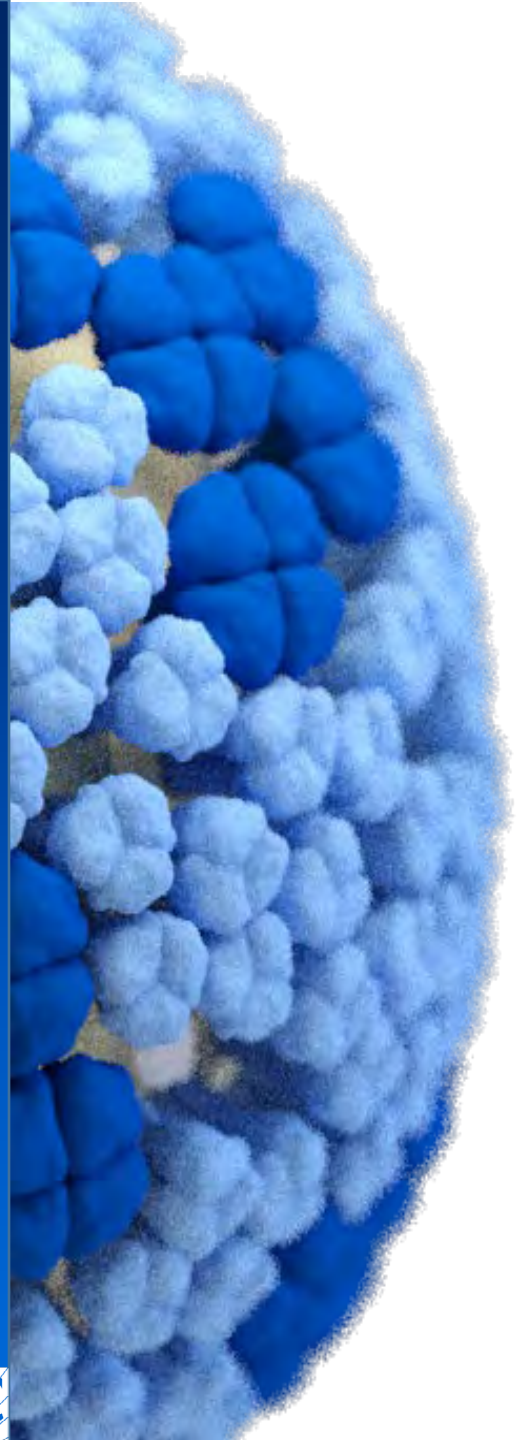

Information For The Vaccine And Related Biological Products Advisory Committee CBER, FDA

Global Influenza Virus Surveillance and Characterization March 5th, 2024

Rebecca Kondor, Ph.D.

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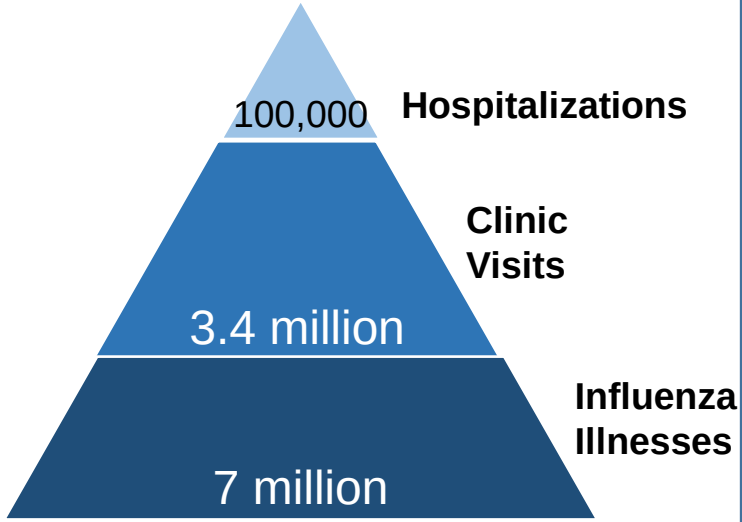
Presentation outline

- **Introduction**
  - Overview on influenza and vaccine antigen selection process
  - WHO Information Meeting on the composition of influenza vaccines for use in the 2024-2025 northern hemisphere influenza season

- **Selected key information supporting committee's recommendations on:**
  - A(H1N1)pdm09 - Vaccine antigen remains unchanged
  - A(H3N2) – Vaccine antigen updated, same recommendation as 2024 Southern Hemisphere
  - B/Victoria lineage - Vaccine antigen remains unchanged
  - B/Yamagata lineage - Vaccine antigen remains unchanged

In 2019-2020 US Season Influenza Vaccine Burden-Prevented Estimates



Past Seasons Estimated Influenza Disease Burden Prevented by Vaccination | CDC

WHO vaccine consultation meeting for the northern hemisphere 2024-2025 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 19 – 22 Feb 2024 in Montreux, Switzerland

- In-person meeting
  - Recommendations for vaccine composition for seasonal/epidemic influenza viruses and candidate vaccine viruses for zoonotic influenza
- Chair: Dr Dayan Wang (Director WHO CC in Beijing, PRC)
- Co-chair: Dr Kanta Subbarao (Director WHO CC in Melbourne, Australia)
- 10 Advisers: Directors of WHO CCs and ERLs
  - Disclosure of interests at the start of meeting

- 32 observers from NICs, WHO CCs, WHO ERLs WHO H5 Ref Labs, national/regional public health agencies and academia; WOAH, FAO and OFFLU
- WHO ROs and HQ staff

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
- **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 as 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
- **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
- **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)

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)?

WHO vaccine recommendations for the northern hemisphere 2024-2025

It is recommended that vaccines for use in the 2024-2025 northern 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 2023-2024 northern hemisphere season but the same as the 2024 southern hemisphere recommendation.**

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

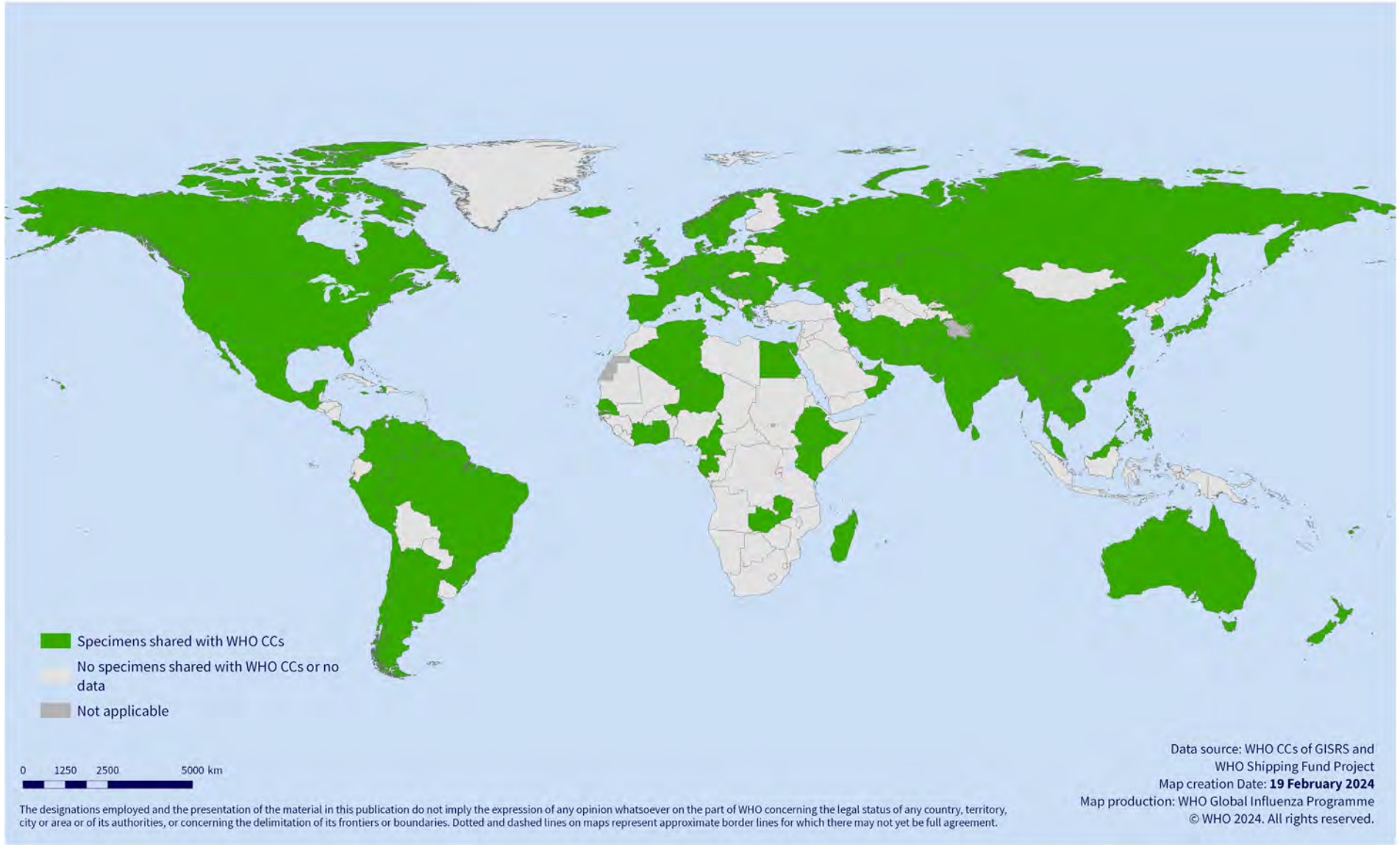
Candidate vaccine viruses & publications

- The WHO recommended candidate viruses for vaccine development and production for NH 2024-25, 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

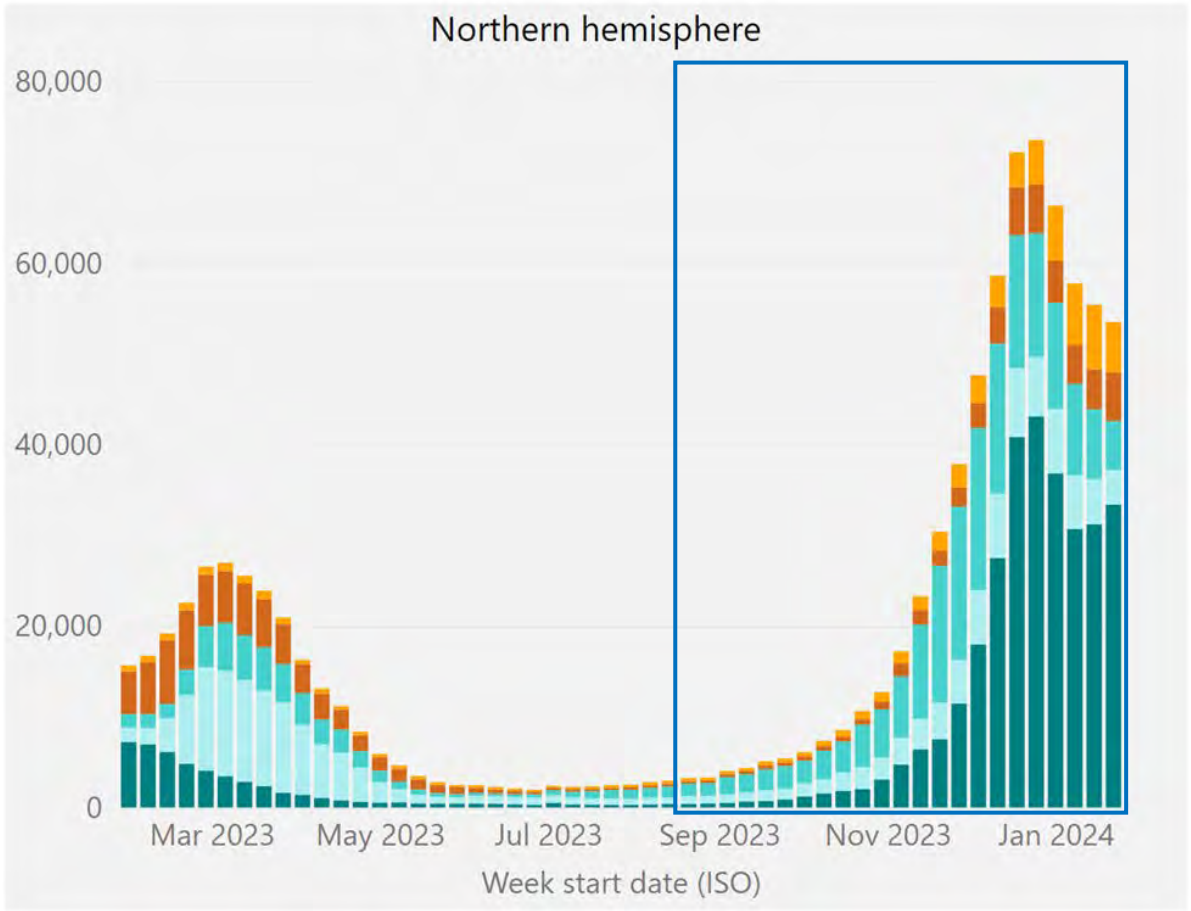
Global Influenza Programme (**GIP**): GISRS-WHOhq@who.int

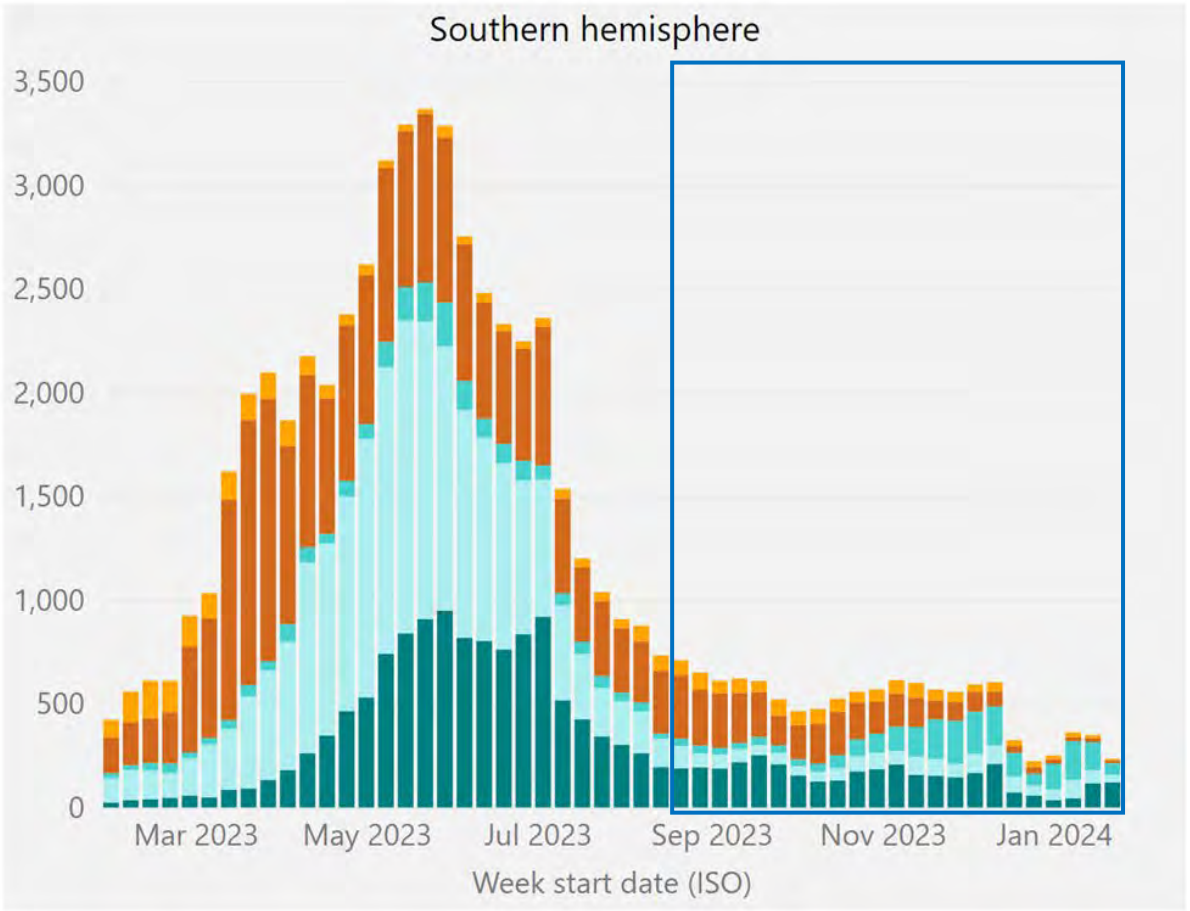
Countries, areas and territories shared viruses with WHO CCs

1 Sep 2023 – 31 Jan 2024



Circulation of influenza viruses by hemisphere



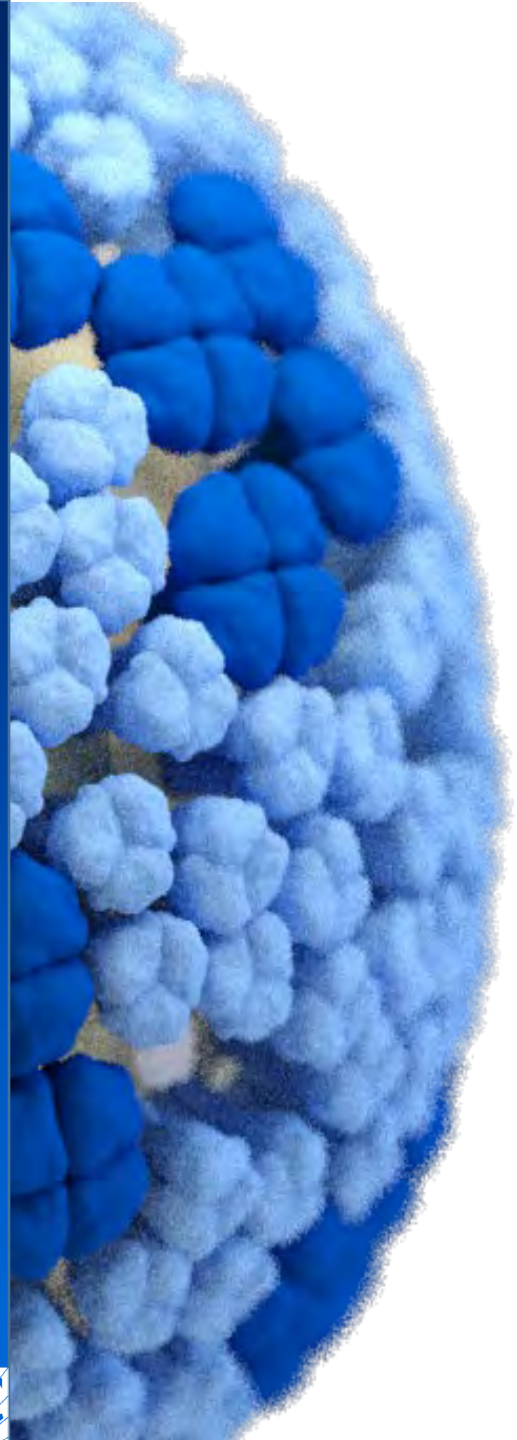


Virus type name A(H1N1)pdm09 A(H3) A (Not subtyped) B (Victoria lineage) B (Yamagata lineage) B (Lineage not determined) A(H1) A(H5)

Select week start date (ISO)

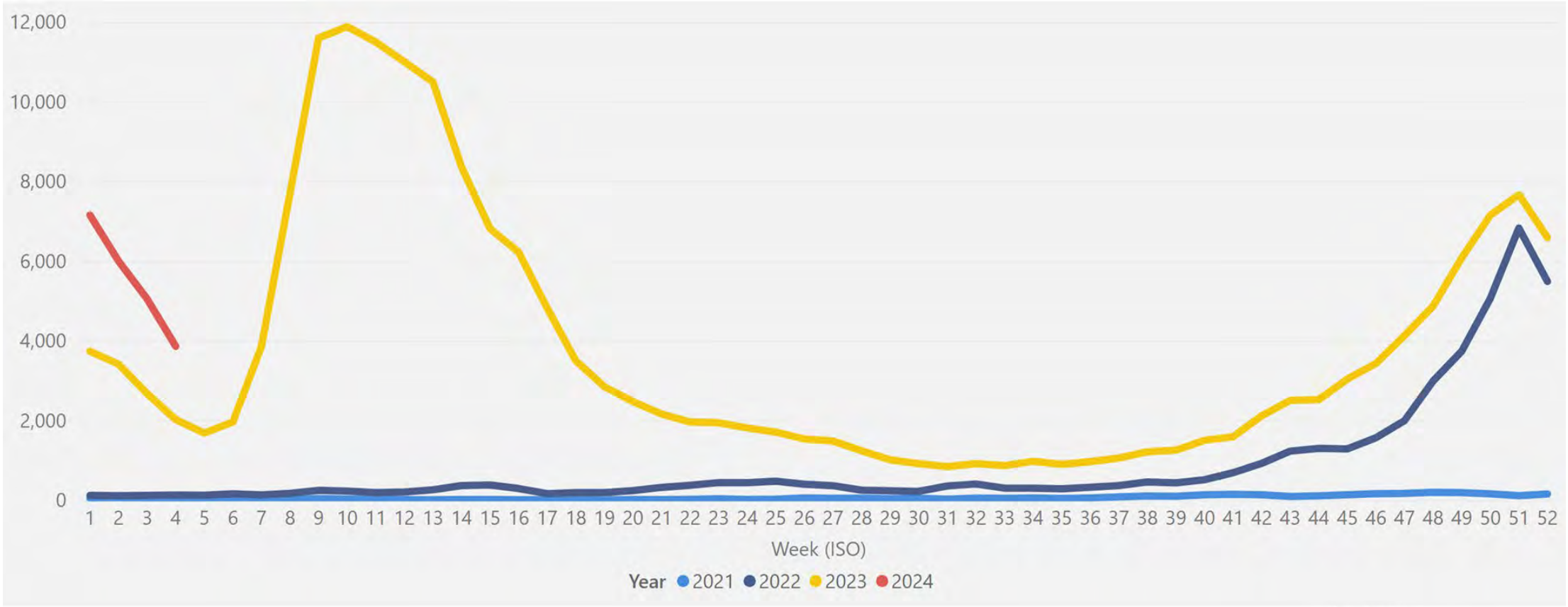
1/30/2023 1/22/2024

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



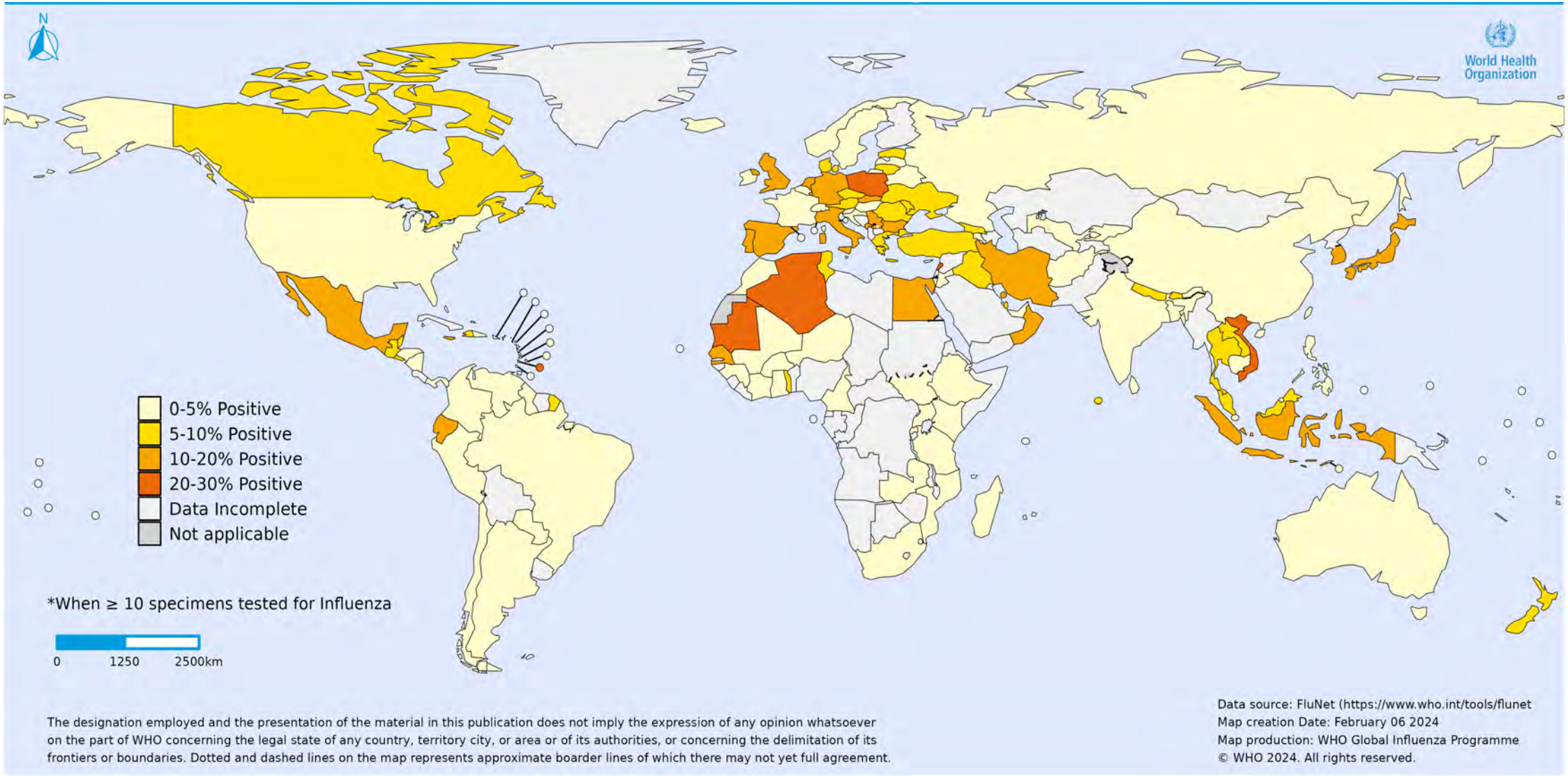
A(H1N1)pdm09 Viruses

Number of A(H1N1)pdm09 viruses detected by GISRS



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

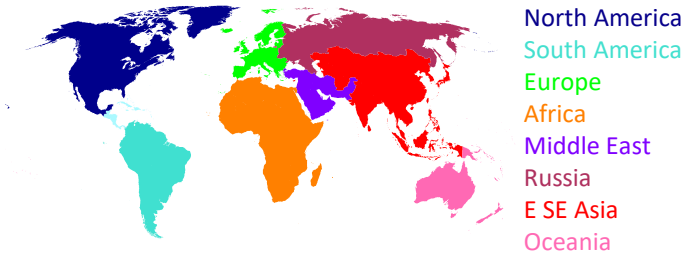
Influenza A(H1N1)pdm09 activity



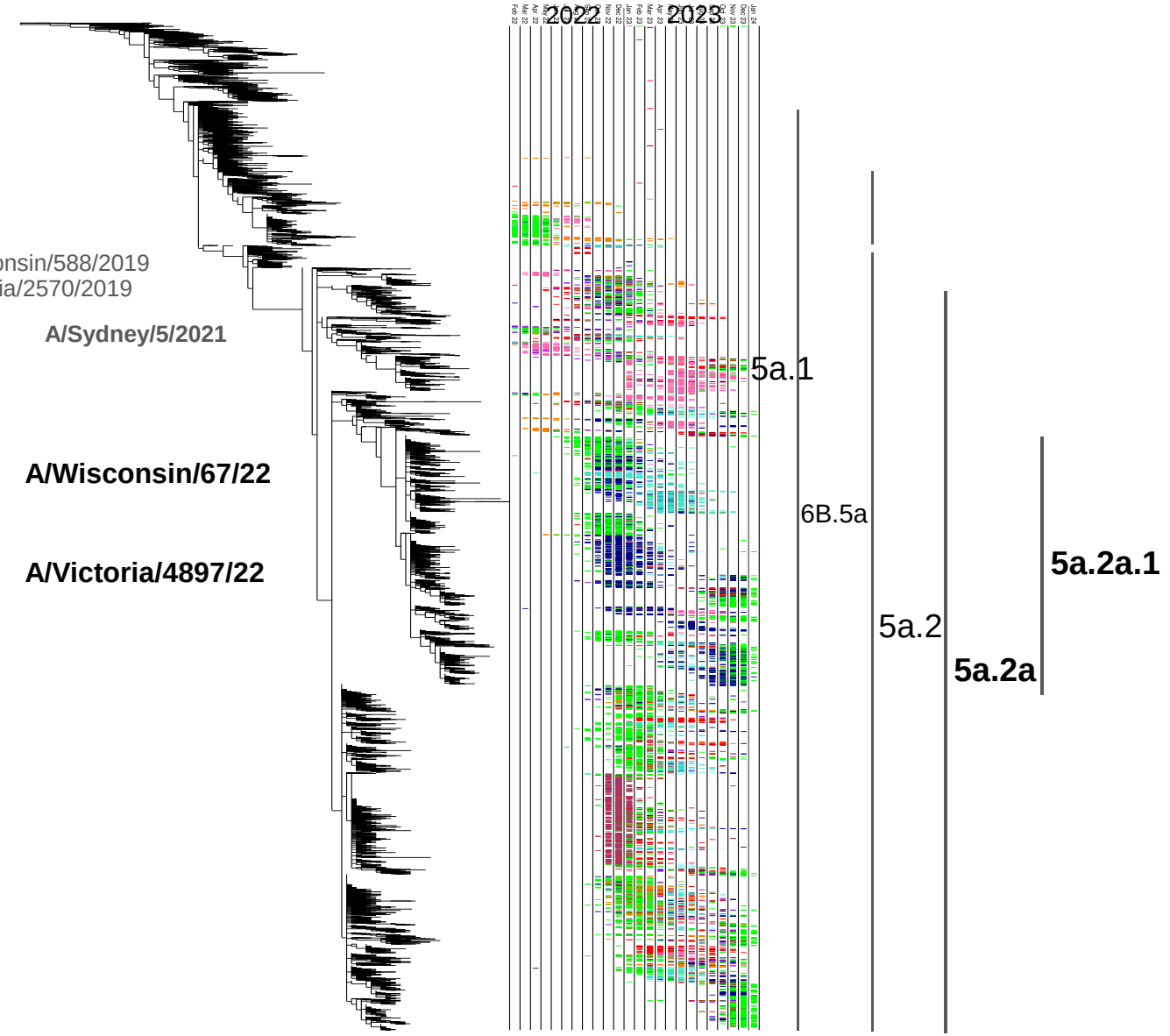
Colour intensity shows the percent of influenza A(H1N1)pdm09 positive among all samples tested during this period per country

Data source: FluNet, (https://www.who.int/tools/flunet), Global Influenza Surveillance and Response System (6 February 2024)

Overall A(H1N1)pdm09 HA phylogeography



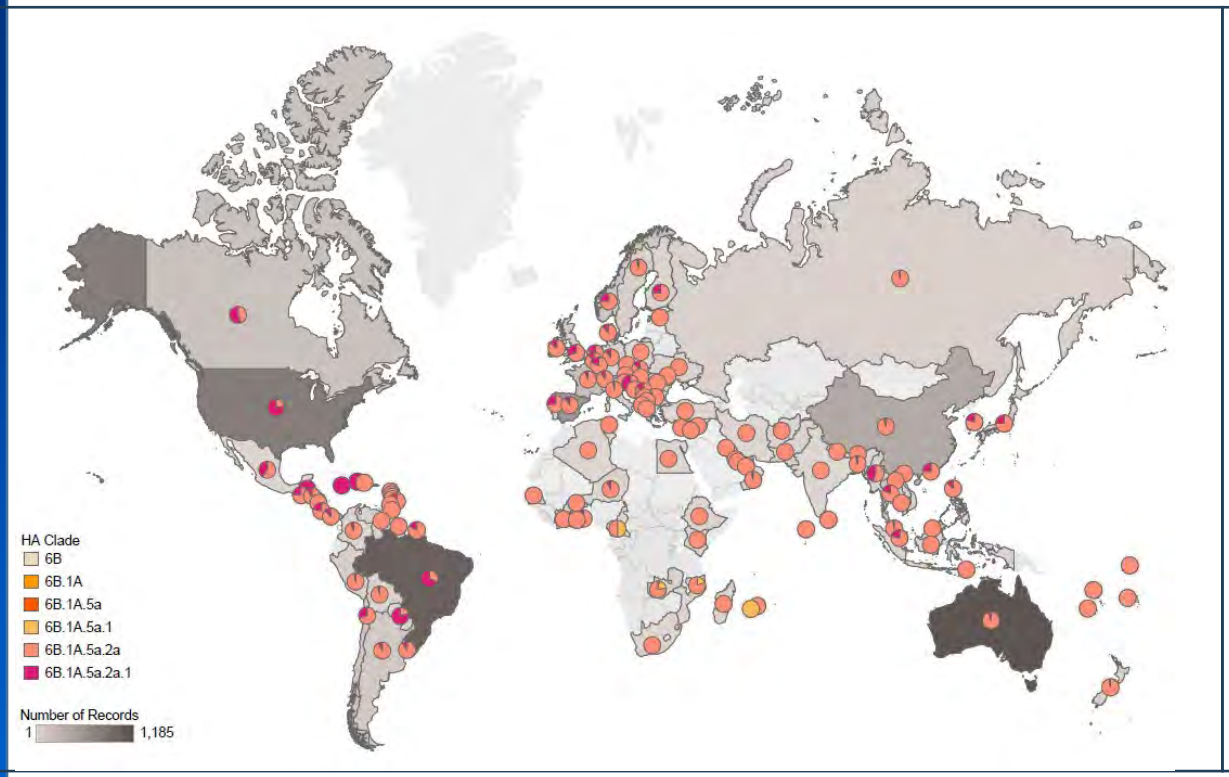
North America
South America
Europe
Africa
Middle East
Russia
E SE Asia
Oceania



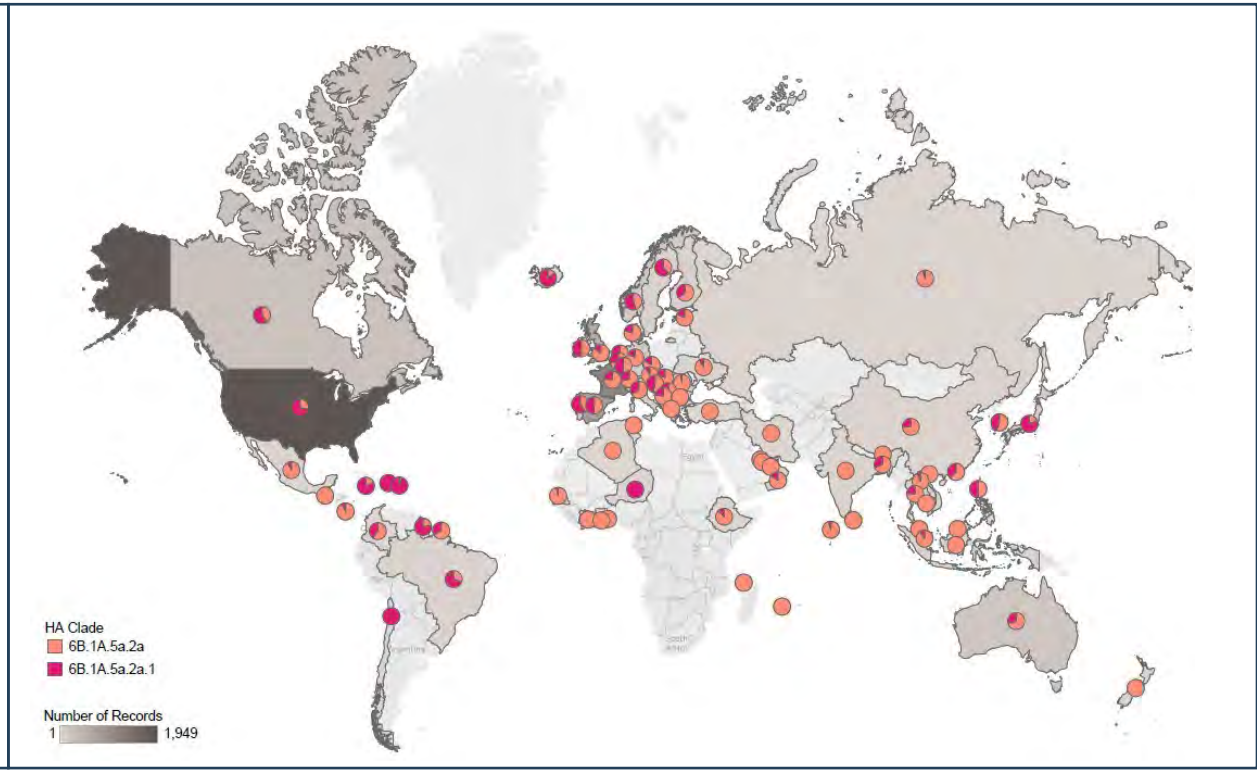
Source: University of Cambridge: Derek Smith and Sarah James

Global A(H1N1)pdm09 HA clade diversity

Collection Dates
February 1, 2023- August 31, 2023



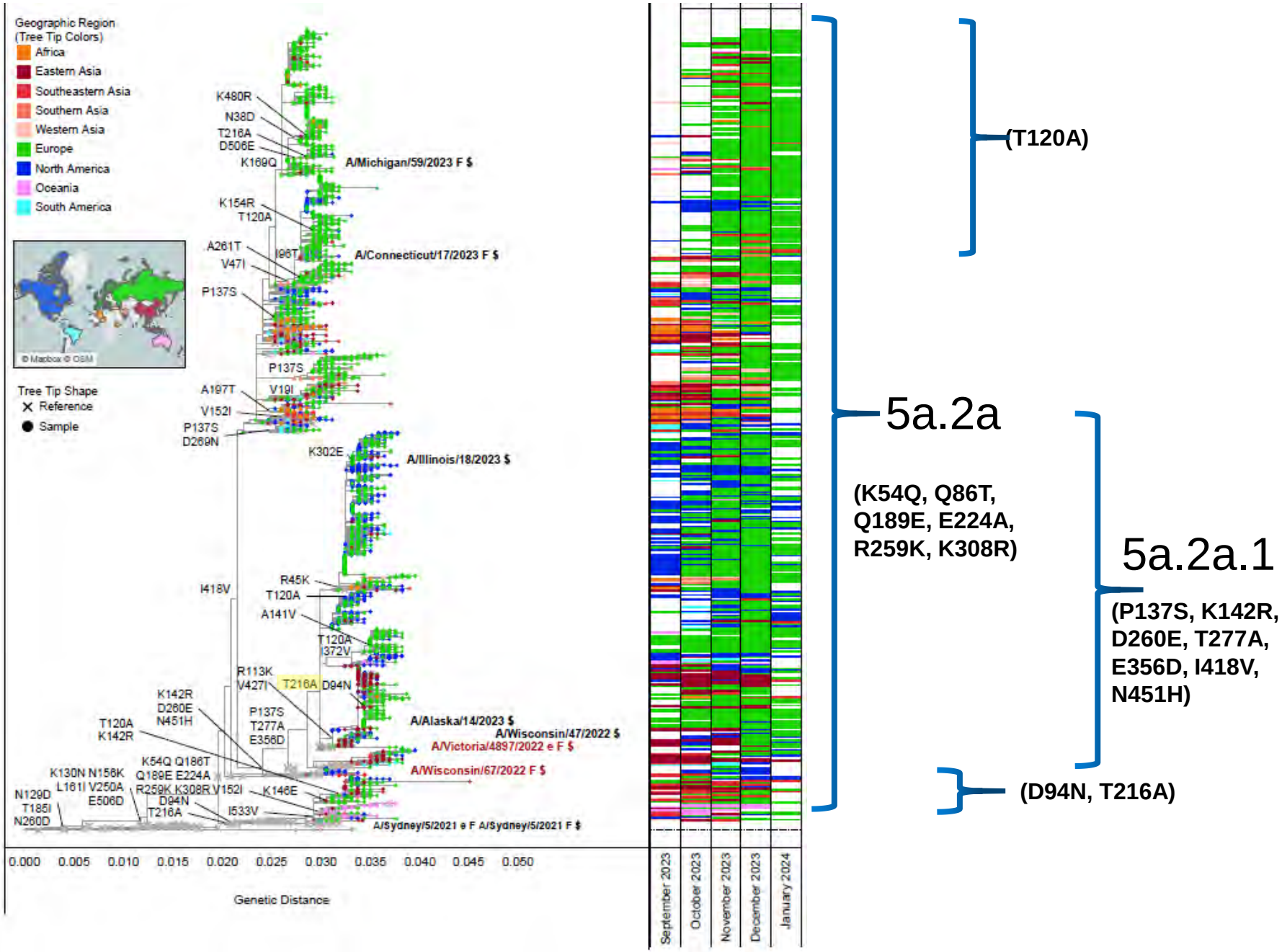
Collection Dates
September 1, 2023- January 31, 2024



Based on HA sequence availability from GISAID EpiFlu™

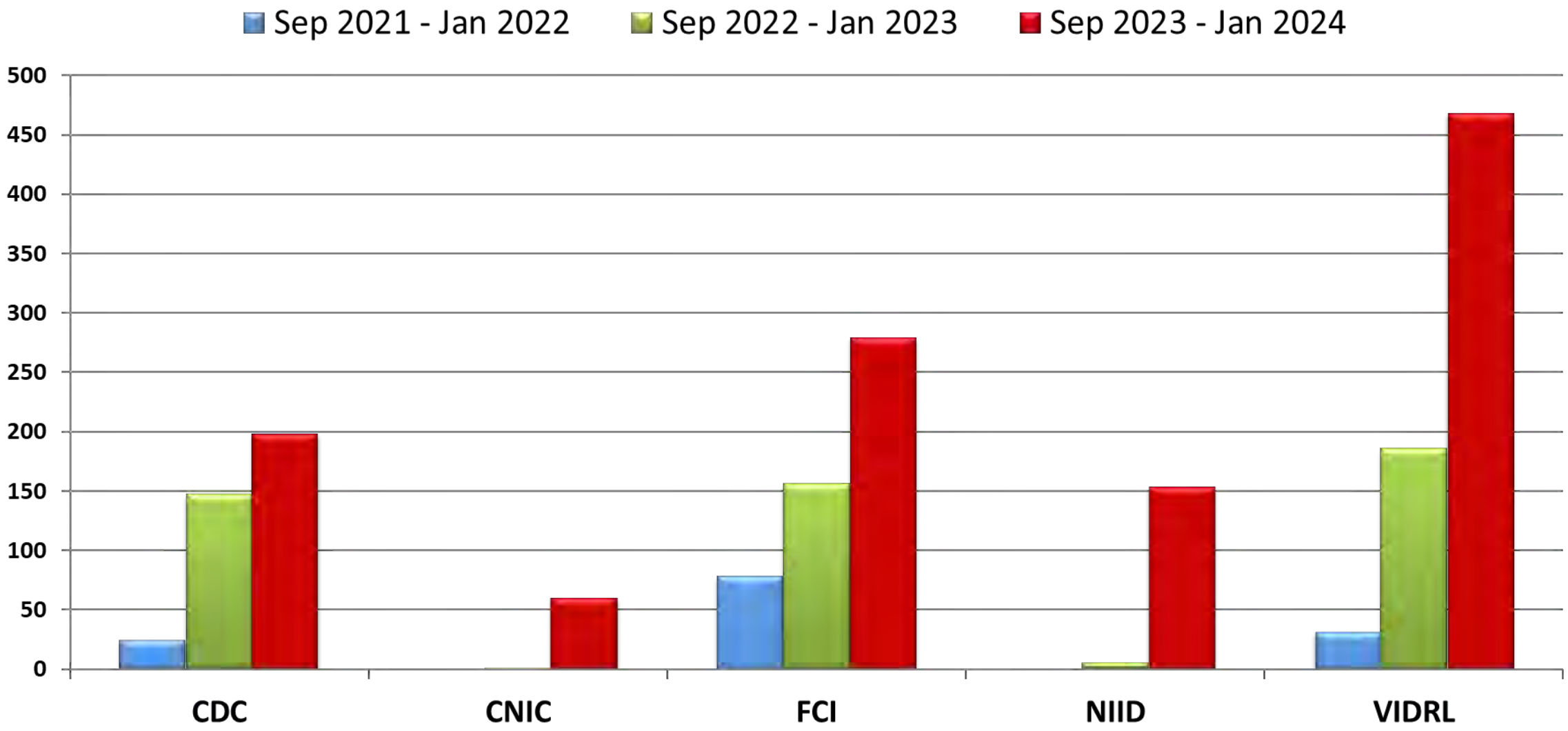
Source: WHO CC CDC, USA

A(H1N1)pdm09 HA phylogenetics and genetic diversity



Source: WHO CC CDC, USA

A(H1N1)pdm09 viruses antigenically characterized



Past 3 reporting periods

Analysis of A(H1N1)pdm09 viruses by ferret antisera to antigens recommended for NH 2023-2024 vaccines

Antisera to northern hemisphere 2023-2024 vaccine virus antigens

A/Wisconsin/67/2022-like (cell) 5a.2a.1

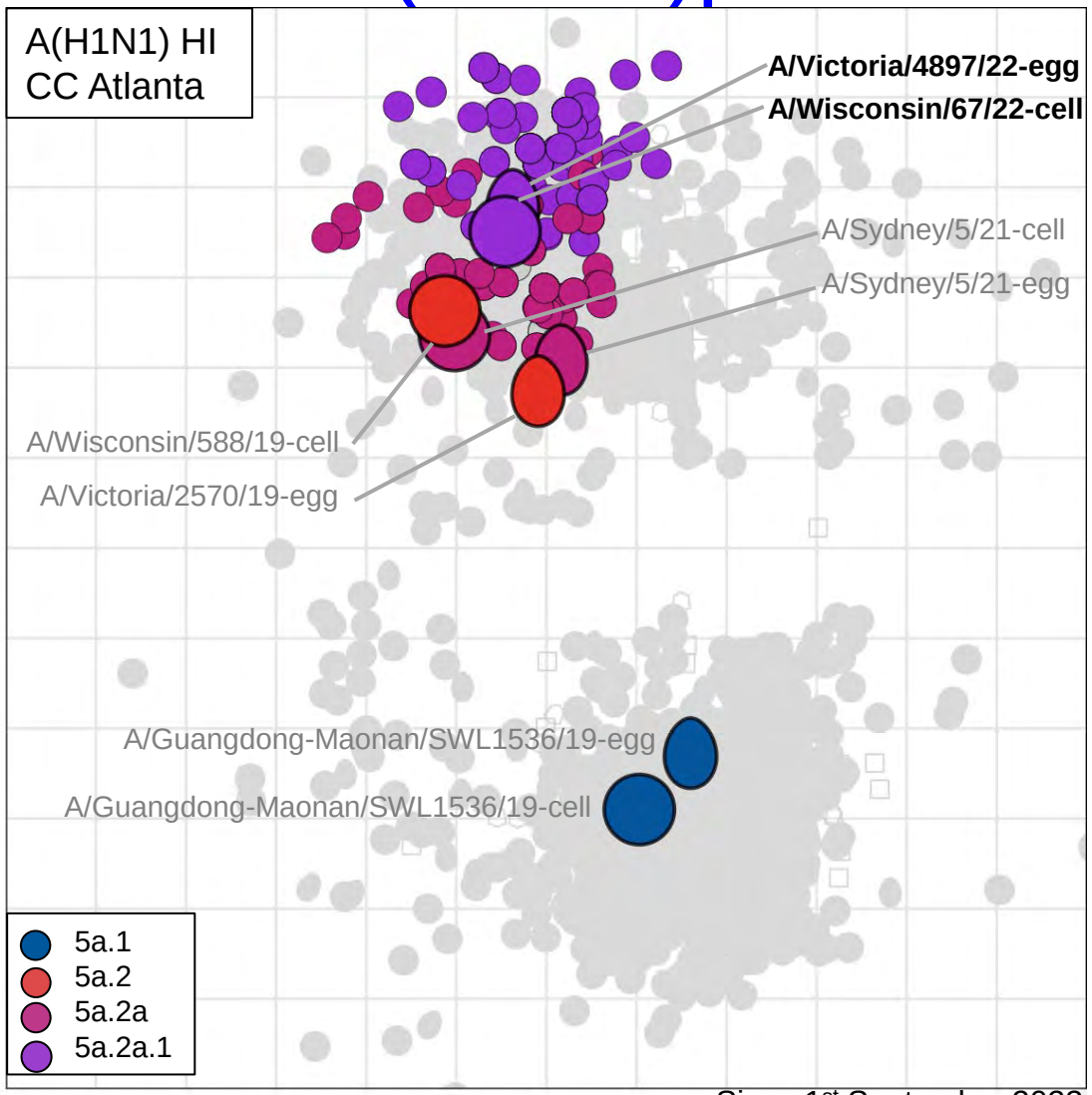
WHO CC	Like (<8 fold)	Low (≥ 8 fold)
CDC	196 (99%)	2 (1%)
CNIC	60 (100%)	0 (0%)
FCI	274 (98%)	5 (2%)
NIID	153 (99%)	1 (1%)
VIDRL	462 (99%)	6 (1%)
TOTAL	1145 (99%)	14 (1%)

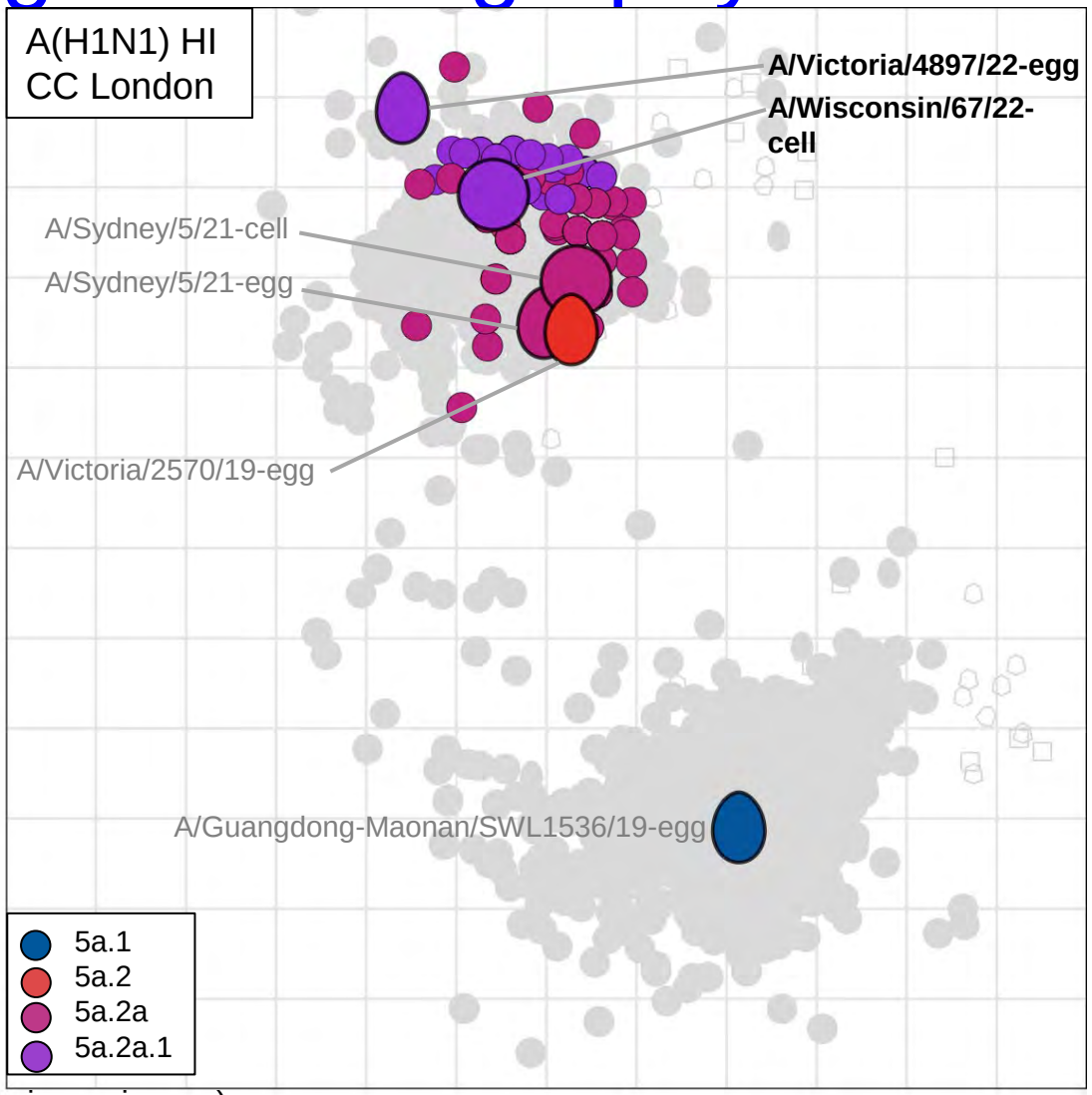
A/Victoria/4897/2022-like (egg) 5a.2a.1

WHO CC	Like (<8 fold)	Low (≥ 8 fold)
CDC	193 (97%)	5 (3%)
CNIC	59 (98%)	1 (2%)
FCI	277 (99%)	2 (1%)
NIID	153 (99%)	1 (1%)
VIDRL	448 (97%)	13 (3%)
TOTAL	1130 (98%)	22 (2%)

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

A(H1N1)pdm09 antigenic cartography 1

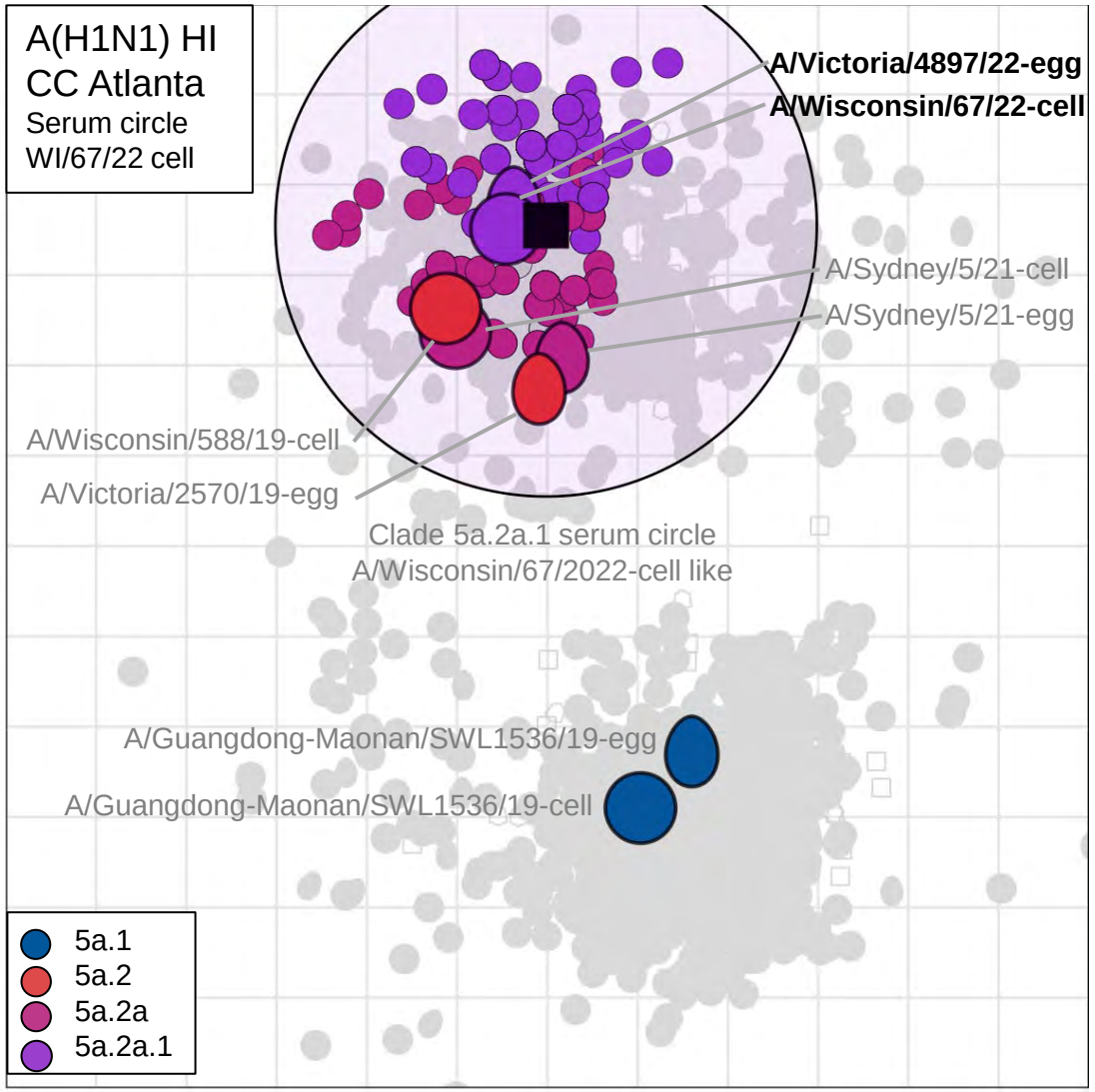


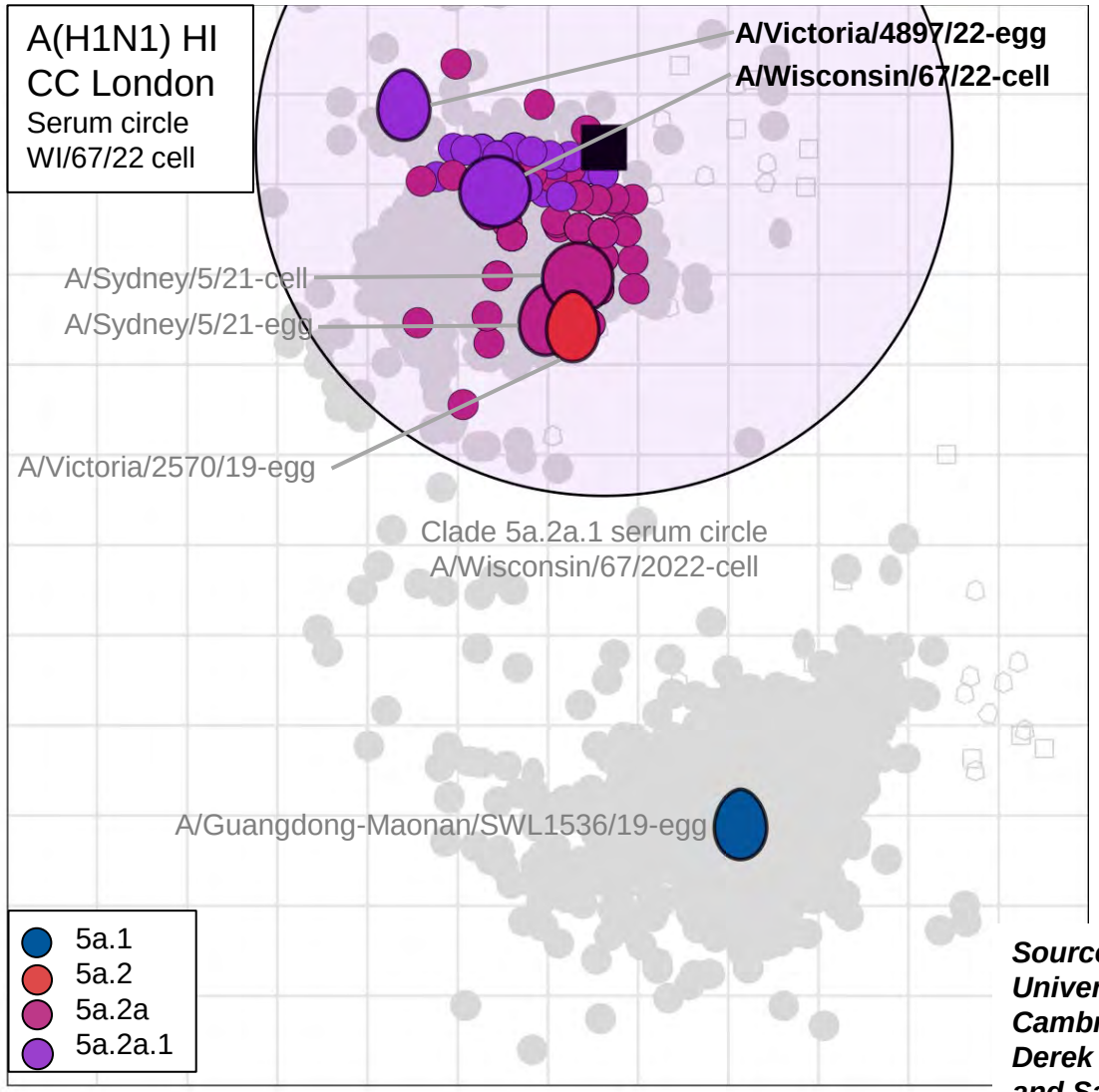


Source: University o Cambridge: Derek Smith and Sarah James

Since 1st September 2023 (older viruses in grey)

A(H1N1)pdm09 antigenic cartography 2





Source: University of Cambridge: Derek Smith and Sarah James

Serum circles (within 8-fold of homologous titers)

NH 2023-2024 post vaccination human serology

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

5a.2a1 | **5a.2a**

WHO CCs
HI Assay

Human Sera Panels
Age/Vaccine/Country

A/Wisconsin/67/2022-Like CELL

Age/Vaccine		Country	WI/67 - CELL CDC	WI/67 - CELL CBER	WI/67 - CELL MHRA	WI/67 - CELL NIID	VIC/4897-LIKE +T216A - VIC/4897 CELL CNIC	VIC/4897-LIKE +T216A - VIC/4897 CELL VIDRL	VIC/4897-LIKE +T216A - AK/14 CELL CDC	WI/47 +T216A +D274N - CELL CDC	WI/47 +T216A +D274N - CELL CNIC	WI/47 +T216A +D274N - CELL MHRA	WI/47 +T216A +D274N - CELL NIID	WI/47 +T216A +D274N - CELL VIDRL	IL/18 +R45K +T216A +K302E - CELL CDC	KAN/AC2330-LIKE +R113K +T216A +V427I - KAN/AC2330 CELL NIID	KAN/AC2330-LIKE +R113K +T216A +V427I - CAT/NSVH102162320 CELL MHRA	CAT/NSA V198281926 +T120A +T216A +I372V - CELL MHRA	DAR/441 +T120A +T216A +P297S +I372V - CELL VIDRL	HX/SWL2916 - CELL CNIC	CT/17 +T120A - CELL CDC	MI/59 +T120A +K169Q - CELL CDC	SYD/5 +D34N +T216A - CELL CDC	SYD/5 +D34N +T216A - CELL CBER	OKI/247 +I161V +H399N - CELL NIID	CAN/366 +T120A +K142R - CELL VIDRL	KAN/AC2311 +T120A +T216A - CELL MHRA	KAN/AC2311 +T120A +T216A - CELL NIID	DAR/463 +T216A +P271S - CELL VIDRL	DAR/517 +T216A +P271S +V295I +V345I - CELL VIDRL
Pediatric (6-35M)	IIV4	USA	49	34				9	√	27				X	27				X		28	√	16	10		X			X	X
Pediatric (CDC: 3-8Y)	ccIIV4 (Flucelvax)	USA	288	92				113	√	√				√	√				√		√	√	117	√		√			41	√
	IIV4	China			36		36	36			X	X		X			X	X	X	X						X	X		20	X
		USA	538	422		394		190	√	√			√	√	√	√			√		√	√	320	234	√	√		√	92	√
Pediatric (9-17Y)	ccIIV4 (Flucelvax)	USA	557	197				219	√	√				√	√				√		√	√	√	√		√			80	√
	IIV4	USA	538	520		577		243	√	√			√	√	√	√			√		√	√	√	√	√	√		√	102	√
Adult (CDC: 18-49Y)	ccIIV4 (Flucelvax)	USA	288	309		394		190	√	√			√	√	160	√			√		166	√	135	√	√	√		√	72	98
	RIV4 (Flublok)	USA	469	394		844		204	√	√			√	√	√	√			√		√	√	226	√	√	√		√	75	√
	IIV4	China			180		216	136			√	√		√			√	√	√	√						√	√		61	√
		Japan	67	78		104			√	√			√		√	√					√	√	√	√	√			√		
		UK			19							X					X	X									X			
		USA	211	204		343		130	√	√			√	√	√	√			√		√	√	√	√	√	√		√	59	√
Older Adult (50-64Y)	IIV4	USA	184	126				109	√	√				√	√				√		√	√	√	√		√			41	√
Elderly (CDC: ≥65Y)	IIV4	China			55		63	45			√	√		√			√	√	√	√						√	√		24	√
		Japan	12	15		22			X	X			X		X	X					X	X	X	X	X			X		
	aIIV4	USA	155	331				56	√	√				√	√				√		√	√	√	√		√			√	√
									0 (0.0)	1 (8.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (16.7)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (16.7)	0 (0.0)	5 (41.7)	2 (16.7)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	11 (84.6)	1 (7.7)

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/ALASKA/14/2023 (AK/14); A/CANBERRA/366/2023 (CAN/366); A/CATALONIA/NSAV198281926/2023 (CAT/NSAV198281926); A/CATALONIA/NSVH102162320/2023 (CAT/NSVH102162320); A/CONNECTICUT/17/2023 (CT/17); A/DARWIN/441/2023 (DAR/441); A/DARWIN/463/2023 (DAR/463); A/DARWIN/517/2023 (DAR/517); A/HUBEI-XIANTAO/SWL2916/2023 (HX/SWL2916); A/ILLINOIS/18/2023 (IL/18); A/KANAGAWA/AC2311/2023 (KAN/AC2311); A/KANAGAWA/AC2330/2023 (KAN/AC2330); A/MICHIGAN/59/2023 (MI/59); A/OKINAWA/247/2023 (OKI/247); A/SYDNEY/5/2021 (SYD/5); A/VICTORIA/4897/2022 (VIC/4897); 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

A(H1N1)pdm09: antiviral susceptibility

Neuraminidase inhibitors

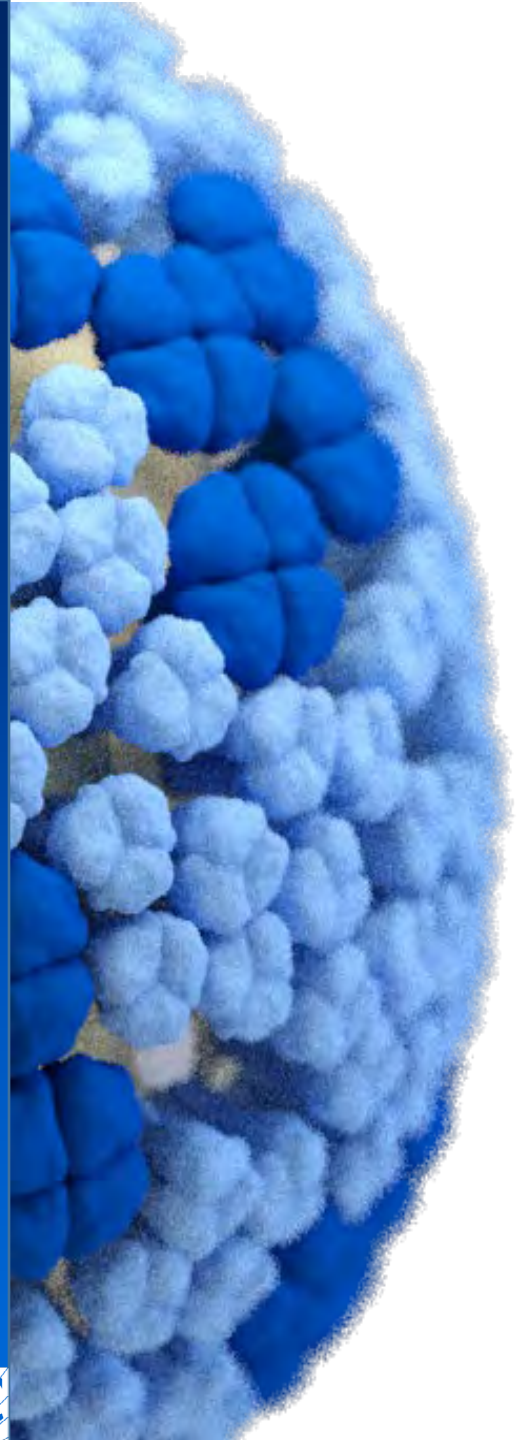
- Of 2089 A(H1N1)pdm09 virus clinical samples and isolates that were examined for neuraminidase inhibitor (NAI) susceptibility by genetic and/or phenotypic analyses,
- 22 viruses showed evidence of reduced susceptibility to NAIs;
  - seven had an H275Y substitution, one had H275Y, I223V and S247N, and 14 had I223V and S247N.
  - 9 of these 22 viruses were tested in phenotypic assays and showed reduced or highly reduced inhibition by NAIs.

Endonuclease inhibitors

- Of 1656 A(H1N1)pdm09 viruses examined by genetic and/or phenotypic analyses,
  - one had a Y24H substitution in the viral polymerase (PA) gene and showed reduced susceptibility to the endonuclease inhibitor baloxavir marboxil in phenotypic assays

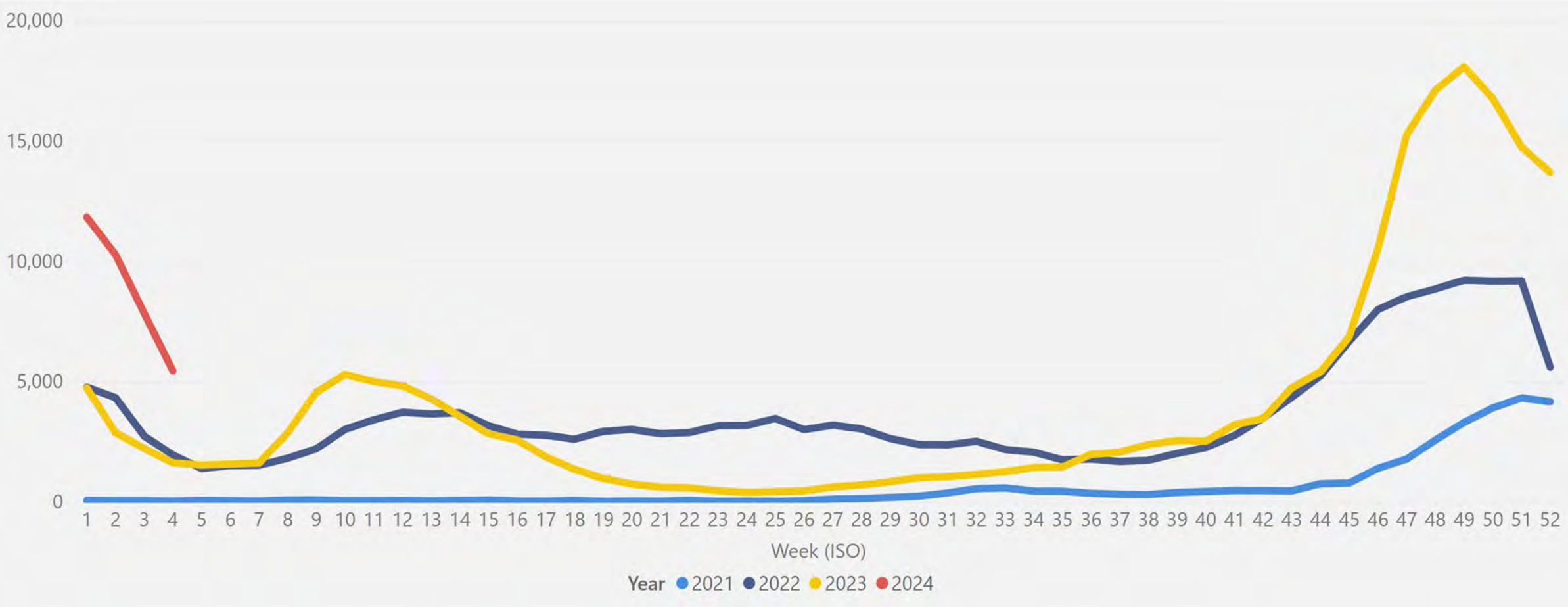
A(H1N1)pdm09 summary

- The data supported A/Wisconsin/67/2022-like and A/Victoria/4897/2022 (HA clade 5a.2a.1) remaining as the vaccine antigens for the 2024-2025 northern hemisphere.
  - A(H1N1)pdm09 viruses circulated globally and predominated in most geographic regions.
  - Phylogenetic analysis of the HA genes from viruses collected since September 1, 2023 showed co-circulation of 5a.2a and 5a.2a.1 with regional differences in which predominated.
  - Post-infection ferret antisera raised against the NH 2023-2024 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.
  - Human sera showed post-vaccination geometric mean titres (GMTs) were not reduced significantly for the recently circulating A(H1N1)pdm09 viruses from both clade 5a.2a and 5a.2a.1 when compared to titers against cell culture-propagated A/Wisconsin/67/2022(H1N1)pdm09-like vaccine viruses.



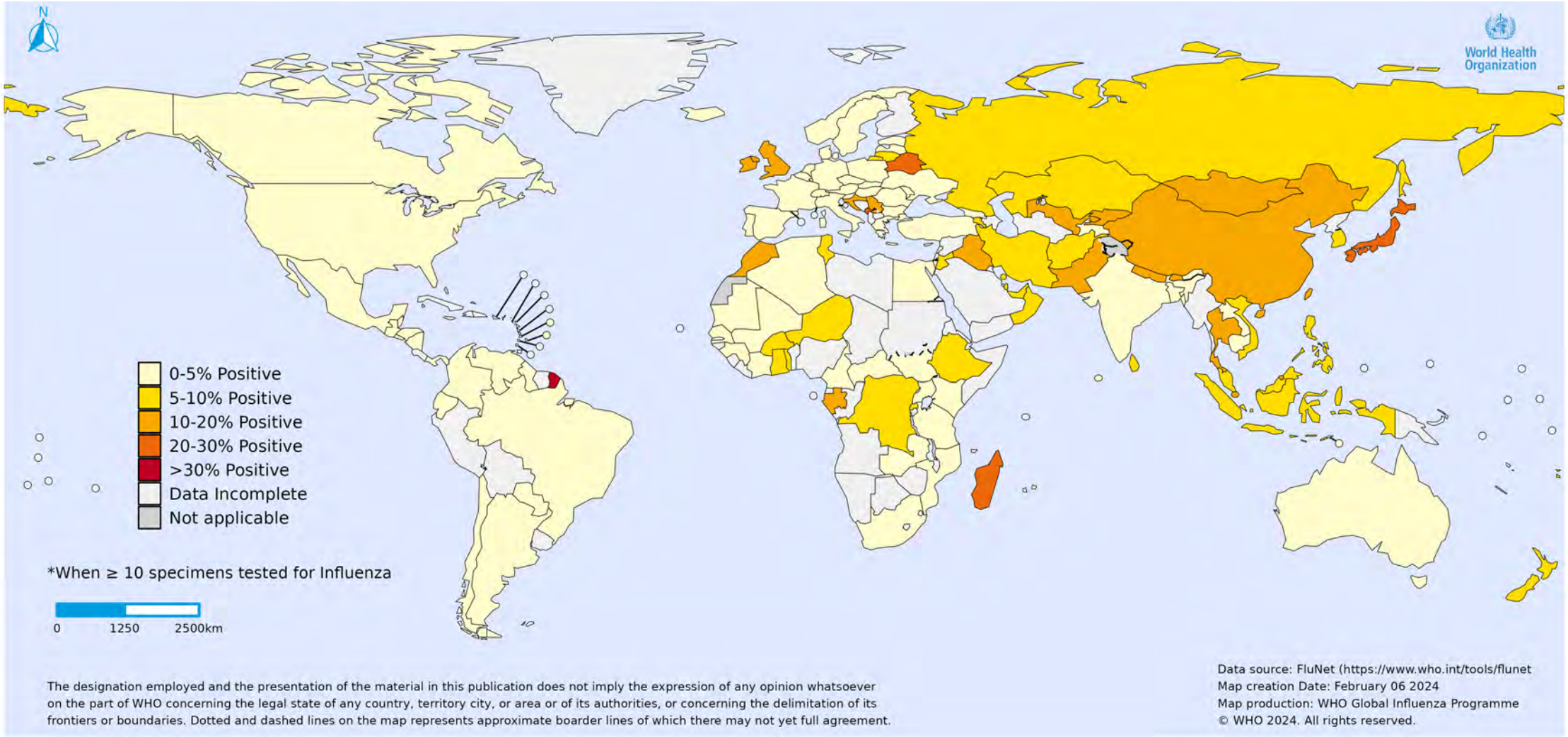
A(H3N2) Viruses

Number of A(H3N2) viruses detected by GISRS



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

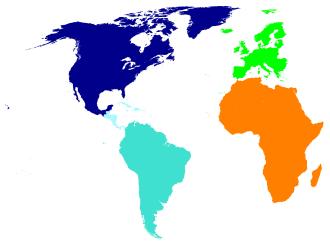
Influenza A(H3N2) activity



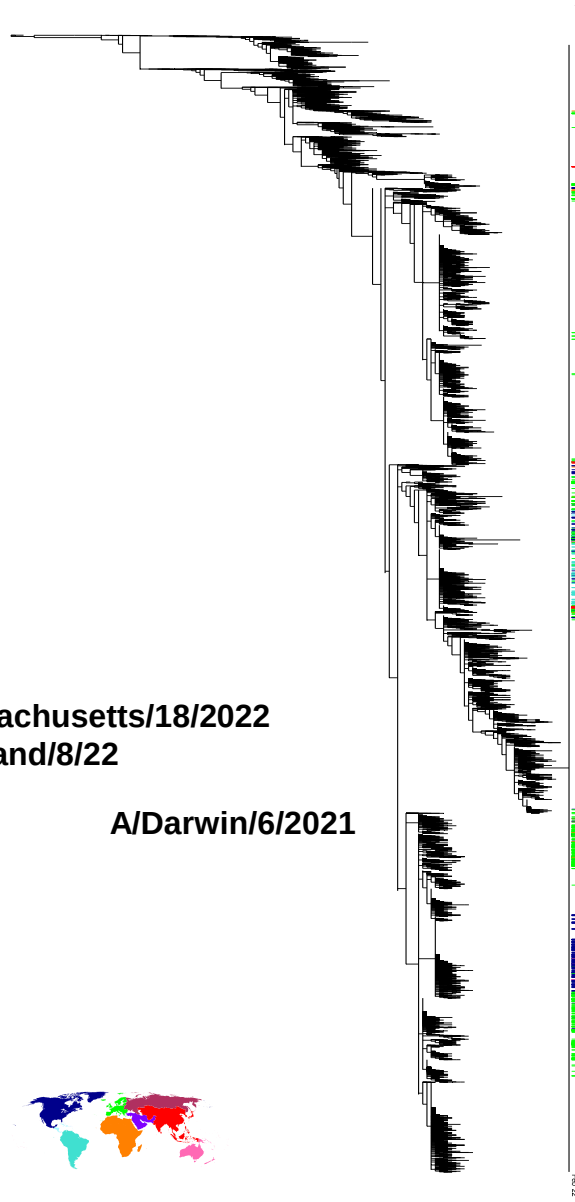
Colour intensity shows the percent of influenza A(H3N2) positive among all samples tested during this period per country

Data source: FluNet, (https://www.who.int/tools/flunet), Global Influenza Surveillance and Response System (6 February 2024)

Overview of A(H3N2) HA phylogeography

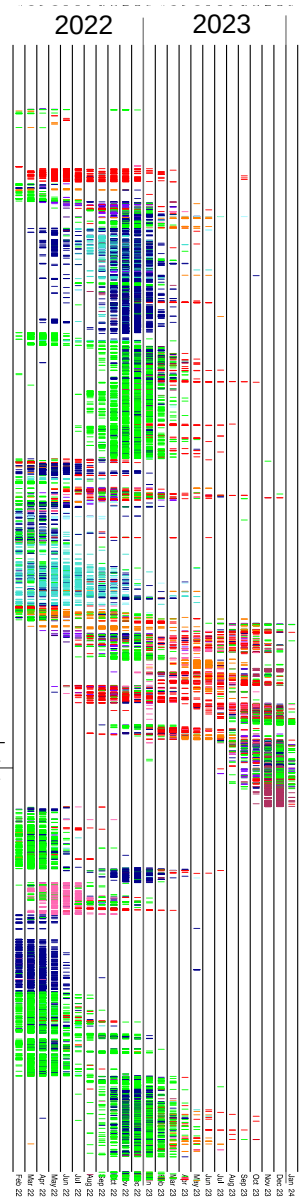


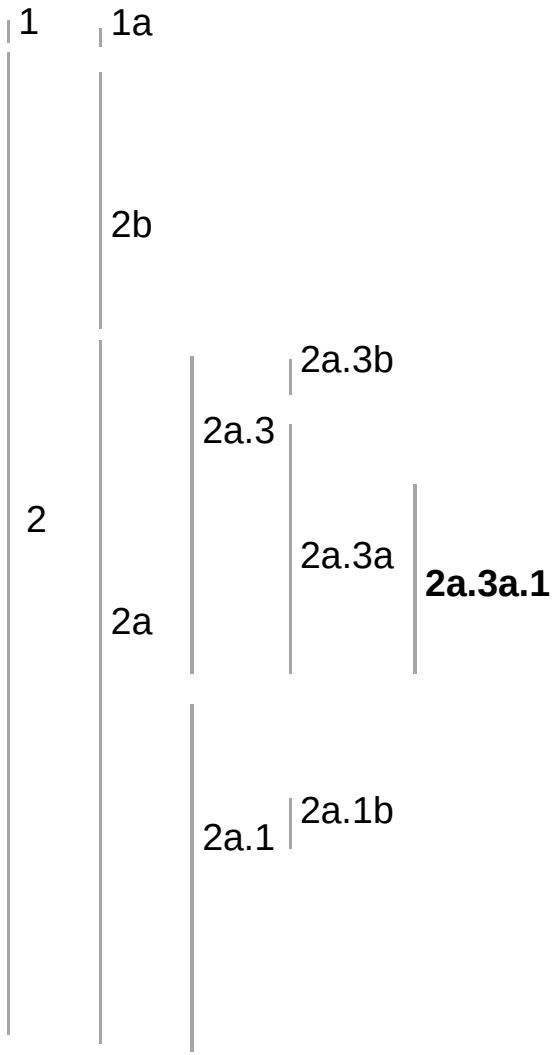
North America
South America
Europe
Africa
Middle East
Russia
E SE Asia
Oceania



A/Massachusetts/18/2022
A/Thailand/8/22

A/Darwin/6/2021

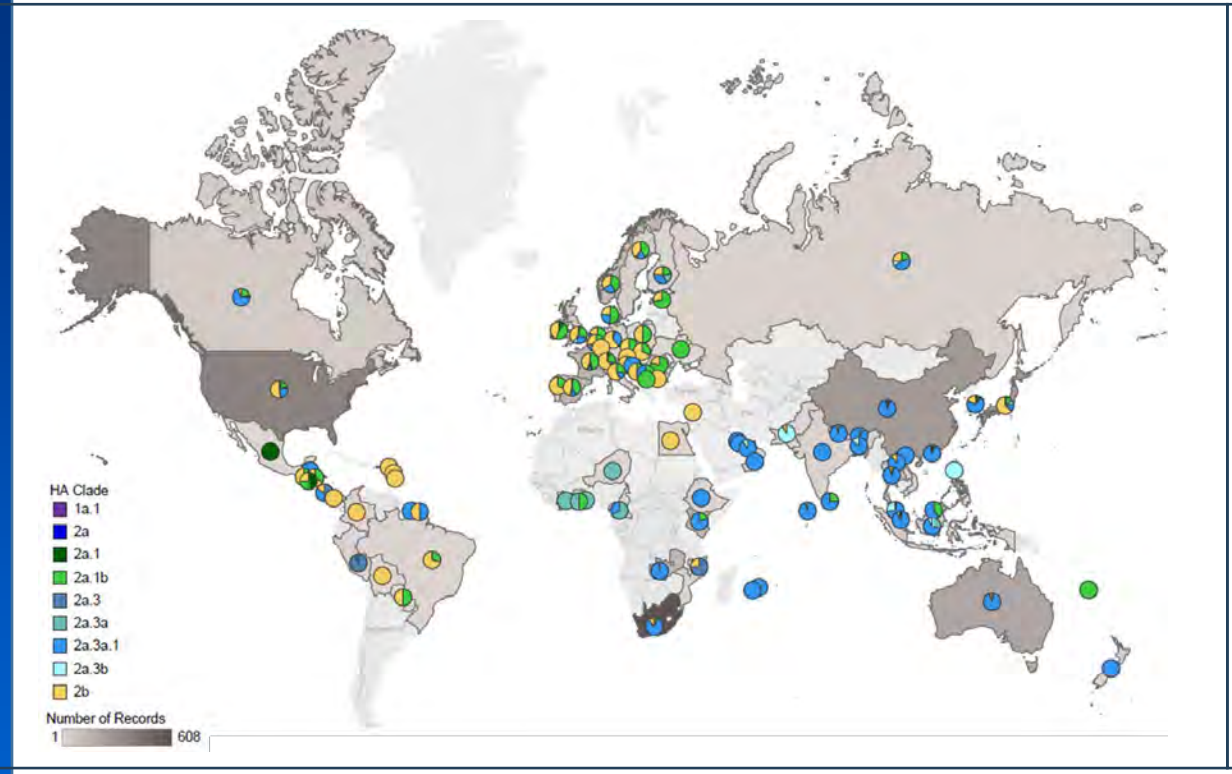




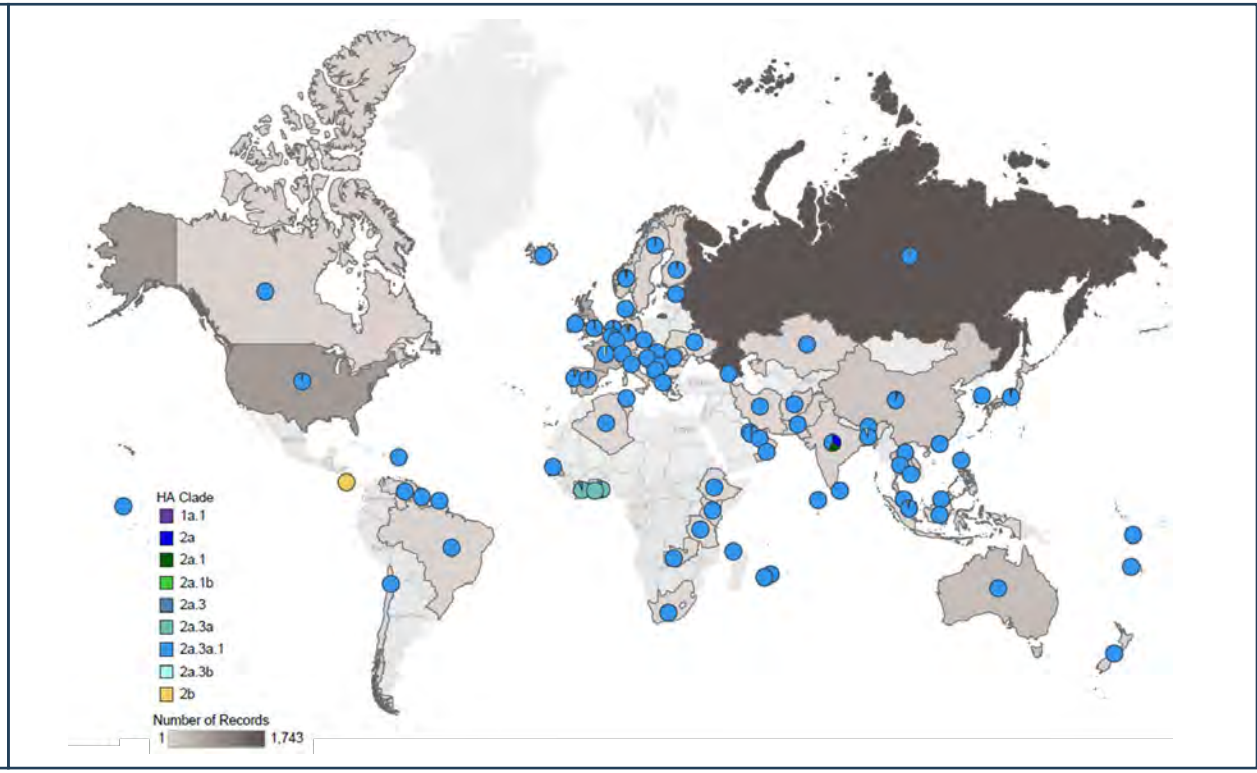
Source: University of Cambridge: Derek Smith and Sarah James

Global A(H3N2) HA clade diversity

Collection Dates
February 1, 2023- August 31, 2023



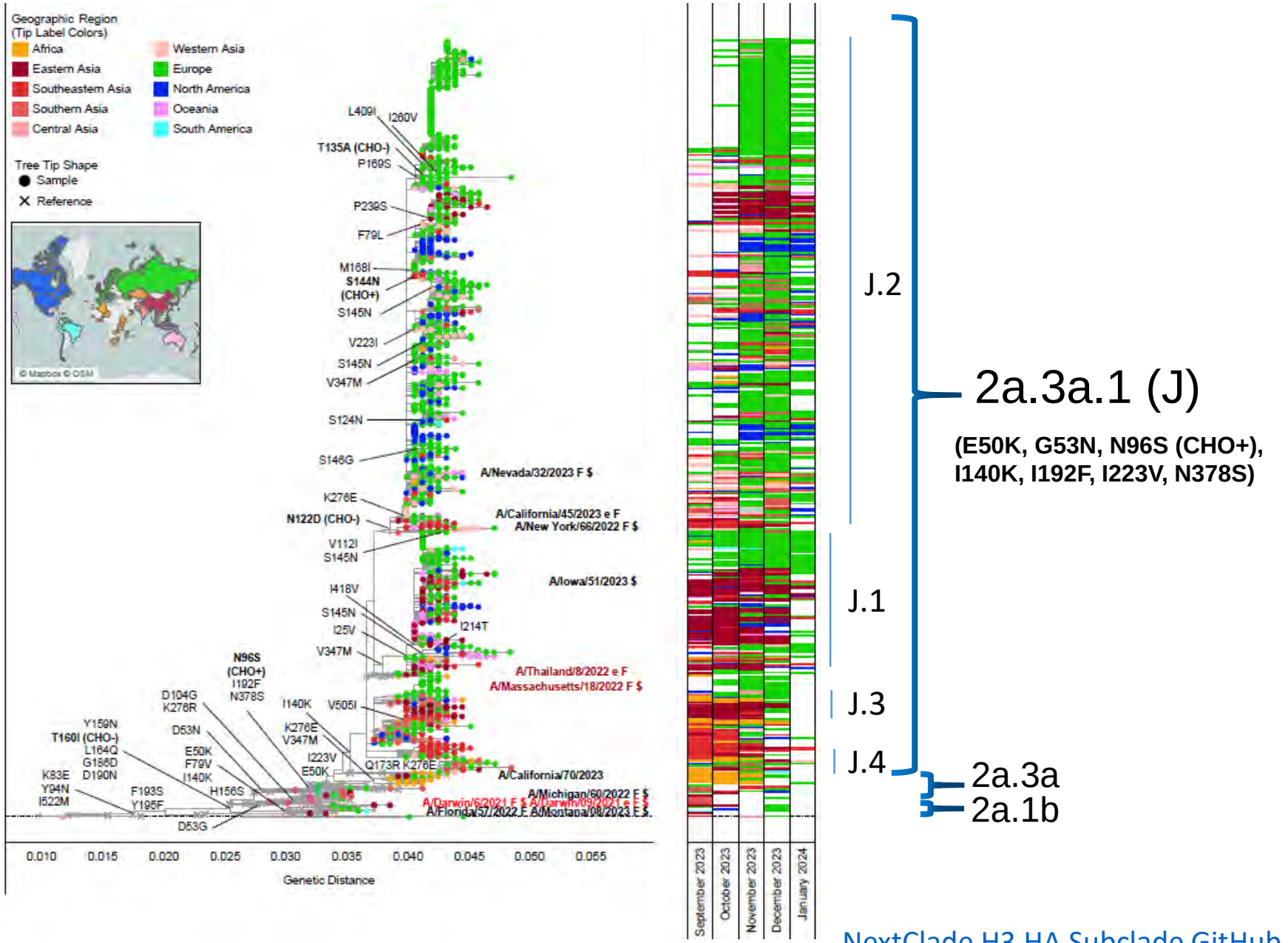
Collection Dates
September 1, 2023- January 31, 2024



Based on HA sequence availability from GISAID EpiFlu™

Source: WHO CC CDC, USA

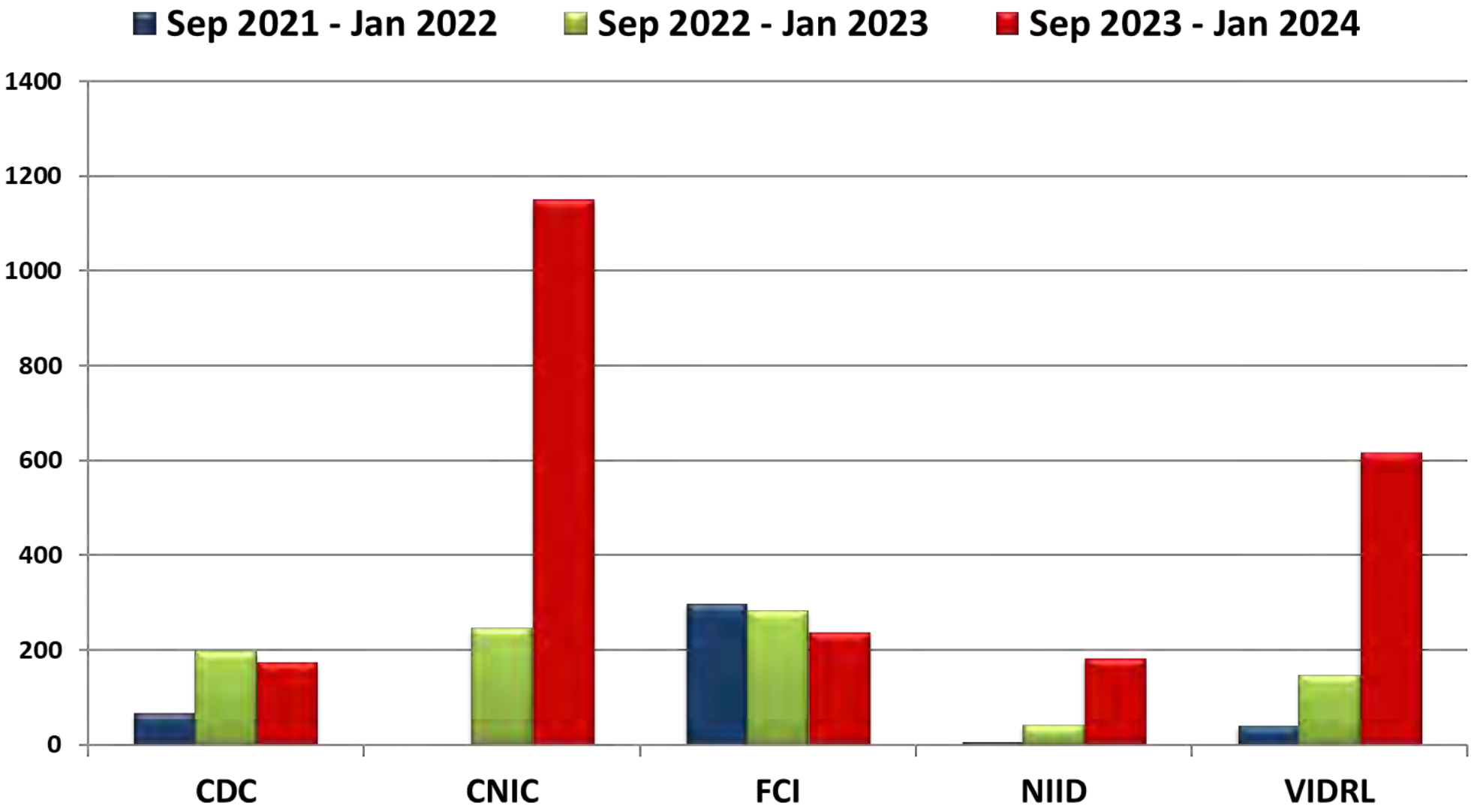
A(H3N2) HA phylogenetics and genetic diversity



NextClade H3 HA Subclade GitHub

Source: WHO CC CDC, USA

A(H3N2) viruses antigenically characterized



Last 3 reporting periods

Analysis of A(H3N2) viruses by antisera to antigens recommended for NH 2023-2024

HI Assay

Antisera to northern hemisphere 2023-2024 antigens (3C.2a1b.2a.**2a**)

A/Darwin/6/2021-like (cell) 2a

WHO CC	Like (<8 fold)	Low (≥ 8 fold)
CDC	174 (100%)	0 (0%)
CNIC	261 (23%)	887 (77%)
FCI	199 (84%)	38 (16%)
NIID	35 (95%)	1 (3%)
VIDRL	577 (94%)	38 (6%)
Total	1246 (48%)	964 (44%)

A/Darwin/9/2021-like (egg) 2a

WHO CC	Like (<8 fold)	Low (≥ 8 fold)
CDC	80 (100%)	0 (0%)
CNIC	370 (32%)	778 (68%)
FCI	236 (100%)	1 (0%)
NIID	50 (94%)	3 (6%)
VIDRL	366 (60%)	249 (40%)
Total	1102 (52%)	1031 (48%)

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

Analysis of A(H3N2) viruses by antisera to antigens recommended for NH 2023-2024 (cont.)

HI Assay

Antisera to southern hemisphere 2024 antigens (3C.2a1b.**2a.3a.1**)

A/Massachusetts/18/2022-like (cell)
2a.3a.1

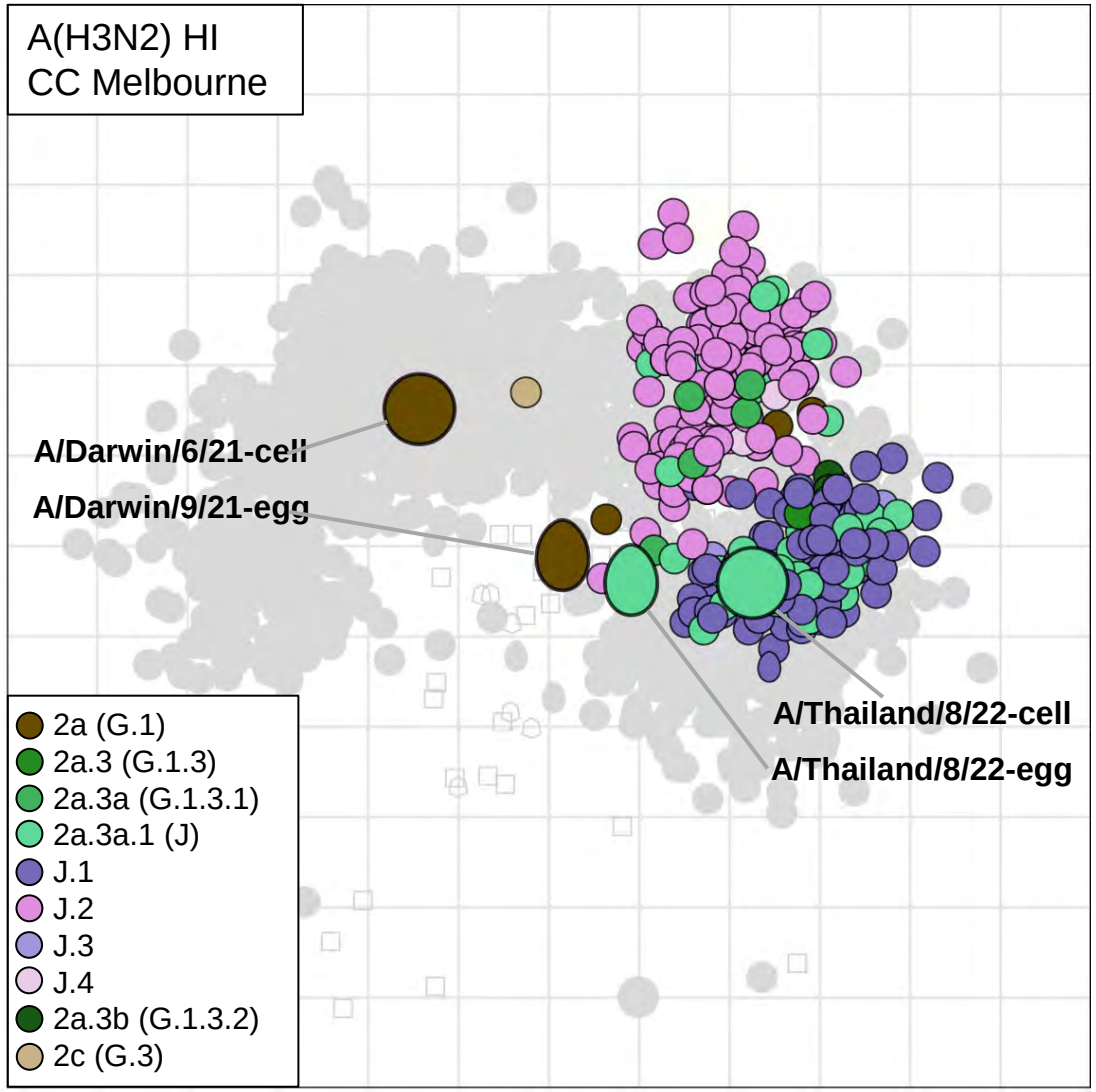
WHO CC	Like (<8 fold)	Low (≥ 8 fold)
CDC	101 (97%)	3 (3%)
CNIC	1046 (91%)	102 (9%)
FCI	195 (82%)	42 (18%)
NIID	19 (100%)	0 (0%)
VIDRL	577 (94%)	38 (6%)
Total	1938 (91%)	185 (9%)

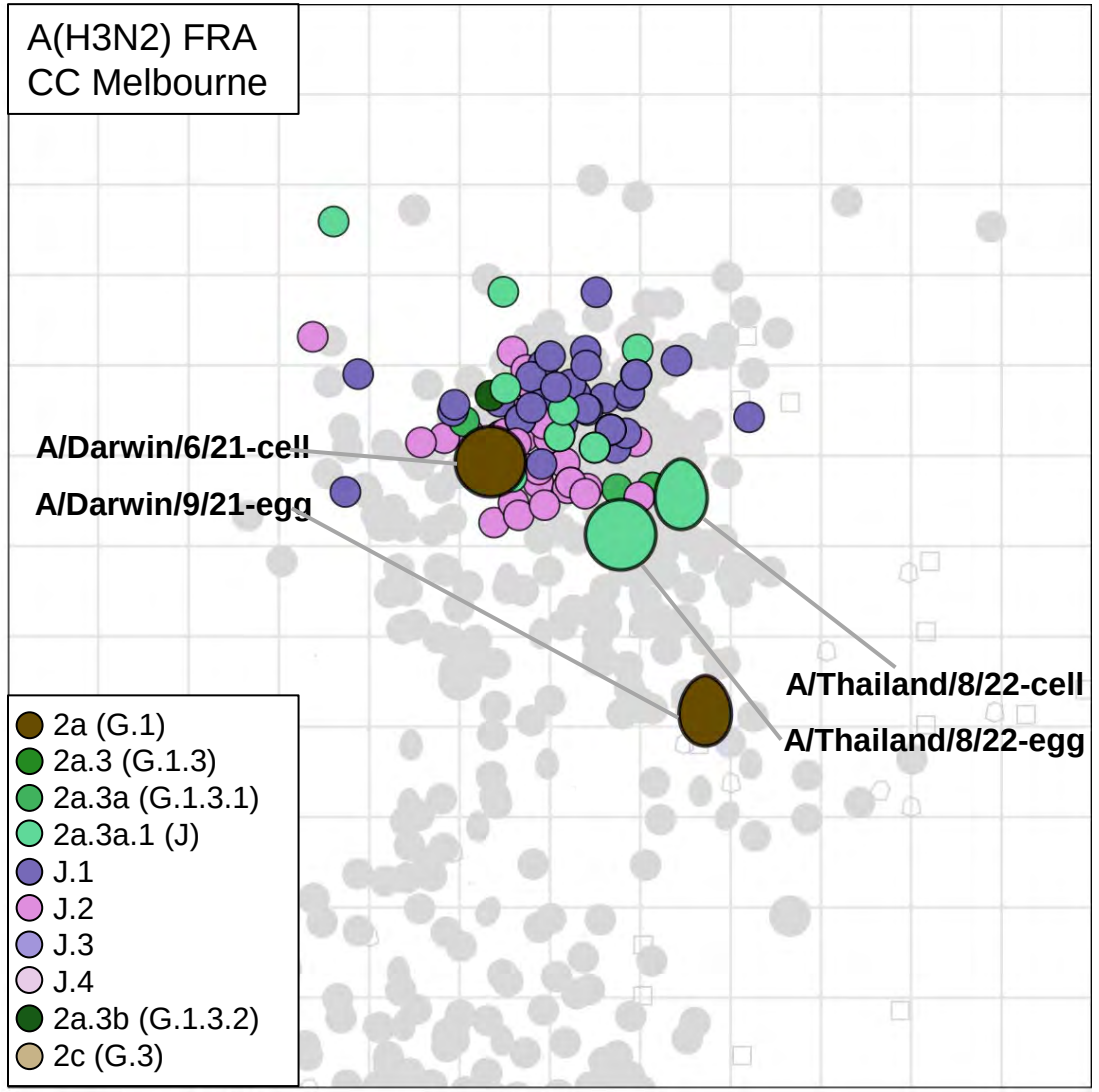
A/Thailand/8/2022-like (egg)
2a.3a.1

WHO CC	Like (<8 fold)	Low (≥ 8 fold)
CDC	99 (95%)	5 (5%)
CNIC	874 (87%)	133 (13%)
FCI	233 (98%)	4 (2%)
NIID	0	0
VIDRL	518 (84%)	97 (16%)
Total	1724 (88%)	239 (12%)

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

A(H3N2) antigenic cartography

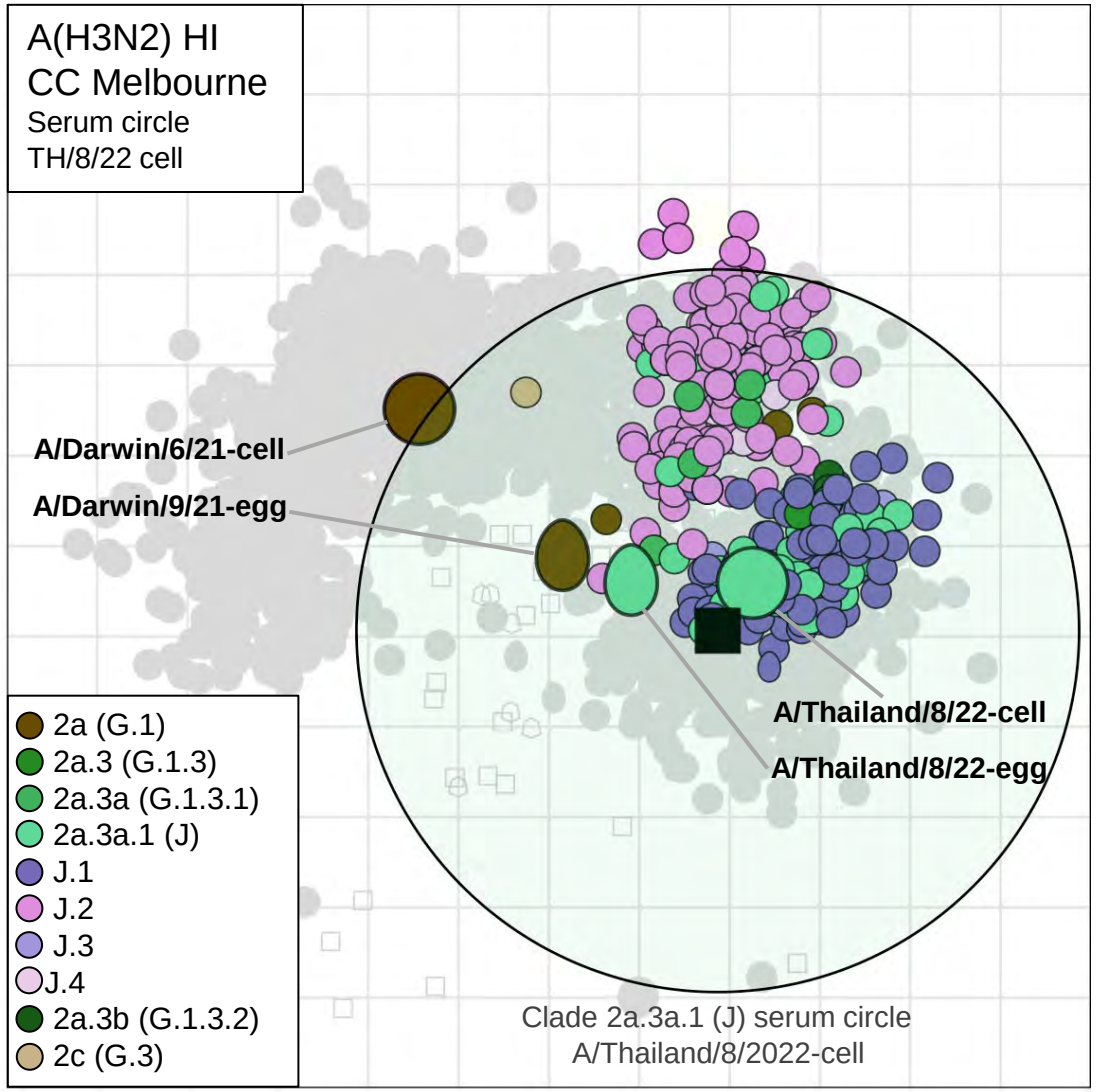


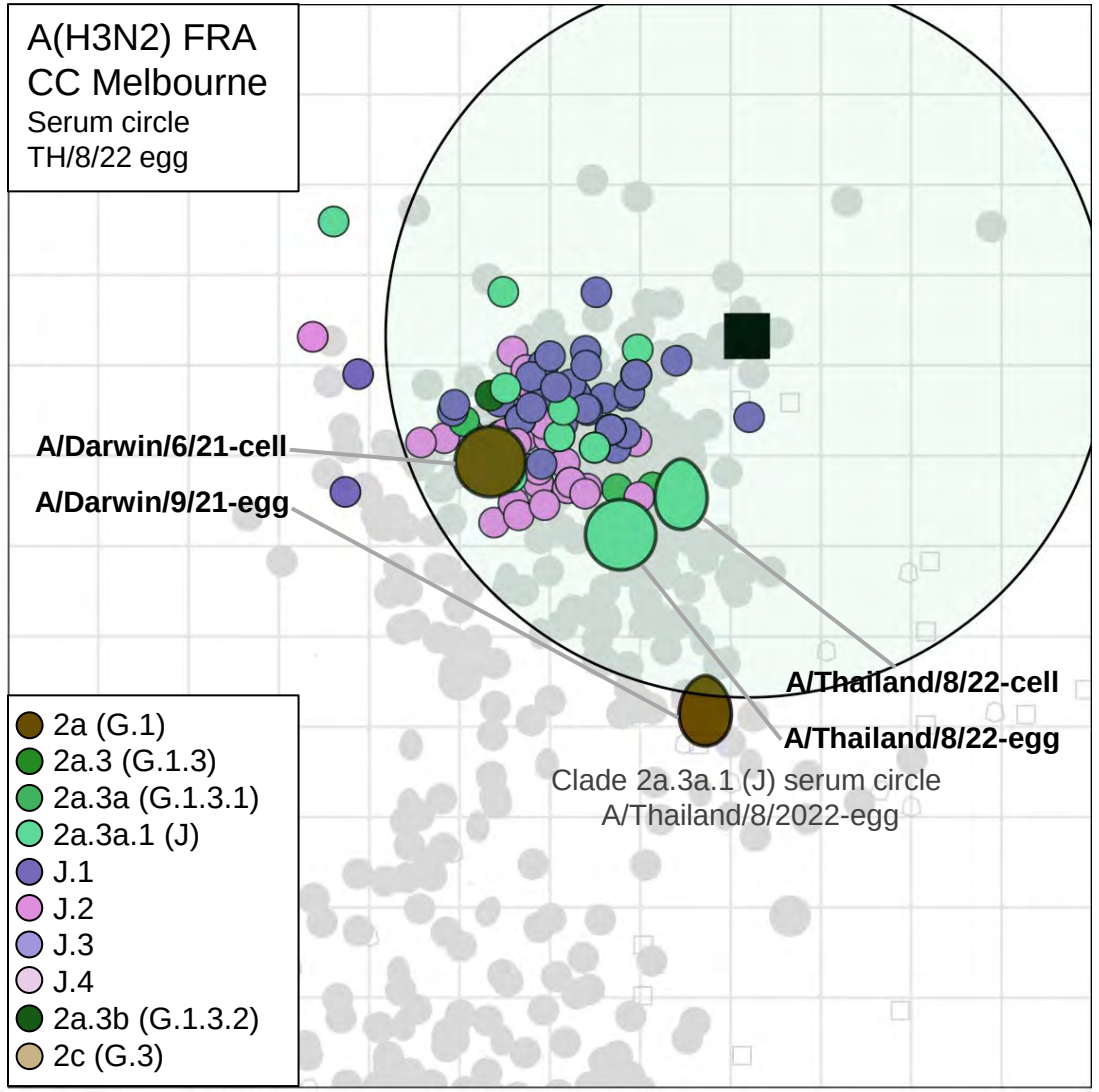


Since 1st September 2023 (older viruses in grey)

University of Cambridge

A(H3N2) antigenic cartography showing antisera reactivity



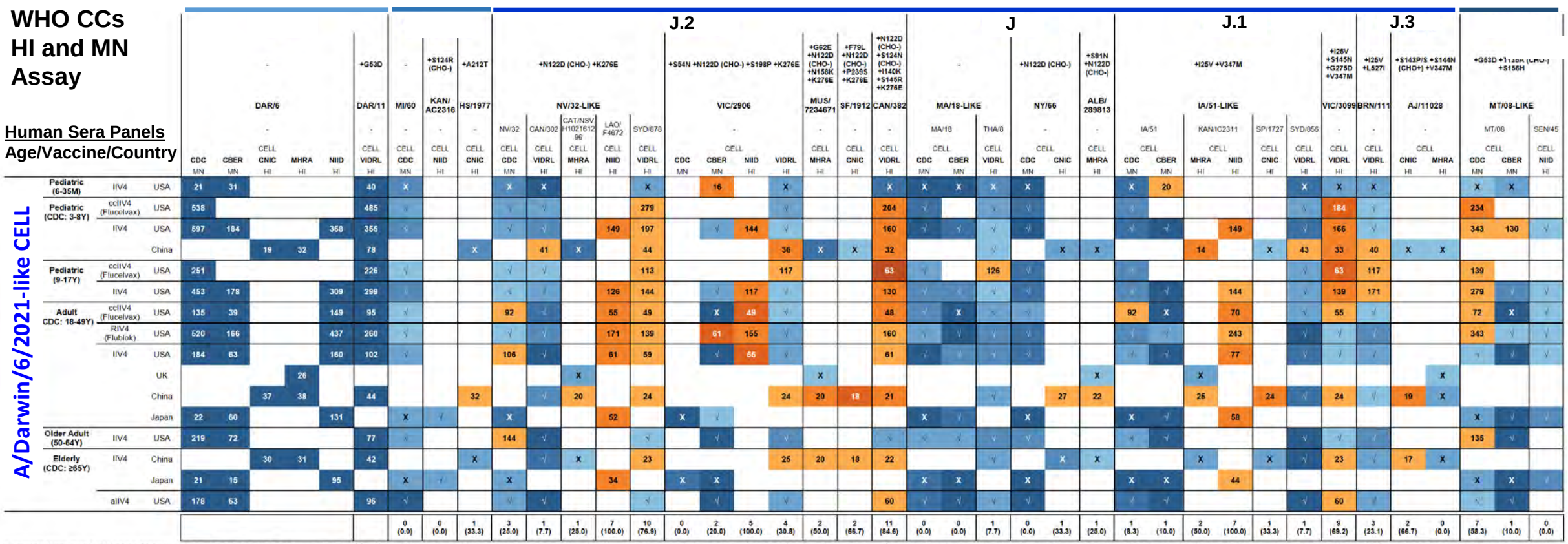


Serum circles (within 8-fold of homologous titers)

University of Cambridge

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

Vaccine: A/Darwin/6/2021-like (2a)



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 CNIC, MHRA, NIID, and VIDRL are indicated in addition to all microneutralization (MN) protocol trends.

Included Strains: A/ALBANIA/289813/2022 (ALB/289813); A/ANHUI-JINAN/11028/2023 (AJ/11028); A/BRUNEI/111/2023 (BRN/111); A/CANBERRA/302/2023 (CAN/302); A/CANBERRA/382/2023 (CAN/382); A/CATALONIA/NSVH102161296/2023 (CAT/NSVH102161296); A/DARWIN/11/2021 (DAR/11); A/DARWIN/6/2021 (DAR/6); A/HENAN-SHIHE/1977/2023 (HS/1977); A/IOWA/51/2023 (IA/51); A/KANAGAWA/AC2316/2023 (KAN/AC2316); A/KANAGAWA/IC2311/2023 (KAN/IC2311); A/LAOS/F4672/2023 (LAO/F4672); A/MASSACHUSETTS/18/2022 (MA/18); A/MICHIGAN/60/2022 (MI/60); A/MONTANA/08/2023 (MT/08); A/MUSCAT/7234671/2023 (MUS/7234671); A/NEVADA/32/2023 (NV/32); A/NEW YORK/66/2022 (NY/66); A/SENDAI/45/2023 (SEN/45); A/SHANGHAI-FENGXIAN/1912/2023 (SF/1912); A/SHANGHAI-PUTUO/1727/2023 (SP/1727); A/SYDNEY/856/2023 (SYD/856); A/SYDNEY/878/2023 (SYD/878); A/THAILAND/8/2022 (THA/8); A/VICTORIA/2906/2023 (VIC/2906); A/VICTORIA/3099/2023 (VIC/3099).

Multiple Sources; compiled by WHO CC CDC, USA

A(H3N2) virus antiviral susceptibility

Neuraminidase inhibitors

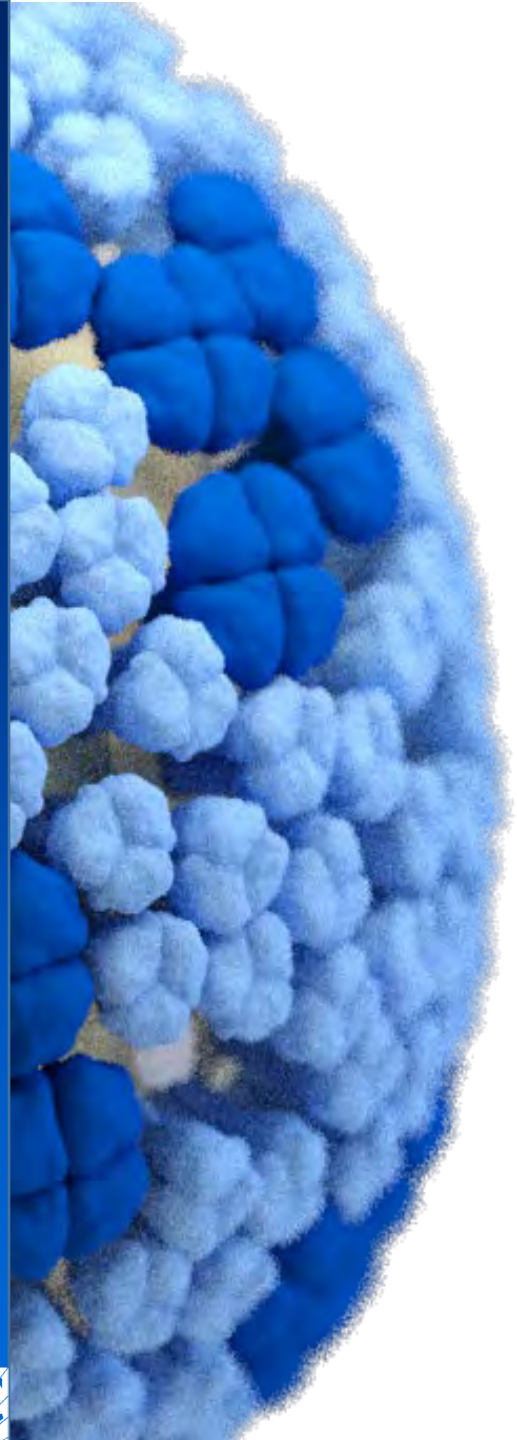
- Of 3,046 A(H3N2) viruses collected and analyzed, none showed genetic or phenotypic evidence of reduced inhibition to neuraminidase inhibitors.

Endonuclease inhibitors

- Of 1,450 A(H3N2) viruses collected and analyzed, four showed genetic or phenotypic evidence of reduced susceptibility to baloxavir marboxil.

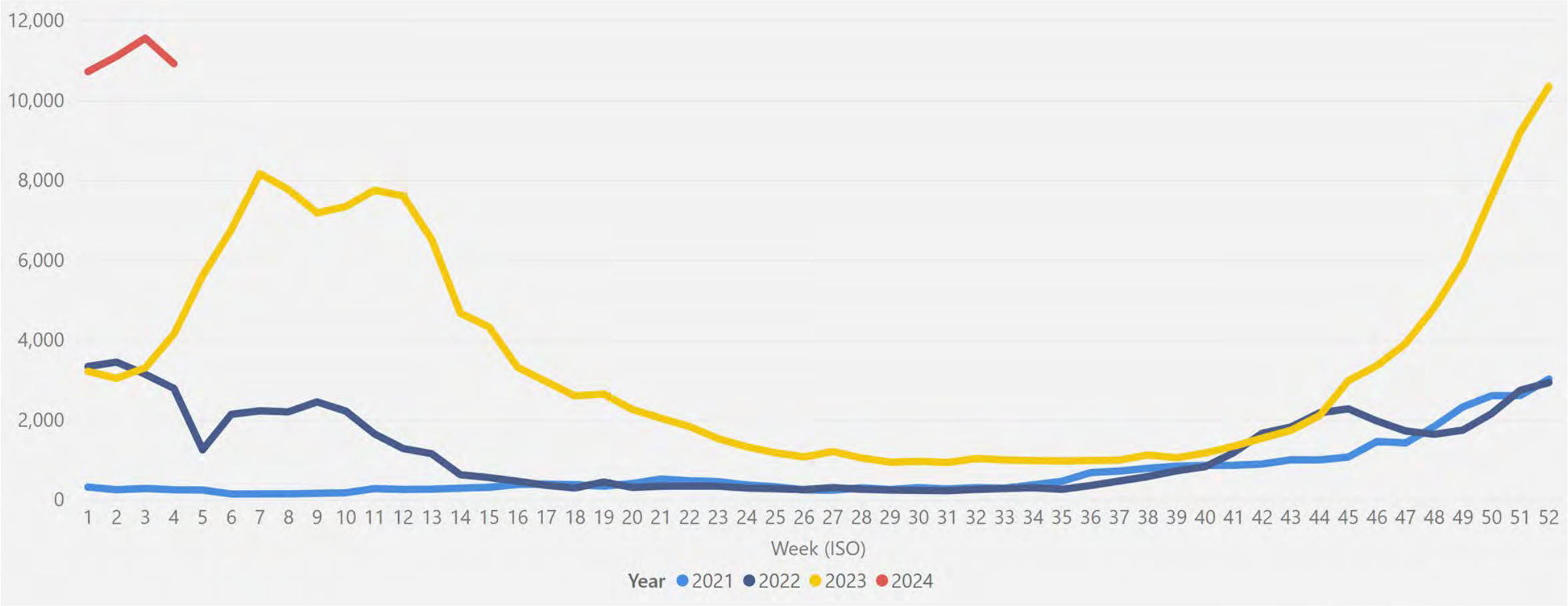
A(H3N2) summary

- The data supported updating the 2024-2025 northern hemisphere vaccine antigen to the same antigen recommended for the 2024 southern hemisphere (A/Massachusetts/18/2022-like (HA clade 2a.3a.1)).
  - A(H3N2) viruses circulated globally and predominated in some geographic regions, namely Asia and Africa.
  - Phylogenetic analysis of the HA genes from viruses collected since September 1, 2023 showed predominance of a single clade: 2a.3a.1, with further diversification into several subclades.
  - Post-infection ferret antisera raised against the NH 2023-2024 A(H3N2) vaccine components (cell culture-propagated A/Darwin/6/2021-like and egg-propagated A/Darwin/9/2021-like) from the clade 2a showed some reductions in inhibition to viruses expressing HA from subclade 2a.3a.1.
  - Post-infection ferret antisera raised against the 2024 SH A(H3N2) vaccine components (cell culture-propagated A/Massachusetts/18/2022-like and egg-propagated A/Thailand/8/2021-like) from the 2a.3a.1 subclade reacted well with most circulating viruses expressing 2a.3a.1.
  - Human sera showed post-vaccination geometric mean titres (GMTs) were significantly reduced for the many viruses representing recently circulating A(H3N2) viruses from clade 2a.3a.1 when compared to titers against cell culture-propagated A/Darwin/6/2021-like (HA clade 2a) vaccine viruses.



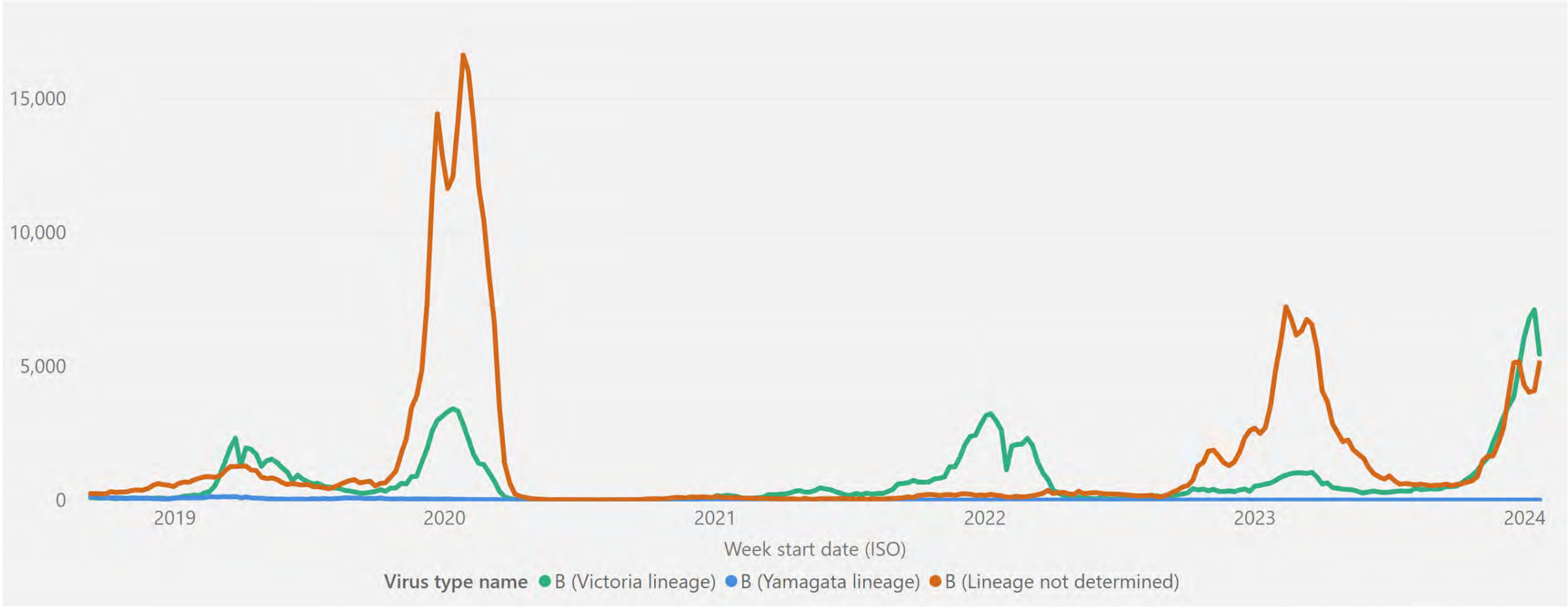
Influenza B Viruses

Number of influenza B viruses detected by GISRS



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

Global circulation of influenza B viruses

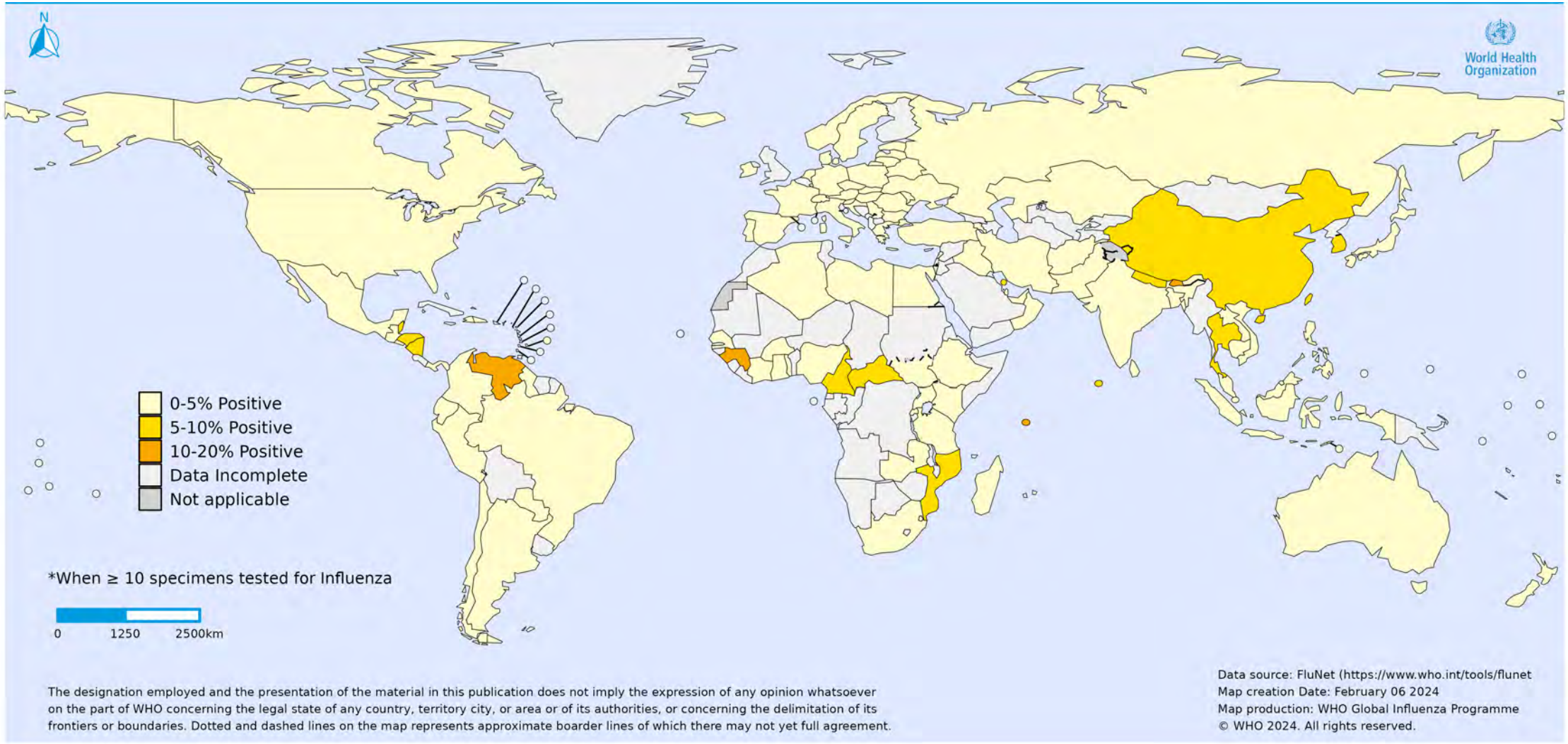


Select week start date (ISO)

9/10/2018 1/28/2024

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

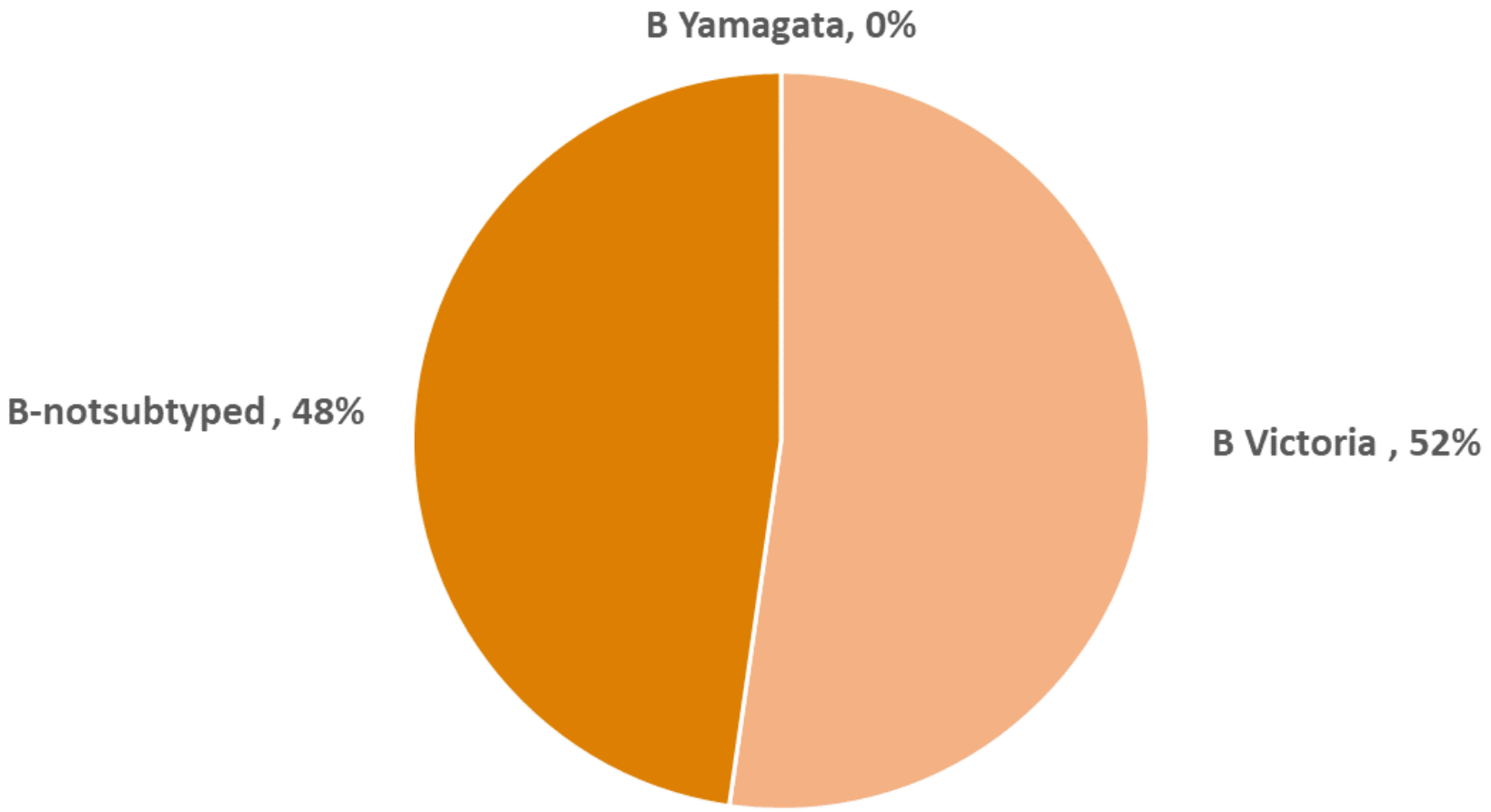
Influenza B virus activity



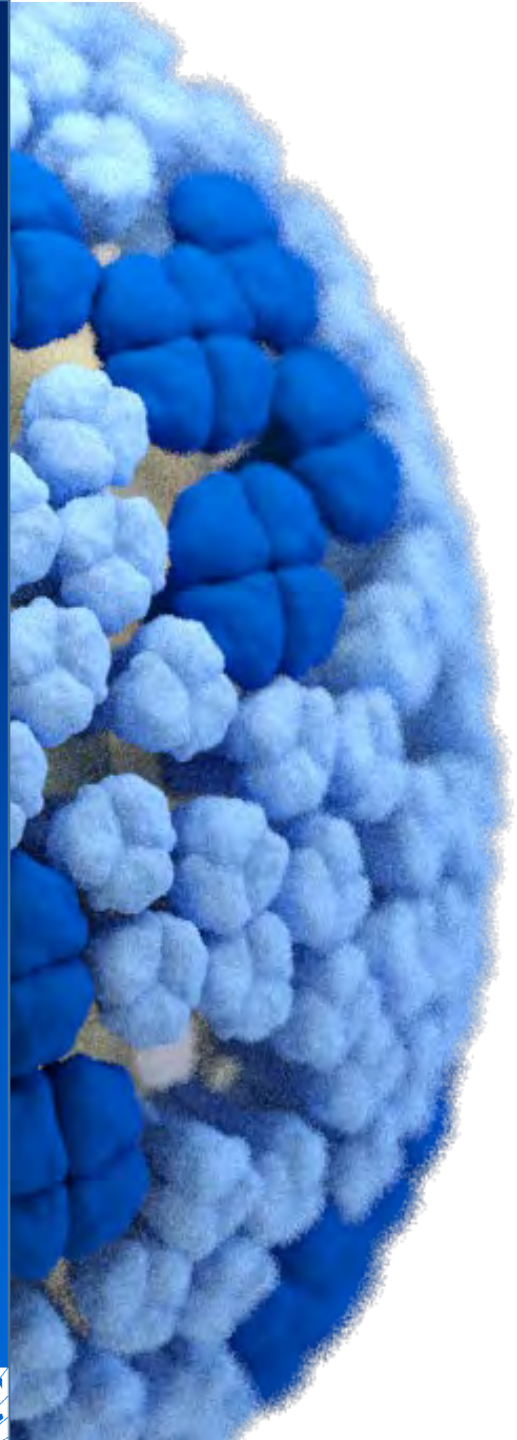
Colour intensity shows the percent of influenza B positive among all samples tested during this period per country

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

Influenza B virus lineages % (1 Sep 2023 – 31 Jan 2024)



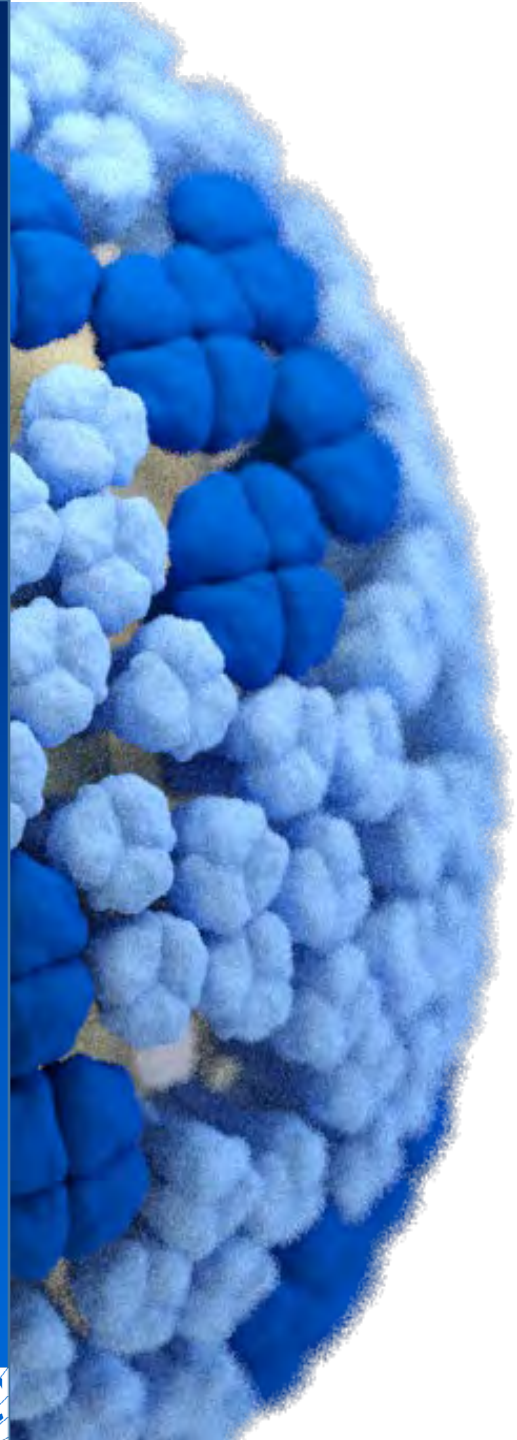
Data source: FluNet, (https://www.who.int/tools/flunet), Global Influenza Surveillance and Response System (6 Feb 2024)



Influenza B/Yamagata Viruses

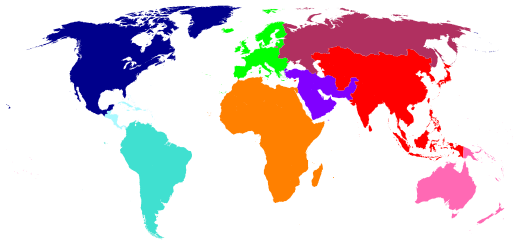
B/Yamagata lineage summary

- 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



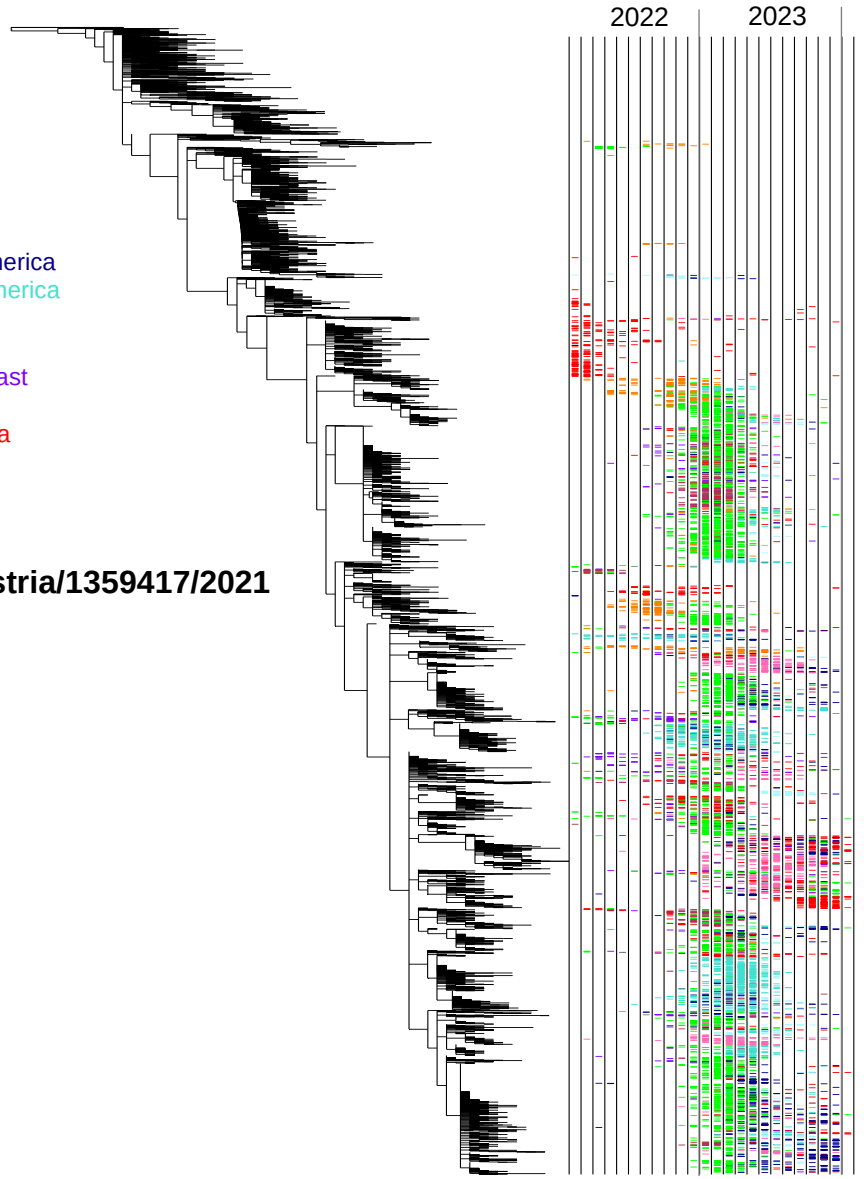
Influenza B/Victoria Viruses

B/Victoria HA phylogenetic tree



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

B/Austria/1359417/2021



1A.1
Δ162 – 163
Double deletion

1A.**3**
Δ162 – 164
Triple deletion

1A.**3a**
N150K
G184E
N197D
R279K

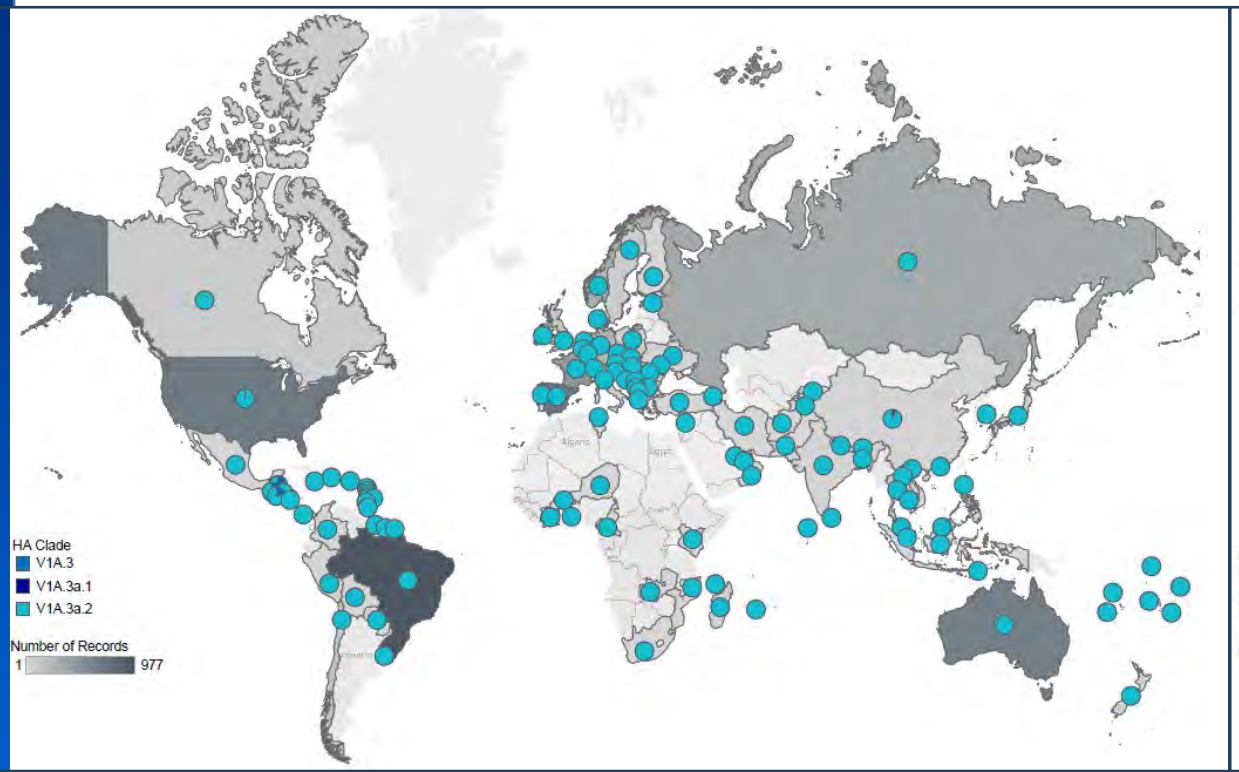
1A.**3a.1**
V220M
P241Q

1A.**3a.2**
A127T
P144L
K203R

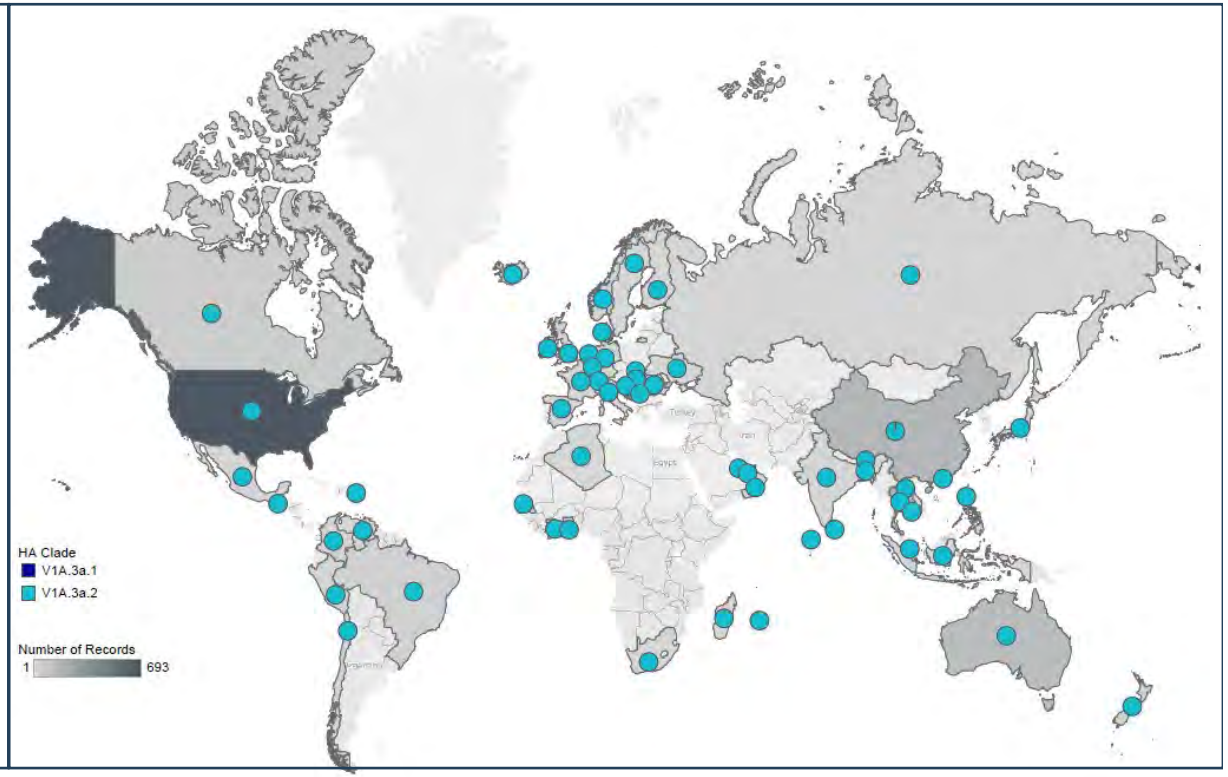
Source: University of Cambridge, UK

Global B/Victoria HA clade diversity

Collection Dates
February 1, 2023- August 31, 2023



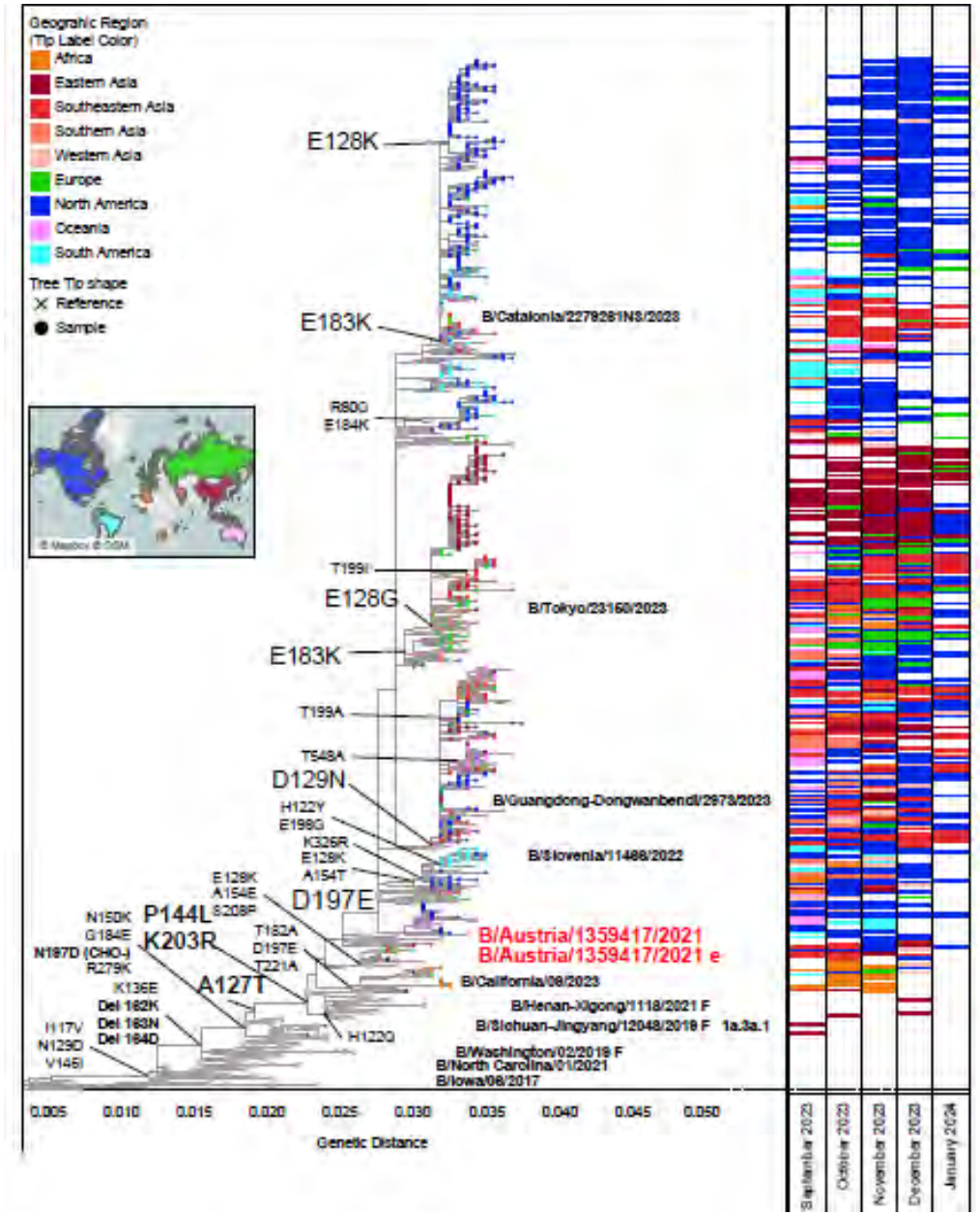
Collection Dates
September 1, 2023- January 31, 2024



Based on HA sequence availability from GISAID EpiFlu™

Source: WHO CC CDC, USA

B/Victoria lineage HA phylogenetics and genetic diversity

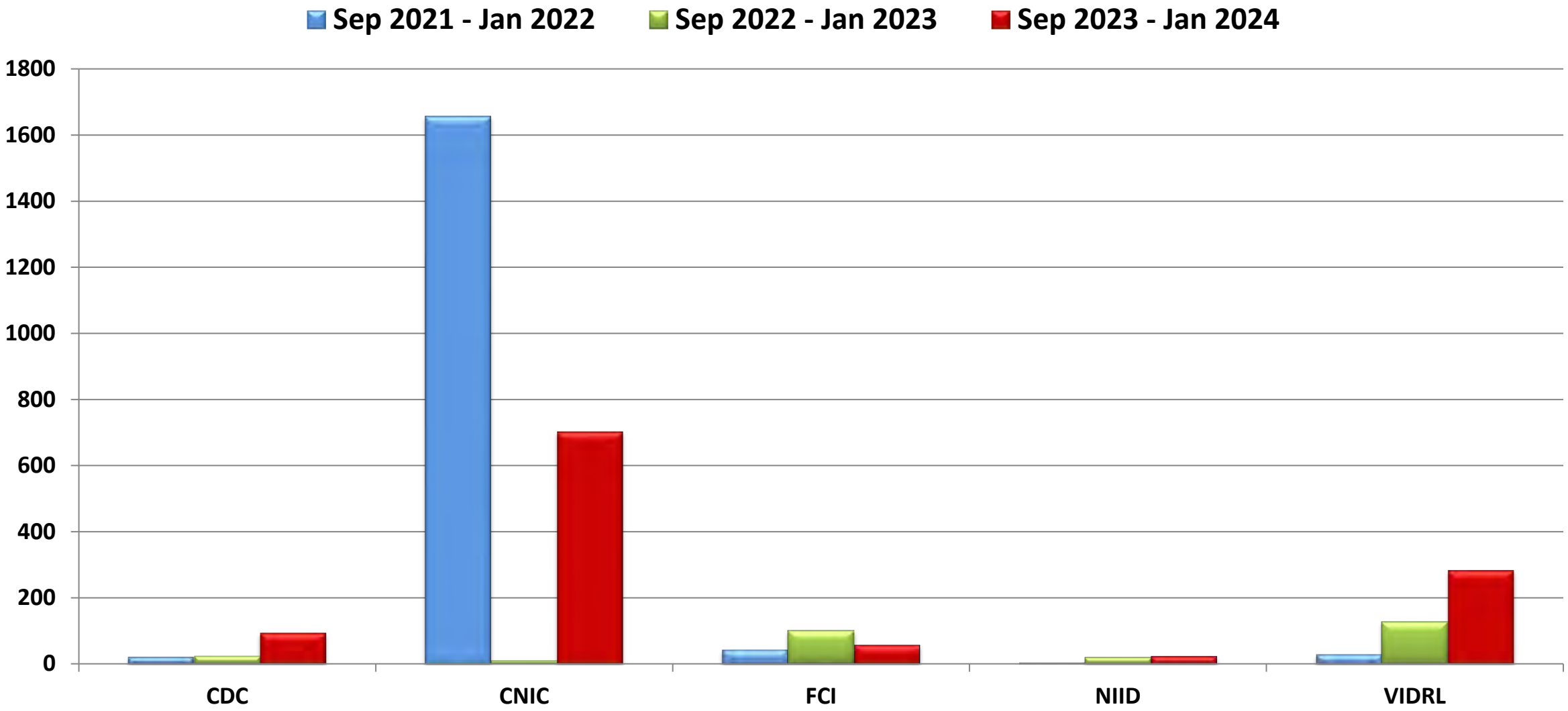


3a.2
(A127T, P144L, K203R)

3a.1
(V220M, P241Q)

Source: WHO CC CDC, USA

Influenza B/Victoria viruses antigenically characterized



Last 3 reporting periods

Antigenic analysis of B/Victoria viruses

Antisera to northern hemisphere 2023-2024 vaccine virus antigens

B/Austria/1359417/2021-like (cell)
3a.2

WHO CC	Like (2-4 fold)	Low (≥ 8-fold)
CDC	95 (100%)	0 (0%)
CNIC	695 (99%)	7 (1%)
FCI	59 (100%)	0 (0%)
NIID	25 (100%)	0 (0%)
VIDRL	284 (100%)	0 (0%)
TOTAL	1158 (99%)	7 (1%)

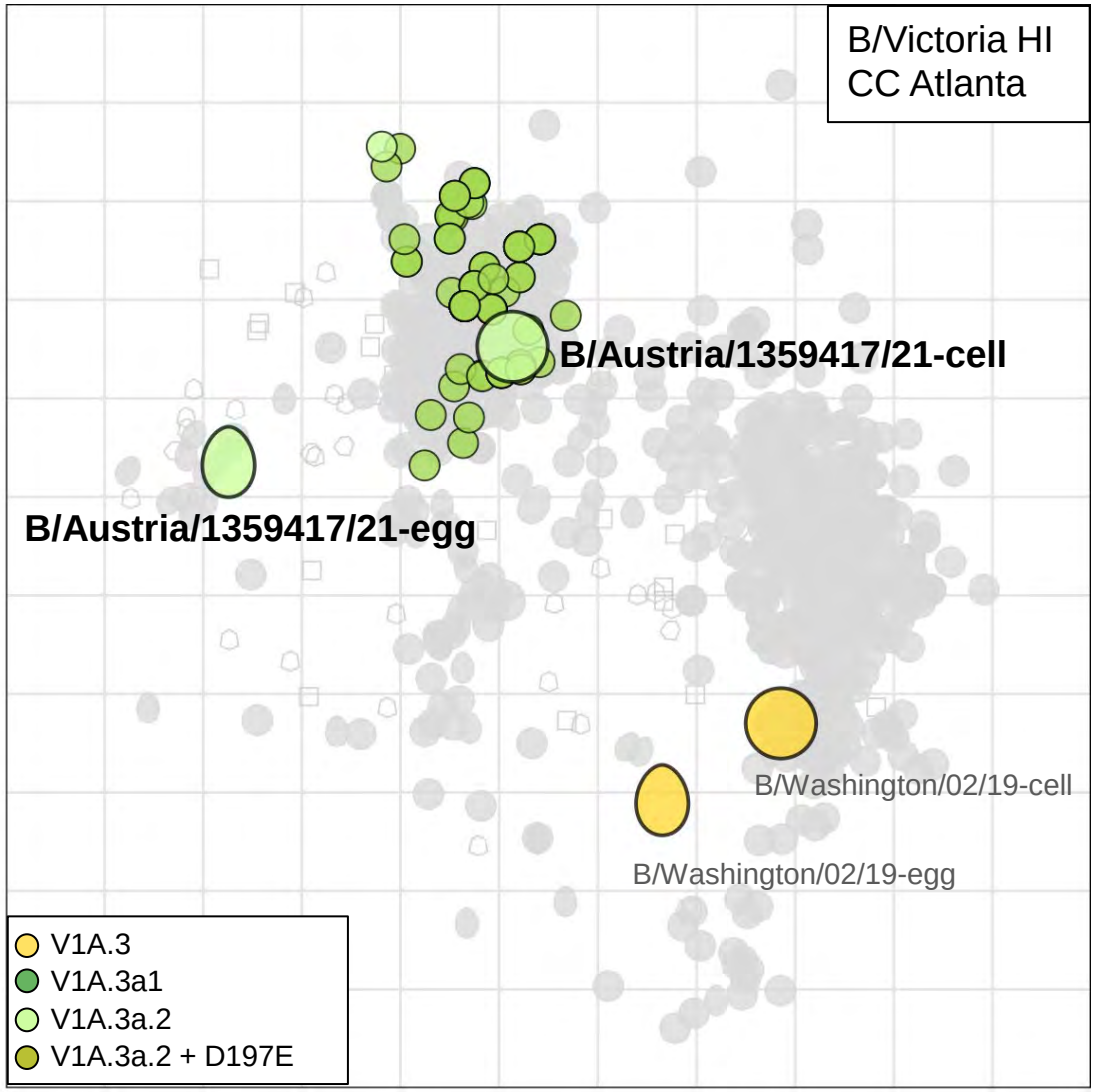
B/Austria/1359417/2021-like (egg)
3a.2

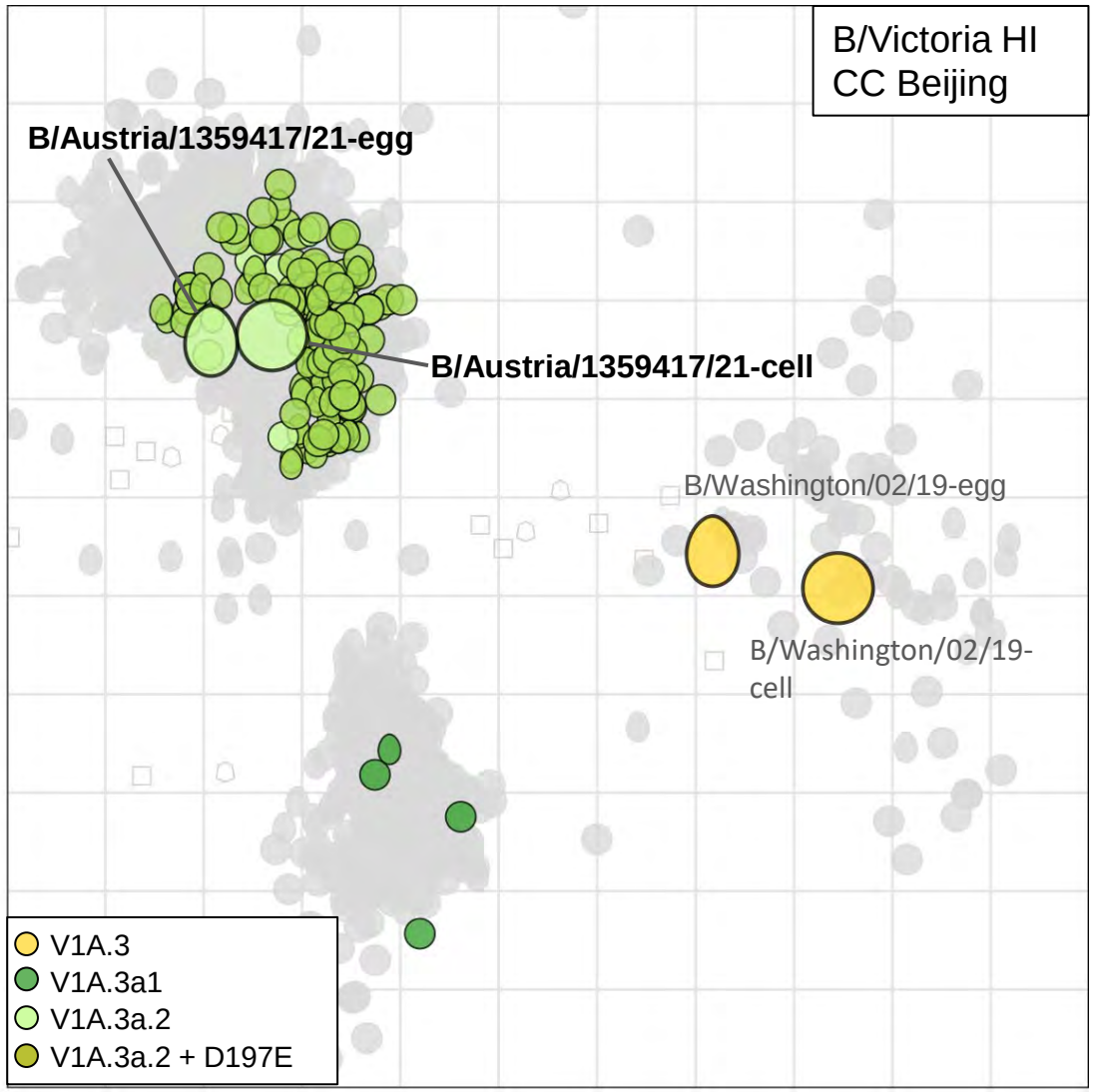
WHO CC	Like (< 8-fold)	Low (≥ 8-fold)
CDC	95 (100%)	0 (0%)
CNIC	692 (99%)	10 (1%)
FCI	59 (100%)	0 (0%)
NIID	25 (100%)	0 (0%)
VIDRL	283 (100%)	1 (0%)
TOTAL	1154 (99%)	11 (1%)

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

B/Victoria antigenic cartography

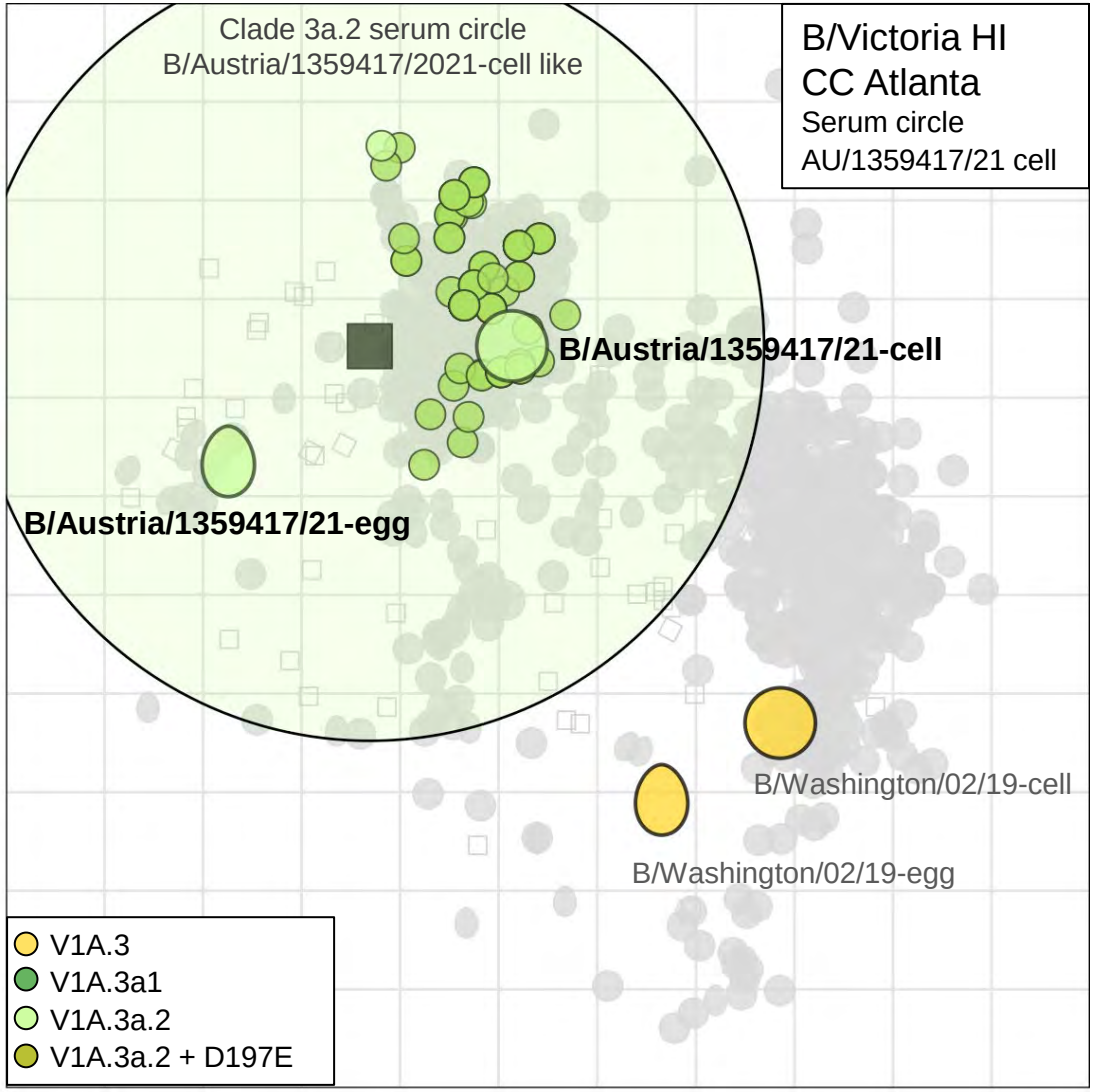
B/Victoria viruses collected since 1st September 2023 (older viruses in grey)

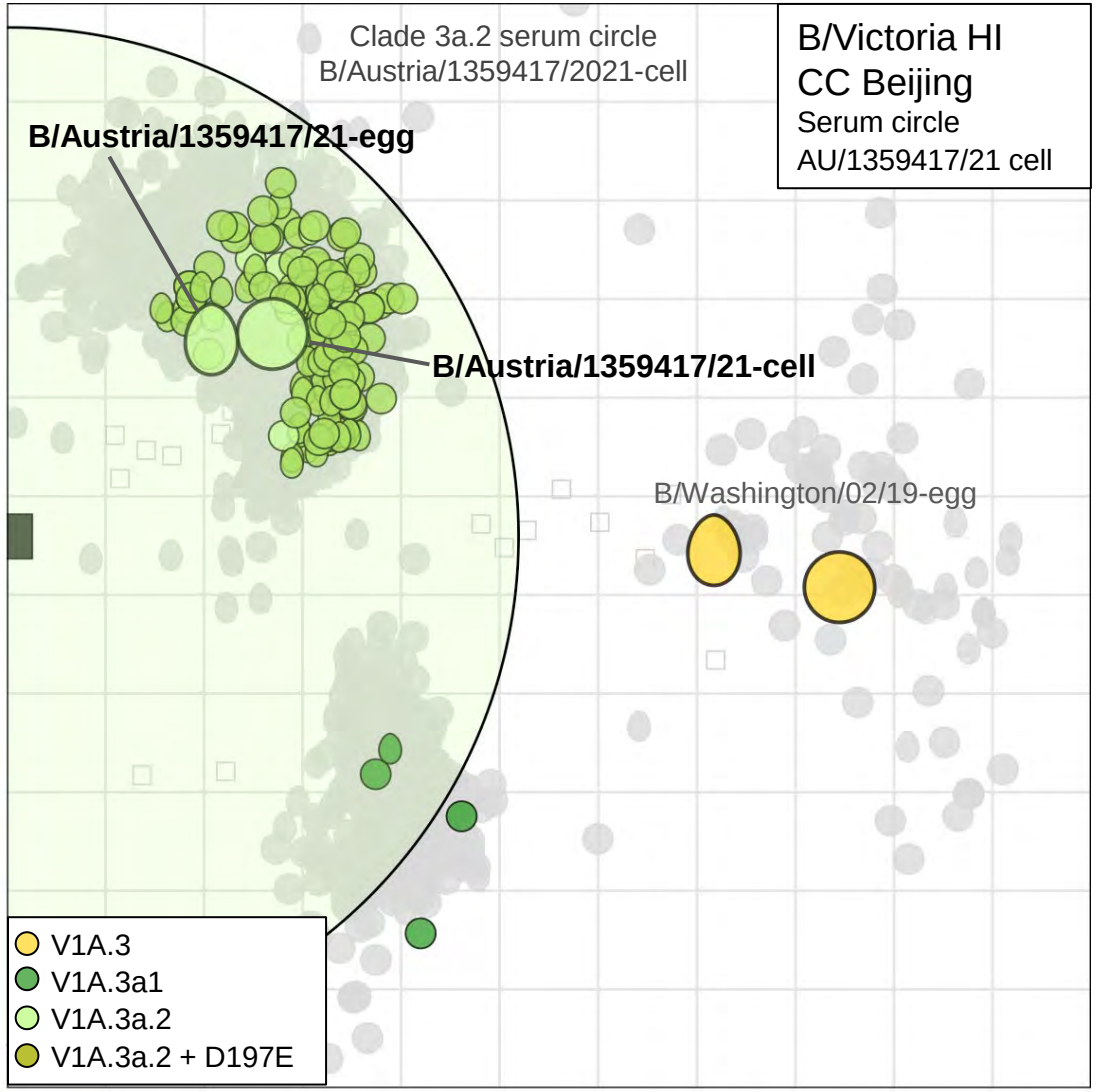




Source: University of Cambridge, UK

B/Victoria reactivity patterns of vaccine antisera





Serum circles (within 8-fold of homologous titers)

Source: University of Cambridge, UK

Human post-vaccination serum analysis of B/Victoria viruses

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

3a.2

3a.2 +D197E

WHO CCs
HI Assay

Human Sera Panels
Age/Vaccine/Country

				AUT/1359417-LIKE						+E128K +A154E +S208P	+E183H	+E183R	+E183K +D197E		+A154T +D197E	-	+T548A	-		+E128G +E183H
				AUT/1359417					SGP/ WUH4618	-	-	-	NOR/10979	CAT/2279261NS	-	-	-	TOKYO/23150	GB/2298	-
				CELL					CELL	CELL	CELL	CELL	CELL	CELL	CELL	CELL	CELL	CELL	CELL	CELL
				CDC	CBER	CNIC	MHRA	NIID	VIDRL	CDC	VIDRL	VIDRL	MHRA	CDC	CBER	CDC	CNIC	VIDRL	MHRA	NIID	CNIC	VIDRL
B/Austria/1359417/2021-like Cell	Pediatric (6-35M)	IIV4	USA	24	22					X				14	X	X						
	Pediatric (CDC: 3-8Y)	ccIIV4 (Flucelvax)	USA	171	130				184	√	√	√		√	√	√		√				√
		IIV4	China			7	9		49		28	28	X				X	√	X		X	28
			USA	144	166			408	139	√	√	√		√	√	√		√		√		√
	Pediatric (9-17Y)	ccIIV4 (Flucelvax)	USA	149	139				155	√	√	√		√	√	√		√				√
		IIV4	USA	251	171			597	234	√	√	√		√	√	√		√		√		√
	Adult (CDC: 18-49Y)	ccIIV4 (Flucelvax)	USA	160	197			320	155	√	√	√		√	√	√		√		√		√
		RIV4 (Flublok)	USA	219	139			640	204	√	√	√		√	√	√		√		√		√
		IIV4	China			16	22		52		√	√	X				X	√	X		X	√
			Japan	58	73			254		√				√	√	√				√		
			USA	109	102			279	98	√	√	√		√	√	√		√		√		√
			UK				202						√						√			
	Older Adult (50-64Y)	IIV4	USA	171	113				190	√	√	√		√	√	√		√				√
	Elderly (CDC: ≥65Y)	IIV4	China			31	73		96		√	√	√				19	√	√		X	√
			Japan	45	82			214		√				√	√	√				√		
		aIIV4	USA	121	149				115	√	√	√		√	√	√		√				√
										0 (0.0)	1 (8.3)	1 (8.3)	0 (0.0)	1 (8.3)	0 (0.0)	0 (0.0)	1 (33.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (8.3)

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.

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

Multiple Sources; compiled by WHO CC CDC, USA

B/Victoria lineage antiviral susceptibility

NA inhibitors

- 1,663 influenza B/Victoria lineage viruses collected since 1 September 2023 were analyzed by genetic and/or phenotypic analysis
  - Four showed evidence of reduced or highly reduced inhibition by NAIs.

Endonuclease inhibitors

- Of 951 B/Victoria lineage viruses collected and analyzed in this period, none showed evidence of reduced susceptibility to baloxavir.

Influenza B/Victoria lineage virus summary

- The data supported B/Austria/1359417/2021 (HA clade 3a.2) remaining as the vaccine antigens for the 2024-2025 northern hemisphere.
  - B/Victoria lineage viruses co-circulated with influenza A viruses in all geographic regions.
  - Phylogenetic analysis of the HA genes from viruses collected since September 1, 2023 showed clade 3a.2 viruses predominated.
  - Post-infection ferret antisera raised against the NH 2023-2024 B/Victoria lineage vaccine components (B/Austria/1359417/2021-like) from the 3a.2 well recognized the diversity observed in 3a.2 viruses.
  - Human sera showed post-vaccination geometric mean titres (GMTs) were not reduced significantly for the recently circulating B/Victoria lineage viruses from HA clade 3a.2 when compared to titers against cell culture-propagated B/Austria/1359417/2021-like vaccine viruses.

Support and Disclaimer

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