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

Global Influenza Virus Surveillance and Characterization October 10th, 2024

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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.

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; WOA, 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

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)?

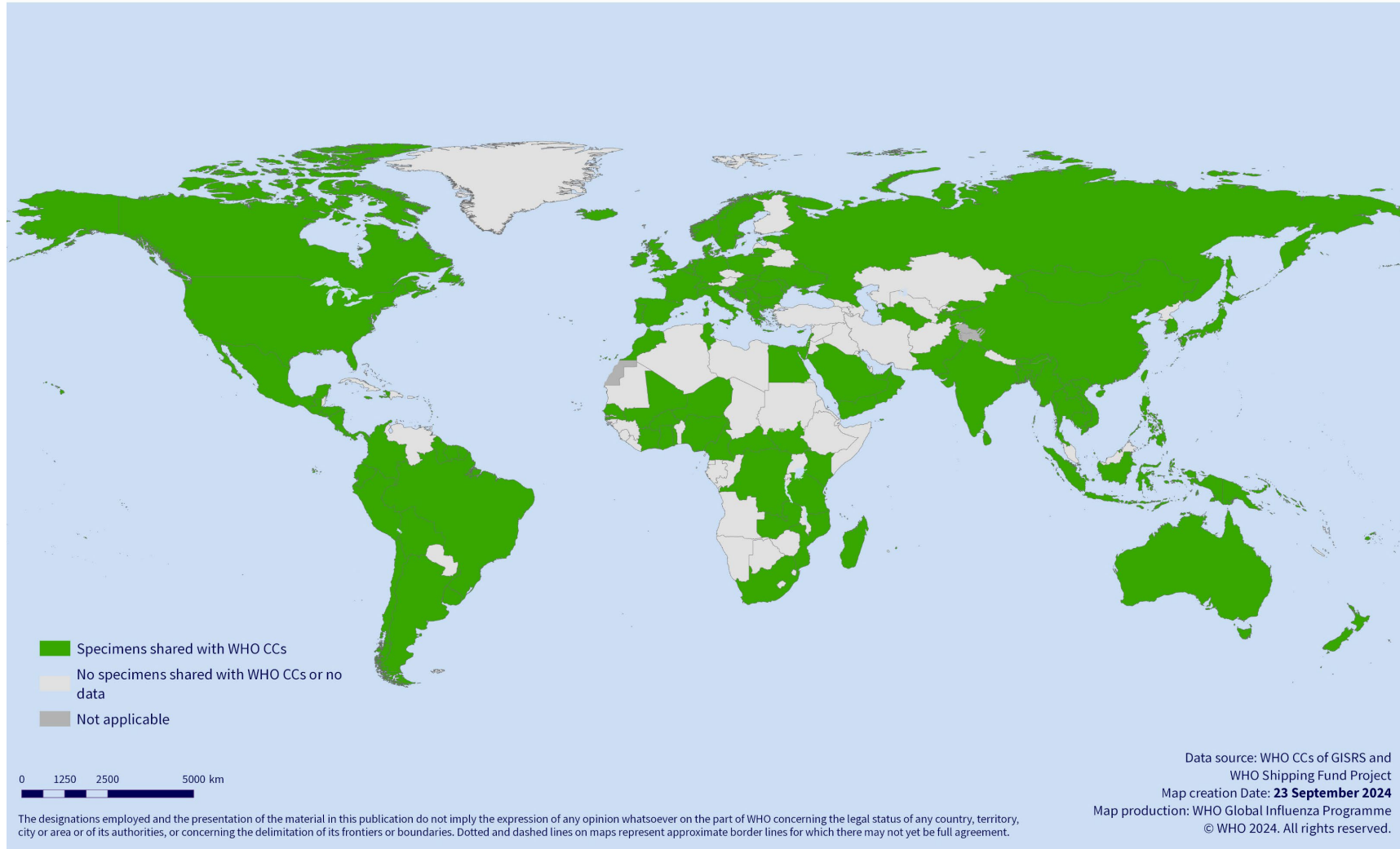
Data used to address key vaccine update questions

- **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 cartography, 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

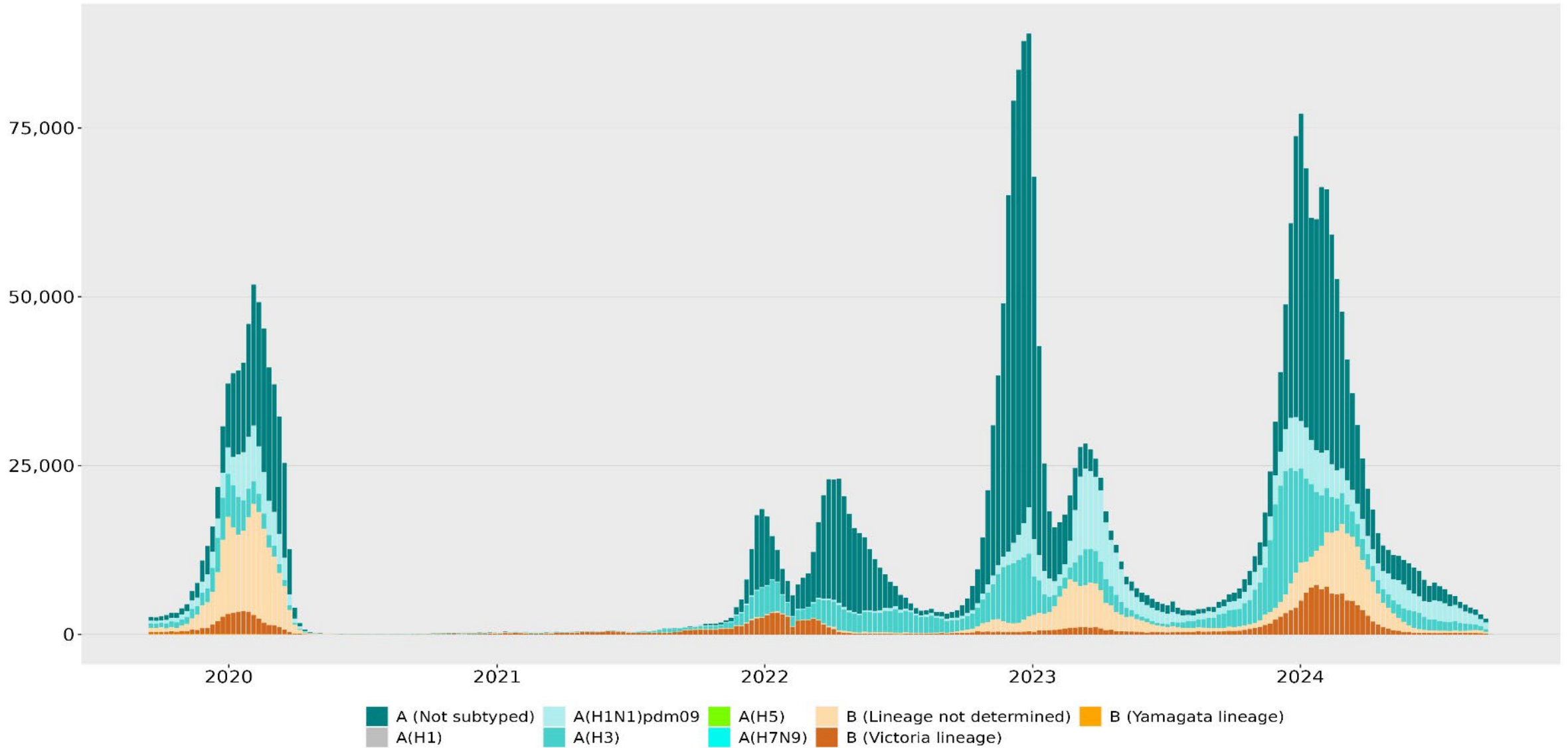
Countries, areas and territories sharing specimens with WHO Collaborating Centres (WHO CCs) from February to August 2024



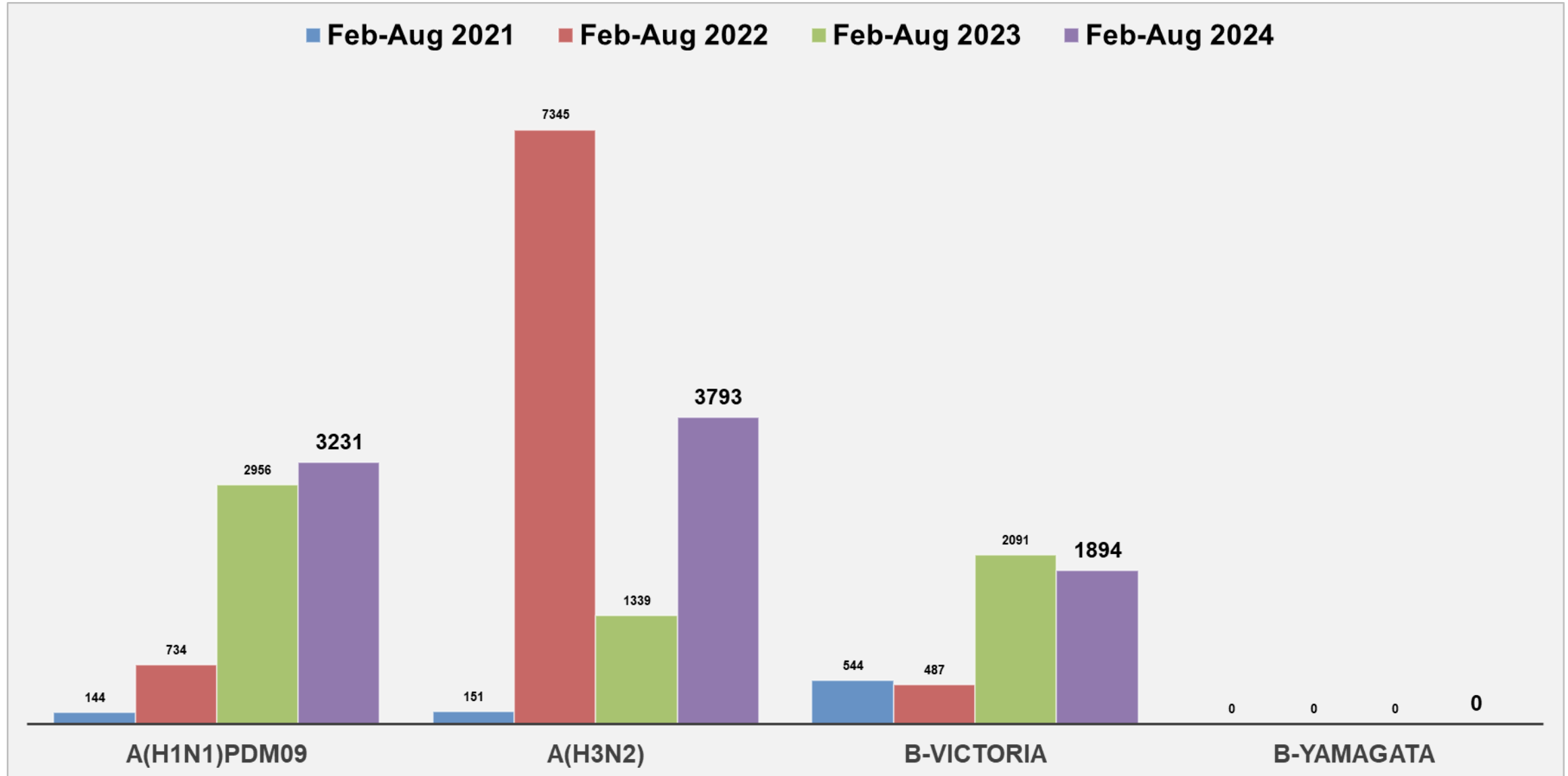
The designations employed and the presentation of the material in this publication do not imply the expression of any opinion whatsoever on the part of WHO concerning the legal status of any country, territory, city or area or of its authorities, or concerning the delimitation of its frontiers or boundaries. Dotted and dashed lines on maps represent approximate border lines for which there may not yet be full agreement.



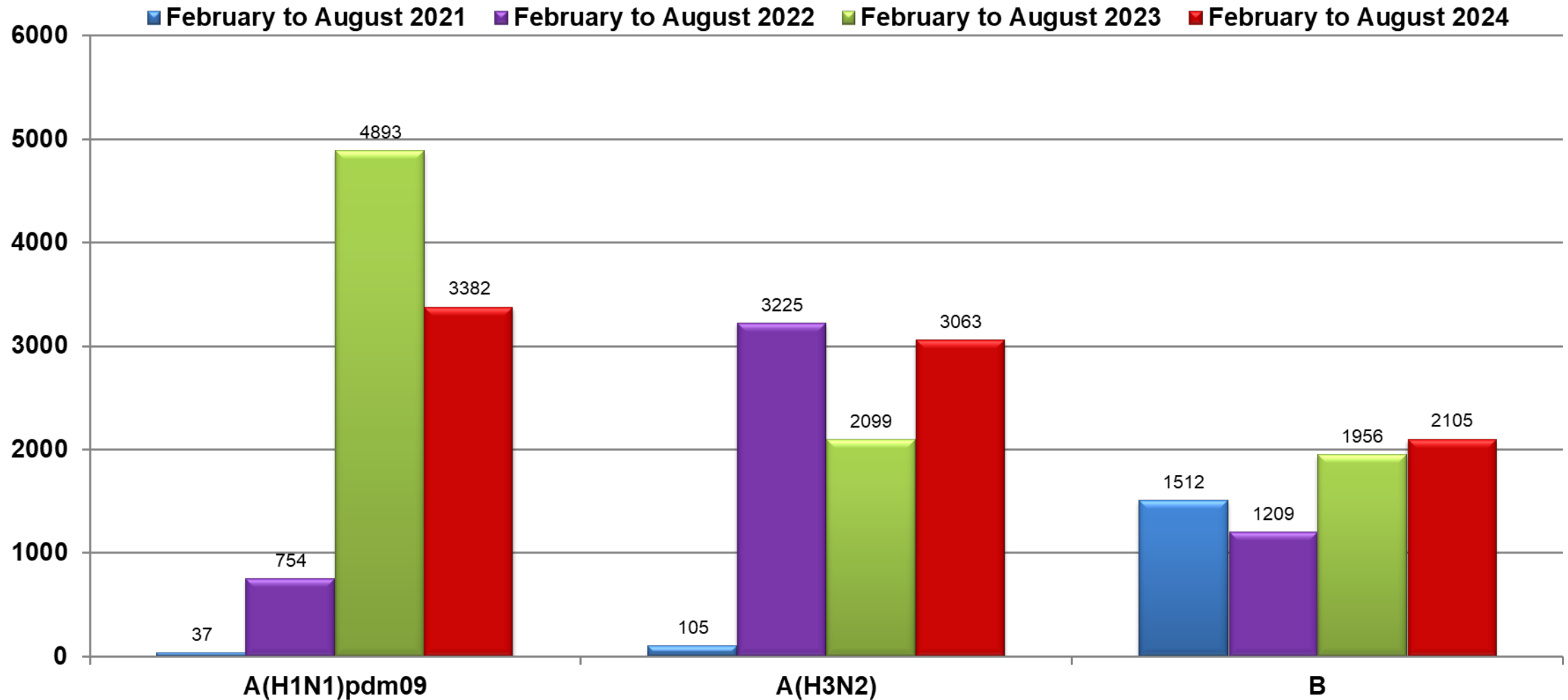
Global circulation of influenza viruses



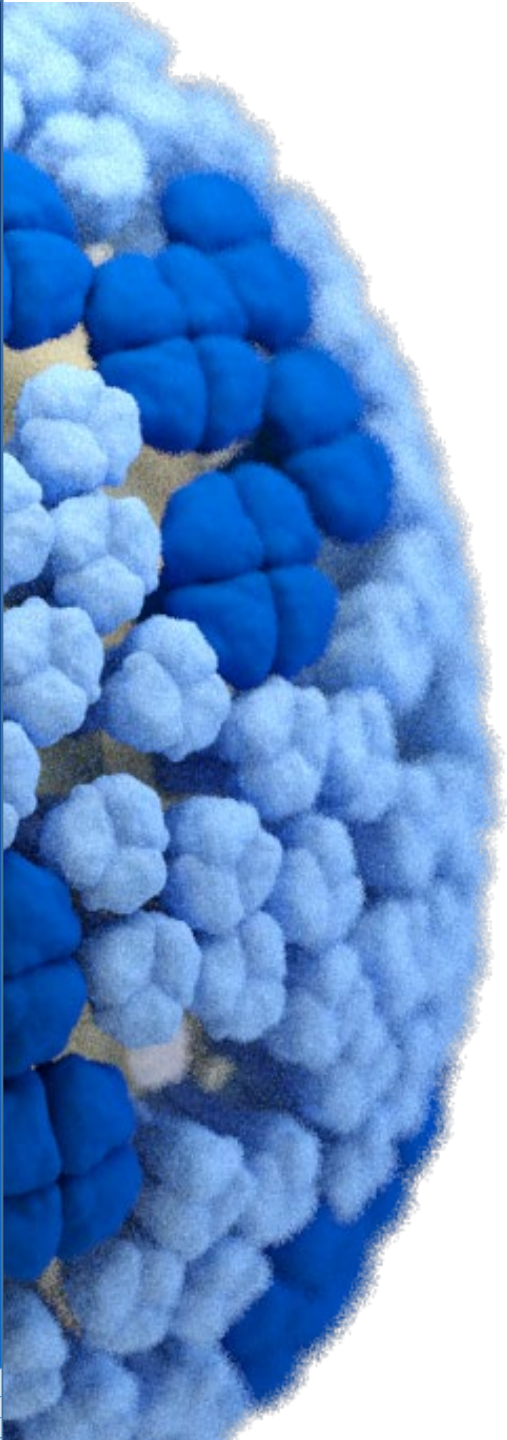
Influenza viruses genetically characterized by WHO CCs over the past 4 southern hemisphere seasons



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

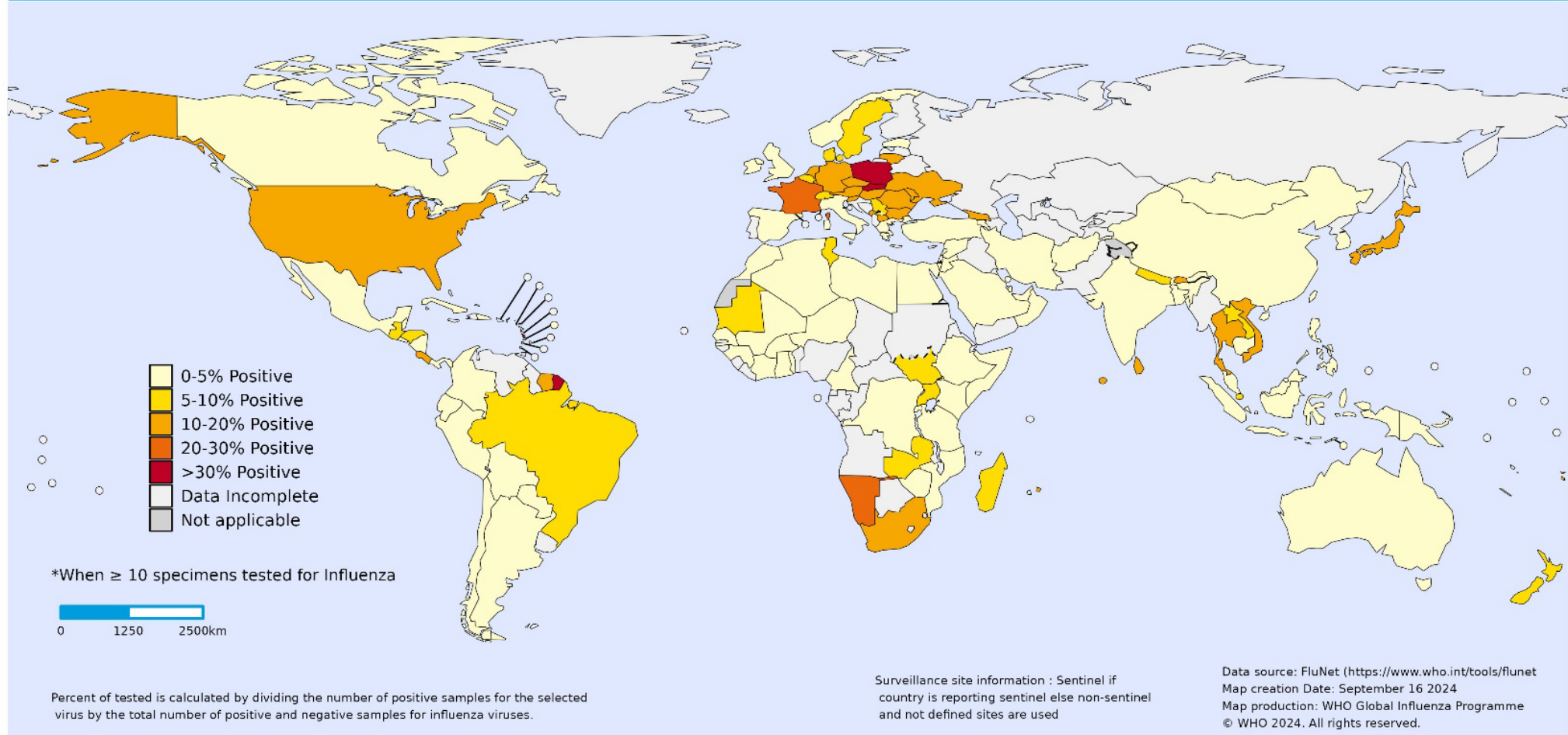


A(H1N1)pdm09 Viruses



Influenza A(H1N1)pdm09 virus activity

Influenza A(H1N1)pdm09, February 2024 to August 2024, percent of all samples tested



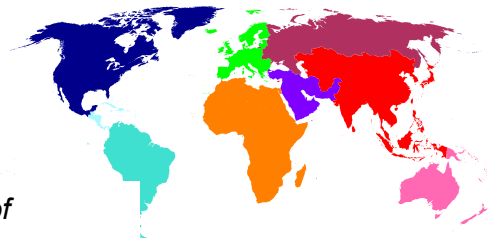
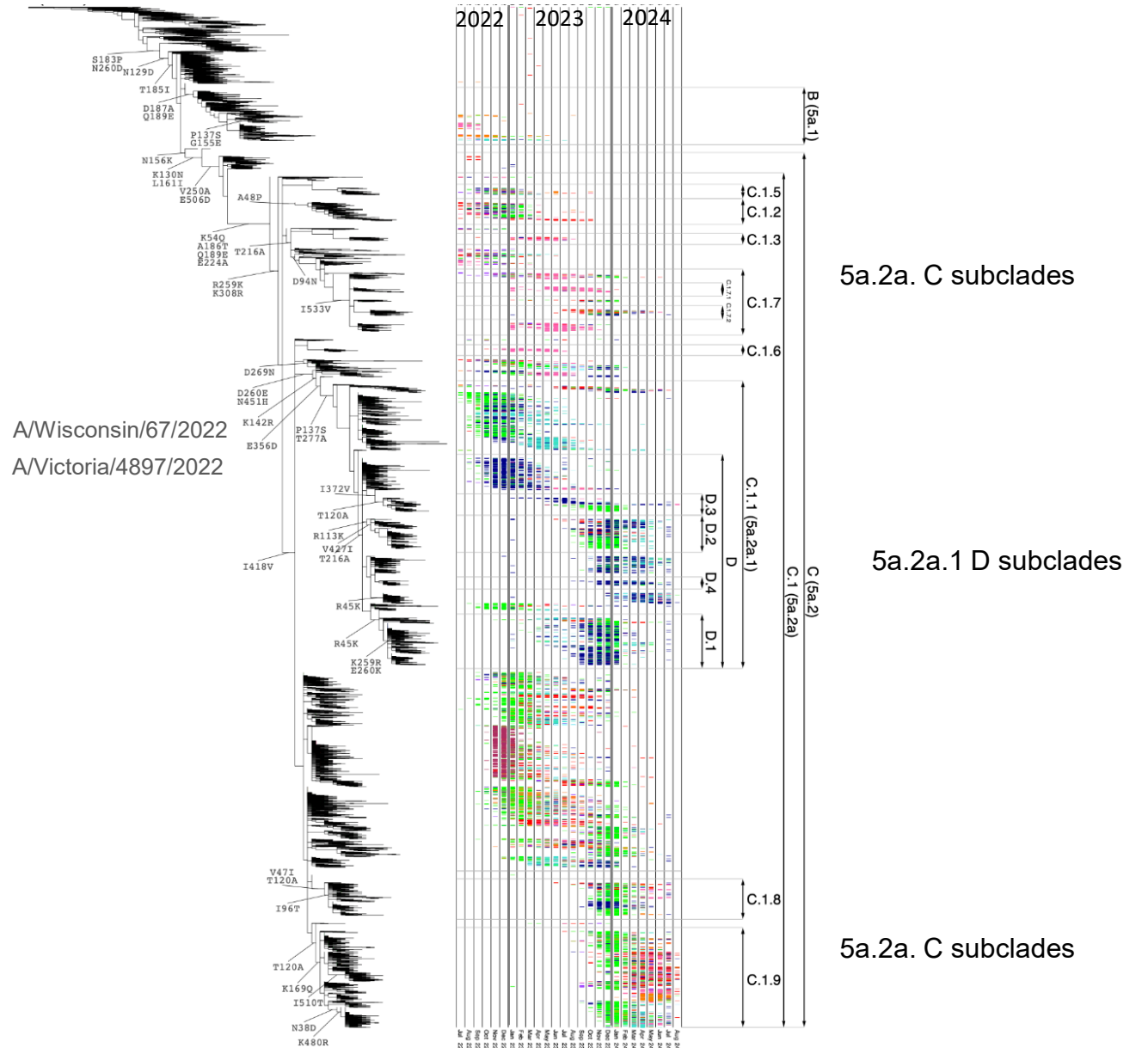
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Colour intensity shows the percent of influenza A(H1N1)pdm09 positive among all samples tested during this period per country

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

A(H1N1)pdm09 HA phylogeography

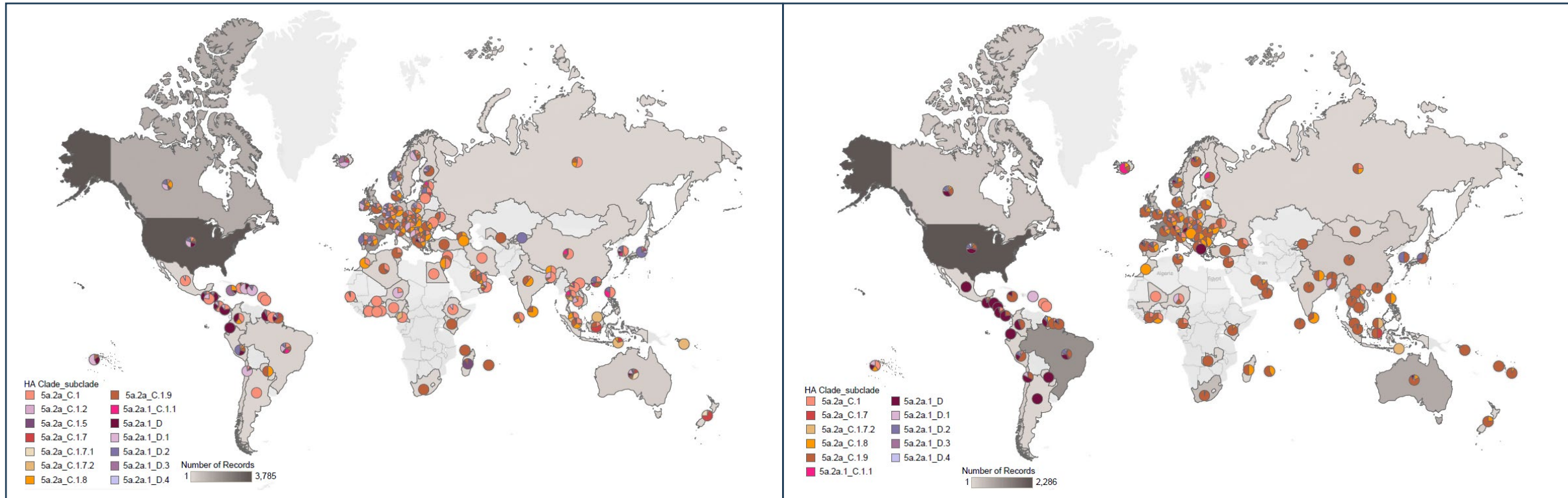


Source: University of Cambridge, UK

Global A(H1N1)pdm09 HA clade diversity

Collection Dates
September 1, 2023 - January 31, 2024

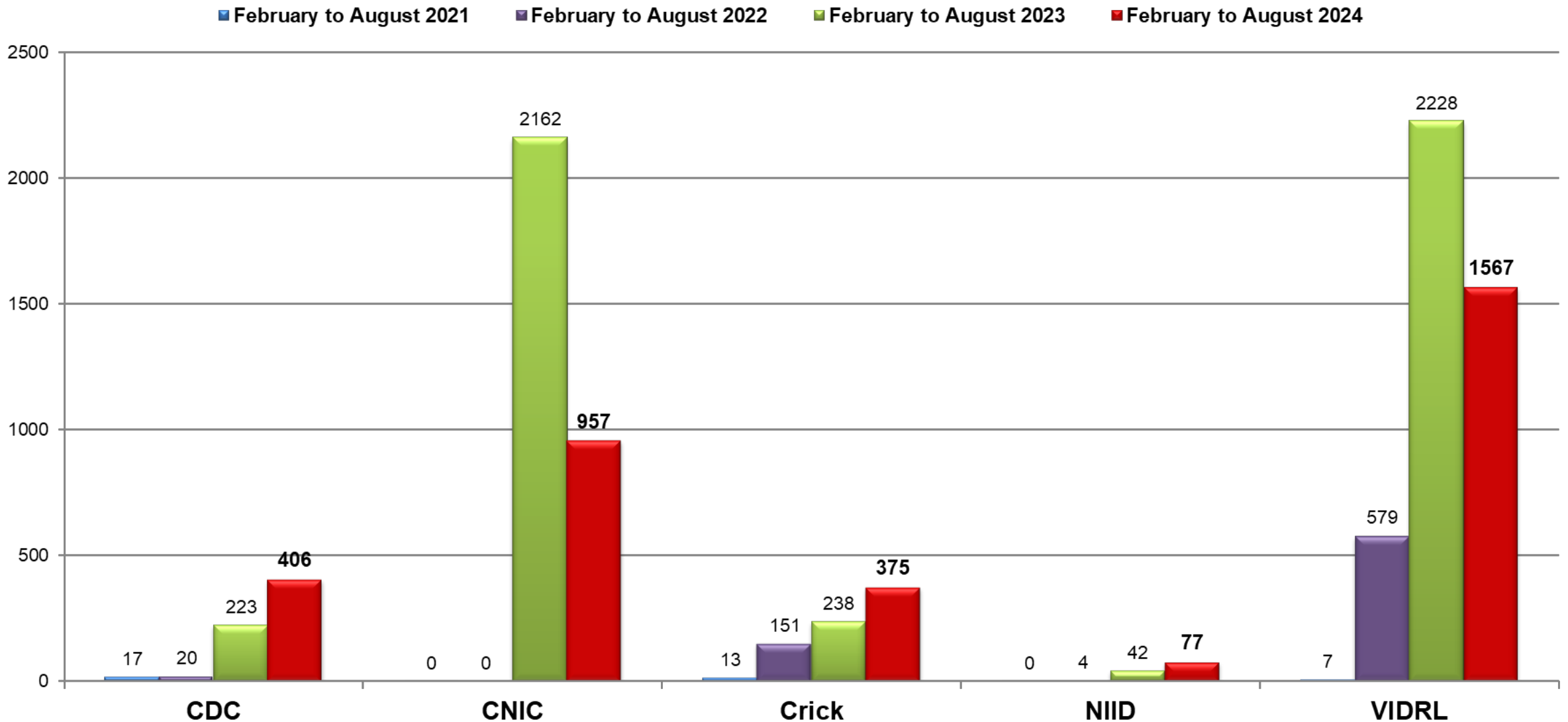
Collection Dates
February 1, 2024 – August 31, 2024



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)**

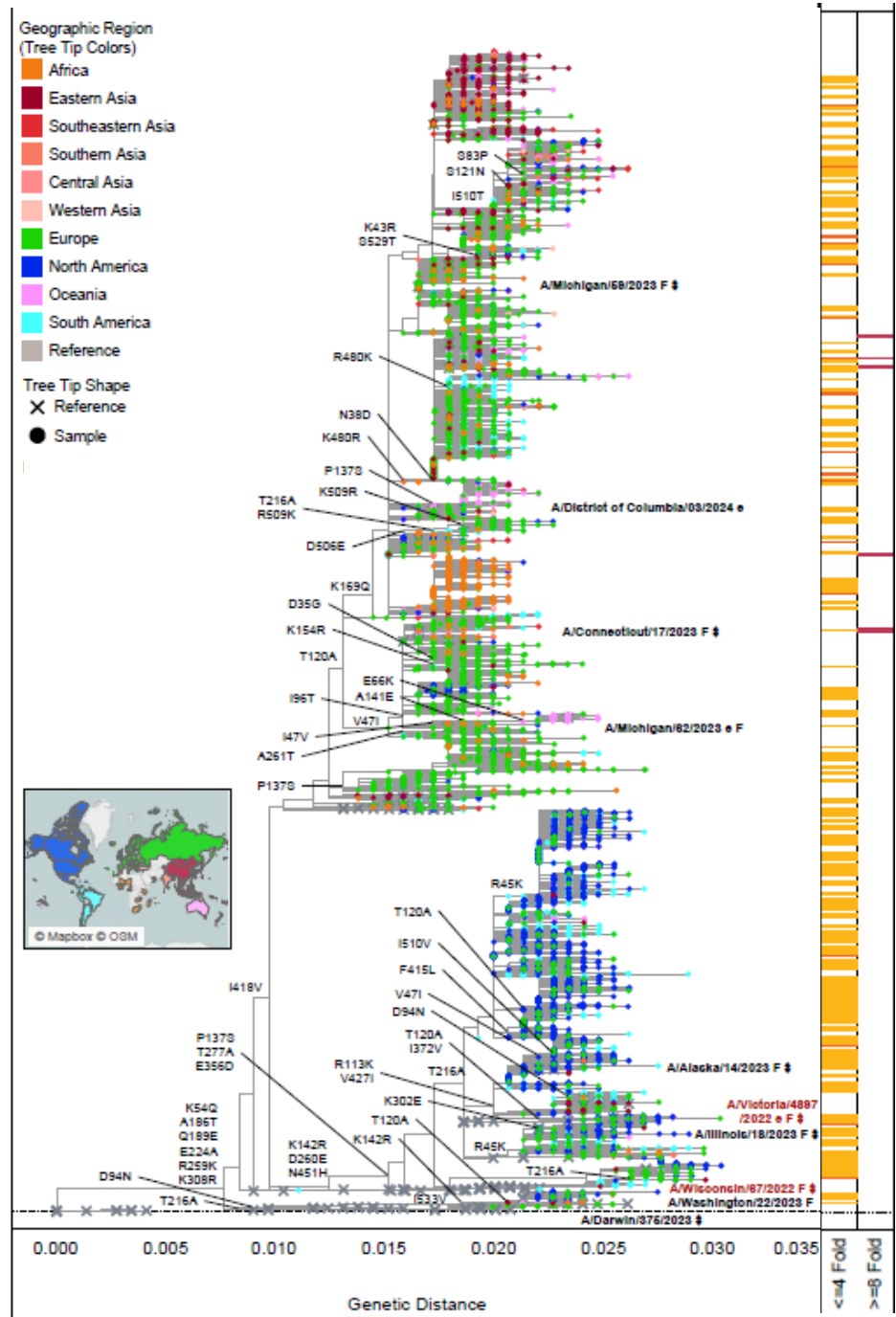
**A/Victoria/4897/2022-like (egg)
C.1.1 (5a.2a.1)**

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



Sera Panel
Antigenic Characterization
by HI Fold Reduction
to A/Wisconsin/67/2022 cell

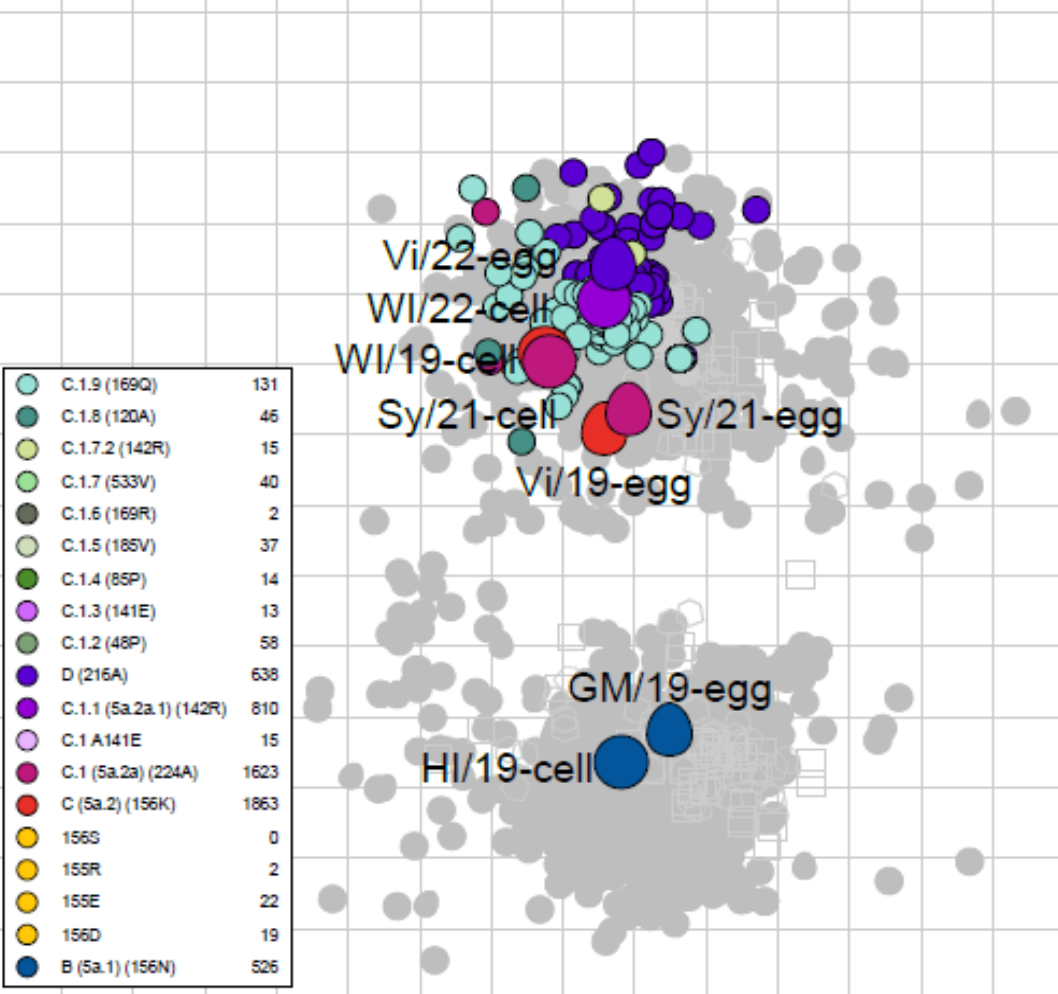
■ <=2 ■ =8
■ =4

5a.2a
(C.1, C.1.7, C.1.7.2, C.1.8, C.1.9)

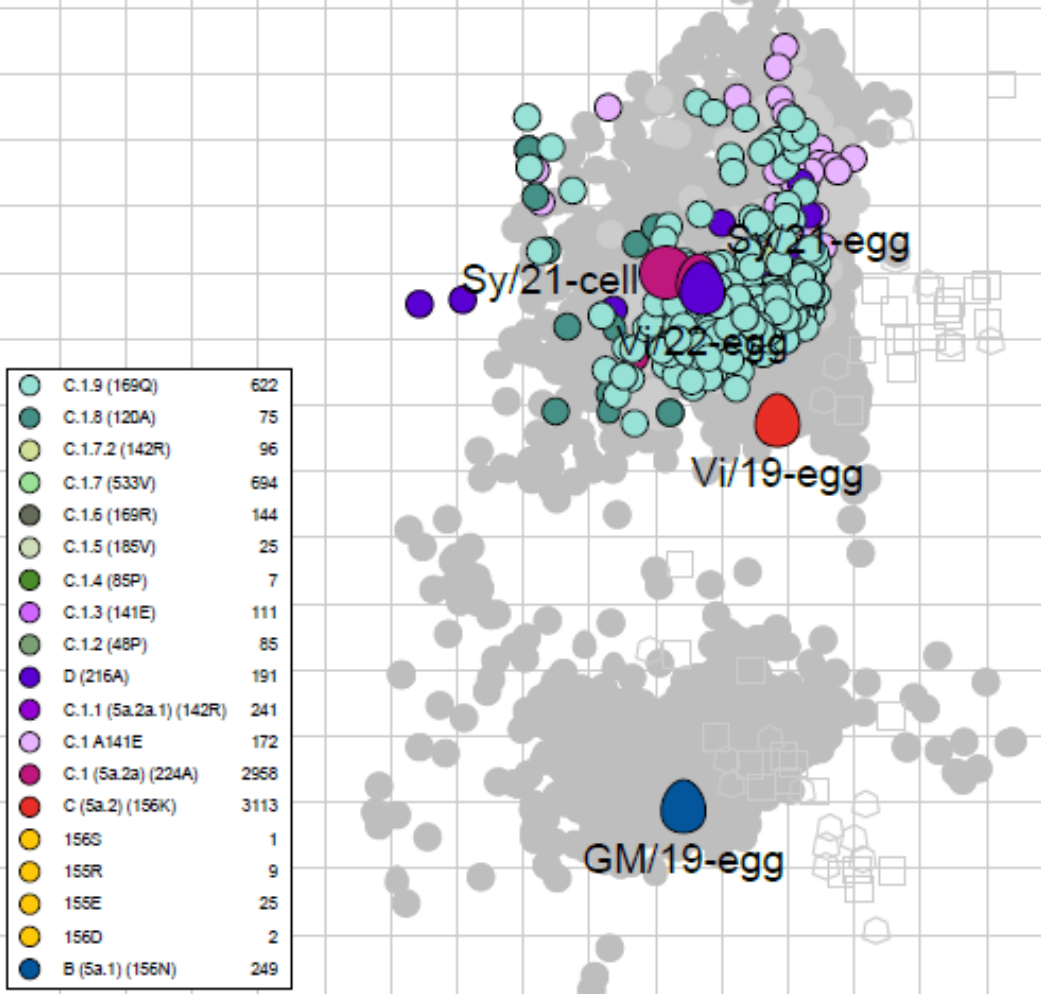
5a.2a.1
(C.1.1, D, D.1, D.2, D.3, D.4)

A(H1N1)pdm09 antigenic cartography

CDC A(H1N1) by clade (since March 2024)



VIDRL A(H1N1) by clade (since March 2024)



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)
			WI/67		GA/12	VIC/4897		+V1521					+T120A		+T120A +A141E	+T120A +K154R	+K169Q					+T120A +K169Q	+P137S +K169Q	+A141E +K169Q	+K169Q +T216A	+R45K +T216A	+R45K +T216A +K302E	+R113K +T216A				+T120A +T216A					
			-		-	-		-					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				
			CELL	MHRA	NIID	CELL	CELL	CDC	CNIC	CELL	NIID	VIDRL	CELL	NIID	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	NIID	MHRA	VIDRL					
AWISCONSIN/67/2022-LIKE CELL	Adult	ccIV4 (Flucelvax)	Australia	320	735	557	184	459	√	249	286	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√			
		IIV4	Australia	151	223	243	76	147	√	85	128	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√		
			Peru	61	113	135	29	48	√	√	55	√	√	X	√	√	√	X	√	√	√	√	√	X	√	√	√	√	√	√	√	√	√	√	√	X	
	Elderly	allIV4	Australia	34	59	70	17	35	X	19	27	√	X	X	X	√	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)	2 (50.0)	0 (0.0)	3 (75.0)	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.



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.

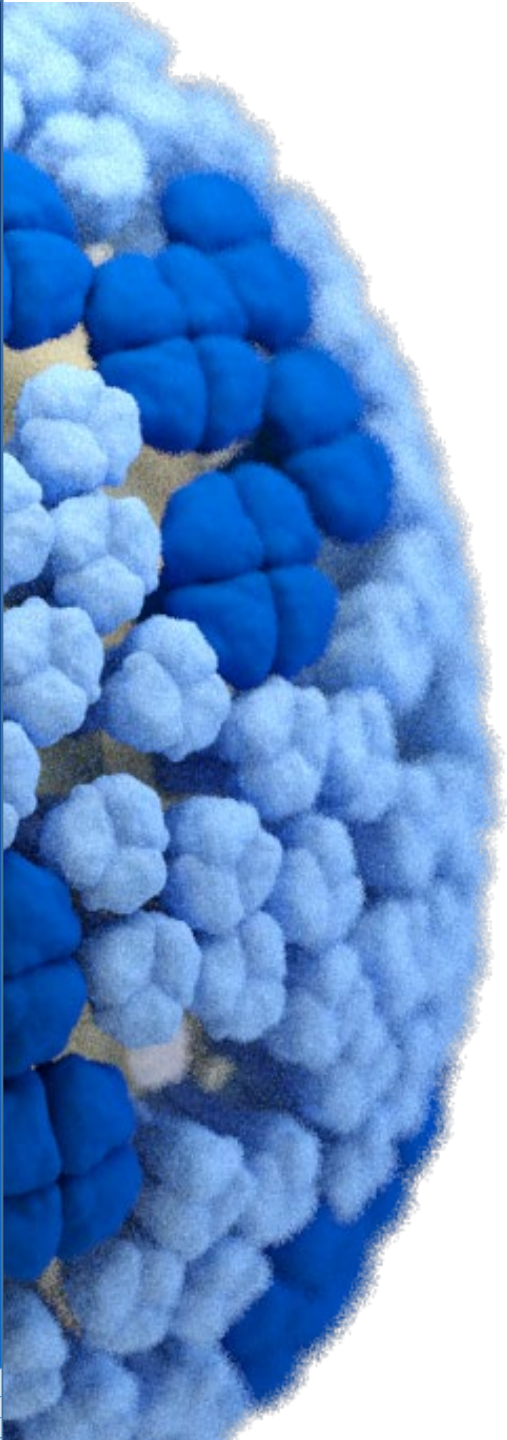
A(H1N1)pdm09 summary (1): global circulation and HA diversity

- 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

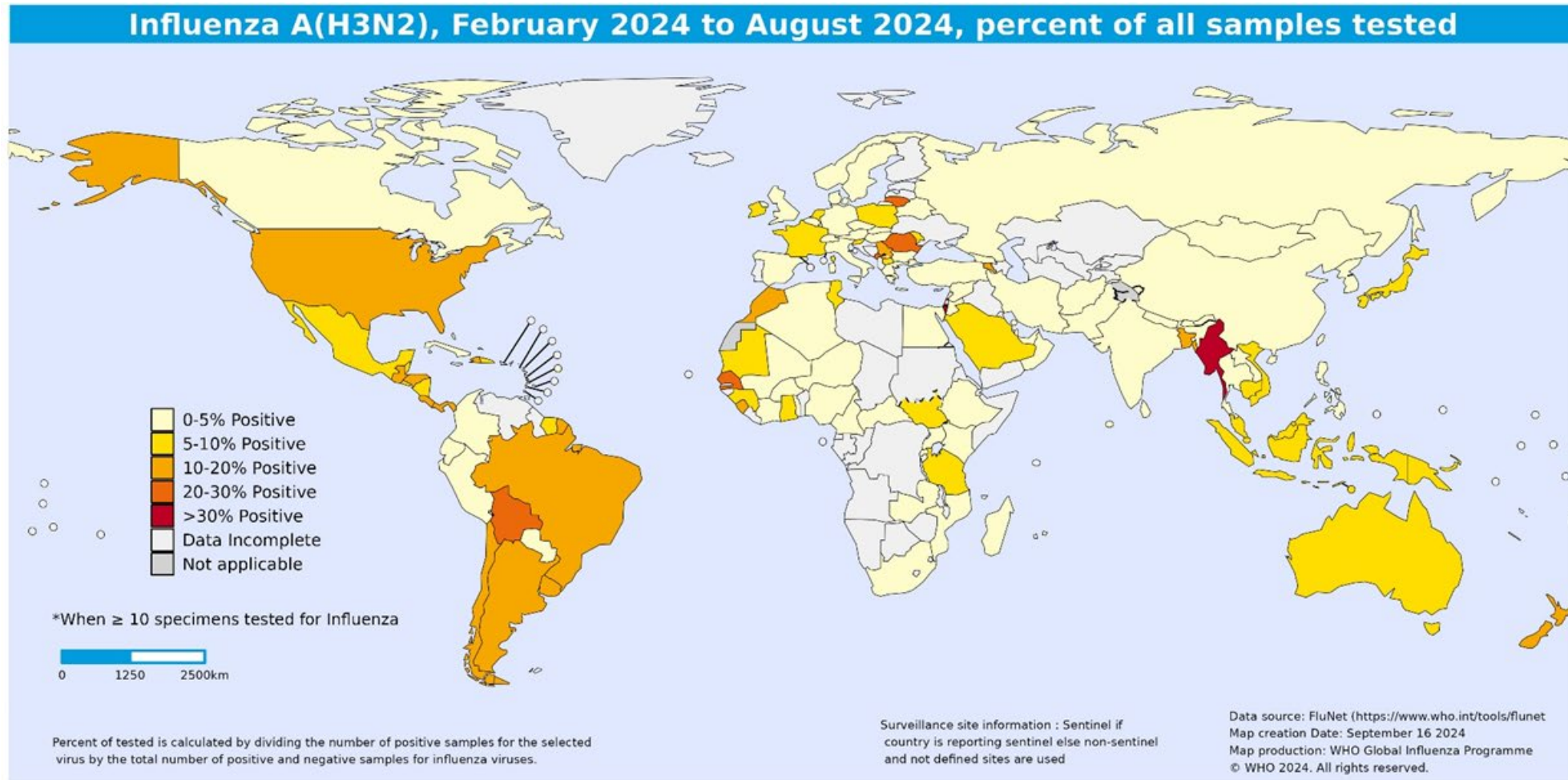
A(H1N1)pdm09 summary (2): antigenic characteristics

- 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



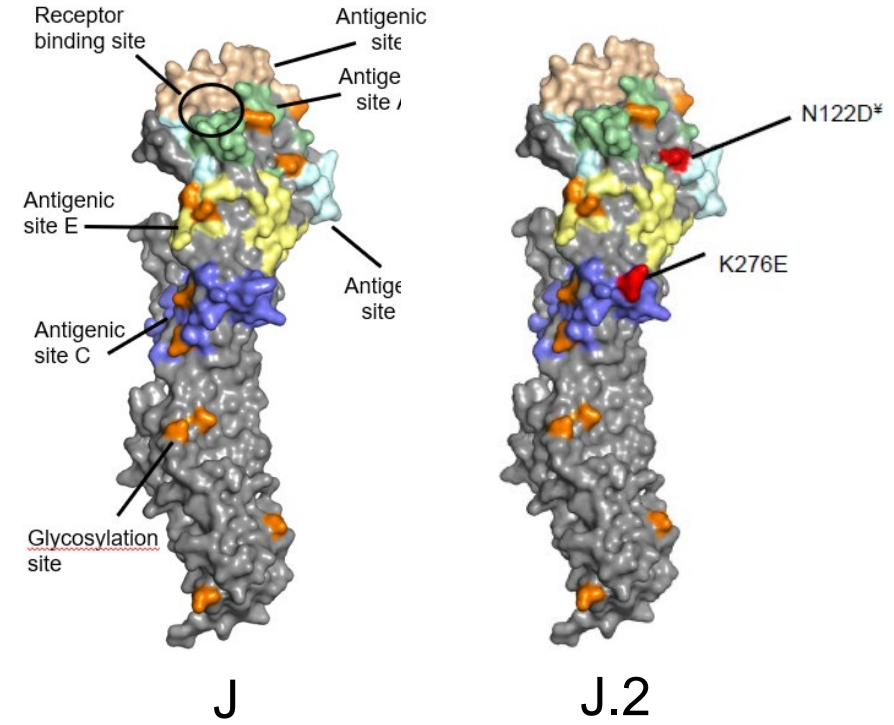
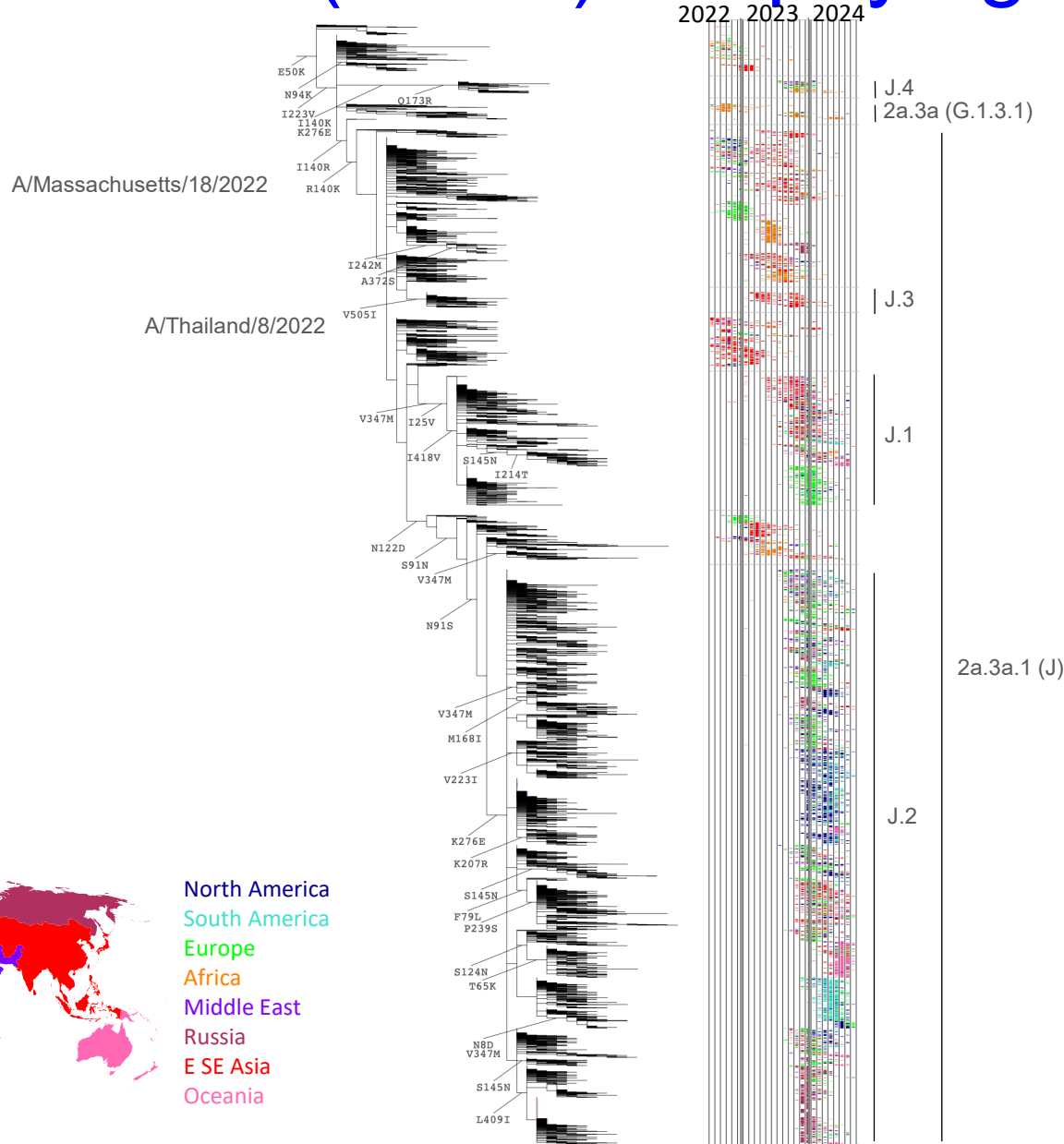
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Colour intensity shows the percent of influenza A(H3N2) positive among all samples tested during this period per country

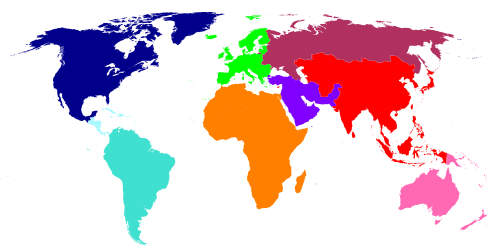
Data source: FluNet, (<https://www.who.int/tools/flunet>), Global Influenza Surveillance and Response System (16 September 2024)

A(H3N2) HA phylogeography



E50K, I140K, I223V

N122D (CHO-), K276E

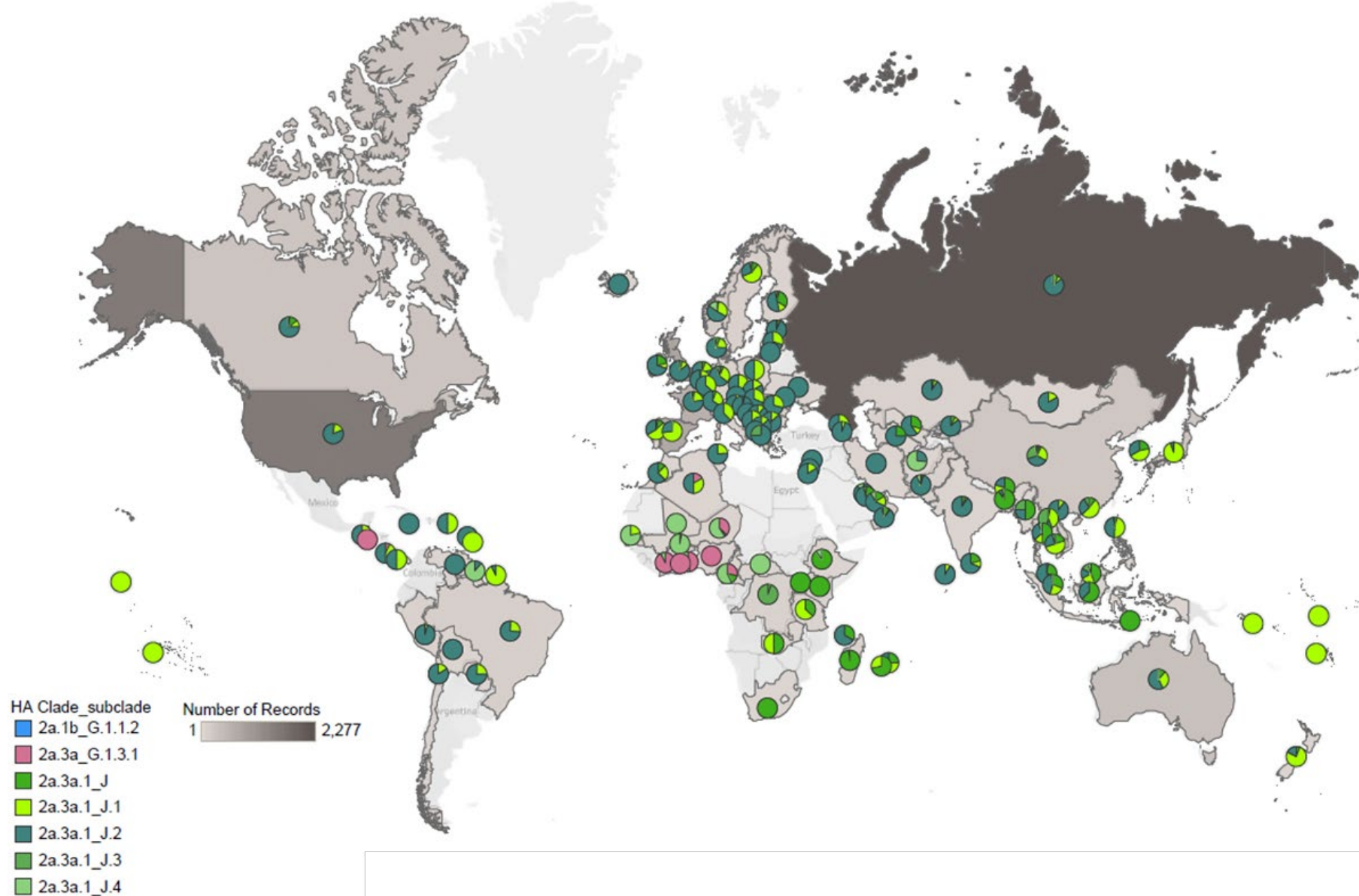


- North America
- South America
- Europe
- Africa
- Middle East
- Russia
- E SE Asia
- Oceania

Source: University of Cambridge, UK

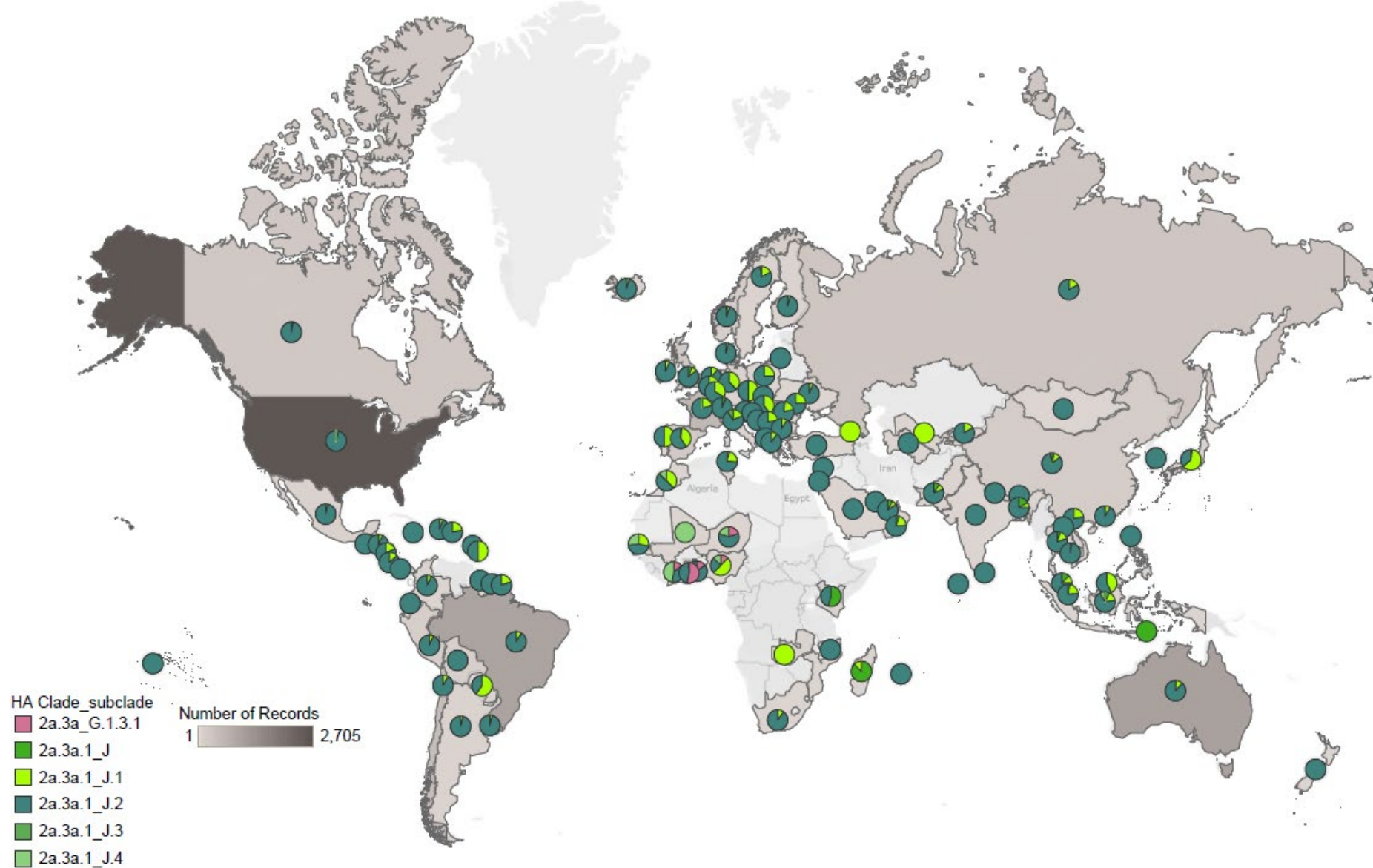
HA subclade: <https://clades.nextstrain.org/>

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



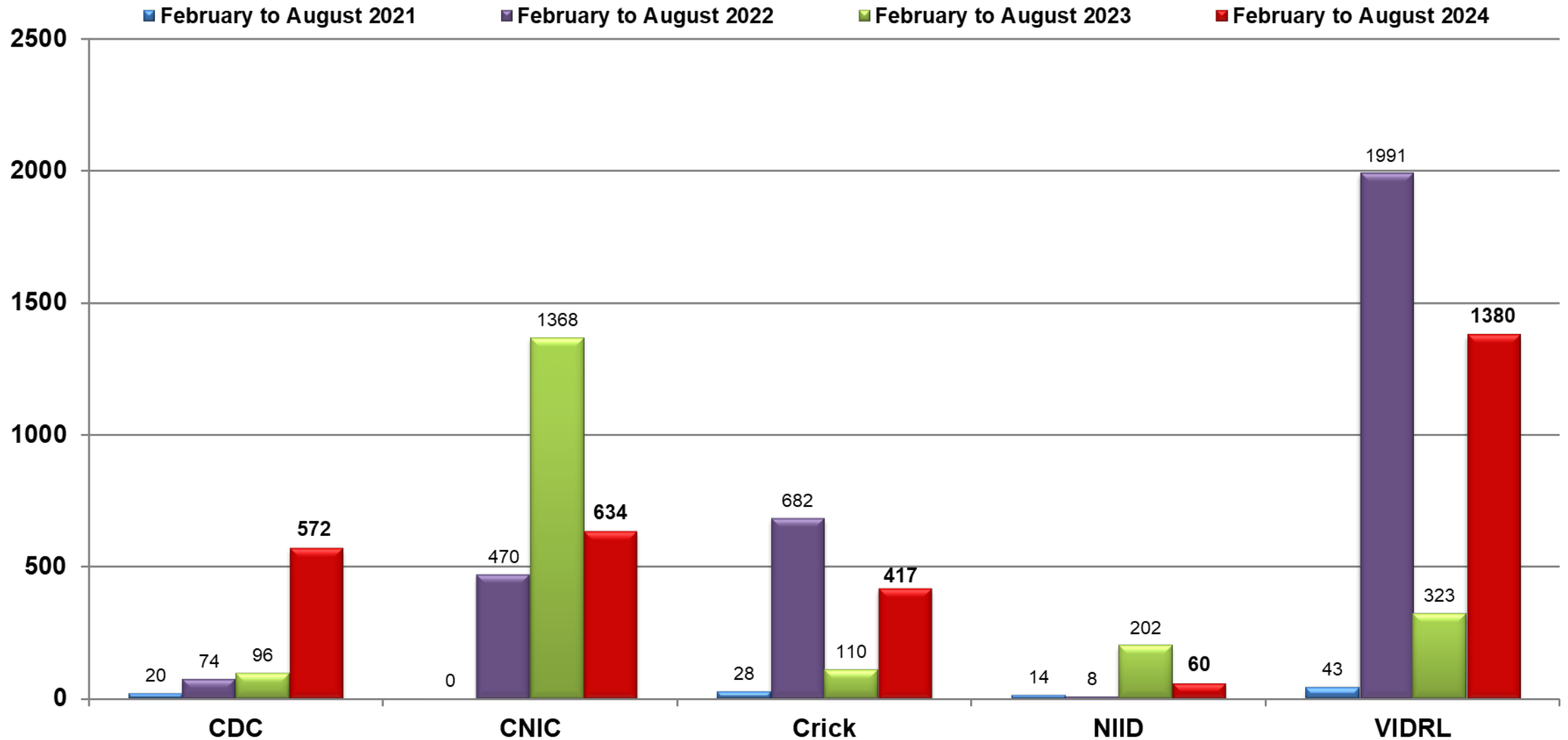
Source: WHO CC CDC, USA

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 (\geq 8 fold)	WHO CC	Like (<8 fold)	Low (\geq 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 \geq 8-fold lower than vaccine strain homologous titer

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

VN
Assay

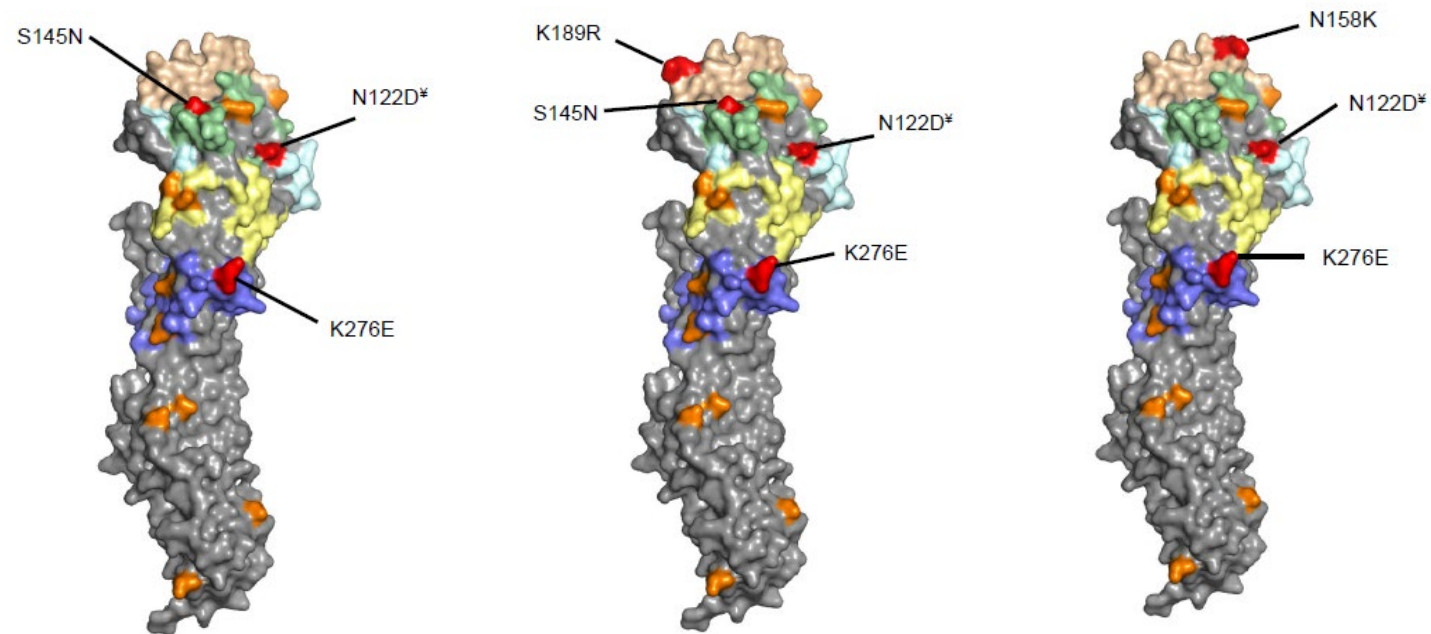
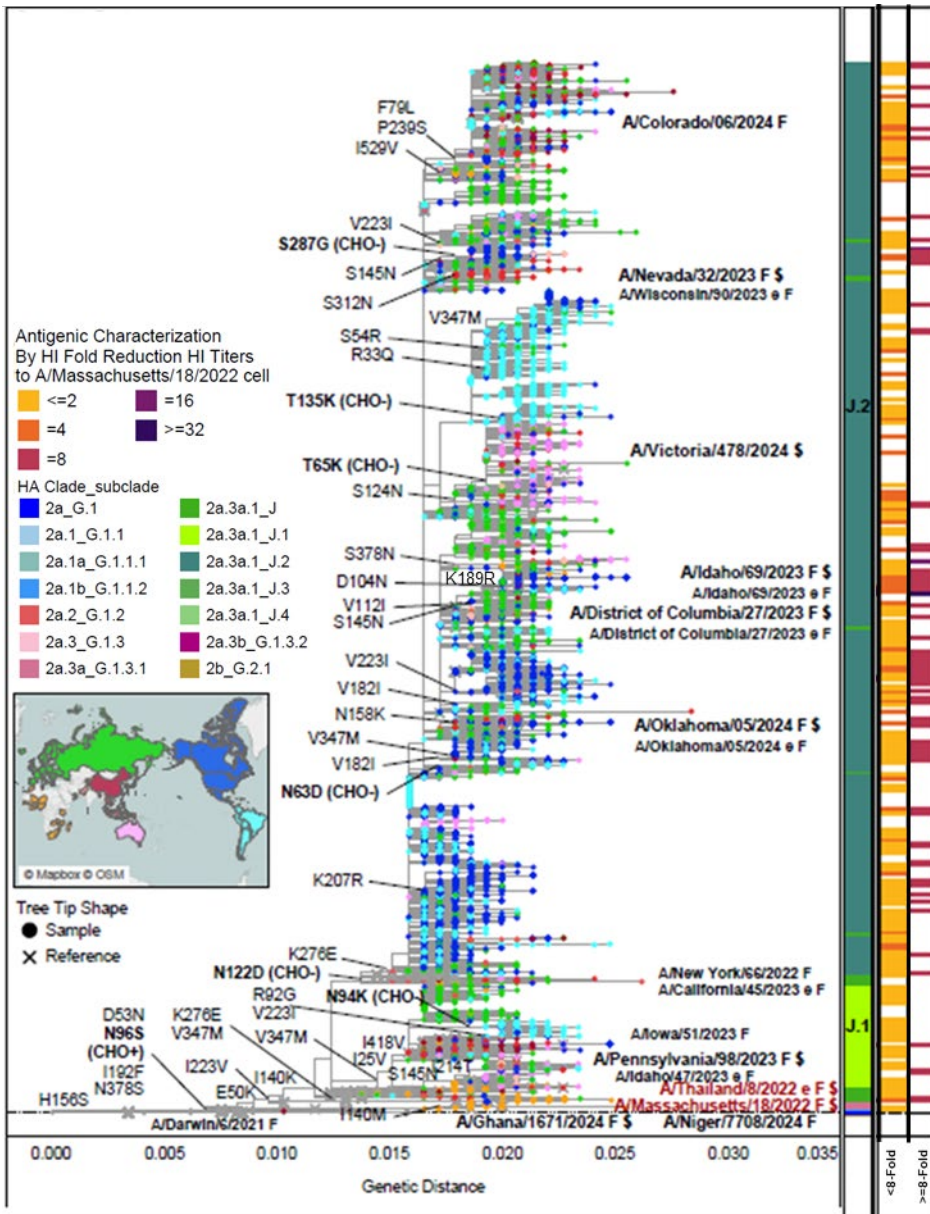
Antisera to southern hemisphere 2024 antigens (2a.3a.1)

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	77 (70%)	33 (30%)
FCI	127 (91%)	13 (9%)	VIDRL	21 (36%)	37 (64%)
VIDRL	52 (90%)	6 (10%)	Total	98 (58%)	70 (42%)
Total	321 (92%)	29 (8%)			

“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

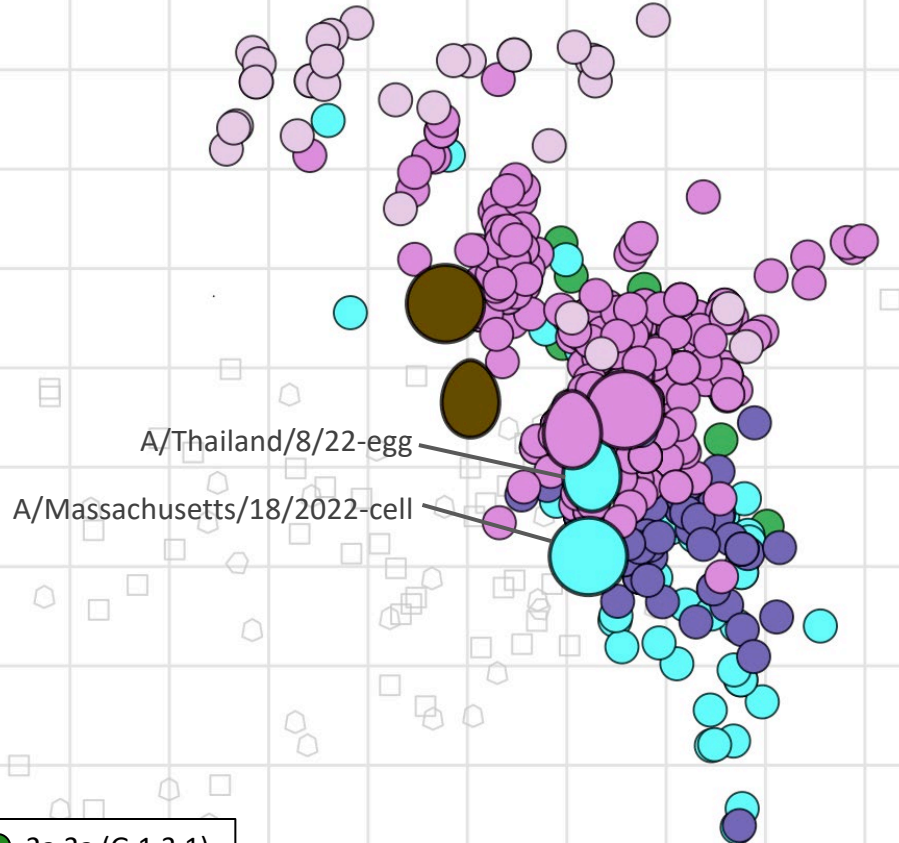
A(H3N2) HI Assay

Post-infection reference ferret antiserum

	HA Clade (Subclade)	HA Substitutions	SIAT	Egg	SIAT	SIAT	Egg	SIAT	Passage
			A/Massachusetts /18/2022	A/Thailand /08/2022	A/Sydney /856/2023	A/Croatia/ 10136RV/2023	A/Croatia/ 10136RV/2023	A/Slovenia /49/2024	
			2a.3a.1 (J)	2a.3a.1 (J)	2a.3a.1 (J.1)	2a.3a.1 (J.2)	2a.3a.1 (J.2)	2a.3a.1 (J.2)	
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 (Am1A12)
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

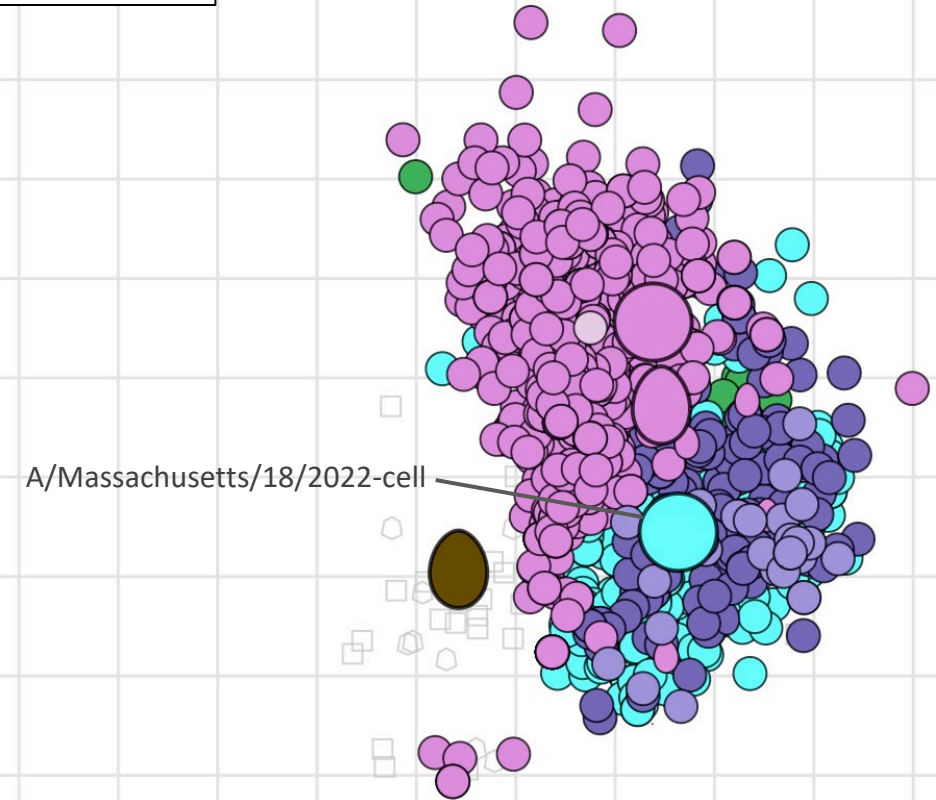
A(H3N2) antigenic cartography

A(H3N2) HI
CC London



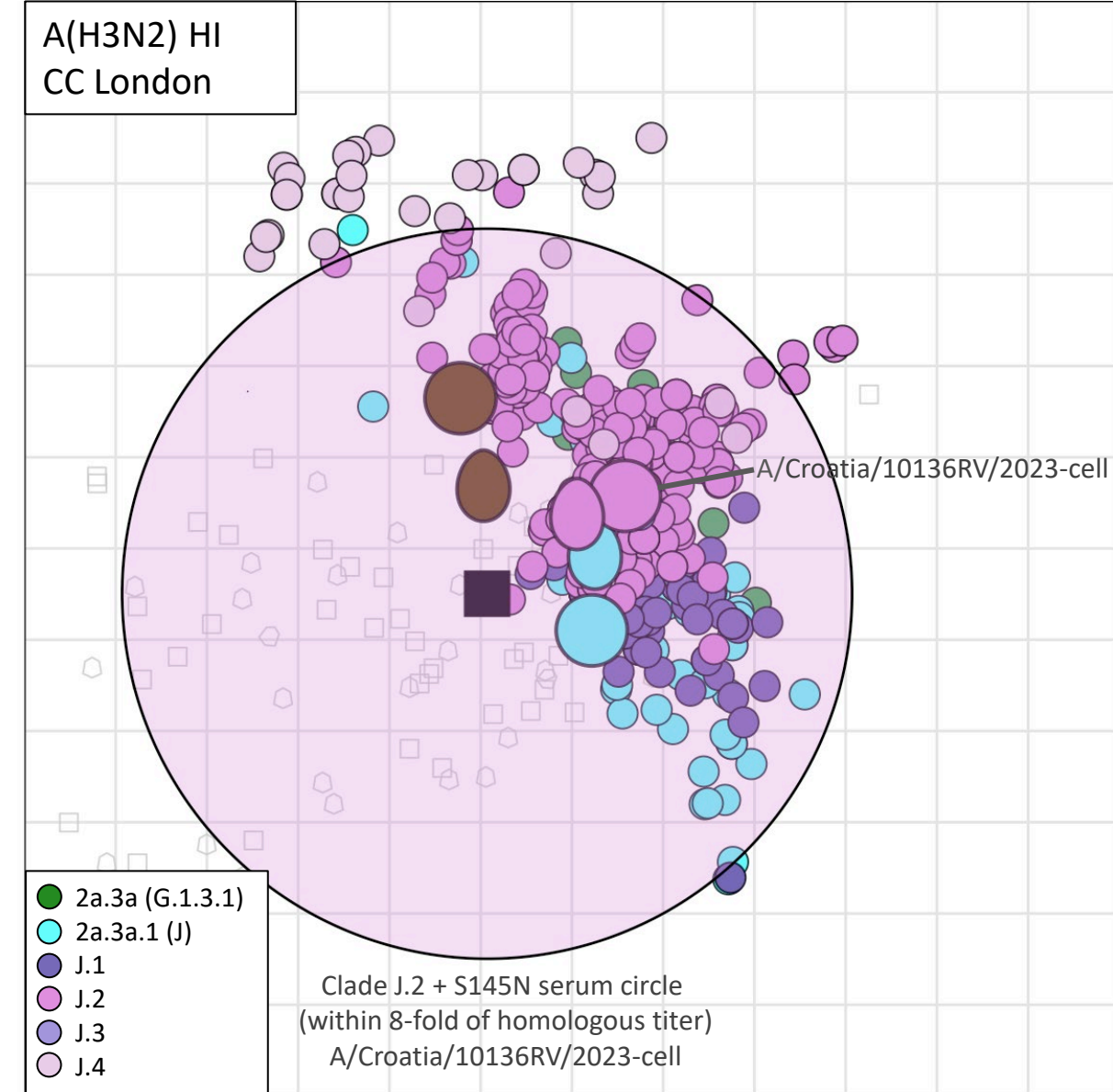
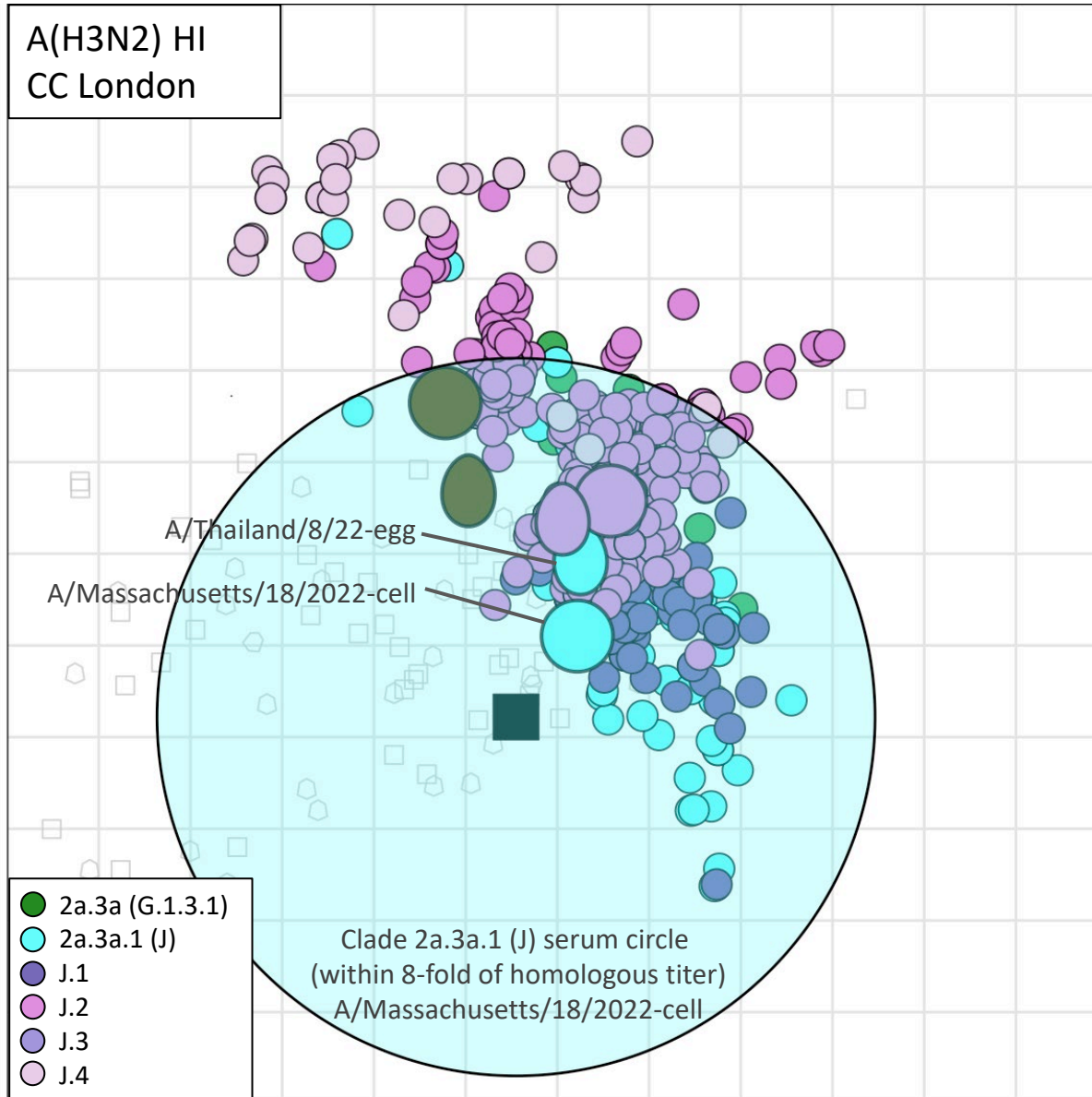
- 2a.3a (G.1.3.1)
- 2a.3a.1 (J)
- J.1
- J.2
- J.3
- J.4

A(H3N2) HI
CC Melbourne



- 2a.3a (G.1.3.1)
- 2a.3a.1 (J)
- J.1
- J.2
- J.3
- J.4

A(H3N2) antigenic cartography



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

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

HA Clade
Subclade

2a.3a.1

K189R

J

J.1

J.2

J.4

A/Massachusetts/18/2022-like Cell

		MA/18-LIKE				S145N				S145N				S145N				S145N K189R				N158K		+P239S		+Q173R +K189R	+K140 +I190R												
		MA/18				PA/88-LIKE		YAM/77		NV/32-LIKE		SYD/761-LIKE		DC/27-LIKE				VIC/478-LIKE				OK/05-LIKE		SYD/711-LIKE		BFA/3131	GHA/1871												
		CELL		CELL		CELL		CELL		CELL		CELL		CELL		CELL		CELL		CELL		CELL		CELL		CELL	CELL												
		CDC MN	CBER MN	MHRA HI	NIID HI	CDC MN	CBER MN	CNIC HI	VIDRL HI	CDC MN	VIDRL HI	SYD/761 HI	LSBOA/218 HI	CDC MN	CBER MN	MHRA HI	MHRA HI	NIID HI	VIDRL HI	CDC MN	CBER MN	CNIC HI	MHRA HI	NIID HI	VIDRL HI	CDC MN	CBER MN	MHRA HI	NIID HI	VIDRL HI	VIDRL HI	VIDRL HI	VIDRL HI						
Adult	ccIV4 (Fluceivax) Australia	422	97	217	125	422	638							119	60		118			223	64	294	74		184	138	143	109	115	180	19			184	228	112	174		
	IIV4 Australia	282	80	178	82	271	398							82	47	100	82			138	48	211	87		161	103	108	82	88	115	22				188	67	147		
	Peru	190	55	88	48	88	228							102													48	41	81		27				86		87		
Elderly	aiIV4 Australia	299	67	130	82	234	288							88	38	95	77	58		108			87		130		80	75	135	148	30				165		130		
	IIV4 Hong Kong	228												68						121									72	121							83		

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 V 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.



Multiple Sources; compiled by WHO CC CDC, USA

2a.3a
G.1.3.1

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



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)

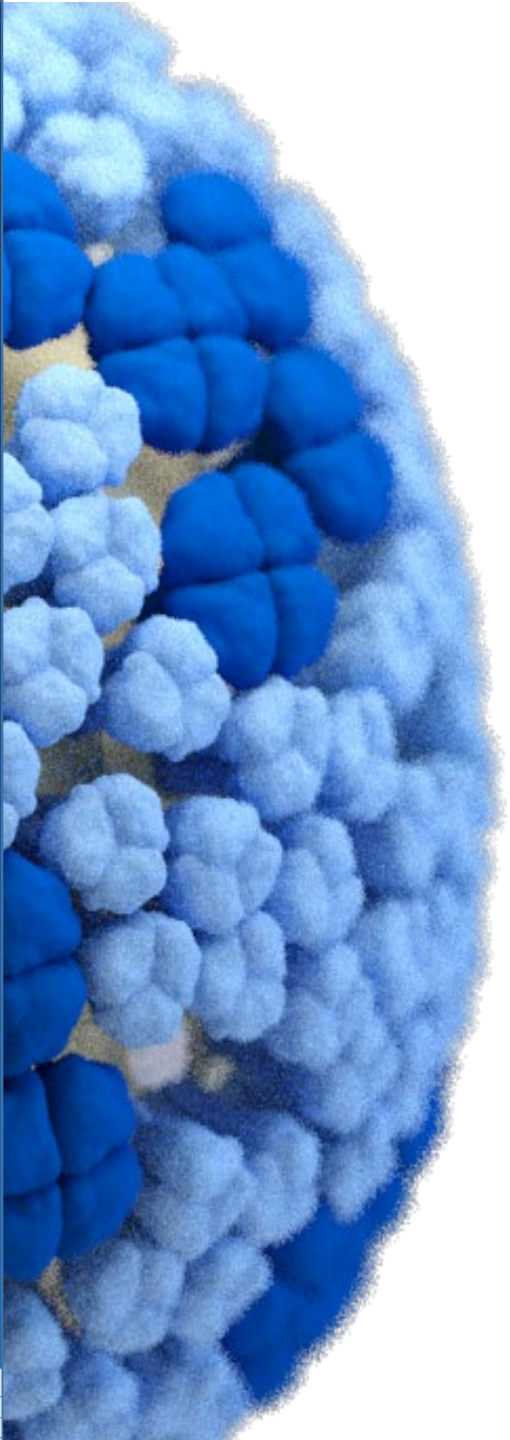
A(H3N2) summary (2): antigenic characteristics

- 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.

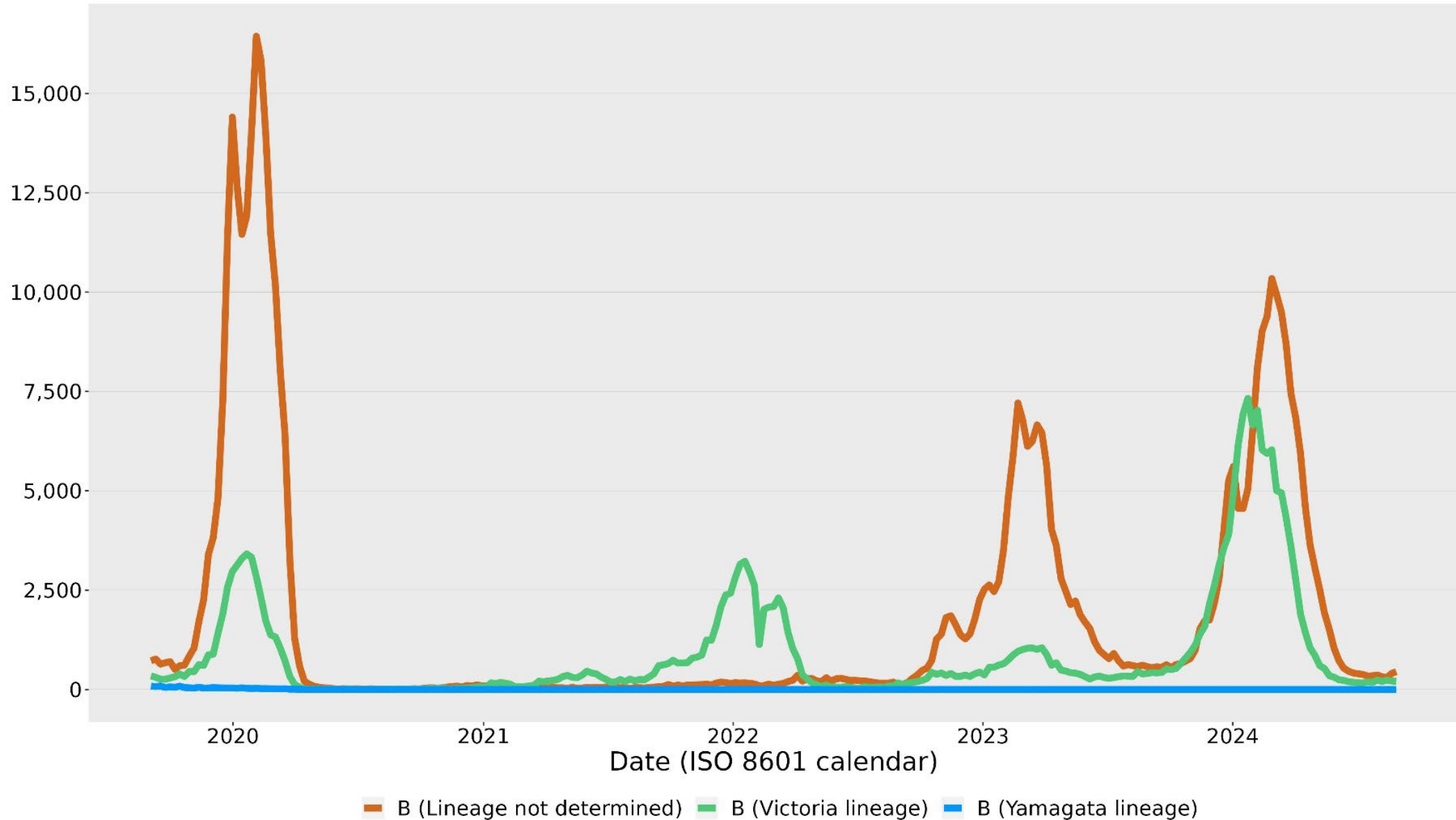
A(H3N2) summary (3): antigenic characteristics

- 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.**

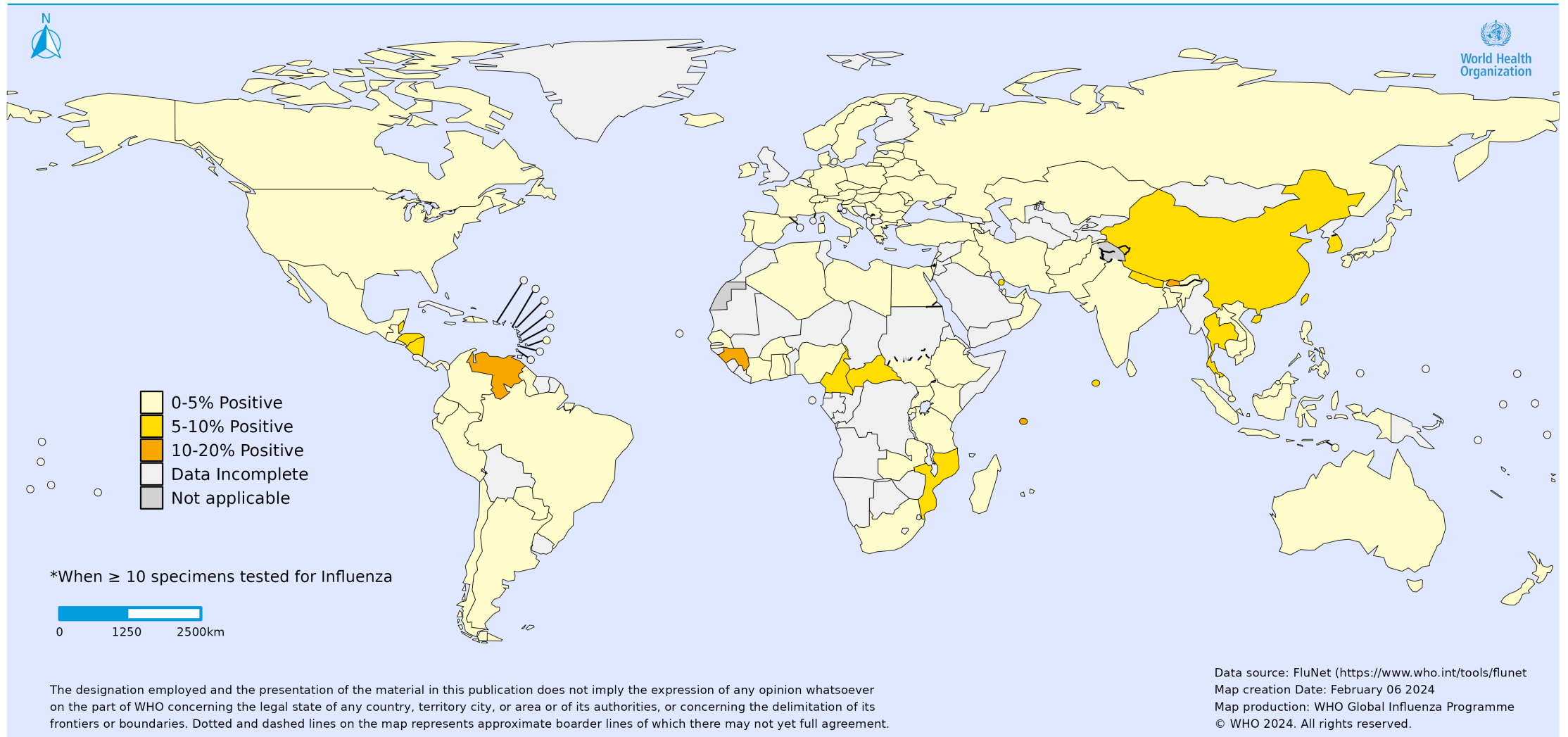
Influenza B Viruses



Global circulation of influenza B viruses



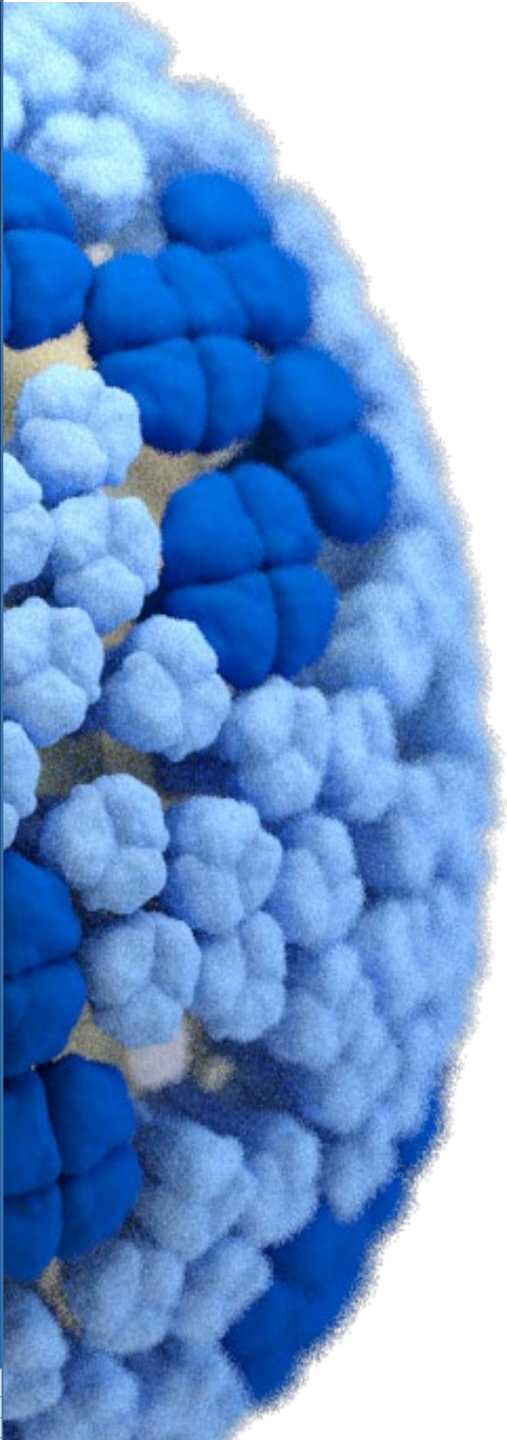
Influenza B virus activity



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

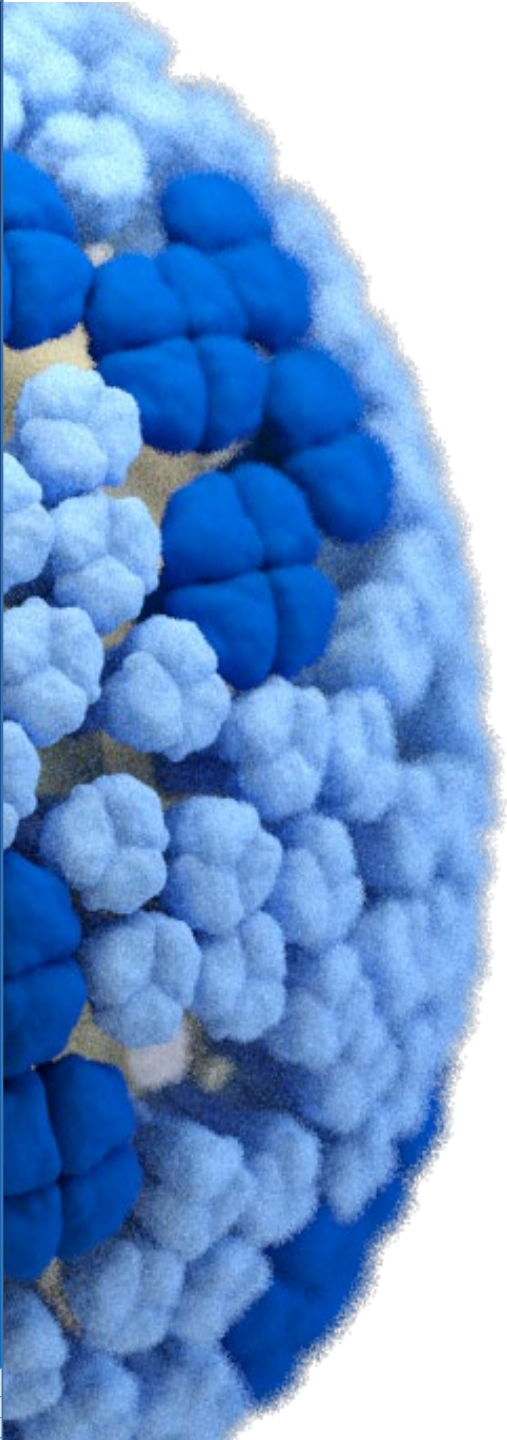
Influenza B/Yamagata Viruses



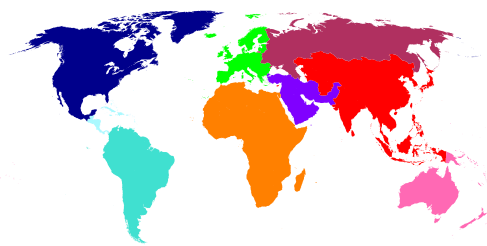
B/Yamagata lineage summary

- 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

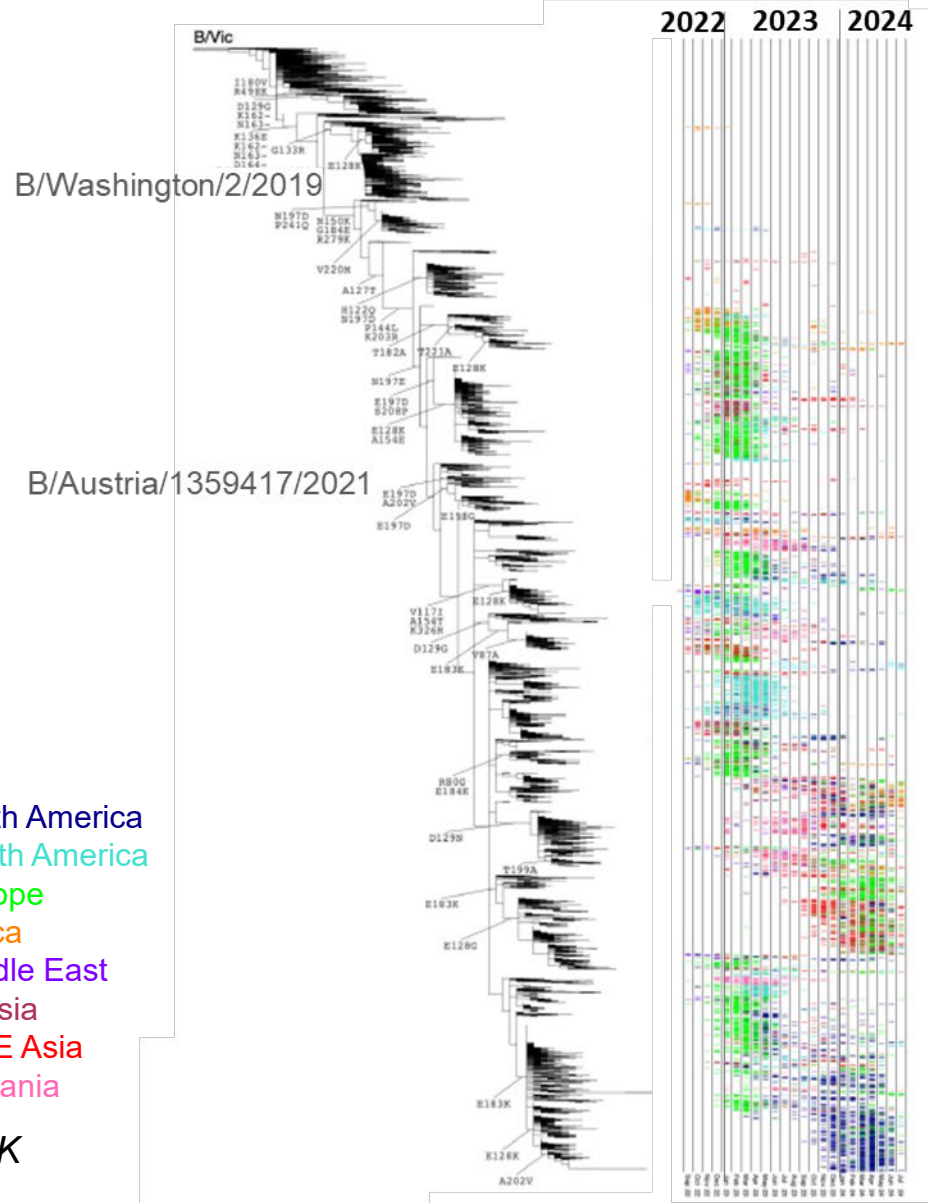


B/Victoria HA phylogeography



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

Source: University of Cambridge, UK



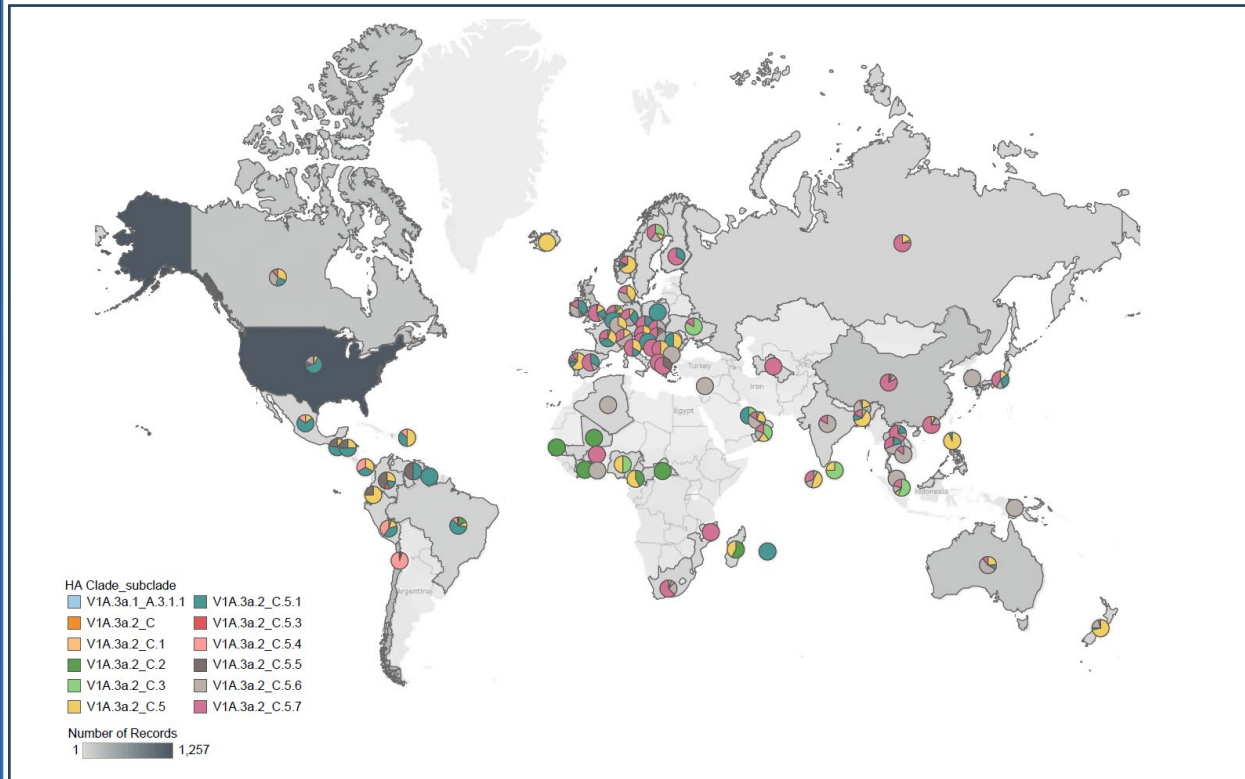
V1A.3a.1
 C.1
 C.2
 V1A.3a.2
 C.3
 C.4
 C.5
 D197E
 C.5.1

C.5.2
 C.5.4
 C.5.3
 C.5.5
 C.5.6
 C.5.7

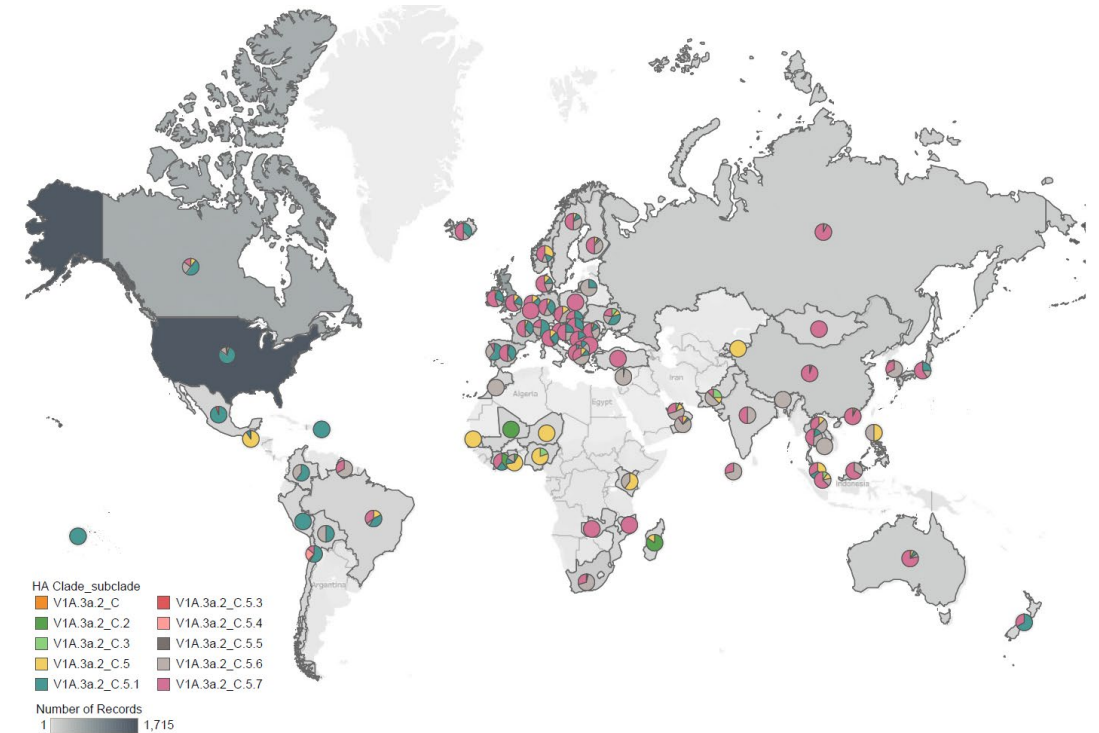
3a.2
 (A127T, P144L, K203R)

Global B/Victoria HA clade diversity

Collection Dates
September 1, 2023- January 31, 2024



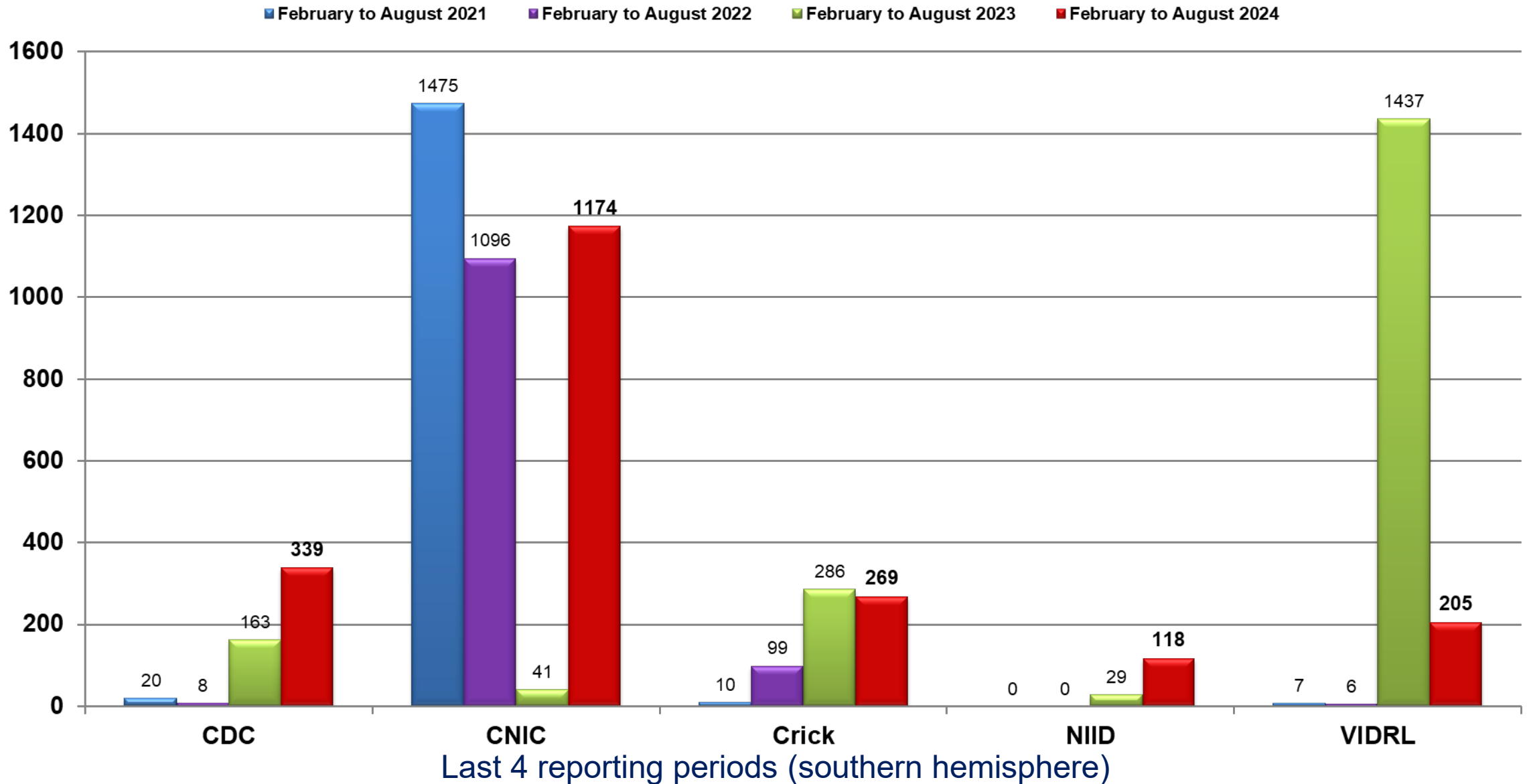
Collection Dates
February 1, 2024- August 31, 2024



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



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

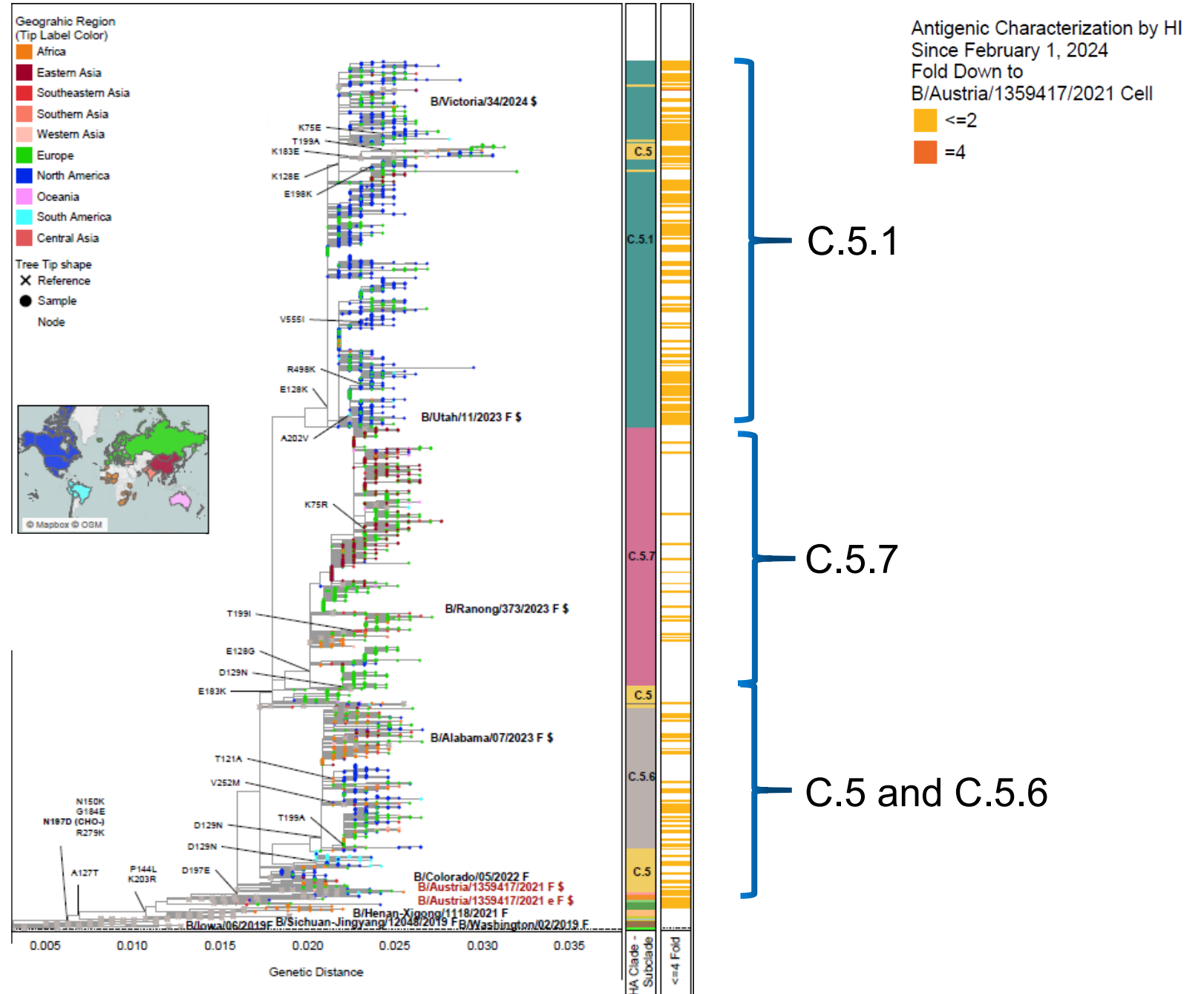
Antisera to southern hemisphere 2024 vaccine virus antigens

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%)

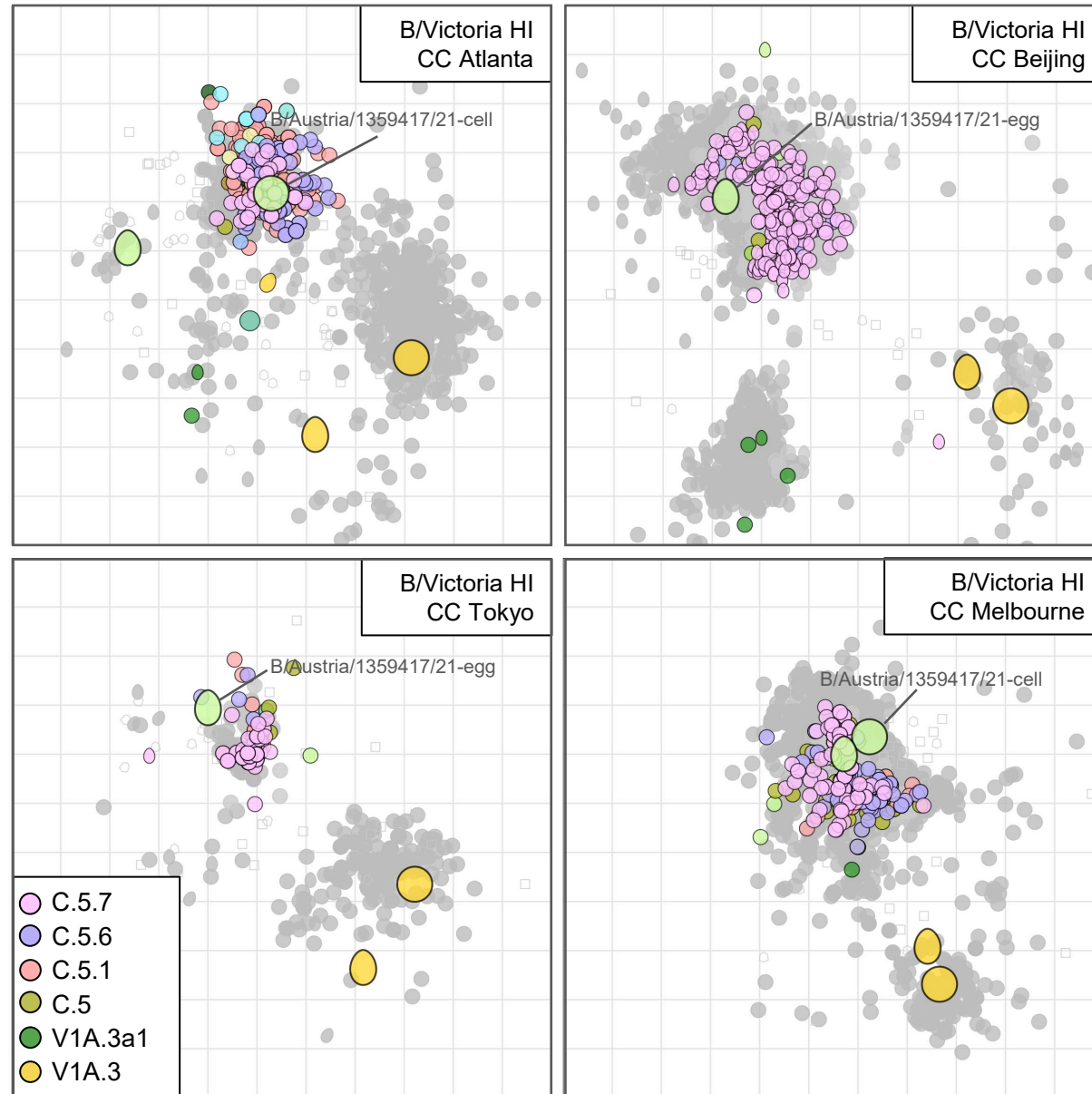
“Low” represented titers ≥ 8 -fold lower than vaccine strain homologous titer

B/Victoria Integrated Genotype and Phenotype Analysis

Source: WHO CC CDC, USA



B/Victoria antigenic cartography



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)					C.5.1 (V1A.3a.2)					C.5.6 (V1A.3a.2)					C.5.7 (V1A.3a.2)													
			AUT/1359417-LIKE					VIC/34-LIKE					AL/07-LIKE					RAN/373-LIKE													
			AUT/1359417					VIC/34					AL/07					RAN/373													
			SGP/WUH4618					CHIBA/22					KAN/IC2360					DAR/6													
			CELL		CELL	CELL		CELL	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	cclIV4 (Flucelvax)	Australia	236	169	605	472	446	184	√	√	√	√	√	√	√	√	76	√	√	√	√	√	√	√	√	√	√	√	√	√
		IIIV4	Australia	67	39	147	112	194	80	√	√	√	√	√	√	√	√	√	21	√	√	√	√	X	√	√	√	√	√	X	√
			Peru	113	70	299	343	381	269	√	102	√	√	√	√	√	√	√	29	√	√	√	√	√	√	√	√	√	√	√	√
	Elderly	allIV4	Australia	89	55	204	184	211	95	√	√	√	√	√	√	√	√	25	√	√	√	√	√	√	√	√	√	√	√	√	√
		IIIV4	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



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

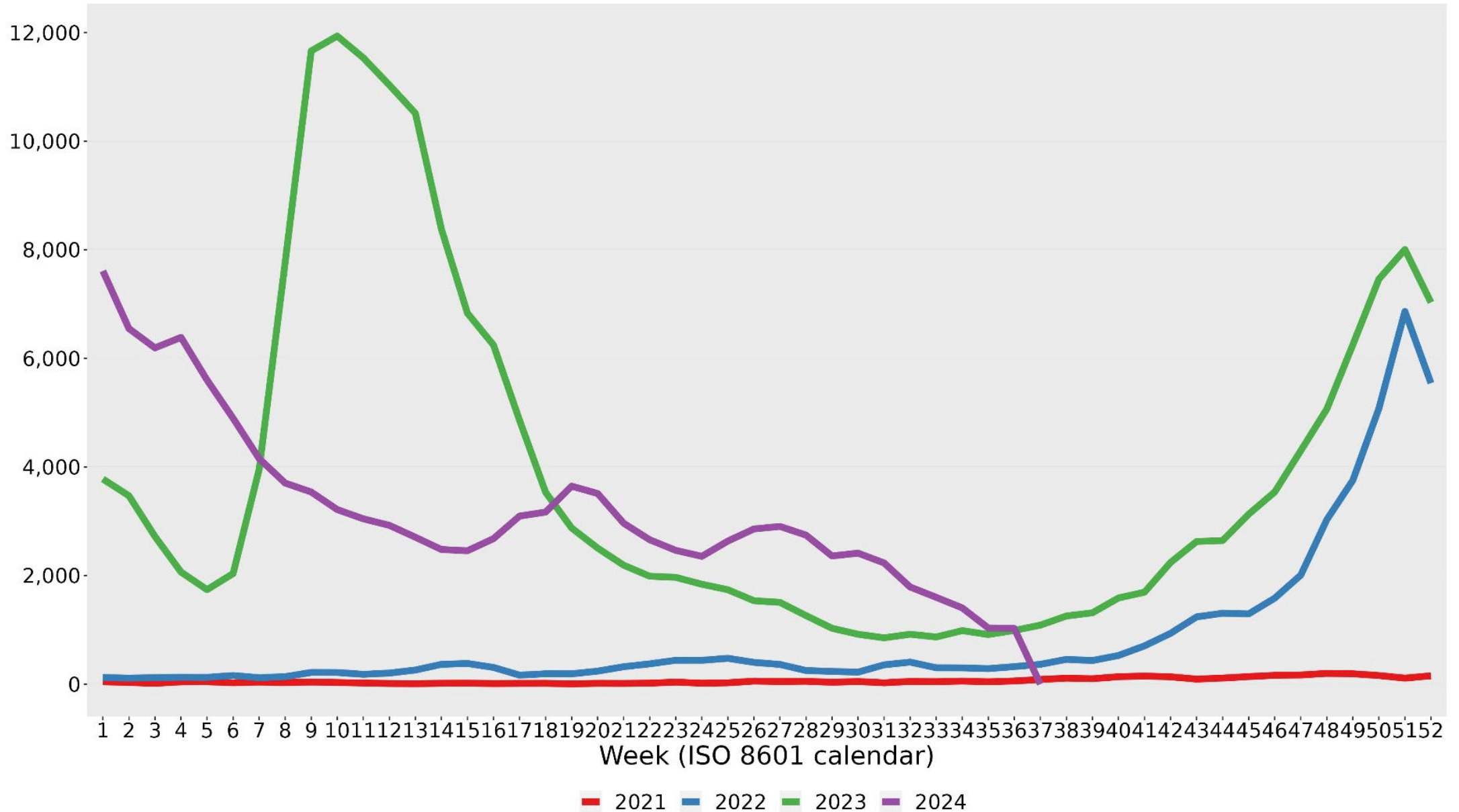
The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention.

These projects have been funded in part with federal funds from US Health and Human Services (National Institutes of Health, Centers for Disease Control, and the Biomedical Advanced Research and Development Authority).

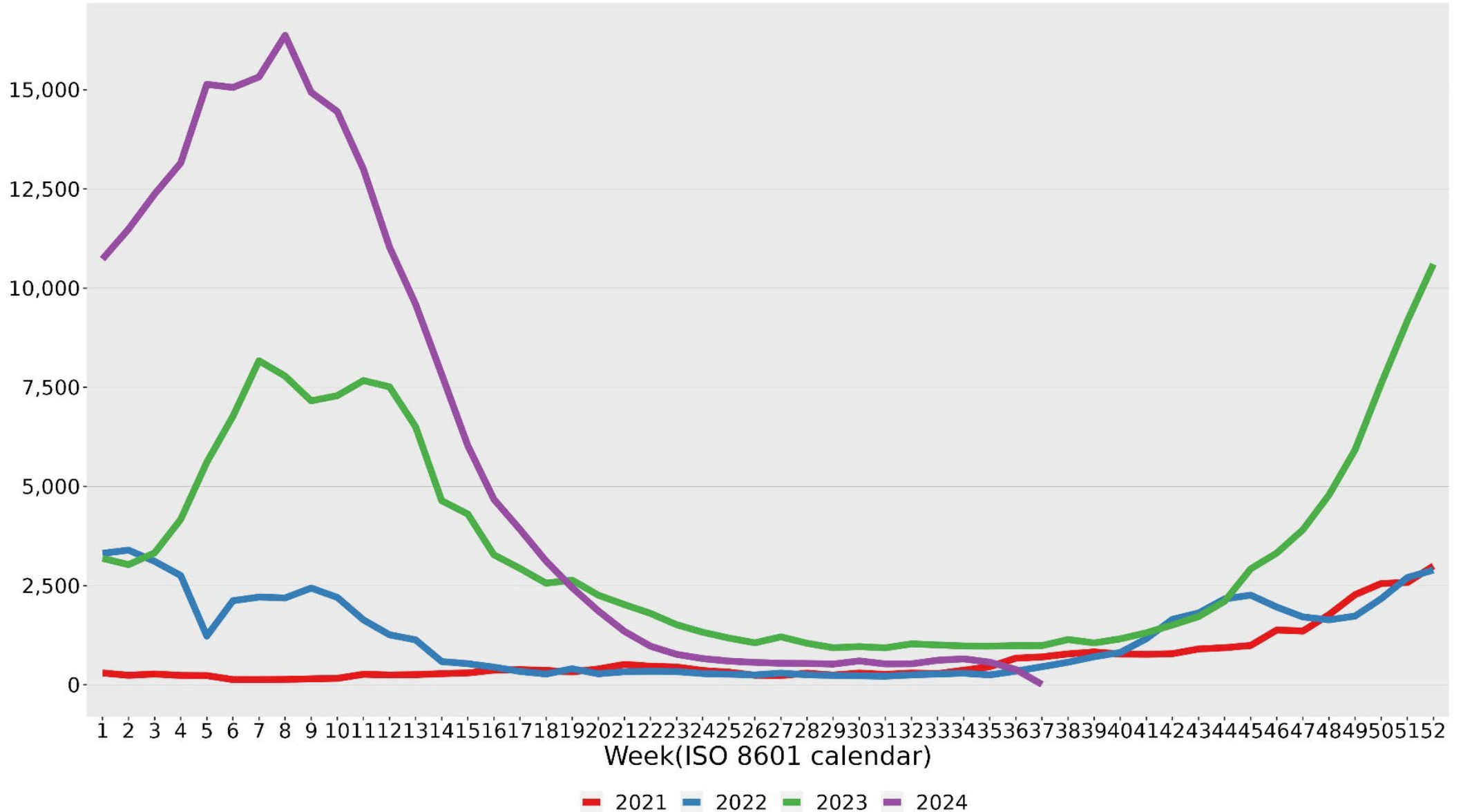


Additional Slides

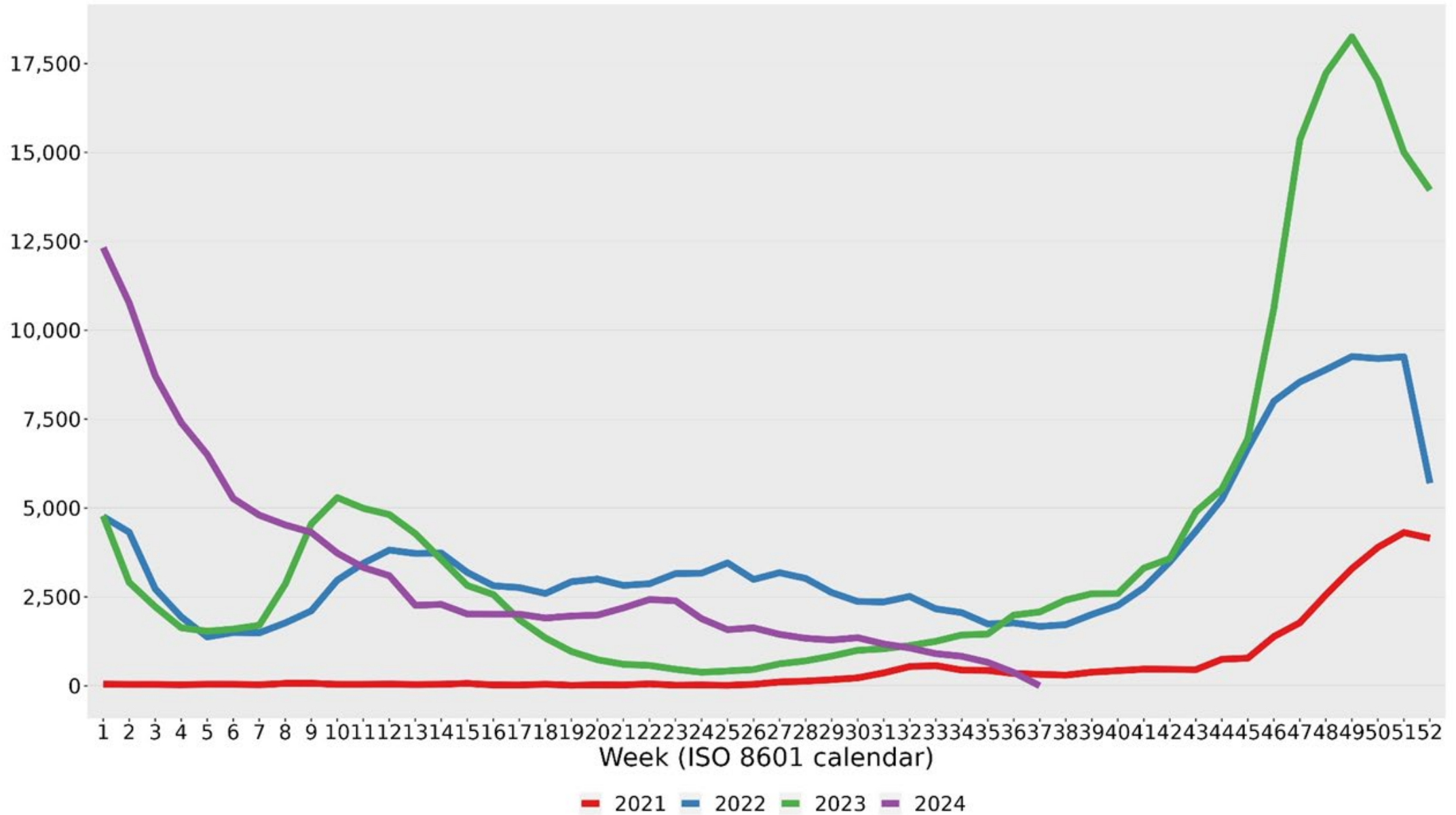
Number of A(H1N1)pdm09 viruses detected by GISRS



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 (VAXIGRIPTETR A, 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)