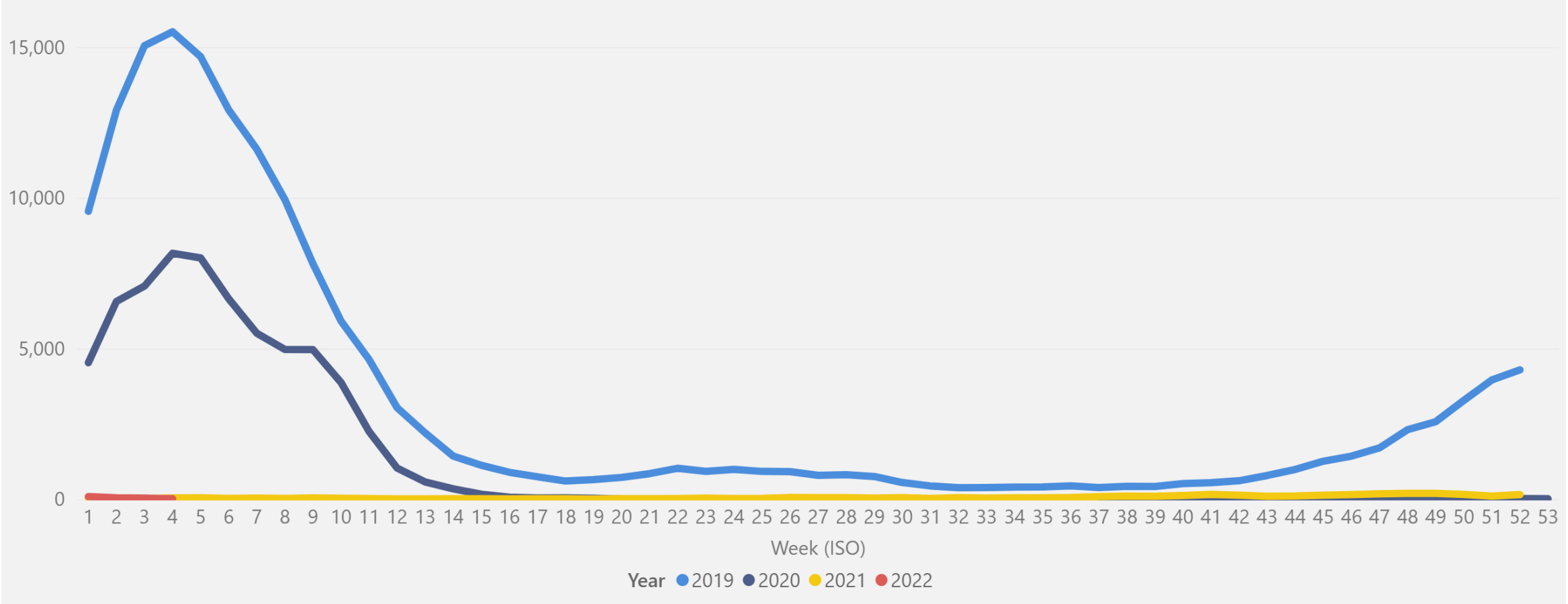
World Health Organization



A(H1N1)pdm09 Viruses

September 2021 – February 2022

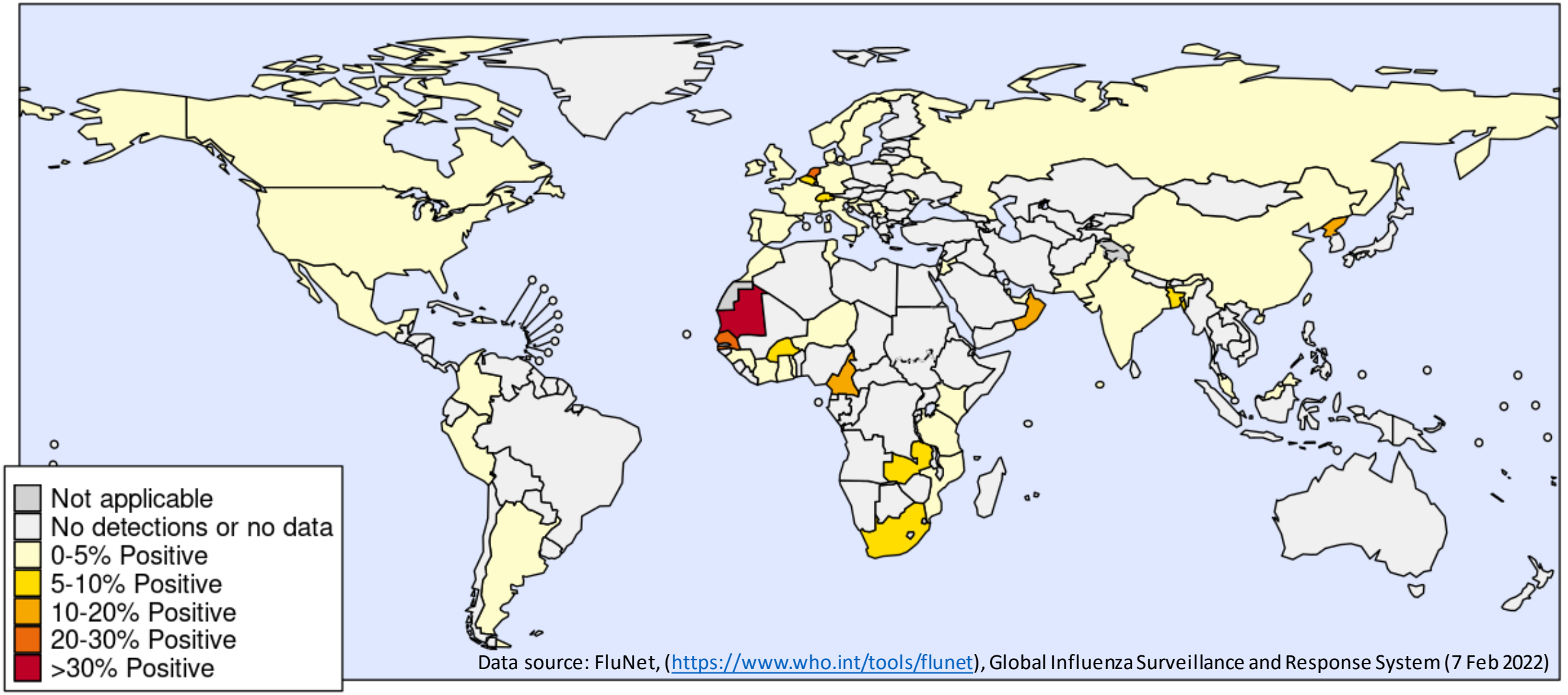
Number of A(H1N1)pdm09 Viruses Detected By GISRS



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

Influenza A(H1N1)pdm09 Activity

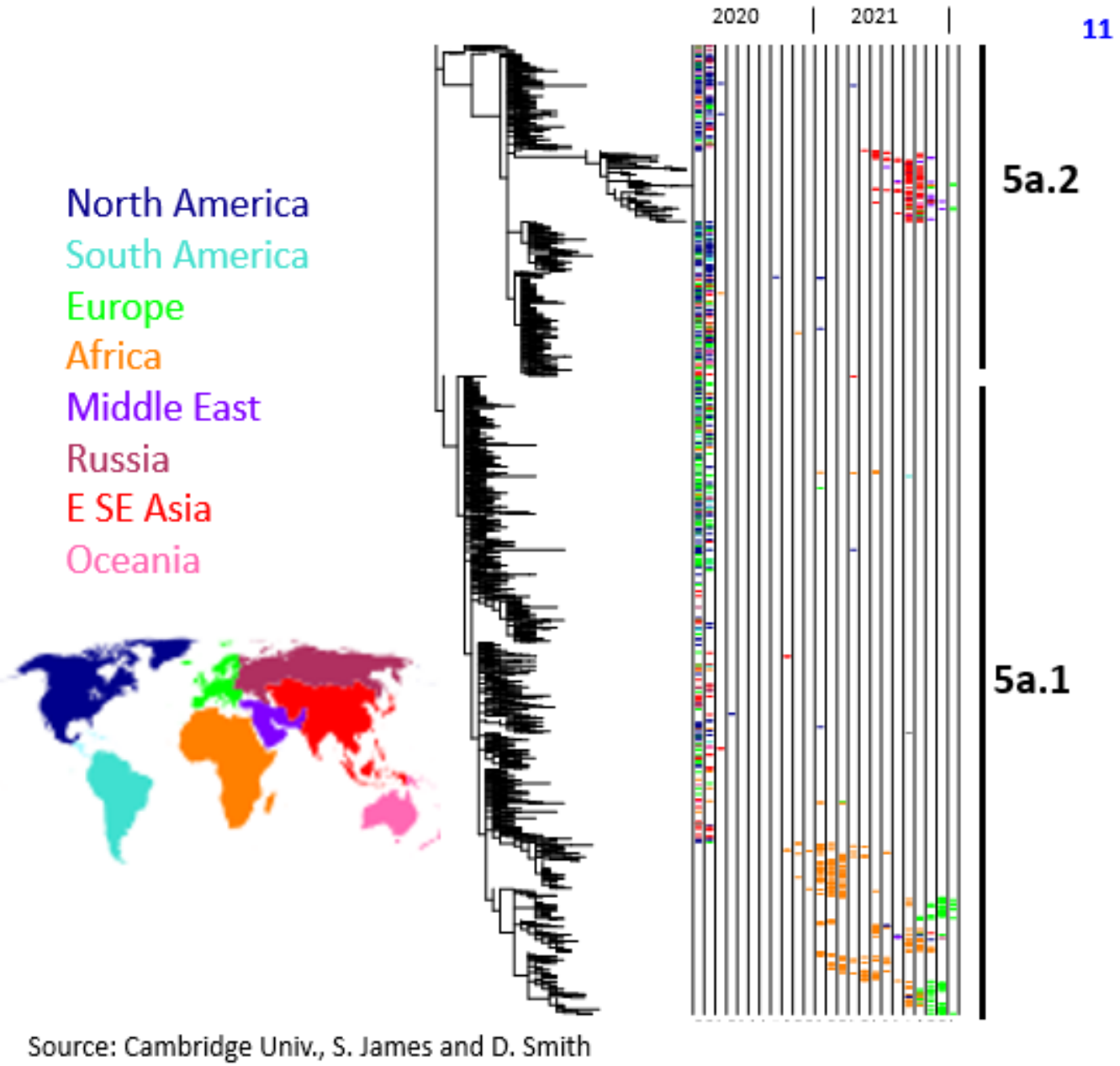
Influenza A(H1N1)pdm09, September 2021 to January 2022, percent of all samples tested



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

A(H1N1)pdm09 HA Phylogeography

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

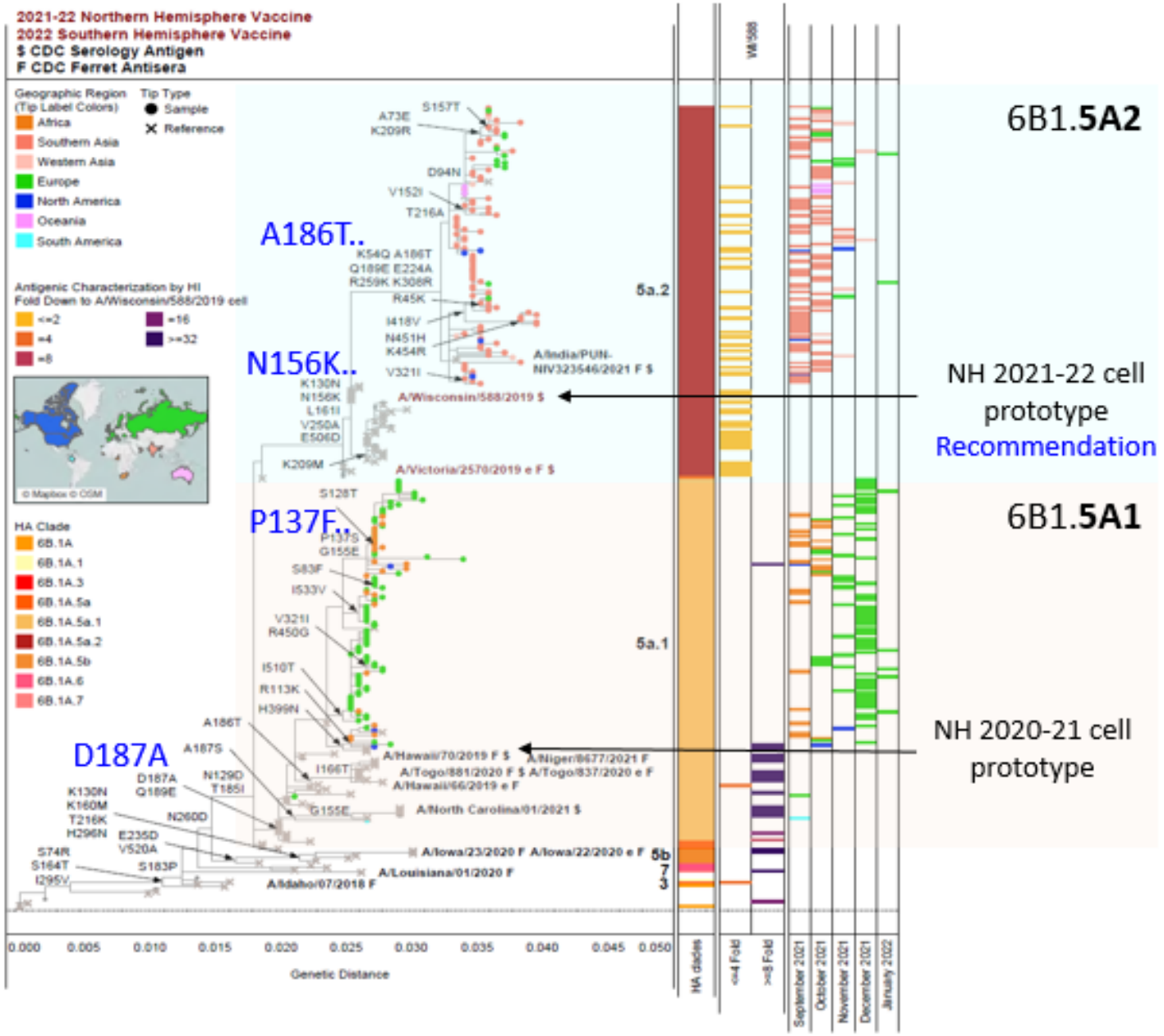


Source: Cambridge Univ., S. James and D. Smith

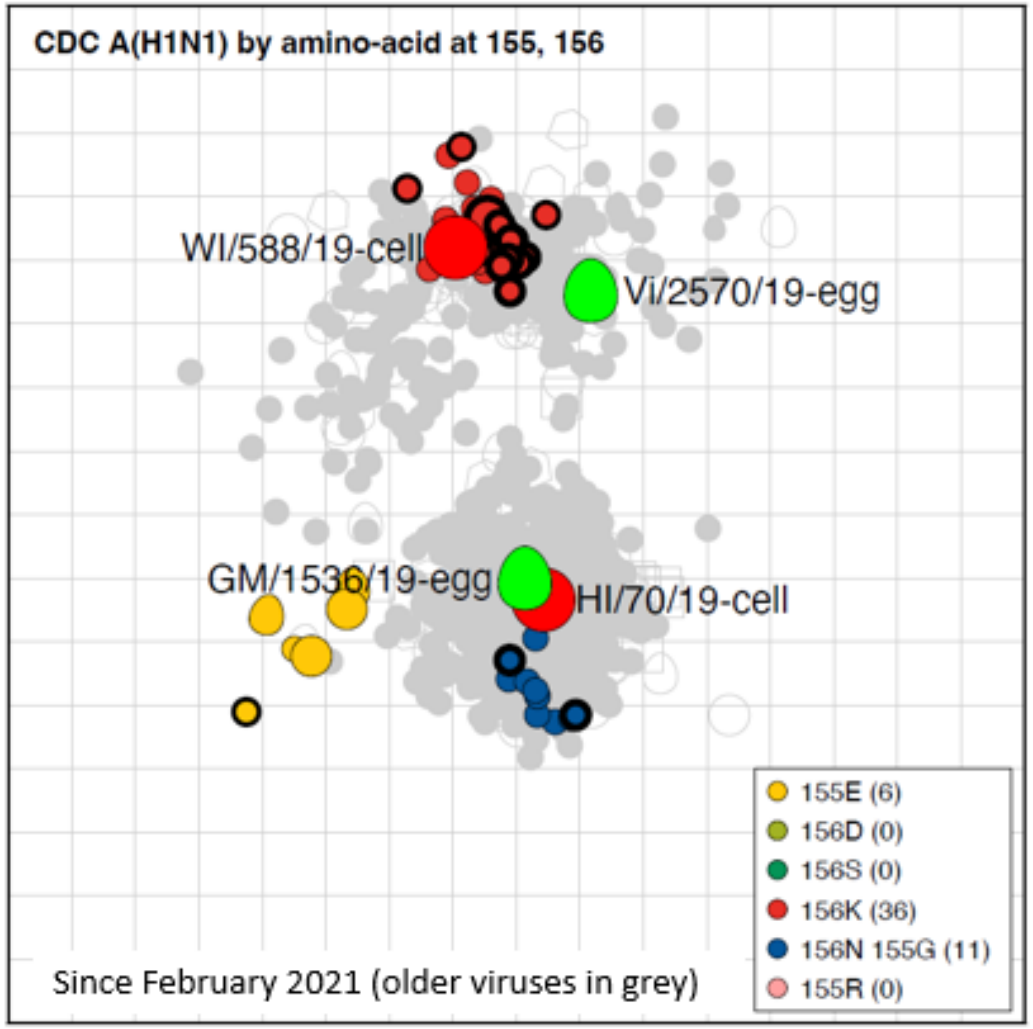
Recent A(H1N1)pdm09 HA Phylogeography

Two major 6B.1.5A subclades

- 5A1 (e.g., HI/70)
  - NH 2020-21 vaccine antigen
  - Often share D187A, Q189E
  - Few with G155E (NC/01) or P137S and G155E
  - Recent viruses from West Africa and Europe
- 5A2 HA (e.g., WI/588)
  - NH 2021-2022 vaccine virus
  - Often share N156K
  - Recent viruses, primarily in India (e.g., IND/PUN-..) have acquired more changes
    - K54Q, A186T, Q189E, E224A, R259K, and K308R



A(H1N1)pdm09 Antigenic Cartography



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

- The viruses with HA from 6B.1A subclades **5a.1** (187A) and **5a.2** (156K) form two antigenically distinct groups
  - Virus of each subclade cluster with respective vaccine reference viruses
- Few 5a.1 viruses with G155E are antigenically distinguishable

Human Post-vaccination Sera Analysis of A(H1N1)pdm09 Viruses

NH 2021-2022 Vaccine (5a.2) Sera			5a.2			5a.1		
			+N156K *WI/588 SIAT	+N156K +Q223R VIC/2570 EGG	+A186T +Q189E +E224A IND/PUN-NIV323546 SIAT	+D187A +Q189E HI/70 SIAT	+G155E +A187S NC/01 SIAT	+I166T +A186T TGO/881 SIAT
A/WISCONSIN/588/2019 SIAT	Pediatric (6-35M)	USA	IIV4	43	√	√	11	11	10
	Pediatric (3-8Y)	USA	ccIIV4 (Flucelvax)	83	√	√	√	46	51
			IIV4	331	√	190	171	126	204
	Pediatric (9-17Y)	USA	ccIIV4 (Flucelvax)	502	√	√	√	166	260
			IIV4	243	√	√	√	130	√
	Adult	USA	ccIIV4 (Flucelvax)	453	√	299	√	155	√
			RIV4 (Flublok)	874	√	178	394	204	243
			IIV4	260	√	139	√	98	√
		Japan	IIV4	48	√	√	√	32	√
		UK	IIV4	60	√	34	√	45	√
	Older Adult (50-64Y)	USA	IIV4	149	√	77	√	106	√
	Elderly	Japan	IIV4	19	X	X	X	X	X
		USA	IIV4-HD	135	√	89	√	70	√

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/HAWAII/70/2019 (HI/70); A/INDIA/PUN-NIV323546/2021 (IND/PUN-NIV323546); A/NORTH CAROLINA/01/2021 (NC/01); A/TOGO/881/2020 (TGO/881); A/VICTORIA/2570/2019 (VIC/2570); A/WISCONSIN/588/2019 (WI/588).

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

GMT ratio lowerbound (90% CI)
0.0 — 1.0

Human Post-vaccination Sera Analysis of A(H1N1)pdm09 Viruses

- Inhibits both 5a.2 and most 5a.1 viruses
  - Exceptions
    - Very young pediatric (6-35 Month old)
    - G155E viruses (e.g., NC/01), which were less frequently detected

NH 2021-2022 Vaccine (5a.2) Sera

				5a.2			5a.1		
				+N156K	+Q223R	+A186T +Q189E +E224A	+D187A +Q189E		+I166T +A186T
				*WI/588	VIC/2570	IND/PUN-NIV323546	HI/70	NC/01	TGO/881
				SIAT	EGG	SIAT	SIAT	SIAT	SIAT
A/WISCONSIN/588/2019 SIAT	Pediatric (6-35M)	USA	IIV4	43	√	√	11	11	10
	Pediatric (3-8Y)	USA	ccIIV4 (Flucelvax)	83	√	√	√	46	51
			IIV4	331	√	190	171	126	204
	Pediatric (9-17Y)	USA	ccIIV4 (Flucelvax)	502	√	√	√	166	260
			IIV4	243	√	√	√	130	√
	Adult	USA	ccIIV4 (Flucelvax)	453	√	299	√	155	√
			RIV4 (Flublok)	874	√	178	394	204	243
			IIV4	260	√	139	√	98	√
		Japan	IIV4	48	√	√	√	32	√
		UK	IIV4	60	√	34	√	45	√
	Older Adult (50-64Y)	USA	IIV4	149	√	77	√	106	√
	Elderly	Japan	IIV4	19	X	X	X	X	X
		USA	IIV4-HD	135	√	89	√	70	√

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.

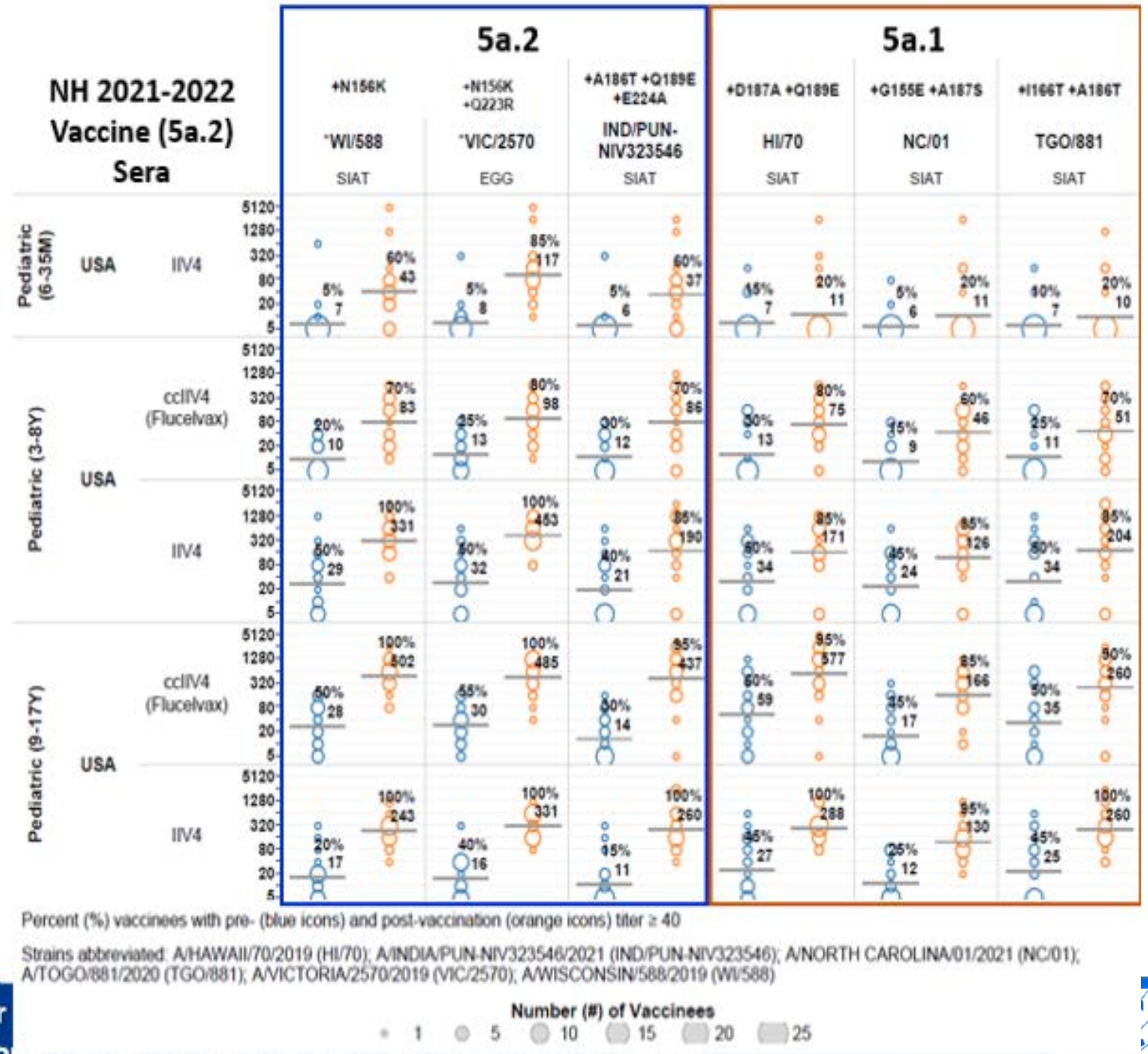
Strain abbreviations: A/HAWAII/70/2019 (HI/70); A/INDIA/PUN-NIV323546/2021 (IND/PUN-NIV323546); A/NORTH CAROLINA/01/2021 (NC/01); A/TOGO/881/2020 (TGO/881); A/VICTORIA/2570/2019 (VIC/2570); A/WISCONSIN/588/2019 (WI/588).

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

GMT ratio lowerbound (90% CI)
0.0 — 1.0

Pediatric Human Post-vaccination Sera Analysis of A(H1N1)pdm09 Viruses (Individual Responses)

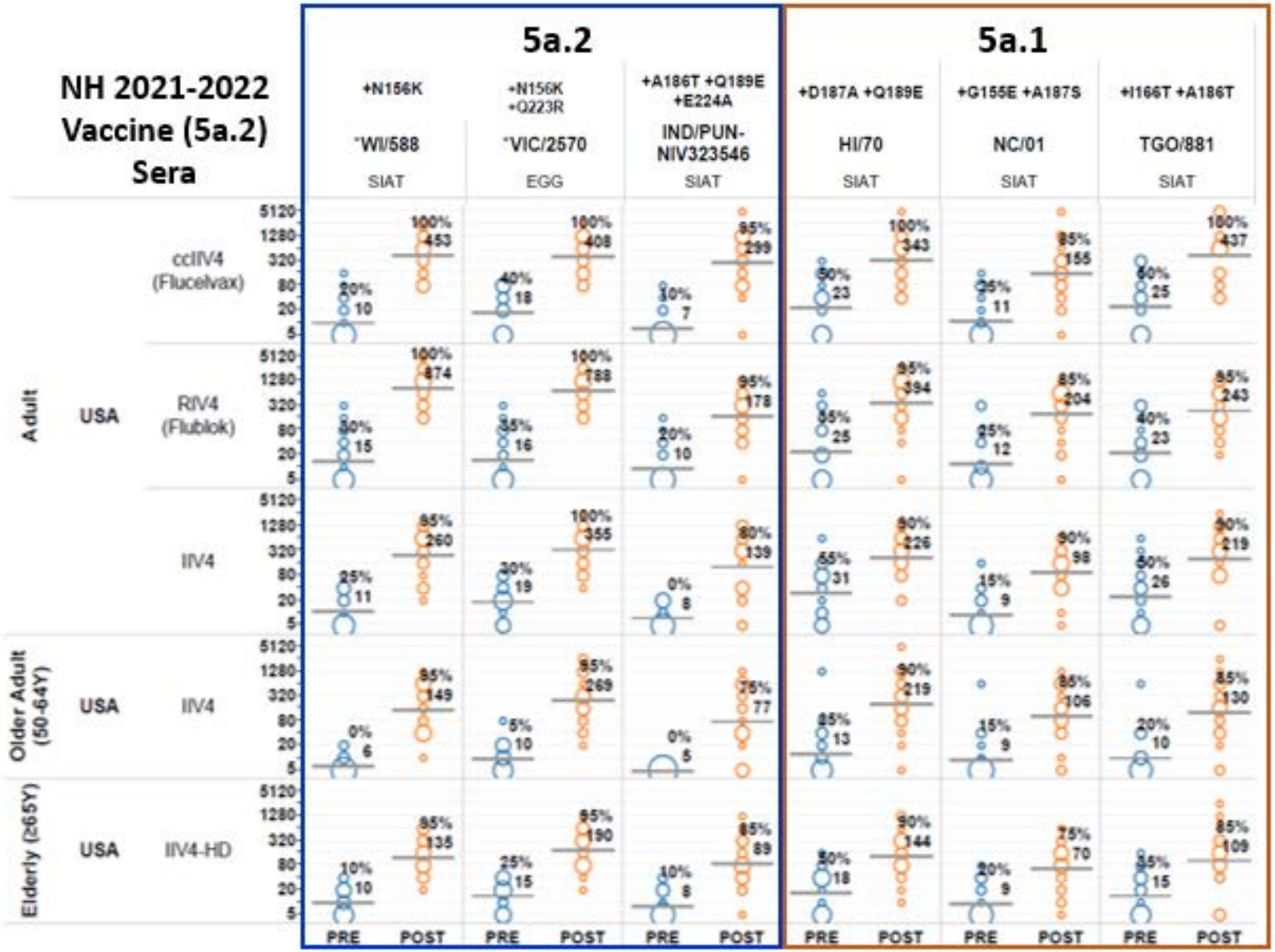
- 6-35 month panel
  - ~60% have HI titer increase >40 to 5a.2 viruses
    - Including IND/PUN (5a.2+ 186T..)
  - Poor reactivity with 5a.1 viruses
  - Similar pattern as naive ferrets
- Older pediatric panels (3-17 y)
  - Increase titers to both 5a.2 and 5a.1 viruses
    - Back boost (HI/70 (5a.1))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



Adult Human Post-vaccination Sera Analysis of A(H1N1)pdm09 Viruses (Individual Responses)

Adults and ≥ 65 years of age

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



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

Strains abbreviated: A/HAWAII/70/2019 (HI/70); A/INDIA/PUN-NIV323546/2021 (IND/PUN-NIV323546); A/NORTH CAROLINA/01/2021 (NC/01); A/TOGO/881/2020 (TGO/881); A/VICTORIA/2570/2019 (VIC/2570); A/WISCONSIN/588/2019 (WI/588)

Number (#) of Vaccinees

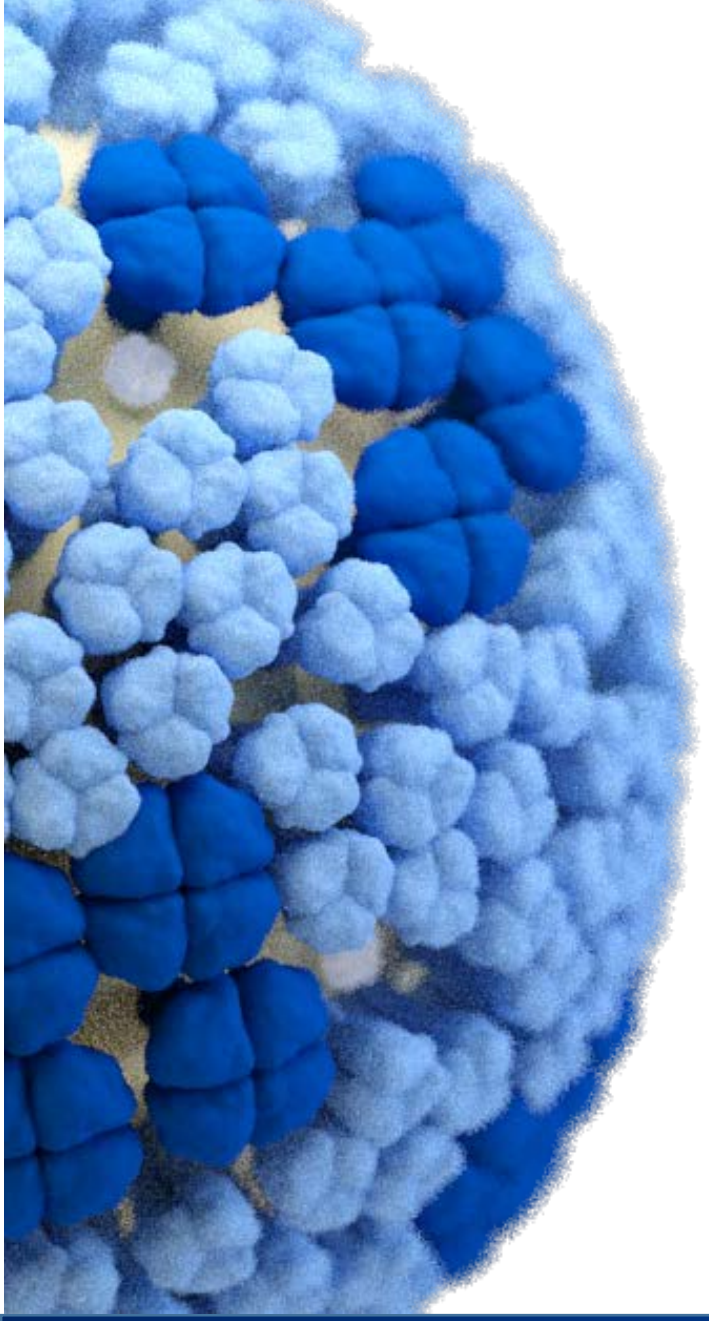
1 5 10 15 20 25

A(H1N1)pdm09 Summary (1)

- A(H1N1)pdm09 viruses have been detected in Africa, Europe, the Middle East, southern Asia, Oceania and sporadically in a few other regions
- The great majority of HA gene sequences belonged to clade 6B.1A5a, subclades;
  - 5a.1 (D187A, Q189E) HA proteins predominant in Africa and Europe
    - Some HA's share with additional substitutions P137S and G155E
  - 5a.2 (K130N, N156K, L161I, V250A) HA proteins were predominant in the Middle East, southern Asia and Oceania
    - Many recent virus have additional HA substitutions K54Q, **A186T**, Q189E, E224A, R259K and K308R (e.g., IND/PUN-..)
- Ferret antisera show that HA clade 5a.1 viruses are antigenically distinct from HA clade 5a.2 viruses

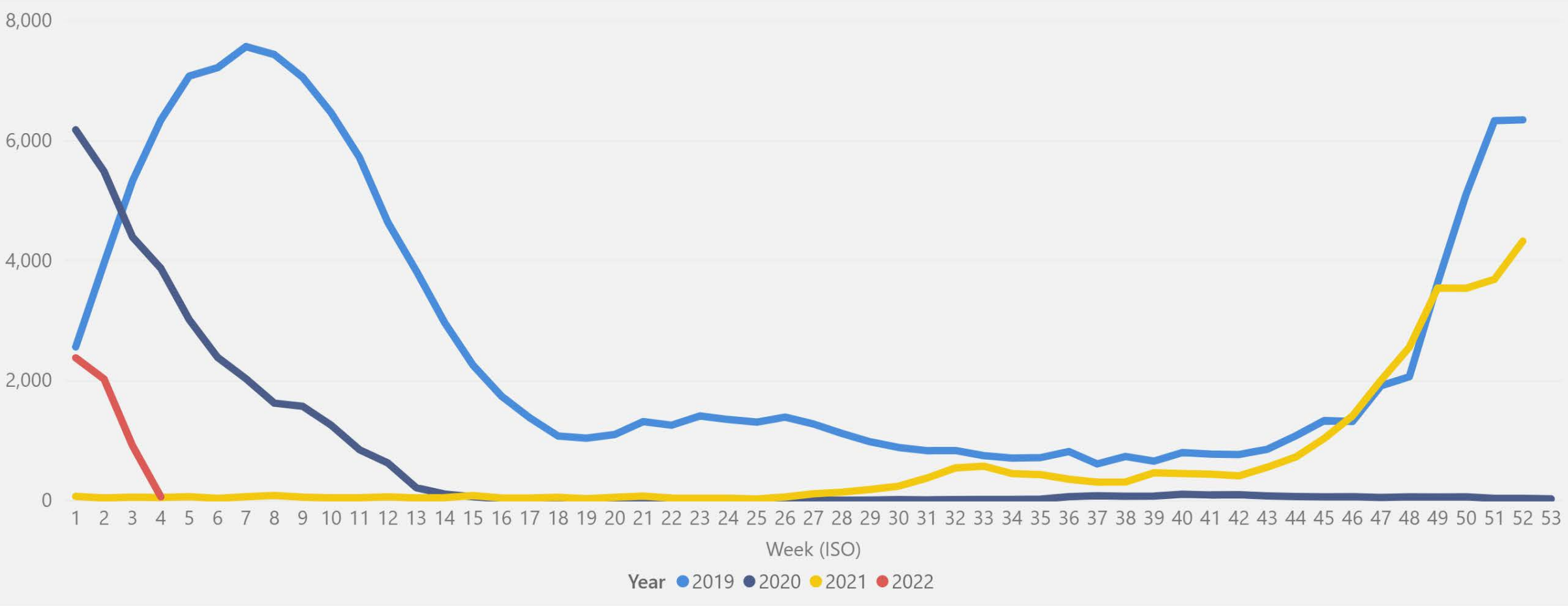
A(H1N1)pdm09 Summary (2)

- Post vaccination sera collected from humans vaccinated with NH 2021-2022 vaccines (Immunized with HA subclade 5a.2 antigens)
  - GMTs against viruses representing HA subclade 5a.2 (N156K) were generally recognized well, as were most of those in subclade 5a.1 (D187A, Q198E).
    - Vaccine induced antibodies that cross react with 5a.1
      - Likely because of B-cell memory response, since 5a.1 viruses circulated previously and were a component of 2020-2021 vaccine
    - Exception were the 6-35 month old sera panels
      - Only react with 5a.2 viruses
- None of the viruses tested showed evidence of reduced inhibition by neuraminidase inhibitors (n=190) or reduced susceptibility to the endonuclease inhibitor baloxavir (n=158).



A(H3N2) Viruses
September 2021 - February 2022

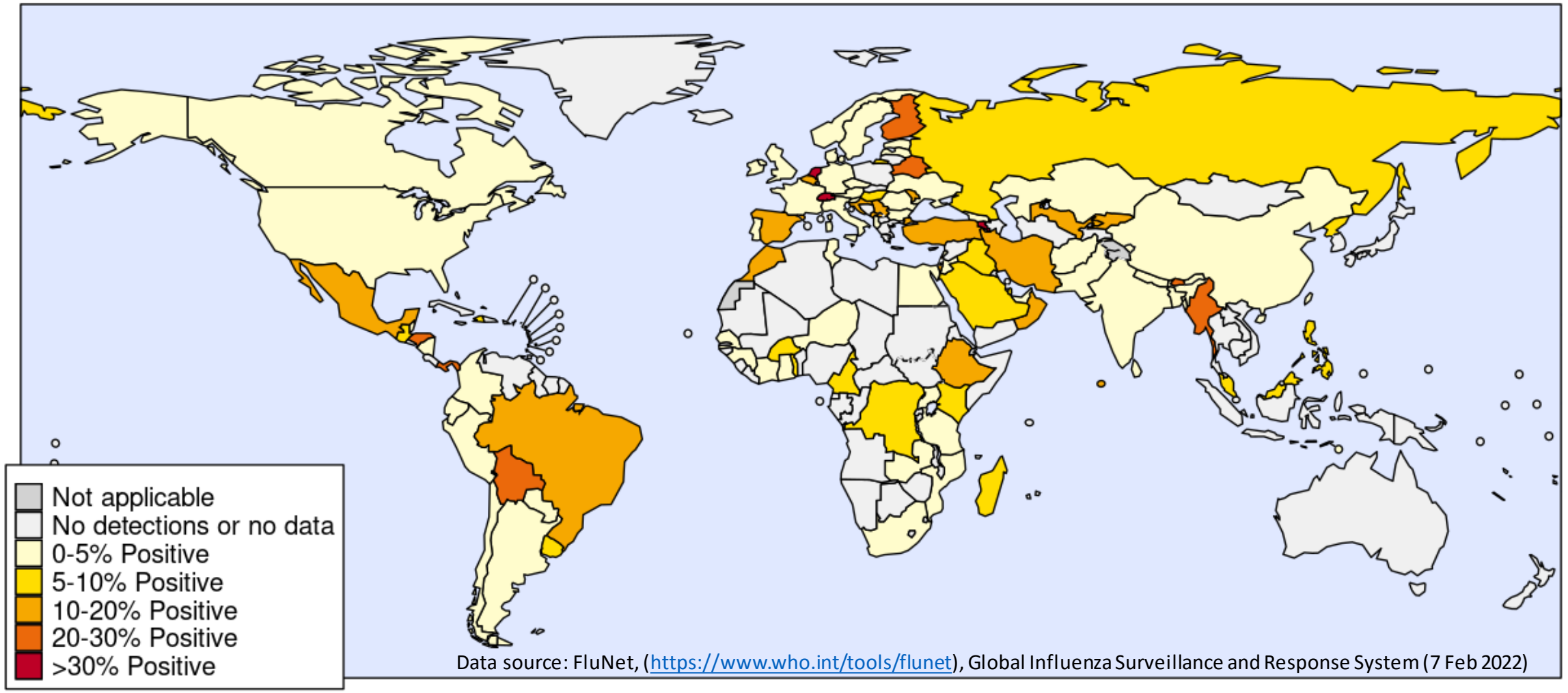
Number of A(H3N2) Viruses Detected by GISRS



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

Influenza A(H3N2) Activity

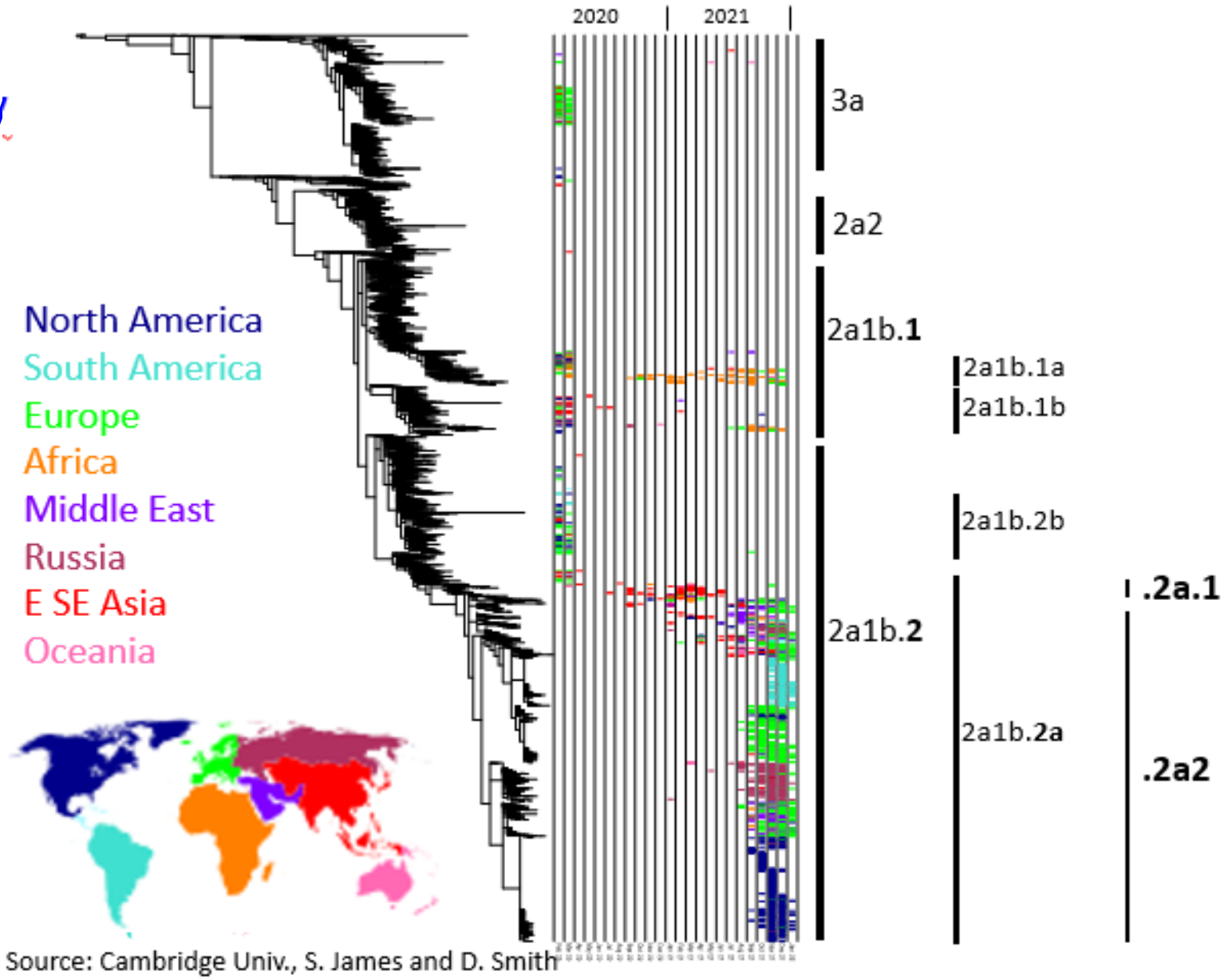
Influenza A(H3N2), September 2021 to January 2022, percent of all samples tested



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

A(H3N2) HA Phylogeography

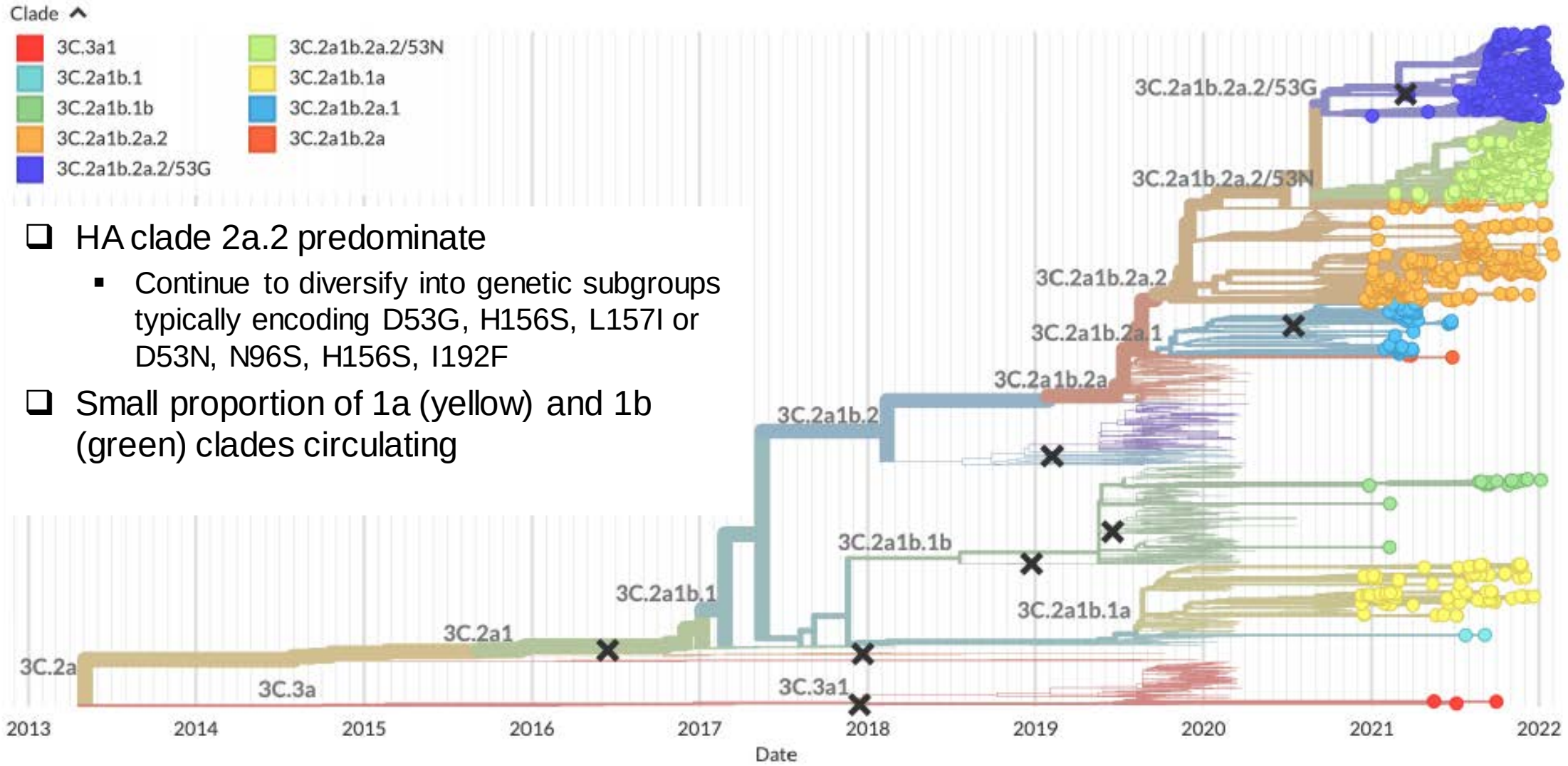
- Two major clades survived the COVID-19 bottleneck
  - 2a1b.**1**
    - 1a and 1b subclades in Africa and Europe
  - 2a1b.**2a**
    - **2a.1** in Asia, decreased in 2021
    - **2a.2** in Europe, Russia, North and South America increased in 2021-22



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

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

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



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

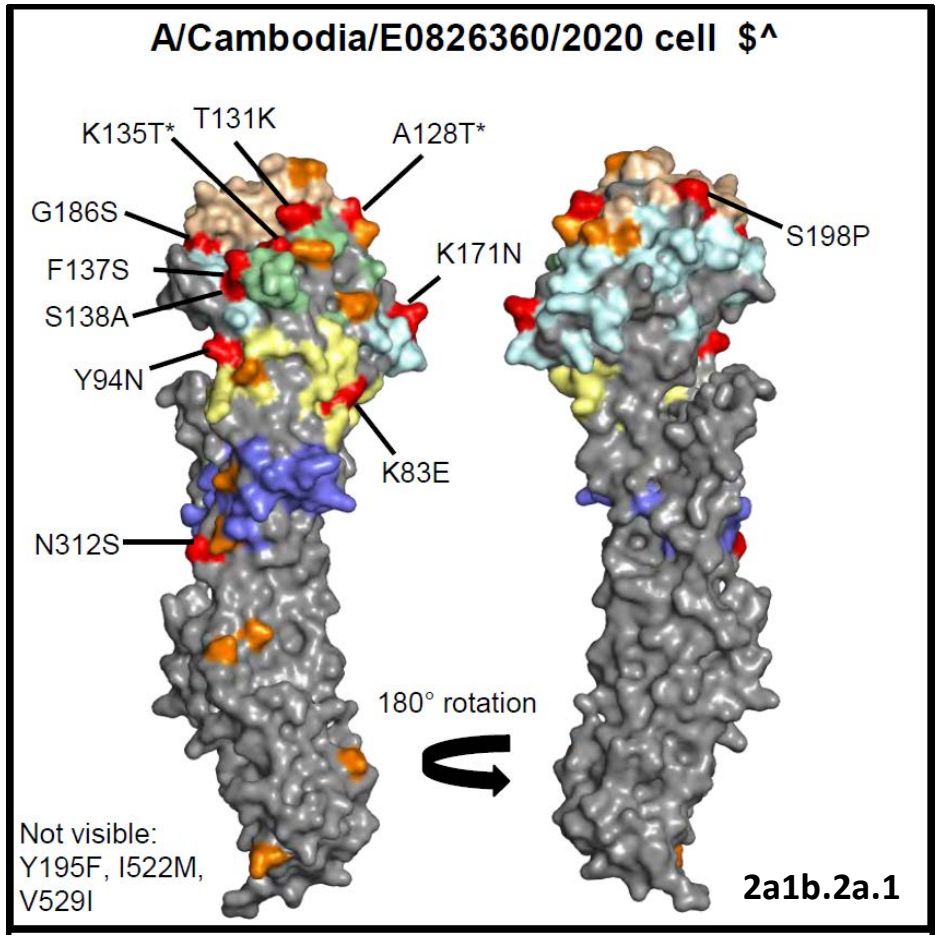
Global Circulation of A(H3N2) HA Clades

Source: Nextflu Based on HA sequence available as of 02/12/2022

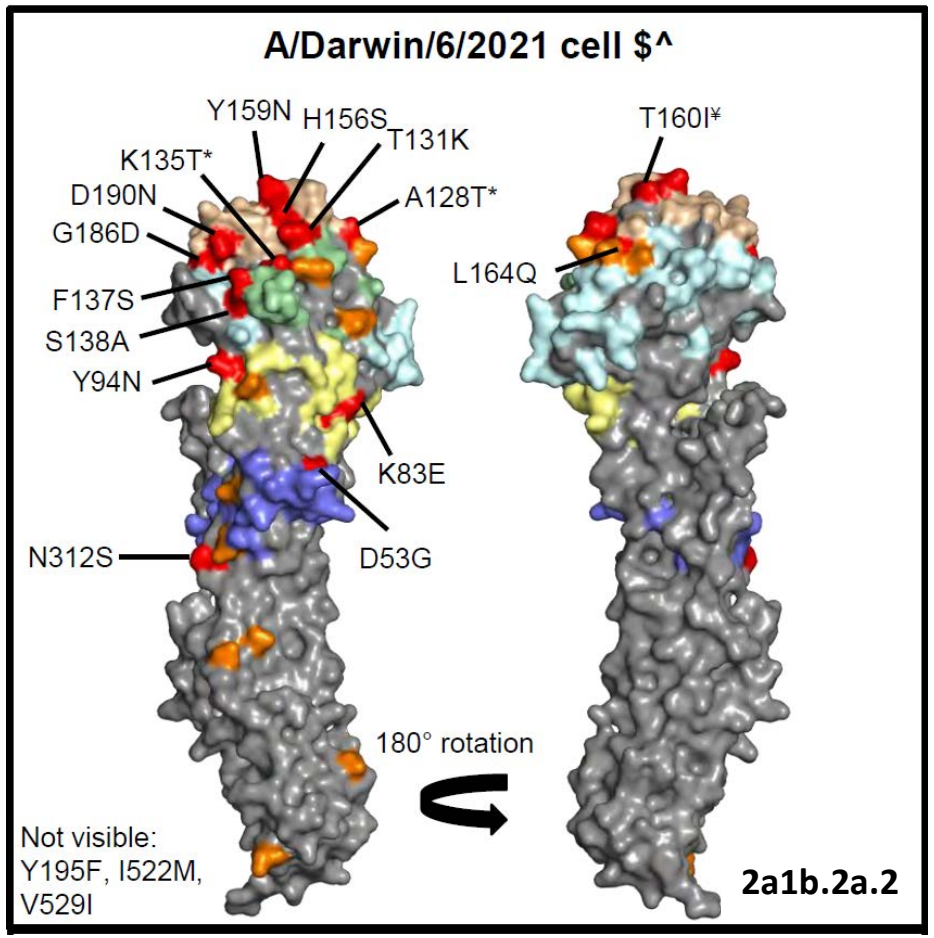
- HA clade 2a.2 predominate and show global distribution
  - Predominance of subclades differ regionally (e.g., **D53G, H156S, L157I** in North America (e.g., U.S.) vs **D53N, D96N, H156S, I192F** in Western Europe (e.g., Netherlands and Sweden) and South America (e.g., Brazil)
- HA clade 1a viruses circulating in Africa (e.g., Côte d'Ivoire, Ghana, Niger, Nigeria, Ethiopia, Togo)
- HA clade 1b viruses sporadically identified (i.e., Armenia, France, Kenya, Madagascar, South Africa)

Location of Substitutions on H3 HA Monomer

NH 2021-22 Vaccine Prototype



SH 2022 Vaccine Prototype



Differences from A/Hong Kong/45/2019 shown

Source: U.S. CDC

- HA Clade 2a1b.**2a.2** (e.g., Darwin/6) have additional substitutions (i.e., H156S, Y159N, T160I, L164Q, S186D, D190N) compared to A/Cambodia/e0826360/2020

Analysis of A(H3N2) Viruses By Antisera to Antigens Recommended for NH 2021-2022

HI Assay

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

WHO CC	Like (2-4 fold)	Low (≥ 8 fold)
FCI	50 (17%)	246 (83%)
VIDRL	10 (25%)	30 (75%)
Total	60 (18%)	276 (82%)

A/Cambodia/e0826360/2020-like (egg)

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

VN Assay

WHO CC	Like (2-4 fold)	Low (≥ 8 fold)
CDC	4 (6%)	63 (94%)
NIID	0 (0%)	5 (100%)
FCI	16 (18%)	75 (82%)
VIDRL	13 (52%)	12 (48%)
TOTAL	33 (18%)	155 (82%)

WHO CC	Like (2-4 fold)	Low (≥ 8 fold)
CDC	22 (33%)	45 (67%)
NIID	0 (0%)	5 (100%)
TOTAL	22 (31%)	50 (69%)

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

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

Analysis of A(H3N2) Viruses By Antisera to Antigens Recommended for SH 2022

HI Assay

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

WHO CC	Like (2-4 fold)	Low (≥ 8 fold)
FCI	259 (88%)	37 (13%)
VIDRL	25 (63%)	15 (38%)
Total	284 (85%)	52 (15%)

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

WHO CC	Like (2-4 fold)	Low (≥ 8 fold)
FCI	207 (70%)	89 (30%)
VIDRL	7 (18%)	33 (83%)
Total	214 (64%)	122 (36%)

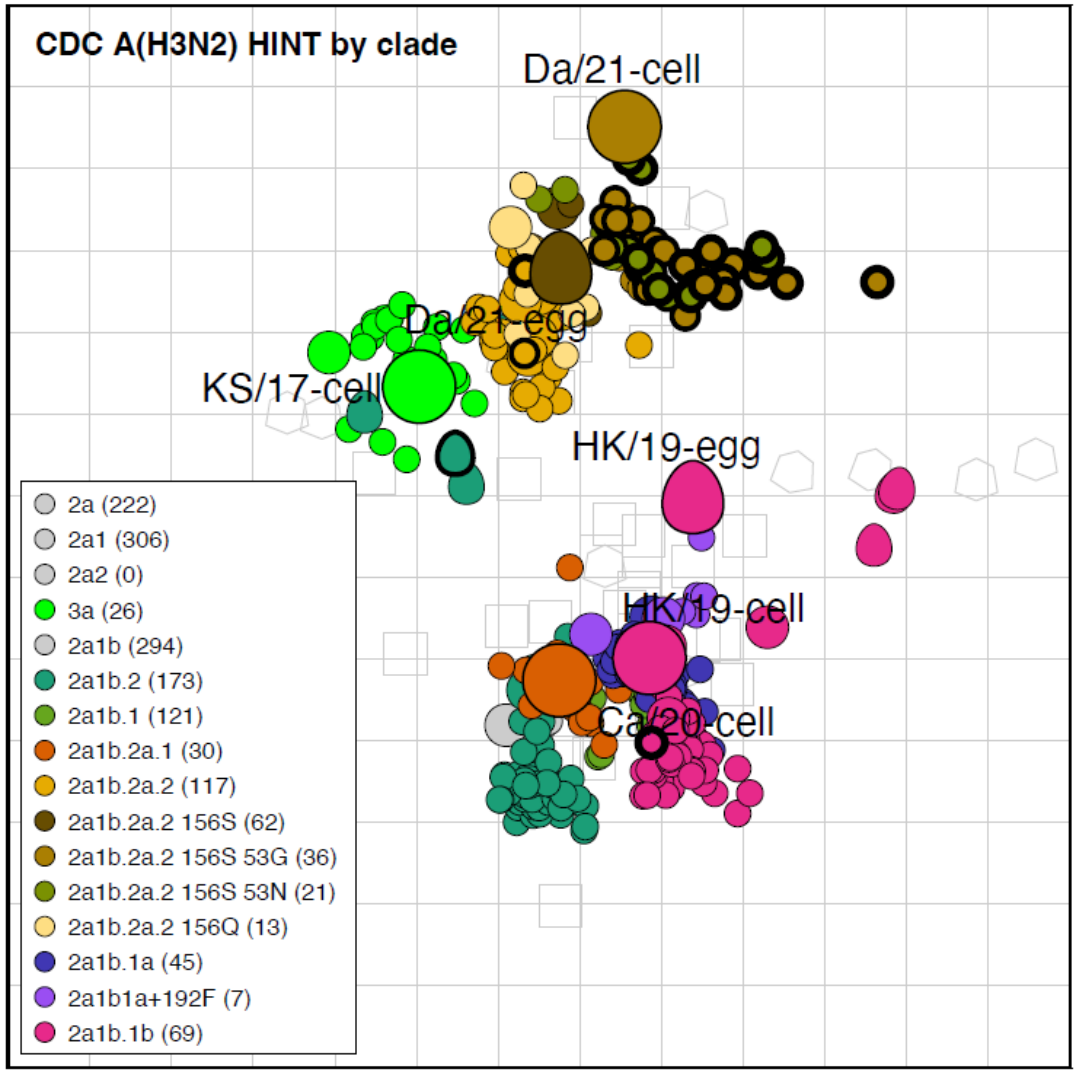
VN Assay

WHO CC	Like (2-4 fold)	Low (≥ 8 fold)
CDC	66(99%)	1(1%)
FCI	259(88%)	37(13%)
NIID	5 (100%)	0 (0%)
VIDRL	19 (73%)	7 (27%)
TOTAL	349(89%)	45 (11%)

WHO CC	Like (2-4 fold)	Low (≥ 8 fold)
CDC	64(98%)	1(2%)
FCI	207(70%)	89(30%)
NIID	4 (80%)	1 (20%)
VIDRL	17 (65%)	9 (35%)
TOTAL	292(74%)	100(26%)

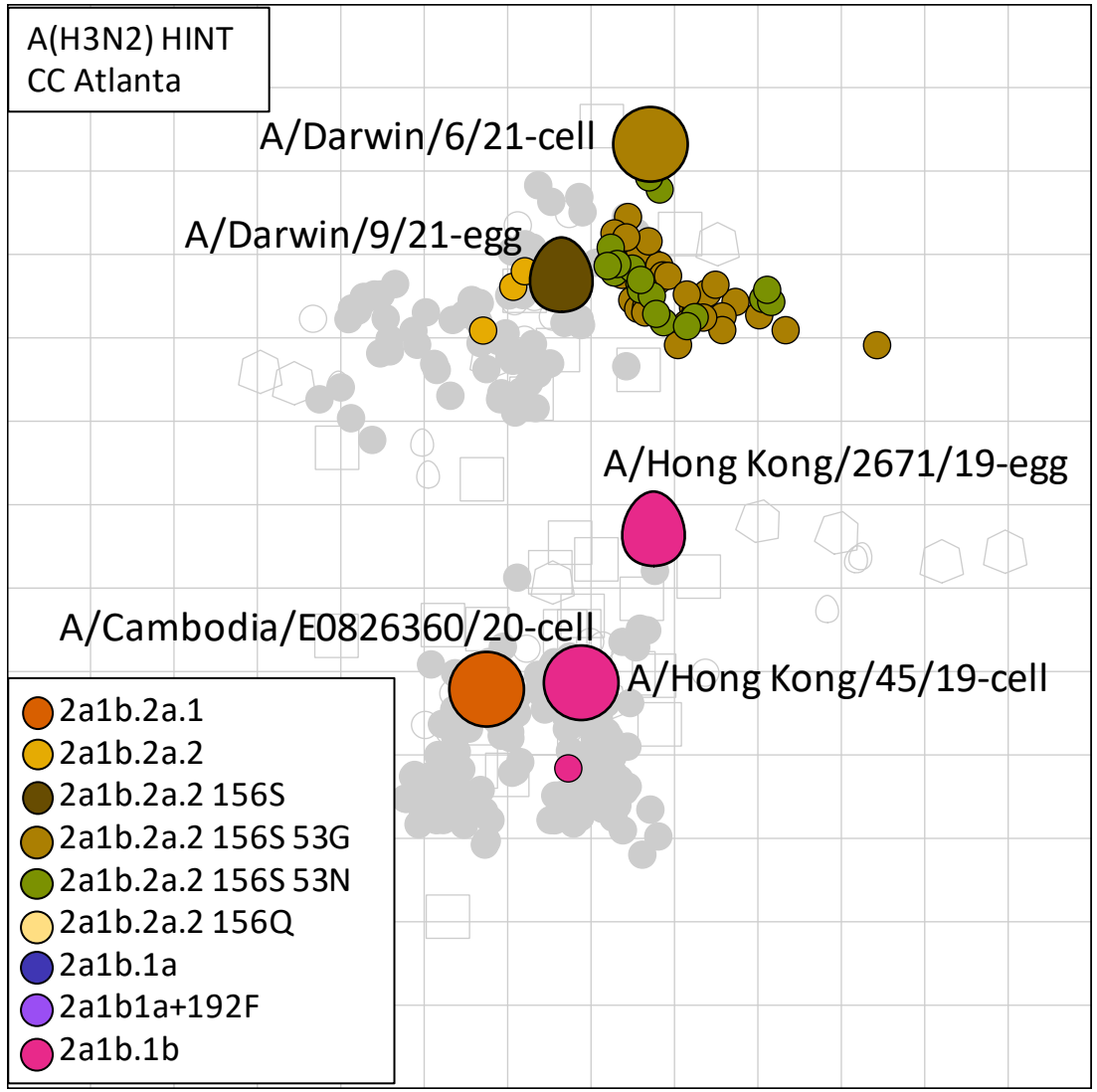
Reference viruses are in HA clade 3C.2a1b.**2a.2**. Showing data from viruses isolated from swabs collected from September to January 2022

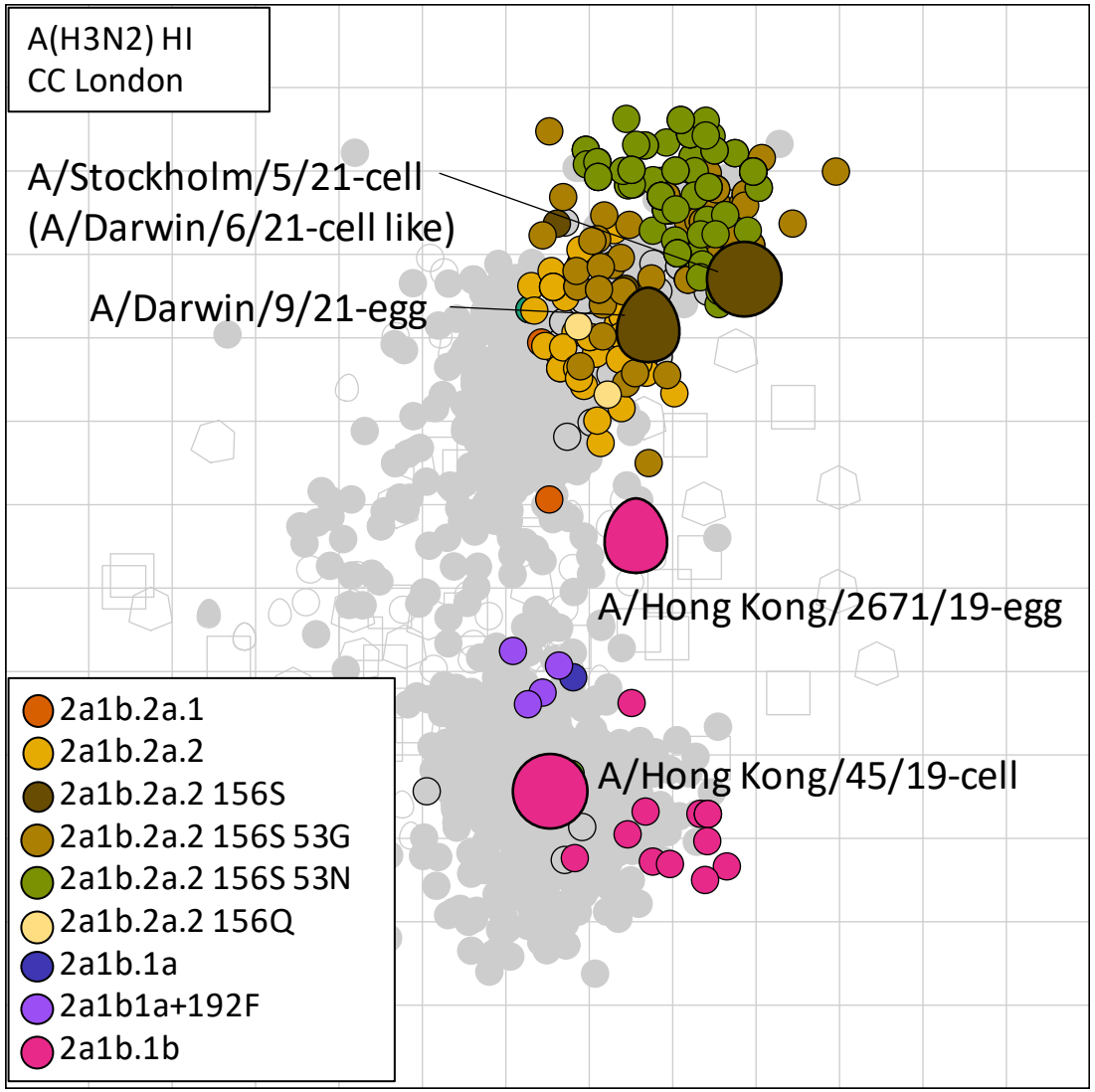
A(H3N2) Antigenic Cartography



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

A(H3N2) Antigenic Cartography





Source: Cambridge Univ., S. James and D. Smith **Last 6 months, 2021-08 to 2022-02, older viruses in grey**

Human Post-vaccination Sera Analysis of A(H3N2) Viruses

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

NH 2021-2022 Vaccine (2a.1)			2a.1		1a	1b	2a.2		
			*CAM/E0826360	+T160K(CHO-) +S186R CAM/E0826360	+G186D +D190N +I192F TGO/771	- HK/45	+D53G +H156S DAR/06	+D53G +H156S +L157I +S262N MD/02	+D53N +N96S (CHO+) +H156S +I192F AK/01
			SIAT	EGG	SIAT	SIAT	SIAT	SIAT	SIAT
A/CAMBODIA/E0826360/2020 SIAT	Pediatric (6-35M)	USA	IIV4	21	X	10	X	11	8	X
	Pediatric (3-8Y)	USA	ccIIV4 (Flucelvax)	171	√	√	√	89	86	106
			IIV4	211	√	√	√	113	113	117
	Pediatric (9-17Y)	USA	ccIIV4 (Flucelvax)	368	√	√	√	77	72	59
			IIV4	139	√	√	√	63	49	46
	Adult	USA	ccIIV4 (Flucelvax)	394	√	√	√	121	178	155
			RIV4 (Flublok)	171	√	√	√	65	44	57
			IIV4	95	√	√	√	36	26	40
		Japan	IIV4	11	X	X	X	7	6	7
		UK	IIV4	29	X	X	X	14	13	14
	Older Adult (50-64Y)	USA	IIV4	70	√	√	√	46	37	√
	>64 Y	Japan	IIV4	18	X	X	X	X	13	X
		USA	IIV4-HD	89	√	√	√	36	46	46

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/CAMBODIA/E0826360/2020 (CAM/E0826360); A/DARWIN/06/2021 (DAR/06); A/HONG KONG/45/2019 (HK/45); A/MARYLAND/02/2021 (MD/02); A/TOGO/771/2020 (TGO/771).

Source: U.S. CDC

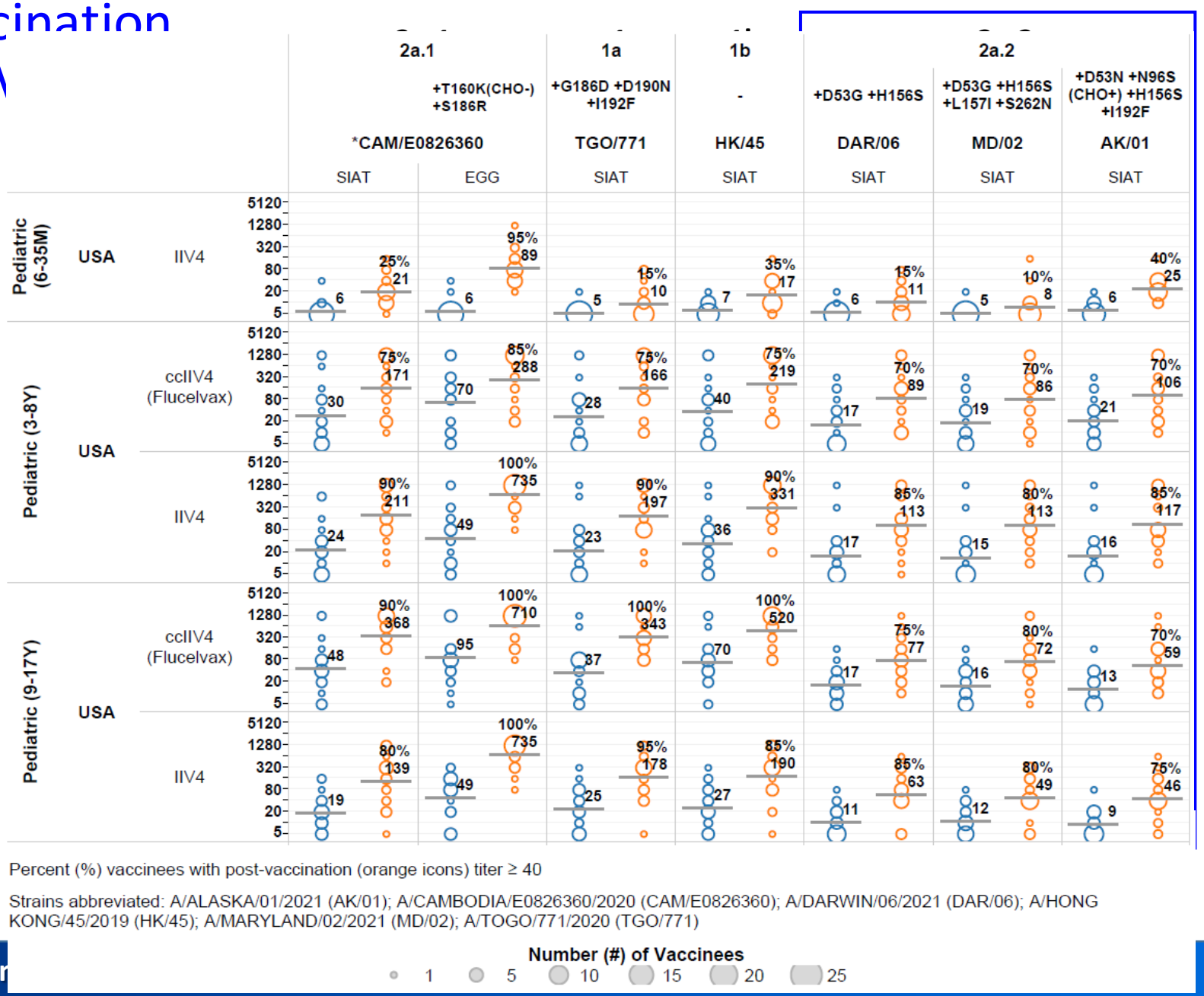
Statistically non-inferior = √
Statistically non-inferior but reference virus GMT < 40 = X

GMT ratio lowerbound (90% CI)
0.0 — 1.0

Pediatric Human Post-vaccination Sera Analysis of A(H3N2) V

NH 2021-2022 Vaccine (2a.1), Individual Responses

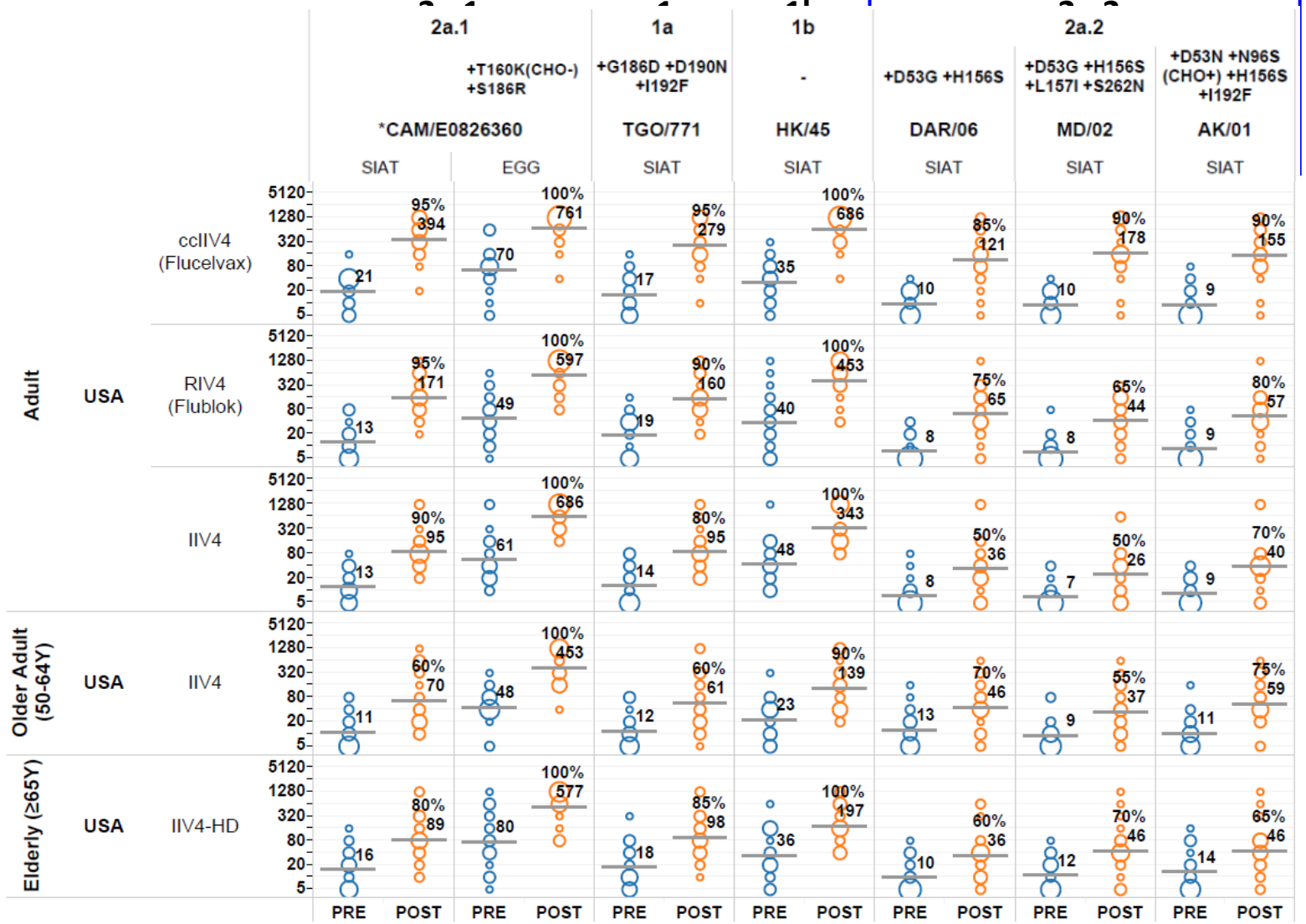
- 6-35 M panel
  - Limited response
    - Only 25% have titers ≥ 40
- Older pediatric panels
  - Vaccination increased titers to HA clade 1a, 1b, 2a.1 and 2a.2 viruses
  - Back boost (HK/45 (1b)
  - Forward boost
    - Recent 1a (TGO/771)
    - Multiple 2a.2 variants
      - DAR/06 (D53G, H156S)
   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



Adult Human Post-vaccination Sera Analysis of A(H3N2) Viruses

NH 2021-2022 Vaccine (2a.1), Individual Responses

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



A(H3N2) Summary (1): Global Circulation and Phylogeny

- In many countries, areas and territories reporting influenza A viruses, A(H3N2) subtype predominated
  - Most countries in Europe, North America, the Middle East, South America and some countries in Africa (e.g., Côte d'Ivoire, Ethiopia, Kenya, Uganda and Togo)
- HA phylogenetics: circulating A(H3N2) viruses in this period belonged to 3C.2a1b subclades including:
  - 1a, 1b, 2a.1 and 2a.2
  - 2a.2 HA clade viruses predominated in this period and continue to diversify into genetic groups that typically encode:
    - D53G, H156S, L157I

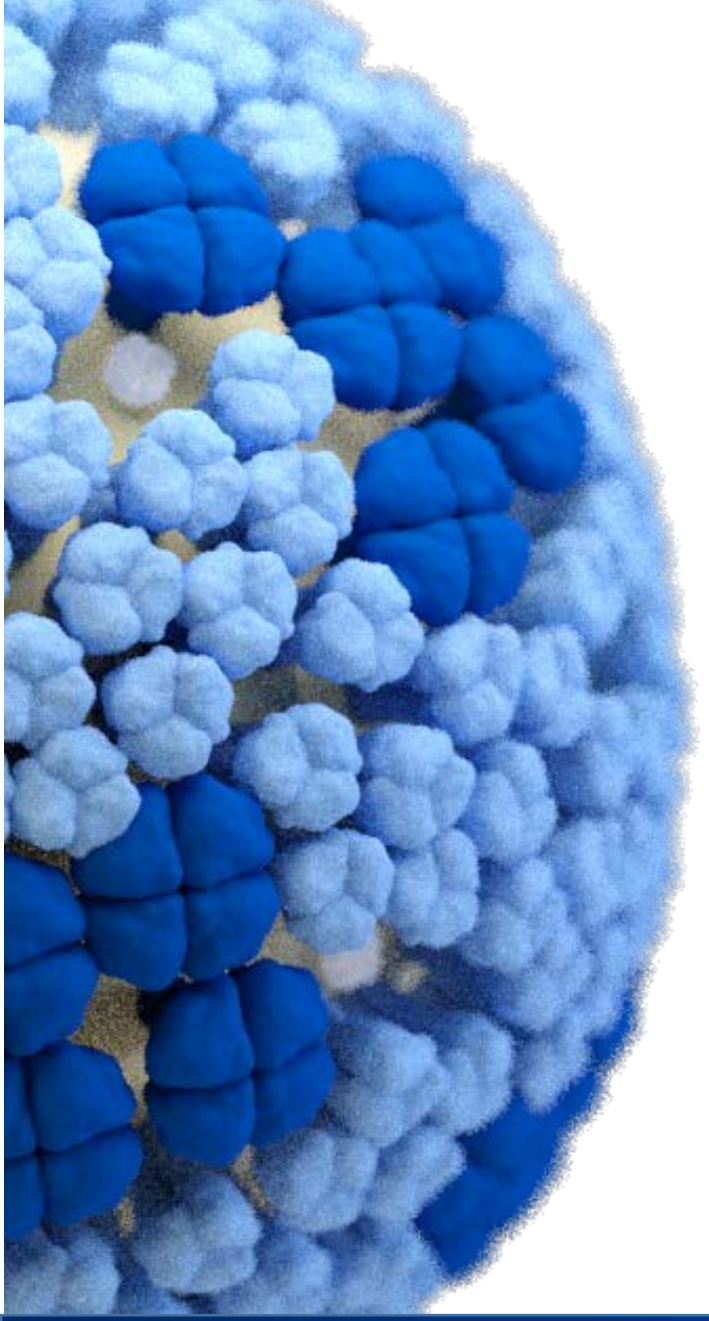
    or
    - D53N, N96S, H156S, I192F

A(H3N2) Summary (2): Antigenic Characteristics

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

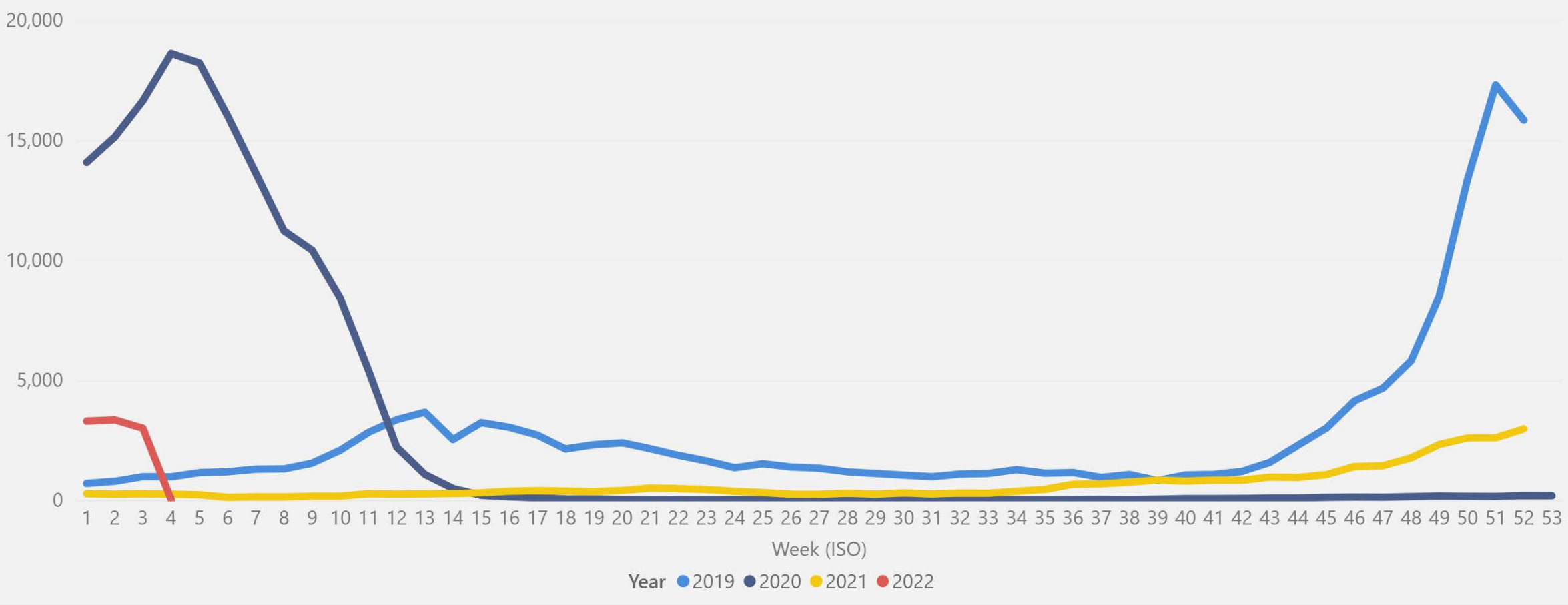
A(H3N2) Summary (3)

- Human serology studies with serum panels from individuals vaccinated with A/Cambodia/e0826360/2020-like (2a.1) viruses:
  - Post-vaccination GMTs were significantly reduced against cell culture-propagated 2a.2 viruses
    - Viruses with HA in 2a.2 subclades (e.g., D53N or D53G) all showed very similar reactivity patterns
    - Nevertheless, the 2a.1 vaccine provided forward boost against 1a and 2a.2 viruses and often majority of individuals had neutralizing titers > 40
- Antiviral Susceptibility
  - Genetic and/or phenotypic testing showed 1 of the 1023 A(H3N2) viruses collected after September 2021 showed reduced inhibition to neuraminidase inhibitors.
  - Of 962 A(H3N2) viruses collected and analyzed after September 2021, none showed genetic or phenotypic evidence of reduced susceptibility to baloxavir.



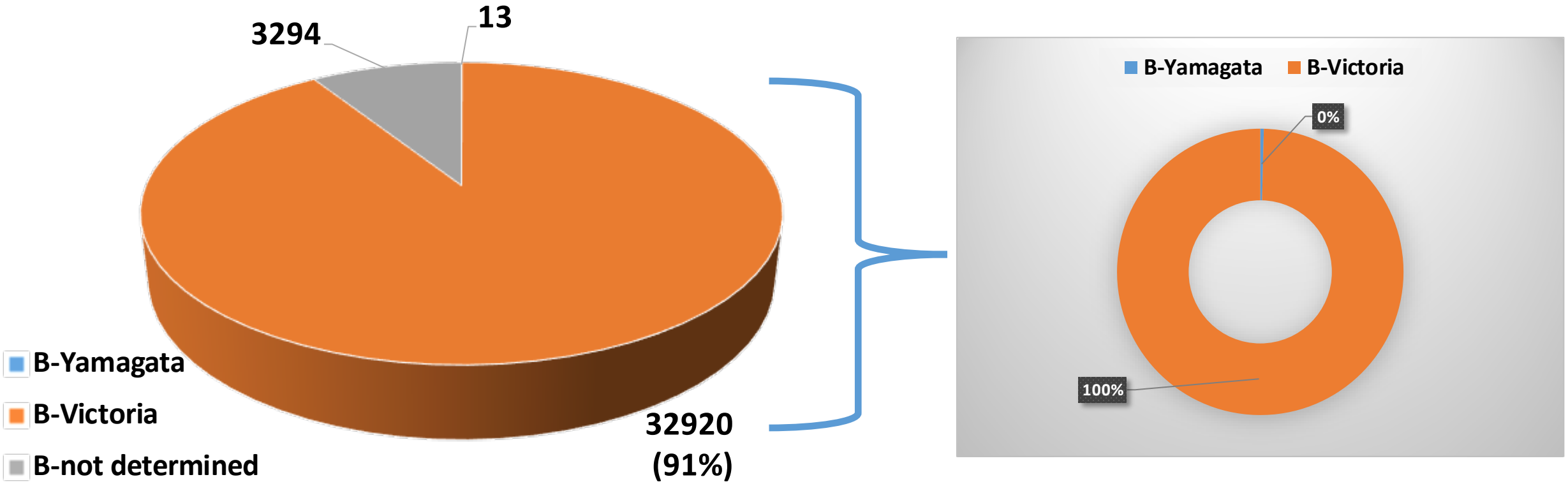
Influenza B Viruses
September 2021 - February 2022

Number of B Viruses Detected By GISRS



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

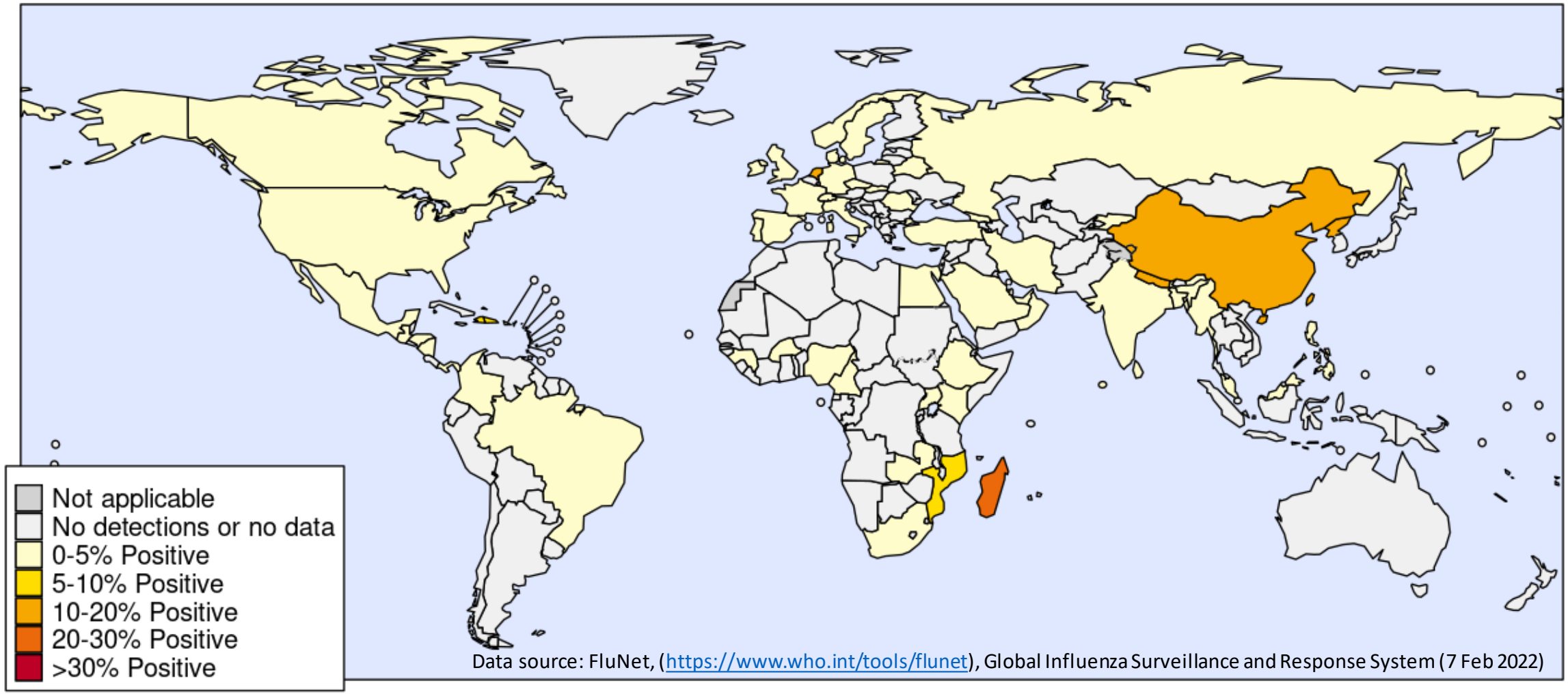
Influenza B Viruses Ascribed to Lineages: Numbers and Percentage (Sep 2021 – Jan 2022)



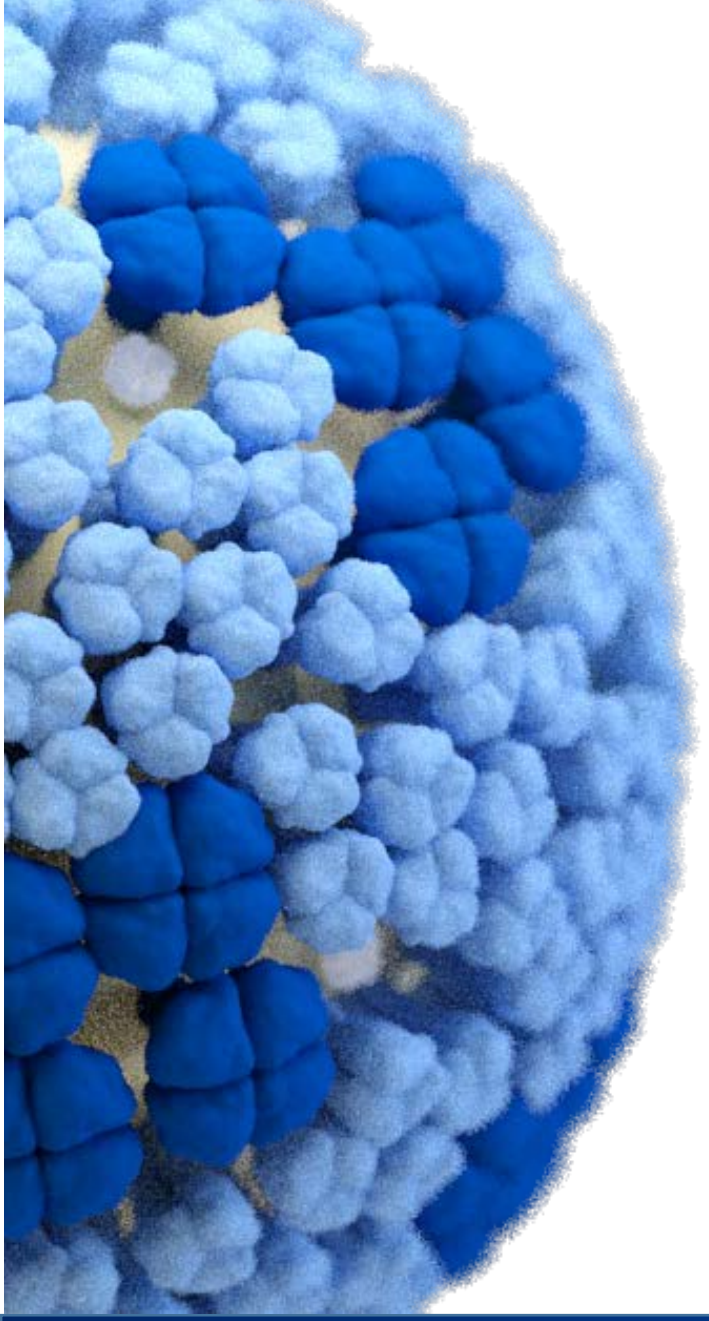
Data source: FluNet, (https://www.who.int/tools/flunet), Global Influenza Surveillance and Response System (7 Feb 2022)

Influenza B Viruses Activity

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



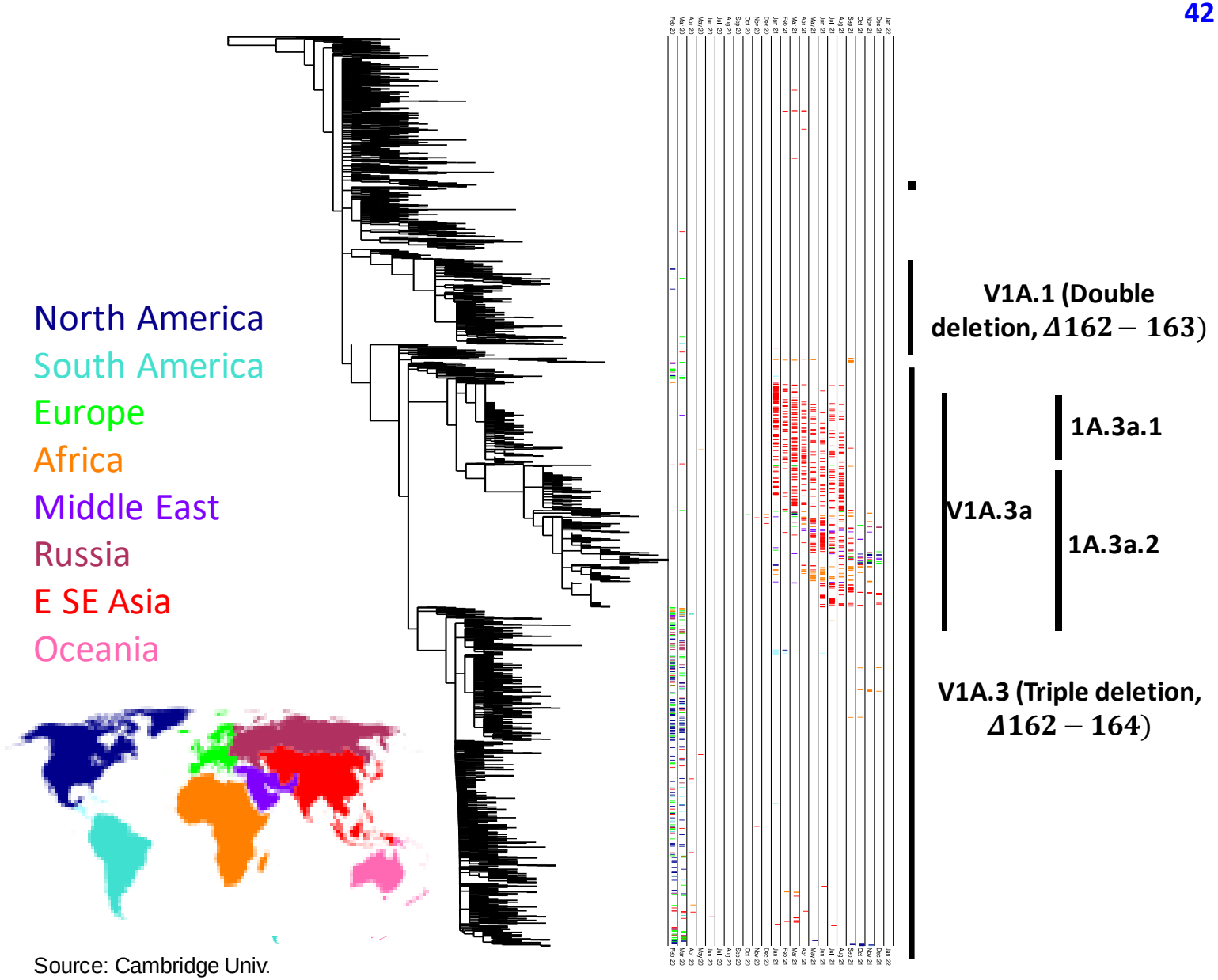
Colour intensity shows the percent of influenza B positive among all samples tested during this period per country



B/Victoria Lineage Viruses

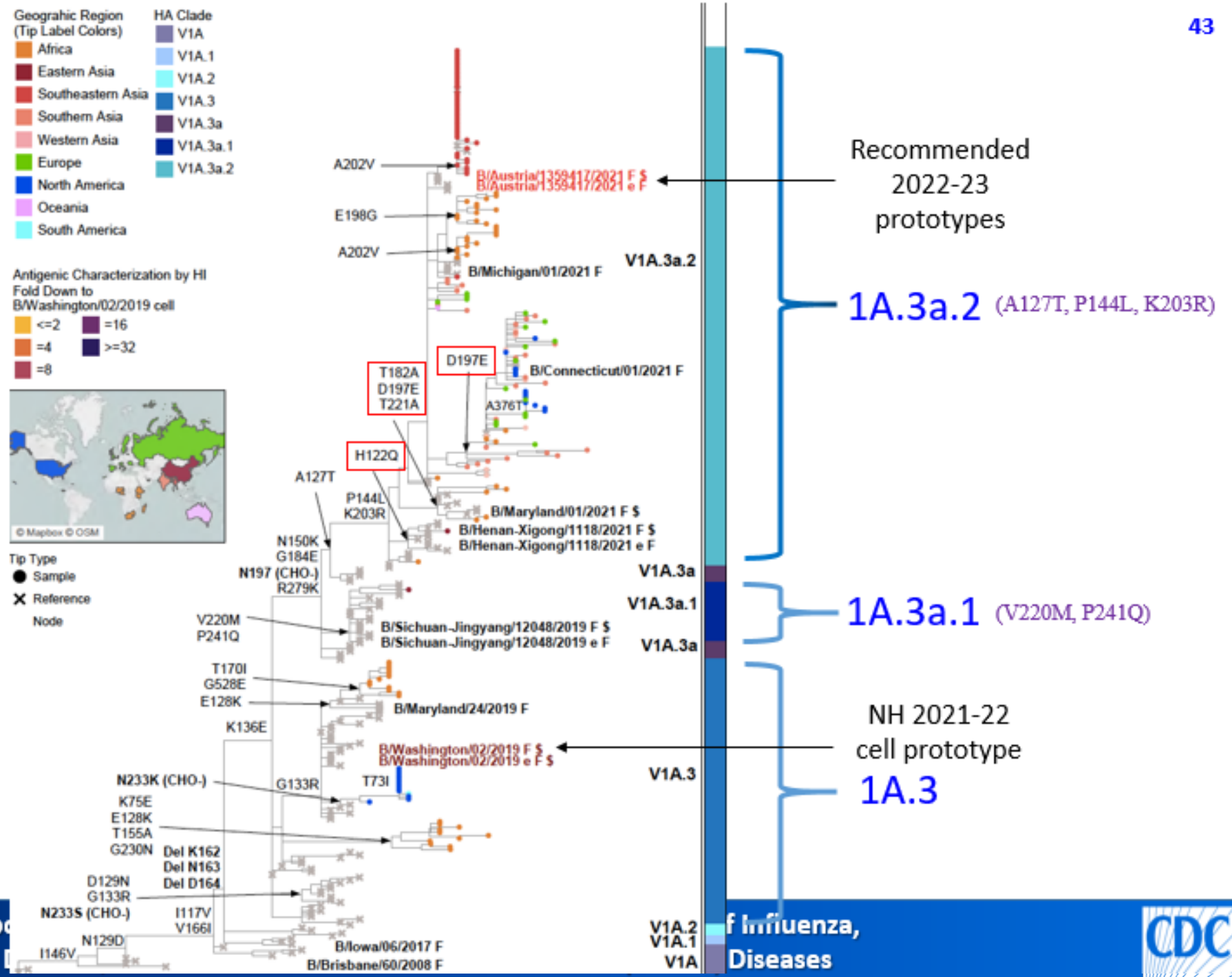
Influenza B/Victoria HA Phylogeography

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



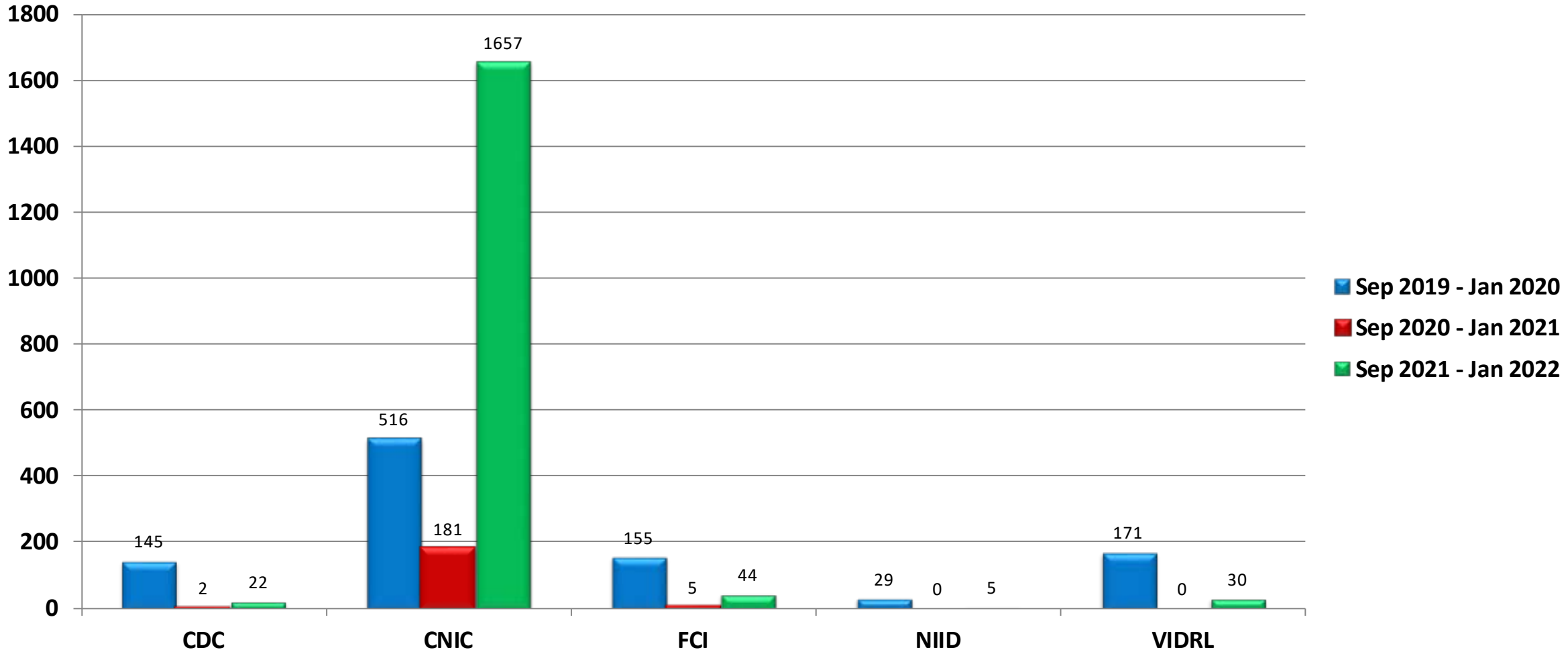
Source: Cambridge Univ.

B/Victoria HA Phylogenetics



WHO CC
CDC, USA

Influenza B Viruses Antigenically Characterized During The Last 3 Reporting Periods



Analysis of B/Victoria Viruses By Antisera to Antigens Recommended for NH 2021-2022

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

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

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

WHO CC	Like (2-4 fold)	Low (≥ 8 fold)
CDC	17 (77%)	5 (23%)
CNIC	550 (33%)	1107 (67%)
FCI	5 (11%)	39 (89%)
NIID	5 (100%)	0 (0%)
VIDRL	2 (14%)	12 (86%)
TOTAL	579 (33%)	1163 (67%)

Analysis of B/Victoria Viruses By Antisera to Antigens Recommended for SH 2022

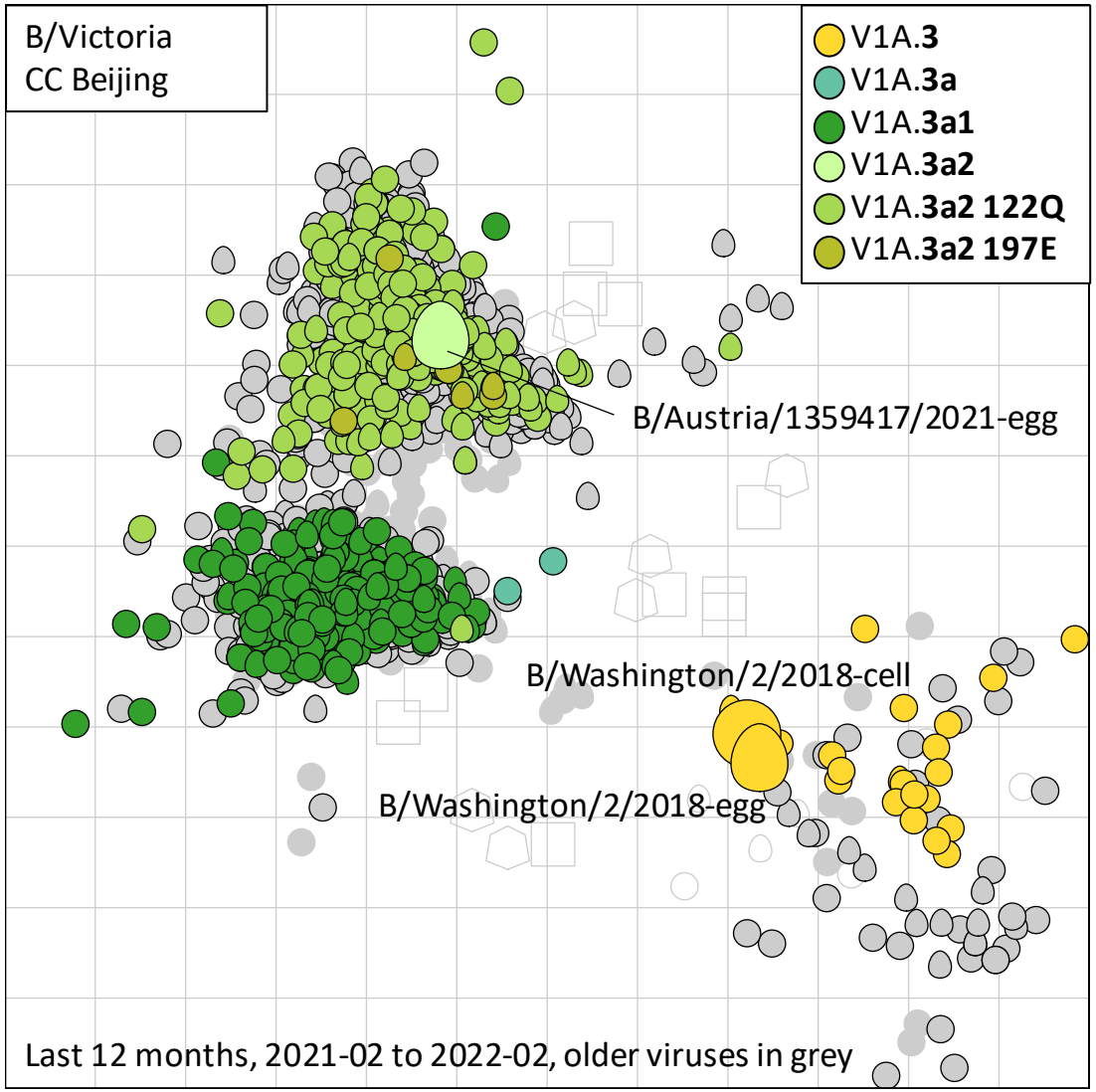
B/Austria/1359417/2021-like (cell)

WHO CC	Like (2-4 fold)	Low (≥ 8 fold)
CDC	5 (45%)	6 (55%)
CNIC	1315 (88%)	180 (12%)
FCI	39 (89%)	5 (11%)
NIID	5 (100%)	0 (0%)
VIDRL	25 (83%)	5 (17%)
TOTAL	1389 (88%)	196 (12%)

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

WHO CC	Like (2-4 fold)	Low (≥ 8 fold)
CDC	6 (55%)	5 (45%)
CNIC	1329 (89%)	166 (11%)
FCI	39 (89%)	5 (11%)
NIID	5 (100%)	0 (0%)
VIDRL	30 (100%)	0 (0%)
TOTAL	1409 (89%)	176 (11%)

Antigenic Cartography



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

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

Human Post-vaccination Serum Analysis

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

NH 2021-2022 Vaccine (V1A.3)

B/WASHINGTON/02/2019 MDCK

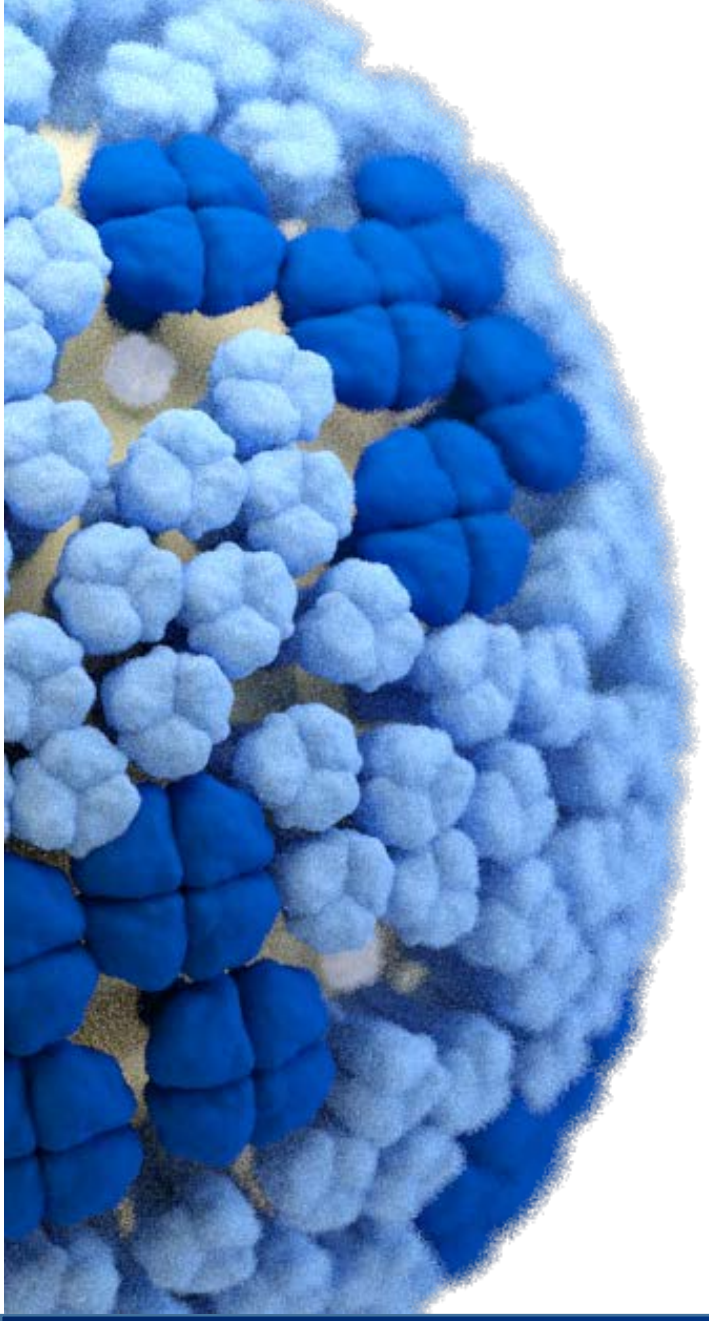
			V1A.3		V1A.3a.1	V1A.3a.2		
			*WA/02	+N197S(CHO-) WA/02	+V220M +P241Q SIC/12048	+A127T +P144L +K203R AUT/1359417	+H122Q +A127T +P144L +K203R HEN/1118	+A127T +P144L +T182A +D197E +K203R +T221A MD/01
			MDCK	EGG	MDCK	MDCK	MDCK	MDCK
Pediatric (6-35M)	USA	IIV4	25	X	X	X	13	15
Pediatric (3-8Y)	USA	ccIIV4 (Flucelvax)	39	X	X	X	X	X
		IIV4	95	√	√	√	√	√
Pediatric (9-17Y)	USA	ccIIV4 (Flucelvax)	139	√	√	√	√	√
		IIV4	49	√	√	√	√	√
Adult	USA	ccIIV4 (Flucelvax)	67	43	37	36	31	44
		RIV4 (Flublok)	95	√	57	48	51	59
		IIV4	63	√	39	43	43	√
	Japan	IIV4	24	X	X	X	X	X
	UK	IIV4	49	√	√	√	√	√
Older Adult (50-64Y)	USA	IIV4	63	√	√	√	√	√
Elderly	Japan	IIV4	27	X	X	X	X	X
	USA	IIV4-HD	75	√	√	√	√	√

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: B/AUSTRIA/1359417/2021 (AUT/1359417); B/HENAN-XIGONG/1118/2021 (HEN/1118); B/MARYLAND/01/2021 (MD/01); B/SICHUAN-JINGYANG/12048/2019 (SIC/12048); B/WASHINGTON/02/2019 (WA/02).

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

GMT ratio lowerbound (90% CI)
0.0 — 1.0



B/Yamagata Lineage Viruses

B/Yamagata Lineage Virus Detections

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

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

B/Yamagata: Future Considerations

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

Summary of Influenza B Viruses (1)

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

Summary of Influenza B Viruses (2)

- Occasional B/Yamagata/16/88 lineage viruses have been reported in FluNet during this reporting period (13 specimens) but none have been confirmed by WHO Collaborating Centres
- No viruses of B/Yamagata/16/88 lineage have been available for analysis during this period

Acknowledgements

- WHO Collaborating Centers in Beijing, Melbourne, London and Tokyo and WHO Geneva staff
  - GISRS; National Influenza Centers
  - University of Cambridge partners
- Essential Regulatory Laboratories
- US partners:
  - Association of Public Health Laboratories
  - United States Air Force School of Aerospace Medicine (USAFSAM)
  - Naval Health Research Center (NHRC)
- Fitness forecasting partners in Europe and US
  - M. Lässig, M. Łuksza
  - T. Bedford, R. Neher
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  - Special thanks to Rebecca Kondor, Min Levine, Larisa Gubareva and John Steel

Support and Disclaimer

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