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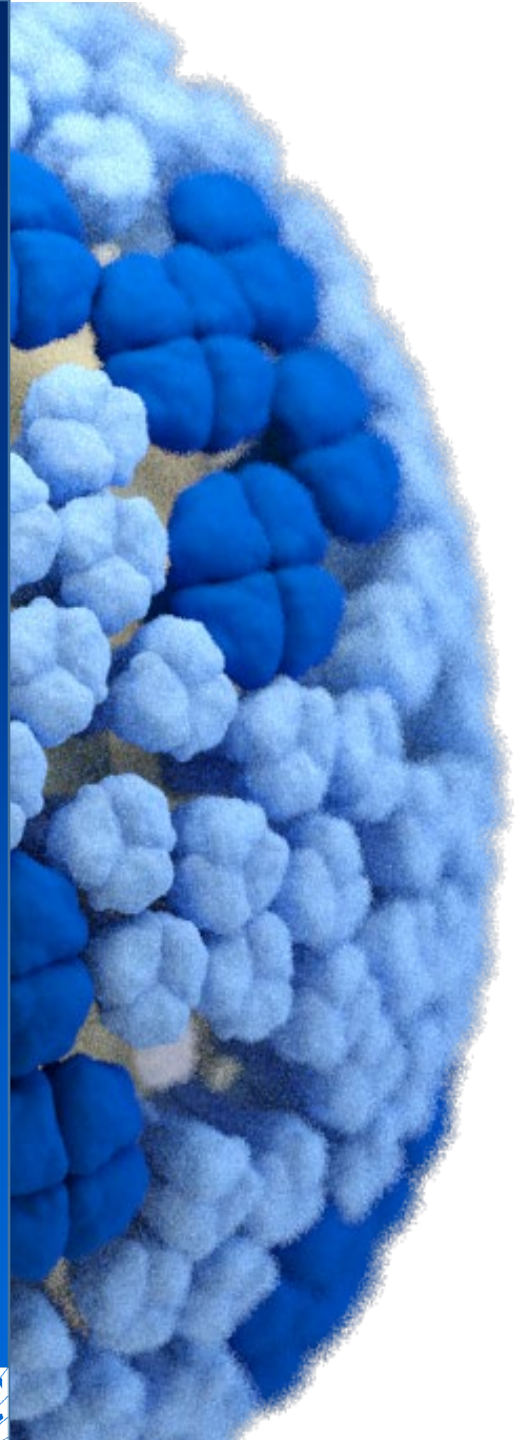


WHO-CC for Influenza | VSDB | Influenza Division | NCIRD

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

Global Influenza Virus Surveillance and Characterization October 10th, 2024

Rebecca Kondor, Ph.D.
Interim Director, WHO Collaborating Center for Surveillance, Epidemiology and Control of Influenza
Influenza Division, National Center for Immunization and Respiratory Diseases
Centers for Disease Control and Prevention
Atlanta, GA 30333

WHO vaccine consultation meeting for the southern hemisphere 2025 influenza vaccine

Continuous surveillance conducted by Global Influenza Surveillance and Response System (GISRS)

- WHO GIP, WHO CCs, NICs, WHO ERLs, WHO H5 Reference Laboratories
- Supported by countries and partners worldwide

WHO Vaccine Consultation Meeting 23 – 26 Sep 2024 in Melbourne, Australia

- In-person meeting
  - Recommendations for vaccine composition for seasonal/epidemic influenza viruses and candidate vaccine viruses for zoonotic influenza
- Chair: Dr. Ian Barr (Deputy Director WHO CC in Melbourne, Australia)
- 10 Advisers: Directors of WHO CCs and ERLs
  - Disclosure of interests at the start of meeting
- 45 observers from NICs, WHO CCs, WHO ERLs, WHO H5 Ref Labs, national/regional/global public health agencies, institutions and academia; WOAH, FAO and OFFLU
- WHO ROs and HQ staff

WHO vaccine recommendations for the southern hemisphere 2025

It is recommended that vaccines for use in the 2025 southern hemisphere influenza season contain the following:

Trivalent: Egg-based Vaccines
- **an A/Victoria/4897/2022 (H1N1)pdm09-like virus antigen;**
- **an A/Croatia/10136RV/2023 (H3N2)-like virus antigen*; and**
- **a B/Austria/1359417/2021 (B/Victoria lineage)-like virus.**

Trivalent: Cell-, recombinant protein- or nucleic acid-based Vaccines
- **an A/Wisconsin/67/2022 (H1N1)pdm09-like virus antigen;**
- **an A/District of Columbia/27/2023 (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 2024 southern hemisphere season and from the 2024-25 northern hemisphere season**

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

Candidate vaccine viruses & publications

- The WHO recommended candidate viruses for vaccine development and production for SH 2025, and FAQ;
  - https://www.who.int/teams/global-influenza-programme/vaccines/who-recommendations
- Candidate vaccine viruses and reagents
  - https://www.who.int/teams/global-influenza-programme/vaccines/who-recommendations/candidate-vaccine-viruses
- Guidance to tropical and subtropical countries: which formulation (northern hemisphere vs. southern hemisphere) and when to start vaccination:
  - https://www.who.int/teams/global-influenza-programme/vaccines/vaccine-in-tropics-and-subtropics
- Zoonotic influenza summary reports and candidate vaccine viruses on H5/H7/H9 and variant influenza vaccine viruses:
  - https://www.who.int/teams/global-influenza-programme/vaccines/who-recommendations
  - https://www.who.int/teams/global-influenza-programme/vaccines/who-recommendations/zoonotic-influenza-viruses-and-candidate-vaccine-viruses

Global Influenza Programme (GIP): GISRS-WHOhq@who.int

Goal and key questions addressed for virus vaccine antigen recommendations

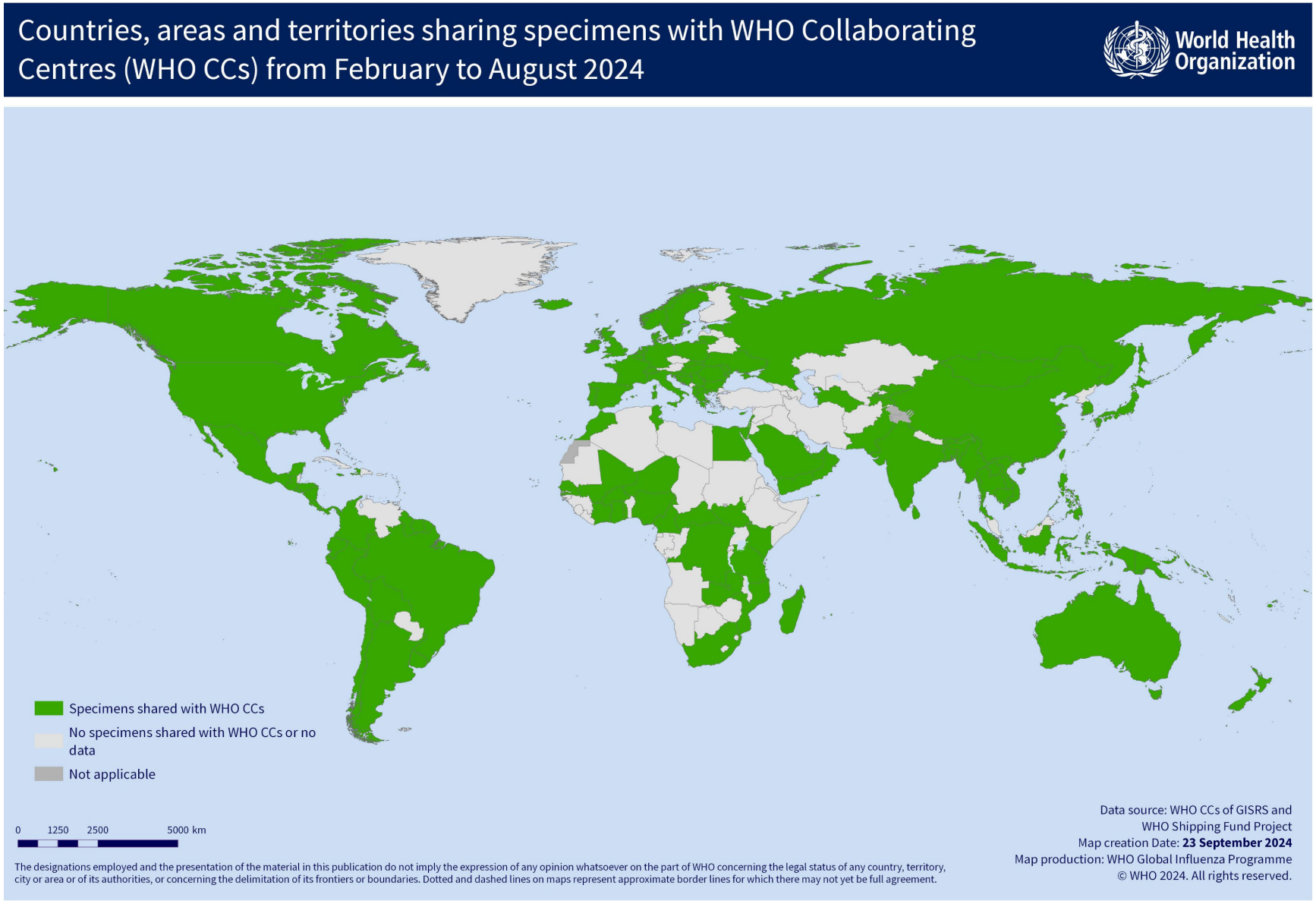
- **Goal of WHO committee on influenza vaccine composition**
  - Identify influenza virus antigen(s) that will elicit immunity against diverse/diverging viruses that will likely co-circulate in the future. Ideal antigens confer breadth of immunity to multiple subclades of viruses and reduce risk(s). It is not trying to "match" just one strain of influenza virus that will circulate.
- **Key questions for each of the antigens (3 or 4) targeted by the vaccine**
  - Are/were there significant epidemics and where were they?
  - What are the influenza A subtypes/influenza B lineages?
    - What are the genetic clades/subclades in circulation and where?
    - What genetic diversity has been observed within subclades (surface proteins/genome)?
    - Are the viruses with new genetic changes/variants spreading geographically?
    - Are the viruses with new variants 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 subclades (i.e., does it confer breadth of protection)?

Data used to address key vaccine update questions

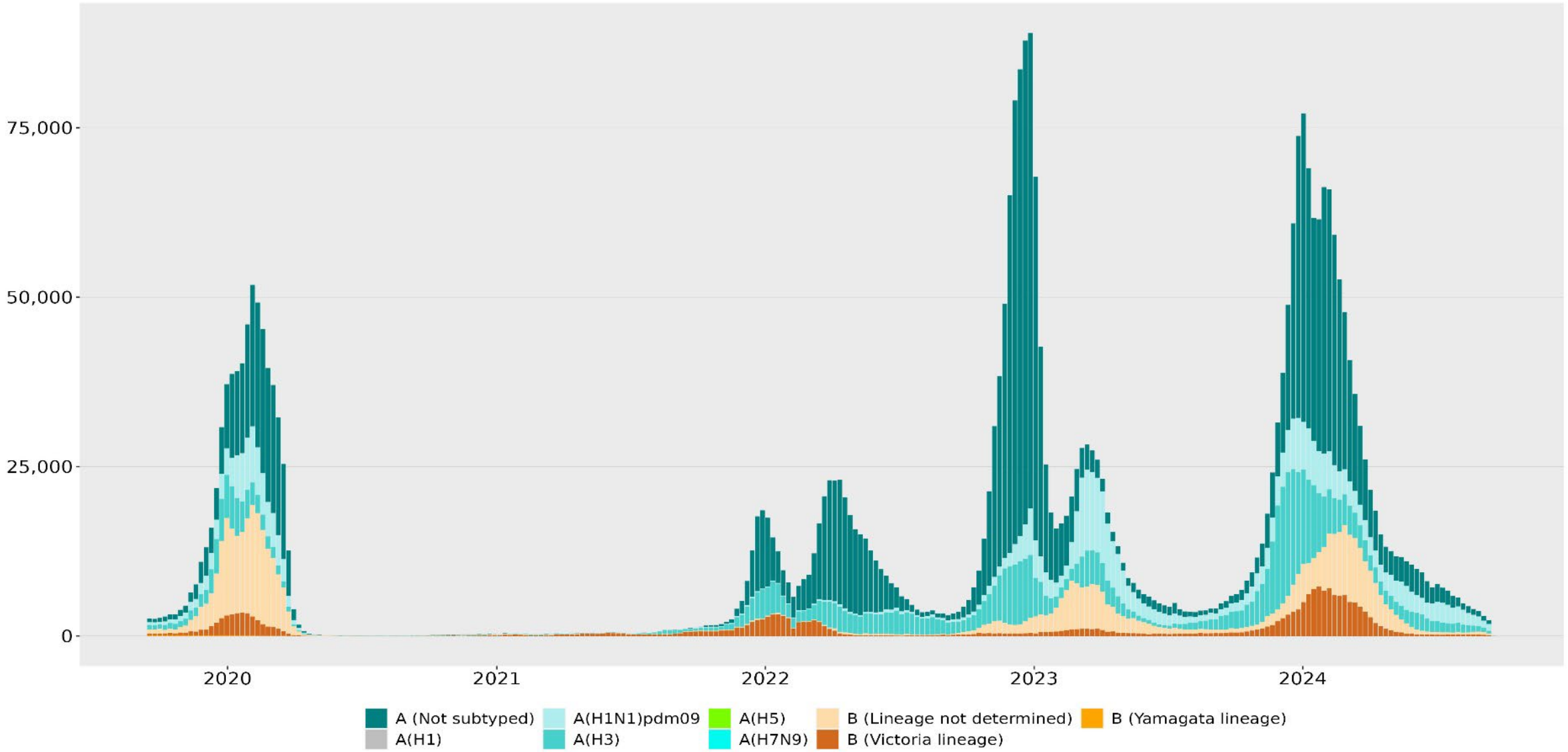
- **Epidemiologic and clinical data**
  - Where are recent epidemics occurring, are they unusual in magnitude or disease
- **Virus surveillance (GISRS: Global Influenza Surveillance and Response System)**
  - GISRS labs test 50-150 thousand samples per week year-round and identify influenza positive 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 for characterization and CVV development
- **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 reassortment, patterns of parallel/convergent evolution
- **Antigenic characterization of representative emerging viruses**
  - Level of antigenic drift from progenitors and/or vaccine references
    - Naïve animal models (ferrets) 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 evaluated as potential candidate vaccines (two-way characterization)
- **Post vaccination human serology studies**
  - Comparative analysis of co-circulating antigenic variants to identify those that pose the greatest risk of immune escape
- **Human population immunity studies**
  - Analysis of antibody levels in US population to vaccine reference viruses and representative circulating viruses
- **Vaccine effectiveness studies (global consortium-GIVE)**
  - VE comparisons across sites/subtype, 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- global and regional estimates
- **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)

Countries, areas and territories shared viruses with WHO CCs

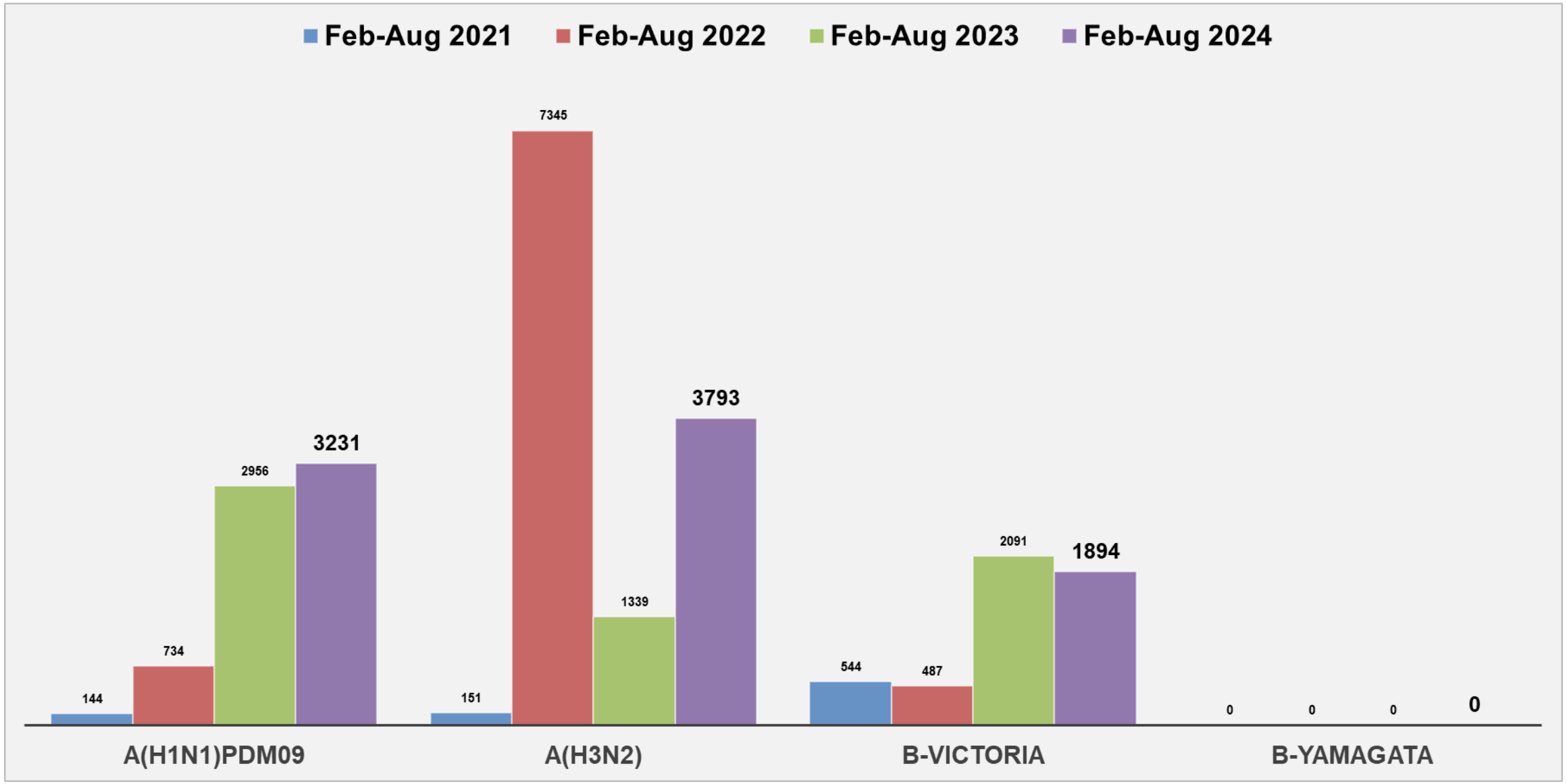
1 Feb 2024 – 31 Aug 2024



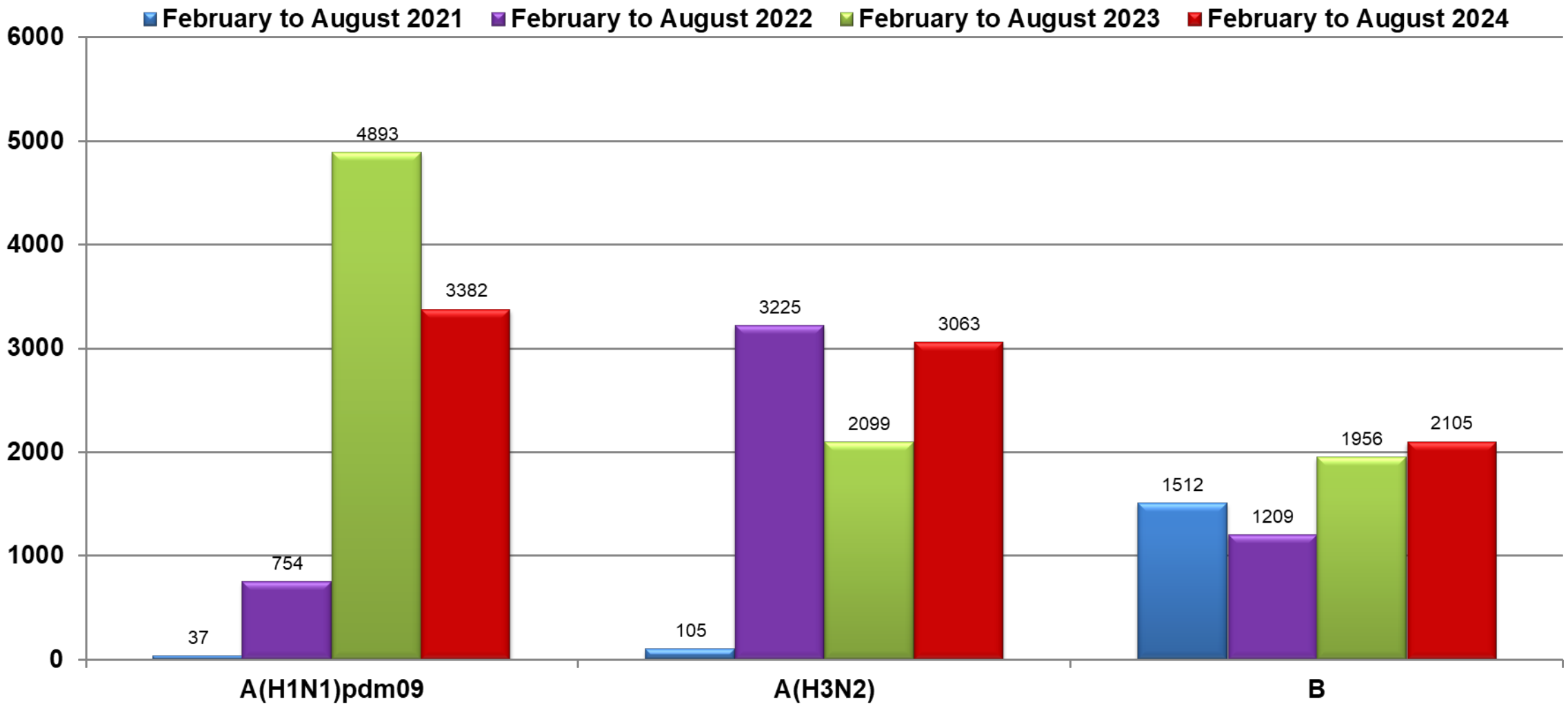
Global circulation of influenza viruses

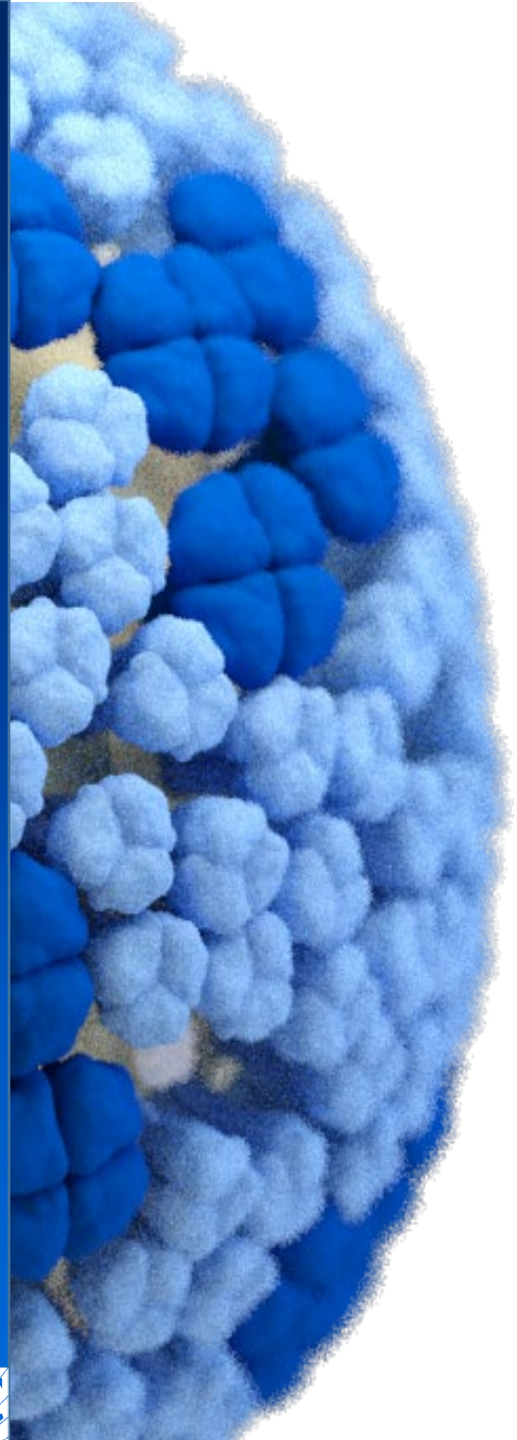


Influenza viruses genetically characterized by WHO CCs over the past 4 southern hemisphere seasons



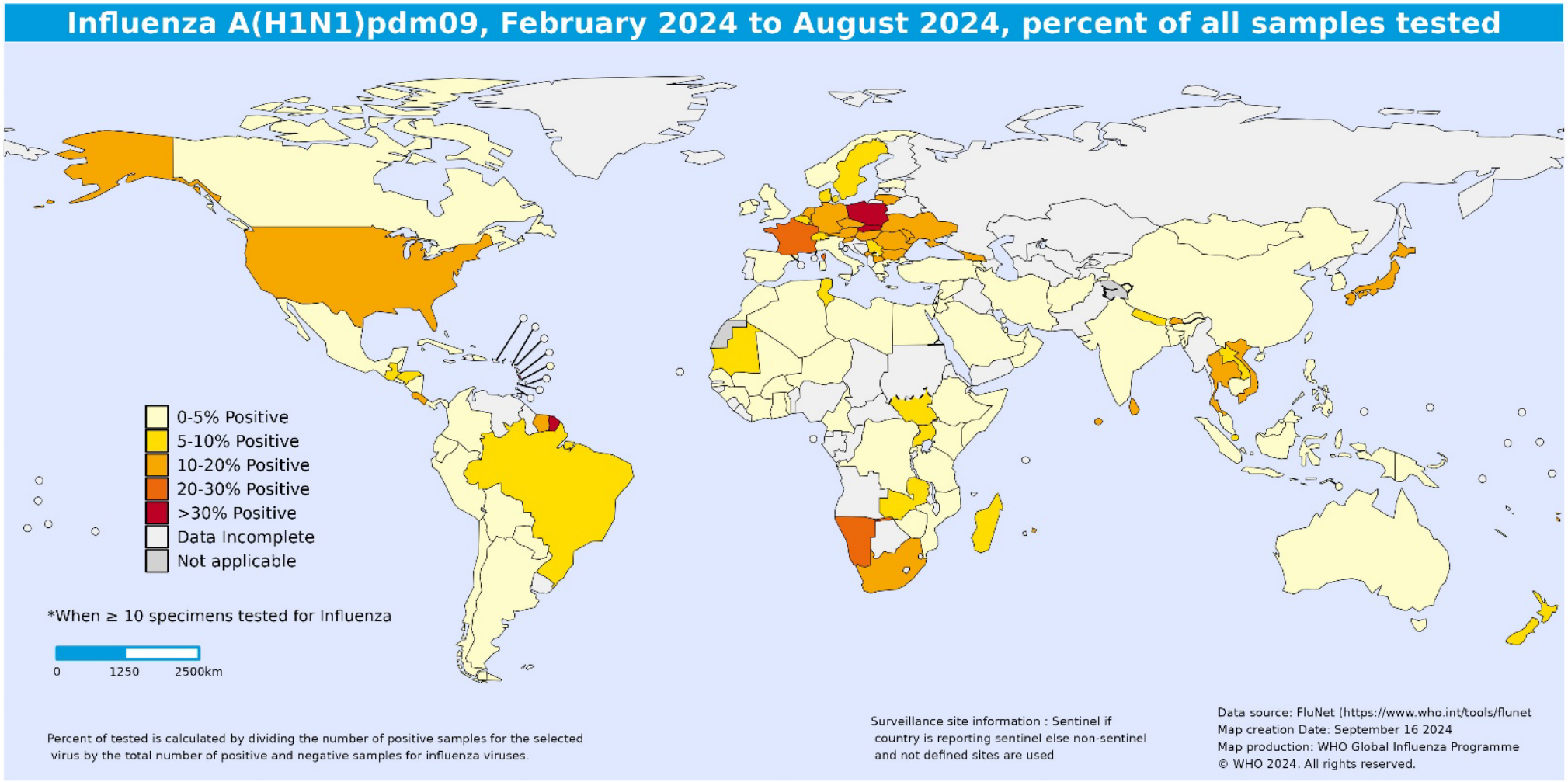
Influenza viruses antigenically characterized by WHO CCs over the past 4 southern hemisphere seasons





A(H1N1)pdm09 Viruses

Influenza A(H1N1)pdm09 virus activity

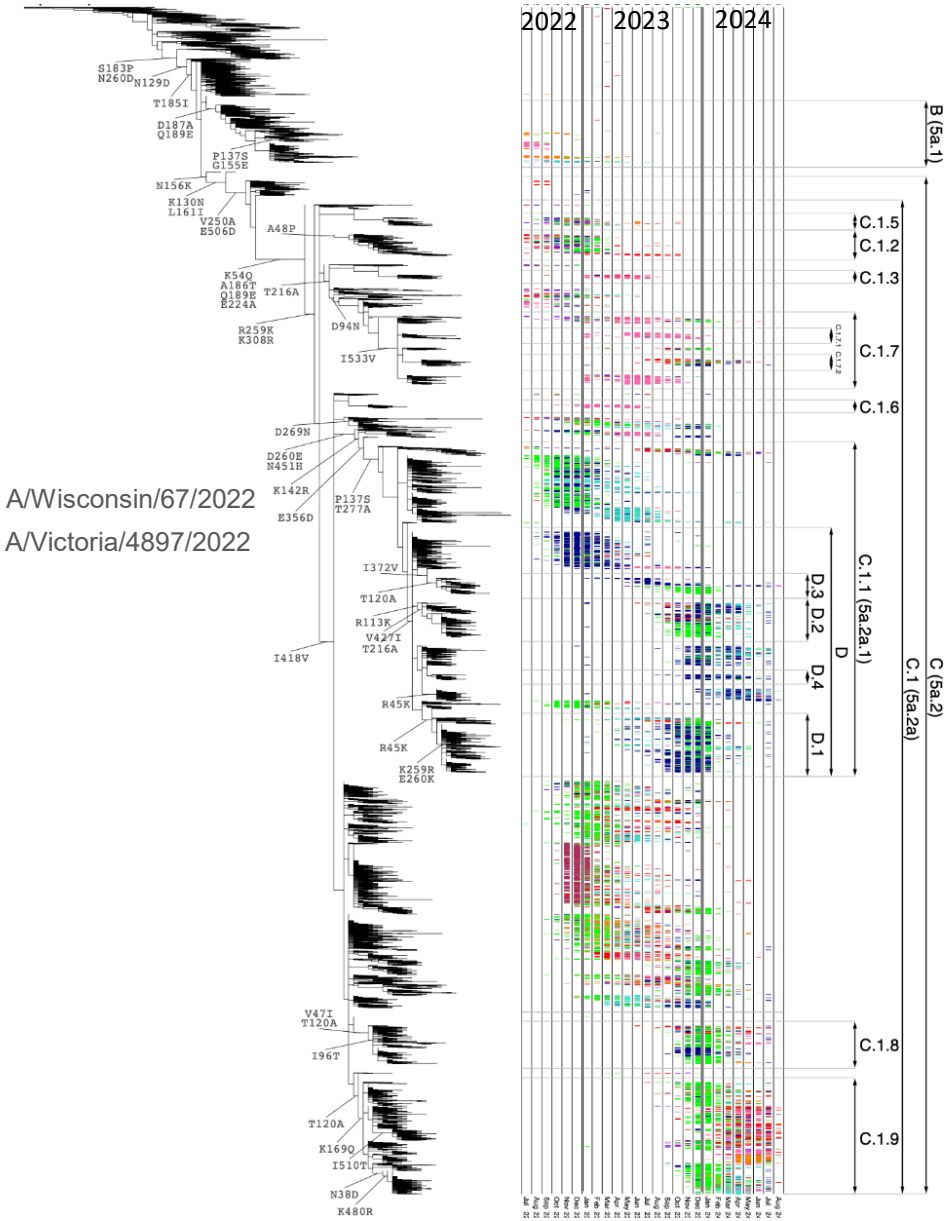


World Health Organization

Colour intensity shows the percent of influenza A(H1N1)pdm09 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 (16 September 2024)

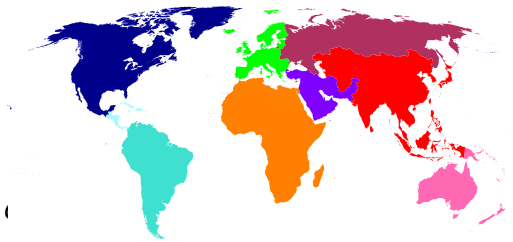
A(H1N1)pdm09 HA phylogeography



5a.2a. C subclades

5a.2a.1 D subclades

5a.2a. C subclades



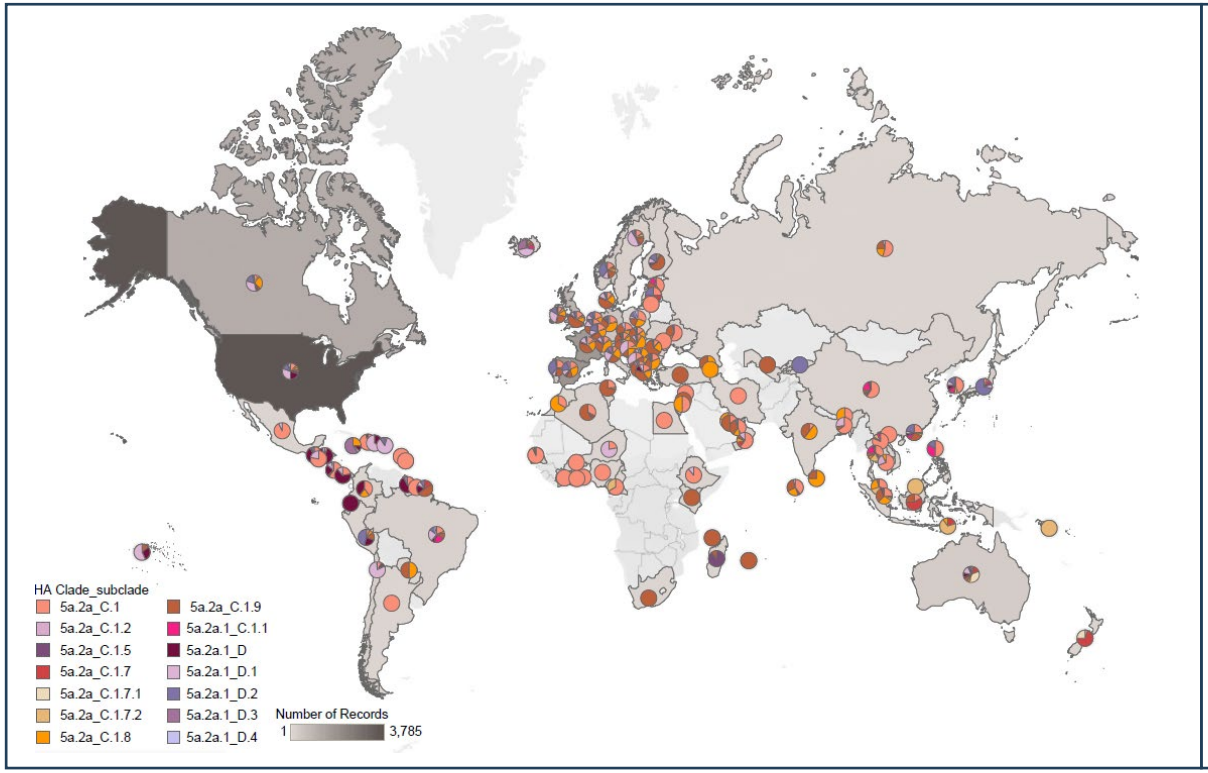
North America
South America
Europe
Africa
Middle East
Russia
E SE Asia
Oceania

Source: University of Cambridge, UK

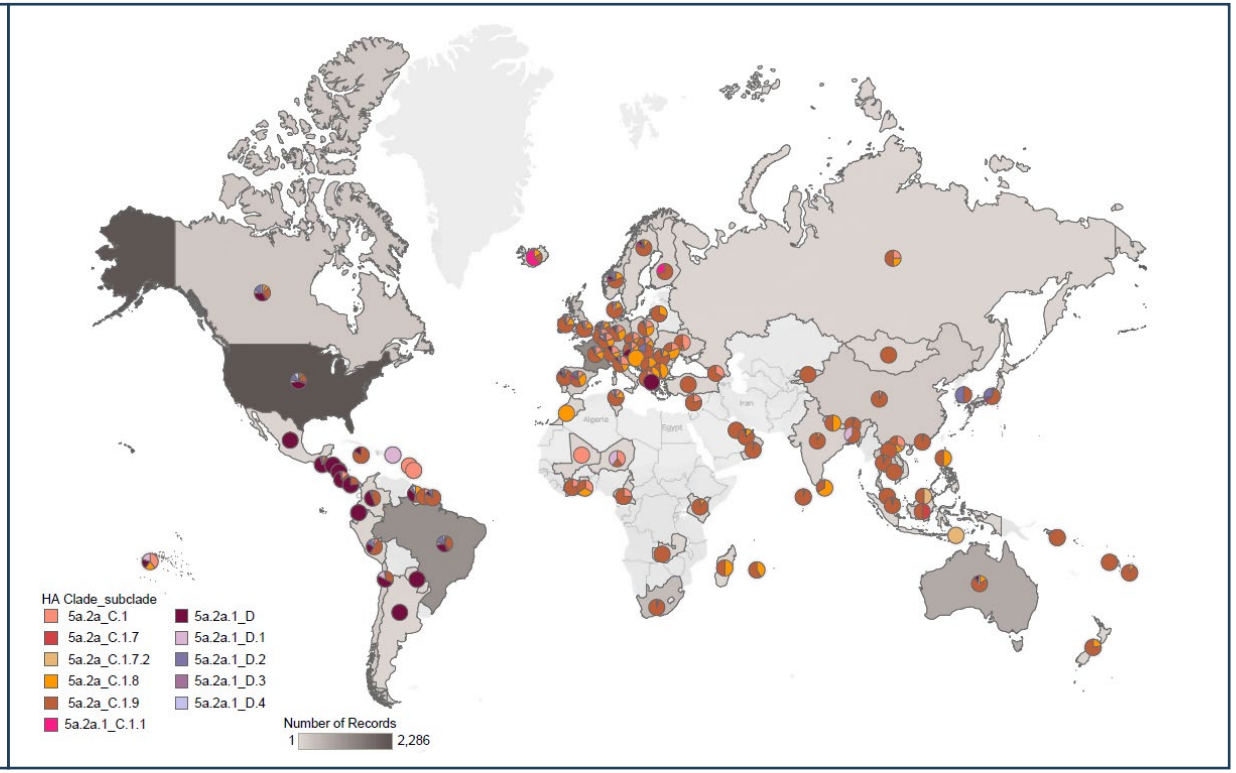
HA subclade: https://clades.nextstrain.org/

Global A(H1N1)pdm09 HA clade diversity

Collection Dates
September 1, 2023 - January 31, 2024



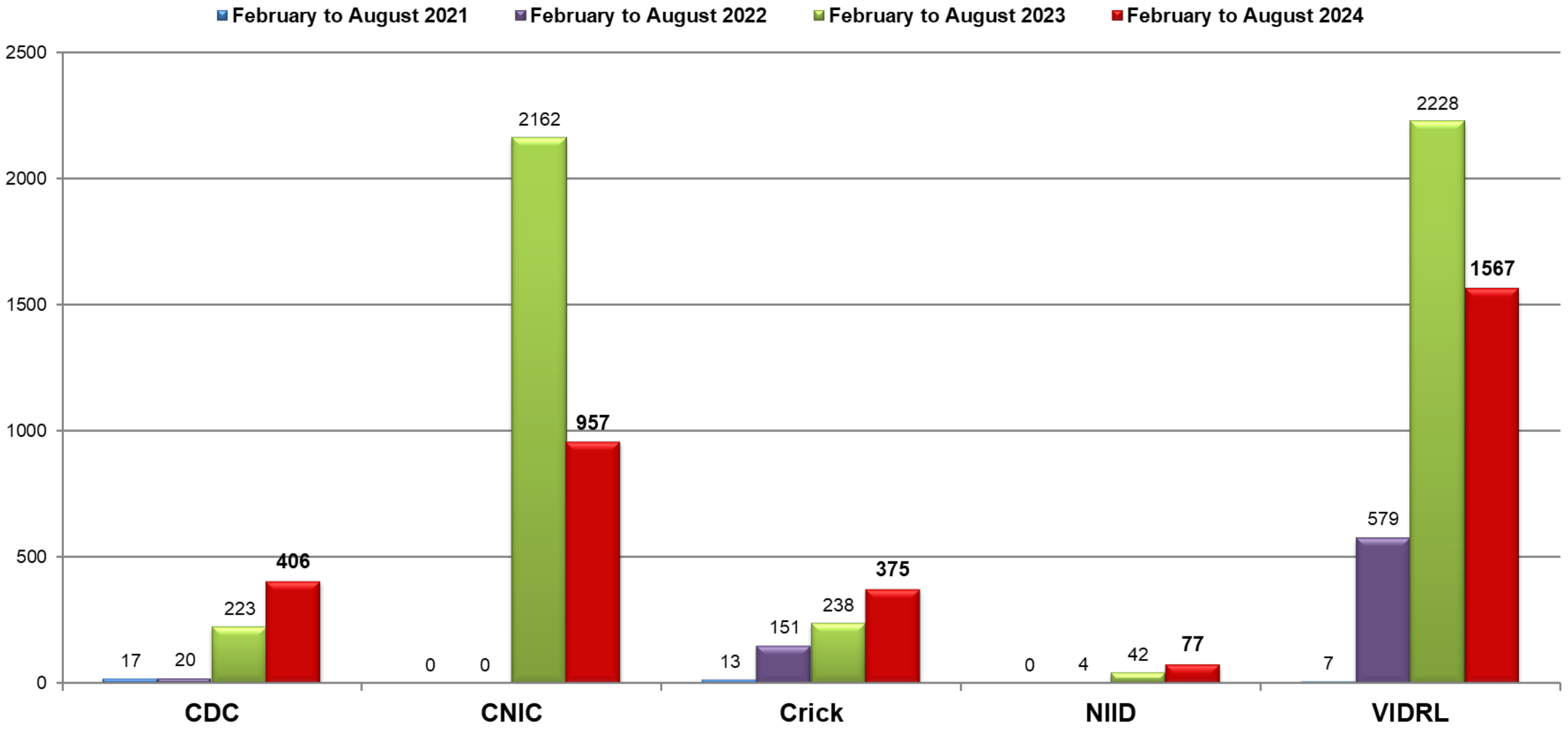
Collection Dates
February 1, 2024 – August 31, 2024



Based on HA sequence availability from GISAID EpiFlu™

Source: WHO CC CDC, USA

A(H1N1)pdm09 viruses antigenically characterized during the past 4 reporting periods



Past 4 reporting periods (southern hemisphere)

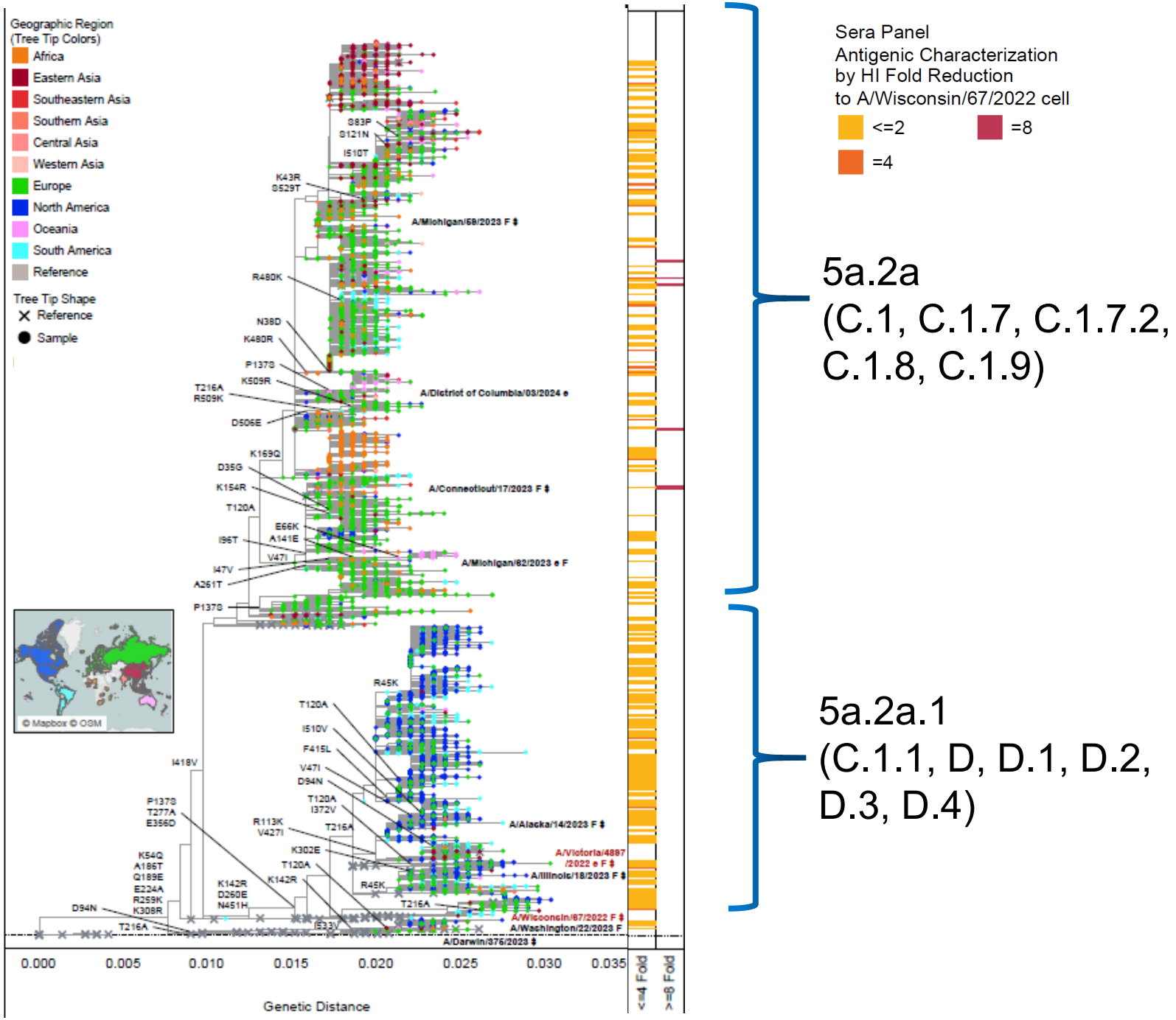
Antigenic analysis of A(H1N1)pdm09 viruses in HI assays by WHO CCs

Antisera to southern hemisphere 2024 vaccine virus antigens

A/Wisconsin/67/2022-like (cell) D (5a.2a.1)			A/Victoria/4897/2022-like (egg) C.1.1 (5a.2a.1)		
WHO CC	Like (<8 fold)	Low (≥ 8 fold)	WHO CC	Like (<8 fold)	Low (≥ 8 fold)
CDC	400 (99%)	6 (1%)	CDC	406 (100%)	0 (0%)
CNIC	933 (97%)	24 (3%)	CNIC	925 (97%)	32 (3%)
FCI	371 (99%)	4 (1%)	FCI	374 (100%)	1 (0%)
NIID	76 (99%)	1 (1%)	NIID	77 (100%)	0 (0%)
VIDRL	1547 (99%)	20 (1%)	VIDRL	1539 (98%)	28 (2%)
TOTAL	3327 (98%)	55 (2%)	TOTAL	3321 (98%)	61 (2%)

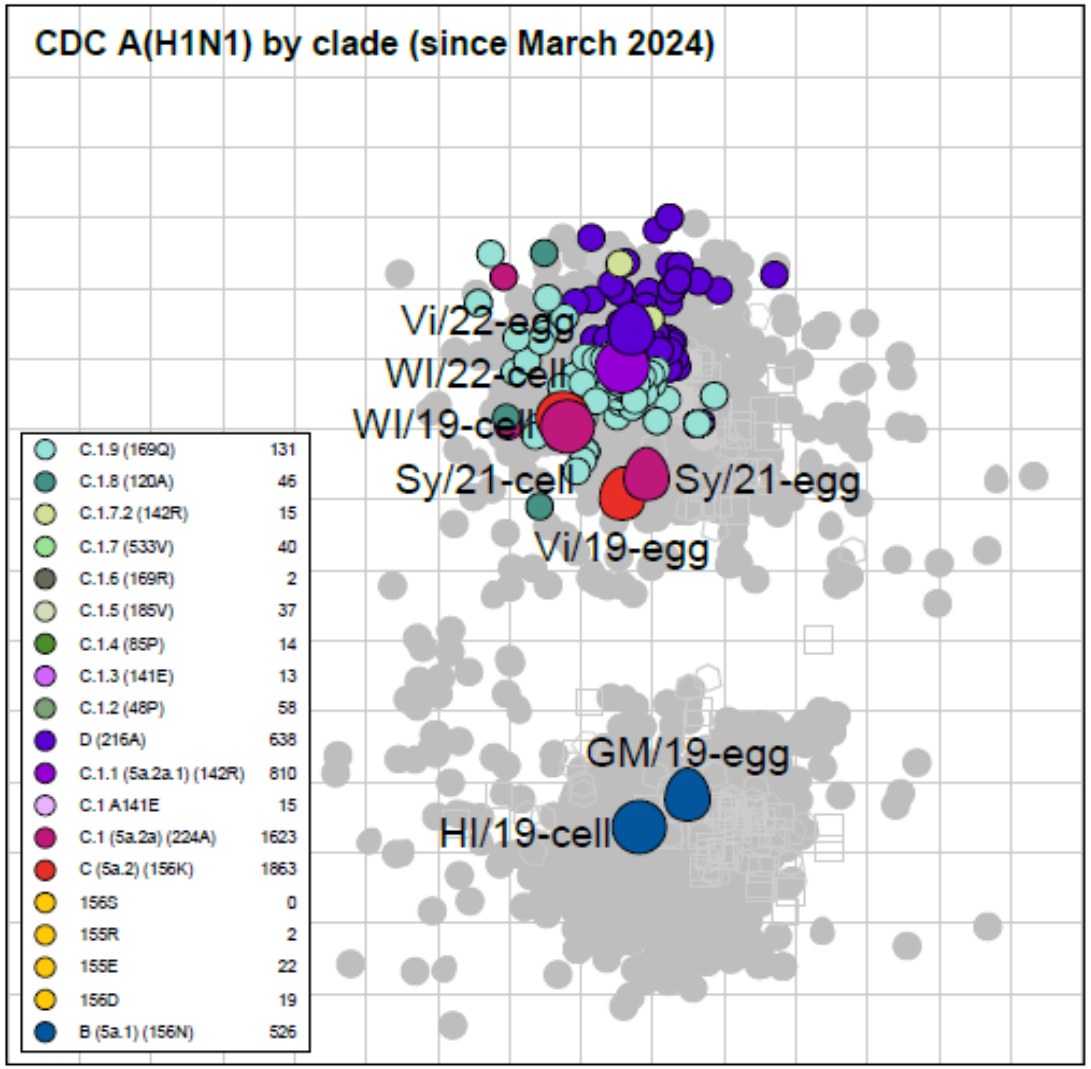
"Low" reactor represented titers ≥ 8-fold lower than vaccine strain homologous titer by HI

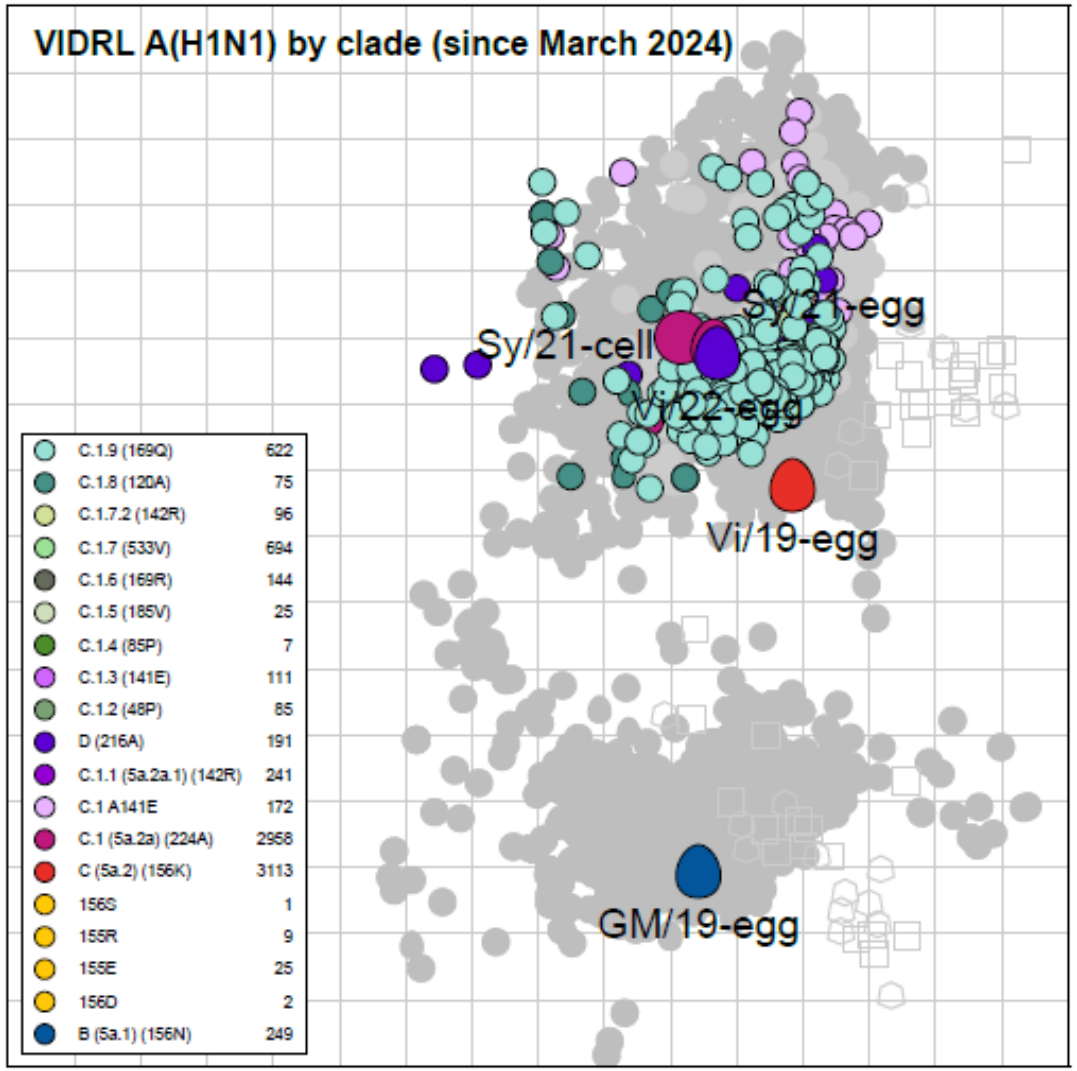
A(H1N1)pdm09 Integrated Genotype and Phenotype Analysis



Source: WHO CC CDC, USA

A(H1N1)pdm09 antigenic cartography





Vi/22 – A/Victoria/4897/2022
WI/22 – A/Wisconsin/67/2022
WI/19 – A/Wisconsin/588/2019
Sy/21 – A/Sydney/5/2021
Vi/19 – A/Victoria/2570/2019
GM/19 – A/Guangdong-Maonan/SWL1536/19

Source: University of Cambridge: Derek Smith and Sarah James

Human post-vaccination serum analysis of A(H1N1)pdm09 viruses

Vaccine: A/Wisconsin/67/2022-like C.1.1 (5a.2a.1)

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

				C.1.1 (5a.2a.1)				D (5a.2a.1)	C.1.7.1 (5a.2a)					C.1.8 (5a.2a)					C.1.9 (5a.2a)									D (5a.2a.1)	D.1 (5a.2a.1)		D.2 (5a.2a.1)				D.3 (5a.2a.1)
				-				+T216A	+V152I					+T120A		+T120A +A141E	+T120A +K154R		+K169Q				+T120A +K169Q	+P137S +K169Q	+A141E +K169Q	+K169Q +T216A		+R45K +T216A	+R45K +T216A +K302E		+R113K +T216A				+T120A +T216A
				WI/67			GA/12	VIC/4897	DAR/375					CT/17-LIKE		AUC/11	BAL/2117		MI/59-LIKE				VIC/317	TAR/13	YOK/26	LISBOA/188		VIC/1429	IL/18		AK/14-LIKE				VIC/1959
				-			-	-	-					CT/17		-	-		MI/59	GD/SWL2511	JT/SWL1586		SGP/KK1423	-	-	-	-	-	-		AK/14		AKITA/1	NOR/79	-
				CELL			CELL	CELL	CELL					CELL		CELL	CELL		CELL	CELL	CELL		CELL	CELL	CELL	CELL		CELL	CELL		CELL		CELL	CELL	CELL
				CDC	MHRA	NIID	VIDRL	CNIC	CDC	CNIC	MHRA	NIID	VIDRL	CDC	NIID	CNIC	VIDRL	MHRA	CDC	CNIC	CNIC	MHRA	VIDRL	VIDRL	VIDRL	NIID	MHRA	VIDRL	CDC	MHRA	CDC	MHRA	NIID	MHRA	VIDRL
A/WISCONSIN/67/2022-LIKE CELL	Adult	ccIIV4 (Flucelvax)	Australia	320	735	557	184	459	√	249	286	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	434	√	378	√	√	√
		IIV4	Australia	151	223	243	76	147	√	85	128	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√
			Peru	61	113	135	29	48	√	√	55	√	X	√	√	√	X	√	√	√	√	√	X	X	X	√	√	X	√	√	√	35	√	√	X
	Elderly	aIIV4	Australia	34	59	70	17	35	X	19	27	√	X	X	√	X	X	√	X	X	X	√	X	X	X	√	√	X	X	30	X	24	√	√	X
		IIV4	Hong Kong	36					X					X					X											X		X			
									0 (0.0)	3 (75.0)	4 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (50.0)	0 (0.0)	3 (75.0)	0 (0.0)	0 (0.0)	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.

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

Neuraminidase inhibitors

- Of 3,300 A(H1N1)pdm09 virus clinical samples and isolates that were examined for neuraminidase inhibitor (NAI) susceptibility by genetic and/or phenotypic analyses, 63 viruses showed evidence of reduced susceptibility to NAIs.

Endonuclease inhibitors

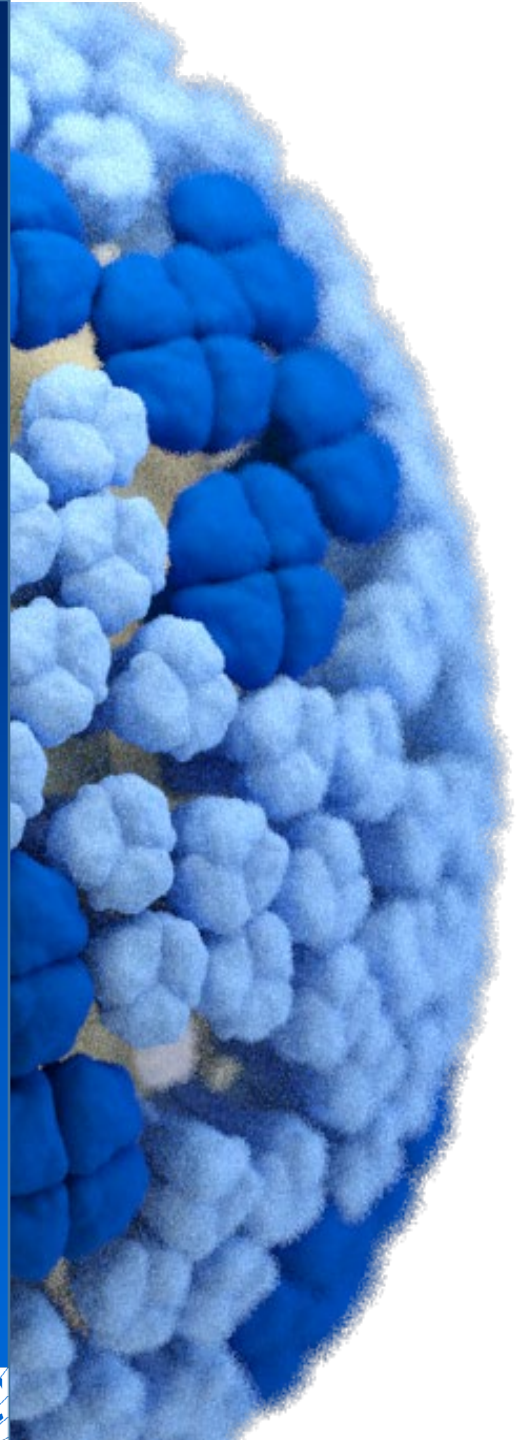
- Of 2,612 A(H1N1)pdm09 viruses examined by genetic and/or phenotypic analyses, one had the PA substitution I38V and one had I38N.

A(H1N1)pdm09 summary (1): global circulation and HA diversity

- A(H1N1)pdm09 viruses circulated globally and predominated in several geographic regions.
- The hemagglutinin (HA) genes of viruses that were genetically characterized belonged to clades 5a.2a and 5a.2a.1, with further diversity within their subclades.
- Viruses from both subclades continued to circulate:
  - 5a.2a subclade C.1.9 predominated in most regions, except in North America and some countries in Central and South America where the 5a.2a.1 subclade D predominated

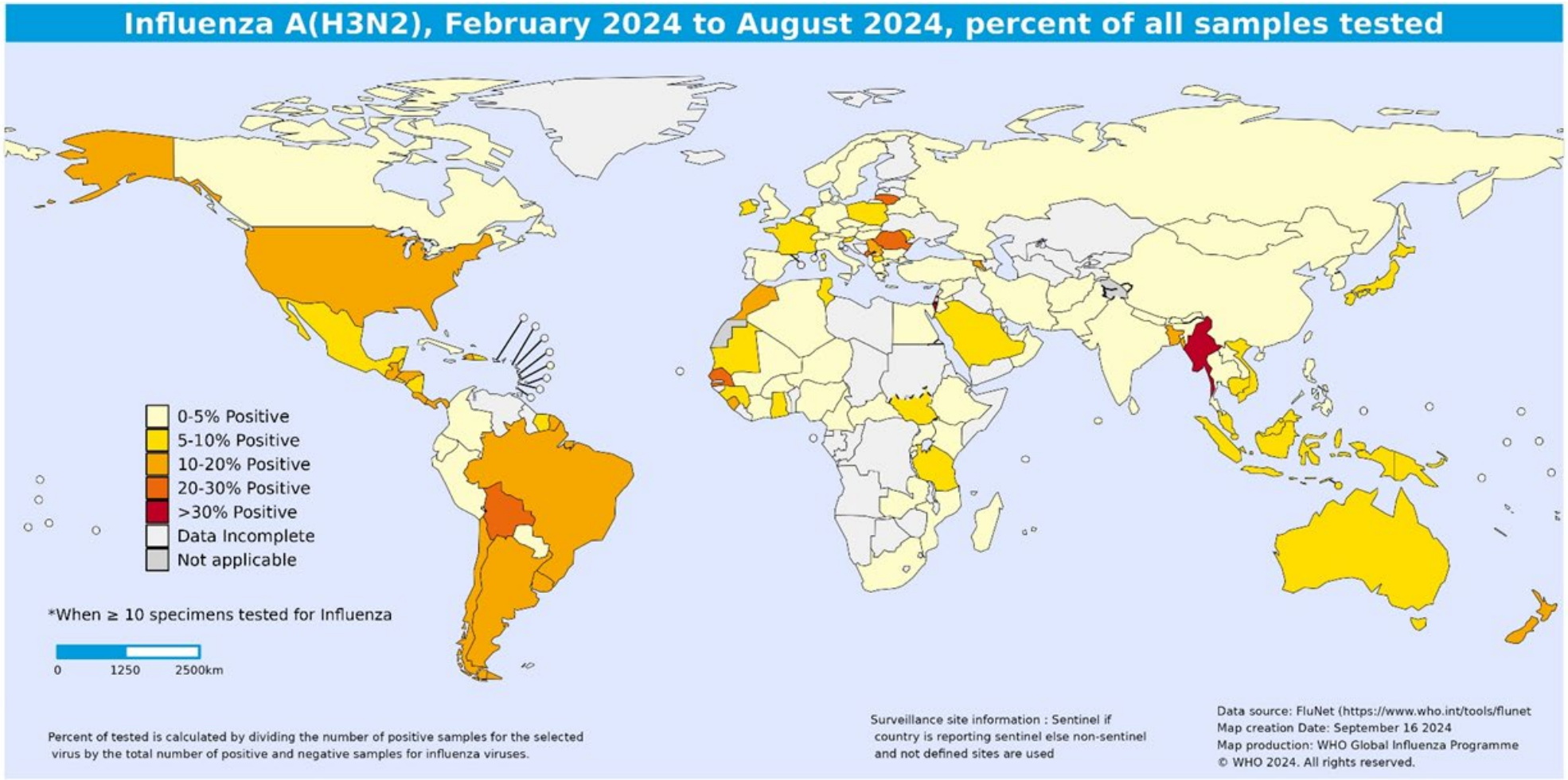
A(H1N1)pdm09 summary (2): antigenic characteristics

- Post-infection ferret antisera raised against the SH 2024 and NH 2024-2025 A(H1N1)pdm09 vaccine components (cell culture-propagated A/Wisconsin/67/2022 and egg-propagated A/Victoria/4897/2022) from the 5a.2a.1 subclade recognized 5a.2a and 5a.2a.1 viruses well.
- Post-vaccination GMTs were not reduced significantly for most recently circulating A(H1N1)pdm09 viruses when compared to the responses to cell culture-propagated A/Wisconsin/67/2022 (H1N1)pdm09-like vaccine reference viruses.
- **The data supported A/Wisconsin/67/2022-like (C.1.1 (5a.2a.1)) and A/Victoria/4897/2022-like (D (5a.2a.1)) to remain as the vaccine antigens for the 2025 southern hemisphere.**



A(H3N2) Viruses

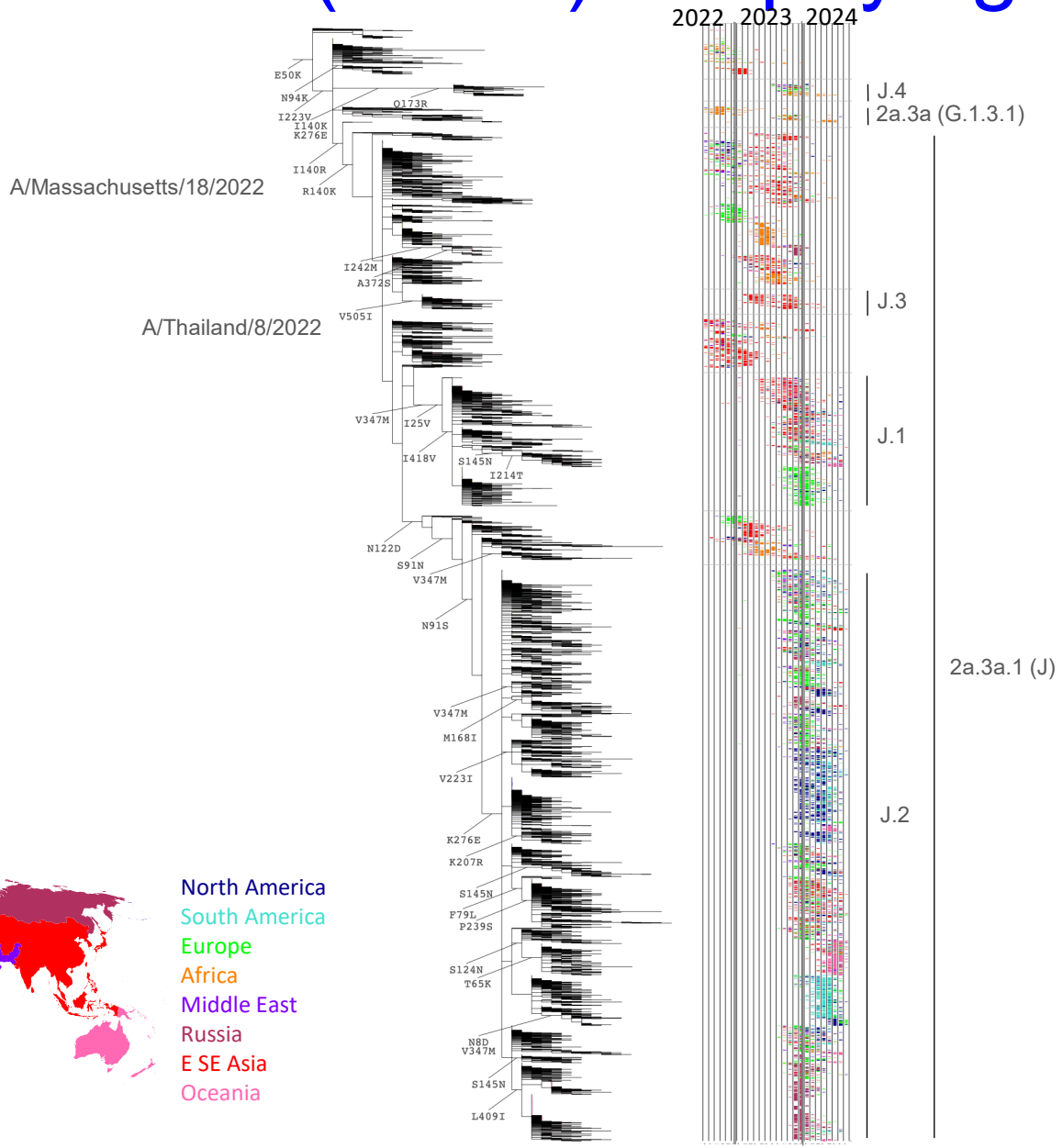
Influenza A(H3N2) virus activity

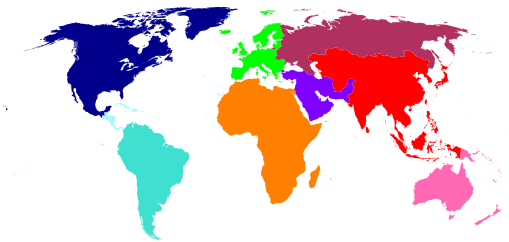


Colour intensity shows the percent of influenza A(H3N2) positive among all samples tested during this period per country

Data source: FluNet, (https://www.who.int/tools/flunet), Global Influenza Surveillance and Response System (16 September 2024)

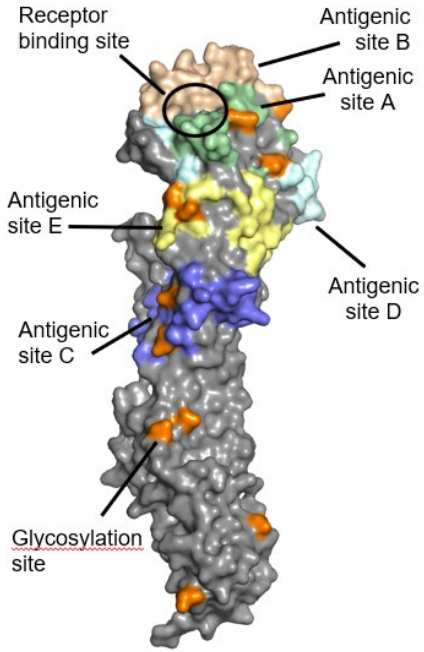
A(H3N2) HA phylogeography

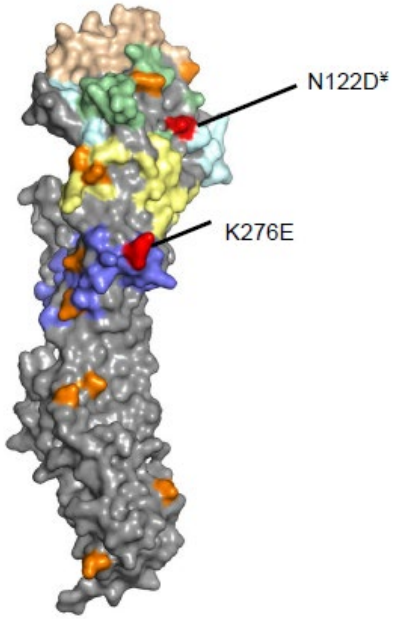




North America
South America
Europe
Africa
Middle East
Russia
E SE Asia
Oceania

Source: University of Cambridge, UK





J

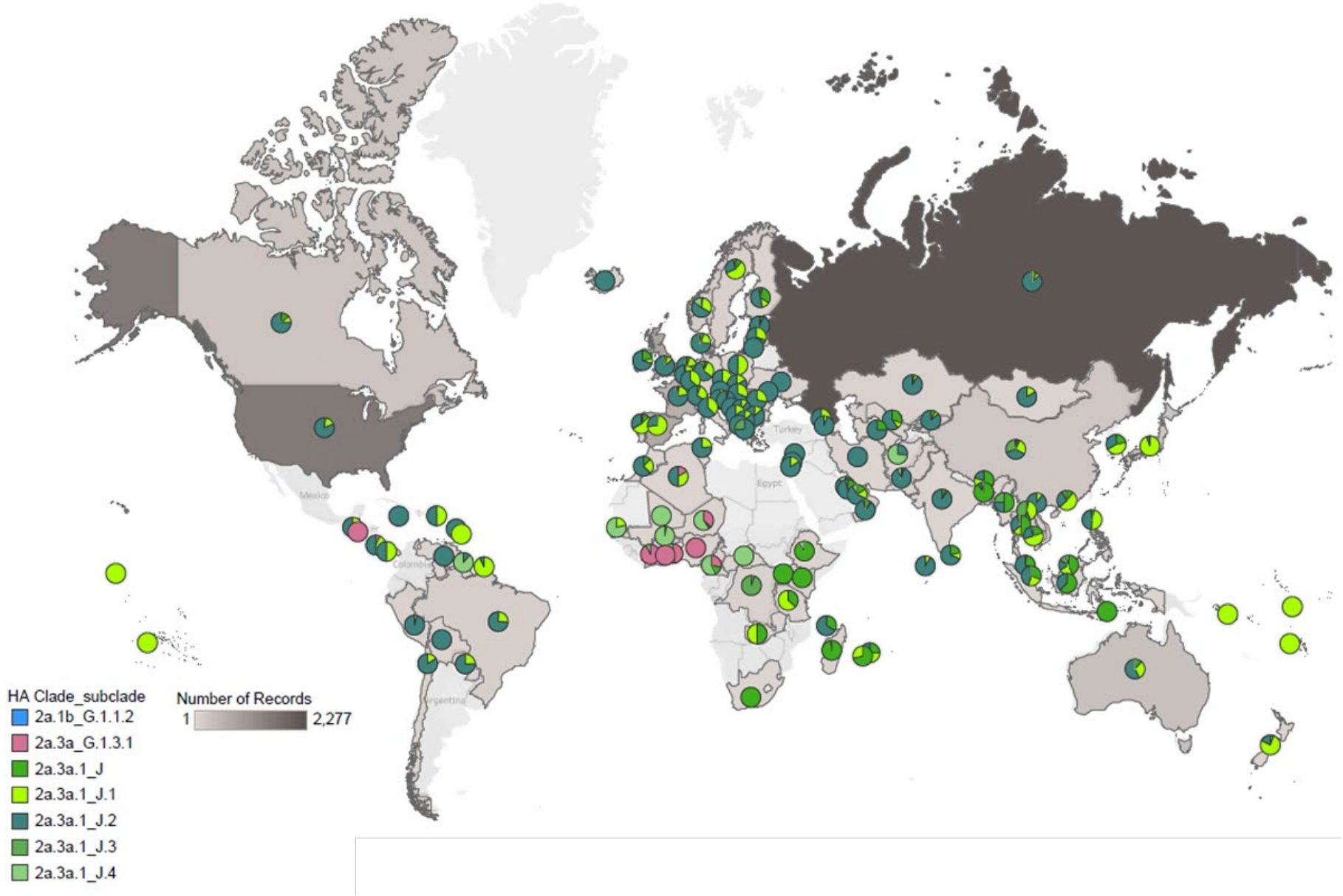
E50K, I140K, I223V

J.2

N122D (CHO-), K276E

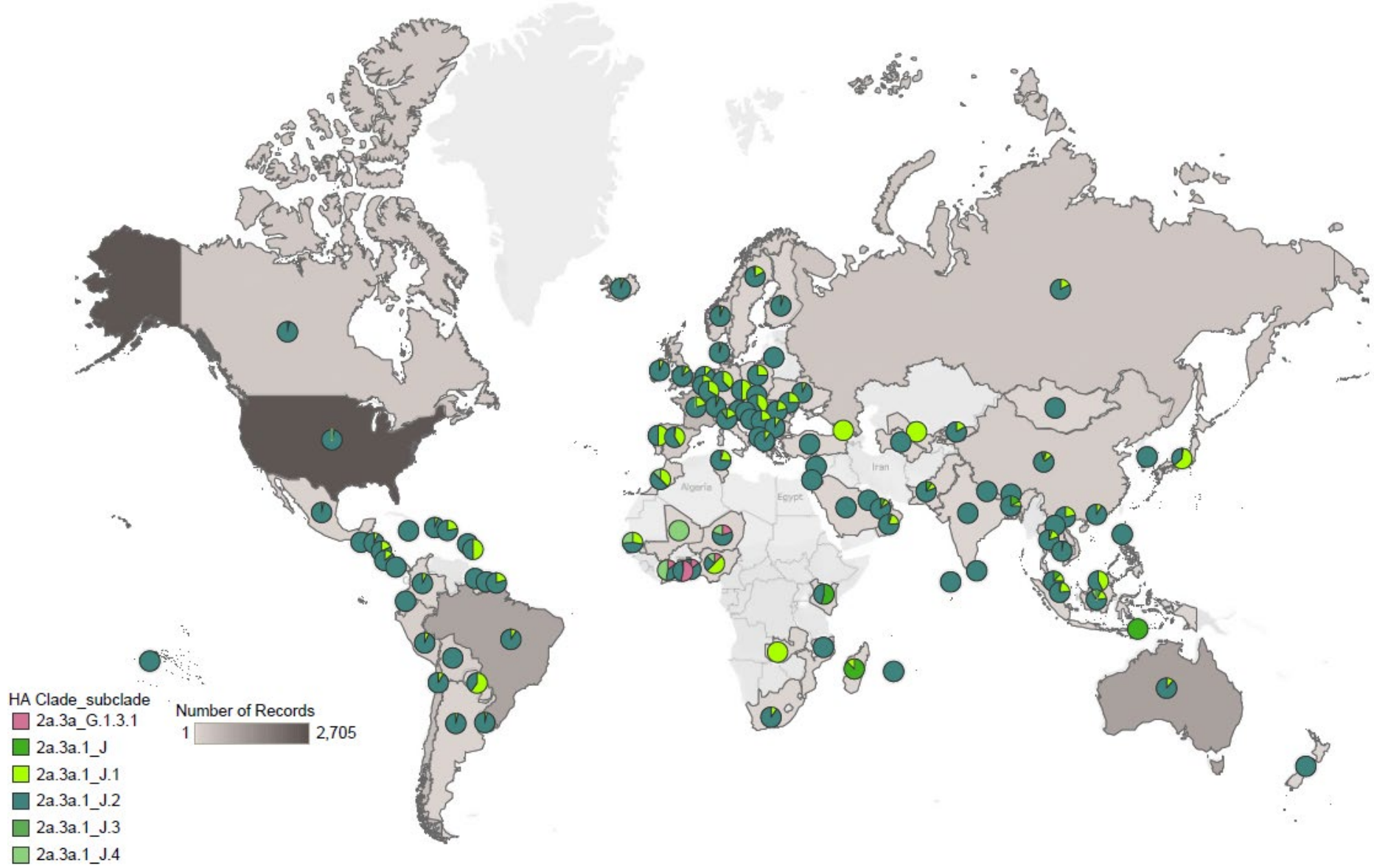
HA subclade: https://clades.nextstrain.org/

Global A(H3N2) HA clade diversity: Sep 2023 to Jan 2024



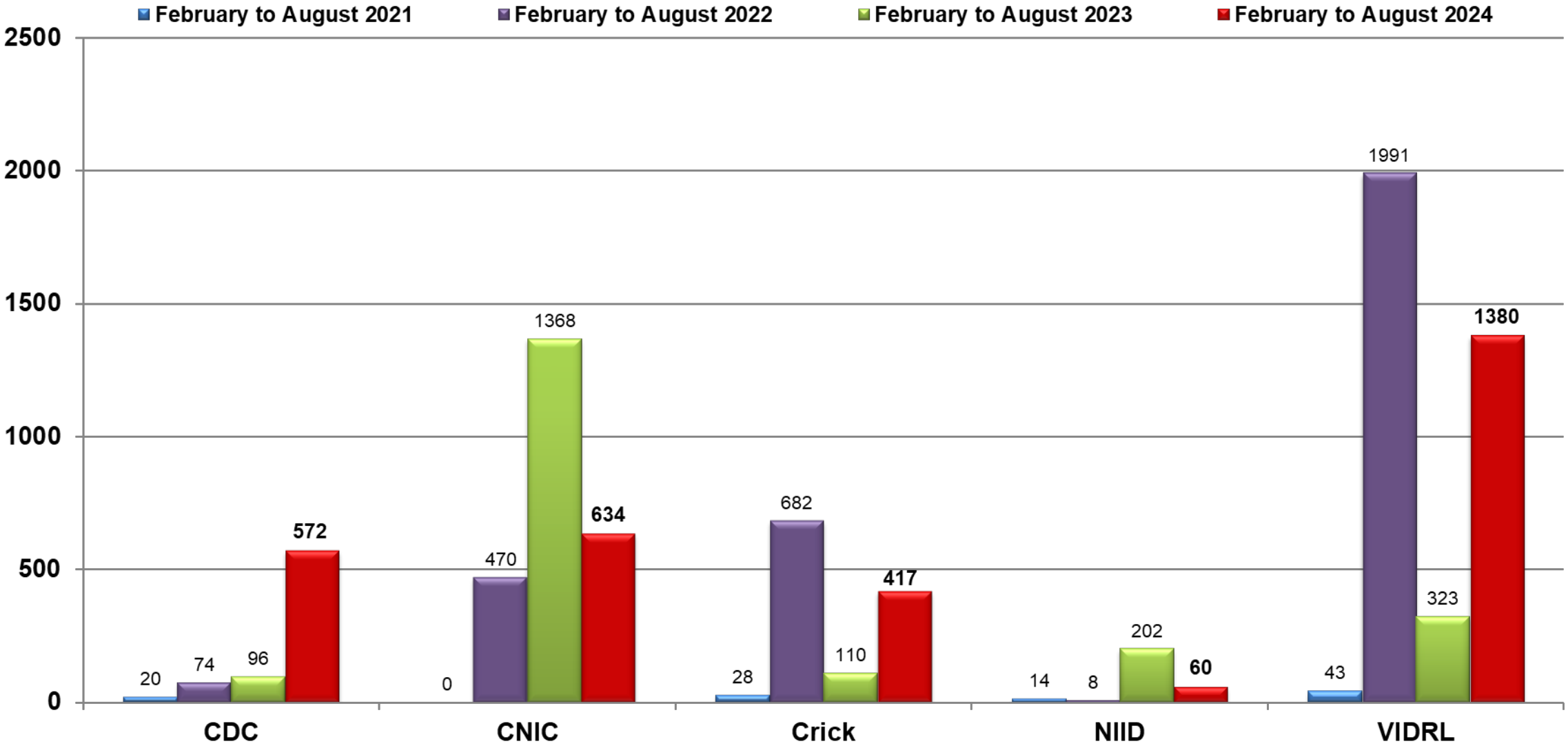
Source: WHO CC CDC, USA

Global A(H3N2) HA clade diversity: Feb 2024 to Aug 2024



Source: WHO CC CDC, USA

A(H3N2) viruses antigenically characterized during the past 4 reporting periods



Last 4 reporting periods (southern hemisphere)

Antigenic analysis of A(H3N2) viruses in **HI** assays by WHO CCs

HI Assay

Antisera to southern hemisphere 2024 antigens (2a.3a.1)

A/Massachusetts/18/2022-like Cell (2a.3a.1)			A/Thailand/8/2022-like Egg (2a.3a.1)		
WHO CC	Like (<8 fold)	Low (≥ 8 fold)	WHO CC	Like (<8 fold)	Low (≥ 8 fold)
CDC	450 (79%)	122 (21%)	CDC	513 (90%)	59 (10%)
CNIC	403 (64%)	231 (36%)	CNIC	331 (52%)	303 (48%)
FCI	258 (62%)	159 (38%)	FCI	313 (75%)	104 (25%)
NIID	58 (97%)	2 (3%)	NIID	58 (97%)	2 (3%)
VIDRL	1271 (92%)	108 (8%)	VIDRL	776 (56%)	604 (44%)
Total	2440 (80%)	622 (20%)	Total	1991 (65%)	1072 (35%)

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

Antigenic analysis of A(H3N2) viruses in **VN** assays by WHO CCs

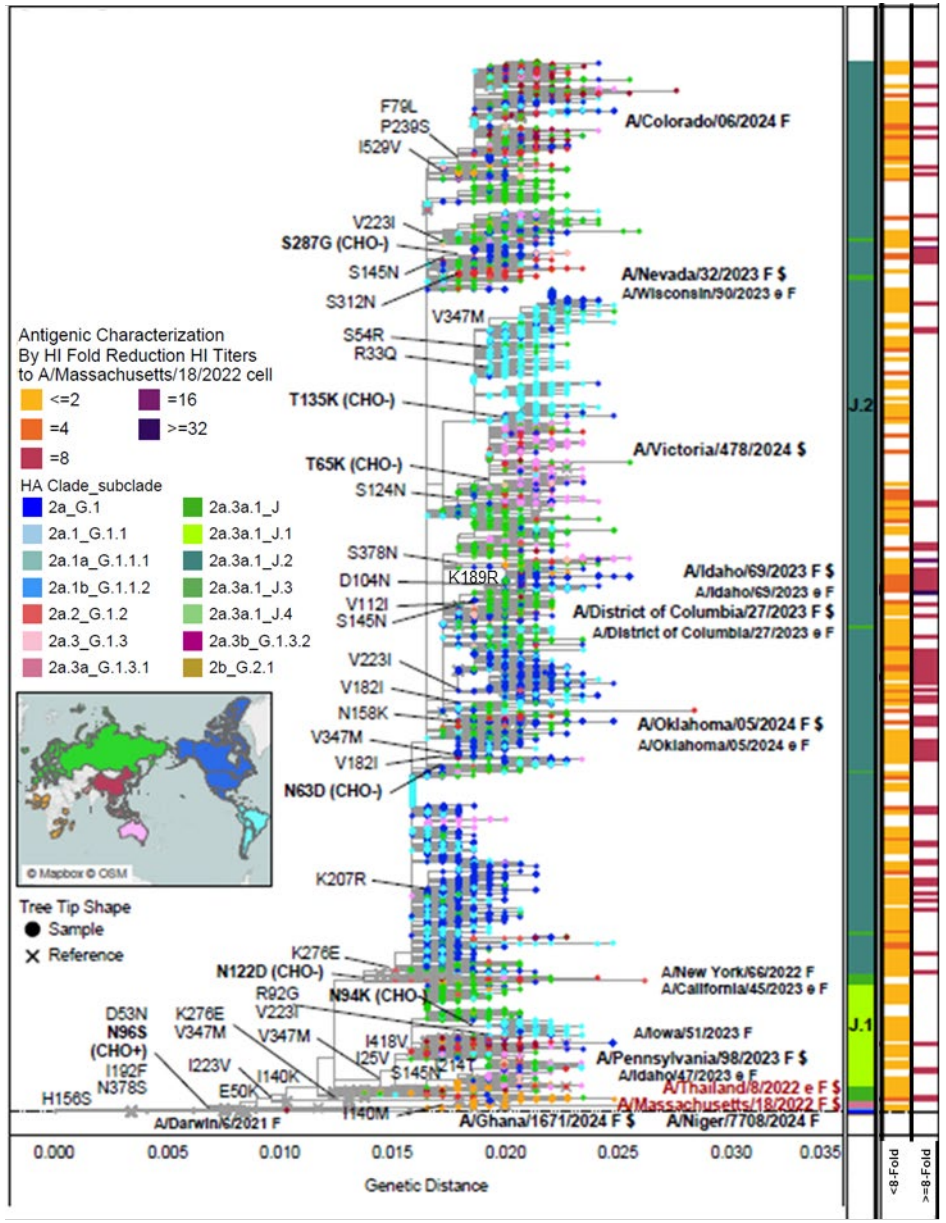
VN Assay

Antisera to southern hemisphere 2024 antigens (2a.3a.1)

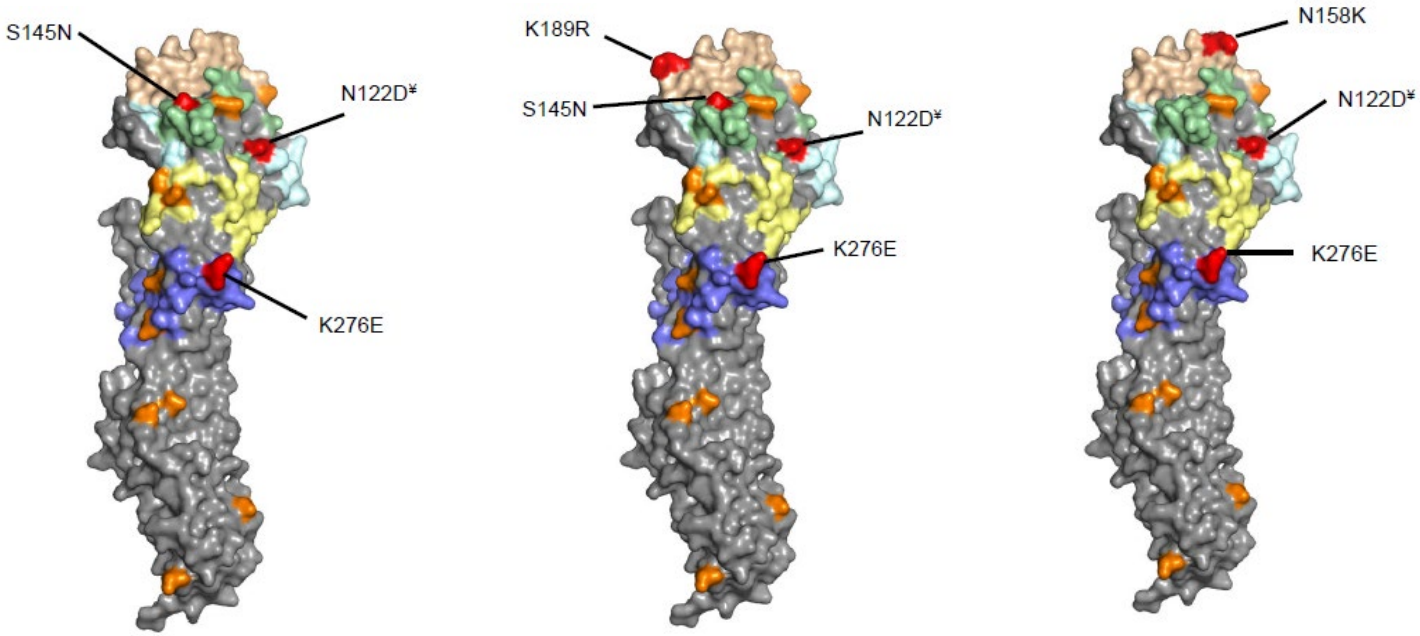
	A/Massachusetts/18/2022-like Cell 2a.3a.1			A/Thailand/8/2022-like Egg 2a.3a.1	
WHO CC	Like (<8 fold)	Low (≥ 8 fold)	WHO CC	Like (<8 fold)	Low (≥ 8 fold)
CDC	142 (93%)	10 (7%)			
FCI	127 (91%)	13 (9%)	FCI	77 (70%)	33 (30%)
VIDRL	52 (90%)	6 (10%)	VIDRL	21 (36%)	37 (64%)
Total	321 (92%)	29 (8%)	Total	98 (58%)	70 (42%)

"Low" reactor represented titers ≥ 8-fold or >8-fold lower than vaccine strain homologous titer depending on WHO CC

A(H3N2) Integrated Genotype and Phenotype Analysis



- The majority of viruses express HA clade 2a.3a.1 from subclade J.1 and J.2
- Additional HA substitutions emerging throughout the tree
- Ferret antisera to A/Massachusetts/18/2022-like viruses show reduced to poor reactivity with some viruses; either HA substitution S145N, N158K or K189R or in combination



Emerging subclades in J.2

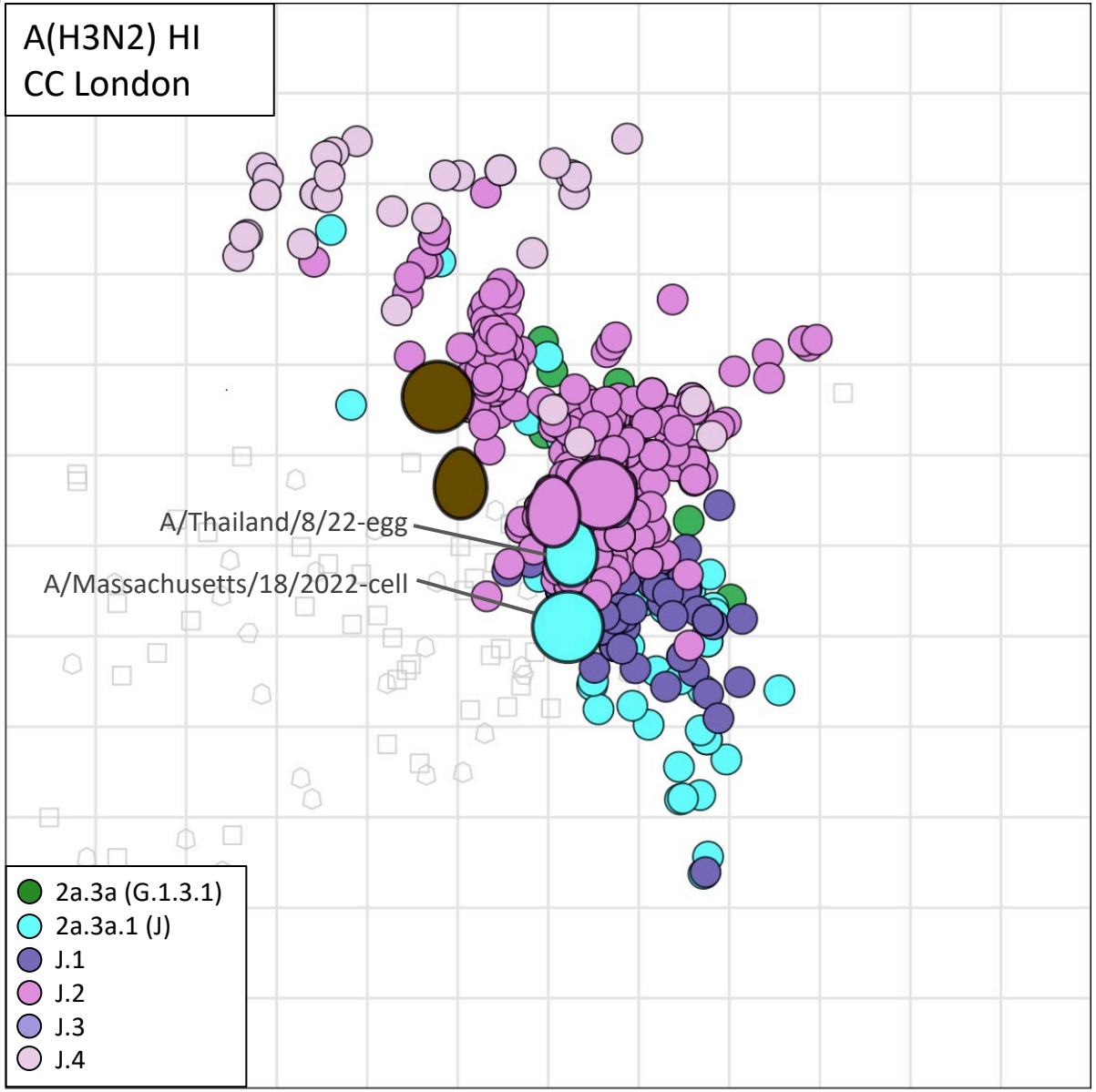
WHO CC CDC, USA

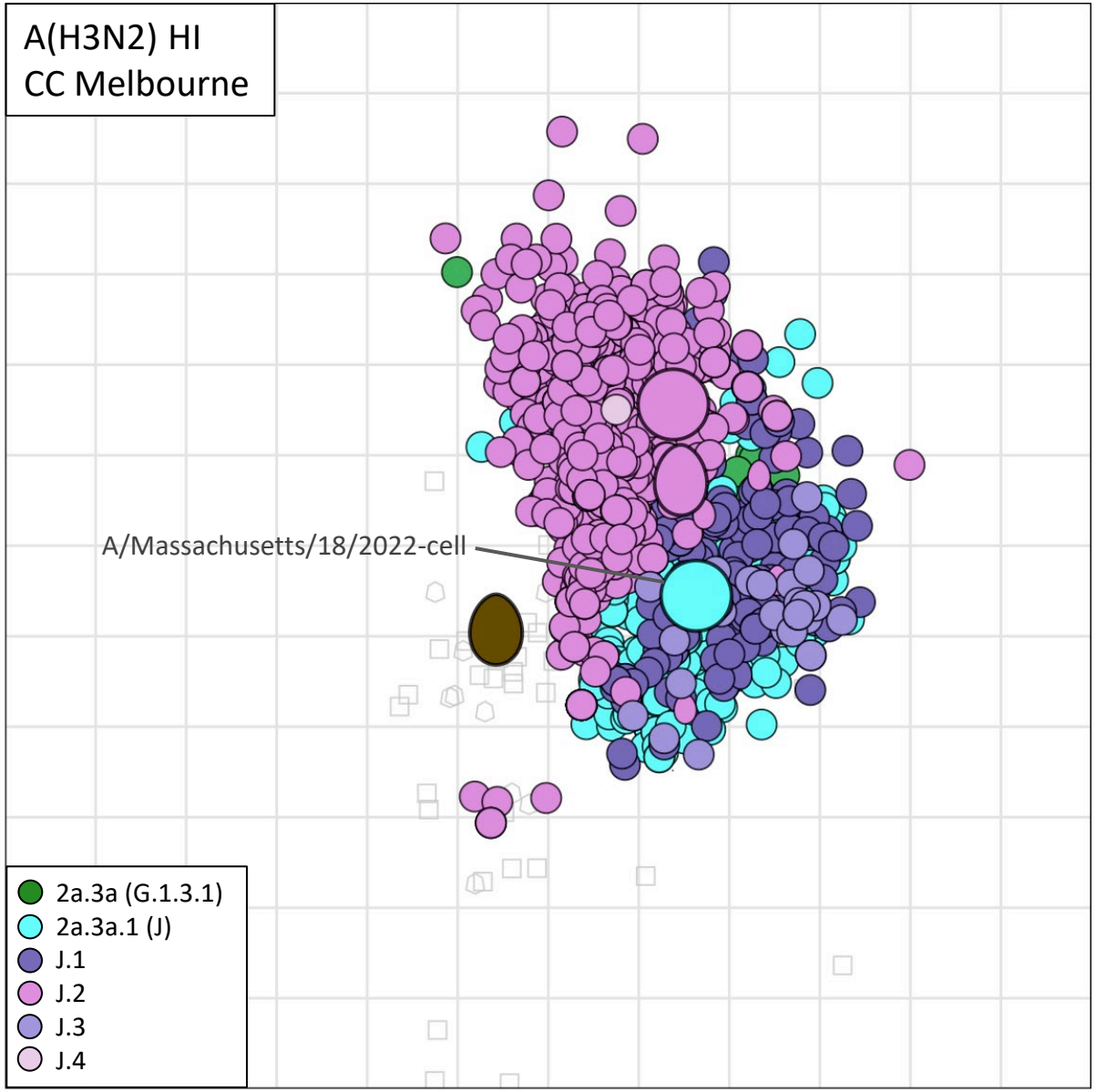
A(H3N2) HI Assay

			Post-infection reference ferret antiserum						
	HA Clade (Subclade)	HA Substitutions	SIAT A/Massachusetts /18/2022 2a.3a.1 (J)	Egg A/Thailand /08/2022 2a.3a.1 (J)	SIAT A/Sydney /856/2023 2a.3a.1 (J.1)	SIAT A/Croatia/ 10136RV/2023 2a.3a.1 (J.2)	Egg A/Croatia/ 10136RV/2023 2a.3a.1 (J.2)	SIAT A/Slovenia /49/2024 2a.3a.1 (J.2)	Passage
REFERENCE VIRUSES									
A/Massachusetts/18/2022	2a.3a.1 (J)		**640**	1280	1280	160	320	160	SIAT3/SIAT1
A/Thailand/08/2022	2a.3a.1 (J)		320	**1280**	640	320	640	320	E3/E1
A/Sydney/856/2023	2a.3a.1 (J.1)		320	640	**640**	80	160	80	SIAT1/SIAT2
A/Croatia/10136RV/2023	2a.3a.1 (J.2)	S145N	40	160	160	**160**	160	160	SIAT3
A/Croatia/10136RV/2023	2a.3a.1 (J.2)	S145N	320	640	640	640	**640**	640	E3 (Am1Al2)
A/Slovenia/49/2024	2a.3a.1 (J.2)	N158K	<40	160	<40	80	40	**1280**	MDCKx/SIAT3
TEST VIRUSES									
A/Saudi Arabia/6095/2024	2a.3a (G.1.3.1)		40	80	40	80	80	80	SIAT1
A/Iasi/567841/2024	2a.3a.1 (J.1)		320	640	640	160	320	80	SIAT1/SIAT1
A/Belgium/4741/2024	2a.3a.1 (J.2)		160	320	160	160	160	160	SIAT1
A/Prahova/566118/2024	2a.3a.1 (J.2)		160	320	160	160	160	160	SIAT1/SIAT1
A/Spain/2603/2024	2a.3a.1 (J.2)		160	320	160	160	320	160	SIAT1
A/Cameroon/5947/2024	2a.3a.1 (J.2)		80	160	160	160	160	80	SIAT1
A/Denmark/2186/2024	2a.3a.1 (J.2)		80	160	160	160	160	160	SIAT2/SIAT1
A/Papeete/OMS24.3.54/2024	2a.3a.1 (J.2)		80	160	160	160	160	160	MDCK2/SIAT1
A/Saudi Arabia/12903/2024	2a.3a.1 (J.2)		80	160	160	160	160	160	SIAT1
A/Tarbes/NOMS24.4.9/2024	2a.3a.1 (J.2)		80	160	160	160	160	160	MDCK2/SIAT1
A/Denmark/2208/2024	2a.3a.1 (J.2)	S145N	80	160	160	160	320	160	SIAT2/SIAT1
A/Spain/2562/2024	2a.3a.1 (J.2)	S145N	80	160	160	160	320	160	SIAT1
A/Cameroon/7167/2024	2a.3a.1 (J.2)	S145N	40	80	80	80	160	80	SIAT1
A/Spain/2381/2024	2a.3a.1 (J.2)	S145N	40	80	80	80	160	80	SIAT1
A/Cameroon/6580/2024	2a.3a.1 (J.2)	S145N	<40	40	40	80	80	80	SIAT1
A/Switzerland/47775/2024	2a.3a.1 (J.2)	K189R	<40	40	<40	80	40	<40	MDCK1/SIAT1
A/Switzerland/59652/2024	2a.3a.1 (J.2)	K189R	<40	40	<40	40	80	<40	SIAT1
A/Cameroon/3172/2024	2a.3a.1 (J.4)		80	160	80	80	80	80	SIAT1

WHO CC London FCI

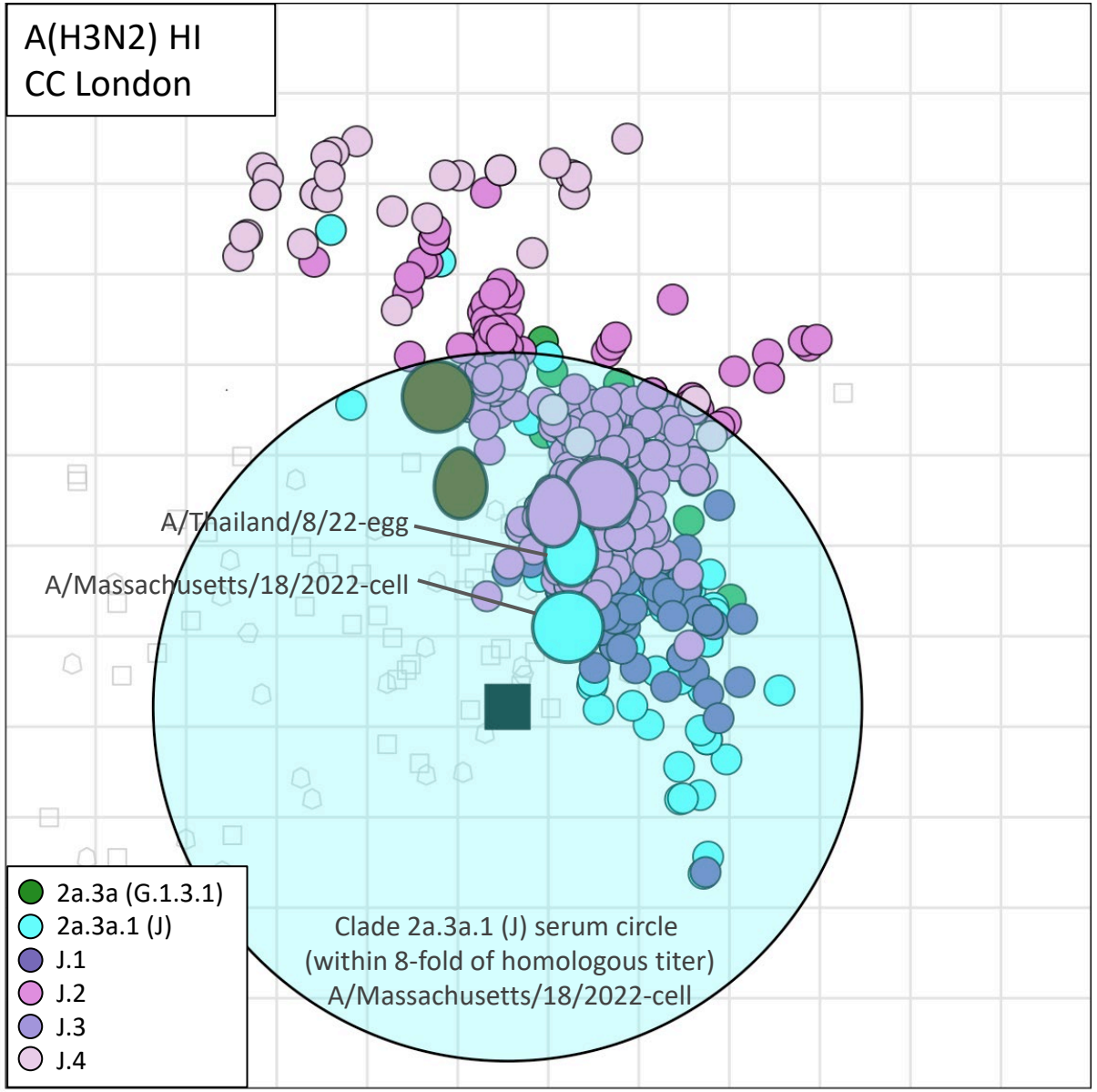
A(H3N2) antigenic cartography

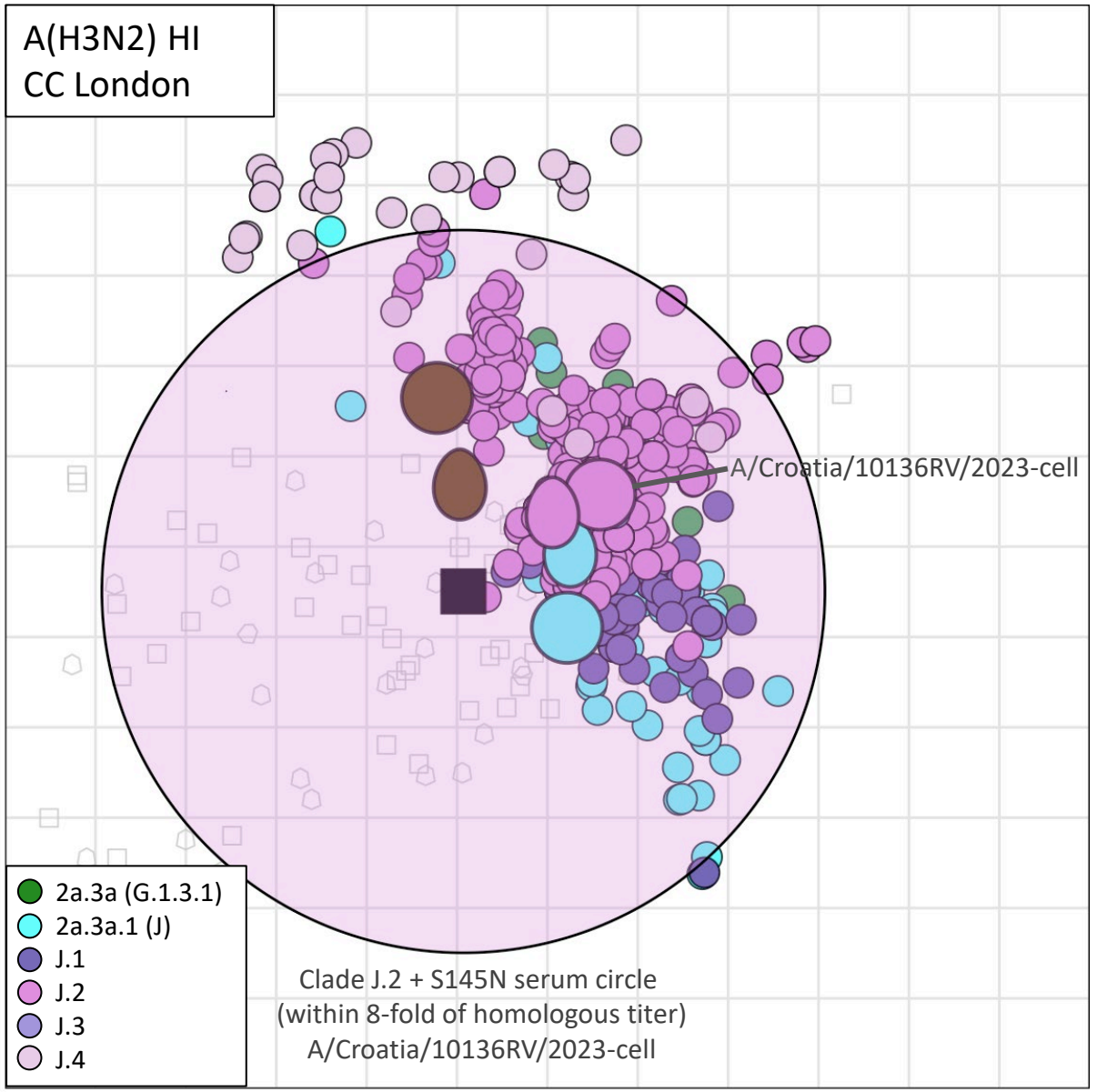




University of Cambridge

A(H3N2) antigenic cartography

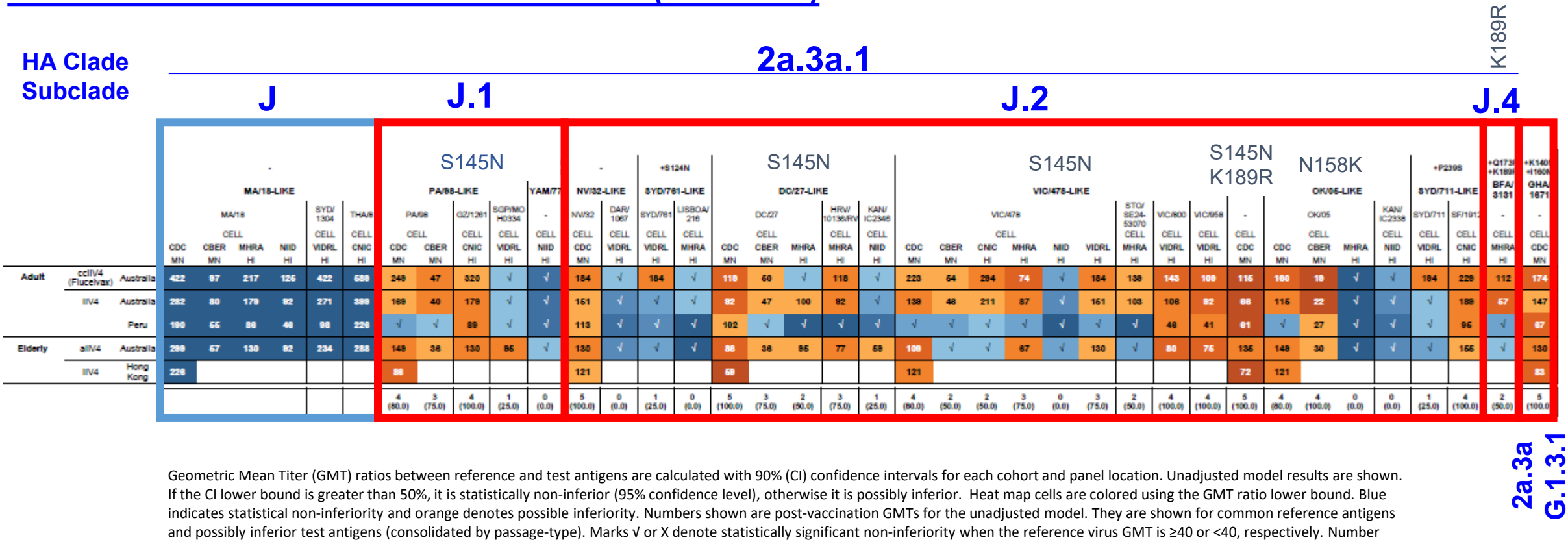




University of Cambridge

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

Vaccine: A/Massachusetts/18/2022-like (2a.3a.1 J)



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.

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(H3N2): antiviral susceptibility

Neuraminidase inhibitors

- Of 3,300 A(H3N2) viruses that were examined for neuraminidase inhibitor (NAI) susceptibility by genetic and/or phenotypic analyses, one showed genetic or phenotypic evidence of reduced inhibition to neuraminidase inhibitors

Endonuclease inhibitors

- Of 3,269 A(H3N2) viruses examined by genetic and/or phenotypic analyses, 11 showed genetic or phenotypic evidence of reduced susceptibility to endonuclease inhibitor baloxavir marboxil

A(H3N2) summary (1): global circulation and HA diversity

- In some countries, areas and territories reporting influenza A viruses, A(H3N2) predominated
  - Significant H3 activity was observed in Central and South America, Northern and Western Africa, Southeast Asia and Oceania transmissions zones

- **HA phylogenetics:**
  - HA of circulating A(H3N2) viruses belonged to clades: 2a.3a and 2a.3a.1
    - Further diversification of 2a.3a.1 into several subclades J.1 to J.4
    - J.2 viruses predominated in most regions with J.1 predominating in some countries in Asia, Africa and South America
    - J.4 and 2a.3a (G.1.3.1) viruses predominated in some countries in Africa
  - Multiple additional HA substitutions have emerged, with several positions showing convergent evolution (e.g., HA substitutions S145N, N158K and K189R)

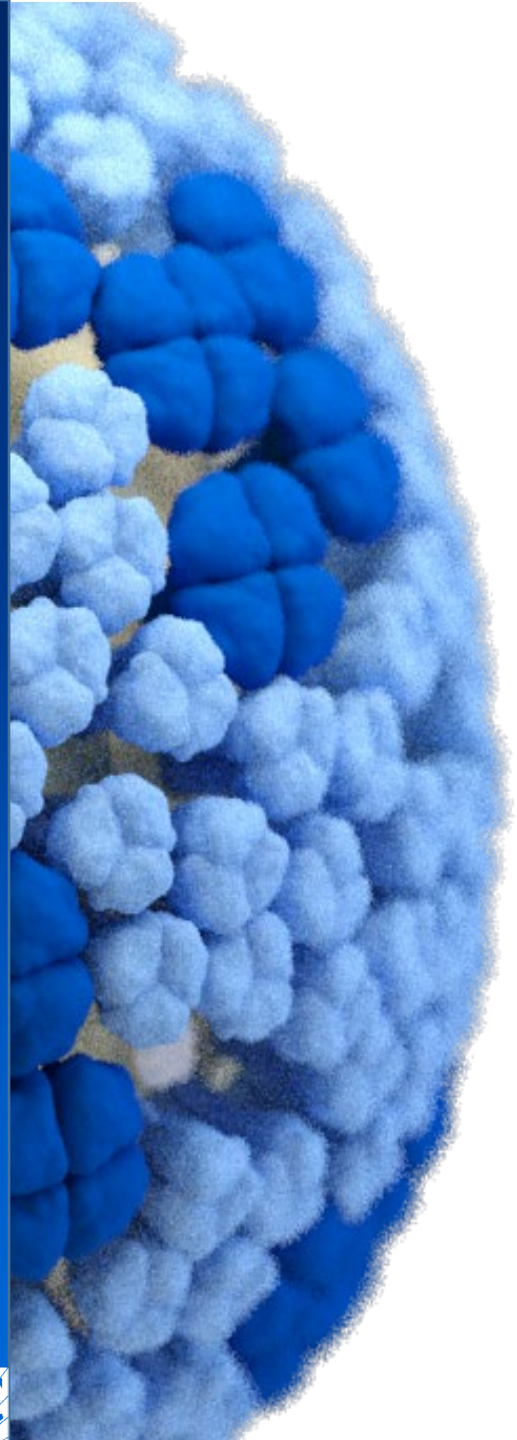
A(H3N2) summary (2): antigenic characteristics

- Post-infection ferret antisera raised against the SH 2024 and NH 2024-2025 A(H3N2) vaccine components (cell culture-propagated A/Massachusetts/18/2022 and egg-propagated A/Thailand/8/2022) from the 2a.3a.1 (J) subclade recognized many viruses expressing J.1 and J.2 well.
  - Reduced to poor recognition was observed for viruses expressing:
    - J.2 subclade with either HA substitution S145N, N158K or K189R or in combination
    - J.4 subclade with HA substitution K189R
- Post-infection ferret antisera raised against reference viruses from HA subclade J.2+S145N (e.g., A/District of Columbia/27/2023 and A/Croatia/10136RV/2023) recognized the majority circulating viruses well.

A(H3N2) summary (3): antigenic characteristics

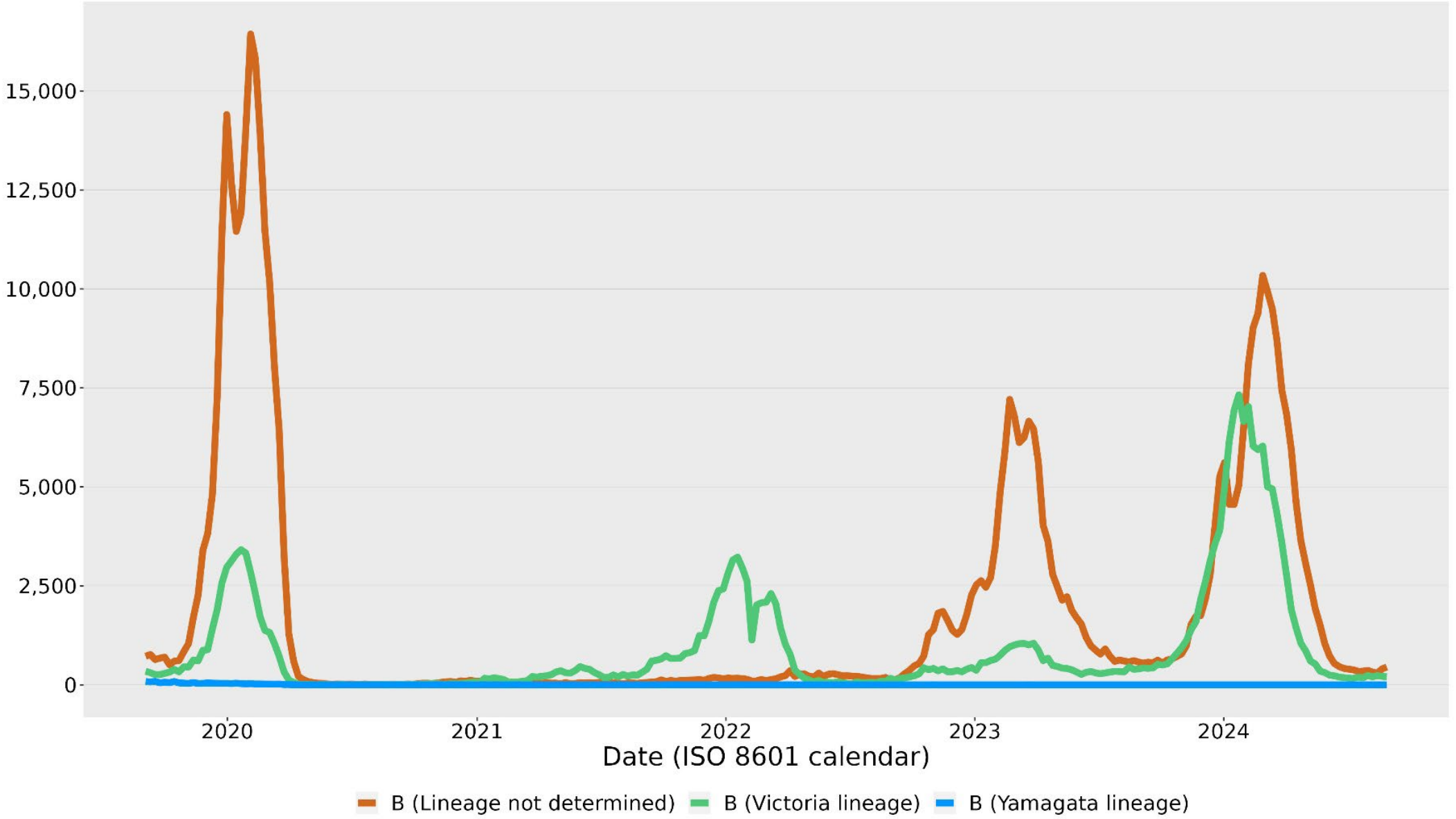
- Post-vaccination GMTs were significantly reduced for many recently circulating A(H3N2) viruses when compared to the responses to cell culture-propagated A/Massachusetts/18/2022-like vaccine reference viruses in most serum panels.

- **The data supported recommending A/District of Columbia/27/2023-like (J.2+S145N) and A/Croatia/10136RV/2023-like (J.2+S145N) as the vaccine antigens for the 2025 southern hemisphere.**

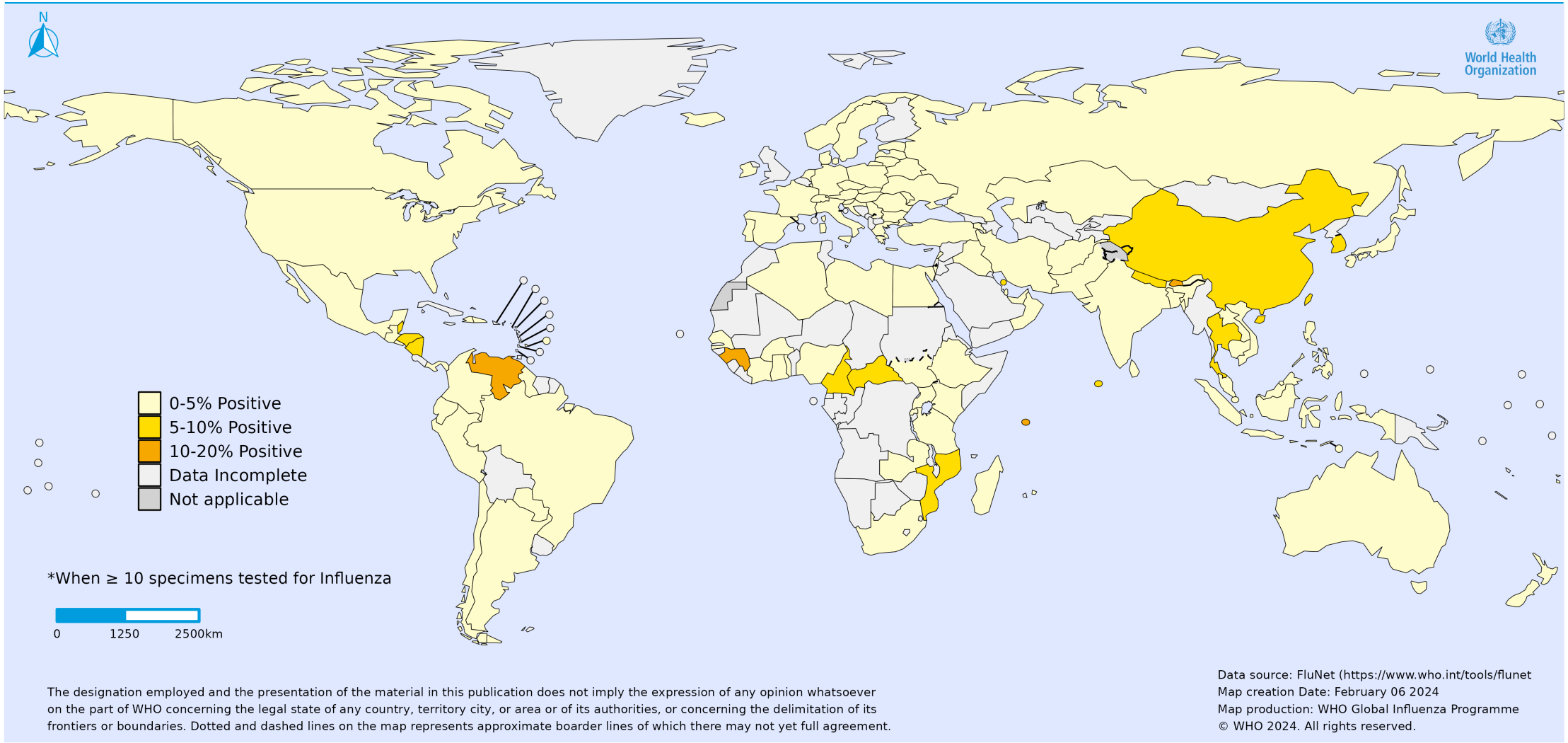


Influenza B Viruses

Global circulation of influenza B viruses

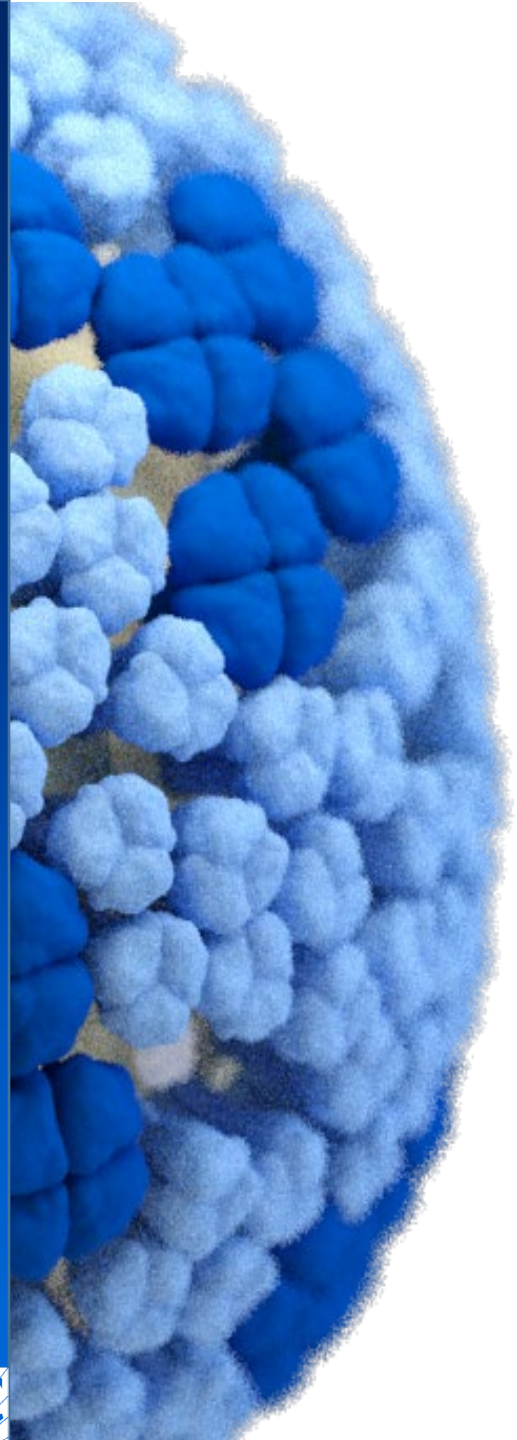


Influenza B virus activity



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

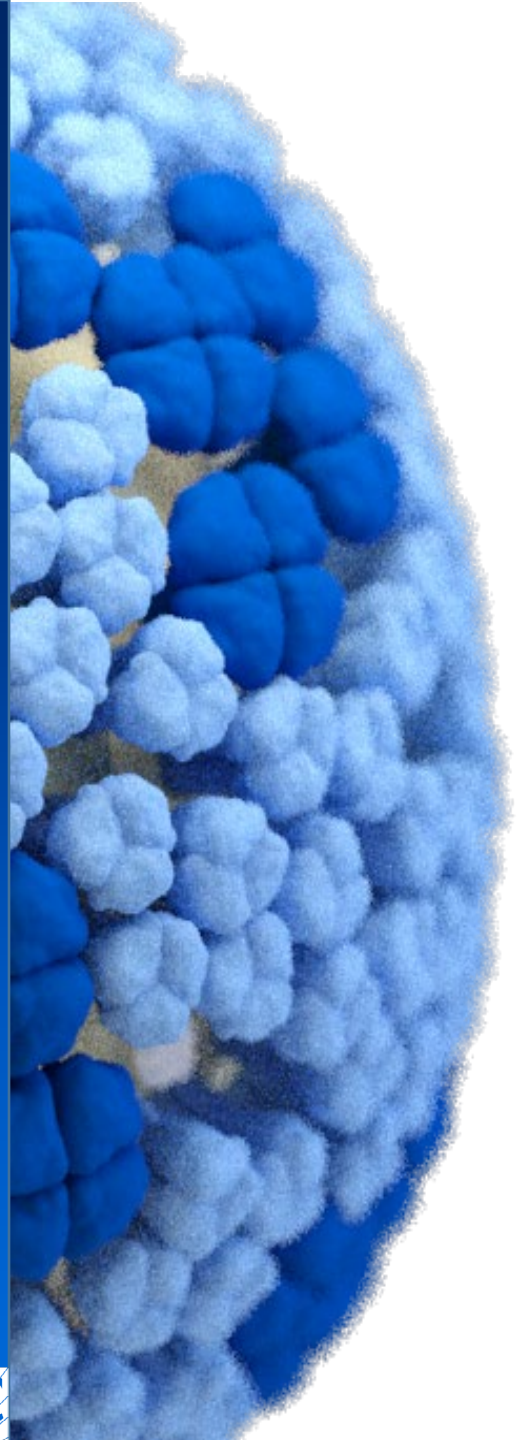
Data source: FluNet, (https://www.who.int/tools/flunet), Global Influenza Surveillance and Response System



Influenza B/Yamagata Viruses

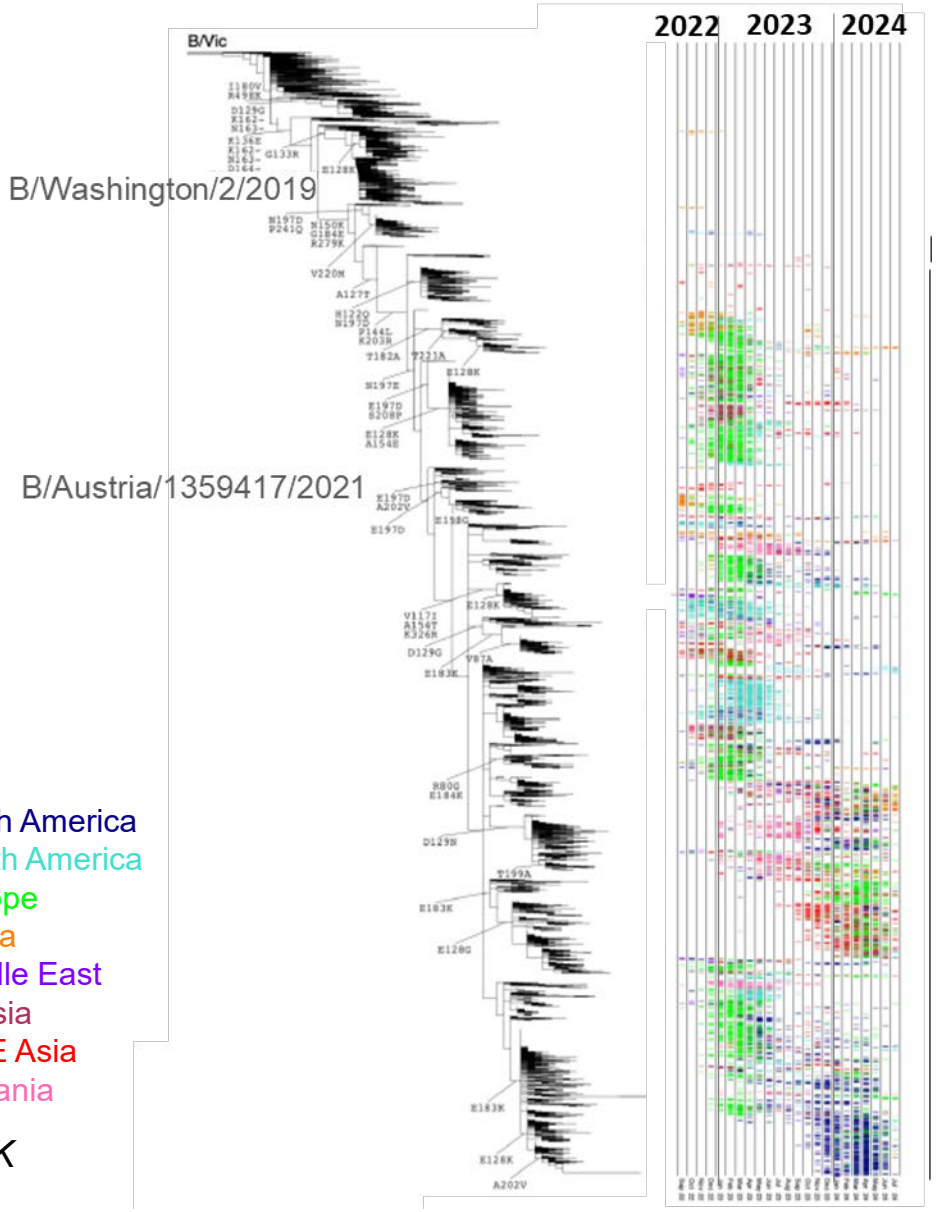
B/Yamagata lineage summary

- There have been no confirmed detections of circulating B/Yamagata/16/88 lineage viruses after March 2020.
- It remains the opinion of the WHO influenza vaccine composition advisory committee that the B/Yamagata lineage antigen should be excluded from influenza vaccines as it is no longer warranted.
- Where quadrivalent vaccines are still used, the B/Yamagata lineage component remains unchanged from previous recommendations:
  - B/Phuket/3073/2013 (B/Yamagata lineage)-like virus



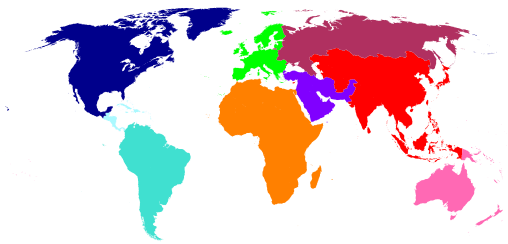
Influenza B/Victoria Viruses

B/Victoria HA phylogeography



3a.2

(A127T, P144L, K203R)



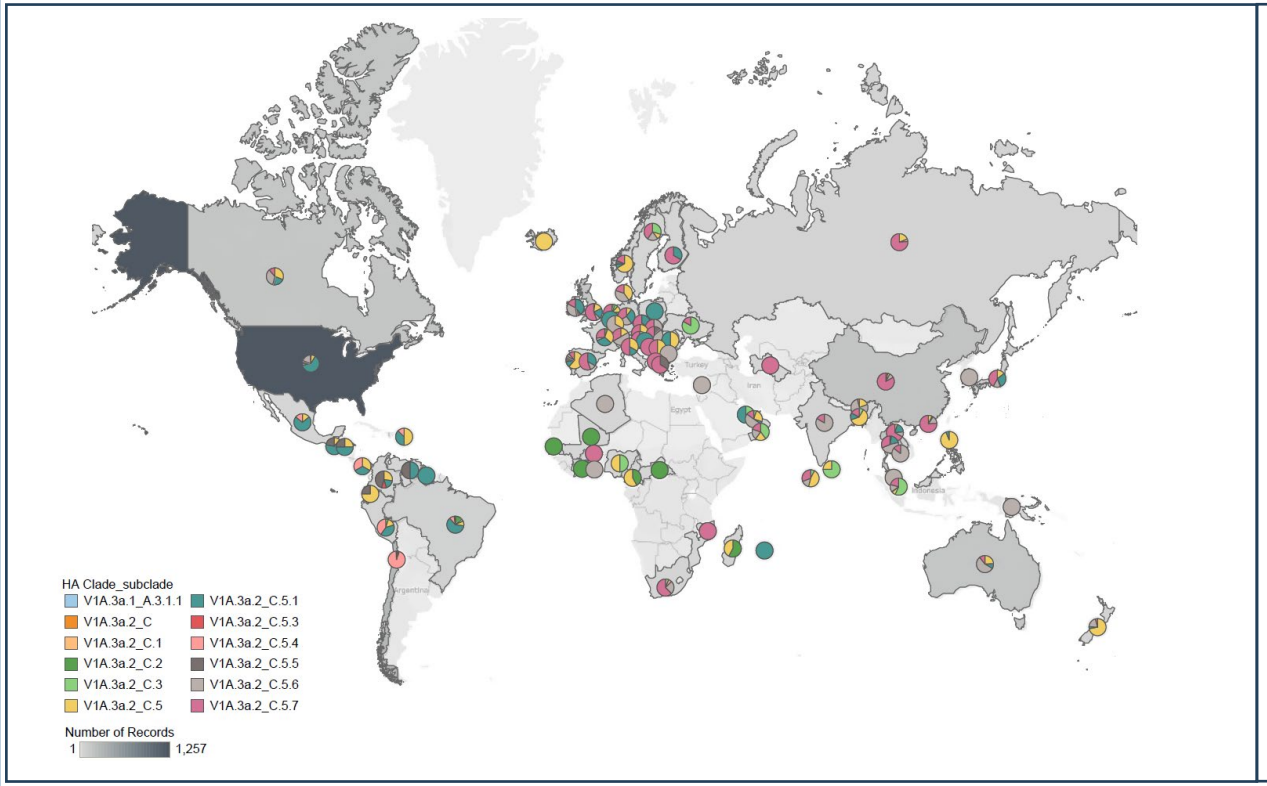
North America
South America
Europe
Africa
Middle East
Russia
E SE Asia
Oceania

Source: University of Cambridge, UK

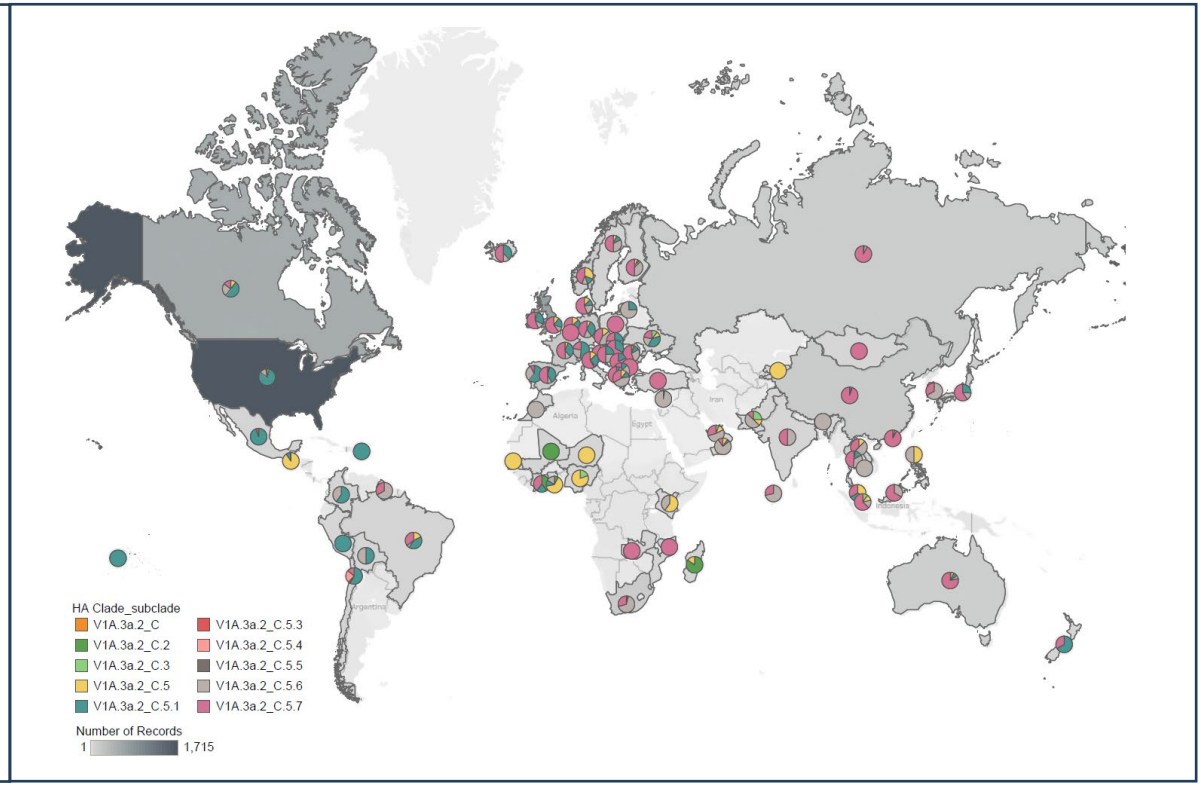
HA subclade: https://clades.nextstrain.org/

Global B/Victoria HA clade diversity

Collection Dates
September 1, 2023- January 31, 2024



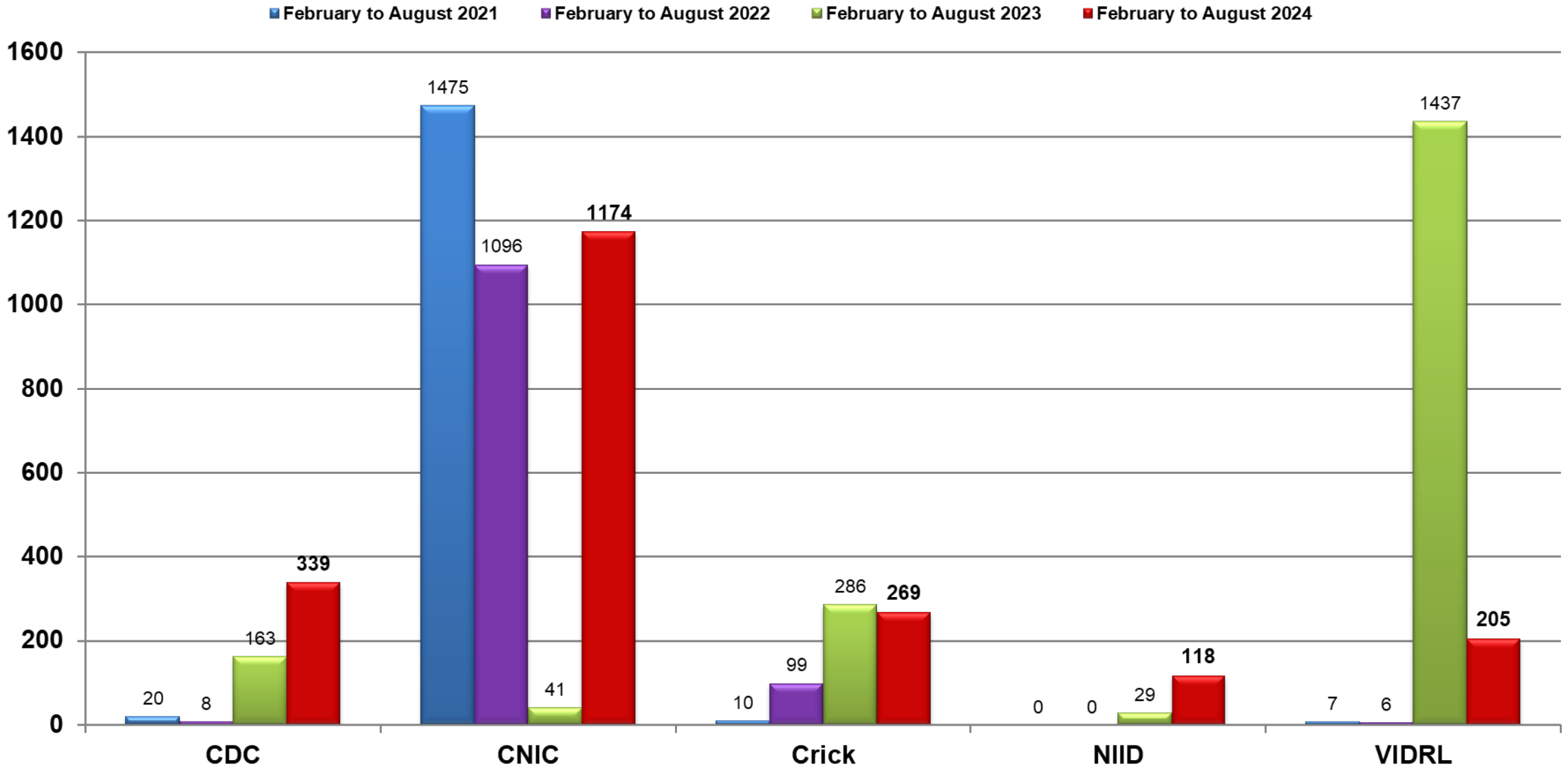
Collection Dates
February 1, 2024- August 31, 2024



Based on HA sequence availability from GISAID EpiFlu™

Source: WHO CC CDC, USA

Influenza B/Victoria viruses antigenically characterized during the past 4 reporting periods



Last 4 reporting periods (southern hemisphere)

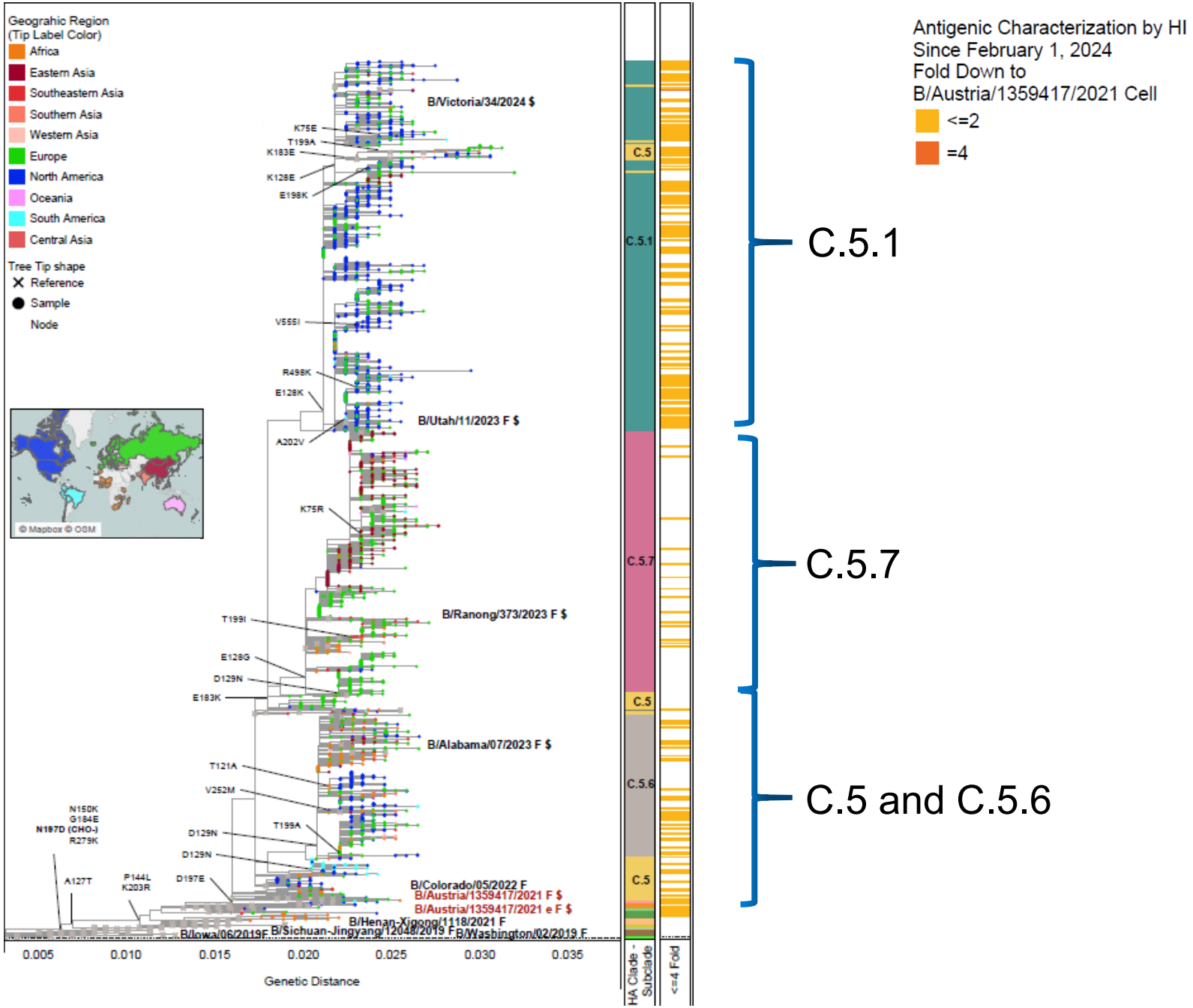
Antigenic analysis of B/Victoria viruses in **HI** assays by WHO CCs

Antisera to southern hemisphere 2024 vaccine virus antigens

B/Austria/1359417/2021-like (cell) V1A.3a.2			B/Austria/1359417/2021-like (egg) V1A.3a.2		
WHO CC	Like (<8 fold)	Low (≥ 8 fold)	WHO CC	Like (< 8-fold)	Low (≥ 8-fold)
CDC	339 (100%)	0 (0%)	CDC	339 (100%)	0 (0%)
CNIC	1165 (99%)	9 (1%)	CNIC	1164 (99%)	10 (1%)
FCI	269 (100%)	0 (0%)	FCI	268 (100%)	1 (0%)
NIID	118 (100%)	0 (0%)	NIID	118 (100%)	0 (0%)
VIDRL	205 (100%)	0 (0%)	VIDRL	205 (100%)	0 (0%)
TOTAL	2096 (100%)	9 (0%)	TOTAL	2094 (99%)	11 (1%)

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

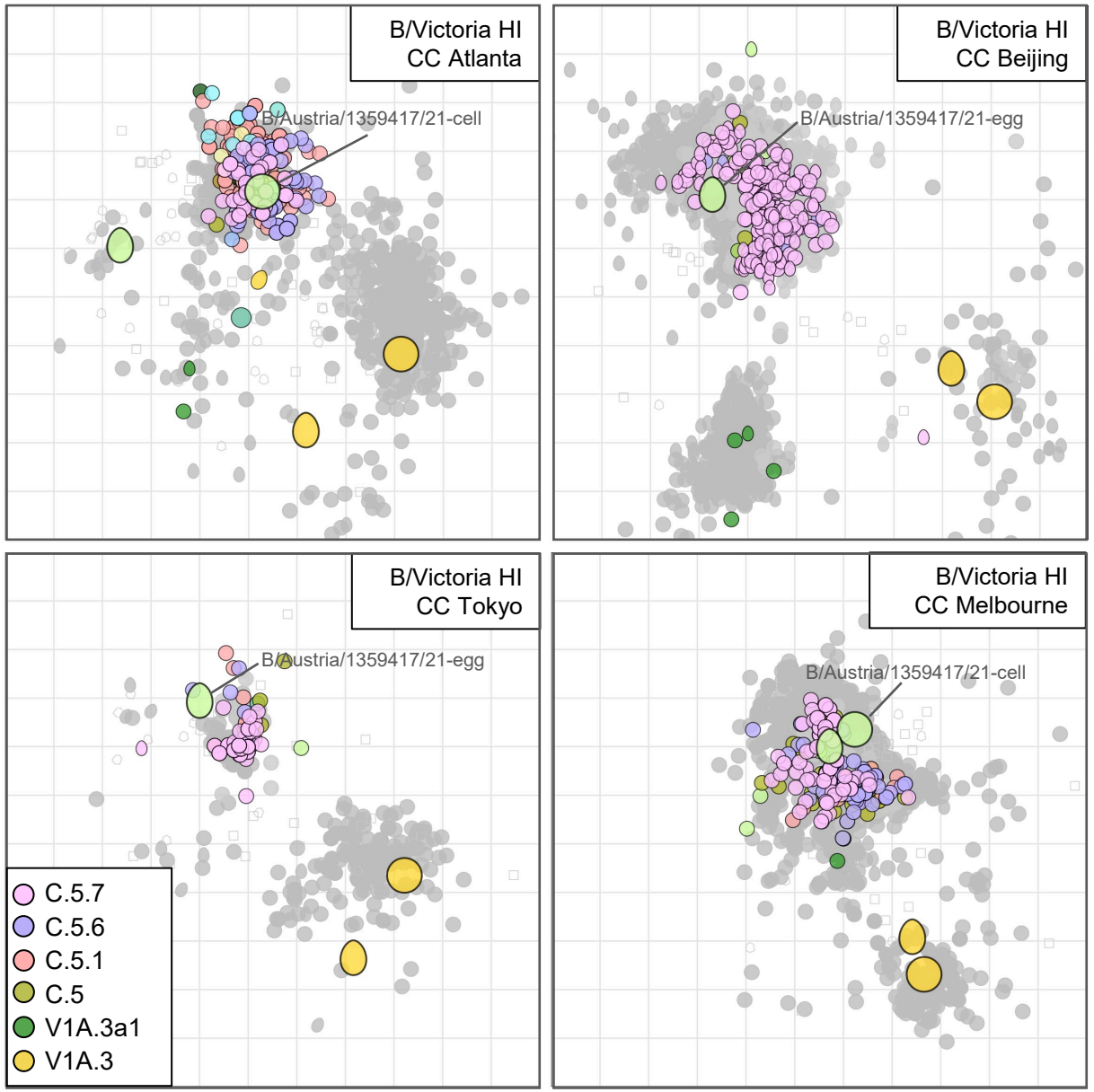
B/Victoria Integrated Genotype and Phenotype Analysis



Source: WHO CC CDC, USA

B/Victoria antigenic cartography

Since 1st September 2023
(older viruses in grey)



Source: University of Cambridge, UK

Human post-vaccination serum analysis of B/Victoria viruses

Vaccine: B/Austria/1359417/2021-like (3a.2 C)

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

				C (V1A.3a.2) AUT/1359417-LIKE						C.5.1 (V1A.3a.2) VIC/34-LIKE										C.5.6 (V1A.3a.2) AL/07-LIKE						C.5.7 (V1A.3a.2) RAN/373-LIKE					
				AUT/1359417					SGP/WUH4618	VIC/34					CHIBA/22	GHA/828	ISL/13541	UT/11		AL/07	KAN/IC2360	SB/1321		VIC/70		RAN/373		DAR/6	LY/1221	NAG/2119	
				CELL					CELL	CELL					CELL	CELL	CELL	CELL		CELL	CELL	CELL		CELL		CELL		CELL	CELL	CELL	
				CDC	CBER	CNIC	MHRA	NIID	VIDRL	CDC	CNIC	MHRA	NIID	VIDRL	NIID	MHRA	MHRA	CDC	CBER	CDC	NIID	CNIC	MHRA	CBER	VIDRL	CDC	MHRA	VIDRL	CNIC	CBER	NIID
B/AUSTRIA/1359417/2021-LIKE	Adult	ccIIV4 (Flucelvax)	Australia	236	169	605	472	446	184	√	√	√	√	√	√	√	√	√	76	√	√	√	√	√	√	√	√	√	√	√	√
		IIV4	Australia	67	39	147	112	194	80	√	√	√	√	√	√	√	√	√	21	√	√	√	√	X	√	√	√	√	X	√
			Peru	113	70	299	343	381	269	√	102	√	√		√	√	√	√	29	√	√	√	√	√	√	√	√	√	√	√	√
	Elderly	aIIV4	Australia	89	55	204	184	211	95	√	√	√	√	√	√	√	√	√	25	√	√	√	√	√	√	√	√	√	√	√	√
		IIV4	Hong Kong	40						X								X		X						X					
										0 (0.0)	1 (25.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	4 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	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.

Human serum panels China, Japan, US and UK vaccinated with 2023-2024 Northern Hemisphere vaccine formulations

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

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

B/Victoria lineage antiviral susceptibility

Neuraminidase inhibitors

- Of 2,153 influenza B/Victoria lineage viruses collected since 1 September 2023 that were examined for neuraminidase inhibitor (NAI) susceptibility by genetic and/or phenotypic analyses, six showed evidence of reduced or highly reduced inhibition by NAIs.

Endonuclease inhibitors

- Of 1,685 B/Victoria lineage viruses collected and analyzed in this period, none showed evidence of reduced susceptibility to baloxavir.

Influenza B/Victoria lineage summary (1): global circulation and HA diversity

- **Only influenza B/Victoria lineage viruses were available for analysis (no B/Yamagata viruses confirmed after March 2020)**

- Though B/Victoria circulated globally, detections were lower than those of influenza A in most regions

- **Phylogenetics of B/Victoria lineage HA genes**
  - Only 3a.2 HA clade viruses circulated (no HA clade 3a.1)
  - Nearly all viruses belong to HA subclades with D197E substitution in HA
  - HA subclade C.5.7 predominated; C.5.1, C.5.6 subclades also co-circulated

Influenza B/Victoria lineage summary (2): antigenic characteristics

- Post-infection ferret antisera raised against the SH 2024 and NH 2024-2025 B/Victoria lineage vaccine components (**B/Austria/1359417/2021-like** viruses) from HA clade 3a.2 well inhibited the vast majority of recently circulating **3a.2** viruses.

- Post-vaccination GMTs were not reduced significantly for most recently circulating B/Victoria lineage viruses when compared to the responses to cell culture-propagated **B/Austria/1359417/2021-like** vaccine reference viruses.

- **The data supported B/Austria/1359417/2021-like (3a.2) to remain as the vaccine antigens for the 2025 southern hemisphere.**

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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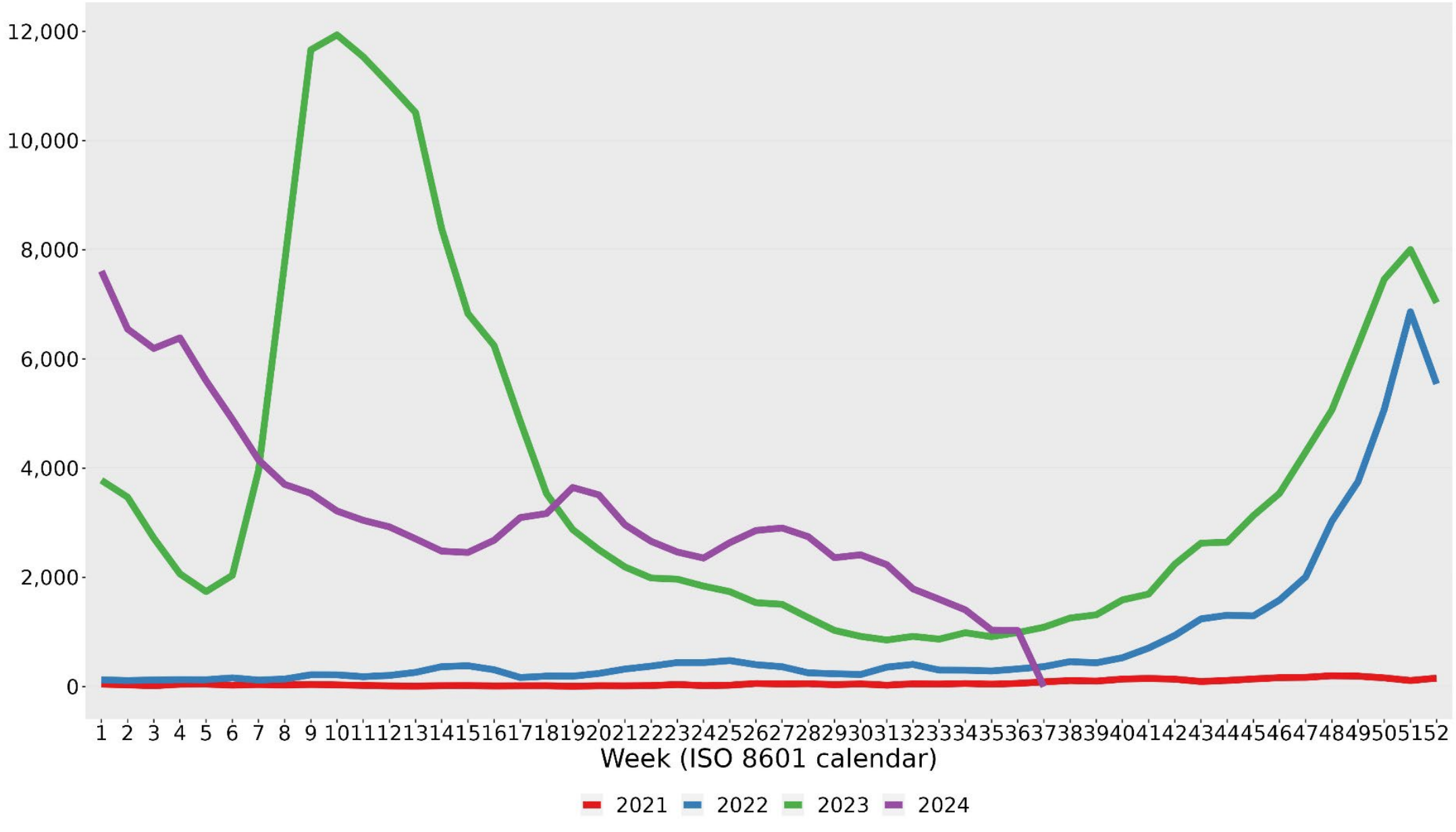
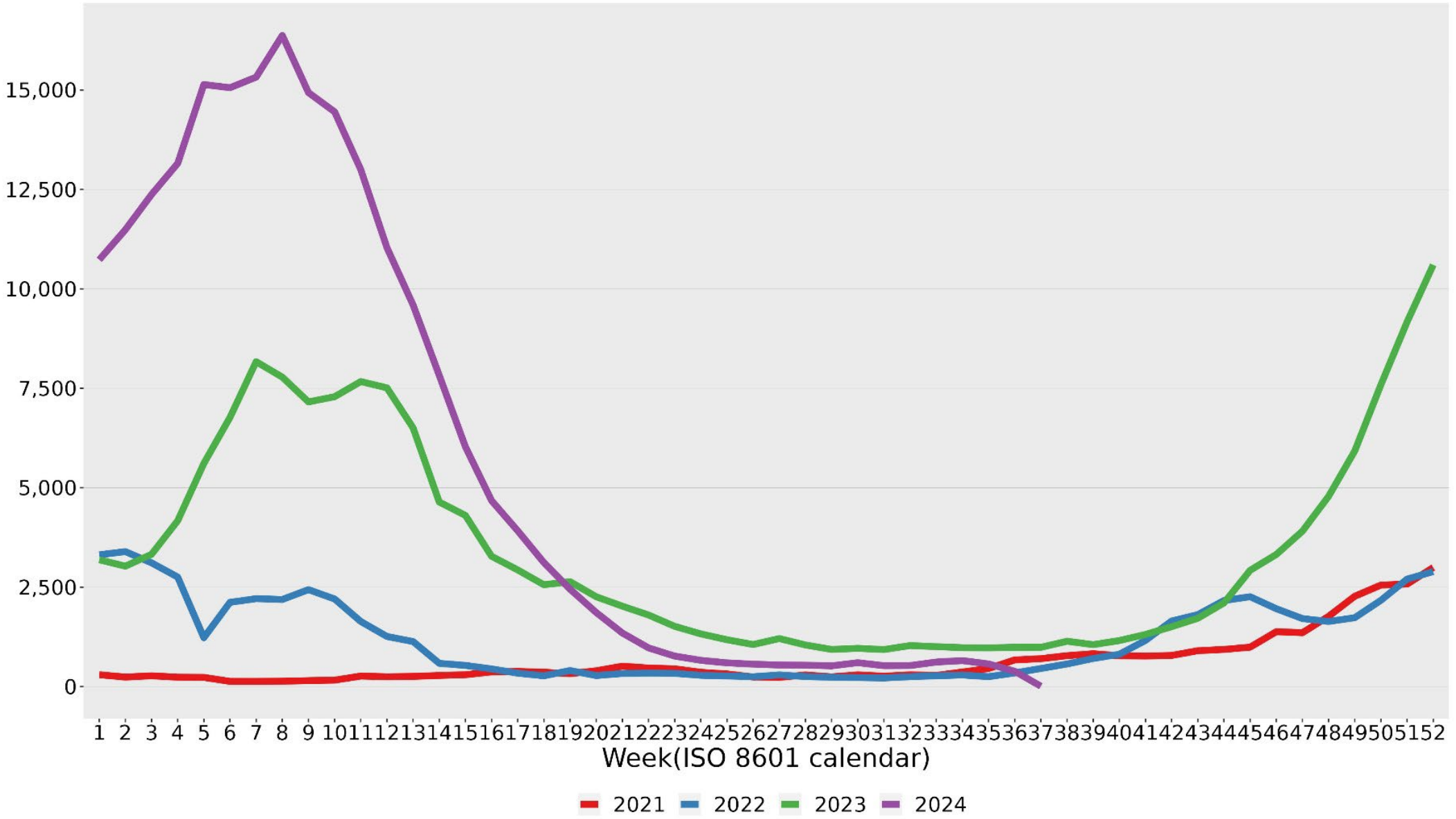
Additional Slides

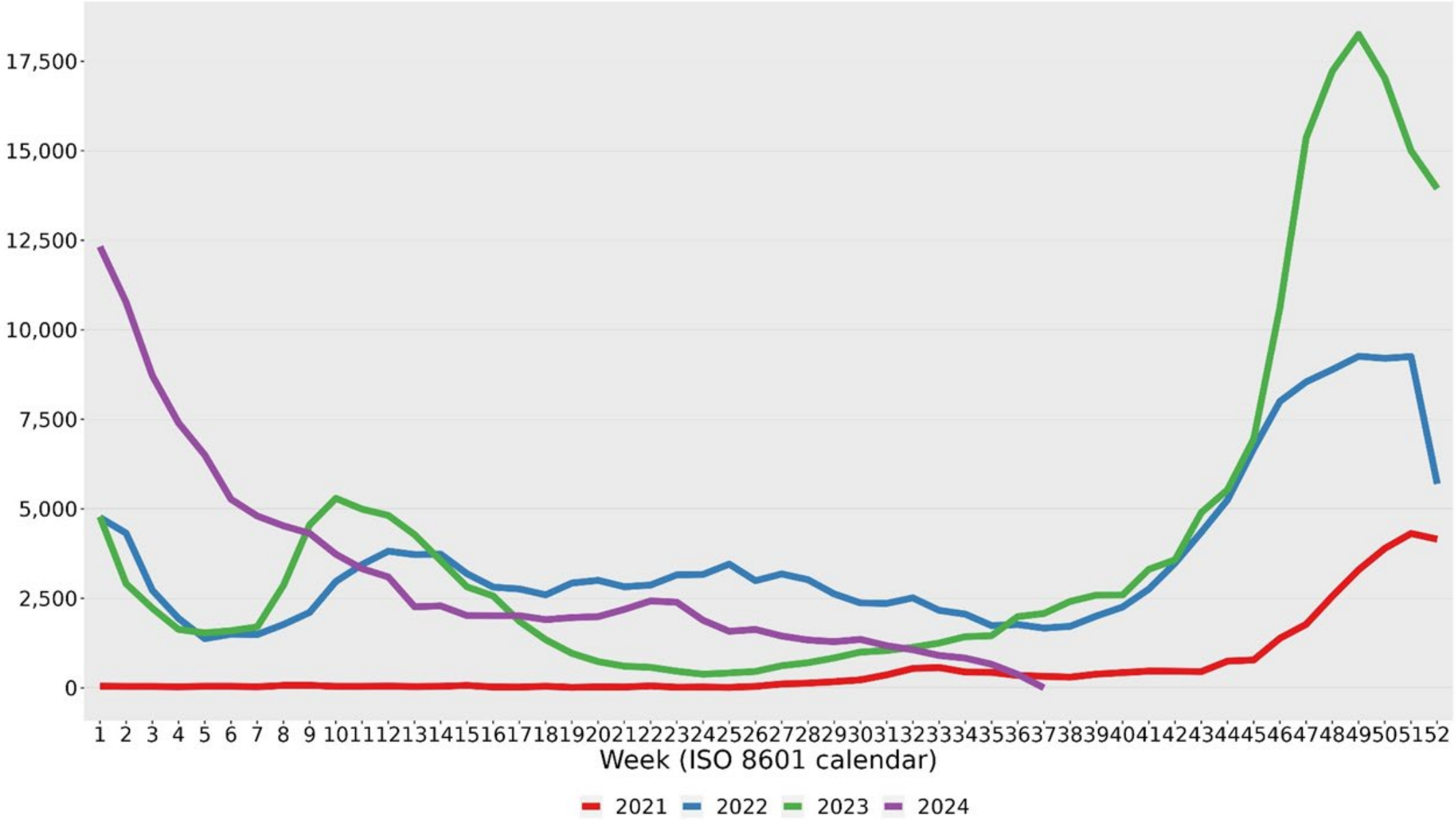
Number of A(H1N1)pdm09 viruses detected by GISRS



Number of influenza B viruses detected by GISRS



Number of A(H3N2) viruses detected by GISRS



Human serum panels from subjects given the 2024 SH influenza vaccine (pre/post-vaccination sera)

Serum Panel	Age range	Median age	N	Vaccine type	Vaccine strains
Adult, Peru, CDC	30-61 years	46 years	20	Egg Quadrivalent (VAXIGRIPTETRA, Sanofi)	A/Victoria/4897/2022 (H1N1)pdm09 - like virus, IVR-238 (A/Victoria/4897/2022)
					A/Thailand/8/2022(H3N2) - like virus, SAN-022 (A/California/122/2022)
					B/Austria/1359417/2021 (B/Victoria lineage) - like virus, B/Michigan/01/2021
					B/Phuket/3073/2013 (B/Yamagata lineage) - like virus, B/Phuket/3073/2013
Adult, Egg Vaccine, Australia, VIDRL	18-63 years	31 years	25	Egg Quadrivalent (FluQuadri, Sanofi-Aventis)	A/Victoria/4897/2022 (H1N1)pdm09 - like virus, IVR-238 (A/Victoria/4897/2022)
					A/Thailand/8/2022(H3N2) - like virus, SAN-022 (A/California/122/2022)
					B/Austria/1359417/2021 (B/Victoria lineage) - like virus, B/Michigan/01/2021
					B/Phuket/3073/2013 (B/Yamagata lineage) - like virus, B/Phuket/3073/2013
Adult, Cell Vaccine, Australia, VIDRL	18-62 years	27 years	25	Cell Quadrivalent (Flucelvax Quad, Seqirus)	A/Georgia/12/2022 (H1N1)pdm09 - like virus, CVR-167 (A/Georgia/12/2022)
					A/Massachusetts/18/2022 (H3N2)- like virus, A/Sydney/1304/2022
					B/Austria/1359417/2021 (B/Victoria lineage) - like virus, B/Singapore/WUH4618/2021
					B/Phuket/3073/2013 (B/Yamagata lineage) - like virus, B/Singapore/INFTT-16-0610/2016
Elderly, Australia, VIDRL	65-80 years	72.5 years	20	Egg Quadrivalent (Fluad Quad, Seqirus)	A/Victoria/4897/2022 (H1N1)pdm09 - like virus, IVR-238 (A/Victoria/4897/2022)
					A/Thailand/8/2022(H3N2) - like virus, IVR-237 (A/Thailand/8/2022)
					B/Austria/1359417/2021 (B/Victoria lineage) - like virus, BVR-26 (B/Austria/1359417/2021)
					B/Phuket/3073/2013 (B/Yamagata lineage) - like virus, BVR-1B (B/Phuket/3073/2013)