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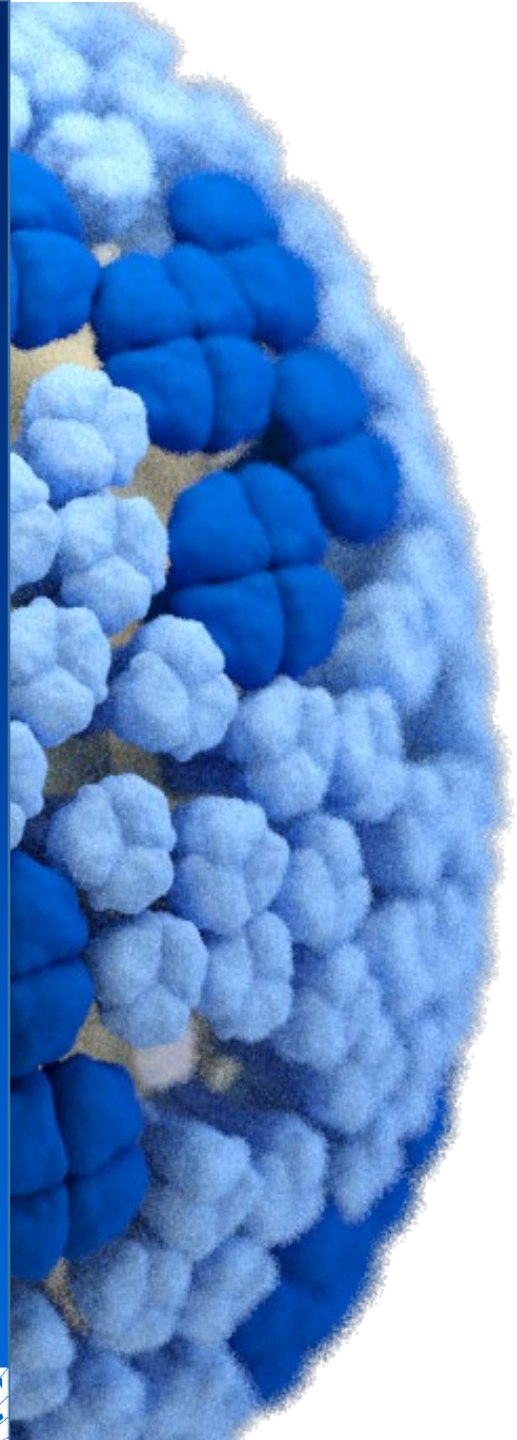

WHO-CC for Influenza | VSDB | Influenza Division | NCIRD

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

Global Influenza Virus Surveillance and Characterization October 5, 2023

David E. Wentworth, Ph.D.

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Director, Coronavirus and Other Respiratory Viruses Division (CORVD)

Influenza Division, National Center for Immunization and Respiratory Diseases

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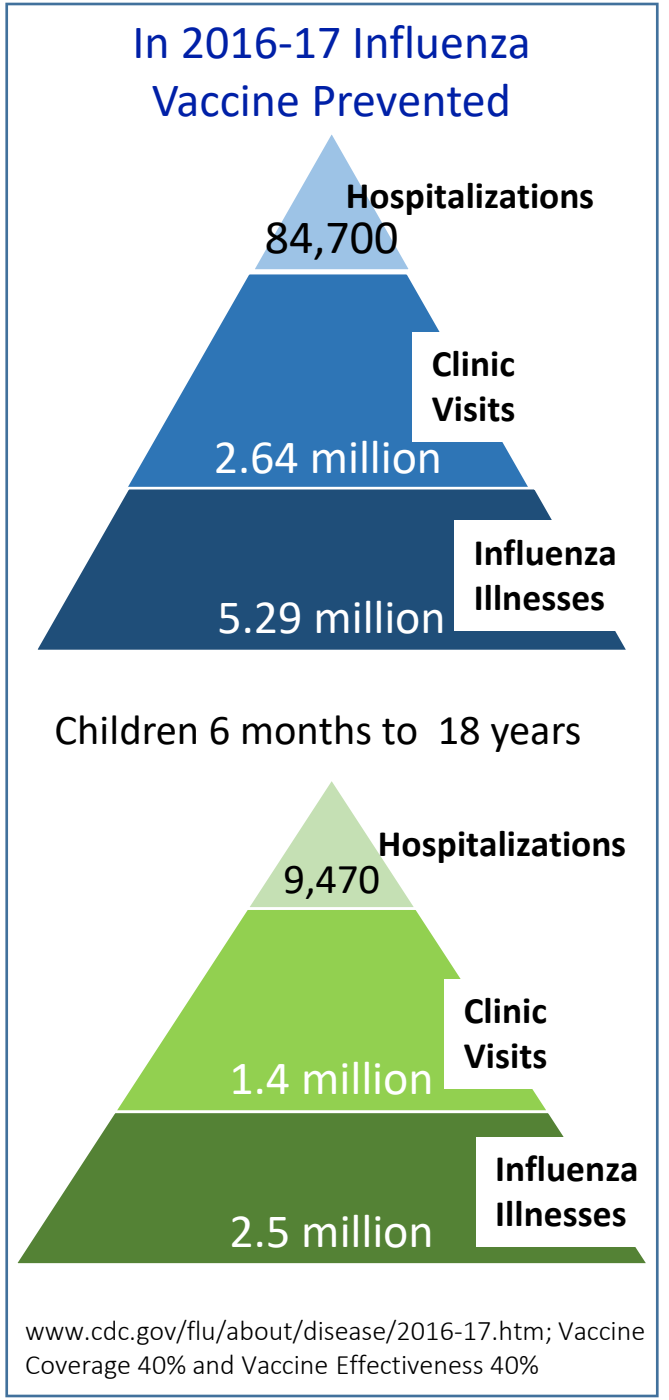
Atlanta, GA 30333

Outline

- Introduction
  - Overview on influenza and vaccine antigen selection process
  - WHO-Vaccine Consultation Meeting, SH 2024 information
- Selected key information supporting committees' recommendations on:
  - A(H1N1)pdm09 - same as N. Hemisphere
  - A(H3N2) - Updated
  - B/Victoria - Vaccine antigen remains unchanged
  - B/Yamagata - Vaccine antigen remains unchanged

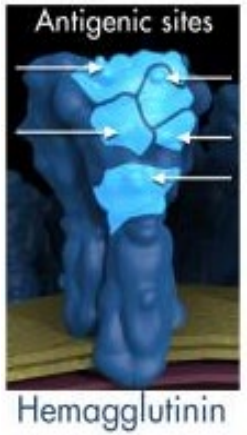


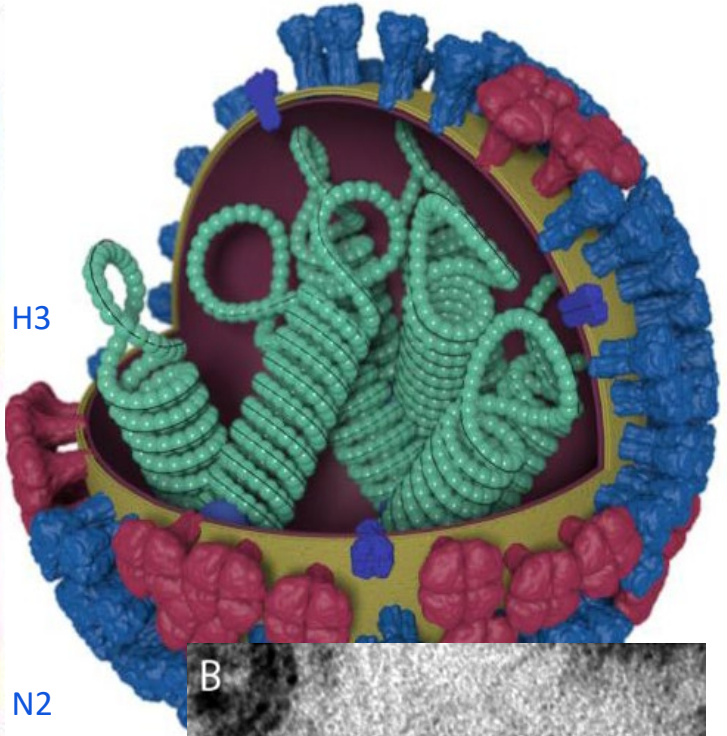
Four different groups of influenza virus infect humans

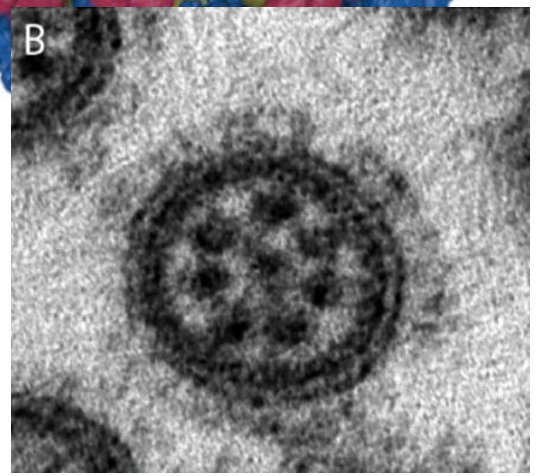
- Co-circulating human influenza viruses
  - Influenza A(H3N2)
  - Influenza A(H1N1)pdm09

  Alphainfluenzavirus
  - Influenza B/Victoria
  - Influenza B/Yamagata

  Betainfluenzavirus
    - Not detected since March 2020
- Major antigens (surface proteins)
  - Hemagglutinin – Virus attachment protein
    - Vaccines induce antibodies to block this protein
  - Neuraminidase – Important for exit from infected cell
    - Antibodies and antiviral drugs inhibit this protein
- Genomes (~13.5Kb): 8 segments negative sense RNA
  - Enables reassortment during coinfections (2 in -> 256 out)



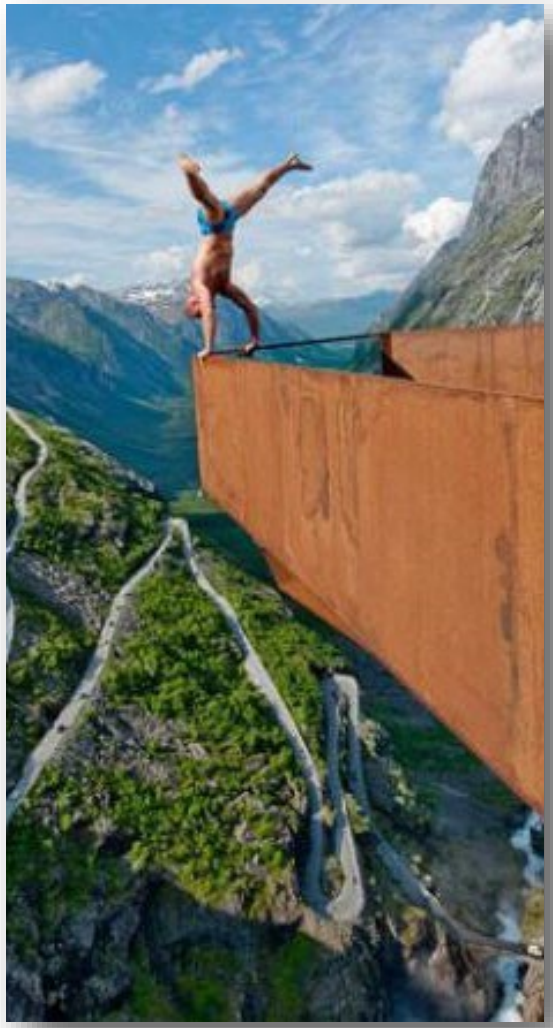




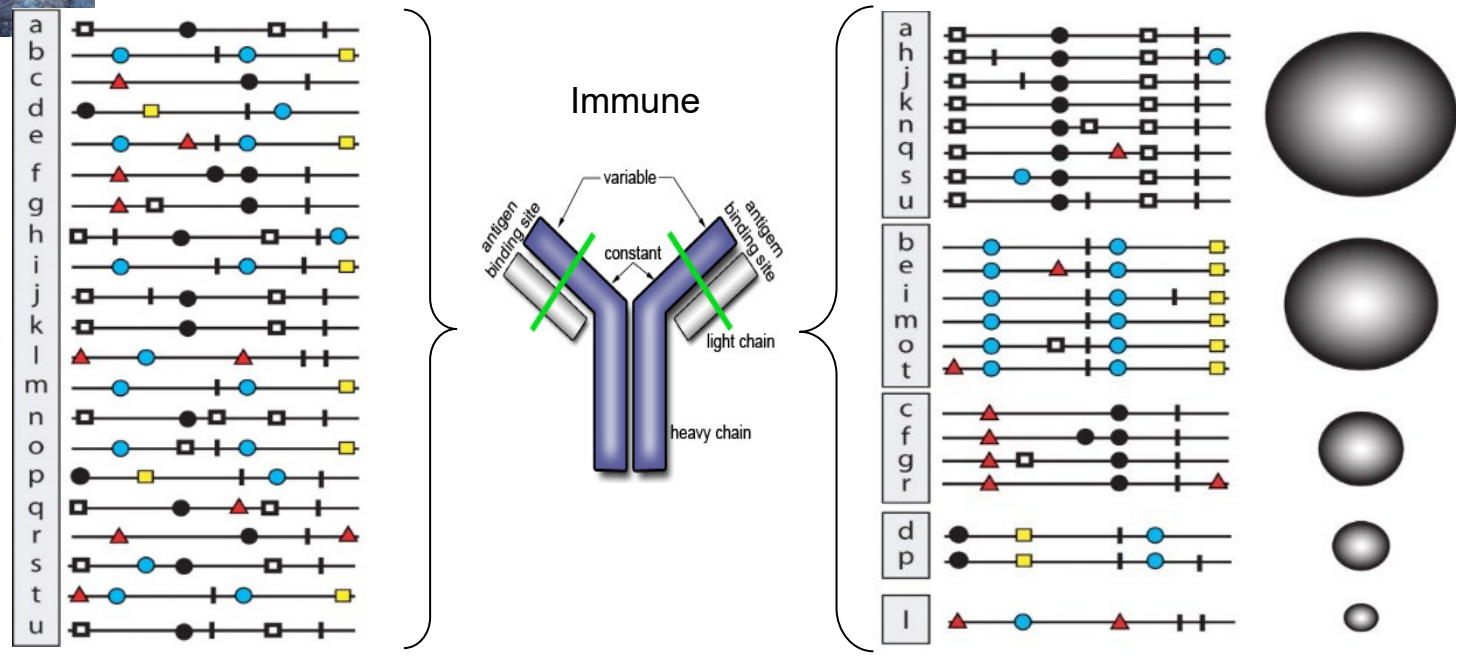
Thin Section EM. T. Noda, et al, Nature 439 (7075):490-492, 2006.

Influenza viruses survive on the edge of catastrophe

- Replication of influenza virus genome is error-prone
  (~1 error/10,000 nucleotides copied)
  - Disadvantage for the virus
    - Close to the threshold of extinction (e.g., many defective viruses every replication cycle)
  - Advantages for the virus
    - Increased adaptability, variants are rapidly selected upon any type of evolutionary pressure (e.g., immune, antiviral drugs, new host)
    - Evolutionary benefit for evading host immunity
- Influenza viruses rapidly and continually evolve
  - Requires continuous comprehensive virus surveillance
  - Necessitates frequent updates to the vaccine



Influenza viruses exist as population of minor variants

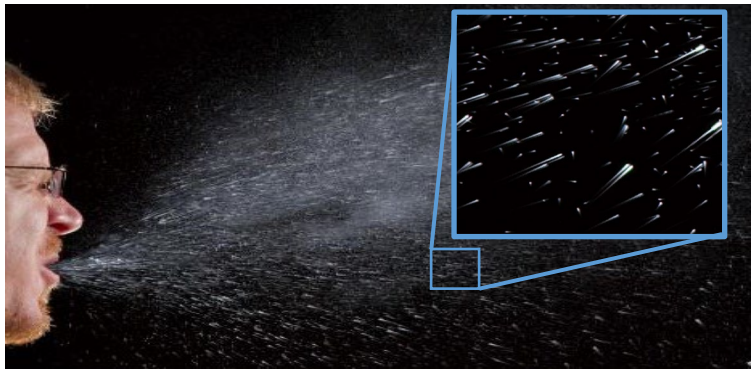


Modified from Domingo E et al. Microbiol. Mol. Biol. Rev. 2012;76:159-216

Evolution

Intra-host

Inter-host



Goal and key questions addressed for virus vaccine antigen recommendations

- Goal
  - Identify antigen(s) that will elicit immunity against diverse/diverging viruses that will likely co-circulate in the future. Ideal antigens confer breadth of immunity to multiple lineages of viruses and reduce risk(s). It is not trying to "match" just one strain of influenza virus that will circulate.
- Key questions for 3-4 viruses targeted by the vaccine
  - Are/were there significant epidemics and where were they?
  - What are the genetic subclades (variants) that have emerged in our population?
  - Are the new emerging variants spreading geographically?
  - Are emerging variant viruses antigenically distinct from prior or contemporary viruses?
  - What is the proportion of the new group(s) and what group(s) is/are likely to predominate?
  - Do current vaccines induce antibodies in humans that protect against co-circulating viruses and/or emerging variants?
  - If new vaccine antigen is warranted, does it elicit antibodies with breadth which recognize multiple important lineages (i.e., does it confer breadth of protection)?

Data Used to Address Key Vaccine Update Questions

- **Epidemiologic and clinical data**
  - Where are recent epidemics occurring, are they unusual in magnitude or disease ?
- **Virus surveillance (GISRS: 70 years in the making)**
  - GISRS labs test 50-150 thousand samples per week year-round and identify influenza positive specimens
    - **Four virus groups**: A(H1N1)pdm09, A(H3N2), B/Victoria, B/Yamagata, enabled by training, diagnostic kits (e.g., Dx rtRT-PCR , EQAP)
  - Regularly share representative specimens to WHO-CCs
- **Genomic characterization of viruses (Influenza changes rapidly and multiple subclades of interest continually emerge)**
  - Primary focus are HA and NA genes, conduct genome constellation analysis and identify reassortants, patterns of parallel/convergent evolution
- **Antigenic characterization of representative emerging viruses**
  - Level of antigenic drift from progenitors and/or vaccine references
    - Naïve animal models used to determine level of antigenic variation ("drift)understand immune response triggered by the proteins on the surface of influenza virus to determine if they would be neutralized by the current vaccine, or have the potential to be a new vaccine
  - Emerging antigenically distinct variants are selected early as new reference viruses for serological analysis and as candidate vaccines (two-way characterization)
- **Post vaccination human serology studies**
  - Comparative analysis of cocirculating antigenic variants to identify those that pose the greatest risk of immune escape
- **Vaccine effectiveness studies (global consortium)**
  - VE lower than expected, decreasing and/or show clade/subclade specific VE differences identified (data on the previous selections and their continued utility)
- **Data integration and comparison among WHO-CCs (shared data methods, reagents, and viruses)**
  - Influenza epidemiology, surveillance, phylogenetics, phylogeography, and antigenic data integration
  - Antigenic chartography, fitness forecasting
- **Availability and characteristics of new candidate vaccine virus antigens**
  - Data generated that illustrates the new antigens induce antibodies that neutralize viruses most likely to co-circulate in upcoming seasons or are cross-protective (progenitors and/or emerging variants)

WHO-Vaccine consultation meeting for the southern hemisphere 2024 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 worldwide
- **WHO Consultation Meeting held 25 – 28 Sep 2023:** data review, analysis and conclusion
  - A hybrid of in-person and virtual meeting
  - Chaired by Drs David Wentworth and Nicola Lewis

  - 10 Advisers: Directors of WHOCCs and ERLs
    - Disclosure of interests at the start of meeting
  - 33 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 29 Sep 2023**

WHO vaccine recommendations for the southern hemisphere 2024

It is recommended that vaccines for use in the 2024 southern hemisphere influenza season contain the following:

Trivalent: Egg-based Vaccines
- **an A/Victoria/4897/2022 (H1N1)pdm09-like virus antigen*;**
- **an A/Thailand/8/2022 (H3N2)-like virus antigen**; 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 antigen*;**
- **an A/Massachusetts/18/2022 (H3N2)-like virus antigen**; and**
- **a B/Austria/1359417/2021 (B/Victoria lineage)-like virus antigen.**

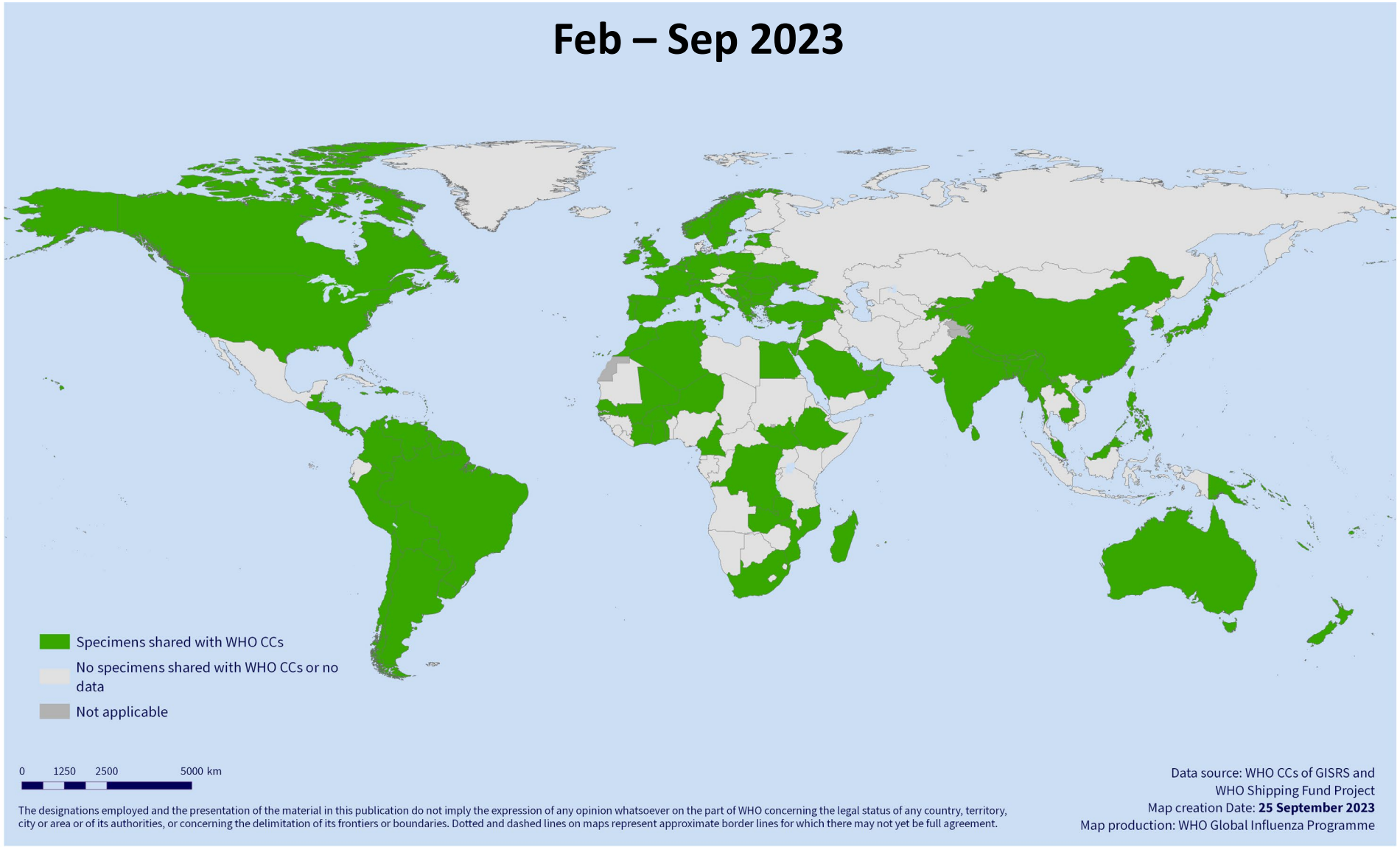
Quadrivalent: egg- or cell culture- or recombinant-based vaccines
- Above 3 components; and a **B/Phuket/3073/2013 (B/Yamagata lineage)-like antigen.**

*** Different from that recommended for the 2023 southern hemisphere season but the same as the NH 2023-24 recommendation.**

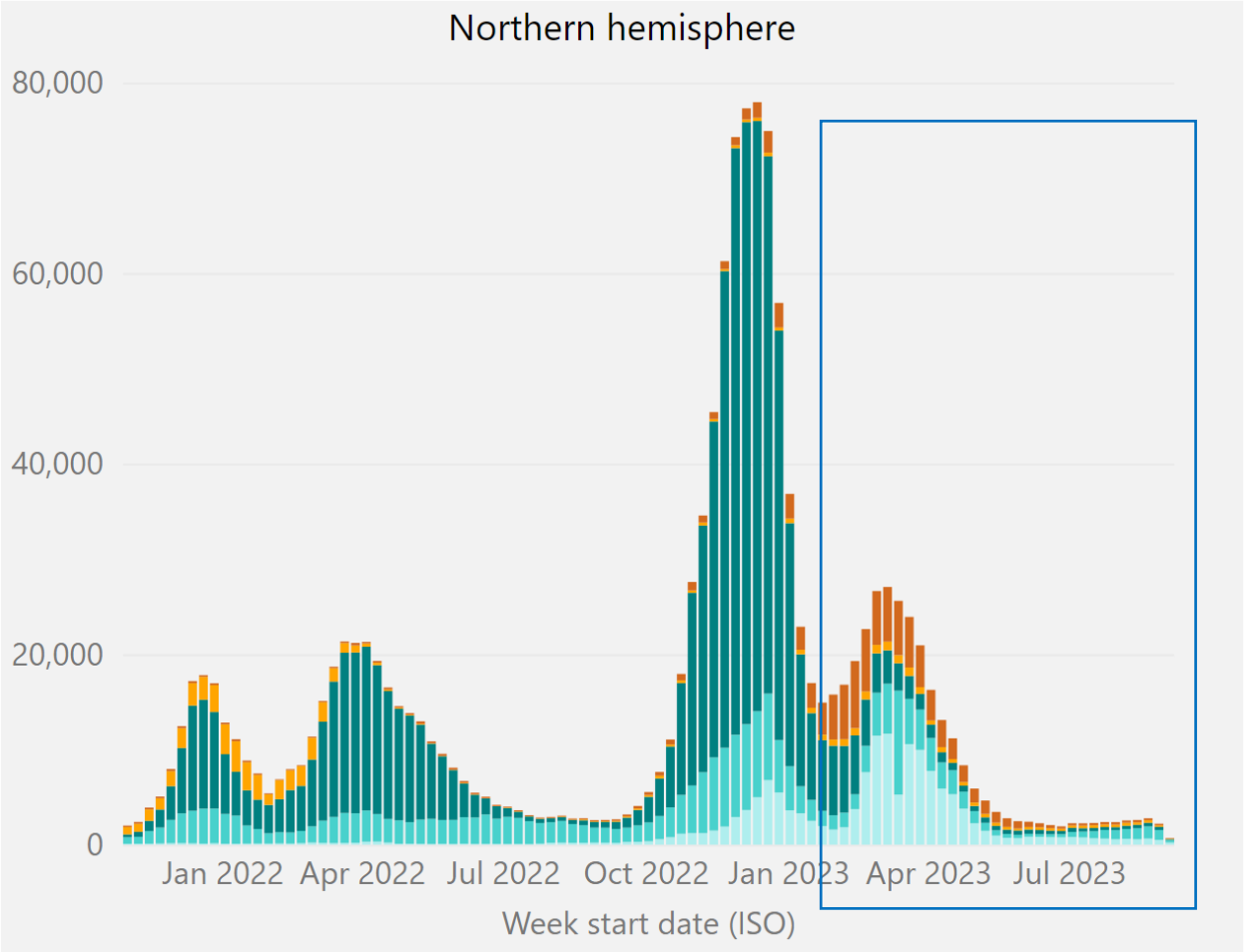
**** Different from that recommended for the 2023 southern hemisphere season and from NH 2023-24 recommendation.**

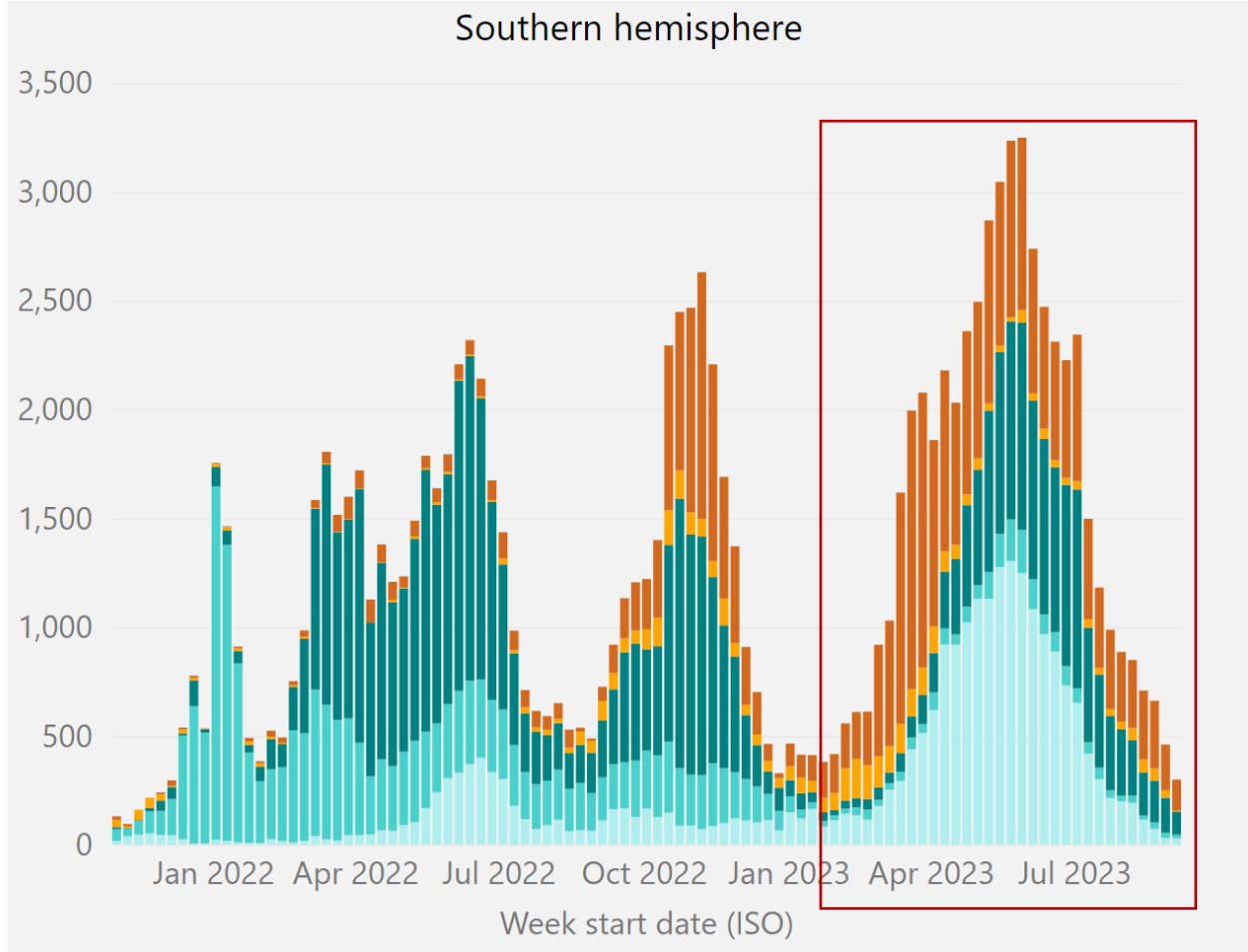
WHO recommendation and technical reports available on the WHO web site: https://www.who.int/teams/global-influenza-programme/vaccines/who-recommendations

Countries, areas and territories shared viruses with WHO CCs



Circulation of influenza viruses by hemisphere



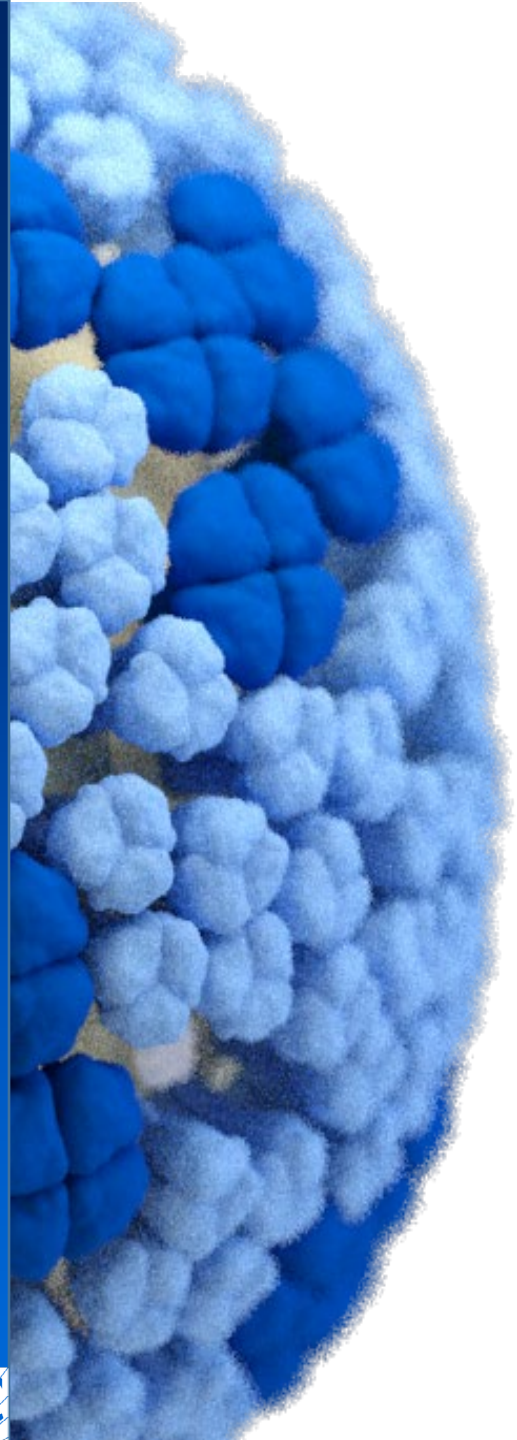


Virus type name A(H1N1)pdm09 A(H3) A (Not subtyped) B (Victoria lineage) B (Yamagata lineage) B (Lineage not determined) A(H1) A(H5)

Select week start date (ISO)

11/1/2021 9/4/2023

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

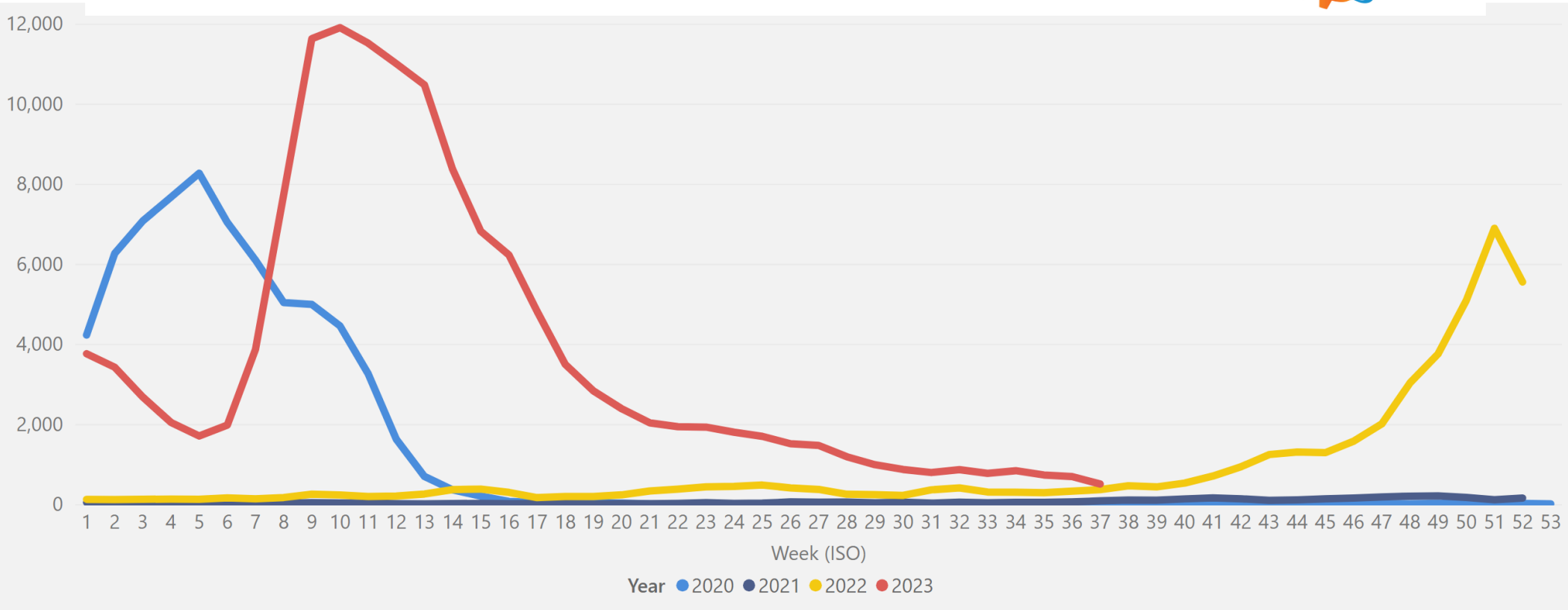


A(H1N1)pdm09 Viruses

Number of A(H1N1)pdm09 viruses detected by GISRS

World Health Organization

GISRS GLOBAL INFLUENZA SURVEILLANCE & RESPONSE SYSTEM

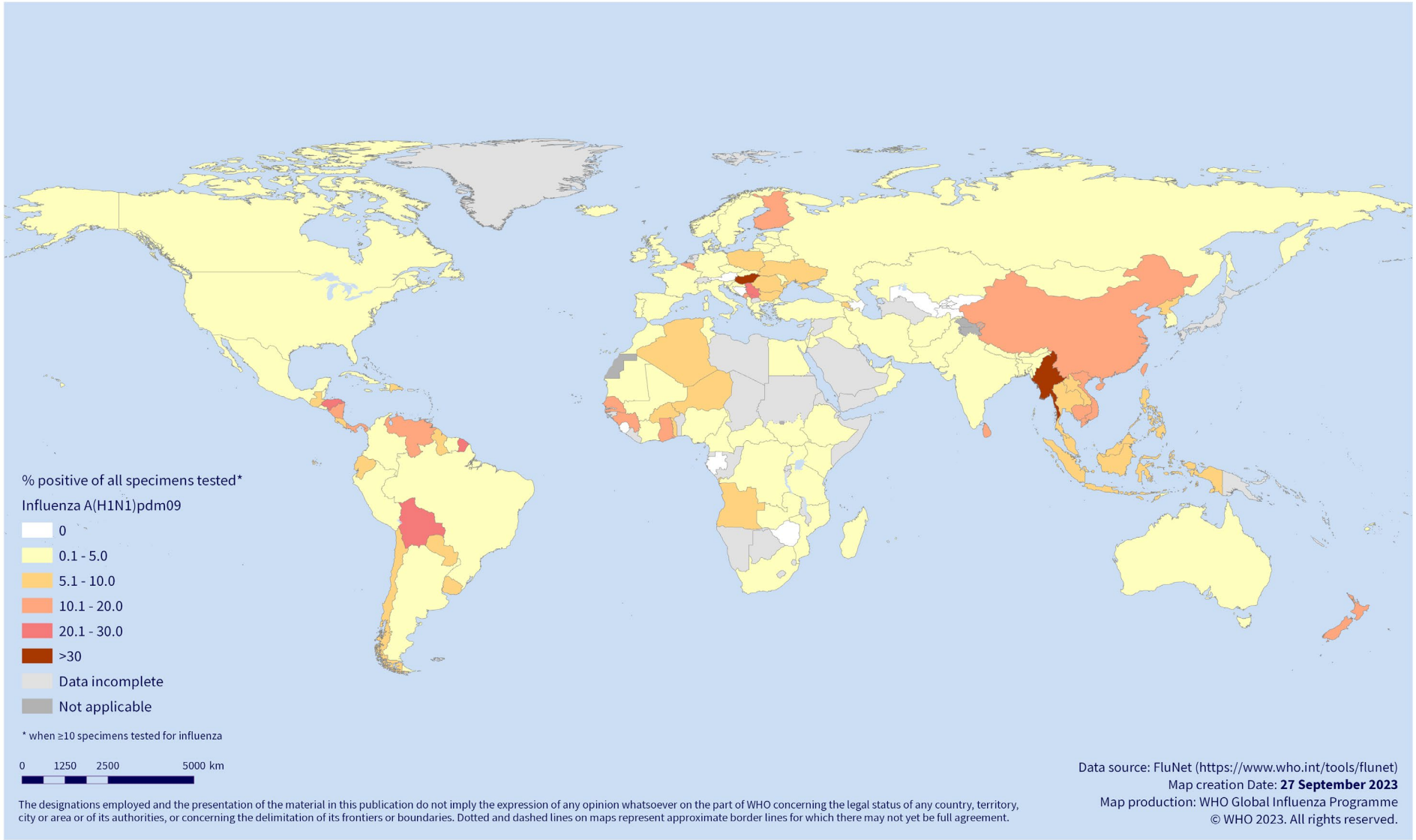


Select Year

2020 2023

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

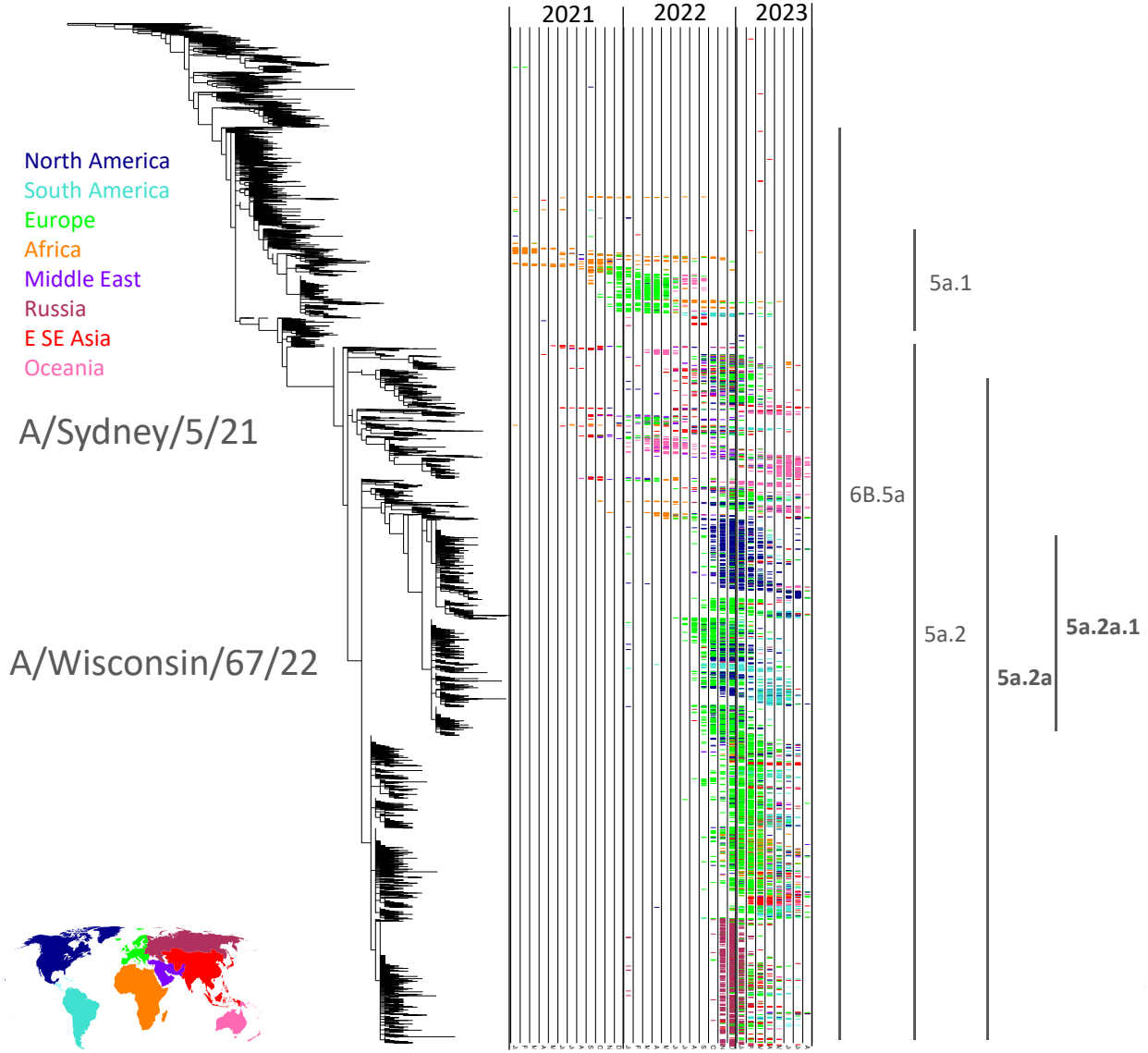
Influenza A(H1N1)pdm09 activity

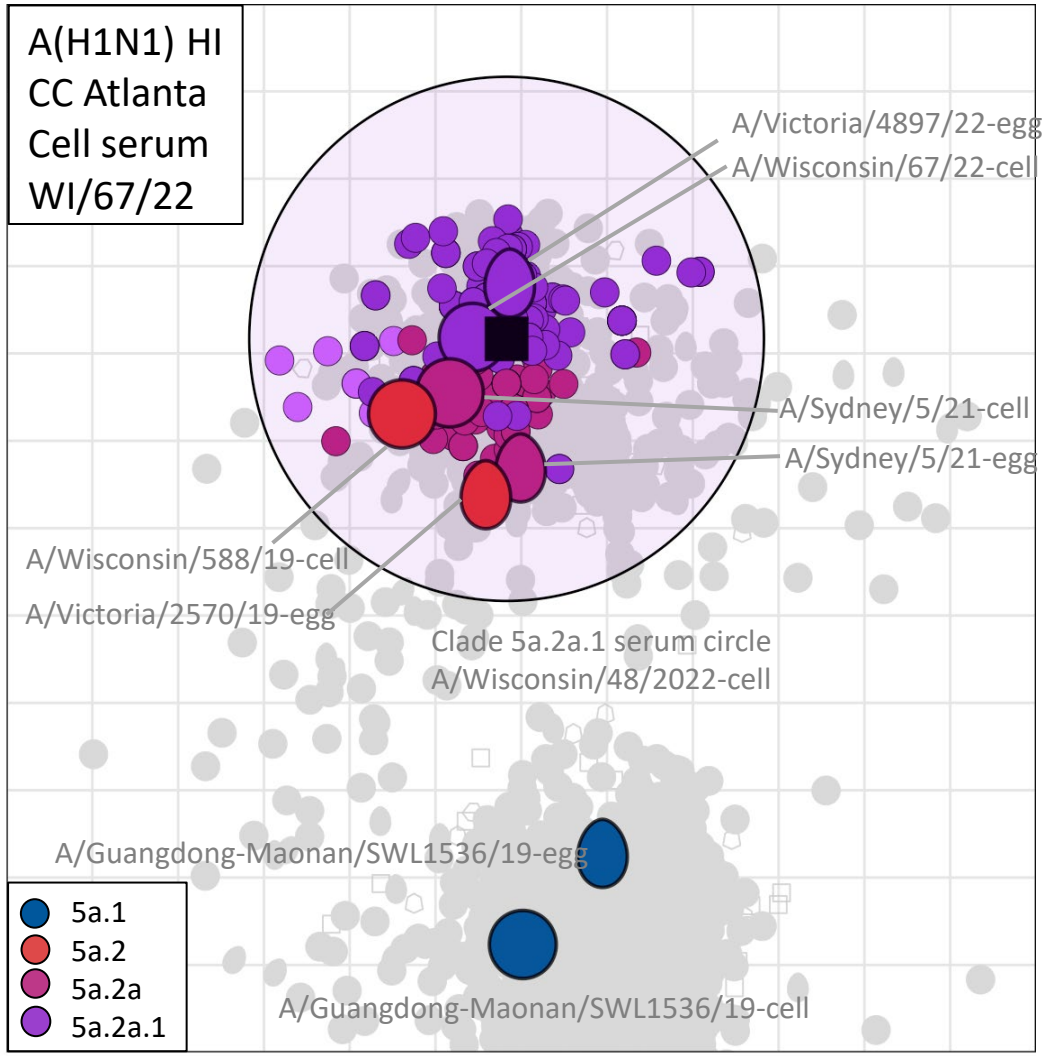


Colour intensity shows the percent of influenza A(H1N1)pdm09 positive among all samples tested during this period per country

Source: Global Influenza Programme (who.int)

Overall A(H1N1)pdm09 HA phylogeography





Since 1st February 2023 (older viruses in grey); Antiserum circles (within 8-fold of homologous titers)

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

Analysis of A(H1N1)pdm09 viruses by ferret antisera to antigens recommended for SH 2023 vaccines

HI Assay

Antisera to southern hemisphere 2023 antigens (5a.2a)

WHO CC	A/Sydney/5/2021-like Cell (5a.2a)	Low (≥ 8 fold)
CDC	222 (100%)	1 (0%)
CNIC	2017 (98%)	34 (2%)
FCI	238 (100%)	0 (0%)
NIID	42 (100%)	0 (0%)
VIDRL	2224 (100%)	4 (0%)
TOTAL	4743 (99%)	39 (1%)

WHO CC	A/Sydney/5/2021-like Egg (5a.2a)	Low (≥ 8 fold)
CDC	76 (99%)	1 (1%)
CNIC	1980 (97%)	71 (3%)
FCI	238 (100%)	0 (0%)
NIID		
VIDRL	2194 (98%)	34 (2%)
TOTAL	4488 (98%)	106 (2%)

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

SH 2023 post vaccination human serology

Vac.: A/Sydney/5/21-like

WHO Collaborating Center (CC): Human Serological Panels
A(H1N1)pdm09 -- HI Protocol [CELL]

				5a.2a												5a.2a.1									5a.1	
				+D94N +T216A				+A48P		+V152I	+T164N (CHO-)	+K169R		+I533V	+A141E +V152I +S190I		-			+T216A					-	
				SYD/5				ME/10		FUKUI/12	TAS/29	SD/31-LIKE		DAR/23	WA/22-LIKE		WI/67			WI/47-LIKE					HI/70	
				-				-		-	-	SD/31	DAR/7	-	WA/22	SYD/44	-			WI/47				VIC/4897	-	
				CELL				CELL		CELL	CELL	CELL	CELL	CELL	CELL	CELL	CELL			CELL				CELL	CELL	
				CDC	CBER	NIID	VIDRL	CDC	CBER	NIID	VIDRL	CDC	VIDRL	VIDRL	CDC	VIDRL	CDC	CBER	NIID	CDC	CBER	NIID	VIDRL	VIDRL	CDC	
A/SYDNEY/5/2021 CELL	Pediatric	IIV4	Australia				69				√		√	√		√							√	√		
	Adult	ccIIV4 (Flucelvax)	Australia	205	229	485	243	√	√	√	√	√	√	√	√	115	√	√	236	√	164	√	√	151	√
		IIV4	Australia	147	358	286	174	√	115	√	√	√	√	√	78	53	√	64	139	94	78	174	√	94	√
	Elderly	aIIV4	Australia	29	120	83	43	X	31	√	√	X	√	√	X	25	X	18	43	X	21	√	√	√	X
								0 (0.0)	2 (66.7)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (25.0)	3 (75.0)	0 (0.0)	2 (66.7)	3 (100.0)	1 (25.0)	3 (100.0)	1 (33.3)	0 (0.0)	2 (50.0)	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: A/DARWIN/23/2023 (DAR/23); A/DARWIN/7/2023 (DAR/7); A/FUKUI/12/2023 (FUKUI/12); A/HAWAII/70/2019 (HI/70); A/MAINE/10/2022 (ME/10); A/SOUTH DAKOTA/31/2023 (SD/31); A/SYDNEY/44/2023 (SYD/44); A/SYDNEY/5/2021 (SYD/5); A/TASMANIA/29/2023 (TAS/29); A/VICTORIA/4897/2022 (VIC/4897); A/WASHINGTON/22/2023 (WA/22); A/WISCONSIN/47/2022 (WI/47); A/WISCONSIN/67/2022 (WI/67).

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

SH 2023 post vaccination human serology

Vac.: A/Sydney/5/21-like

WHO Collaborating Center (CC): Human Serological Panels
A(H1N1)pdm09 -- HI Protocol [CELL]

					5a.2a										5a.2a.1								5a.1
					+D94N +T216A				+A48P		+V152I	+T164N (CHO-)	+K169R		+I533V	+A141E +V152I +S190I	-	+T216A					-
					SYD/5				ME/10		FUKUI/12	TAS/29	SD/31-LIKE		DAR/23	WA/22-LIKE	WI/67	WI/47-LIKE					HI/70
					-				-		-	-	SD/31	DAR/7	-	WA/22	SYD/44	-				VIC/4897	-
					CELL				CELL		CELL	CELL	CELL	CELL	CELL	CELL	CELL	CELL				CELL	CELL
					CDC	CBER	NIID	VIDRL	CDC	CBER	NIID	VIDRL	CDC	VIDRL	VIDRL	CDC	VIDRL	CDC	CBER	NIID	CDC	CBER	NIID	VIDRL	VIDRL	CDC
A/SYDNEY/5/2021 CELL	Pediatric	IIV4	Australia				69				√		√	√		√							√	√	
	Adult	ccIIV4 (Flucelvax)	Australia	205	229	485	243	√	√	√	√	√	√	√	√	115	√	√	236	√	164	√	√	151	√
		IIV4	Australia	147	358	286	174	√	115	√	√	√	√	√	78	53	√	64	139	94	78	174	√	94	√
	Elderly	aIIV4	Australia	29	120	83	43	X	31	√	√	X	√	√	X	25	X	18	43	X	21	√	√	√	X
								0 (0.0)	2 (66.7)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (25.0)	3 (75.0)	0 (0.0)	2 (66.7)	3 (100.0)	1 (25.0)	3 (100.0)	1 (33.3)	0 (0.0)	2 (50.0)	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 den[illegible]es *pos*
der

Demonstrates that changes in site Ca (i.e., P137S and K142R in 5a.2a.1 proteins) subtly change antigenic properties and reduce <u>human</u> antibody recognition.

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

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

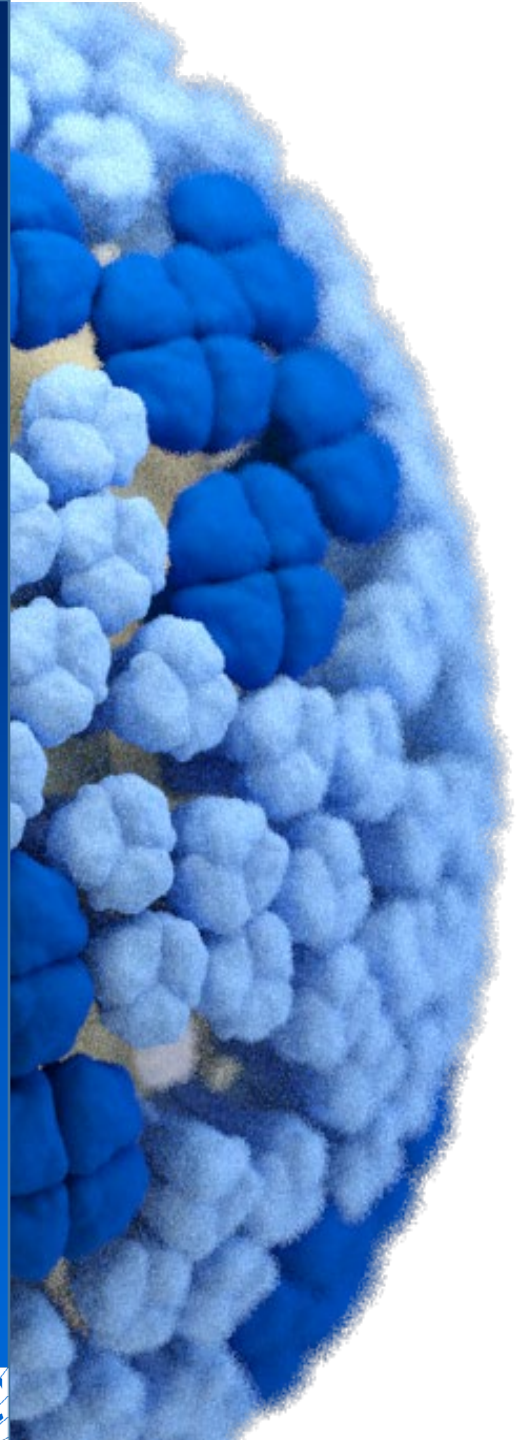
Multiple sources: compiled by WHO CC CDC, USA

A(H1N1)pdm09: antiviral susceptibility

- **NA inhibitors**
  - **Of 5,012** viruses tested – **18** showed resistance in genetic and/or phenotype analyses
- **Endonuclease inhibitors**
  - **Of 1,843** viruses tested – **2** showed resistance in genetic and/or phenotype analyses

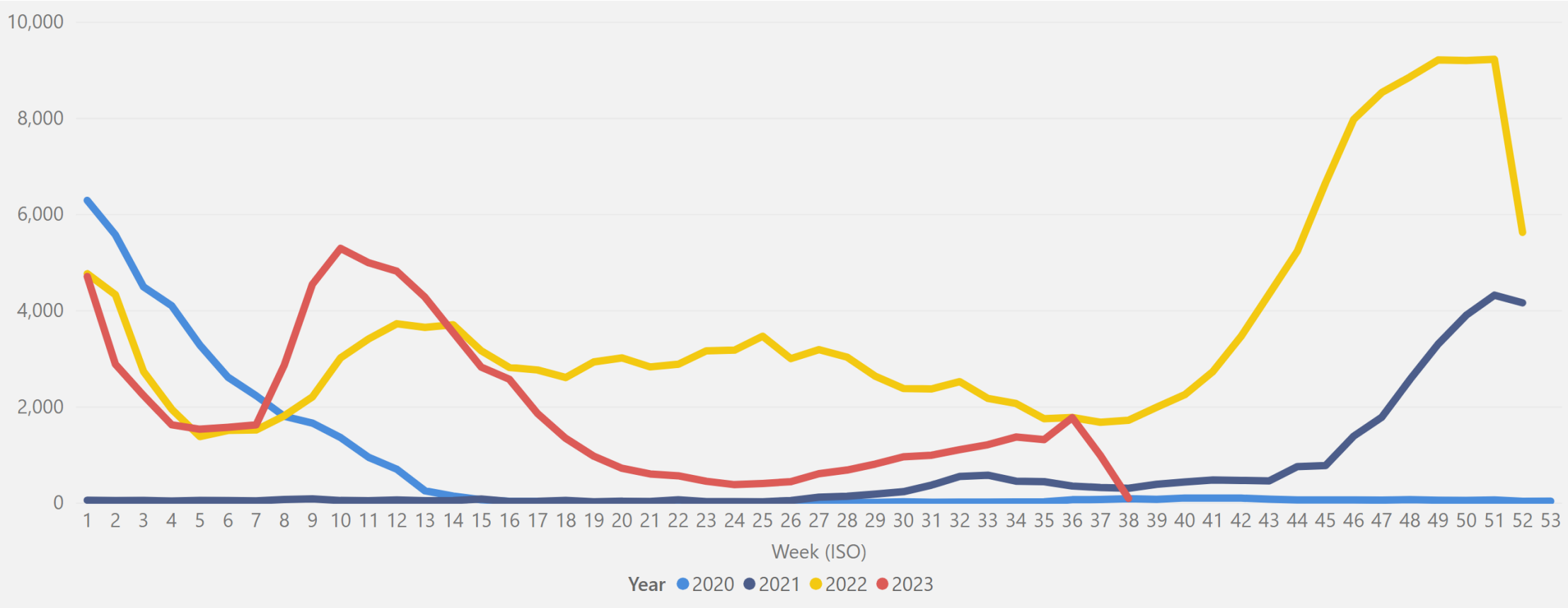
A(H1N1)pdm09 Summary

- Taken together the data supported updating from the southern hemisphere 2023 vaccine antigen (A/Sydney/5/2021-like (HA clade 5a.2a)) to the same antigen recommended for the northern hemisphere 2023-24 (A/Wisconsin/67/2022-like (HA clade 5a.2a.1).
  - A(H1N1)pdm09 viruses circulated globally and predominated in most geographic regions.
  - Phylogenetics analysis of the HA genes from viruses collected since 1 February showed nearly all were subclade 5a.2a (predominated in Oceania, Asia, Africa and Europe) or 5a.2a.1 (predominated in North America, Central America and South America).
  - While **ferret antisera didn't distinguish** between HA clade 5a.2, 5a.2a, or 5a.2a.1 viruses, post vaccination **human sera showed reductions** in geometric mean titers associated with amino acid substitutions in antigenic sites such as Ca.
  - Interim vaccine effectiveness estimates from the southern hemisphere indicate that the vaccines were effective, which is consistent circulation of A/Sydney/5/2021-like (HA clade 5a.2a) viruses.
- Nearly all viruses analyzed showed susceptibility to antivirals



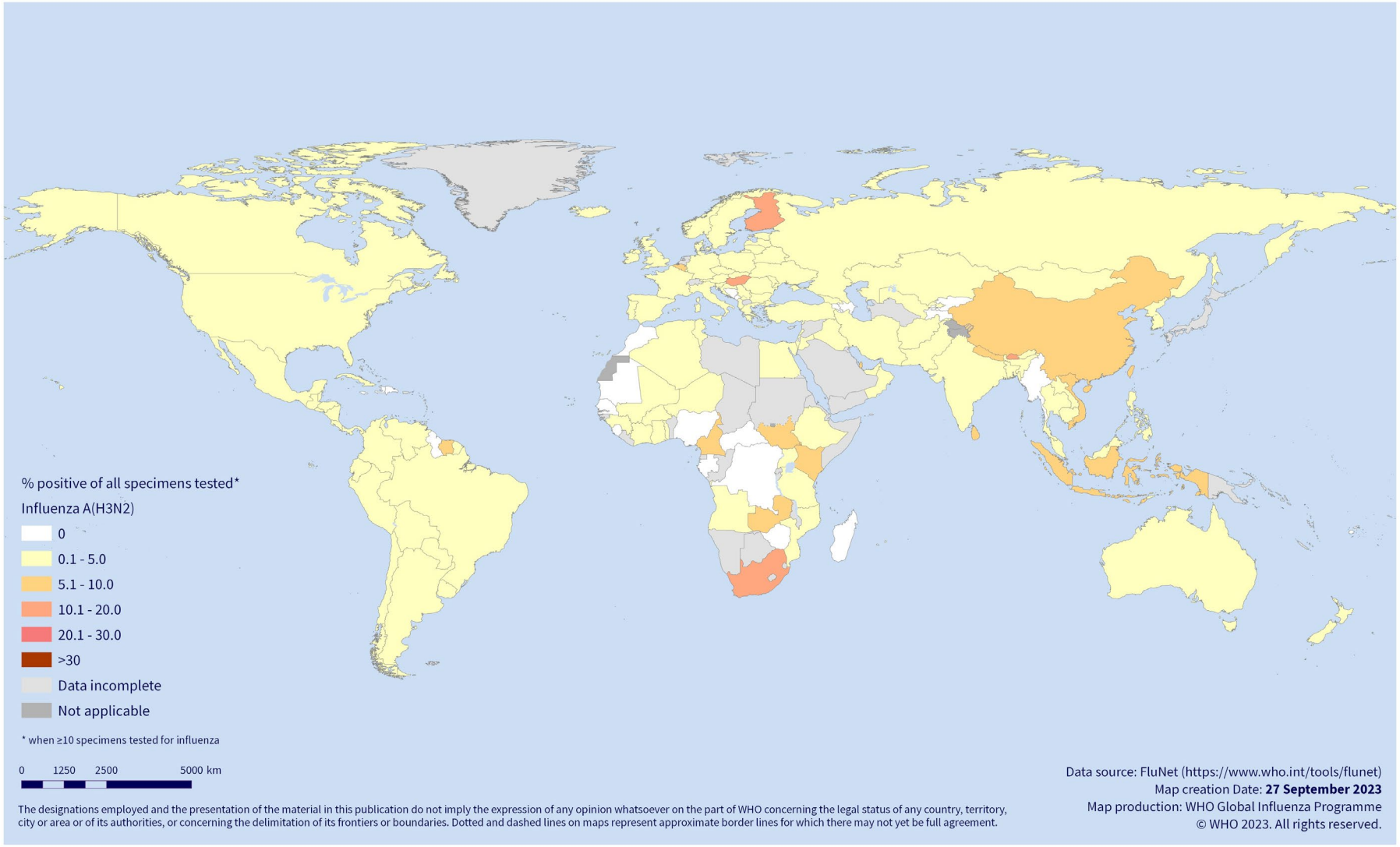
A(H3N2) Viruses

Number of A(H3N2) viruses detected by GISRS



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

Influenza A(H3N2) activity

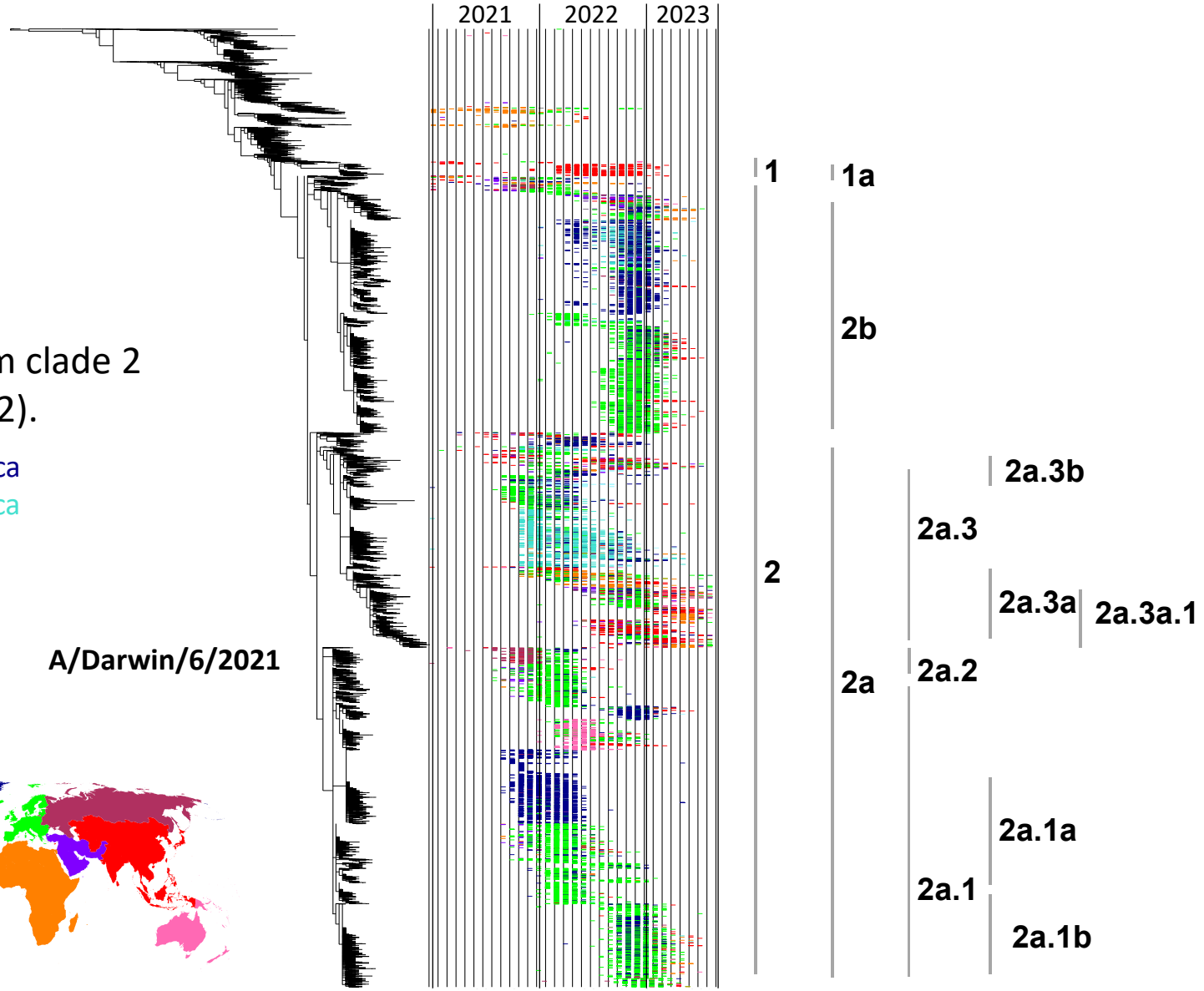


Colour intensity shows the percent of influenza A(H3N2) positive among all samples tested during this period per country

Source: Global Influenza Programme (who.int)

Overview of A(H3N2) HA phylogeography

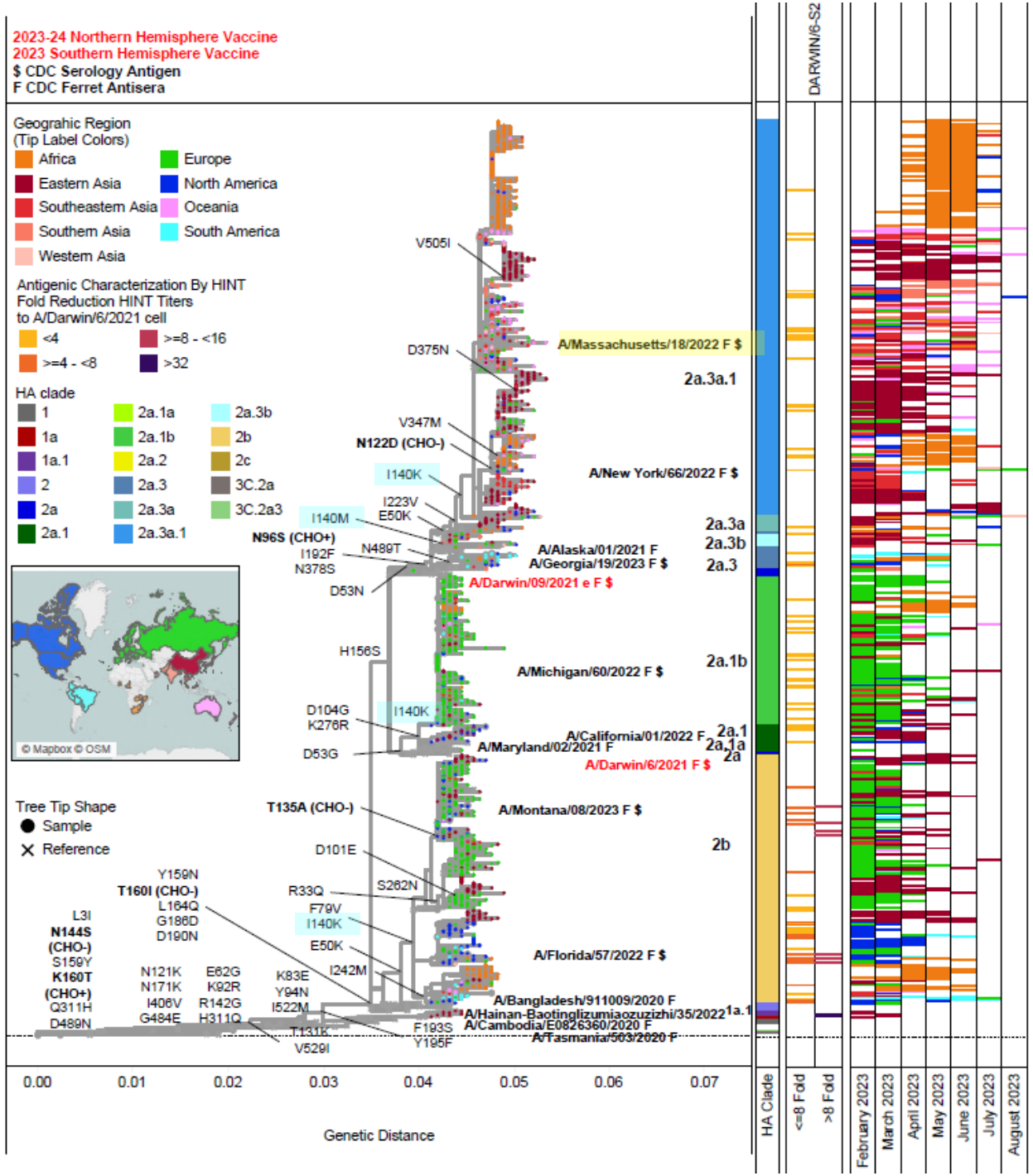
- Nearly all are subclades derived from clade 2 (complete classification 3C.2a1b.2a.2).



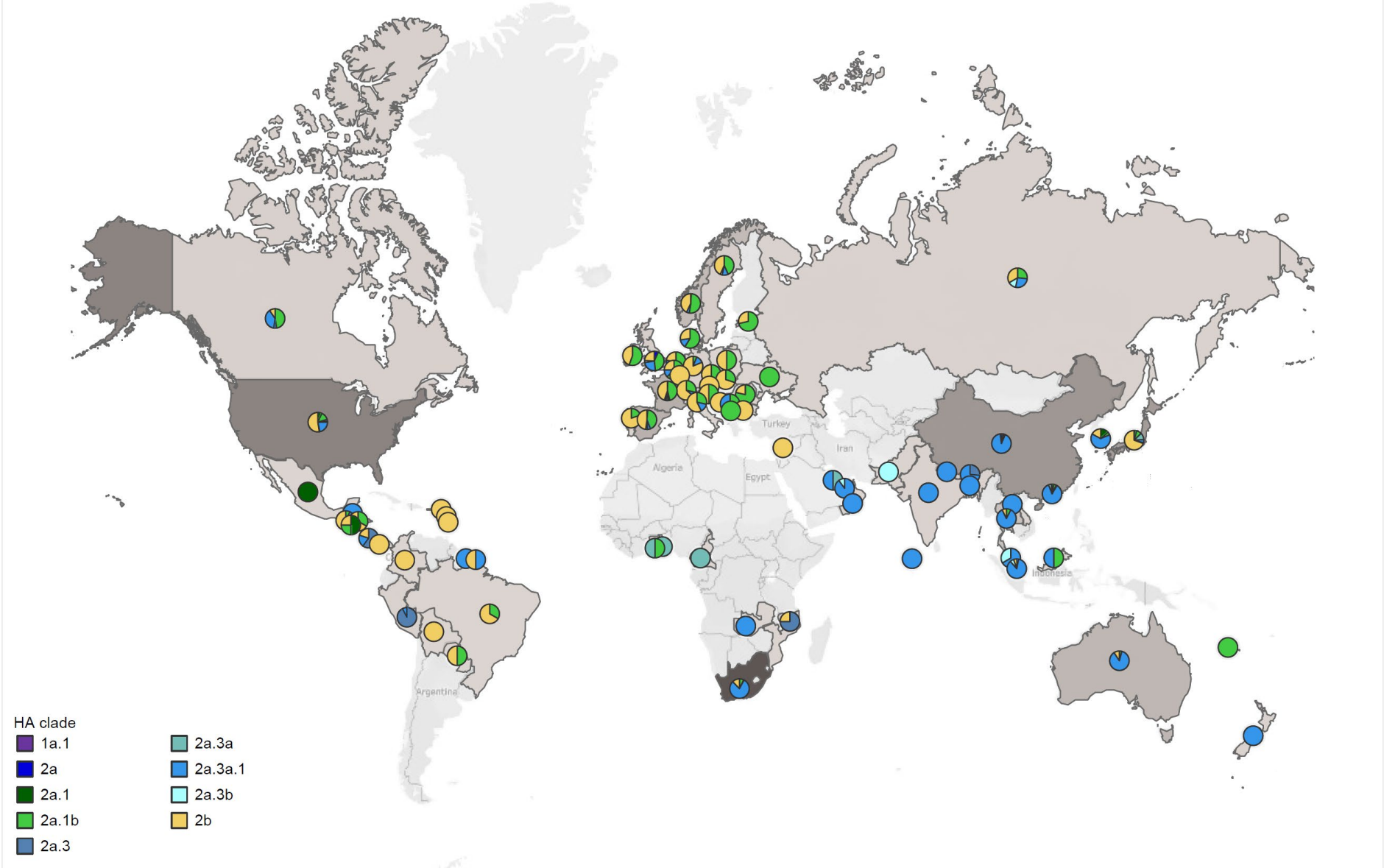
Source: Cambridge Univ., S. James and D. Smith

A(H3N2) HA phylogeography

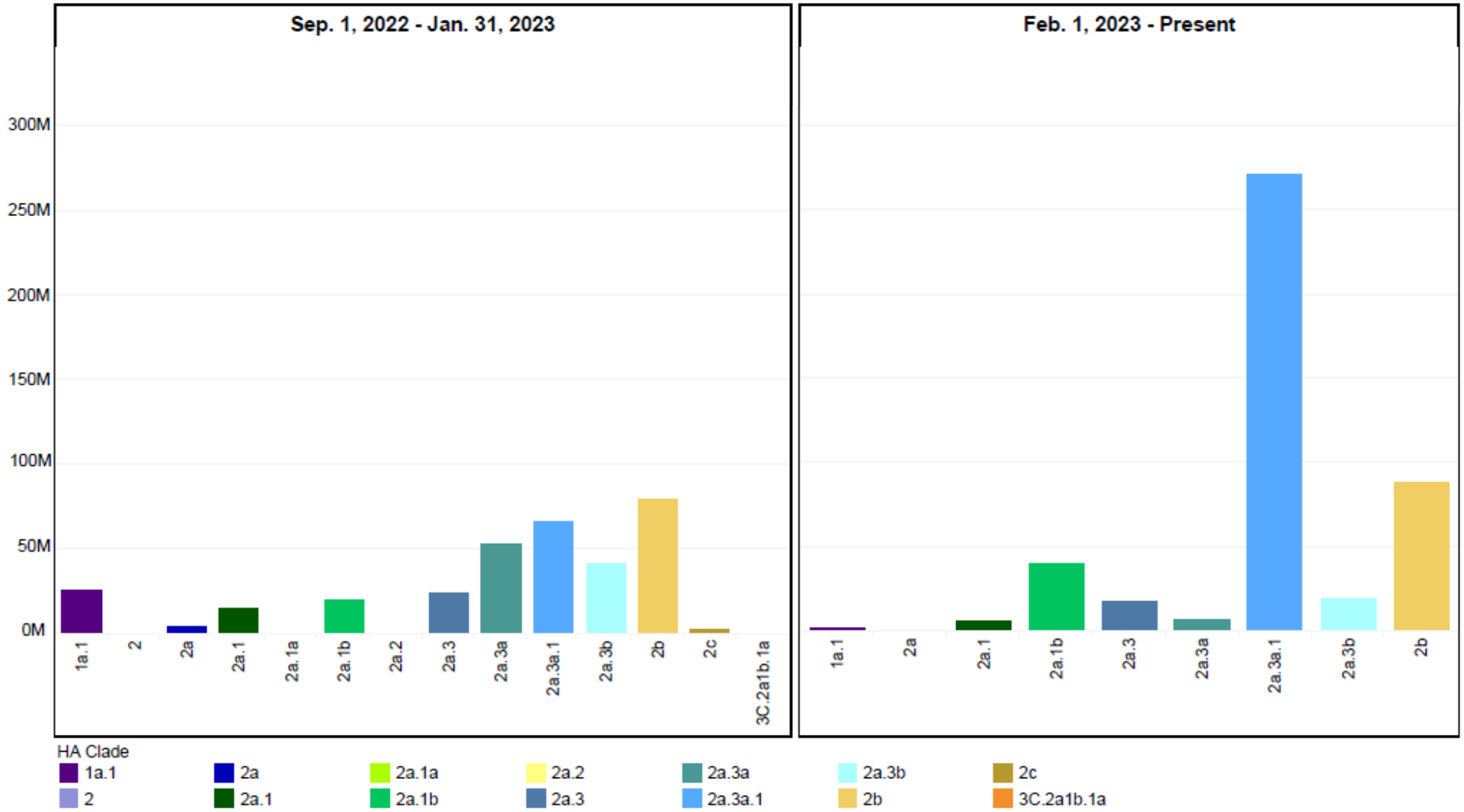
- Major recent clade 2 subclades:
  - 2a.3a.1
    - e.g., A/Massachusetts/18/2022 and A/Thailand/8/2022
    - Africa, Asia, North America, Oceania
  - 2b
    - e.g., A/Florida/57/2022
    - Global distribution
  - 2a.1b
    - e.g., A/Michigan/60/2022
    - North America, Europe
  - Parallel evolution at I140K>M
  - Most reacted well with antisera to A/Darwin/6/2021
    - NH 2023-24 vaccine antigen



Global circulation of A(H3N2) HA clades (Feb.-Aug. 2023)



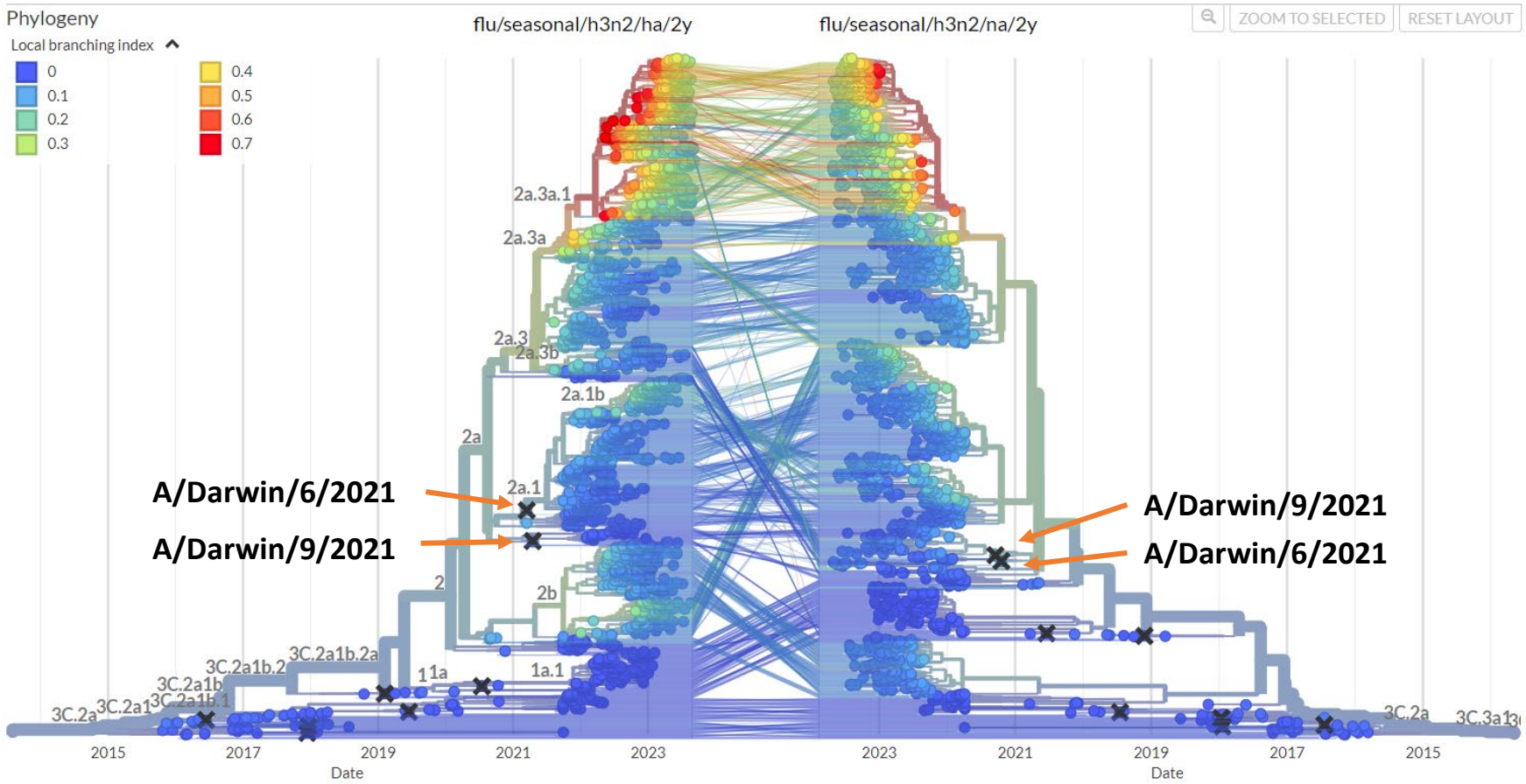
Estimated global infections of A(H3N2) HA clades



Source: CDC: Estimated to reduce impact of sequencing bias regional clade proportions of available sequences were multiplied by regional population size assuming 10% infection rate.

H3 and N2 Phylogenies showing local branching index (LBI)

- LBI is one technique used to identify viruses that may have fitness advantage over other clades
  - Suggest 2a.3a.1 HA and typically corresponding NA genes have higher fitness

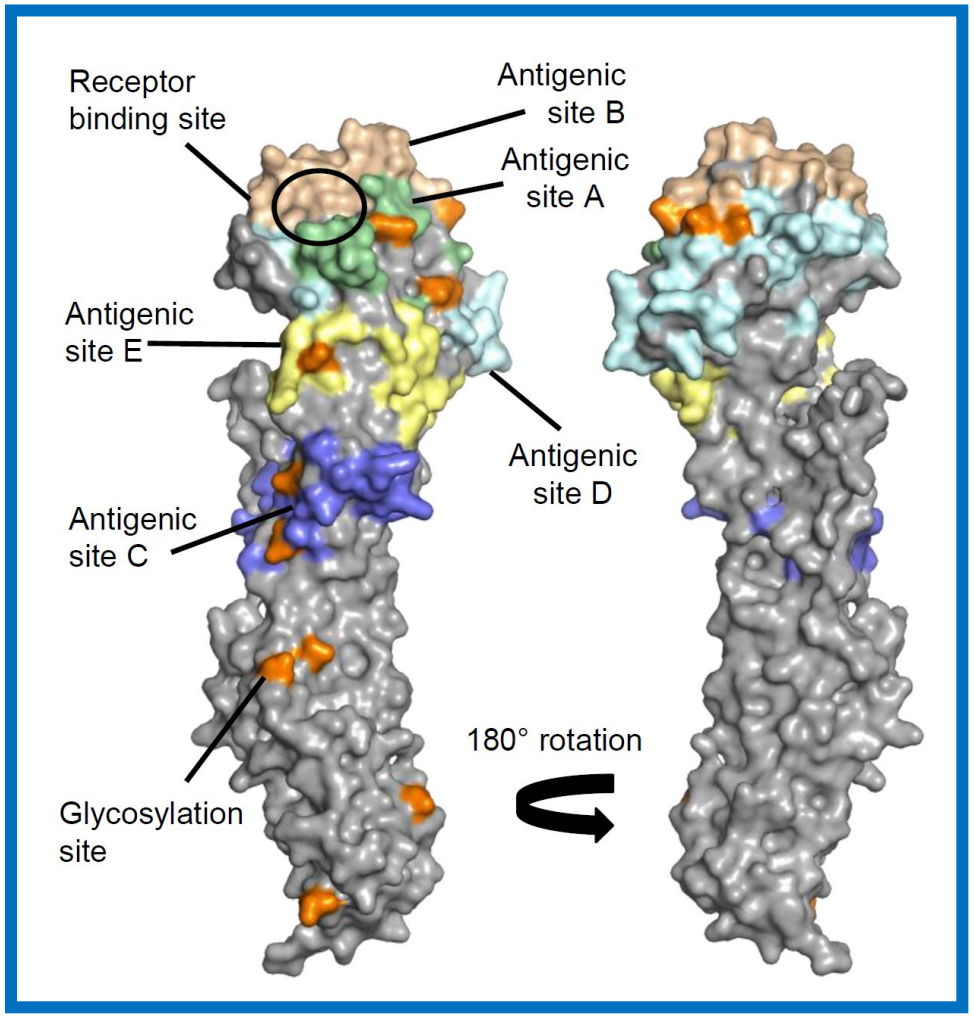


Nextstrain / flu / seasonal / h3n2 / ha / 2y : flu / seasonal / h3n2 / na / 2y

Location of changes in key serology antigens

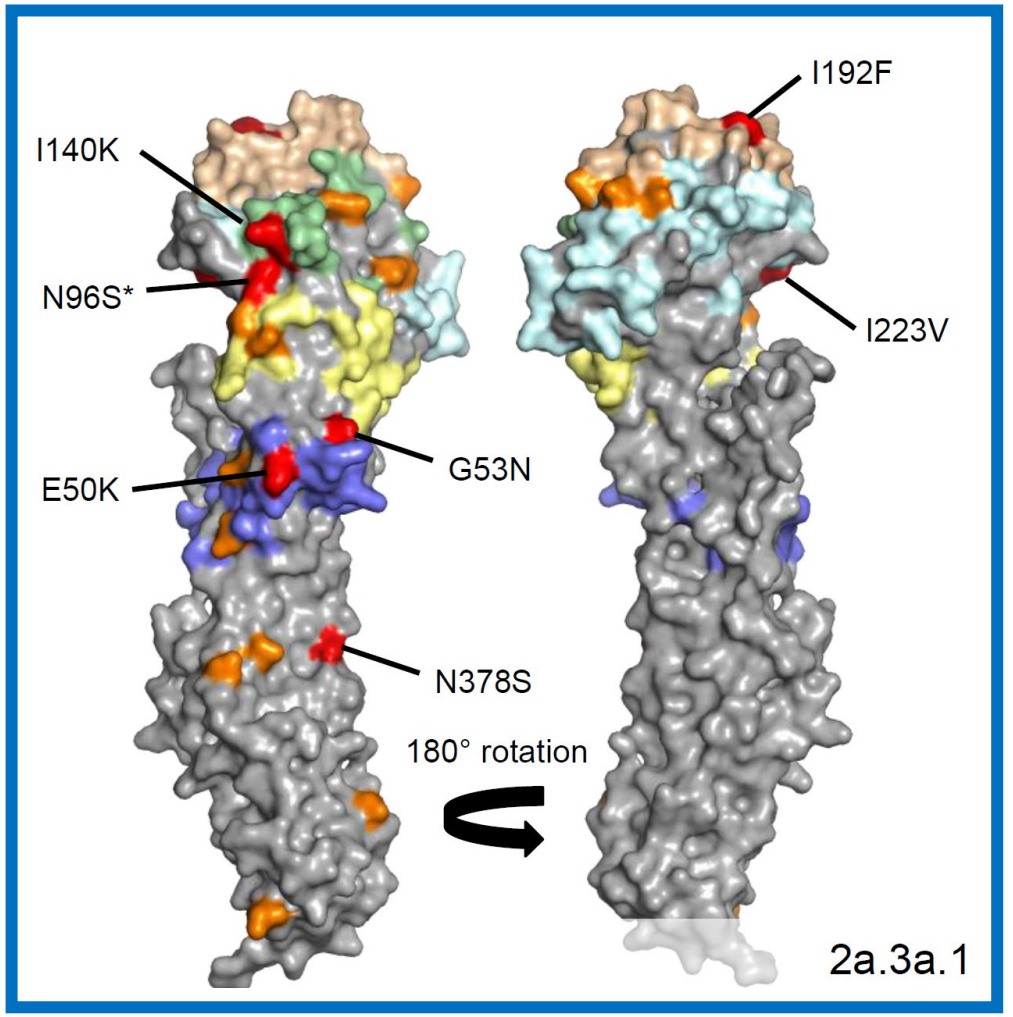
A/Darwin/6/2022 (Cell)

2a



A/Massachusetts/18/2022 (Cell)

2a.3a.1



Analysis of A(H3N2) viruses by antisera to antigens recommended for SH 2023

HI Assay

Antisera to southern hemisphere 2023 antigens (2a)

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

WHO CC	Like (2-4 fold)	Low (≥ 8 fold)
CDC	90 (100%)	0 (0%)
CNIC	783 (57%)	585 (43%)
FCI	108 (98%)	2 (2%)
VIDRL	300 (93%)	23 (7%)
Total	1281 (68%)	610 (32%)

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

WHO CC	Like (2-4 fold)	Low (≥ 8 fold)
CDC	82 (91%)	8 (9%)
CNIC	706 (52%)	662 (48%)
FCI	98 (89%)	12 (11%)
VIDRL	249 (77%)	74 (23%)
Total	1135 (60%)	756 (40%)

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

Antigenic analysis of A(H3N2) viruses (HI)

H3N2, HI

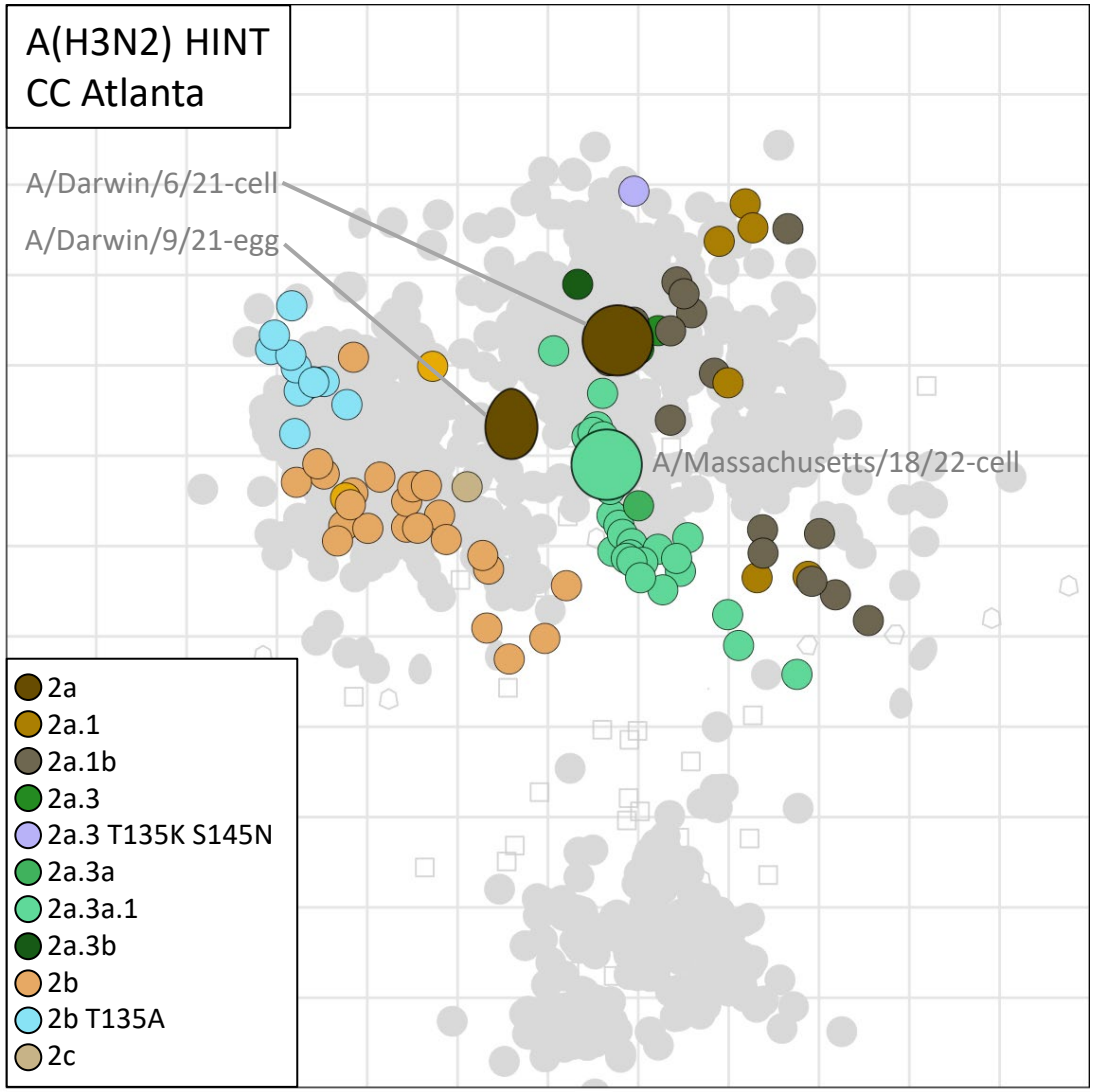
Test Date: 15/08/2023

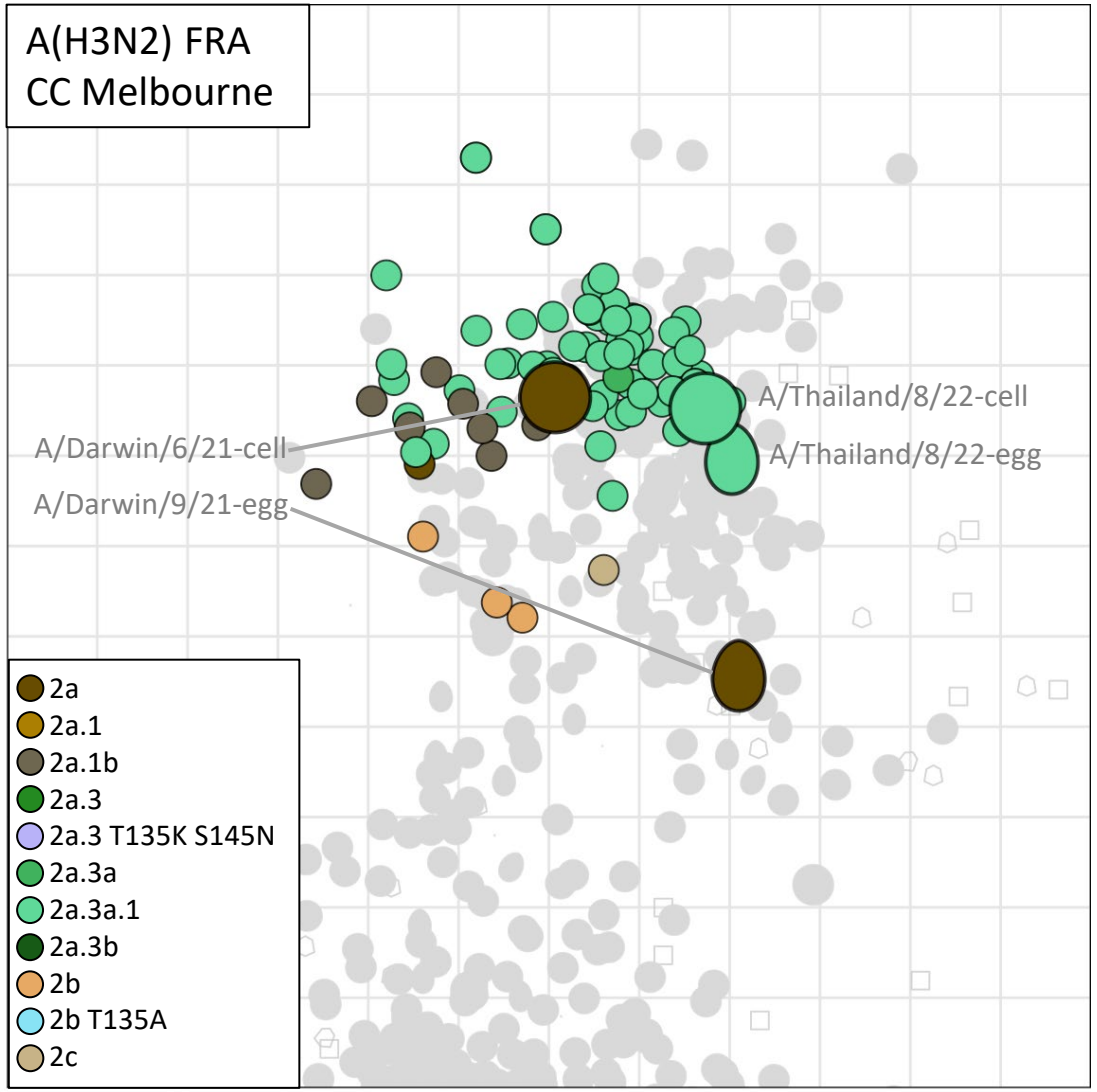
NH- 2023-24 | **SH- 2024**

Fold difference
- <4-fold
- 4-fold
- 8-fold
- >8-fold

	E5 Cambe0826360 A9049 1a	SIAT2 Dar6 A9231 2a	E4 Dar9 A9358 2a	SIAT2 Thai8 A9671 2a.3a.1	E3/D1 Thai8 F0221 2a.3a.1	SIAT1 SthAust389 A9674 2b	Clade	Passage details	Sample Date
REFERENCE ANTIGENS									
A/Cambodia/E0826360/2020e	**640**	320	160	80	160	80	1a	E5	
A/Darwin/6/2021c	80	**1280**	80	40	160	160	2a	SIAT2	
A/Darwin/9/2021e	160	640	**320**	80	320	320	2a	E5	
A/Thailand/8/2022c	80	640	160	**320**	640	80	2a.3a.1	SIAT2	
A/Thailand/8/2022e	160	1280	320	320	**1280**	640	2a.3a.1	E3	
A/South Australia/389/2022c	80	160	80	40	80	**320**	2a.2b	SIAT2	
TEST ANTIGENS									
A/Sydney/510/2023	80	640	80	320	1280	80	2a.3a.1	SIAT1	2023-06-23
A/Sydney/513/2023	80	320	80	320	1280	80	2a.3a.1	SIAT1	2023-06-24
A/Sydney/555/2023	80	320	160	160	640	80	2a.3a.1	MDCK1	2023-07-07
A/Auckland/50/2023	40	320	80	160	1280	40	2a.3a.1	SIATX,SIAT1	2023-04-06
A/Singapore/GP1582/2023	80	640	80	160	640	80	2a.3a.1	SIAT1	2023-02-15
A/Singapore/GP7270/2023	80	640	80	160	1280	80	2a.3a.1	MDCK1,SIAT1	2023-05-24
A/South Australia/48/2023	40	320	80	160	640	40	2a.3a.1	SIAT2	2023-02-22
A/Sydney/639/2023	40	320	40	160	1280	40	2a.3a.1	SIAT1	2023-07-08
A/Sydney/710/2023	<40	320	40	160	640	40	2a.3a.1	SIAT1	2023-07-29
A/Victoria/2107/2023	40	320	40	160	640	40	2a.3a.1	MDCK2	2023-07-29
A/Philippines/52/2023	80	640	80	160	640	40	2a.3b	SIAT2	2023-06-19
A/Brisbane/273/2023	40	640	80	<40	80	40	2a.1b	SIAT2	2023-05-15

A(H3N2) antigenic cartography

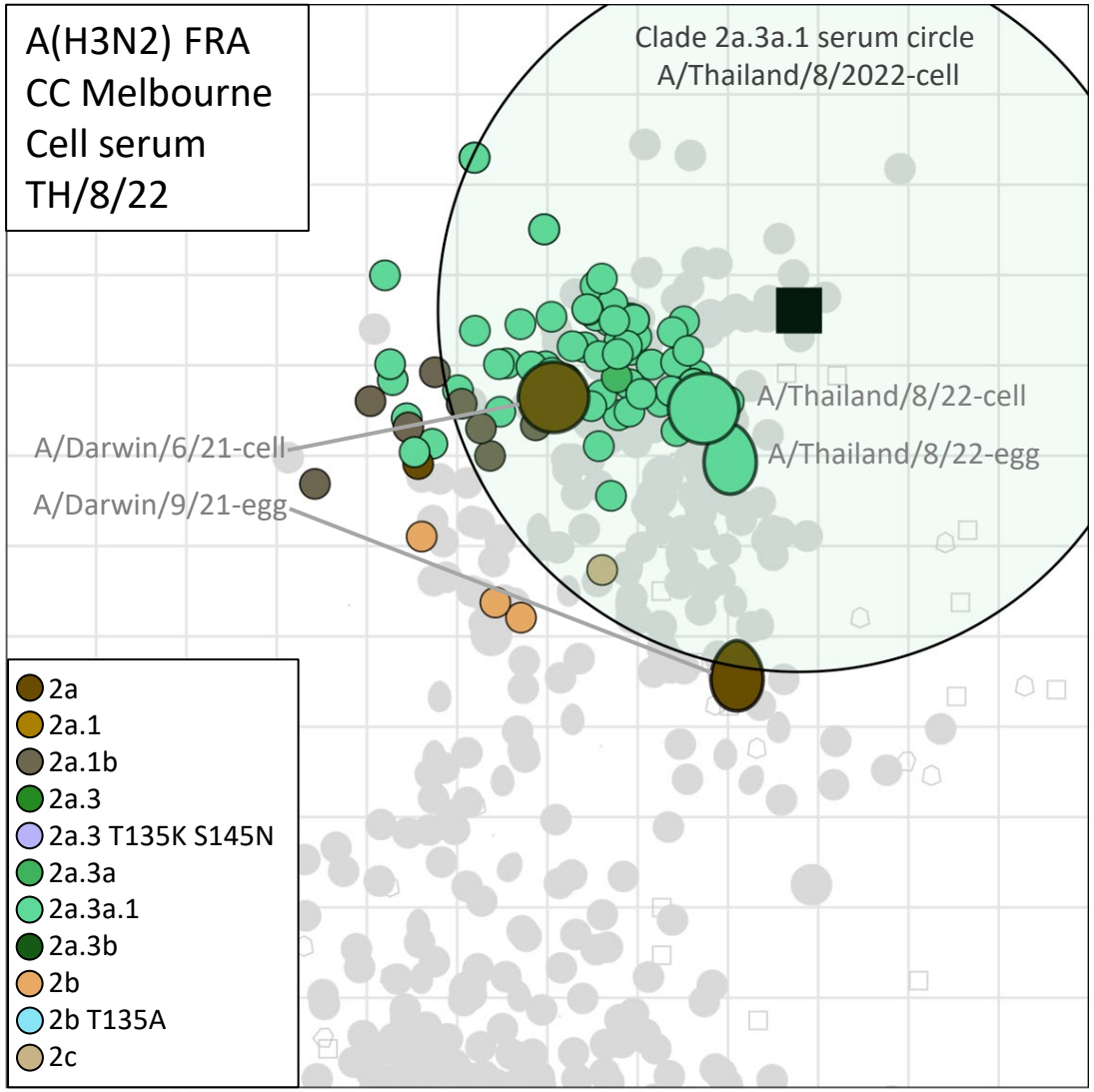


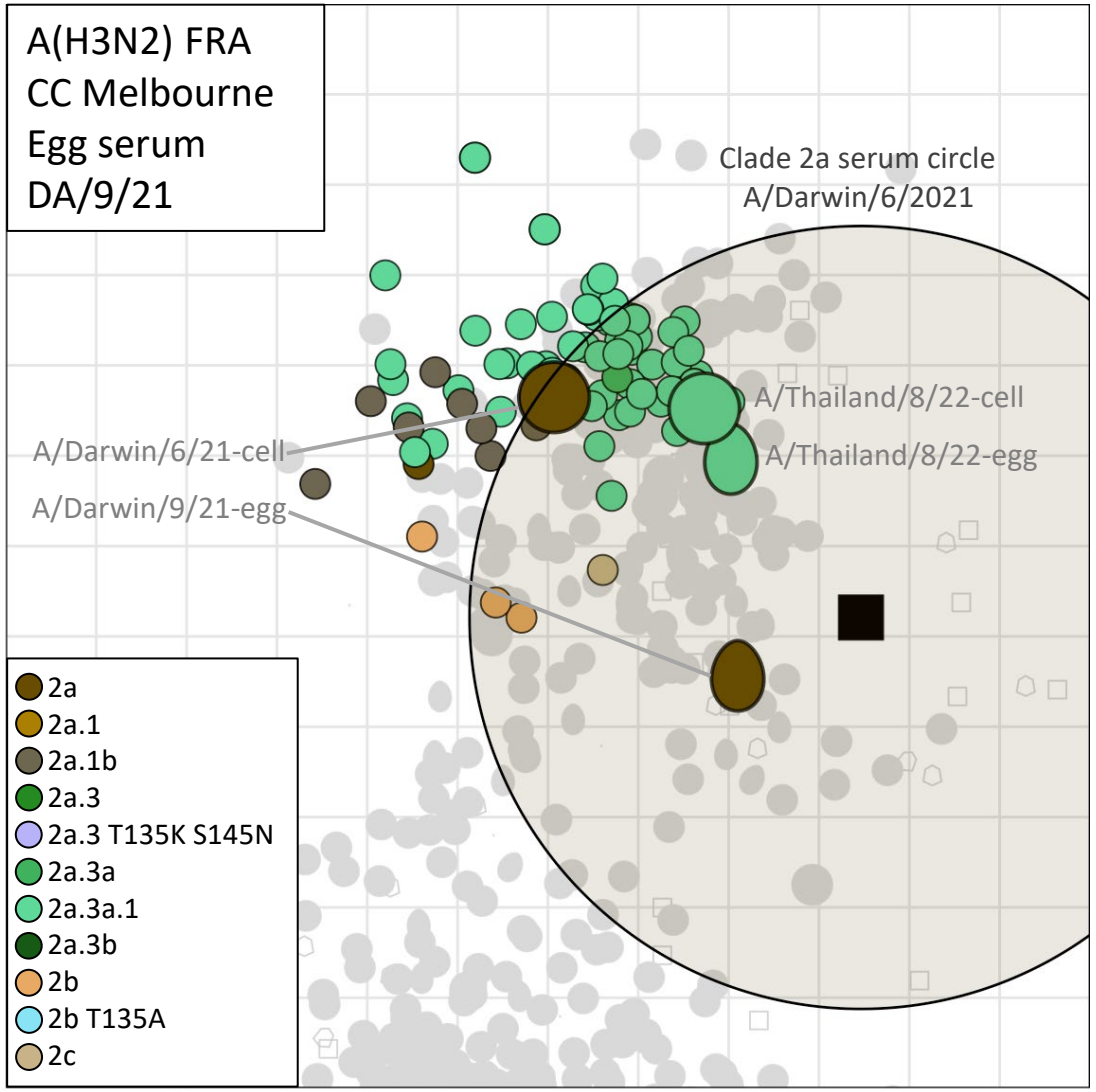


Since 1st February 2023 (older viruses in grey)

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

A(H3N2) antigenic cartography showing antisera reactivity





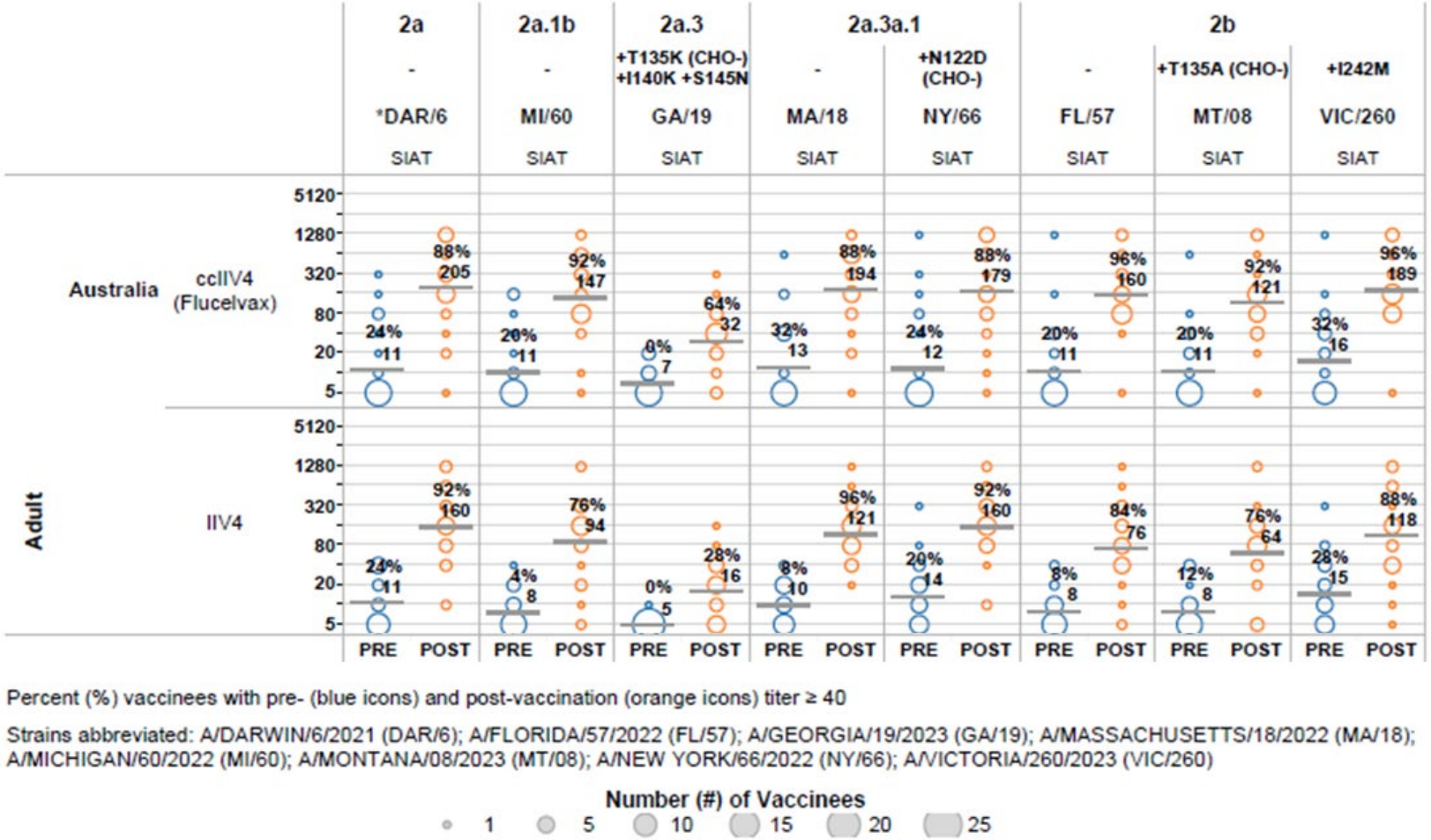
Antiserum circles (within 8-fold of homologous titers)

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

Individual human sera analysis - A(H3N2)

S. hemisphere A/Darwin/6/2021 -like vaccine

- Strong boost in neutralizing antibodies to most emerging HA clades
  - including 2a.3a.1
- Lowest in 2a.3 representative (GA/19), which represents small proportion of viruses.



Source: WHO-CC at CDC

Human post-vaccination sera analysis - A(H3N2) summary

WHO Collaborating Center (CC): Human Serological Panels
A(H3N2) -- HI & MN Protocol [CELL]

					2a - DAR/6-LIKE DAR/6 CELL CDC MN	2a - DAR/6-LIKE DAR/6 CELL CBER MN	2a - DAR/6-LIKE DAR/6 CELL MHRA HI	2a - DAR/6-LIKE DAR/6 CELL NIID MN	2a - DAR/6-LIKE DAR/11 CELL VIDRL HI	2a.1 +K503R AICHI/65 - CELL NIID MN	2a.1b - MI/60-LIKE MI/60 CELL CDC MN	2a.1b - MI/60-LIKE MI/60 CELL CBER MN	2a.1b - MI/60-LIKE LEON/4311 CELL MHRA HI	2a.1b +I214T BRI/273 - CELL CBER MN	2a.1b +I214T BRI/273 - CELL MHRA HI	2a.1b +I214T BRI/273 - CELL VIDRL HI	2a.3 +T135K (CHO-) +I140K +S145N GA/19 - CELL CDC MN	2a.3 +T135K (CHO-) +I140K +S145N GA/19 - CELL CBER MN	2a.3a +T135A (CHO-) +I223V NAG/2100 - CELL NIID MN	2a.3a.1 - MA/18-LIKE MA/18 CELL CDC MN	2a.3a.1 - MA/18-LIKE MA/18 CELL CBER MN	2a.3a.1 - MA/18-LIKE CAN/79 CELL VIDRL HI	2a.3a.1 - MA/18-LIKE NEW/113 CELL VIDRL HI	2a.3a.1 - MA/18-LIKE THA/8 CELL VIDRL HI	2a.3a.1 - MA/18-LIKE YAM/23018 CELL NIID MN	2a.3a.1 - MA/18-LIKE ZAF/R06126 CELL MHRA HI	2a.3a.1 +N122D (CHO-) NY/66 - CELL CDC MN	2a.3a.1 +N63K (CHO-) +N122D (CHO-) +V347M SA/48 - CELL MHRA HI	2a.3a.1 +N63K (CHO-) +N122D (CHO-) +V347M SA/48 - CELL VIDRL HI	2b - FL/57 - CELL CDC MN	2b +T135A (CHO-) MT/08 - CELL CDC MN	2b +T135A (CHO-) MT/08 - CELL CBER MN	2b +T135A (CHO-) +S262N YAM/60 - CELL NIID MN	2b +I242M VIC/260 - CELL CDC MN	2b +I242M VIC/260 - CELL CBER MN	2b +I242M VIC/260 - CELL MHRA HI	2b +I242M VIC/260 - CELL NIID MN	2b +I242M VIC/260 - CELL VIDRL HI	2b +L157F +S262N GRC/ILI_249 - CELL MHRA HI
A/DARWIN/6/2021-LIKE CELL	Pediatric (CDC: 6-35M)	IIV4	2022-23NH	USA	149						√						75			√							√			77	86							
	Pediatric (CDC: 3-8Y)	IIV4	2022-23NH	USA	538						√						57			√							√			√	251							
			2023SH	Australia					102							√					√	√	√					√								√		
	Pediatric (9-17Y)	ccIIV4 (Flucelvax)	2022-23NH	USA	401						√						72			√							√			243	226							
	Adult	ccIIV4 (Flucelvax)	2023SH	Australia	205	147	51	89	184	√	√	74	21	24	6	√	32	21	√	√	70	√	√	100	√	24	√	9	√	√	121	34	√	√	82	14	√	√	21
		IIV4	2022-23NH	USA	309	95					204	30		24			35	27		√	46					8	√			√	√	28			25				
				UK			12						X		X													X							X			7
			2023SH	Australia	160	87	57	51	118	√	94	32	35	22	16	62	16	29	√	√	49	√	√	√	√	7	√	√	√	76	64	28	√	√	28	√		70	16
		IIV3	2023SH	Peru	53		75				√		10		6		26			√						√	√	√		√	√				√			√
	Elderly	aIIV4	2023SH	Australia	226	128	55	187	160	√	√	25	28	23	27	√	19	25	√	√	71	√	√	94	√	17	√	√	√	132	83	39	√	√	45	√	88	√	√
										0 (0.0)	2 (25.0)	4 (100.0)	4 (80.0)	4 (100.0)	4 (80.0)	1 (25.0)	8 (100.0)	4 (100.0)	0 (0.0)	0 (0.0)	4 (100.0)	0 (0.0)	0 (0.0)	2 (50.0)	0 (0.0)	4 (80.0)	0 (0.0)	1 (20.0)	0 (0.0)	4 (50.0)	6 (75.0)	4 (100.0)	0 (0.0)	0 (0.0)	4 (100.0)	1 (20.0)	1 (50.0)	1 (25.0)	3 (60.0)

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.

Hemagglutination inhibition (HI) assay results reported by MHRA and VIDRL are indicated in addition to all microneutralization (MN) protocol trends; Australian/Peruvian and UK/US population cohorts vaccinated with 2023 Southern Hemisphere (SH) and 2022-23 Northern Hemisphere (NH) vaccine formulations (respectively).

Included Strains: A/AICHI/65/2023 (AICHI/65); A/BRISBANE/273/2023 (BRI/273); A/CANBERRA/79/2023 (CAN/79); A/DARWIN/11/2021 (DAR/11); A/DARWIN/6/2021 (DAR/6); A/FLORIDA/57/2022 (FL/57); A/GEORGIA/19/2023 (GA/19); A/GREECE/ILI_249/2023 (GRC/ILI_249); A/LEON/4311/2023 (LEON/4311); A/MASSACHUSETTS/18/2022 (MA/18); A/MICHIGAN/60/2022 (MI/60); A/MONTANA/08/2023 (MT/08); A/NAGANO/2100/2023 (NAG/2100); A/NEW YORK/66/2022 (NY/66); A/NEWCASTLE/113/2023 (NEW/113); A/SOUTH AFRICA/R06126/2023 (ZAF/R06126); A/SOUTH AUSTRALIA/48/2023 (SA/48); A/THAILAND/8/2022 (THA/8); A/VICTORIA/260/2023 (VIC/260); A/YAMAGATA/60/2023 (YAM/60); A/YAMANASHI/23018/2023 (YAM/23018).

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

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

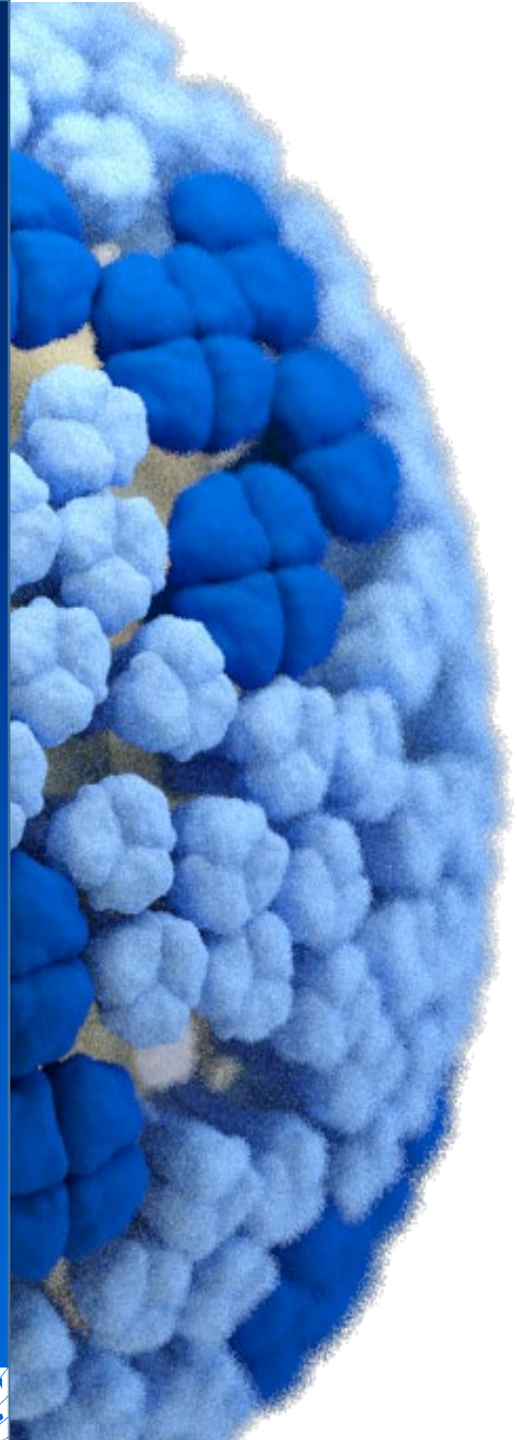
- Most significant reductions in geometric mean titer (GMT) were observed among 2a.1b, 2a.3 and 2b representatives
- Fewer and more subtle reductions in GMT in 2a.3a.1

A(H3N2) virus antiviral susceptibility

- Neuraminidase inhibitors
  - **None of 2,240** A(H3N2) viruses collected and analyzed since 1 February 2023 showed genetic or phenotypic evidence of reduced inhibition to neuraminidase inhibitors.
- Endonuclease (PA) inhibitors
  - **Of 1,092** A(H3N2) viruses collected and analyzed since 1 February 2023, **10** showed genetic or phenotypic evidence of reduced susceptibility to baloxavir marboxil.

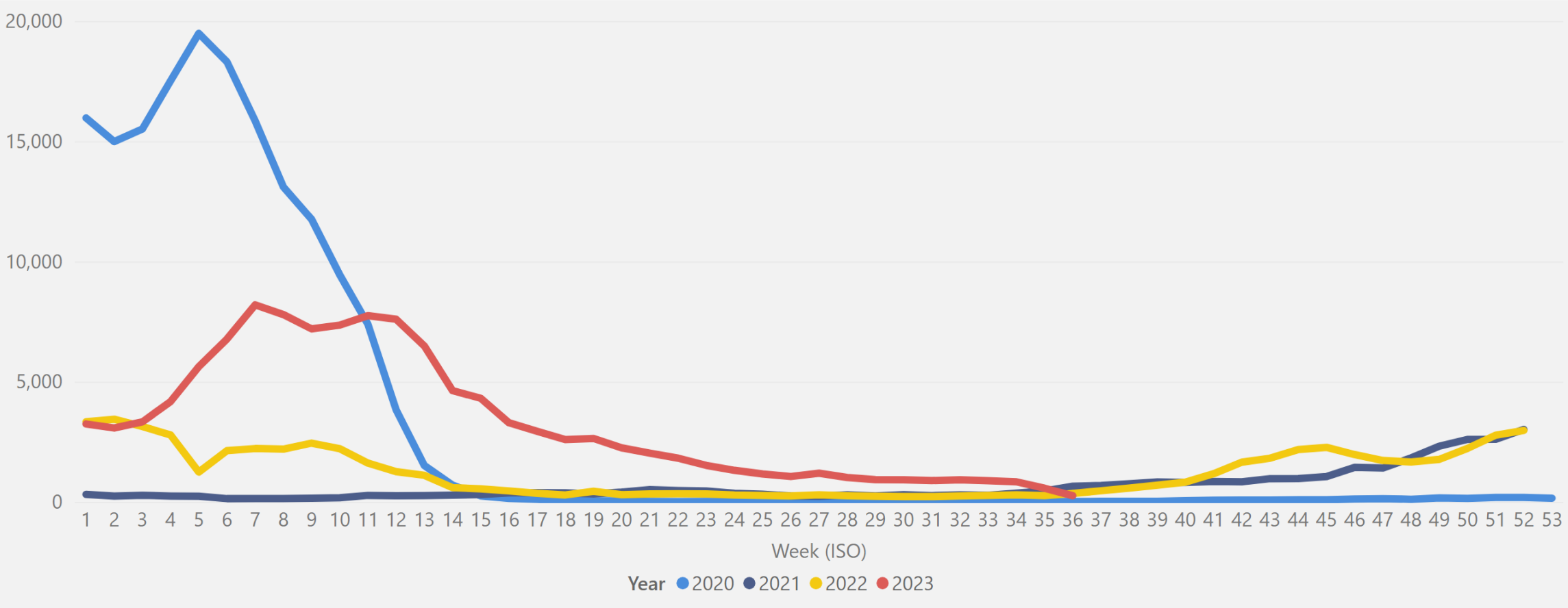
A(H3N2) summary

- Collectively the data indicated that updating the vaccines to contain A/Thailand/8/2022 (H3N2)-like (egg-based) or A/Massachusetts/18/2022 (cell/recombinant-based) for the southern hemisphere 2024 was warranted.
  - A(H3N2) subtype predominated in In some countries, areas and territories
    - Most A(H3N2) activity was observed in southern Africa and in Asia
  - Phylogenetics analysis of the HA genes from viruses in this period showed continued diversification of the HA clade 2a (complete classification 3C.2a1b.2a.**2a**), whereas clade 2b has been stable.
    - Major clades were 2a.3a.1 > 2b > 2a.1b
    - Clade 2a.3a.1 increased in proportion during this period, and predominated where A(H3N2) activity/epidemics occurred.
  - Ferret antisera to:
    - A/Darwin/6/2021-cell (2a) recognized viruses expressing most HA clade 2 derivatives well. Limited reductions were seen among viruses expressing 2b and 2a.3a.1 HA clades and this was more pronounced with A/Darwin/9/2021-egg antisera.
    - A/Massachusetts/18/22-cell or A/Thailand/8/2022 (H3N2)-like (egg-based) reacted well with most viruses circulating particularly those expressing clade 2a.3a.1 HA genes.
  - Overall, most human postvaccination sera (A/Darwin/6/2021-like) reacted well with most emerging lineages including 2a.3a.1. However, some recent HA clade 2a.1b, 2a.3a.1 and 2b virus representative were significantly reduced in some serum panels in some laboratories.
  - Interim vaccine effectiveness estimates from the southern hemisphere were very limited due to low circulation overall.
- Nearly all viruses analyzed showed susceptibility to antivirals



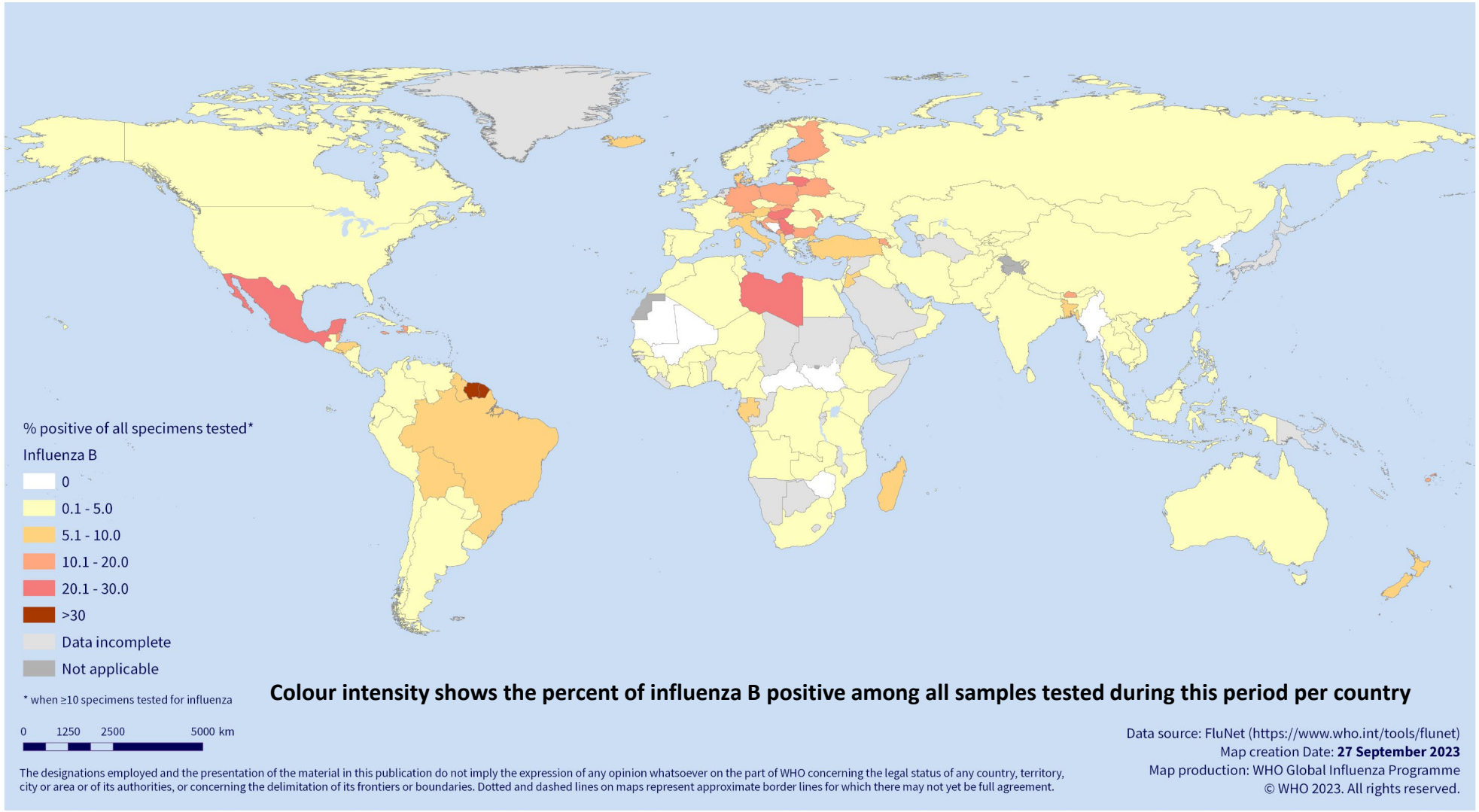
Influenza B Viruses

Number of influenza B viruses detected by GISRS



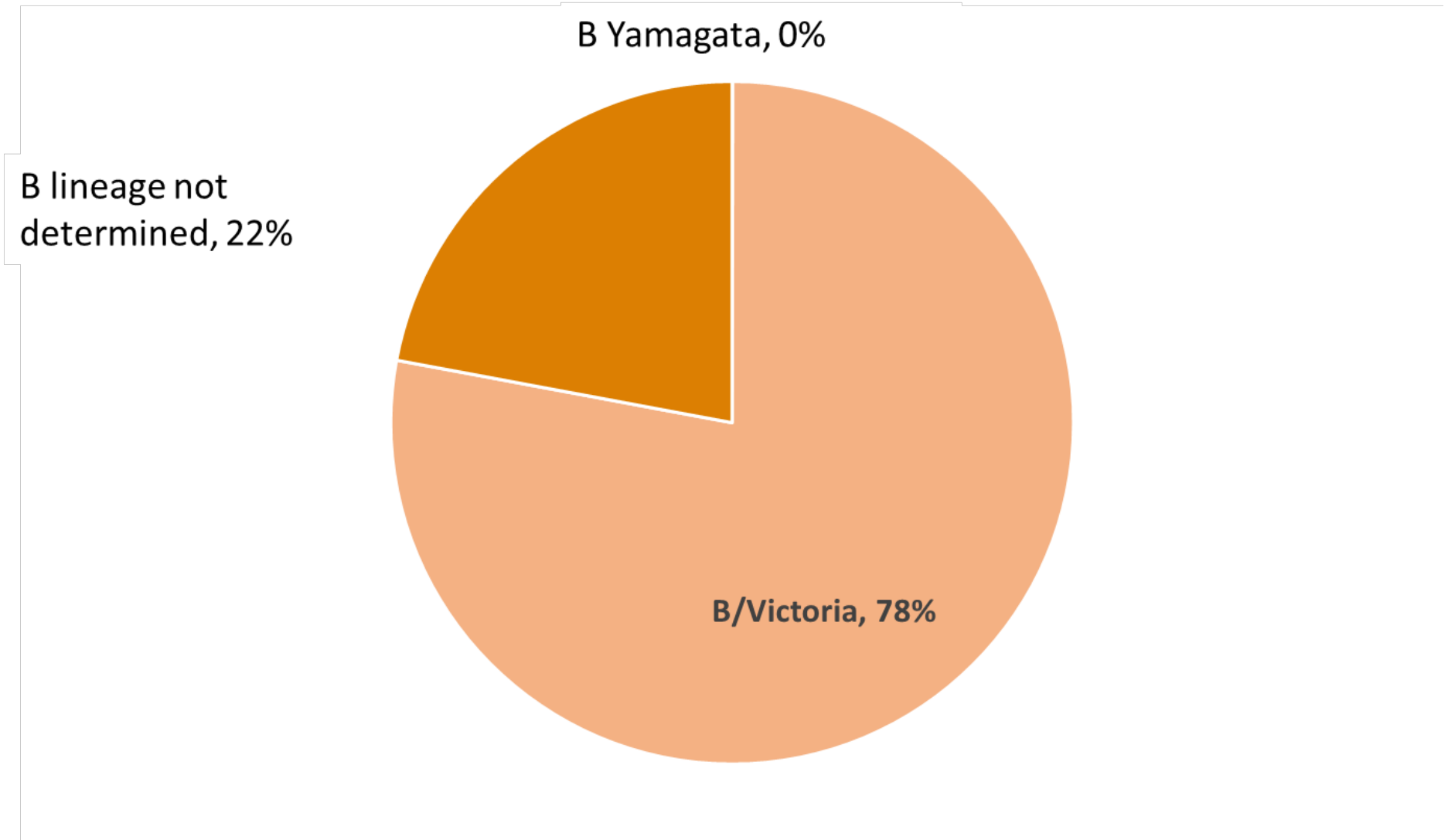
Data source: FluNet, (https://www.who.int/tools/flunet), Global Influenza Surveillance and Response System (GISRS)

Influenza B virus activity

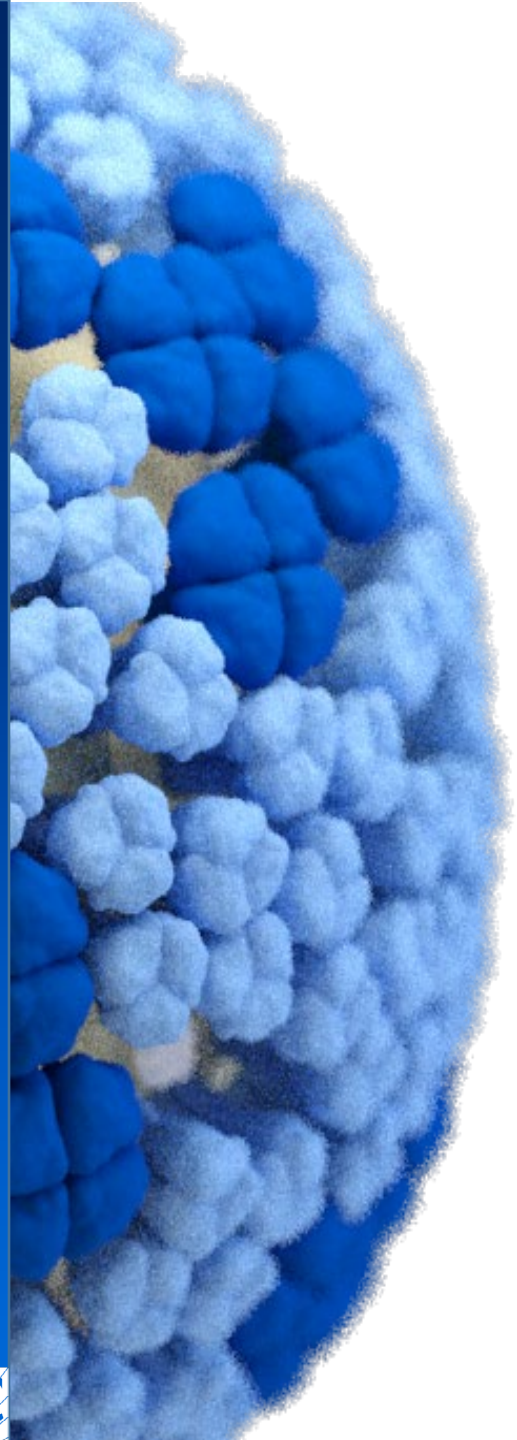


Data source: FluNet, (https://www.who.int/tools/flunet), Global Influenza Surveillance and Response System (27 Sep 2023)

Circulating influenza B virus lineages (Feb 2023 – Aug 2023)

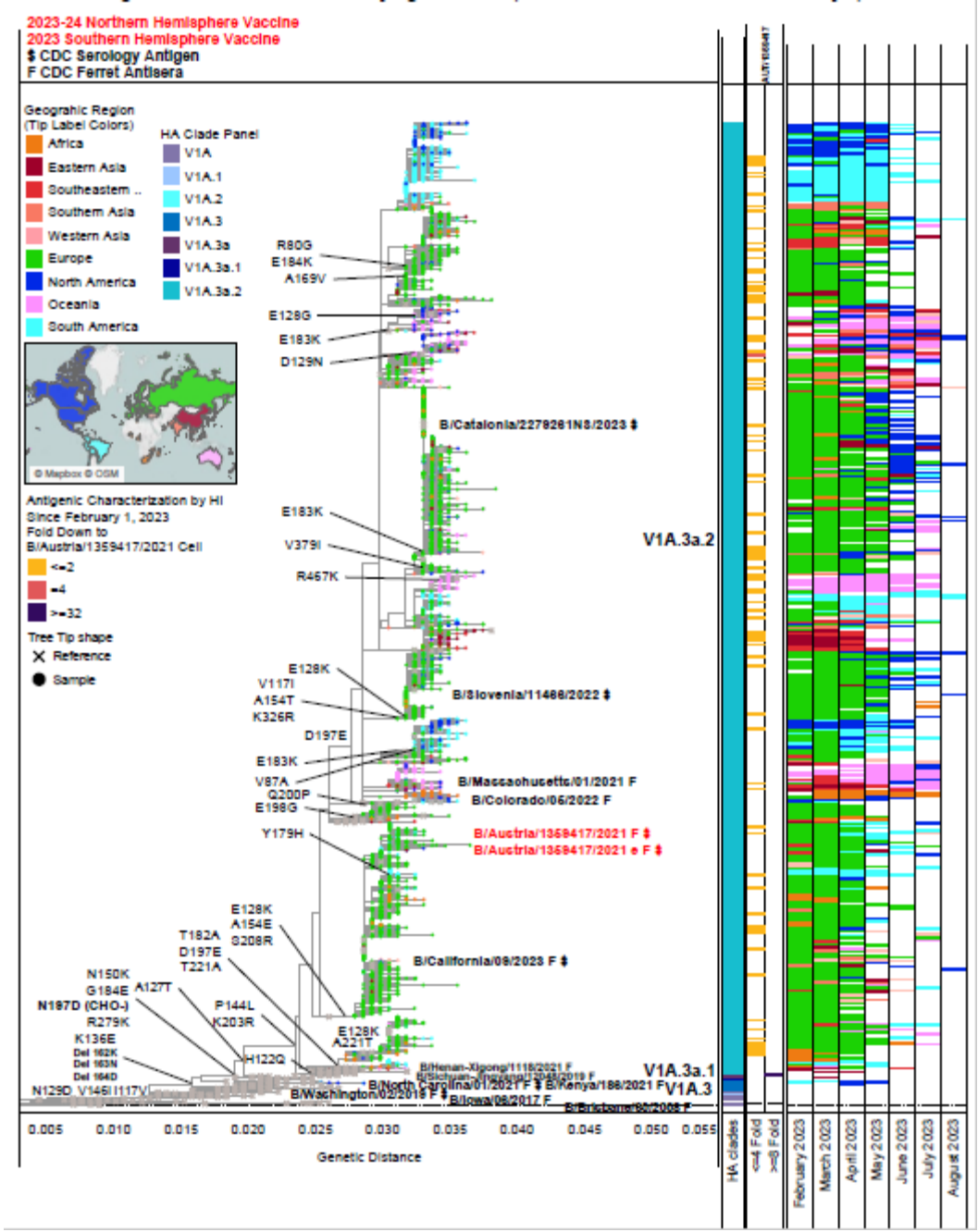


Data source: FluNet, (https://www.who.int/tools/flunet), Global Influenza Surveillance and Response System (15 Sep 2023)



Influenza B/Victoria Viruses

Recent B/Victoria lineage HA phylogenetics



WHO CC
CDC, USA

3a.2
(A127T, P144L, K203R)

B/Austria/1359417/2021

3

Antigenic analysis of B/Victoria viruses

Antisera to southern hemisphere 2022 antigens

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

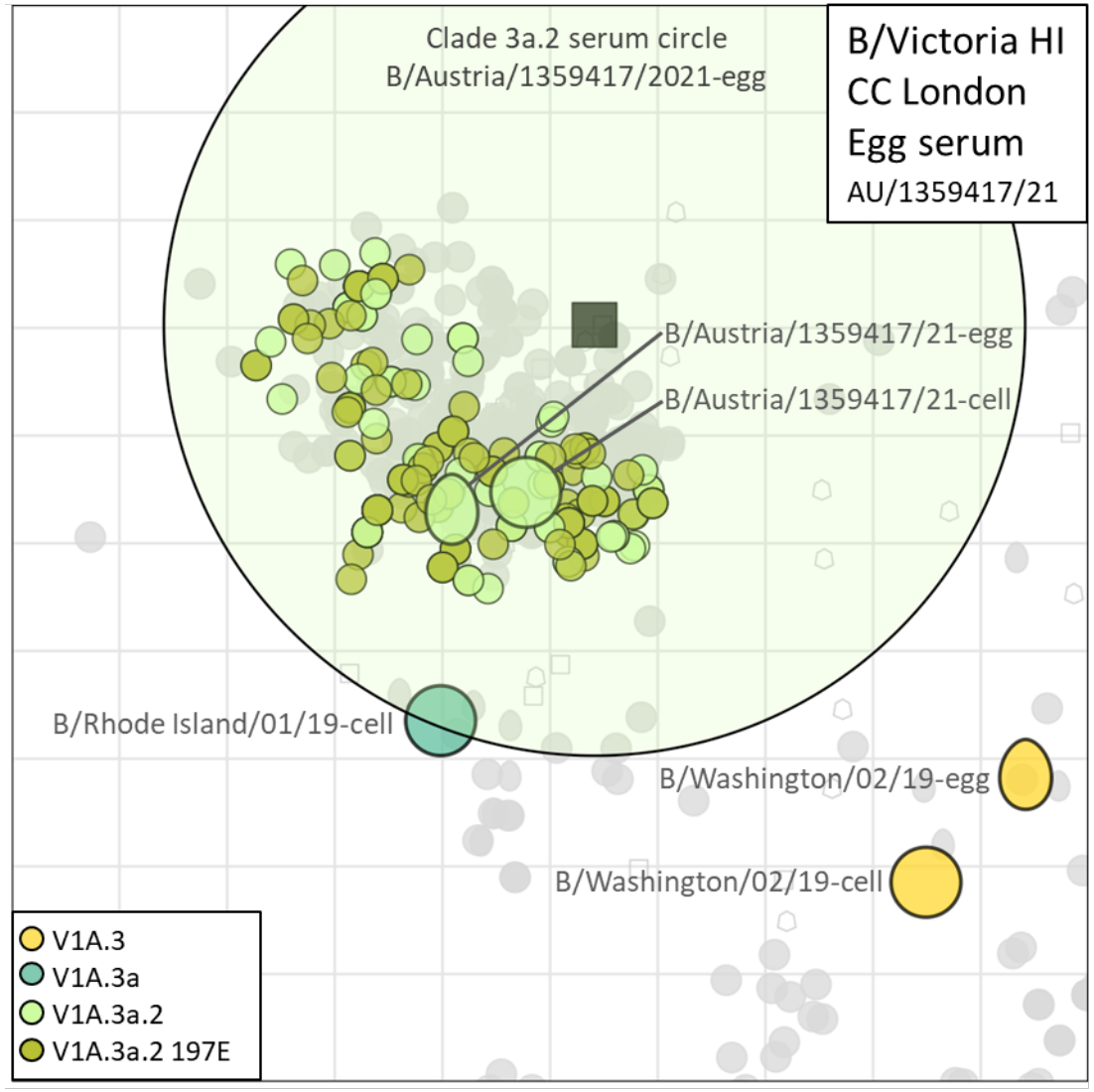
WHO CC	Like (2-4 fold)	Low (≥ 8-fold)
CDC	161 (99%)	2 (1%)
CNIC	40 (98%)	1 (2%)
FCI	285 (100%)	1 (0%)
NIID	29 (100%)	0 (0%)
VIDRL	1436 (100%)	1 (0%)
TOTAL	1951 (>99%)	5 (<1%)

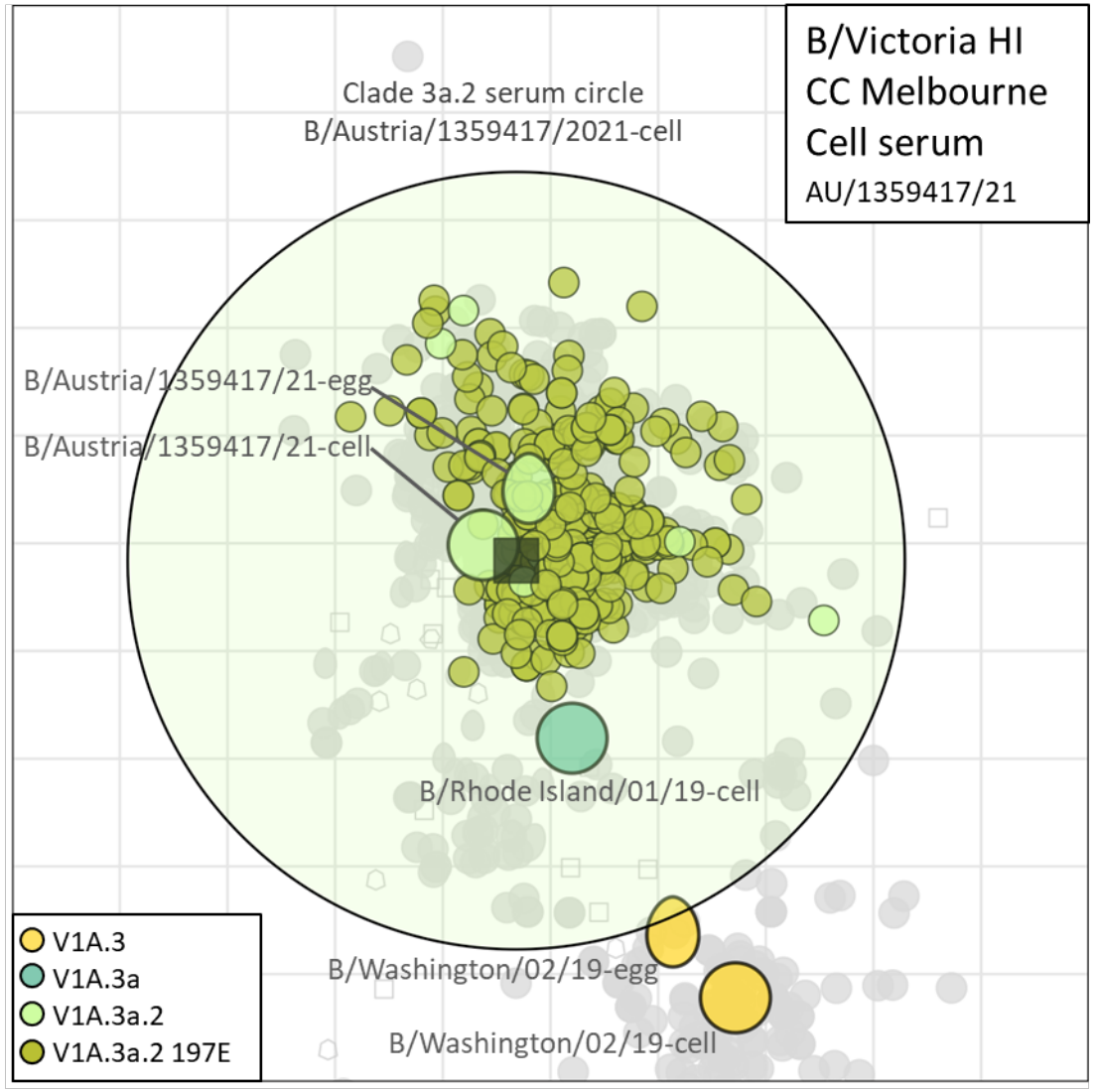
B/Austria/1359417/2021-like (egg)

WHO CC	Like (< 8-fold)	Low (≥ 8-fold)
CDC	161 (99%)	2 (1%)
CNIC	40 (98%)	1 (2%)
FCI	285 (100%)	1 (0%)
NIID	29 (100%)	0 (0%)
VIDRL	1420 (99%)	17 (1%)
TOTAL	1935 (99%)	21 (1%)

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

B/Victoria antigenic cartography





Antiserum circles (within 8-fold of homologous titers)

Human post-vaccination serum analysis of B/Victoria viruses

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

					V1A.3a.2										V1A.3					
					-				+A154T +D197E	+E183K +D197E			+E128G +E183K +D197E	+D197E +T222A +G230D	+E128K +A154E +S208P		-		+N233K (CHO-)			
					AUT/1359417				SVN/11466	CAT/2279261NS-LIKE			TOKYO/22103	OSAKA/01	CA/09-LIKE		WA/02		NC/01			
					-				-	CAT/2279261NS	BUR/4810	CO/05	-	-	CA/09	POL/157	-		-			
					CELL				CELL	CELL	CELL	CELL	CELL	CELL	CELL	CELL	CELL		CELL			
					CDC	CBER	MHRA	NIID	CDC	CDC	MHRA	CBER	NIID	NIID	CDC	MHRA	CDC	CBER	CDC	CBER	MHRA	NIID
B/AUSTRIA/1359417/2021 CELL	Pediatric (CDC: 6-35M)	IIV4	2022-23NH	USA	67				√	√					√		9		9			
	Pediatric (CDC: 3-8Y)	ccIIV4 (Flucelvax)	2022-23NH	USA	178				√	√					√		98		106			
	Adult	ccIIV4 (Flucelvax)	2022-23NH	USA	135				√	√					√		72		89			
			2023SH	Australia	194	236	109	311	√	√	√	√	√	√	√	√	50	15	61	103	61	211
		IIV4	2022-23NH	USA		27						X						6		6		
				UK			52				√					√					31	
			2023SH	Australia	76	43	139	211	√	√	√	√	√	√	√	√	37	9	42	15	94	√
		IIV3	2023SH	Peru	77		130		√	√	√				√	√	31		30		63	
	Elderly	aIIV4	2023SH	Australia	62	36	130	193	√	√	√	X	√	√	√	√	19	7	19	9	34	√
									0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	7 (100.0)	4 (100.0)	7 (100.0)	4 (100.0)	5 (100.0)	1 (33.3)

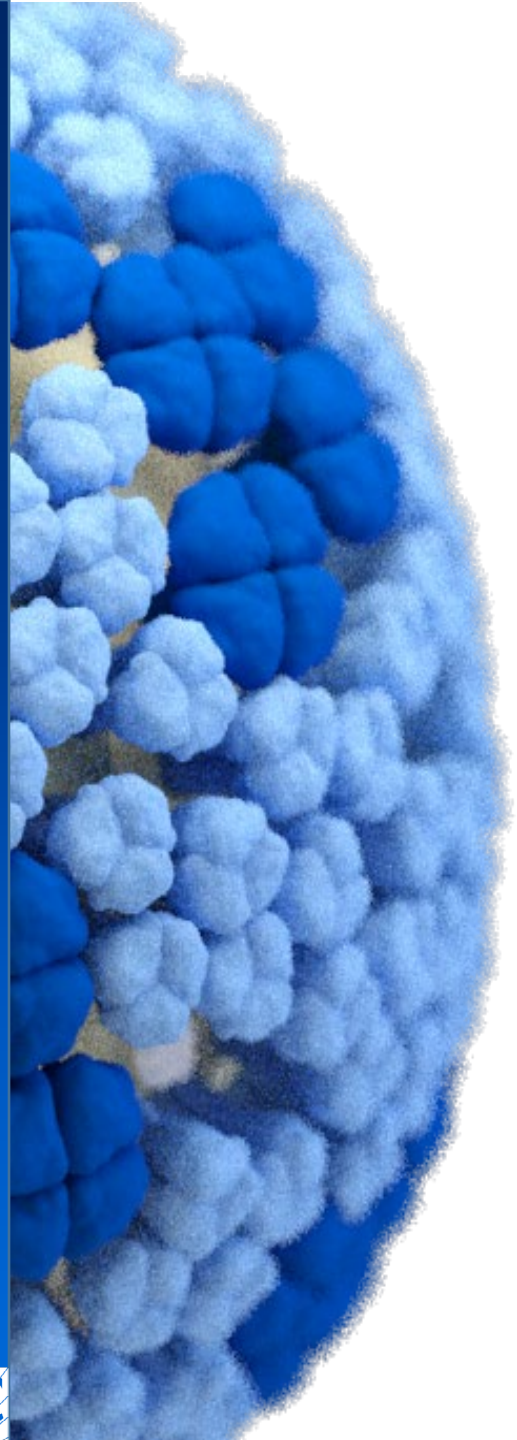
Geometric Mean Titer (GMT) ratios between reference and test antigens are calculated with 90% (CI) confidence intervals for each cohort and panel location. Unadjusted model results are shown. If the CI lower bound is greater than 50%, it is statistically non-inferior (95% confidence level), otherwise 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.

Australian/Peruvian and UK/US population cohorts vaccinated with 2023 Southern Hemisphere (SH) and 2022-23 Northern Hemisphere (NH) vaccine formulations (respectively).

B/Victoria lineage antiviral susceptibility

- **NA inhibitors**
  - **2334** influenza B/Victoria lineage viruses collected since 1 February 2023 were analyzed by genetic and/or phenotypic analysis
    - **Six** showed evidence of highly reduced inhibition by NAIs.
    - **Five** of these viruses had a K360E substitution and one virus had an H134Y substitution in the NA gene.

- **Endonuclease inhibitors**
  - **Of 1,356** B/Victoria lineage viruses collected in this period and analyzed in this period, **none** showed evidence of reduced susceptibility to baloxavir.



Influenza B/Yamagata Viruses

B/Yamagata lineage virus

- There have been no confirmed detections of circulating B/Yamagata/16/88 lineage viruses after March 2020.

- Of 15,878 influenza B viruses collected between 1 February and 31 August 2023 and lineage-tested, no B/Yamagata/16/88 lineage viruses were confirmed.
  - Of the 15 viruses initially identified as B/Yamagata lineage:
    - 13 were confirmed to be B/Victoria lineage viruses or were negative for influenza B
    - 2 were not available for confirmation and did not yield gene sequence data or virus isolates.

B/Yamagata lineage virus (2)

- The absence of confirmed detection of naturally occurring B/Yamagata lineage viruses is indicative of very low risk of infection by B/Yamagata lineage viruses.
- It was the opinion of the WHO influenza vaccine composition advisory committee that while both trivalent and quadrivalent vaccines remain safe and effective, the inclusion of a B/Yamagata lineage antigen in quadrivalent influenza vaccines is no longer warranted, and every effort should be made to exclude this component as soon as practically possible.
- The committee recognizes that national or regional authorities are responsible for approving the composition and formulation of vaccines used in each country and should consider the use & relative benefit(s) of trivalent or quadrivalent influenza vaccines.

Influenza B virus summary

- Only influenza B/Victoria lineage viruses were available for analysis
- Collectively there was not evidence that updating the B/Victoria vaccine antigen (B/Austria/1359417/2021-like (HA clade 3a.2) was needed.
- Phylogenetics analysis of the HA genes showed that 3a.2 (share A127T, P144L and K203R) vastly predominated, had global circulation and continue to diversify while antigenically distinct viruses expressing progenitor clade 3 (1A.3) and 3a.1 HA genes continue to decline.
- Antigenically nearly all the viruses tested are well recognized by ferret antisera to B/Austria/1359417/2021-like viruses (3a.2 HA).
- Post vaccination human antisera well inhibited the diversity of HA clade 3a.2 viruses and the only reductions in GMTs were only detected with most serum panels for viruses that express the progenitor clade 3 (1A.3) HA genes similar to previous vaccine antigens.
- Interim vaccine effectiveness estimates from the Southern hemisphere indicate that the vaccines were highly effective.
- Nearly all viruses analyzed showed susceptibility to antivirals.

Support and Disclaimer

The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention.

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