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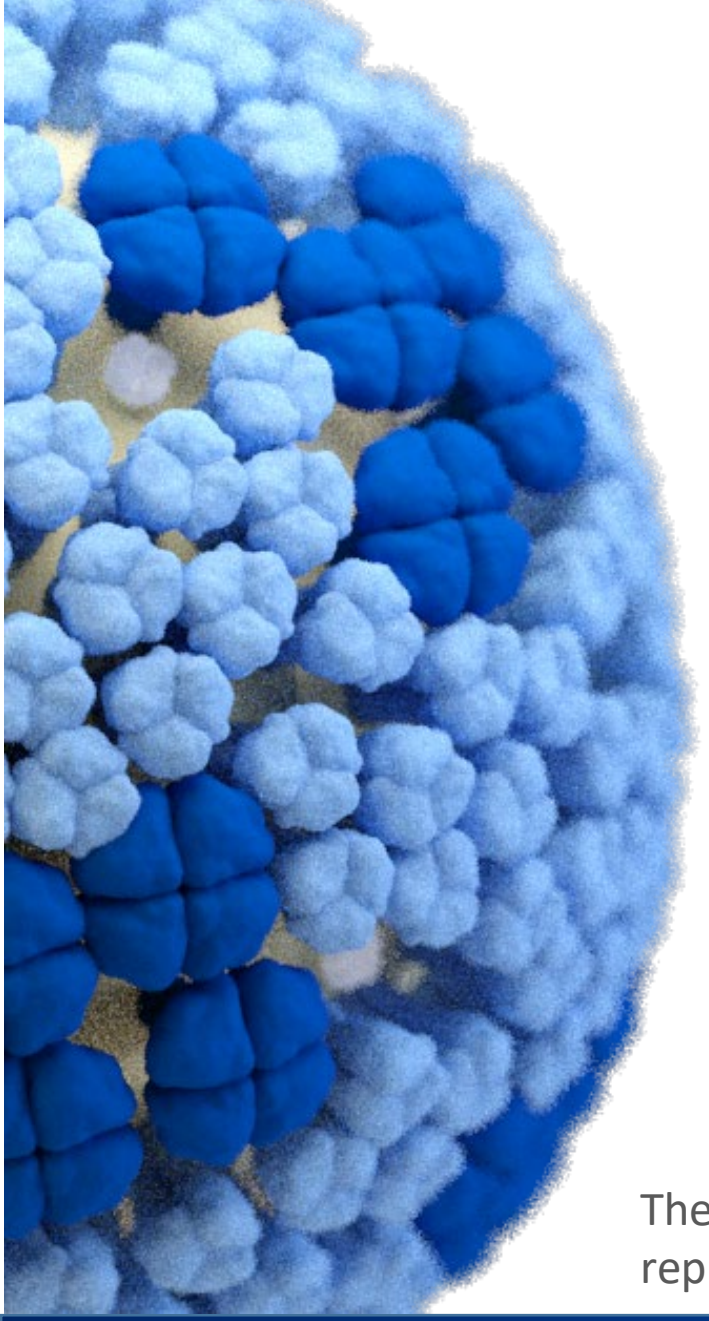


Information For The Vaccine And Related Biological Products Advisory Committee CBER, FDA

Global Influenza Virus Surveillance and Characterization October 6, 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

Outline

- Briefly describe WHO-Vaccine Consultation Meeting, SH-2023 recommendations and influenza virus activity
- A(H1N1)pdm09 Viruses
  - Described to detail key information leading to the recommendation to update the vaccine antigen for SH-2023.
- A(H3N2) Viruses and influenza B Viruses
  - Unchanged, will limit to some of key data

WHO-Vaccine consultation meeting for the southern hemisphere 2023 influenza vaccine

- **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 September 19-22, 2022**
  - A hybrid of in-person and virtual meeting
  - Chaired: Dr Hideki Hasegawa, Co-chair: Dr. David Wentworth
  - 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
  - 35 observers from WHO CCs, WHO ERLs, other GISRS laboratories and academia
  - Experts from WHO Regional offices and Head Quarters

WHO vaccine recommendations for the southern hemisphere 2023

The WHO recommends that quadrivalent vaccines for use in the 2023 southern hemisphere influenza season contain the following:

Egg-based quadrivalent vaccines

- an A/Sydney/5/2021 (H1N1)pdm09-like virus; (updated)
- 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.

Cell culture- or recombinant-based quadrivalent vaccines

- an A/Sydney/5/2021 (H1N1)pdm09-like virus; (updated)
- 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.

The WHO recommends that trivalent vaccines for use in the 2023 southern hemisphere influenza season contain the following:

Egg-based quadrivalent vaccines

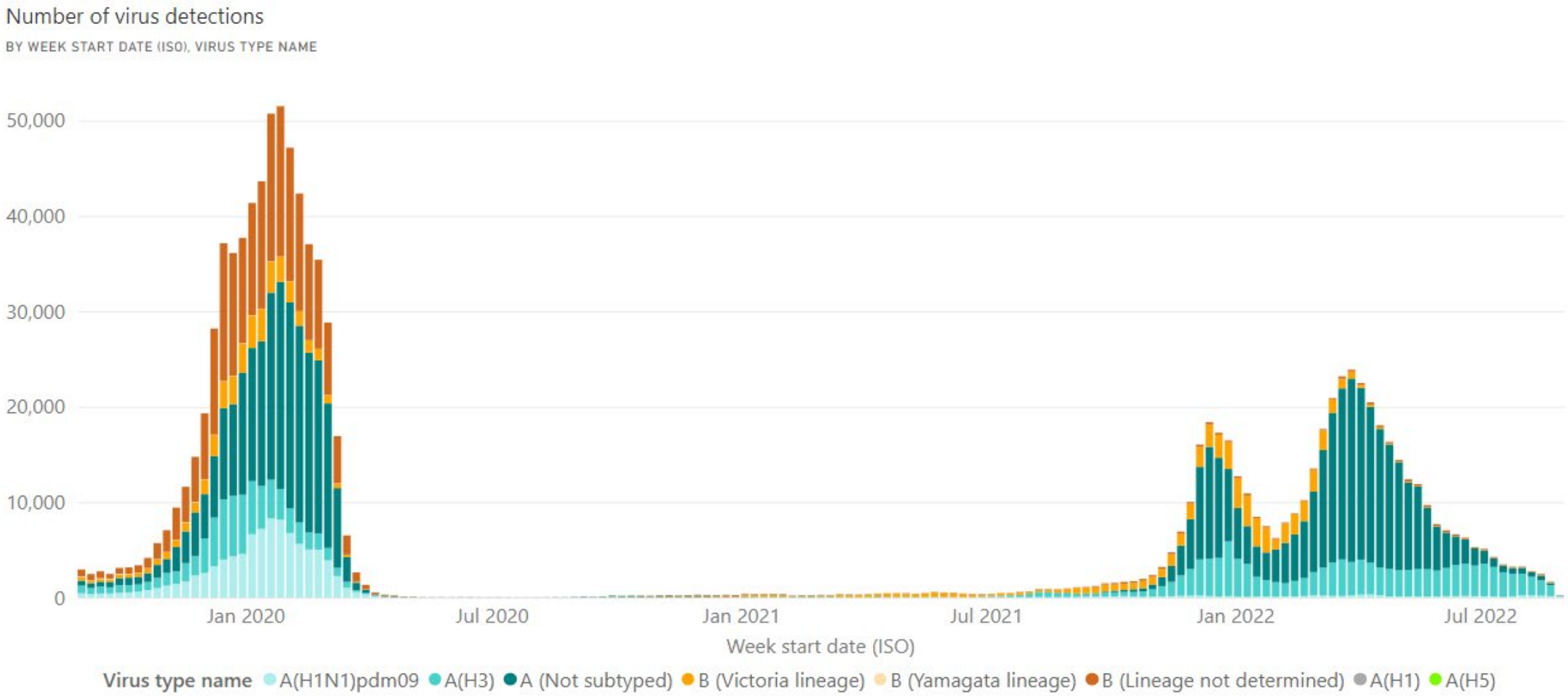
- an A/Sydney/5/2021 (H1N1)pdm09-like virus; (updated)
- an A/Darwin/9/2021 (H3N2)-like virus; and
- a B/Austria/1359417/2021 (B/Victoria lineage)-like virus

Cell culture- or recombinant-based quadrivalent vaccines

- an A/Sydney/5/2021 (H1N1)pdm09-like virus; (updated)
- an A/Darwin/6/2021 (H3N2)-like virus; and
- a B/Austria/1359417/2021 (B/Victoria lineage)-like virus

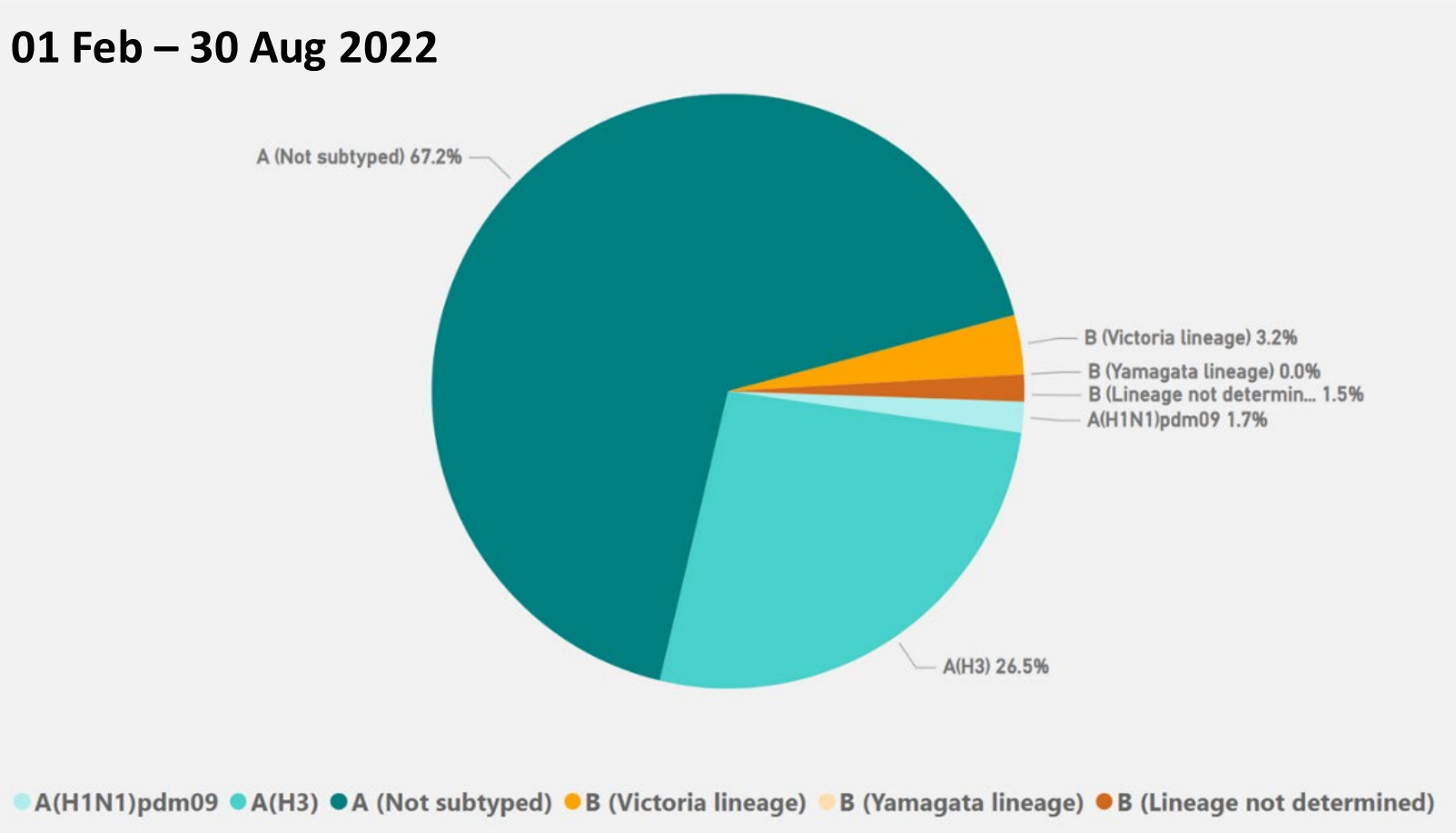
WHO recommendation and technical reports available on the WHO web site: https://www.who.int/teams/global-influenza-programme/vaccines/who-recommendations

Number of specimens positive for influenza



Source: Global Influenza Programme (who.int)

Percentage of influenza A viruses by type/subtype/lineage



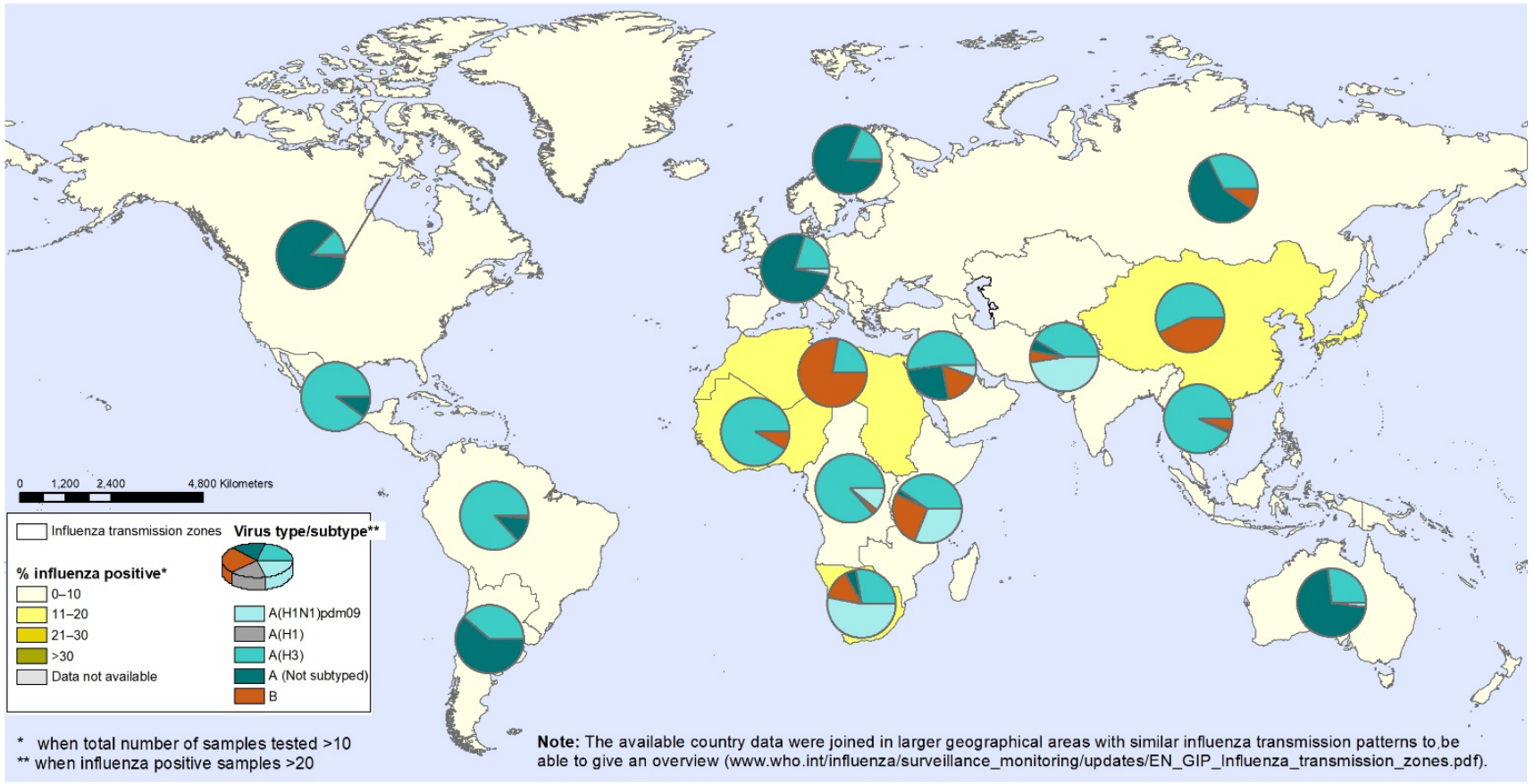
Specimens characterized from Feb 01 – 30 Aug 2022

- 95.4% type A
  - 26.5% A(H3N2)
  - 1.7% A(H1N1)pdm09
  - 67.2% not subtyped
- 3.2 % type B
  - All samples with lineage determined were B/Victoria (1.5%)

Source: Global Influenza Programme (who.int)

Global distribution of influenza viruses

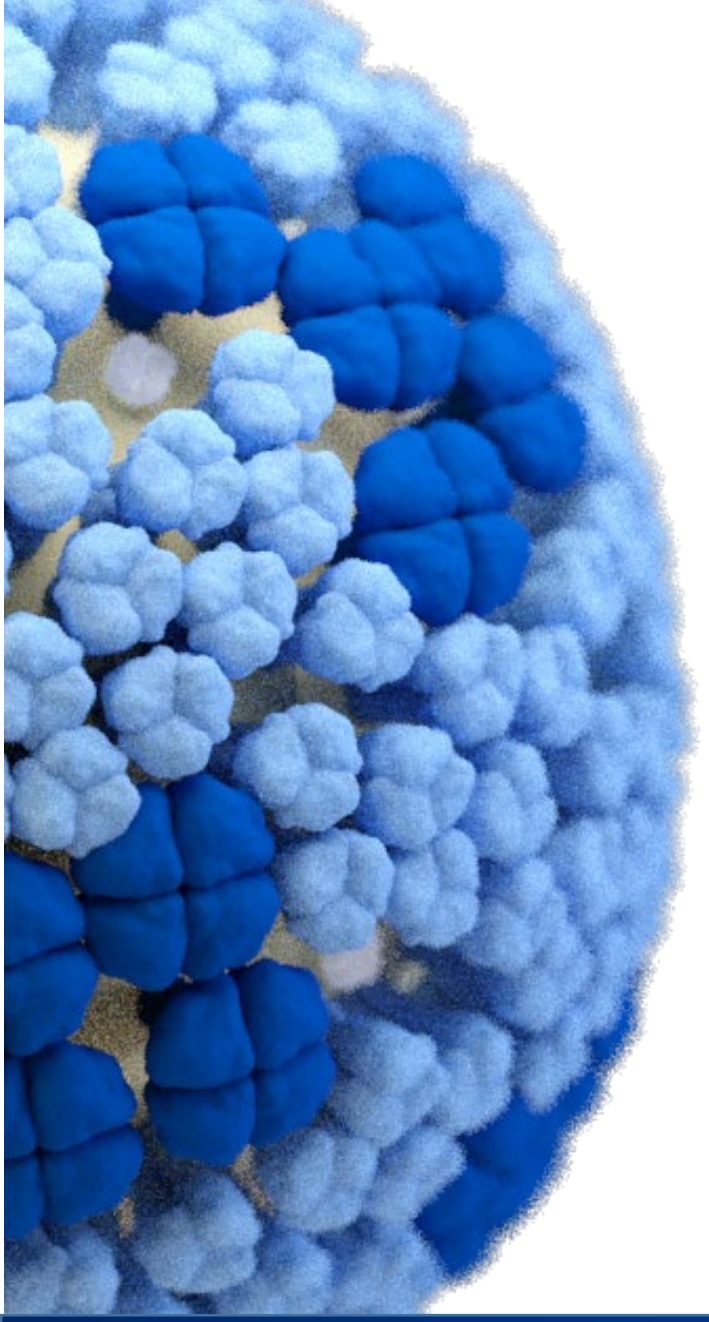
Distribution of influenza virus type/subtype by influenza transmission zone, between February and August 2022



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

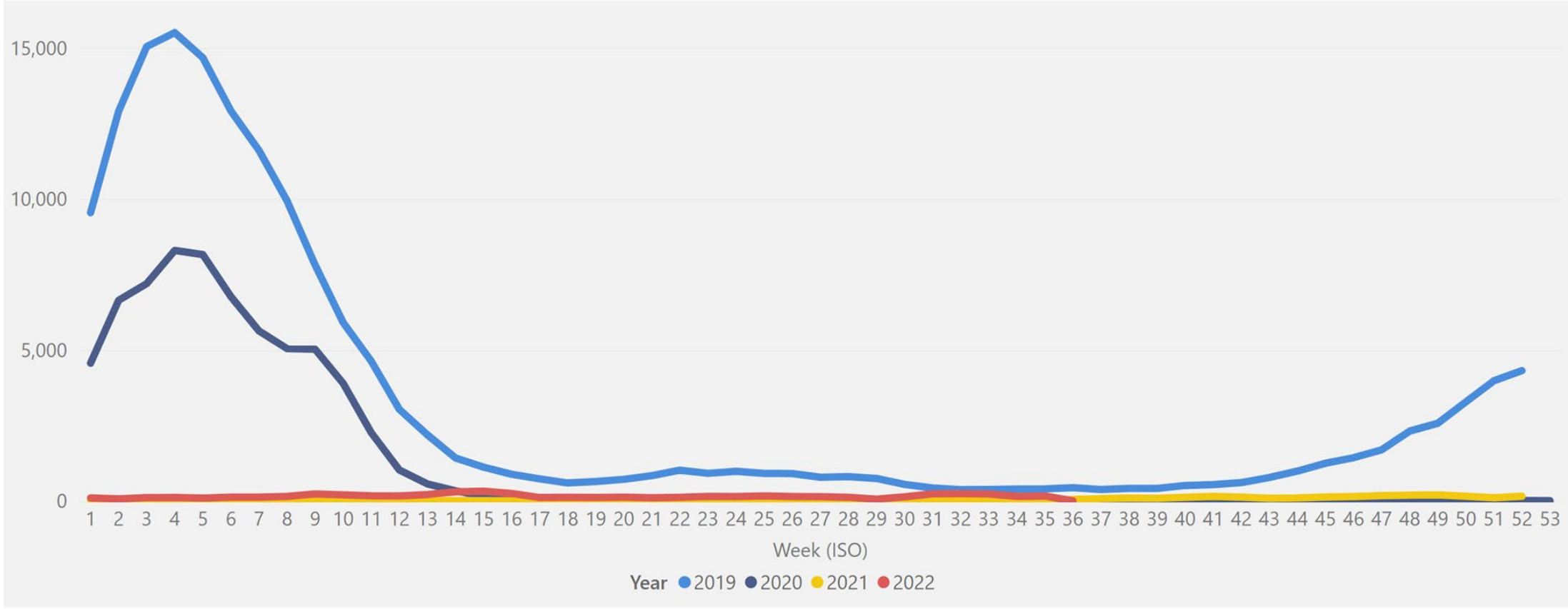
World Health Organization

Source: Global Influenza Programme (who.int)



A(H1N1)pdm09 Viruses

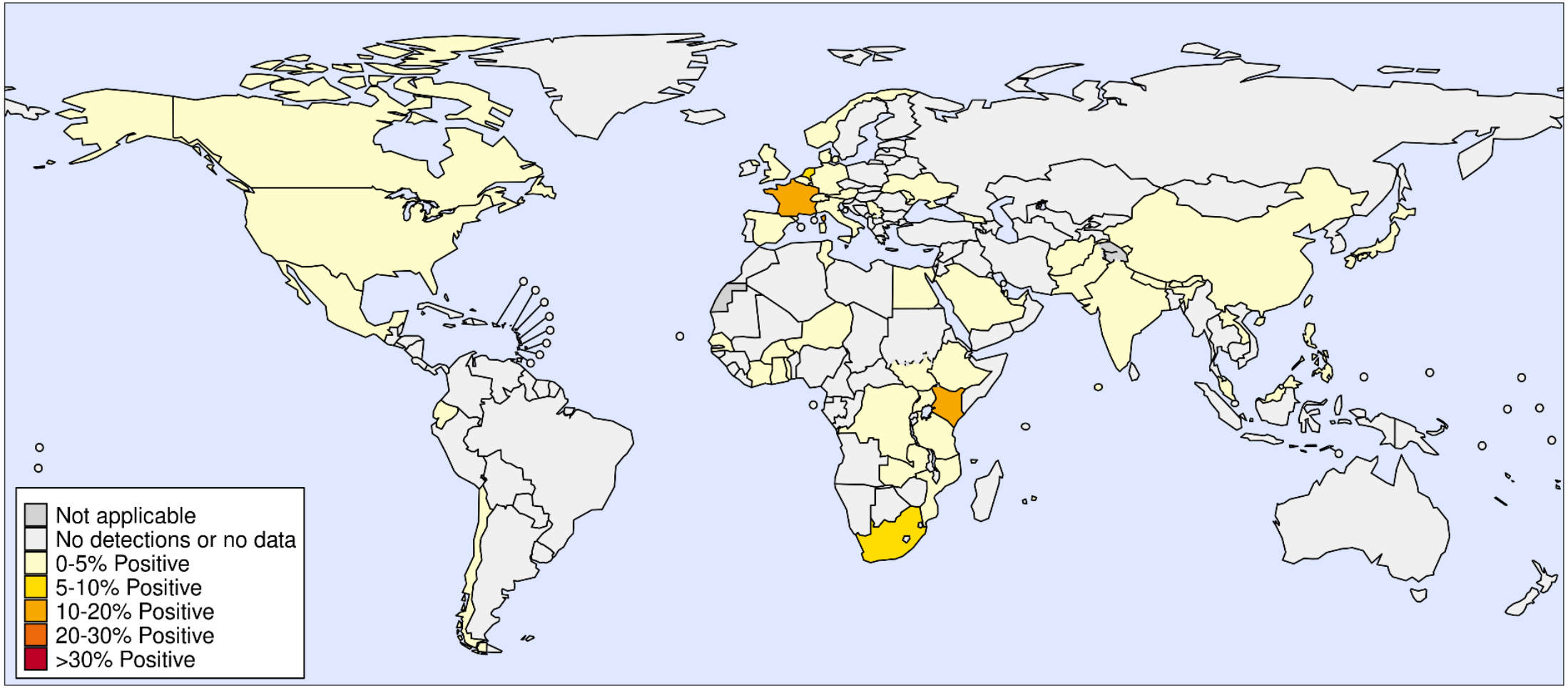
Number of A(H1N1)pdm09 viruses detected by GISRS



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

Influenza A(H1N1)pdm09 activity

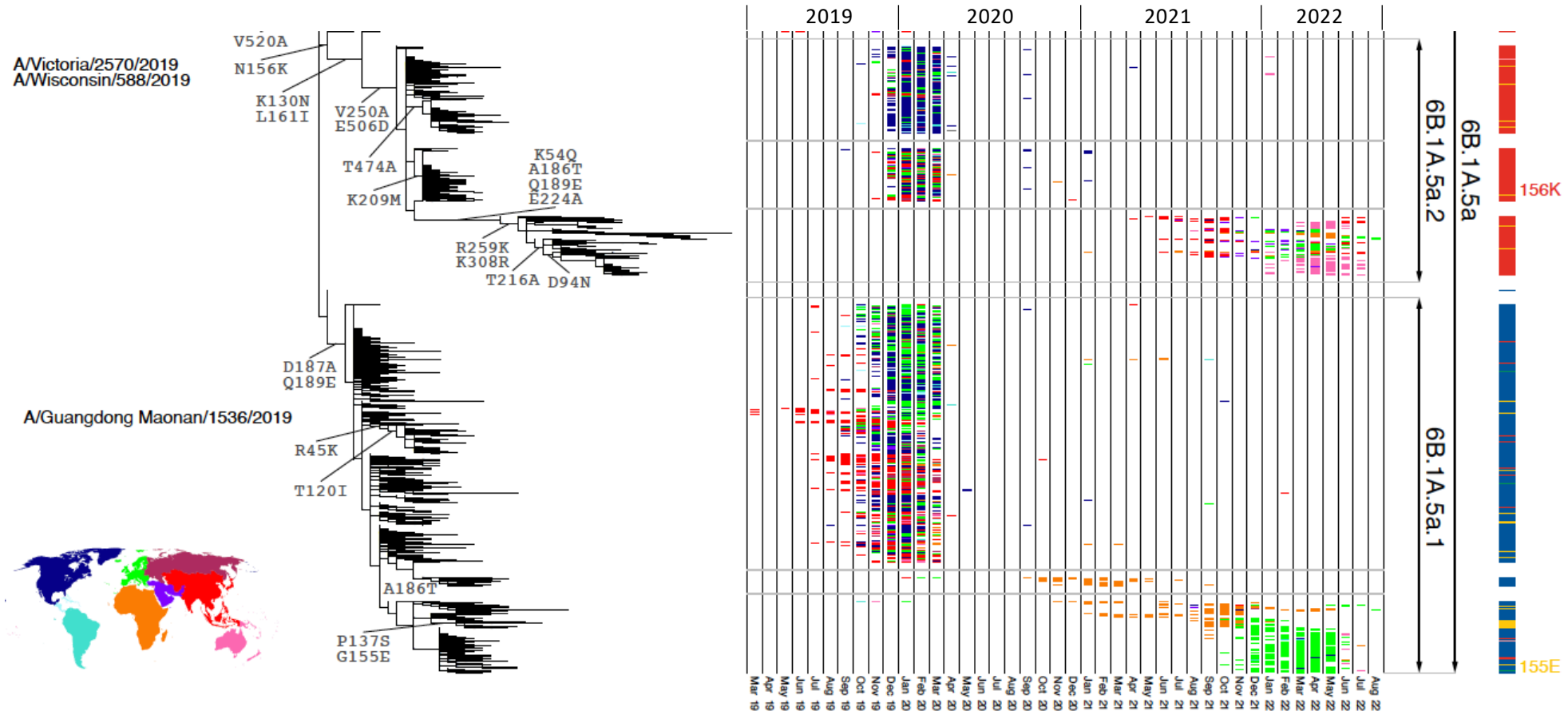
Influenza A(H1N1)pdm09, February 2022 to August 2022, percent of all samples tested



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

Source: Global Influenza Programme (who.int)

Overall A(H1N1)pdm09 HA phylogeography



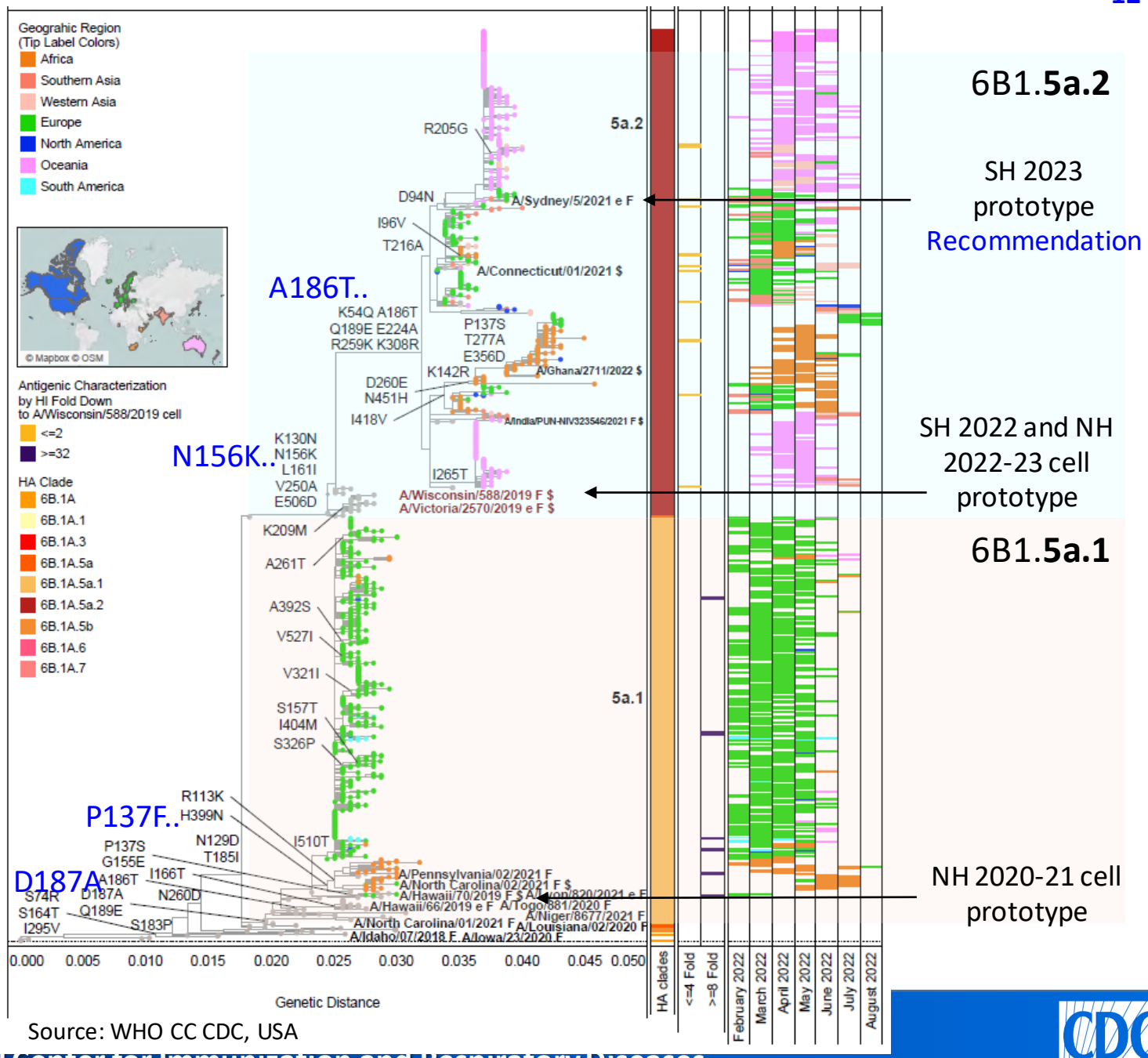
Source: Cambridge Univ., S. James and D. Smith

- Two major 6B.1.5a subclades, emerged prior to the COVID-19 pandemic and descendants continue to circulate
  - 5a.1 HA (e.g., Guangdong Maonan/1536 or HI/70/2019)
  - 5a.2 HA (e.g., Wisconsin/588), continue to diversify

Recent A(H1N1)pdm09 HA phylogeography

Two major 6B.1.5a subclades

- **5a.1** HA (e.g., A/HI/70/2019)
  - Often share D187A and **Q189E** (Sb epitope)
  - Few with P137S (Ca) and **G155E** (Sa)
    - A/NC/02/2021
  - Recent viruses primarily from Africa and Europe
- **5a.2** HA (e.g., A/WI/588/2017)
  - Share K130N, N156K, L161I, V250A, E506D
  - Nearly all recent viruses, have evolved K54Q, **A186T** (Sb), **Q189E** (Sb), **E224A**, R259K, and K308R
    - A/India/PUN-NIV323546/2021
  - Small subgroup have evolved P137S, K142R
    - A/Ghana/2711/2022
  - Recent viruses primarily from Africa, Europe, Oceania
- Parallel evolution of Q189E



Source: WHO CC CDC, USA

Analysis of the changes occurring in H1 HA proteins

Positions shown of note

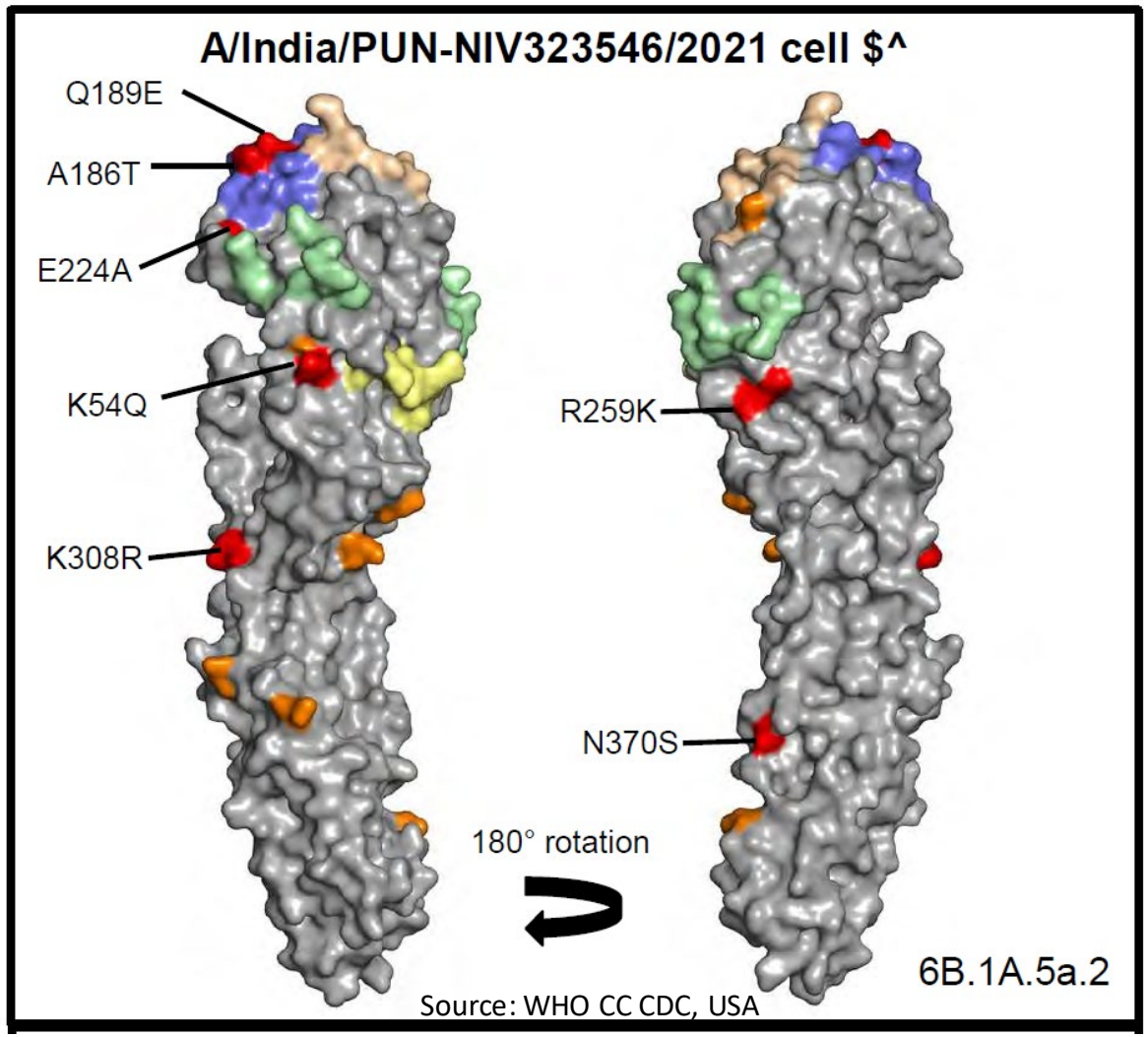
- 5a.1
  - Defining: 156N, 187A, 189E
  - New: 137S, 155E
- 5a.2
  - Defining: 130N, 156K, 161I, V250A
  - Recent: 186T, 189E, 224A
    - 216A > 137S, 142R
- Parallel evolution
  - Q189E > P137S

SeqLogo of Samples collected since 2022–02–01 (n= 1225)

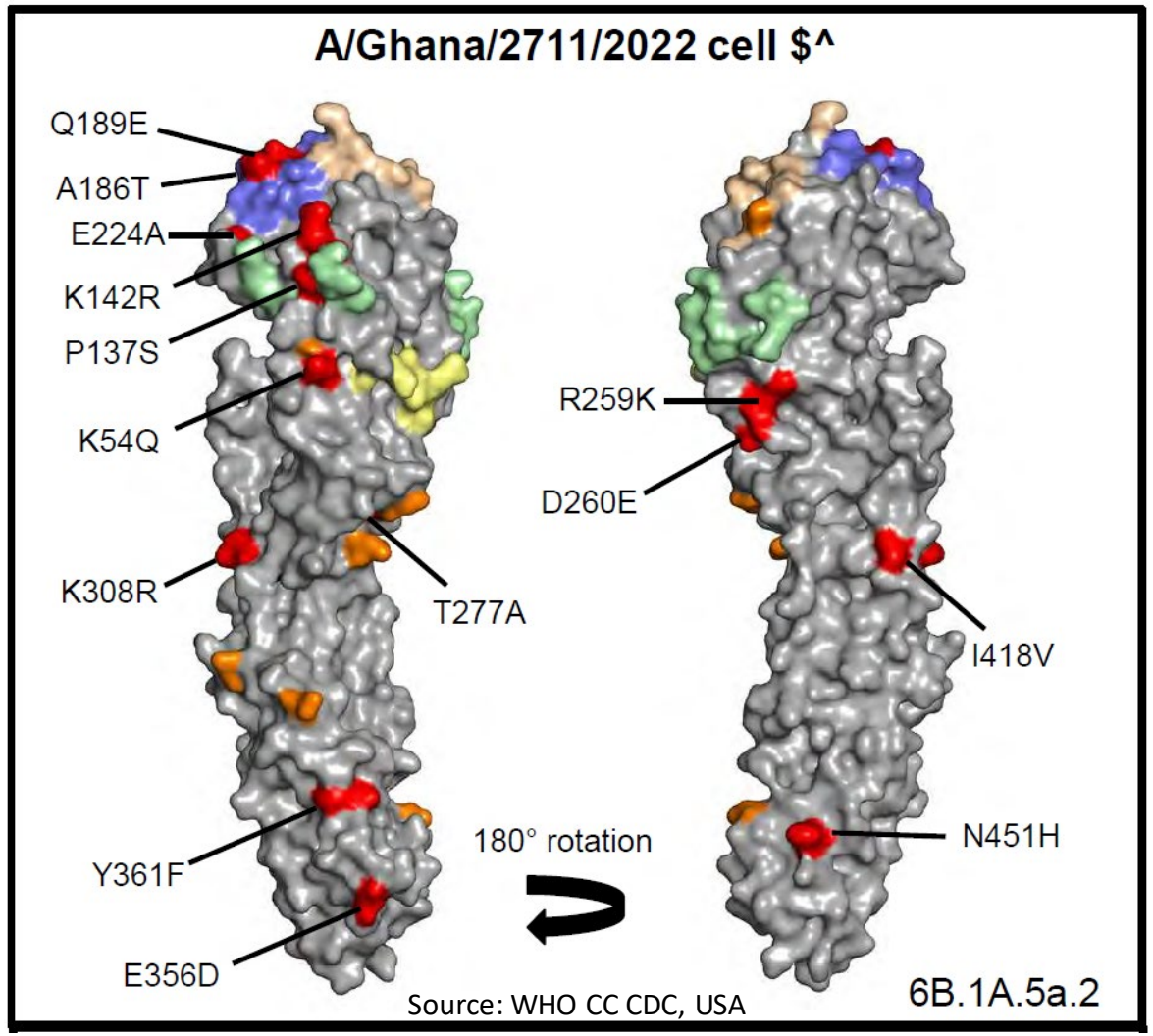
Source: WHO CC CDC, USA

Location of changes in key serology antigens

Majority of Recent 5A.2 HA Proteins



Few Recent 5A.2 HA Proteins



Antigenic analysis of A(H1N1)pdm09 viruses

Antisera to southern hemisphere 2022 antigens (5a.2)

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

WHO CC	Like (2-4 fold)	Low (≥ 8 fold)
CDC	15 (75%)	5 (25%)
CNIC	0	0
FCI	46 (30%)	105 (70%)
NIID	3 (75%)	1 (25%)
VIDRL	532 (92%)	47 (8%)
TOTAL	596 (79%)	158 (21%)

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

WHO CC	Like (2-4 fold)	Low (≥ 8 fold)
CDC	15 (75%)	5 (25%)
CNIC	0	0
FCI	46 (30%)	105 (70%)
NIID	3 (75%)	1 (25%)
VIDRL	532 (92%)	47 (8%)
TOTAL	596 (79%)	158 (21%)

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

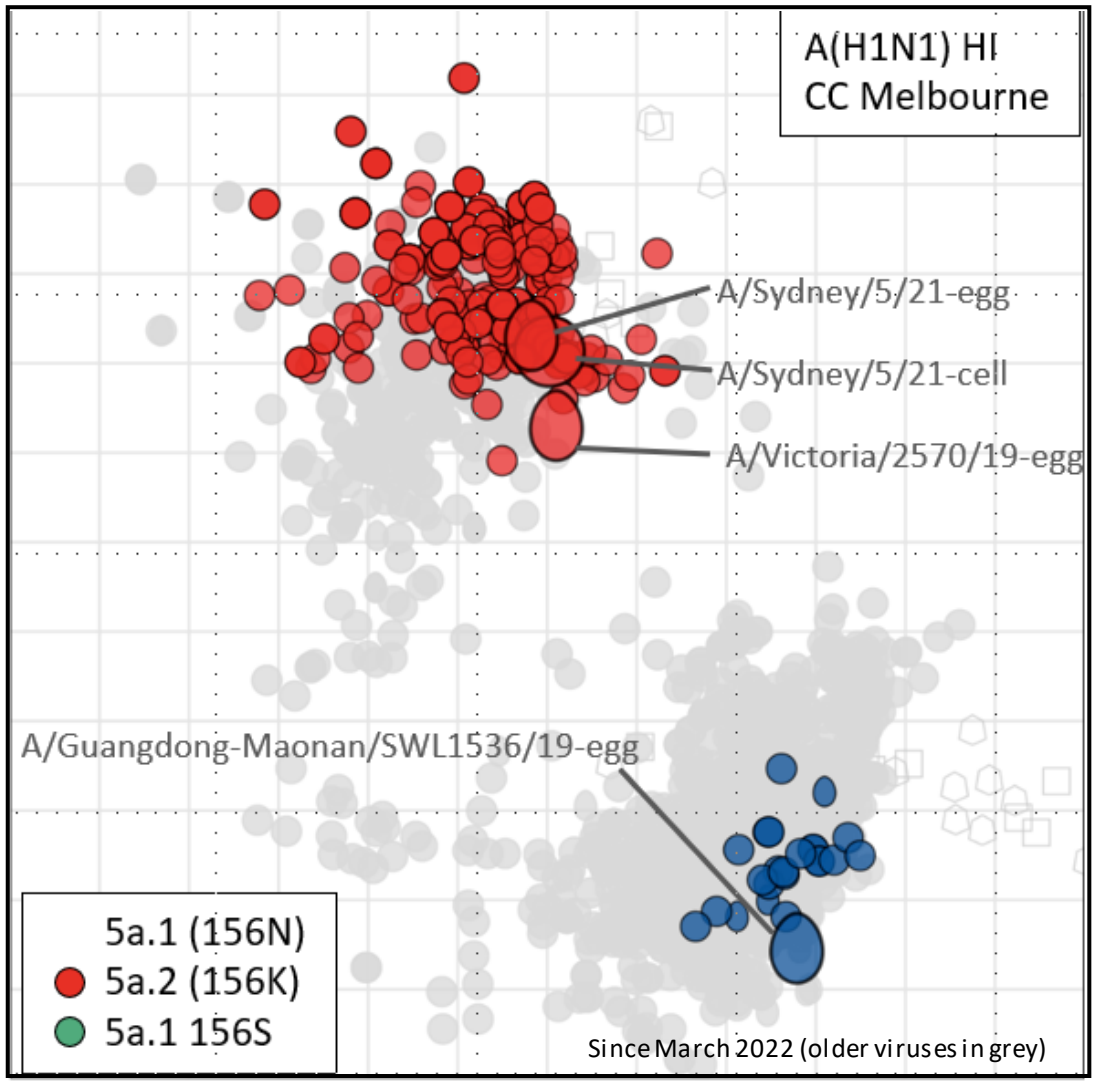
HI analysis of recent H1N1pdm09 viruses

HI analysis with post-infection ferret antisera

Results from VIDRL show the distinct recognition by antisera raised against 5a.1 and 5a.2 viruses

		Haemagglutination inhibition titres						
		Post-infection ferret antisera						
		E4	SIAT1	S3, MDCK1	MDCK1	E4	E3	human
		Guang/SWL1536	Vic2455	Togo881	Vic2570	Vic2570	Syd5	sera
Reference viruses	**Clade**	**A.5a.1**	**A.5a.1**	**A.5a.1**	**A.5a.2**	**A.5a.2**	**A.5a.2**	**pool**
A/Guangdong-Maonan/SWL1536/2019	6B.1A.5a.1	**1280**	2560	2560	<80	<80	80	320
A/Victoria/2455/2019	6B.1A.5a.1	1280	**1280**	1280	<80	<80	80	640
A/Togo/881/2020	6B.1A.5a.1	2560	2560	**2560**	<80	80	160	640
A/Victoria/2570/2019	6B.1A.5a.2	80	80	<80	**320**	320	320	160
A/Victoria/2570/2019	6B.1A.5a.2	80	80	<80	1280	**1280**	1280	640
A/Sydney/5/2021	6B.1A.5a.2	<80	80	<80	2560	1280	**2560**	640
Test viruses								
A/Sydney/894/2022	6B.1A.5a.2	<80	<80	<80	1280	1280	1280	320
A/Perth/184/2022	6B.1A.5a.2	<80	<80	<80	640	1280	1280	320
A/Canberra/222/2022	6B.1A.5a.2	<80	<80	<80	1280	1280	2560	320
A/Darwin/488/2022	6B.1A.5a.2	<80	<80	<80	640	1280	1280	320
A/South Africa/R05765/2022	6B.1A.5a.2	<80	<80	<80	640	640	640	80
A/South Africa/R05258/2022	6B.1A.5a.2	<80	<80	<80	1280	1280	1280	160
A/South Africa/R04994/2022	6B.1A.5a.2	<80	<80	<80	1280	1280	2560	160
A/South Africa/R03645/2022	6B.1A.5a.2	<80	<80	<80	1280	1280	2560	160
A/Sydney/877/2022	6B.1A.5a.1	1280	2560	2560	**<80**	**<80**	**80**	640
A/Sydney/866/2022	6B.1A.5a.1	2560	2560	2560	**<80**	**80**	**80**	640
A/Sydney/869/2022	6B.1A.5a.1	2560	2560	2560	**<80**	**<80**	**80**	640
A/South Africa/R05655/2022	6B.1A.5a.1	1280	1280	1280	**<80**	**<80**	**<80**	320

A(H1N1)pdm09 antigenic cartography



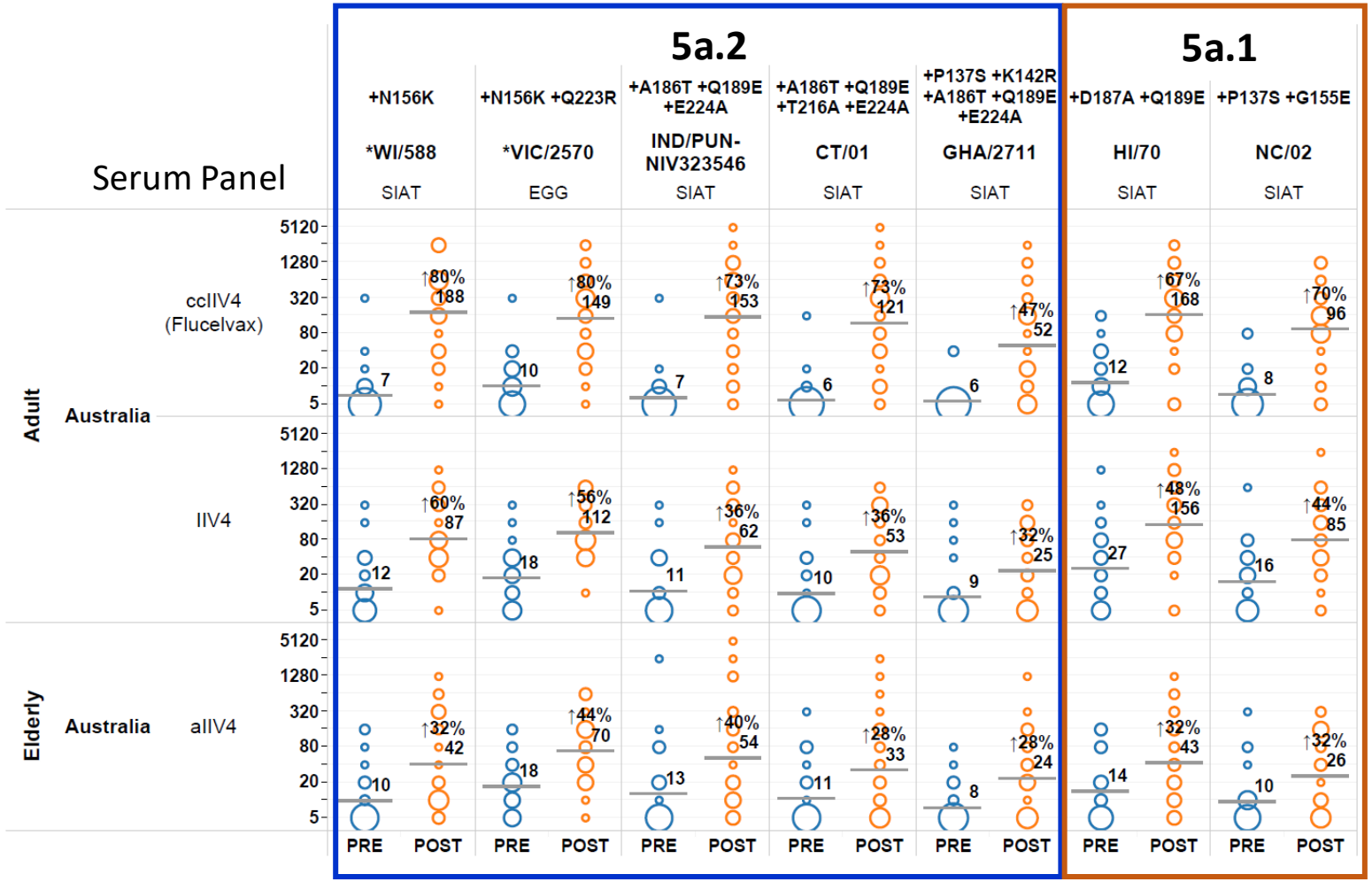
Source: S. James D. Smith Univ. of Cambridge

- 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

Adult human post-vaccination sera: individual responses

U.S. CDC results with SH-2022 (5a.2) adult and ≥ 65 post-vaccination sera

- Increased antibody titers against bot 5a.2 and 5a.1 viruses
  - Often more than 70% of individuals have titer ≥ 40
- Back boost - HI/70 (5a.1)
- Forward boost – recent 5a.2 and 5a. representatives
- Lowest GMTs observed with GHA/2711 antigen



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

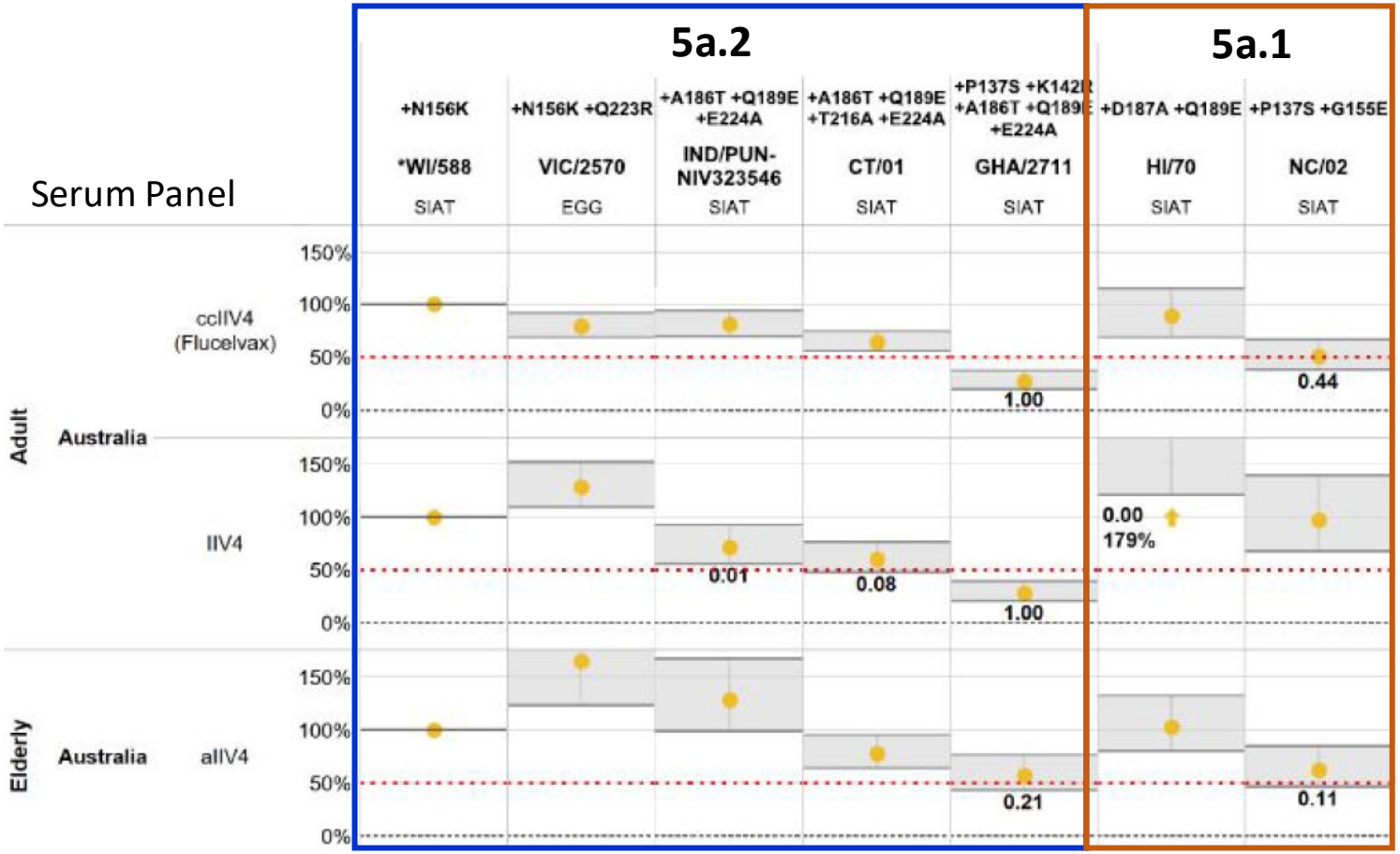
Strains abbreviated: A/CONNECTICUT/01/2021 (CT/01); A/GHANA/2711/2022 (GHA/2711); A/HAWAII/70/2019 (HI/70); A/INDIA/PUN-NIV323546/2021 (IND/PUN-NIV323546); A/NORTH CAROLINA/02/2021 (NC/02); A/VICTORIA/2570/2019 (VIC/2570); A/WISCONSIN/588/2019 (WI/588)

Source: WHO CC CDC, USA

Post vaccination human serology – GMT reductions vs cell culture-propagated A/Wisconsin/588/2019

U.S. CDC results with SH-2022 (5a.2) adult and ≥ 65 post-vaccination sera

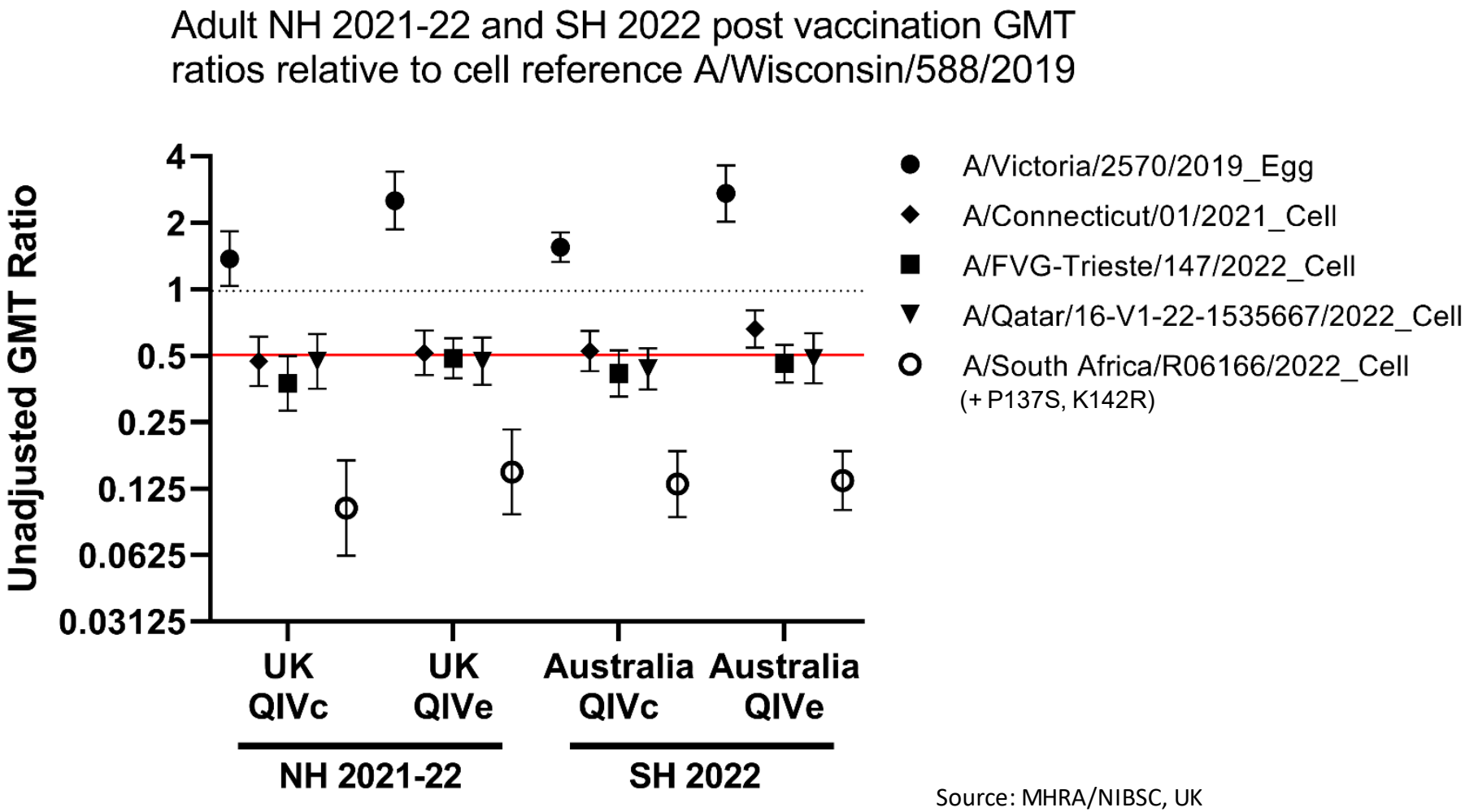
- Inhibition by vaccine induced antibodies decreased as changes in 5a.2 HA proteins have evolved
  - IND/PUN and CT/01 show modest reductions
    - A186T, Q189E, and E224 (+T216A in CT/01)
  - GHA/2711 showed marked reduction in GMT
    - A186T, Q189E, E224, T216A + P137S and K142R



GMT ratios as percentages. The dashed red line is the noninferiority threshold (50% GMT ratio). Unadjusted GMT Ratios lower bounds above this line are statistically noninferior to the applied reference antigen (p•values > 0.01 shown). The y.axis is restricted to ratios in [0%, 175%] with ratios above the upper limit denoted with an arrow ([I]) and displaying the GMT ratio (Rt). These ratios are always significant. Strains abbreviated: A/CONNECTICUT/01/2021 (CT/01); A/GHANA/2711/2022 (GHA/2711); A/HAWAII/70/2019 (HI/70); A/INDIA/PUN·NIV323546/2021 (IND/PUN·NIV323546); A/NORTH CAROLINA/02/2021 (NC/02); A/VICTORIA/2570/2019 (VIC/2570); A/WISCONSIN/588/2019 (WI/588).

Post vaccination human serology – GMT reductions vs cell culture-propagated A/Wisconsin/588/2019

U.K. MHRA results with four panels of adult post-vaccination sera



Source: MHRA/NIBSC, UK

Post vaccination human serology – summary of GMT reductions

WHO Collaborating Center (CC): Human Serological Panels — **2022 Southern Hemisphere and 2021-22 Northern Hemisphere panels**

A(H1N1)pdm09 -- HI Protocol [CELL]

Newer 5a.2 viruses

					5a.2																			5a.1								
					+N156K WI/588-LIKE					+A186T +Q189E +E224A IND/PUN-NIV323546-LIKE			+A186T +Q189E +T216A +E224A CT/01-LIKE								+P137S +K142R +A186T +Q189E +E224A GHA/2711-LIKE			- GUAN/SWL1536-LIKE		+D187A +Q189E HI/70	+P137S NAG/1	+P137S +G155E NC/02			+I510T BRIS/50-LIKE	
					WI/588				VIC/2570	IND/PUN-NIV323546		DAR/7	CT/01				FVG/147	QAT/16-V1-22-1535667	SYD/173	GHA/2711	ZAF/R06166	ZAF/R04778	GUAN/SWL1536	ZAF/R04202	-	-	-			BRIS/50	PRT/211528
					CELL				CELL	CELL		CELL	CELL				CELL	CELL	CELL	CELL	CELL	CELL	CELL	CELL	CELL	CELL			CELL	CELL
					CDC	CBER	NIBSC	NIID	VIDRL	CDC	NIID	VIDRL	CDC	CBER	NIBSC	NIID	VIDRL	NIBSC	NIBSC	VIDRL	CDC	NIBSC	VIDRL	VIDRL	VIDRL	CDC	NIID	CDC	CBER	NIID	VIDRL	NIBSC
A/WISCONSIN/588/2019-LIKE CELL	Pediatric (3-8Y)	ccIIV4 (2021-22 NH)	USA						69			√					√			√			√	√	√						√	
		IIV4 (2021-22 NH)	USA						61			√					√			√			√	√	√						√	
	Pediatric (9-17Y)	ccIIV4 (2021-22 NH)	USA						136			√					√			√			√	√	√						√	
		IIV4 (2021-22 NH)	USA						65			√					√			√			√	√	√						√	
	Adult	ccIIV4 (Flucelvax)	Australia	188	266	80	279	32	√	√	X	√	√	42	106	X	33	35	X	52	10	X	X	X	√	168	96	84	146	X	35
			UK (NIBSC)			165									78			62	78			17										√
		IIV4	Australia	87	271	103	135	17	√	√	X	53	√	√	57	X	47	50	X	25	14	X	X	X	√	√	√	41	√	X	√
			UK (NIBSC)			50									26			24	24			7										√
	Elderly	aIIV4	Australia	45	210	30	100	15	√	√	X	√	146	17	37	X	17	18	X	26	8	X	X	X	√	√	28	26	61	X	16
									0 (0.0)	0 (0.0)	0 (0.0)	1 (33.3)	1 (33.3)	4 (80.0)	3 (100.0)	0 (0.0)	5 (100.0)	5 (100.0)	0 (0.0)	3 (100.0)	5 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (33.3)	2 (66.7)	3 (100.0)	2 (66.7)	0 (0.0)	2 (40.0)

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/50/2022 (BRIS/50); A/CONNECTICUT/01/2021 (CT/01); A/DARWIN/7/2022 (DAR/7); A/FVG-TRIESTE/147/2022 (FVG/147); A/GHANA/2711/2022 (GHA/2711); A/GUANGDONG-MAONAN/SWL1536/2019 (GUAN/SWL1536); A/HAWAII/70/2019 (HI/70); A/INDIA/PUN-NIV323546/2021 (IND/PUN-NIV323546); A/NAGASAKI/1/2022 (NAG/1); A/NORTH CAROLINA/02/2021 (NC/02); A/PORTUGAL/211528/2022 (PRT/211528); A/QATAR/16-V1-22-1535667/2022 (QAT/16-V1-22-1535667); A/SOUTH AFRICA/R04202/2022 (ZAF/R04202); A/SOUTH AFRICA/R04778/2022 (ZAF/R04778); A/SOUTH AFRICA/R06166/2022 (ZAF/R06166); A/SYDNEY/173/2022 (SYD/173); 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 Lower-Bound (90% CI) 0.000 — 1.000

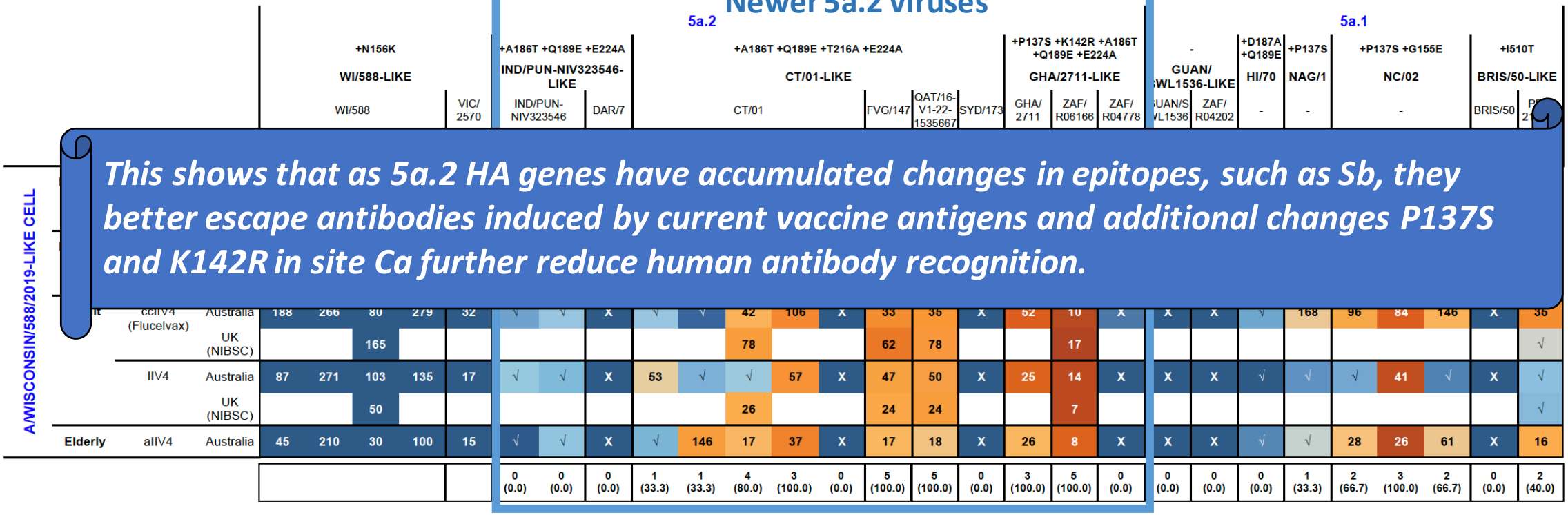
Multiple sources: compiled by WHO CC CDC, USA

Post vaccination human serology – summary of GMT reductions

WHO Collaborating Center (CC): Human Serological Panels — **2022 Southern Hemisphere and 2021-22 Northern Hemisphere panels**

A(H1N1)pdm09 -- HI Protocol [CELL]

Newer 5a.2 viruses



This shows that as 5a.2 HA genes have accumulated changes in epitopes, such as Sb, they better escape antibodies induced by current vaccine antigens and additional changes P137S and K142R in site Ca further reduce human antibody recognition.

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/50/2022 (BRIS/50); A/CONNECTICUT/01/2021 (CT/01); A/DARWIN/7/2022 (DAR/7); A/FVG-TRIESTE/147/2022 (FVG/147); A/GHANA/2711/2022 (GHA/2711); A/GUANGDONG-MAONAN/SWL1536/2019 (GUAN/SWL1536); A/HAWAII/70/2019 (HI/70); A/INDIA/PUN-NIV323546/2021 (IND/PUN-NIV323546); A/NAGASAKI/1/2022 (NAG/1); A/NORTH CAROLINA/02/2021 (NC/02); A/PORTUGAL/211528/2022 (PRT/211528); A/QATAR/16-V1-22-1535667/2022 (QAT/16-V1-22-1535667); A/SOUTH AFRICA/R04202/2022 (ZAF/R04202); A/SOUTH AFRICA/R04778/2022 (ZAF/R04778); A/SOUTH AFRICA/R06166/2022 (ZAF/R06166); A/SYDNEY/173/2022 (SYD/173); A/VICTORIA/2570/2019 (VIC/2570); A/WISCONSIN/588/2019 (WI/588).

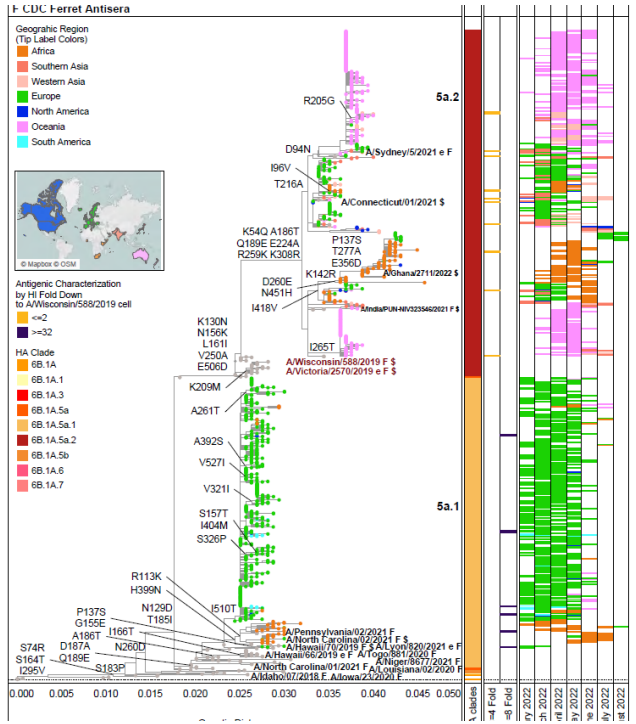
Statistically non-inferior = √
Statistically non-inferior but reference virus GMT < 40 = X

GMT Ratio Lower-Bound (90% CI)
0.000 — 1.000

Multiple sources: compiled by WHO CC CDC, USA

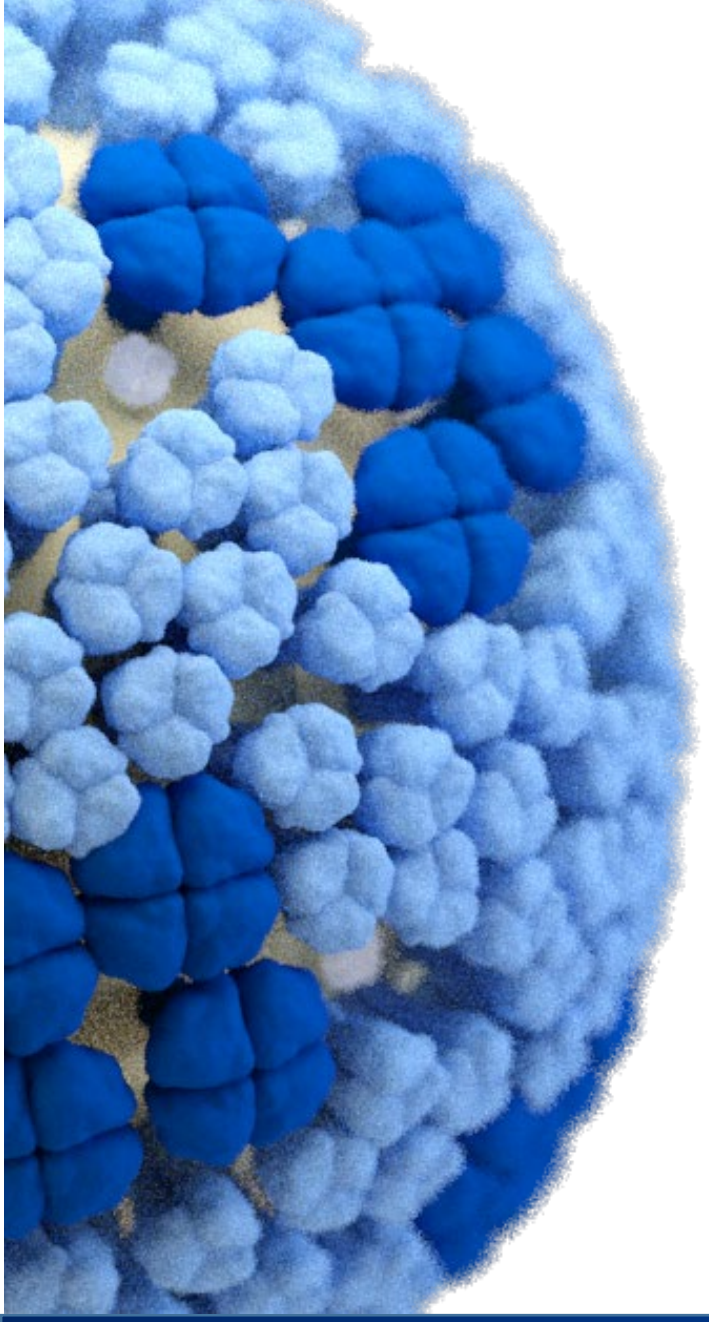
A(H1N1)pdm09 – Summary (1):global circulation and phylogeny

- Globally, relatively few A(H1N1)pdm09 viruses with collection dates after January 2022 have been detected
- The HA genes of all are in clade 6B.1A.5a (**5a**)
- Two 5a subclades have circulated in 2022
  - 5a.1 – encode D187A, Q189E, predominantly circulating in Europe
  - 5a.2 – encode K130N, N156K, L161I, V250A, have global circulation
  - 5a.2 HA genes have further evolved and **all recent HA** proteins have K54Q, A186T, Q189E, E224A, R259K, K308R (e.g., A/Sydney/5/2021)
    - A number of smaller genetic groups emerging



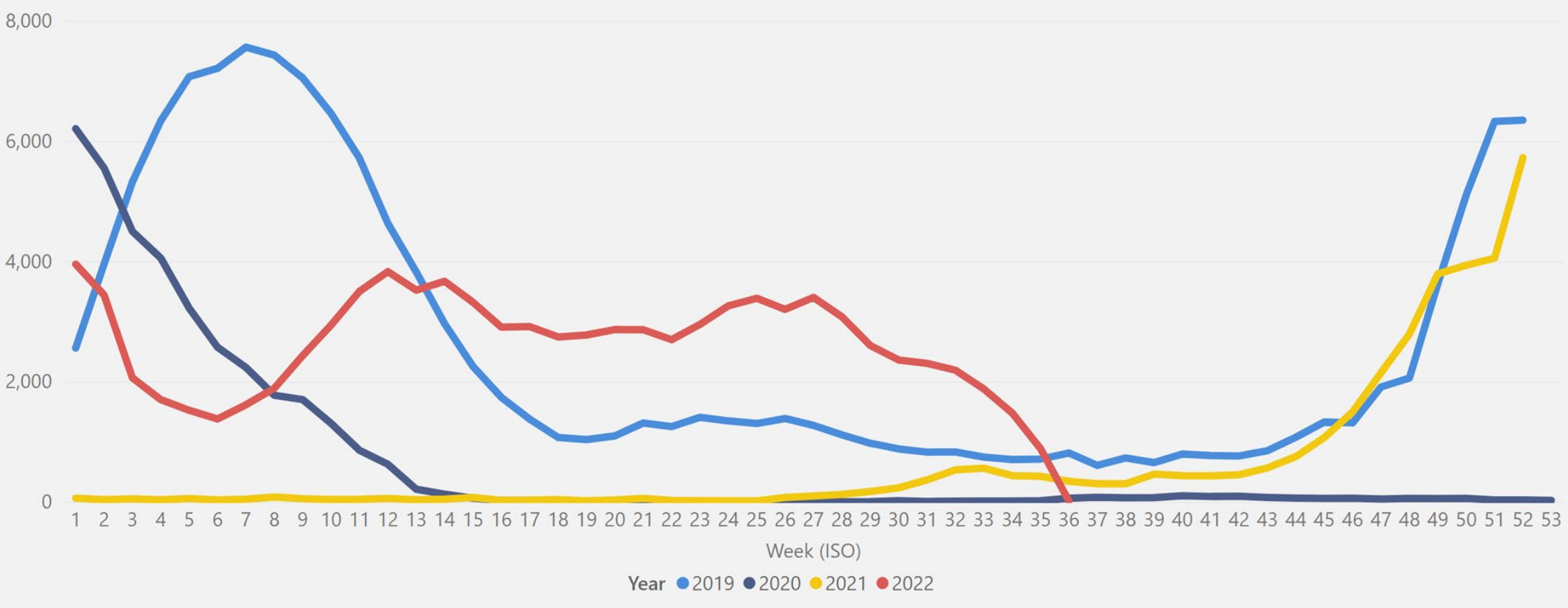
A(H1N1)pdm09 – Summary (2): antigenicity, and human serology

- Antigenic analysis showed
  - 5a.1 and 5a.2 HA proteins form two distinct groups
  - Ferret antisera to A/Sydney/5/2021 cell- and egg-propagated virus well recognized representative recent 5a.2 viruses
- Analysis with human post-vaccination sera showed 5a.2 HA genes have accumulated changes that facilitate escape from antibodies induced by current vaccine antigens.
  - Poorest inhibition was observed in recent viruses that have K142R and P137S substitutions in HA and these represent a small proportion of circulating viruses



A(H3N2) Viruses

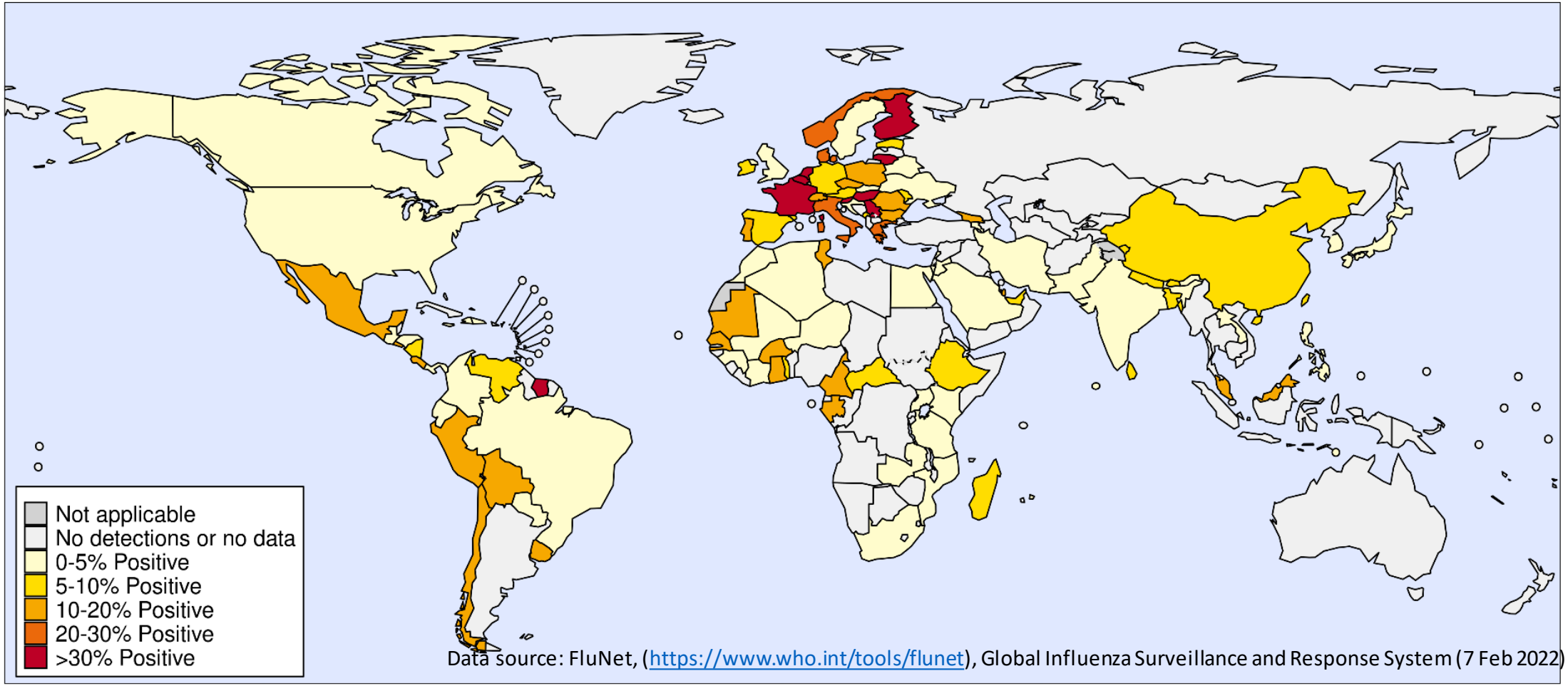
Number of A(H3N2) viruses detected by GISRS



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

Influenza A(H3N2) activity

Influenza A(H3N2), February 2022 to August 2022, percent of all samples tested

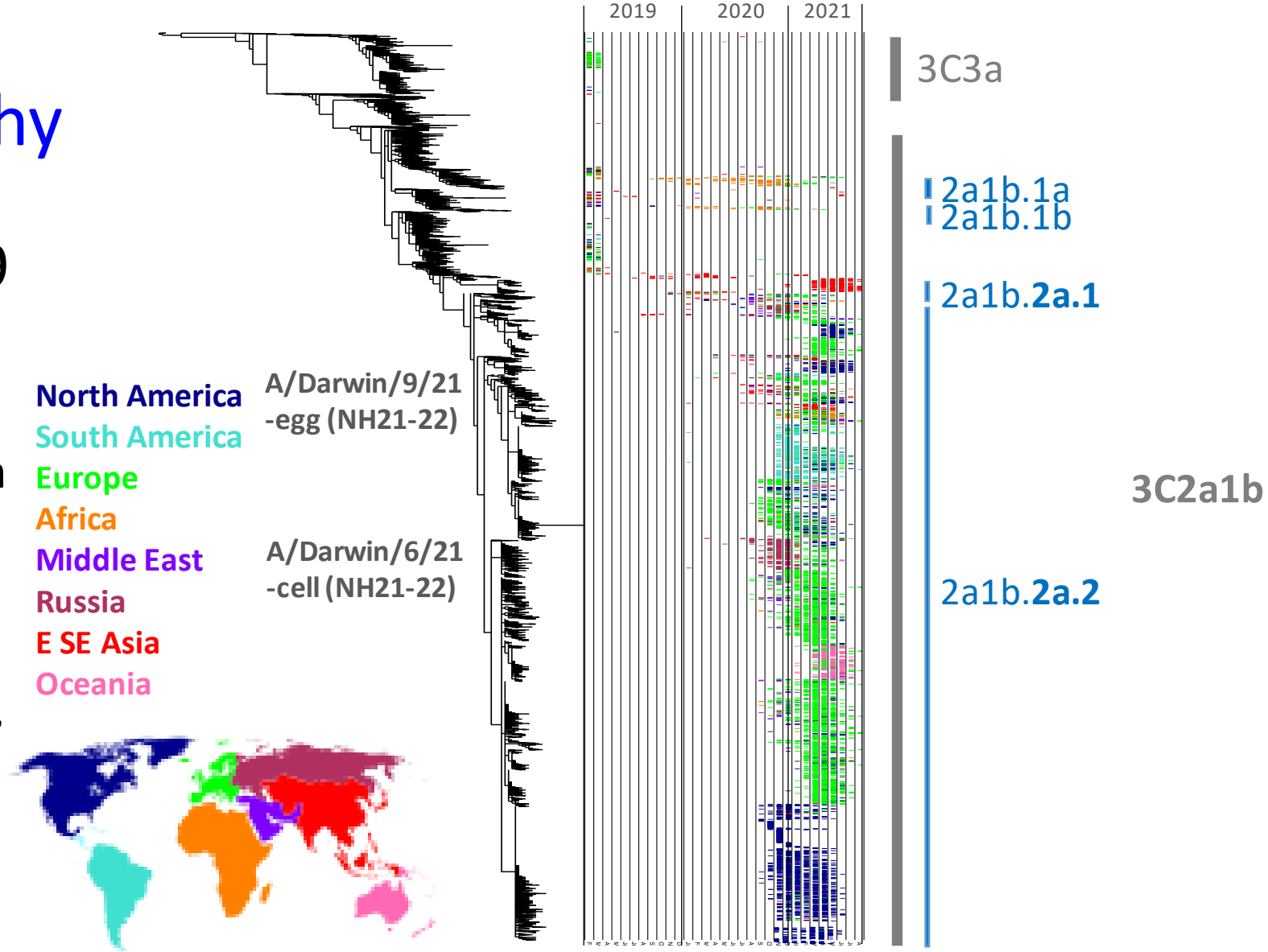


Colour intensity shows the percent of influenza A(H3N2) positive among all samples tested during this period per country

Source: Global Influenza Programme (who.int)

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
    - **2a.2** in Europe, Russia, North and South America increased in 2021-22

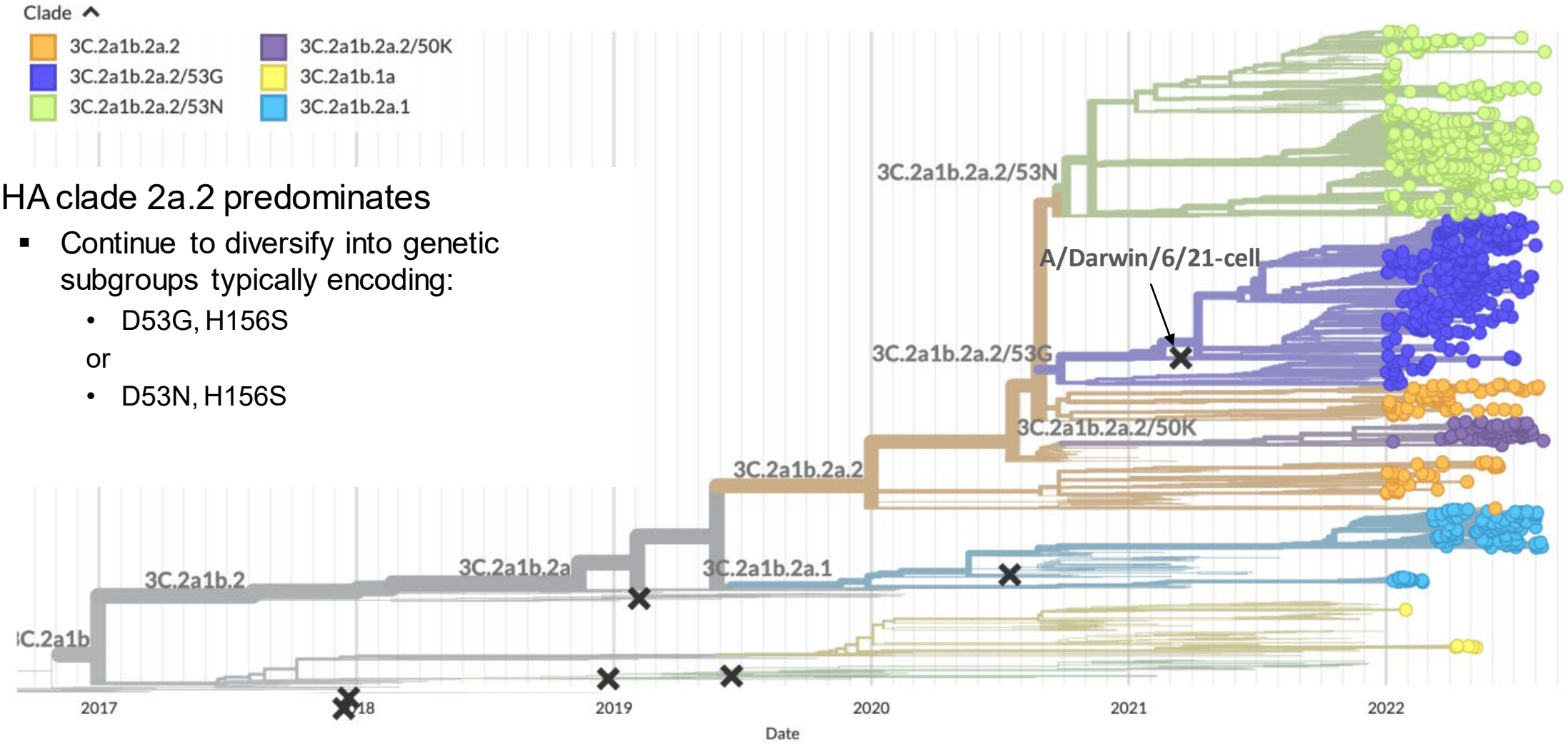


Source: Cambridge Univ., S. James and D. Smith

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

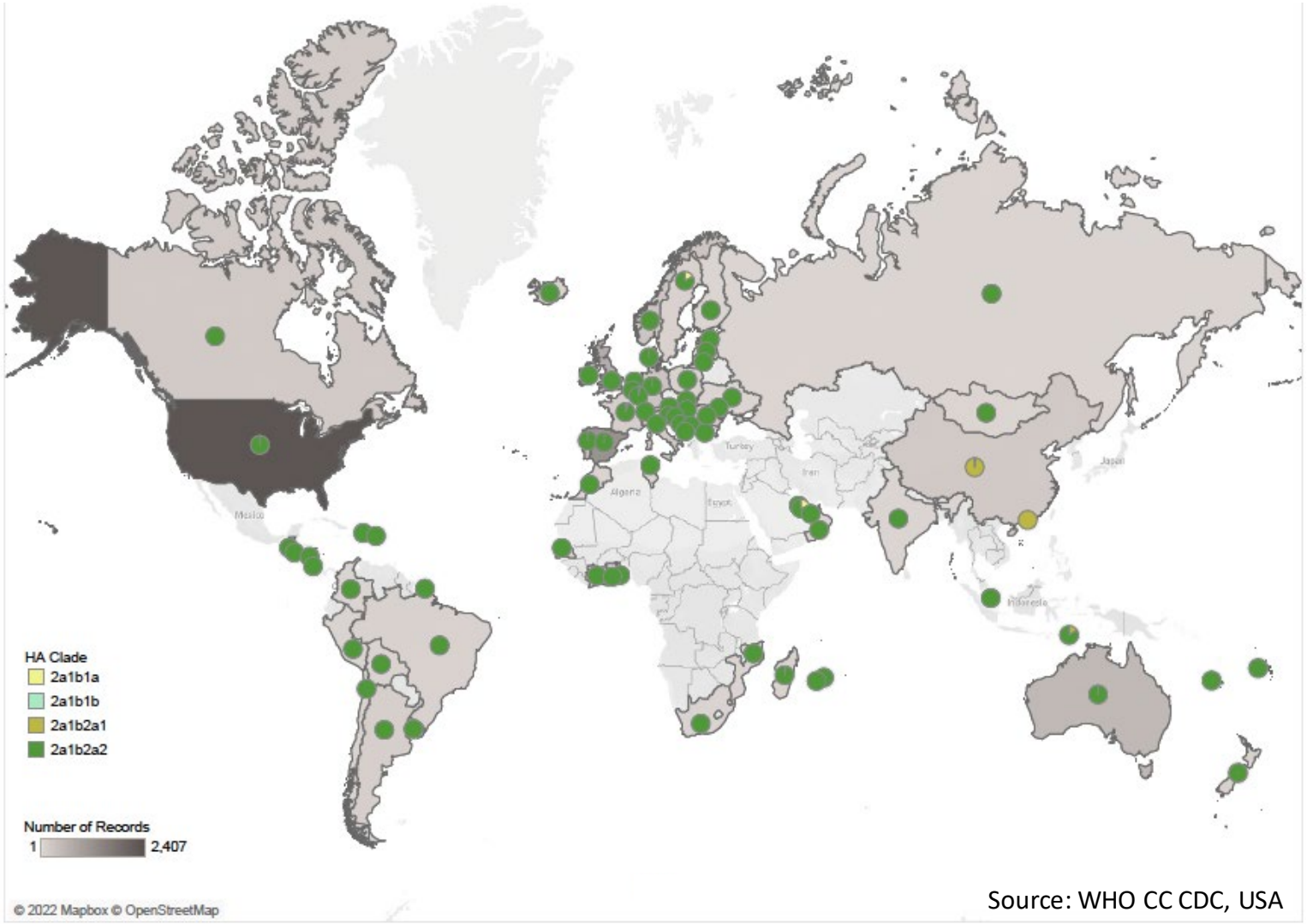
- HA clade 2a.2 predominates
  - Continue to diversify into genetic subgroups typically encoding:
    - D53G, H156S

    or
    - D53N, H156S



Source: Nextflu (J. Huddleston, T. Bedford, J. Lee & R. Neher). Based on HA sequences available as of 09/13/2022

Global circulation of A(H3N2) HA clades



Source: WHO CC CDC, USA

- HA clade 2a.2 predominated and showed global distribution
- HA clade 2a.1 circulated in China and Timor Leste

Analysis of A(H3N2) viruses by antisera to antigens recommended for SH 2022

VN Assay

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

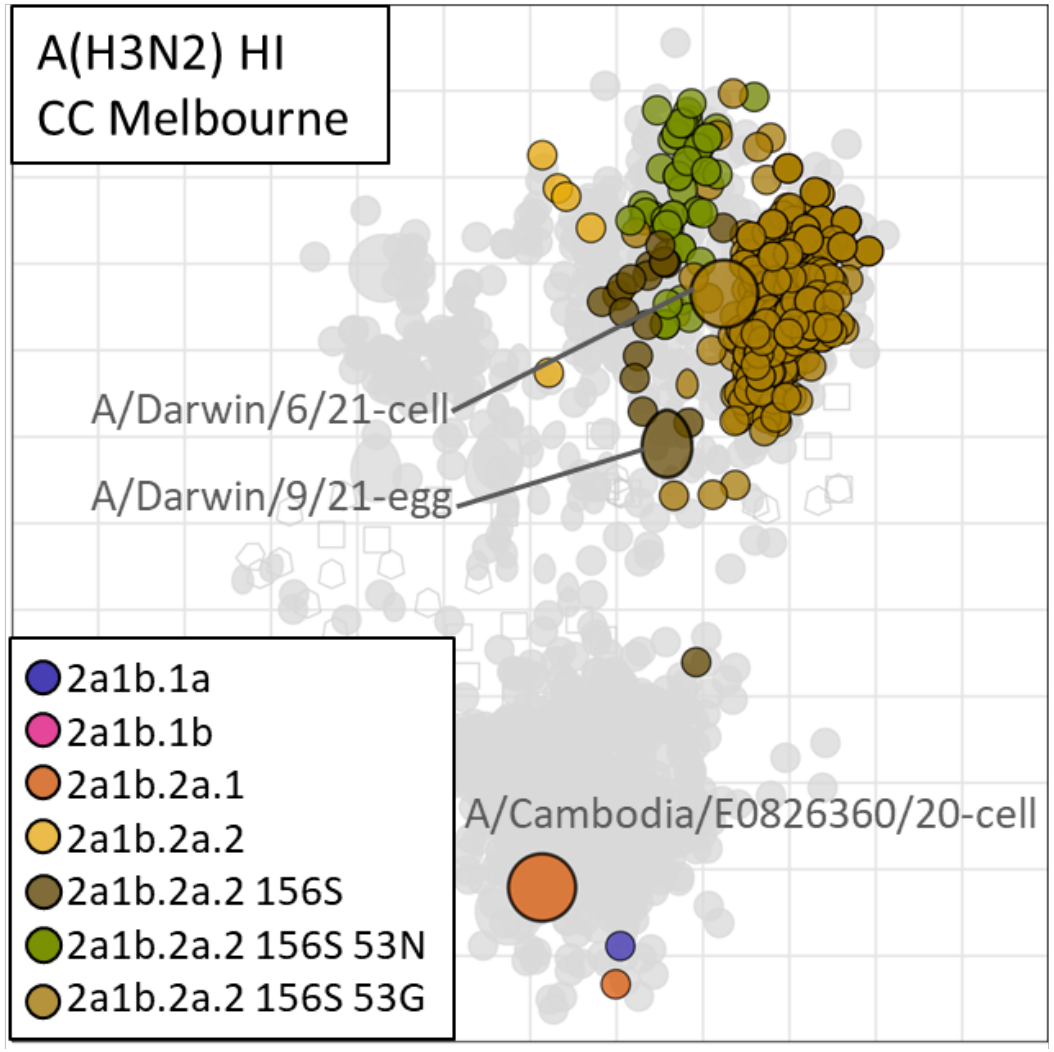
WHO CC	Like (2-4 fold)	Low (≥ 8 fold)
CDC	73 (99%)	1 (1%)
CNIC	60 (100%)	0 (0%)
FCI	202 (98%)	4 (2%)
NIID	17 (100%)	0 (0%)
VIDRL	92 (96%)	4 (4%)
Total	444 (98%)	9 (2%)

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

WHO CC	Like (2-4 fold)	Low (≥ 8 fold)
CDC	69 (93%)	5 (7%)
CNIC	11 (18%)	49 (82%)
FCI	149 (56%)	117 (44%)
NIID	8 (47%)	9 (53%)
VIDRL	80 (83%)	16 (17%)
Total	317 (62%)	196 (38%)

*Reference viruses are in HA clade 3C.2a1b.**2a.2.** Showing data from viruses isolated from swabs collected from 1 Feb – 30 Aug 2022

A(H3N2) antigenic cartography

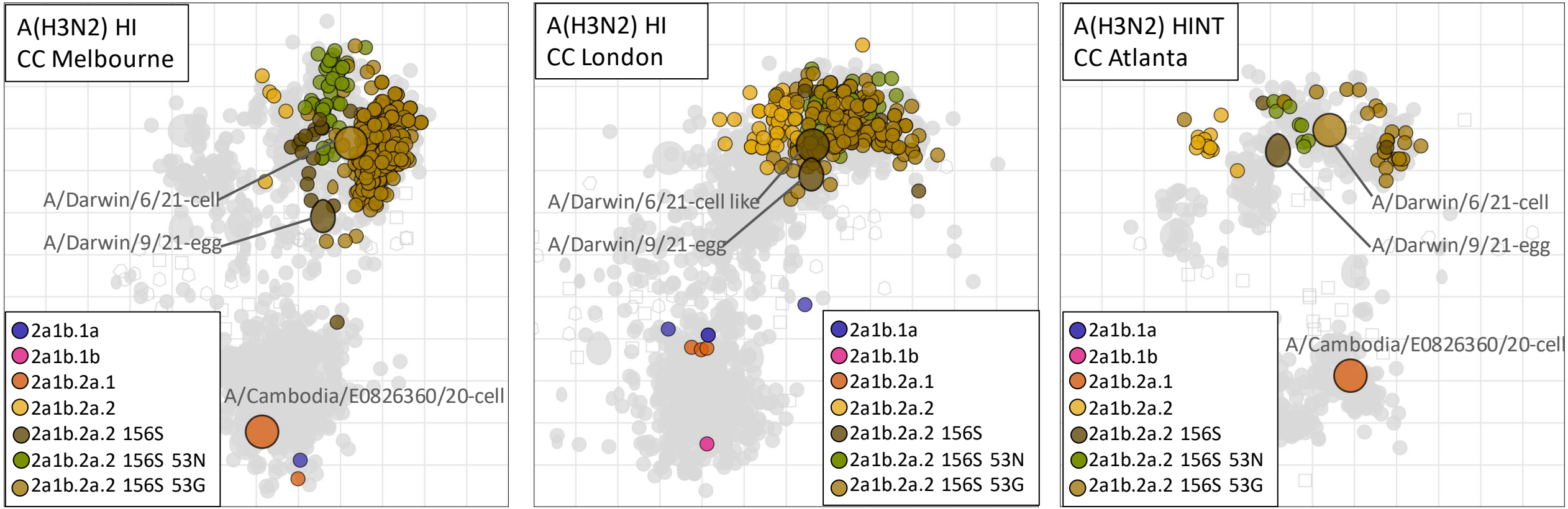


Since March 2022 (older viruses in grey)

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

- HA clade 2a.2 viruses are antigenically distinct from clade 2a.1, 1a and 1b
- SH-23 vaccine virus recommendations
  - A/Darwin/6/2021-cell and A/Darwin/9/2021-egg
  - Antigenically similar to other 2a.2 viruses from multiple subclades (e.g., H156S, H156S & D53G, H156S & D53N)
  - Various subgroups are antigenically closely related (i.e., form overlapping clusters)

A(H3N2) antigenic cartography shows consistent relationship across WHO collaborating centers



Since March 2022 (older viruses in grey)

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

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

- Serum panels show good reactivity with the representative 2a.2 test viruses
  - Geometric mean VN titers against recent representative A(H3N2) 2a.2 and 2a.1 viruses were not significantly reduced compared to titers against cell culture-propagated A/Darwin/6/2021

				SH-2022 Vaccine (2a.2)	2a.2							2a.1
					+D53G +H156S *DAR/6 SIAT	+H156S +D186N +D225G DAR/9 EGG	+D53G +H156S CA/01 SIAT	+D53G +H156S +L157I +S262N MD/02 SIAT	+D53N +N96S (CHO+) +H156S +I192F AK/01 SIAT	+S205F +A212T PA/01 SIAT	+E50K +I140K FL/57 SIAT	- CAM/E0826360 SIAT
A/DARWIN/6/2021 SIAT	Adult	Australia	ccIIV4 (Flucelvax)		171	√	√	√	113	√	94	√
			IIV4		128	√	√	√	√	√	√	√
	>64 Y	Australia	aIIV4		91	√	√	√	√	√	√	√

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/CALIFORNIA/01/2022 (CA/01); A/CAMBODIA/E0826360/2020 (CAM/E0826360); A/DARWIN/6/2021 (DAR/6); A/DARWIN/9/2021 (DAR/9); A/FLORIDA/57/2022 (FL/57); A/MARYLAND/02/2021 (MD/02); A/PENNSYLVANIA/01/2021 (PA/01).

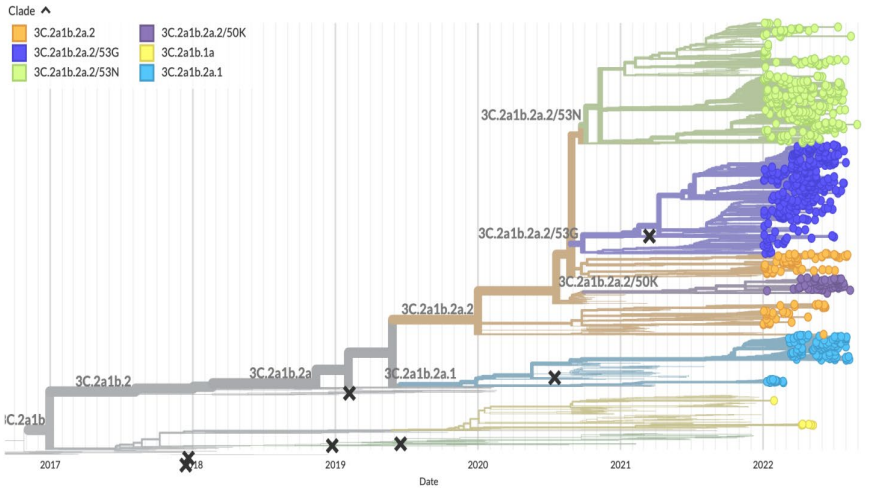
Source: WHO CC CDC, USA

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

GMT ratio lowerbound (90% CI)
0.0 — 1.0

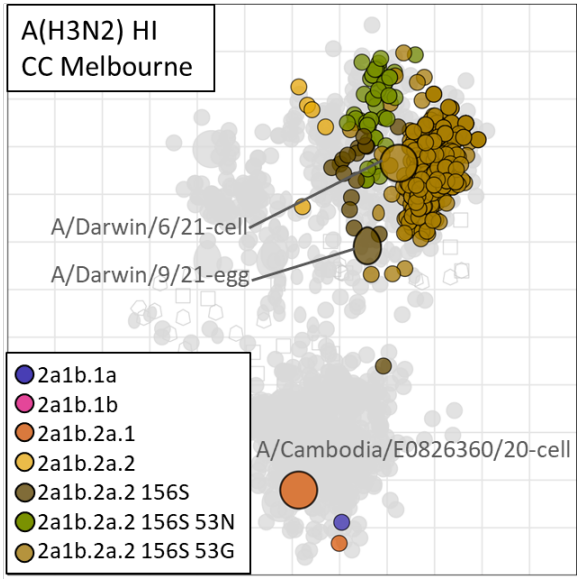
A(H3N2) summary (1): global circulation and phylogeny

- A(H3N2) subtype viruses predominated globally
- HA phylogenetics:
  - The HA of the majority of circulating A(H3N2) viruses in this period belonged to **2a.2** subclade (i.e., 3C.2a1b.**2a.2**)
    - Continue to diversify into genetic groups that typically encode:
      - H156Q
      - H156S and D53G
      - H156S and D53N
      - D53G
  - HA subclade **2a.1** (i.e., 3C.2a1b.2a.1) viruses predominated in China

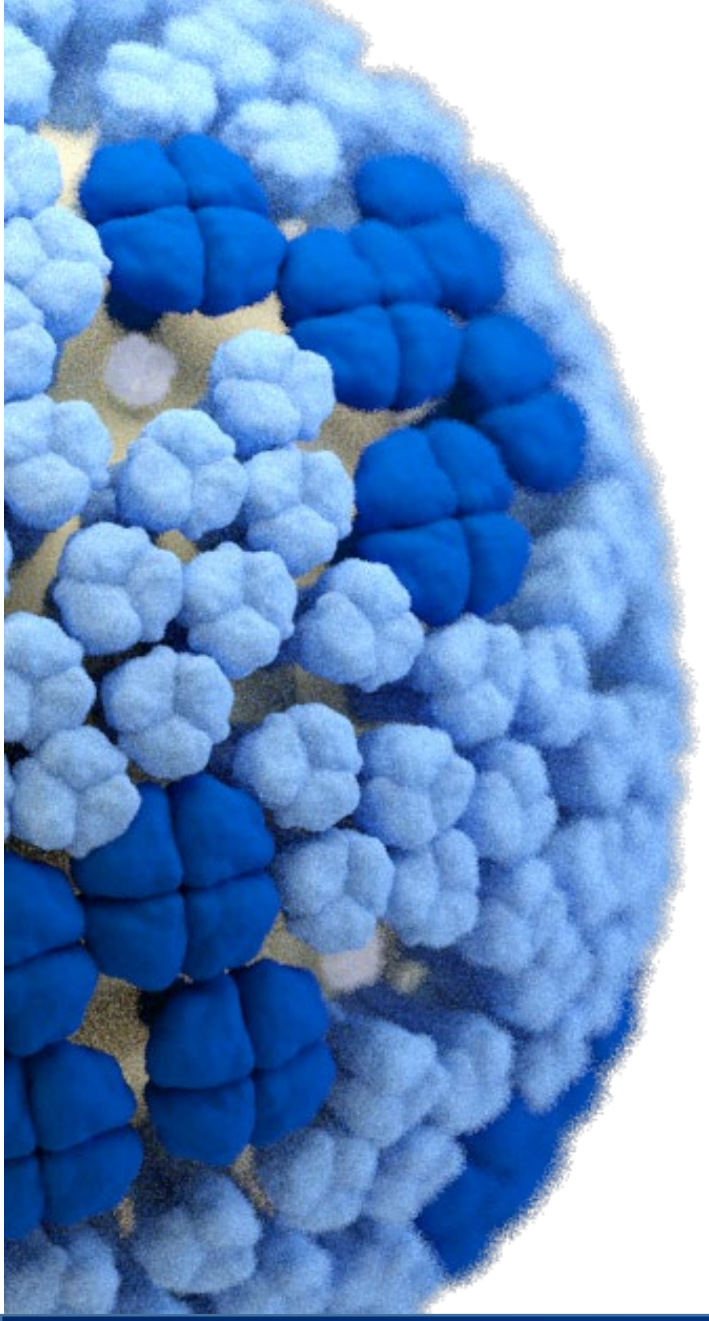


A(H3N2) summary (2): antigenic characteristics and human serology

- Antigenic characteristics
  - Ferret antisera to recommended vaccine viruses (A/Darwin/6/2021-like cell and A/Darwin/9/2021-like egg (HA clade 2a.2) well recognized the majority of viruses circulating in this period
  - Circulating 2a.2 viruses are antigenically related and distinct from 2a.1

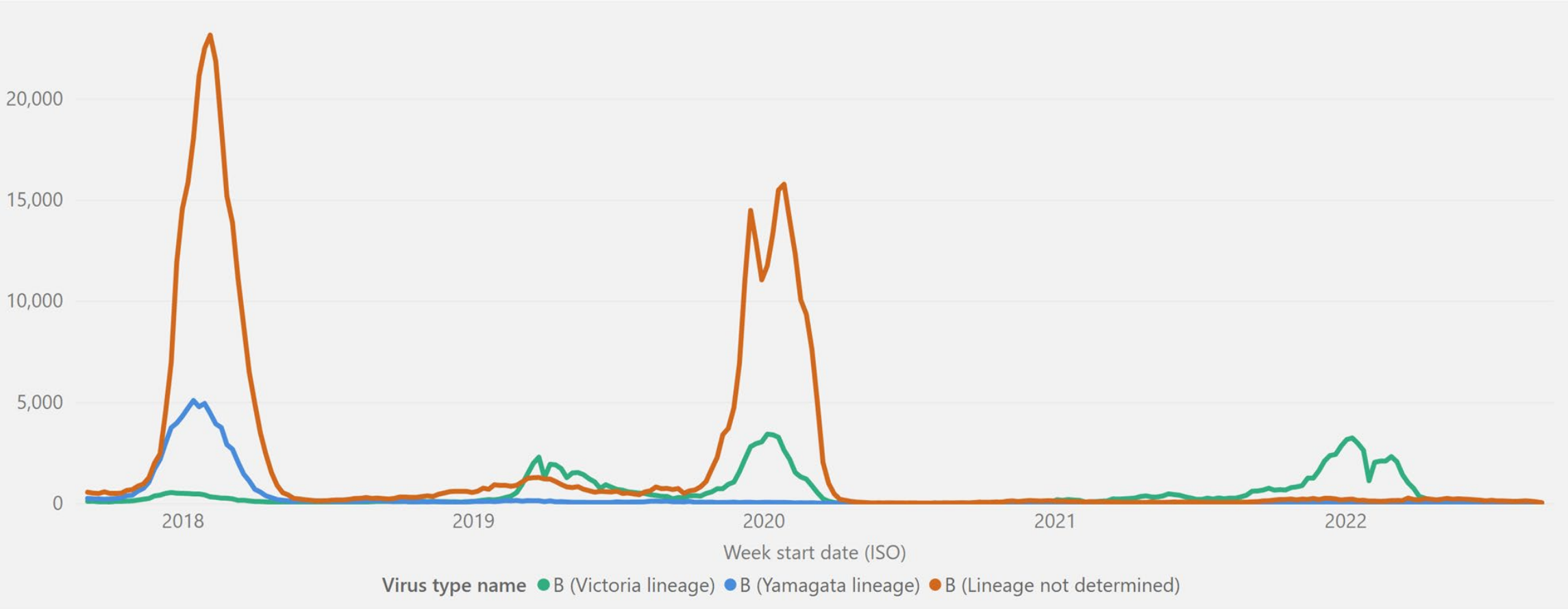


- Human serology studies
  - Serum panels from individuals vaccinated with A/Darwin/6/2021-like and A/Darwin/9/2021-like (2a.2) viruses showed good neutralization of viruses with HA from multiple 2a.2 subclades (e.g., D53N or D53G)



Influenza B Viruses

Global circulation of influenza B viruses

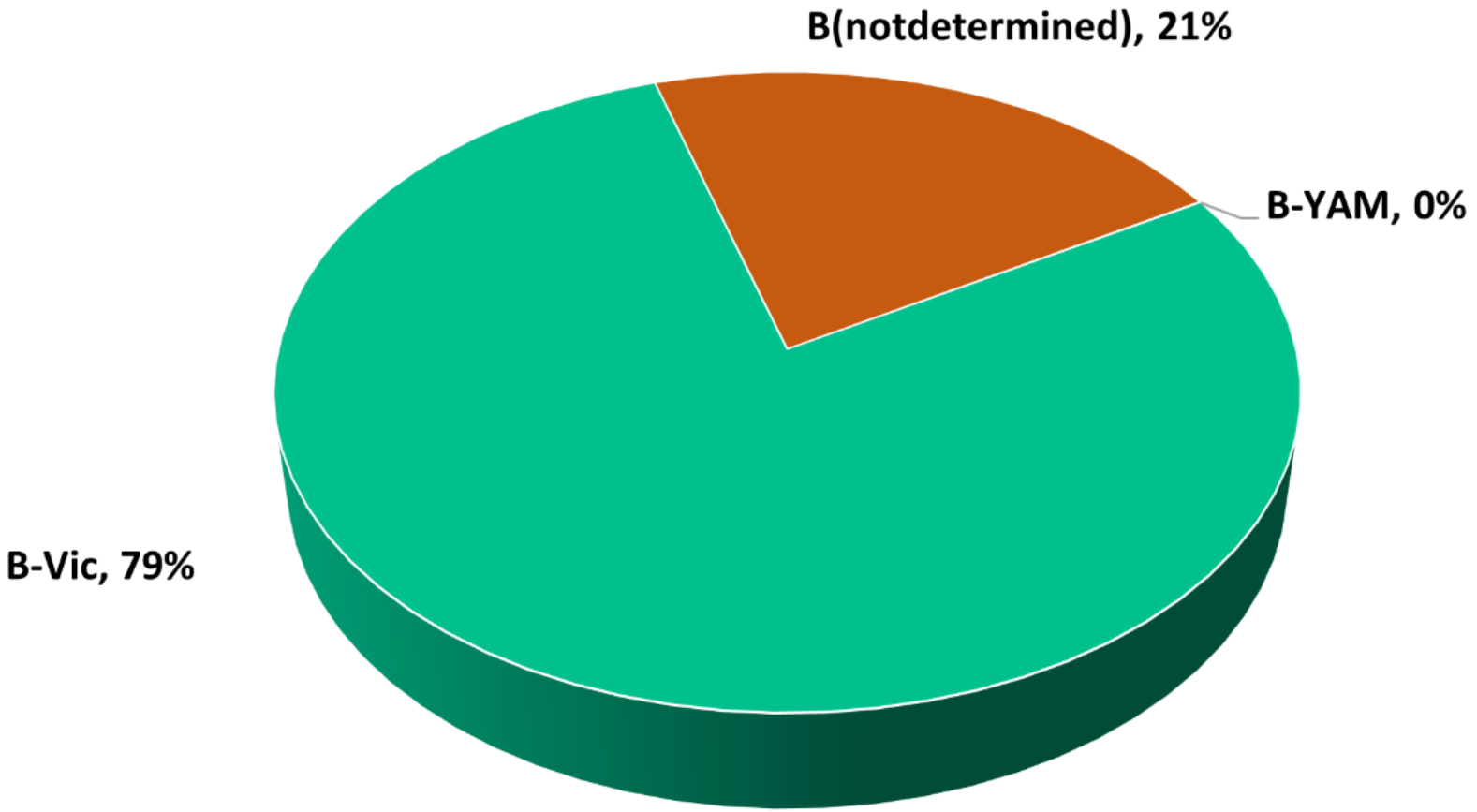


Select week start date (ISO)

9/4/2017 9/5/2022

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

Circulating influenza B virus lineages (Feb – Aug 2022)

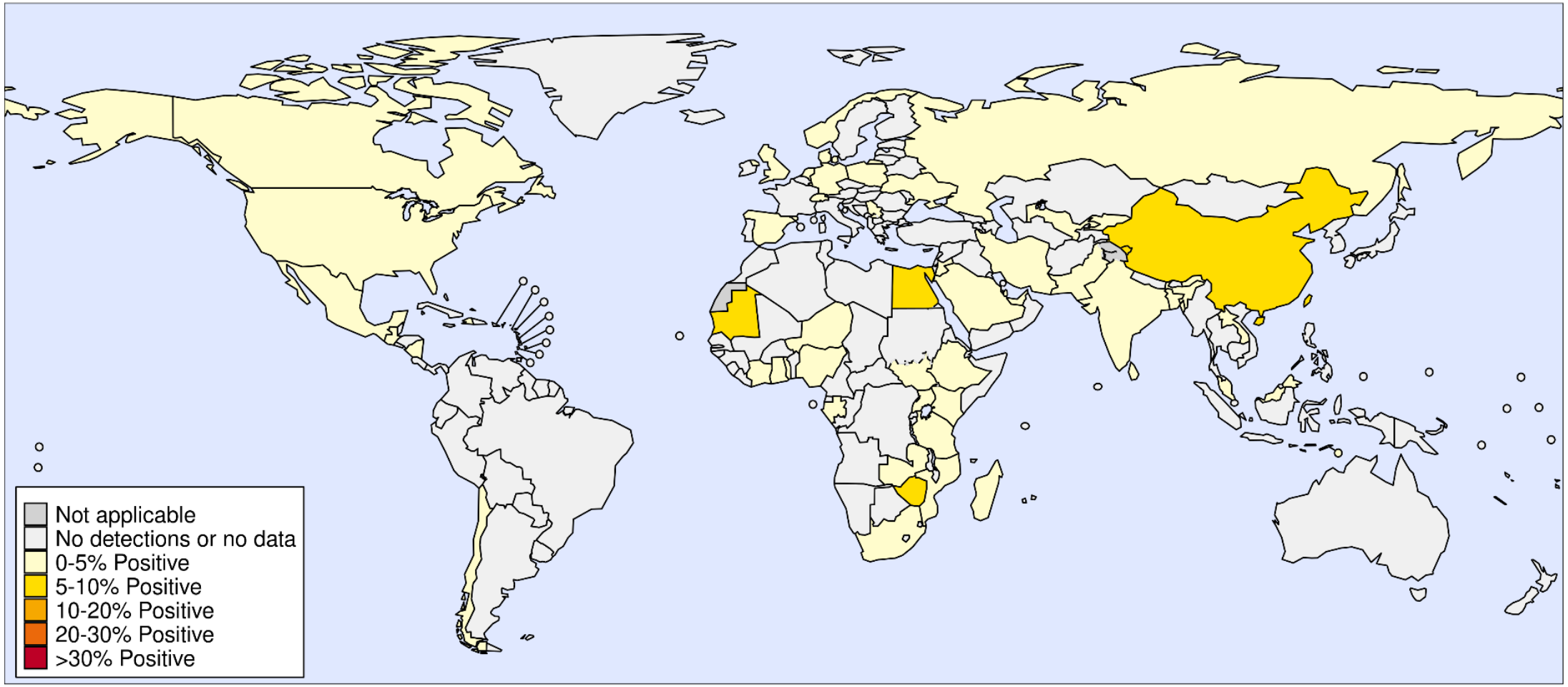


- B lineage summary
  - 79% B/Victoria
  - 0% B/Yamagata
  - 21% not determined

Data source: FluNet, (https://www.who.int/tools/flunet), Global Influenza Surveillance and Response System (17 Sep 2022)

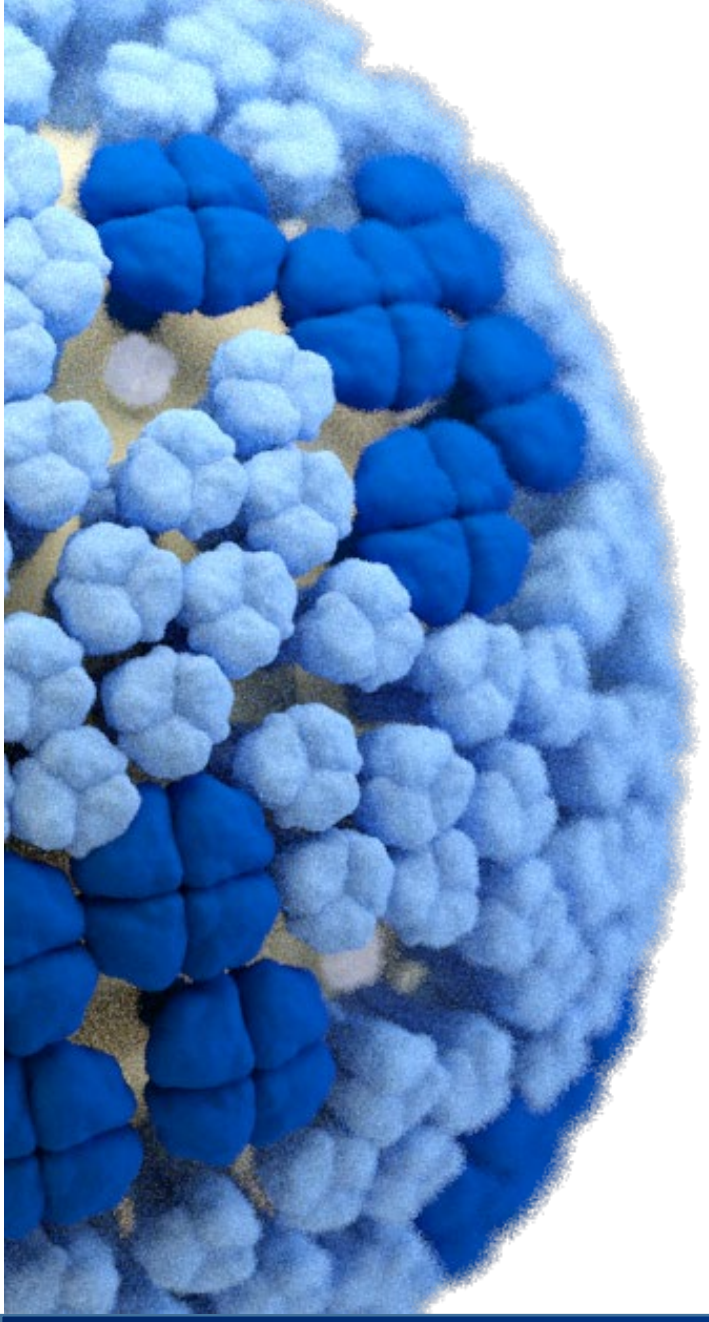
Influenza B virus activity

Influenza B, February 2022 to August 2022, percent of all samples tested



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

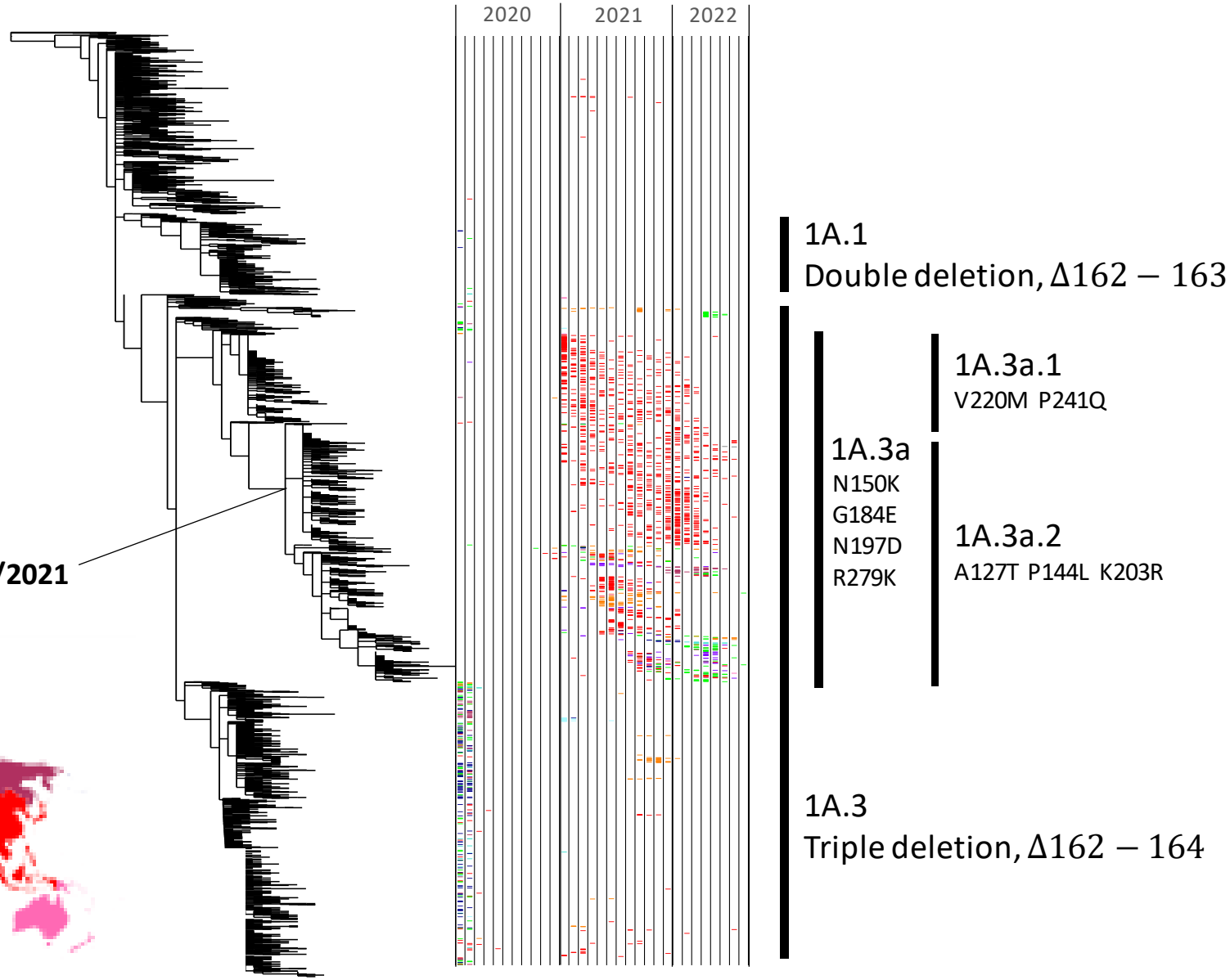
Data source: FluNet, (https://www.who.int/tools/flunet), Global Influenza Surveillance and Response System (9 Sep 2022)



Influenza B/Victoria Viruses

Overview of influenza B/Victoria HA phylogeography

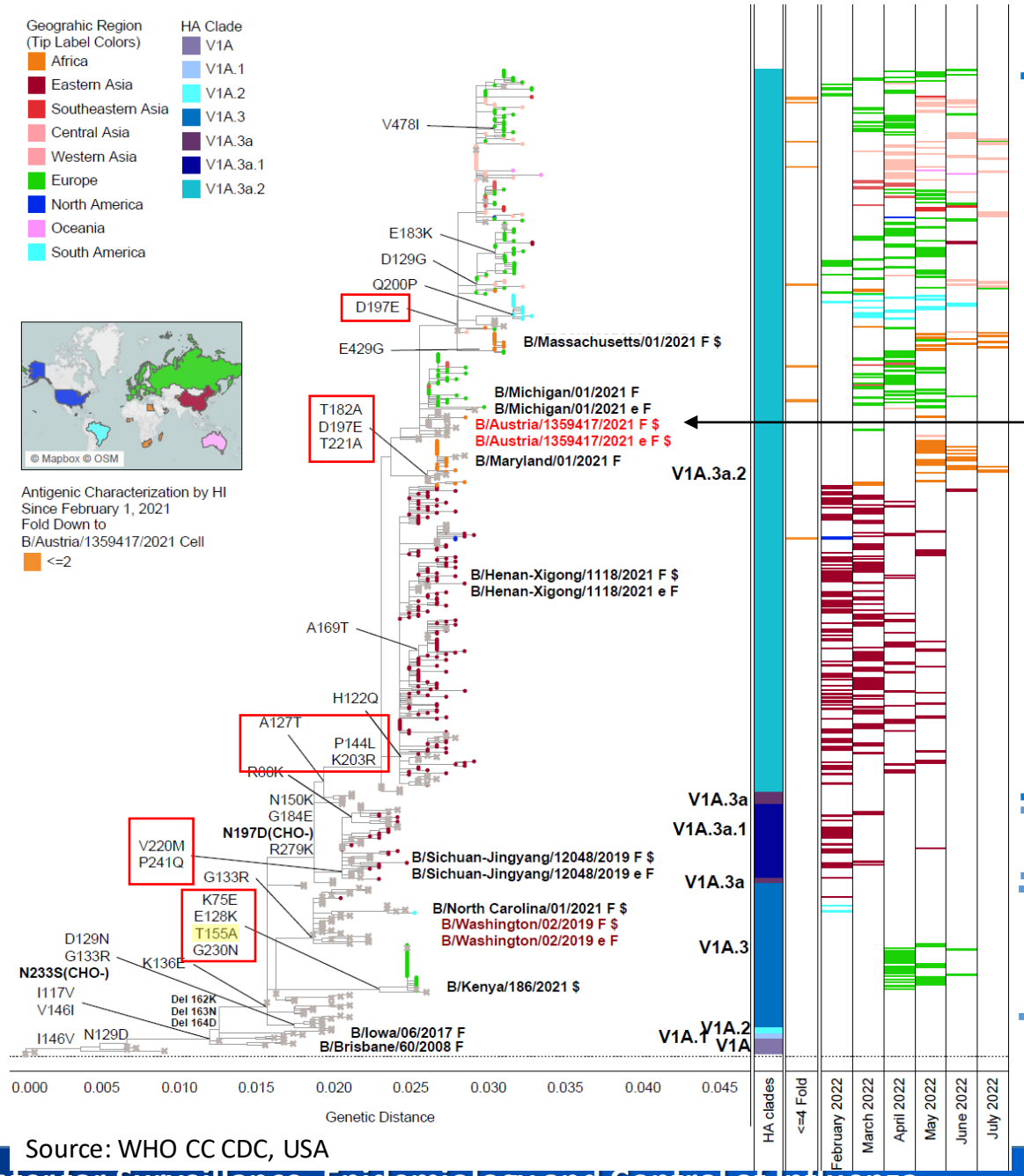
- Two major subclades emerged from the COVID-19 bottleneck
  - 1A.3a.1, primarily in China
  - 1A.3a.2, geographically distributed



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

Recent B/Victoria lineage HA phylogenetics

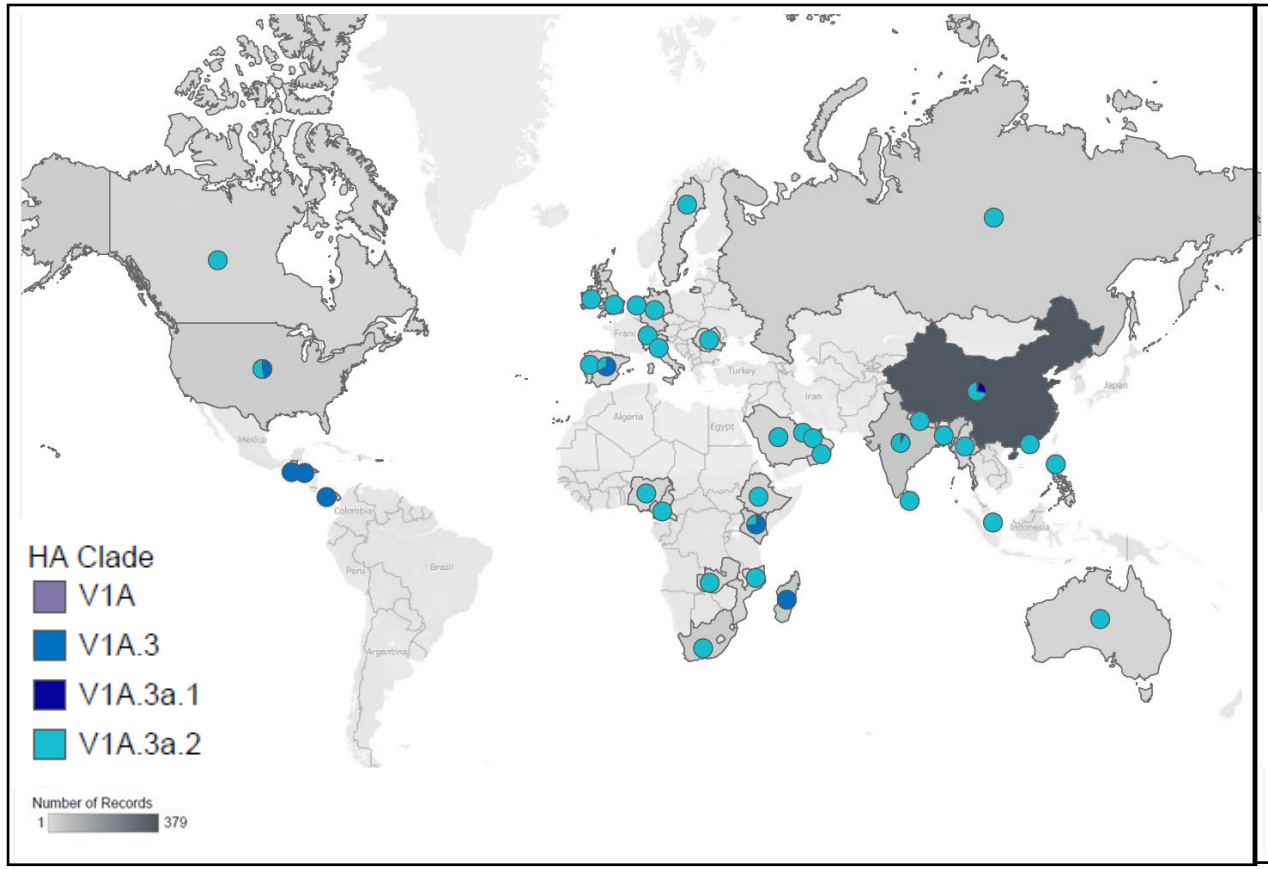
- Clade/sublclade circulation
  - 1A.3 decedents in Kenya and the Netherlands
    - T155A.. (e.g., B/Kenya/186/2021)
  - 1A.3a.1, primarily in China
    - Share V220M, P241Q
  - 1A.3a.2, global distribution
    - Share A127T, P144L, K203R
      - B/Austria/1359417/2021-like
    - Continue to diversify
      - H122Q in China
      - T182A, D197E and T221A in Africa, Europe and North America
      - D197E in globally



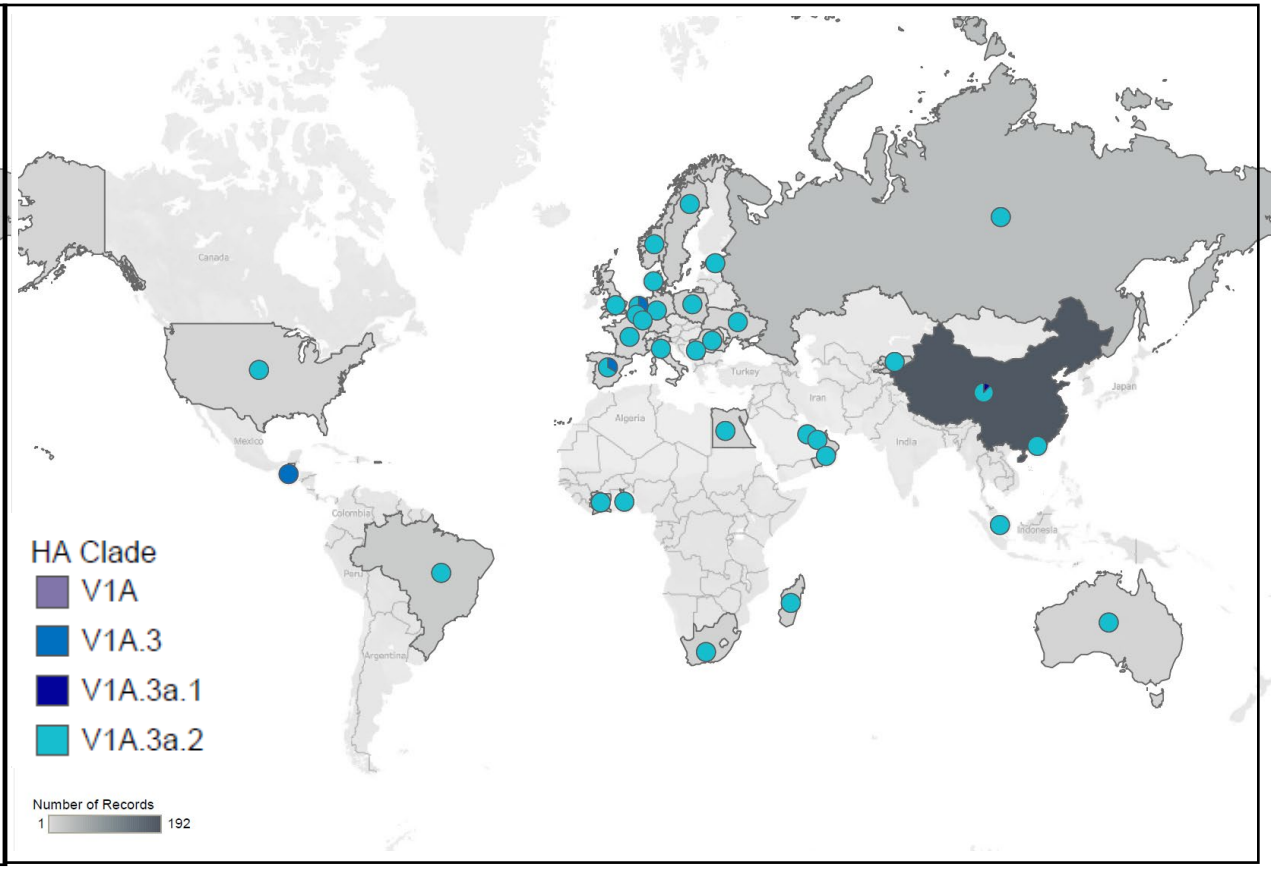
Source: WHO CC CDC, USA

Global B/Victoria HA clade diversity

Collection Dates
September 1, 2021- January 31, 2022



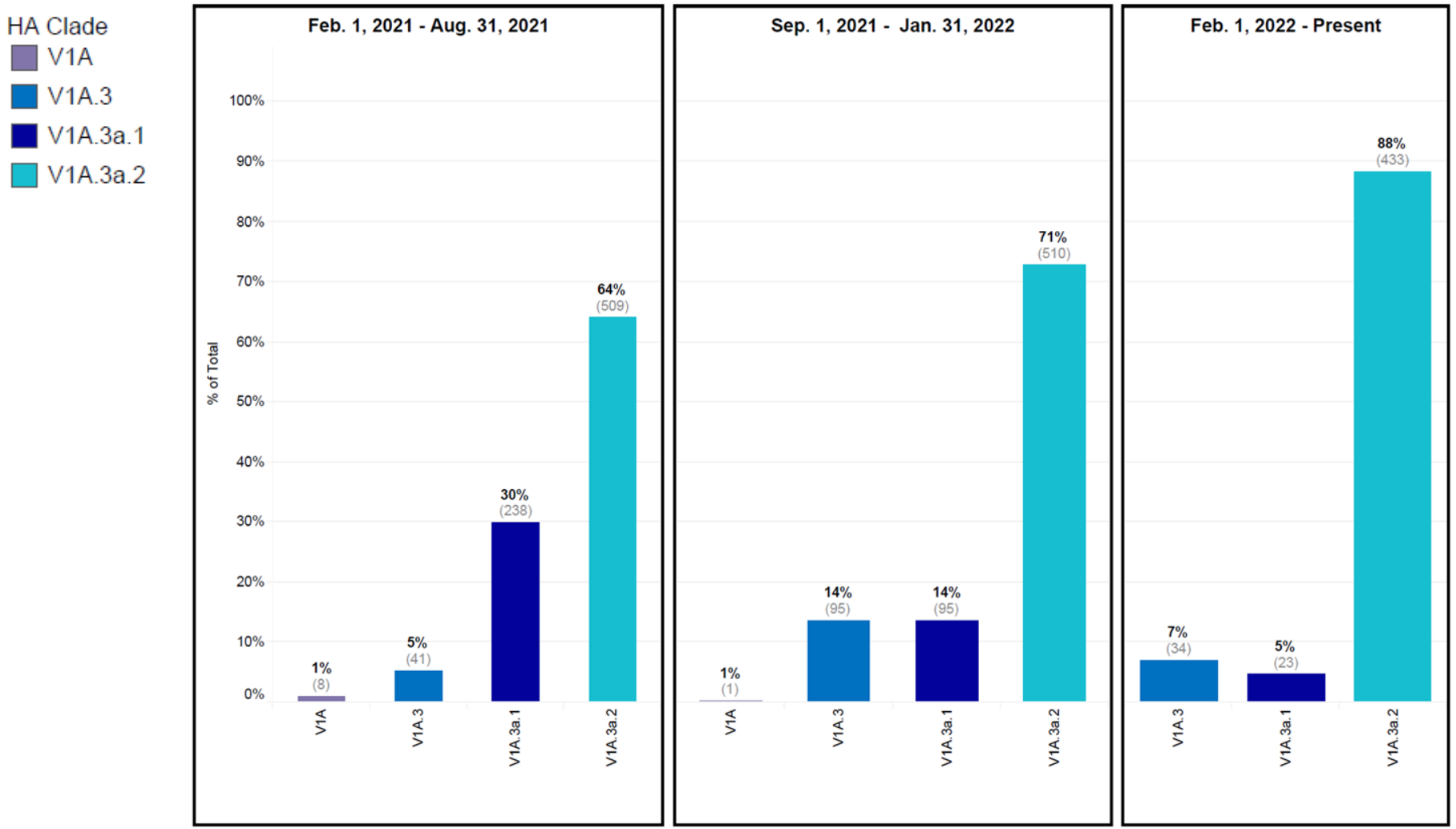
Collection Dates
February 1, 2022- August 31, 2022



Based on HA sequence availability

Source: 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 southern hemisphere 2022 antigens

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

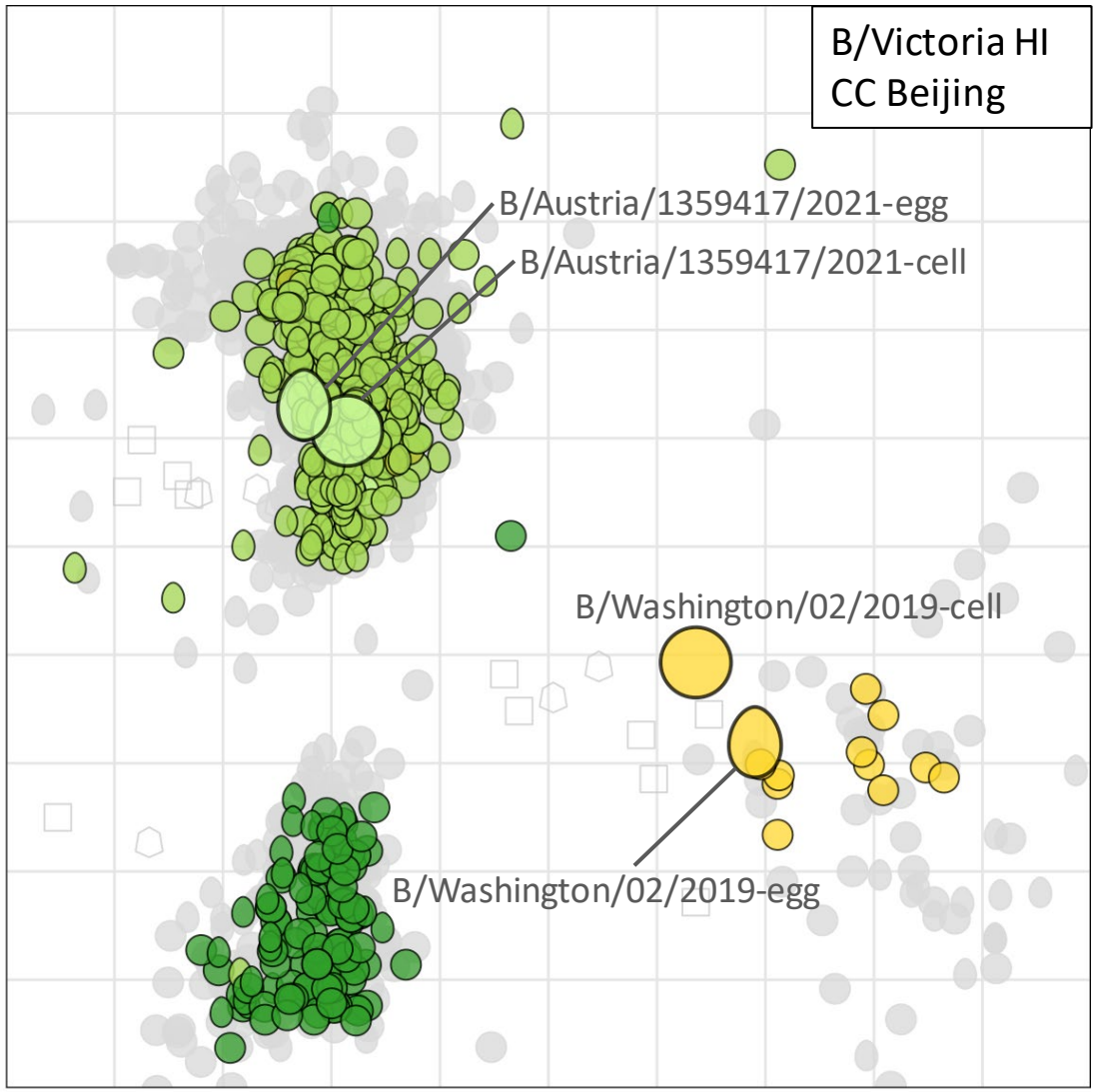
WHO CC	Like (2-4 fold)	Low (≥ 8-fold)
CDC	8 (100%)	0 (0%)
CNIC	1013 (92%)	83 (8%)
FCI	88 (89%)	11 (11%)
NIID	0	0
VIDRL	6 (100%)	0 (0%)
TOTAL	1115 (92%)	94 (8%)

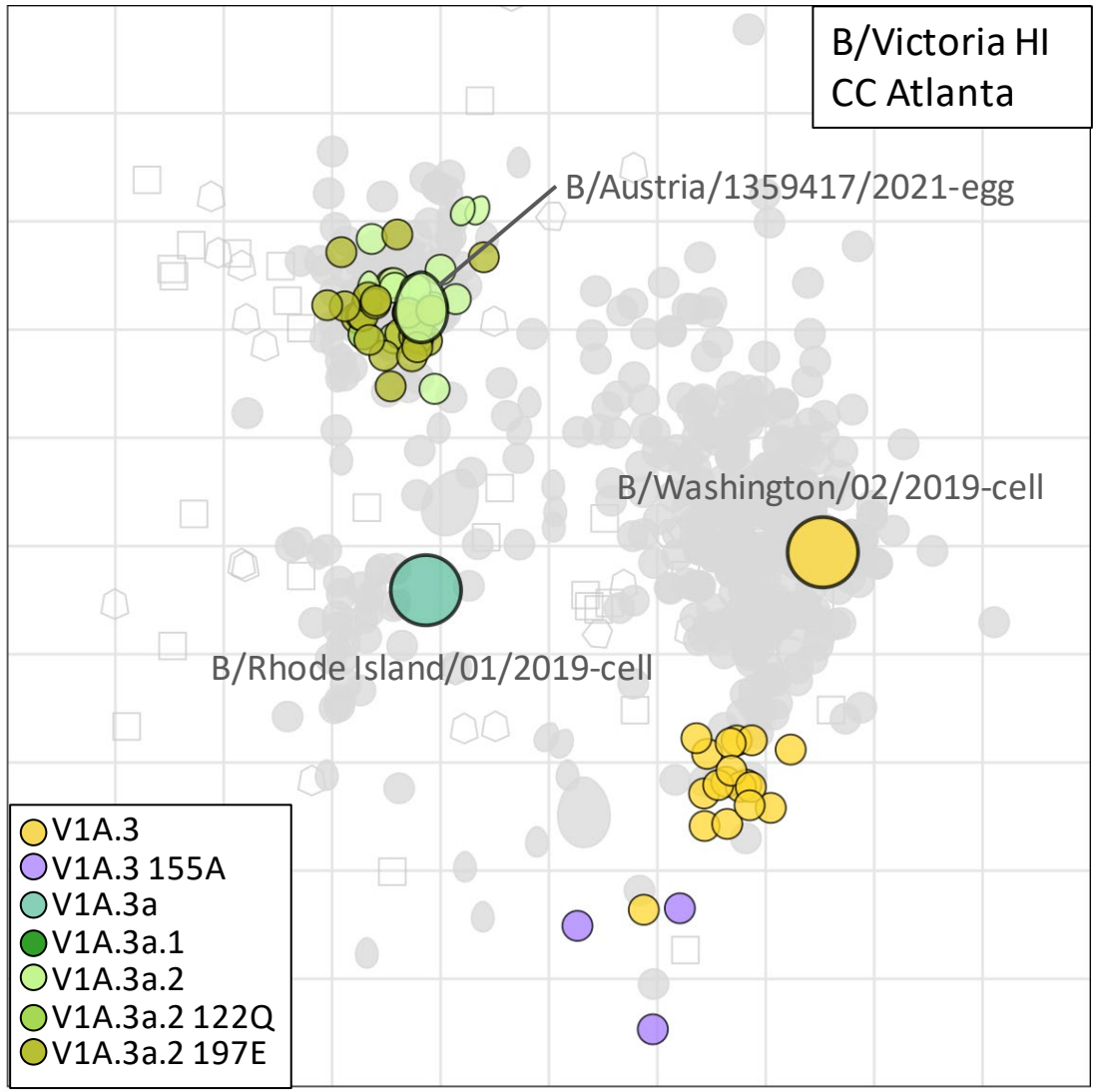
B/Austria/1359417/2021-like (egg)

WHO CC	Like (< 8-fold)	Low (≥ 8-fold)
CDC	8 (100%)	0 (0%)
CNIC	1006 (92%)	90 (8%)
FCI	88 (89%)	11 (11%)
NIID	0	0
VIDRL	6 (100%)	0 (0%)
TOTAL	1108 (92%)	101 (8%)

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

B/Victoria antigenic cartography





Last 12 months September 2021 to August 2022 (older viruses in grey) Source: Cambridge Univ., S. James and D. Smith

Human post-vaccination serum analysis

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

2022 Southern Hemisphere panels

				1A.3a2												1A.3							1A.3a1		
				- AUT/1359417					+D197E MA/01-LIKE						+H122Q HEN/1118-LIKE		+H122Q +INS162K +INS163N +K165DEL GAN/1281	+T182A +D197E +T221A MD/01	- WA/02		+K73E+E128K+T155A+G230N KEN/186	+K73E+E128K+T155A+G230N NLD/10900-LIKE			+N233K (CHO-) NC/01	+V220M +P241Q SIC/12048-LIKE		
				- CELL					MA/01 CELL				POL/95 CELL	SYD/4 CELL	HEN/1118 CELL	SYD/1 CELL	- CELL	- CELL	- CELL		- CELL	NLD/10900 CELL		NLD/11263 CELL	- CELL	SIC/12048 CELL		BEI/1540 CELL
				CDC	CBER	NIBSC	NIID	VIDRL	CDC	CBER	NIBSC	NIID	NIBSC	VIDRL	CDC	VIDRL	NIBSC	CBER	CDC	NIID	CDC	NIBSC	NIID	VIDRL	CDC	CDC	CBER	NIBSC
B/AUSTRIA/ 1359417/2021 CELL	Adult	ccIIV4 (Flucelvax)	Australia	143	57	23	226	71	√	√	X	√	X	√	√	√	X	√	√	√	68	16	√	√	96	√	36	X
		IIV4	Australia	164	62	80	229	80	√	√	√	√	√	√	92	√	√	√	103	√	43	34	109	50	92	√	23	√
	Elderly	aIIV4	Australia	127	56	34	241	72	√	√	X	√	X	√	88	√	X	√	42	117	33	10	99	46	48	65	27	X
									0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (66.7)	0 (0.0)	0 (0.0)	0 (0.0)	2 (66.7)	1 (33.3)	3 (100.0)	3 (100.0)	2 (66.7)	2 (66.7)	3 (100.0)	1 (33.3)	3 (100.0)	0 (0.0)

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.

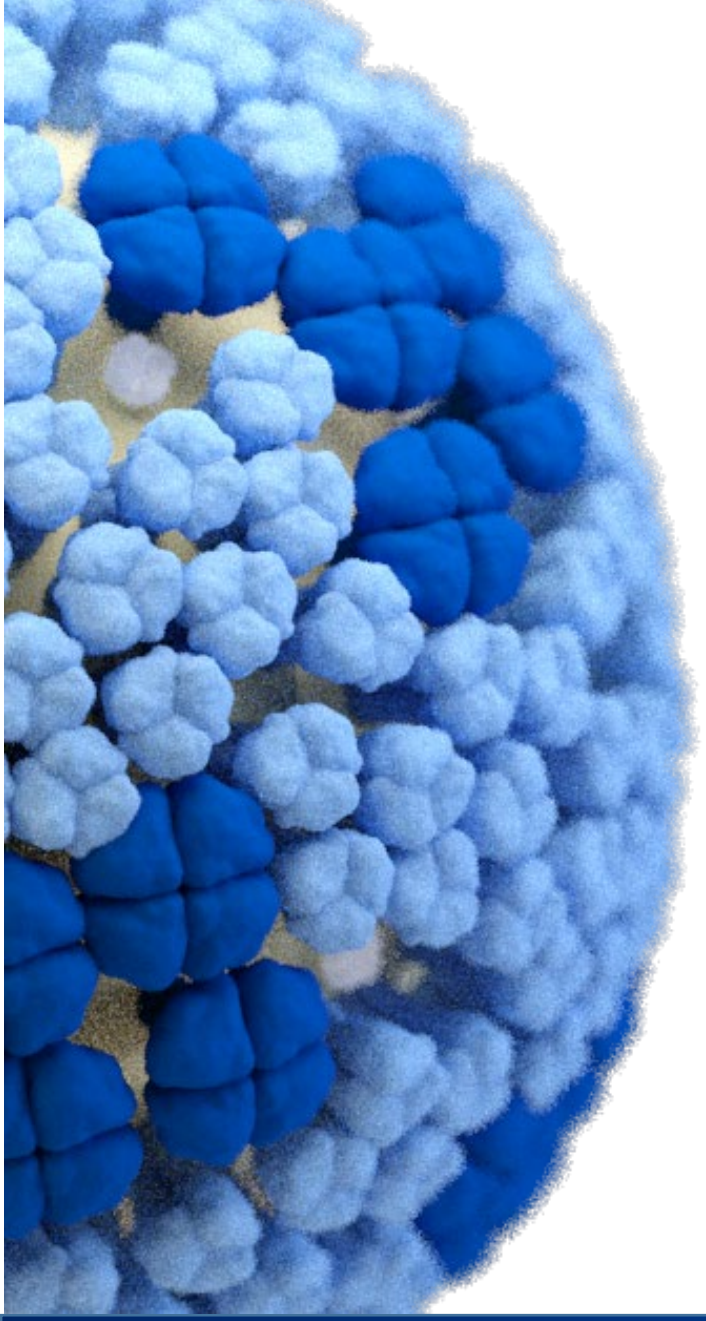
Included Strains: B/AUSTRIA/1359417/2021 (AUT/1359417); B/BEIJING-CHAOYANG/1540/2022 (BEI/1540); B/GANSU-BAIYIN/1281/2022 (GAN/1281); B/HENAN-XIGONG/1118/2021 (HEN/1118); B/KENYA/186/2021 (KEN/186); B/MARYLAND/01/2021 (MD/01); B/MASSACHUSETTS/01/2021 (MA/01); B/NETHERLANDS/10900/2022 (NLD/10900); B/NETHERLANDS/11263/2022 (NLD/11263); B/NORTH CAROLINA/01/2021 (NC/01); B/POLAND/95/2022 (POL/95); B/SICHUAN-JINGYANG/12048/2019 (SIC/12048); B/SYDNEY/1/2022 (SYD/1); B/SYDNEY/4/2022 (SYD/4); B/WASHINGTON/02/2019 (WA/02).

Multiple sources: compiled by WHO CC CDC, USA

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

GMT Ratio Lower-Bound (90% CI)
0.000 — 1.000

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 February- August 2022

- There have been no confirmed detections of circulating B/Yamagata/16/88 lineage viruses after March 2020.
  - No B/Yamagata/16/88 lineage viruses have been available for analysis during this period

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

- Only influenza B/Victoria lineage viruses were detected and circulated at modest levels
  - Parts of Asia (e.g., China) and a few countries in Africa (e.g., Egypt) had higher percent positivity
- HA phylogenetics of B/Victoria lineage viruses
  - All HA genes belonged to clade 1A.3, with a deletion of residues 162-164 and a K136E substitution in HA1
    - A small number of viruses derived from 1A.3 continue to circulate and recent viruses from Kenya and Netherlands have evolved substitutions K75E, E128K, T155A and G230N in HA1
  - Subclade 1A.3a viruses with HA genes encoding further substitutions of N150K, G184E, N197D (resulting in the loss of a glycosylation site) and R279K in HA1 have predominated
    - Two HA subclades have emerged:
      - 3a.1 has V220M and P241Q, seen exclusively in China and are decreasing in number
      - 3a.2 has A127T, P144L and K203R seen in Asia, Africa, Oceania, Europe, North America and South America
        - The majority of contemporary 3a.2 HA's also have D197E change

Influenza B virus summary (2): antigenic characteristics

- **Antigenic characteristics of B/Victoria lineage viruses**
  - Subgroup 1A.**3a.1** and 1A.**3a.2** viruses are **antigenically different**
  - Post-infection ferret antisera raised against **B/Austria/1359417/2021-like** viruses (1A.**3a.2**) inhibited the vast majority of recently circulating viruses well (92%) but recognized 1A.**3a.1** poorly
  - A small number of 1A.**3** viruses, detected in Kenya and the Netherlands, were not recognized well by ferret antisera raised against **B/Washington/02/2019-like** viruses (1A.3) and were poorly recognized by ferret antisera raised against **B/Austria/1359417/2021-like** viruses (3a.2)

Influenza B virus summary (3): human serology

- Human serology studies, using the serum panels from the SH 2022 vaccine (B/Austria/1359417/2021-like)
  - Post vaccination sera well inhibited the majority of recent representative B/Victoria lineage viruses from the 3a.2 subgroup
    - Significant reductions in GMTs were detected with most serum panels for small group of viruses from clade 1A.3 that had additional amino acid substitutions K75E, E128K, T155A and G230N

Support and Disclaimer

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