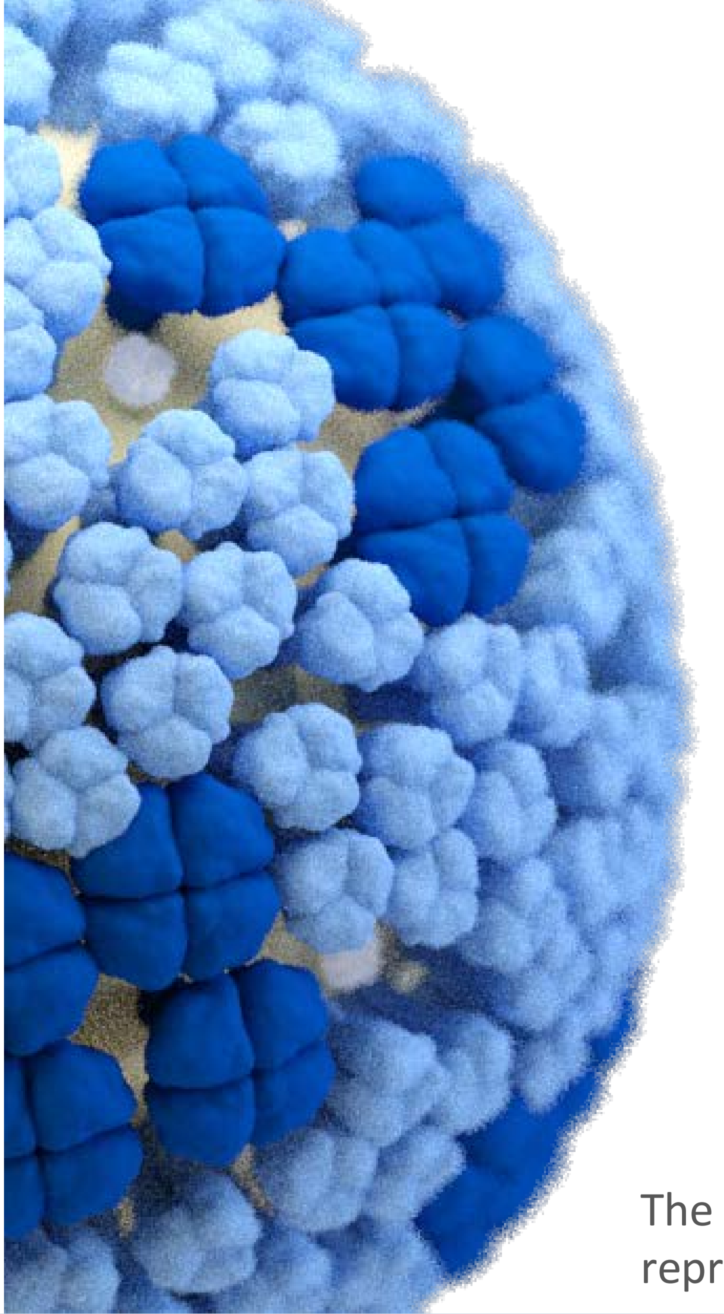
Vaccines and Related Biological Products Advisory Committee Meeting



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

Global Influenza Virus Surveillance and Characterization
September 30, 2021

David E. Wentworth, Ph.D.
Director, WHO Collaborating Center for Surveillance, Epidemiology and Control of Influenza
Chief, Virology Surveillance and Diagnosis Branch
Influenza Division, National Center for Immunization and Respiratory Diseases
Centers for Disease Control and Prevention
Atlanta, GA 30333

Outline

- Overview of the WHO-VCM and Recommendations for the Southern Hemisphere 2022
- Influenza virus activity
- A(H1N1)pdm09, describe major highlights
  - Recommendation is same as the NH 2021-2022 season and SH 2021 recommendation
- A(H3N2), provide details central to the recommendation
  - Update from previous SH 2021 recommendation
  - Similarities and differences from NH 2021-22 recommendation
- B/Victoria lineage viruses, provide details central to the recommendation
  - Update from previous SH 2021 recommendation
- B/Yamagata lineage, will not cover
  - Recommendation remains the same and no circulation of this lineage during this period

WHO Influenza Vaccine Consultation Meeting

- **Year around surveillance conducted by GISRS**
  - WHO Collaborating Centers (WHO CC), National Influenza Centers, WHO Essential Regulatory Laboratories (ERLs), WHO H5 Reference Laboratories
  - Supported by many countries and partners including GISAID
- **WHO consultation meeting held from Sep 13 – 24, 2021**
  - A virtual meeting – 17 hours' time difference among participants
  - Chaired by Dr Kanta Subbarao (pictured right)
  - 10 Advisers: Directors of WHOCCs and ERLs
    - 8 for seasonal influenza and represent their corresponding WHO CCs and ERLs
    - Pictured below (H. Hasegawa, D. Wentworth, J. McCauley, D. Wang, O. Engelhardt, Z. Ye, P. Bamford)

  - 42 observers from WHO CCs, WHO ERLs, academia, H5 Reference laboratories and veterinary sector OFFLU
  - Experts from WHO Regional Offices and Head Quarters

WHO Influenza Vaccine Recommendation

It is recommended that vaccines for use in the 2022 southern hemisphere influenza season contain the following:

Quadrivalent: Egg-based Vaccines

- an A/Victoria/2570/2019 (H1N1)pdm09-like virus*;
- an A/Darwin/9/2021 (H3N2)-like virus*;
- a B/Austria/1359417/2021 (B/Victoria lineage)-like virus*; and

→ **Trivalent**

- a B/Phuket/3073/2013 (B/Yamagata lineage)-like virus

Quadrivalent: Cell- or recombinant-based Vaccines

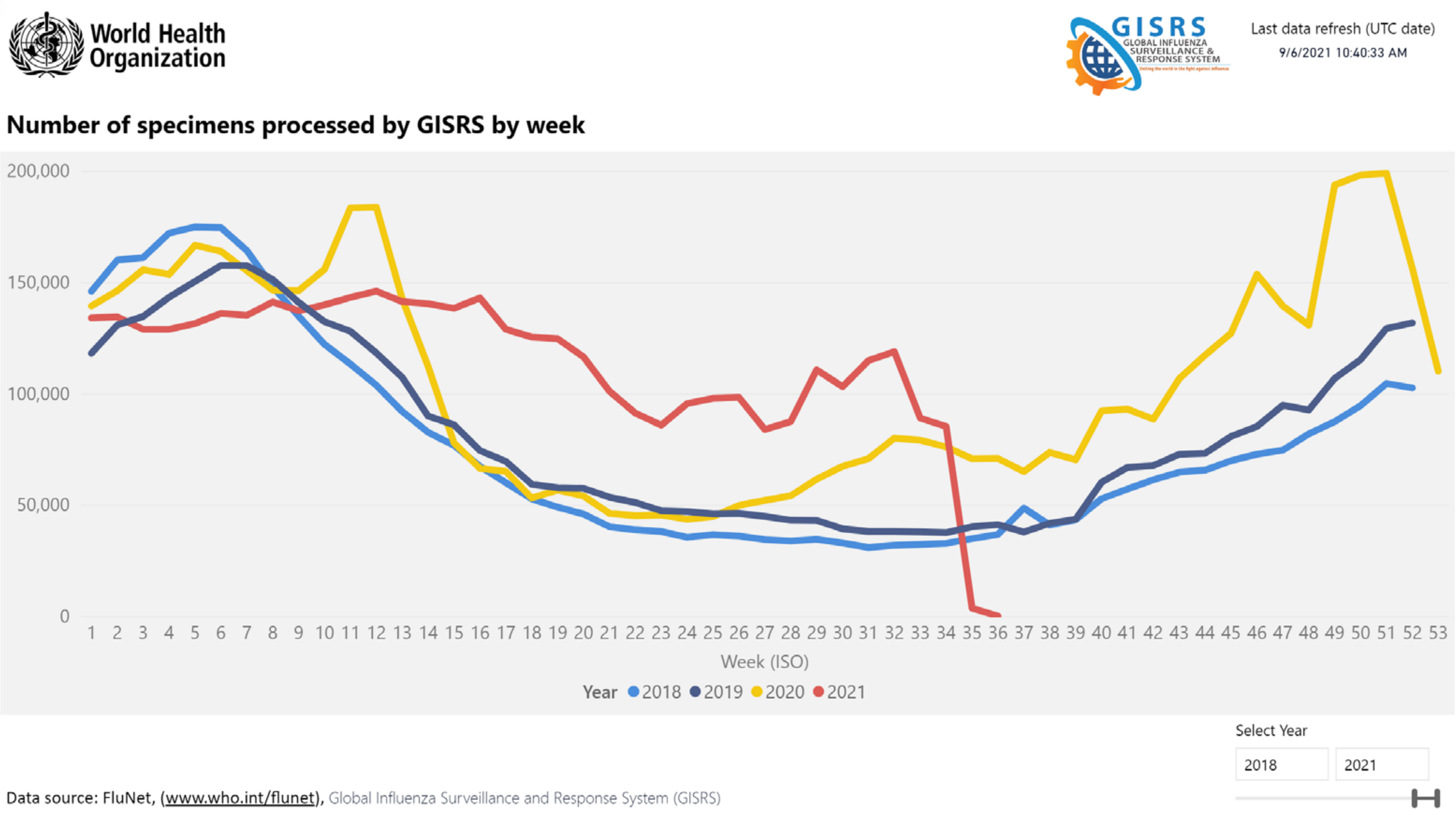
- an A/Wisconsin/588/2019 (H1N1)pdm09-like virus*;
- an A/Darwin/6/2021 (H3N2)-like virus*;
- a B/Austria/1359417/2021 (B/Victoria lineage)-like virus*; and

→ **Trivalent**

- a B/Phuket/3073/2013 (B/Yamagata lineage)-like virus.

* Different from that recommended for the southern hemisphere 2021 season

Number of Specimens Processed by GISRS

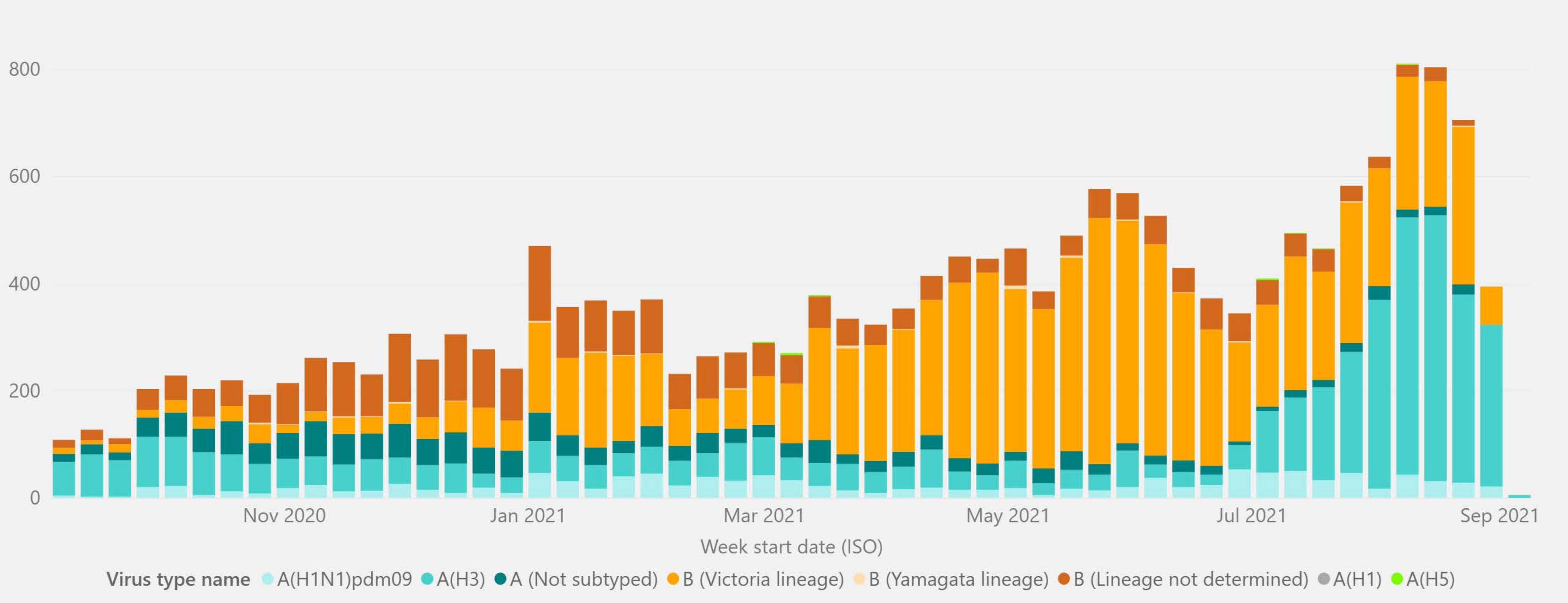


Last data refresh (UTC date)
9/6/2021 10:40:33 AM

Number of specimens processed by GISRS by week

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

Number of Specimens Positive for Influenza by Subtype

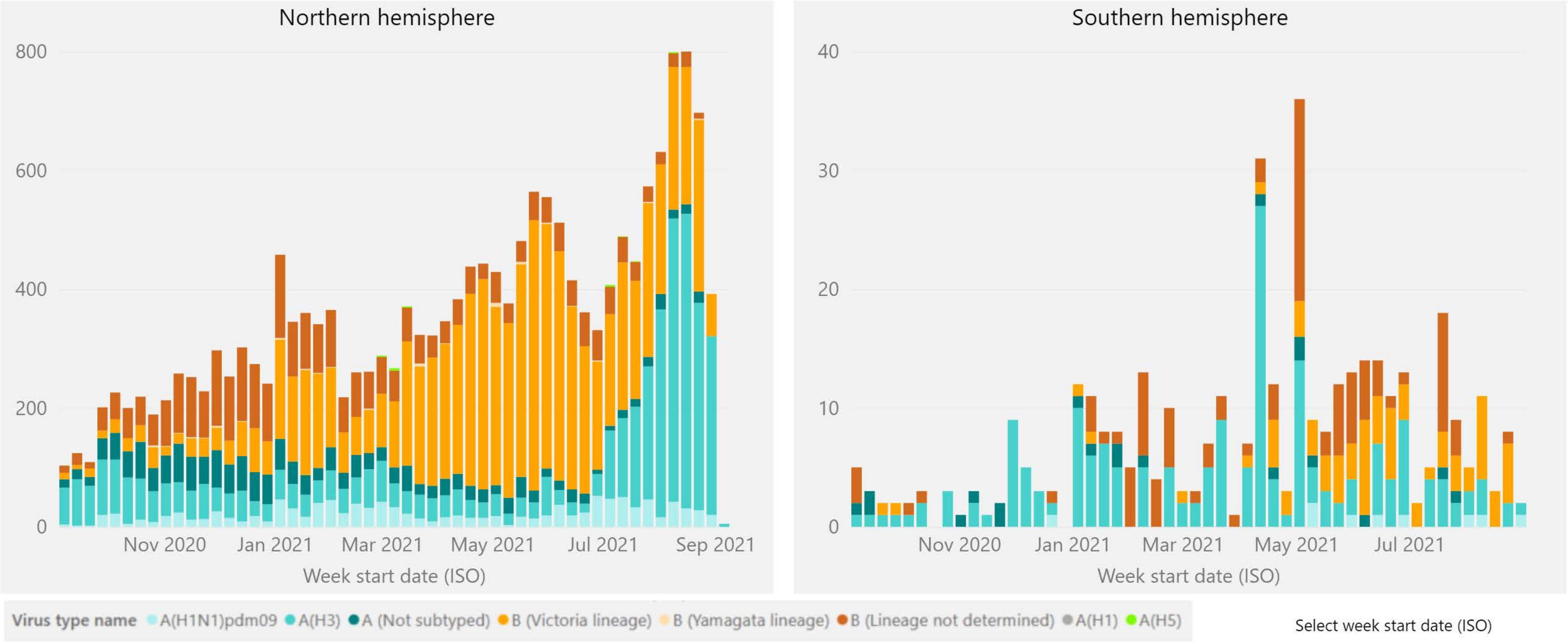


Select week start date (ISO)

9/1/2020 9/6/2021

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

Circulation of Influenza Viruses by Hemisphere



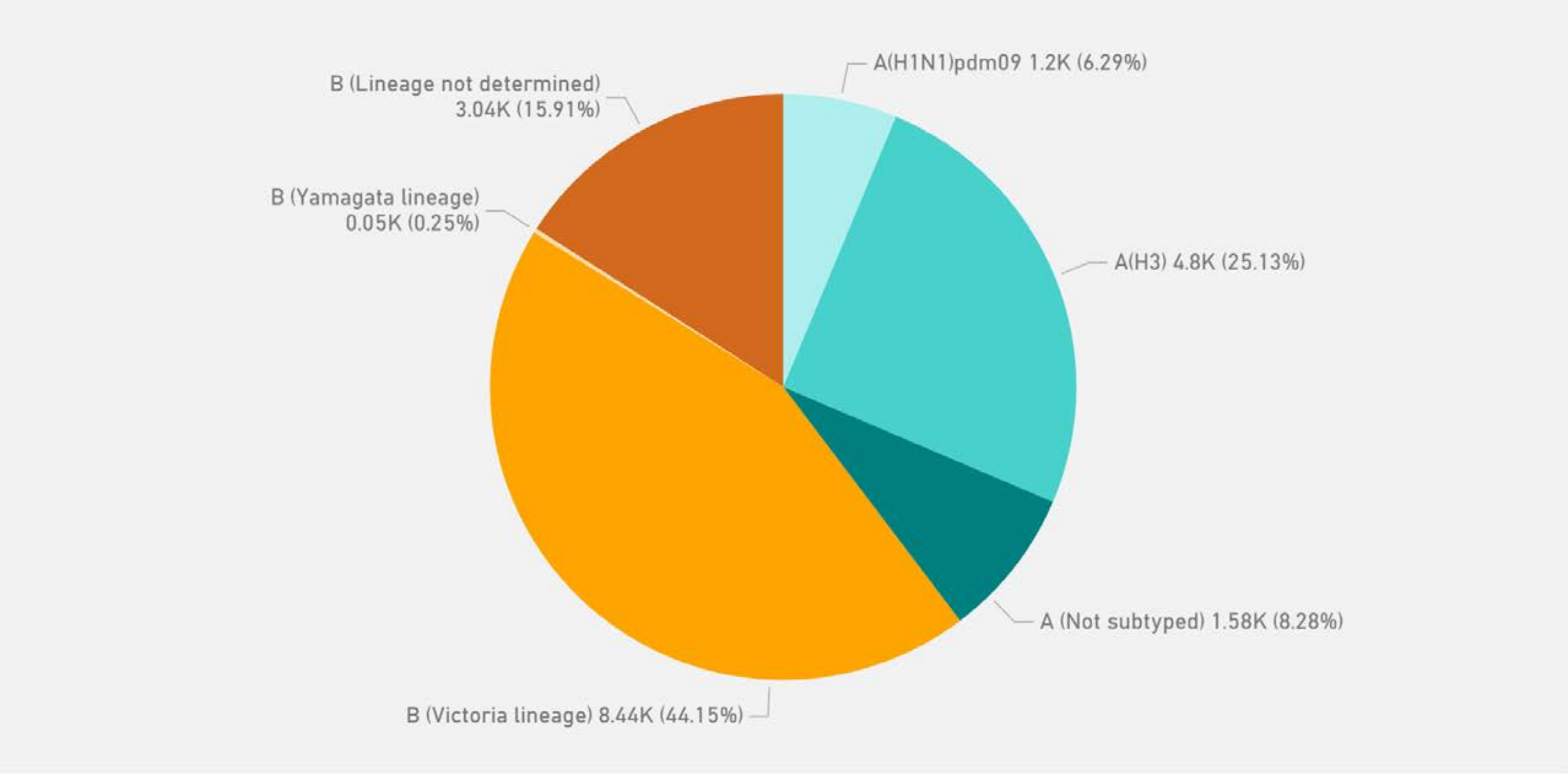
Select week start date (ISO)

9/1/2020 9/6/2021

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

Percentage of Influenza A and B Viruses (Feb – Aug 2021)

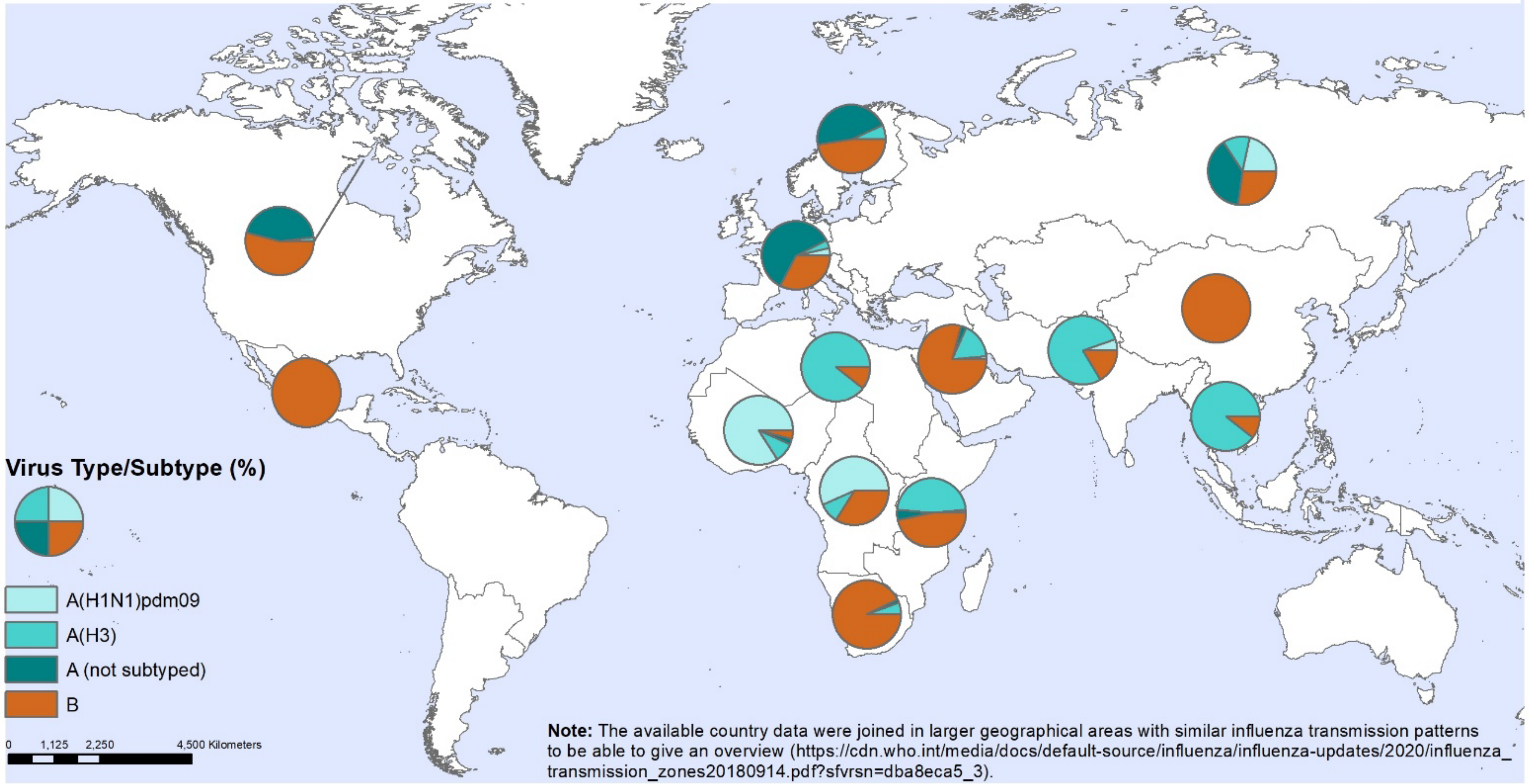
- Type A, 40%
  - H1 -> 20%
  - H3 -> 80%
- Type B, 60%
  - B/Victoria greater than 99%
  - B/Yamagata less than 0.5%



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

Influenza Activity – (Feb – Aug 2021)

Distribution of influenza virus type/subtype by influenza transmission zone, between February and September 2021

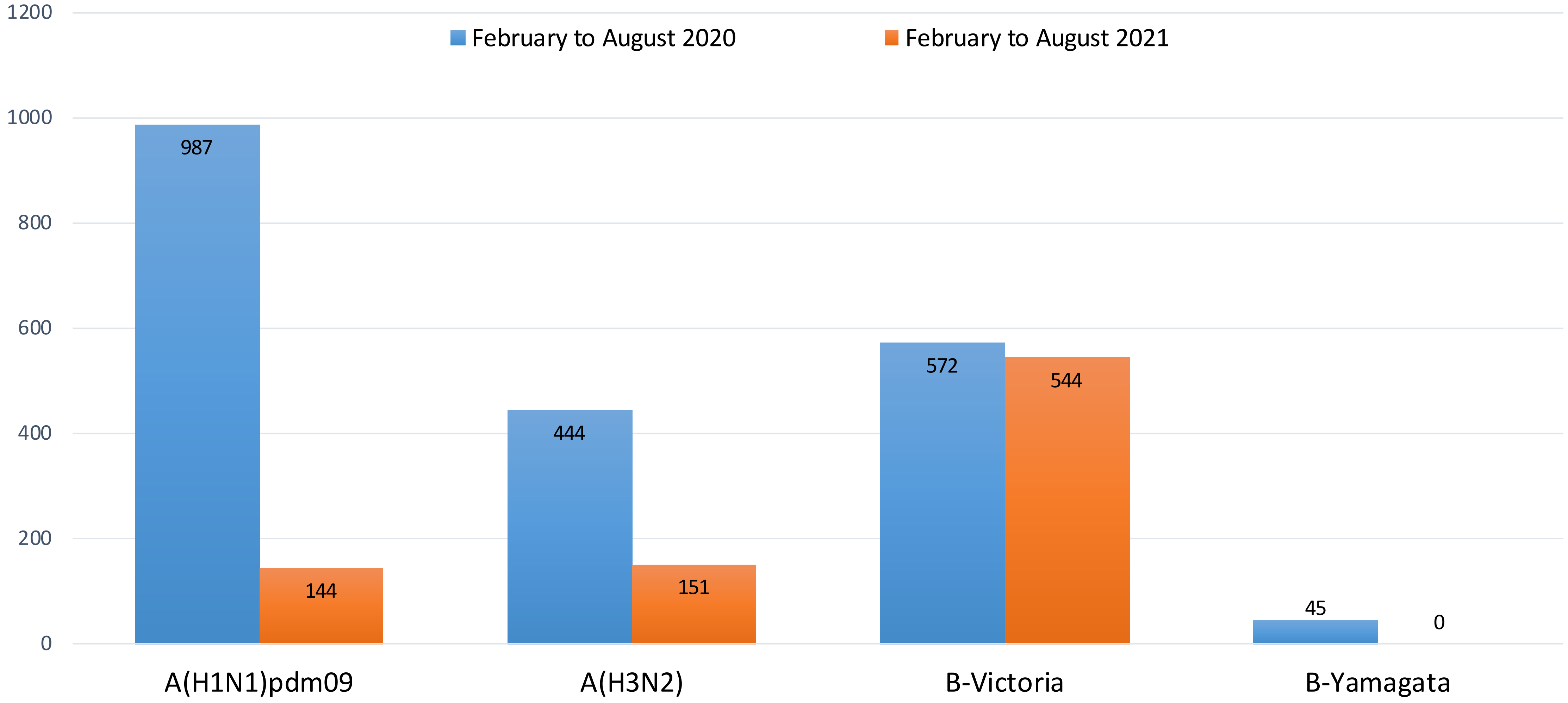


Note: The available country data were joined in larger geographical areas with similar influenza transmission patterns to be able to give an overview (https://cdn.who.int/media/docs/default-source/influenza/influenza-updates/2020/influenza_transmission_zones20180914.pdf?sfvrsn=dba8eca5_3).

Data Source:
WHO/GIP, FluNet (www.who.int/flunet)
as of 13 Sepetember 2021, 07:15 UTC

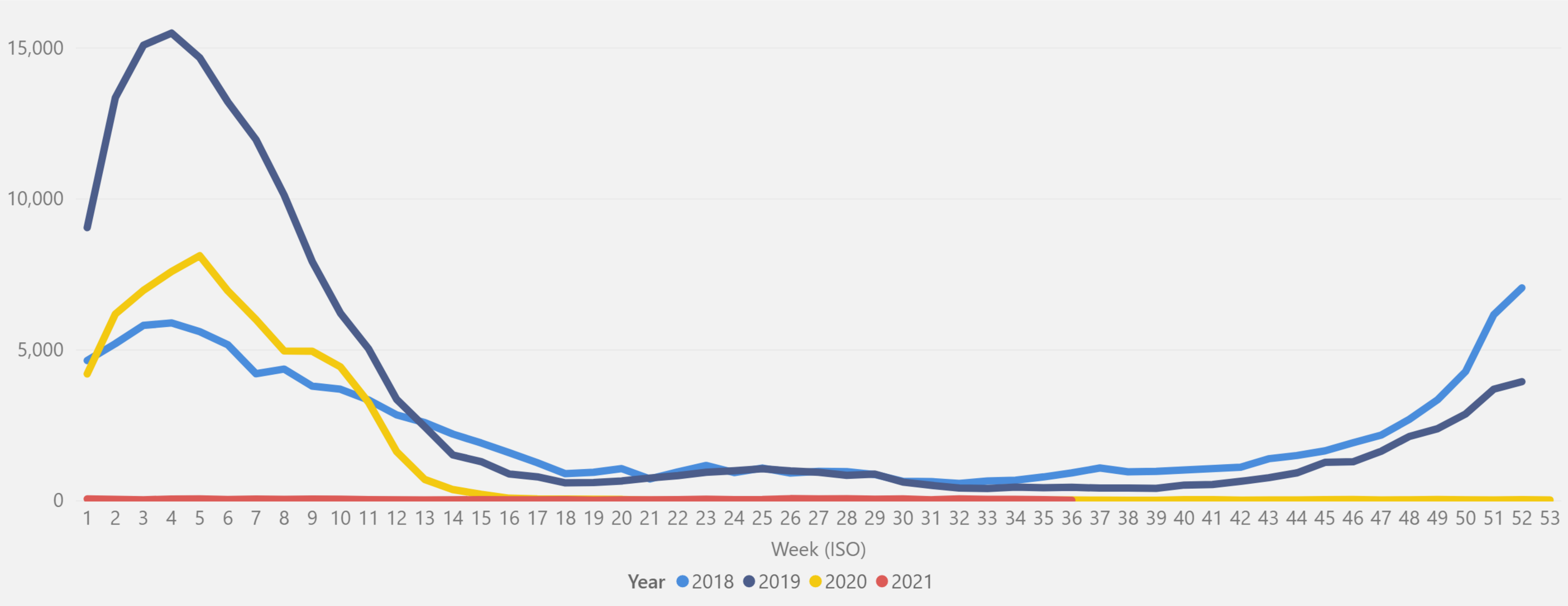
World Health Organization

Influenza Viruses Genetically Characterized By WHO-CCs



A(H1N1)pdm09 Viruses

Number of A(H1N1)pdm09 Viruses Detected by GISRS

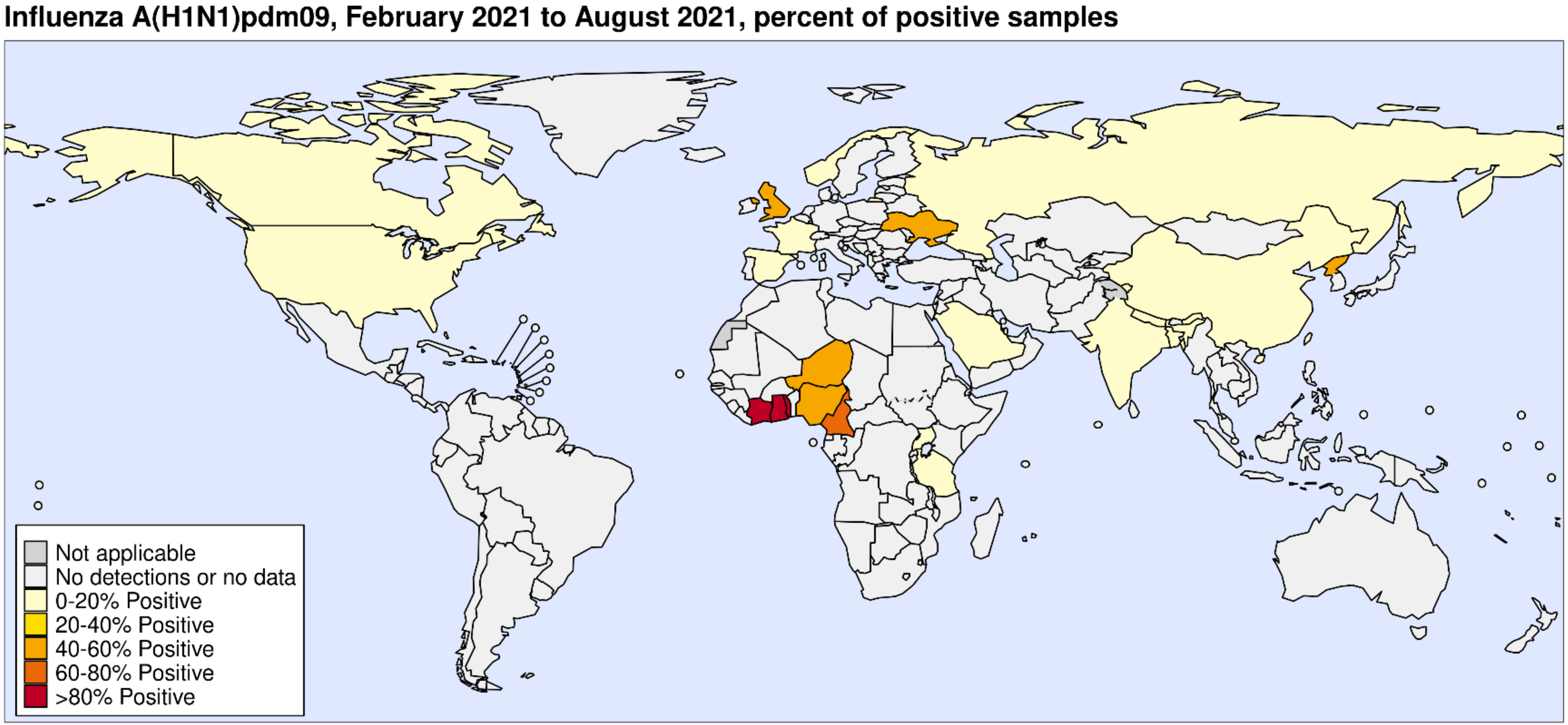


Select Year

2018 2021

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

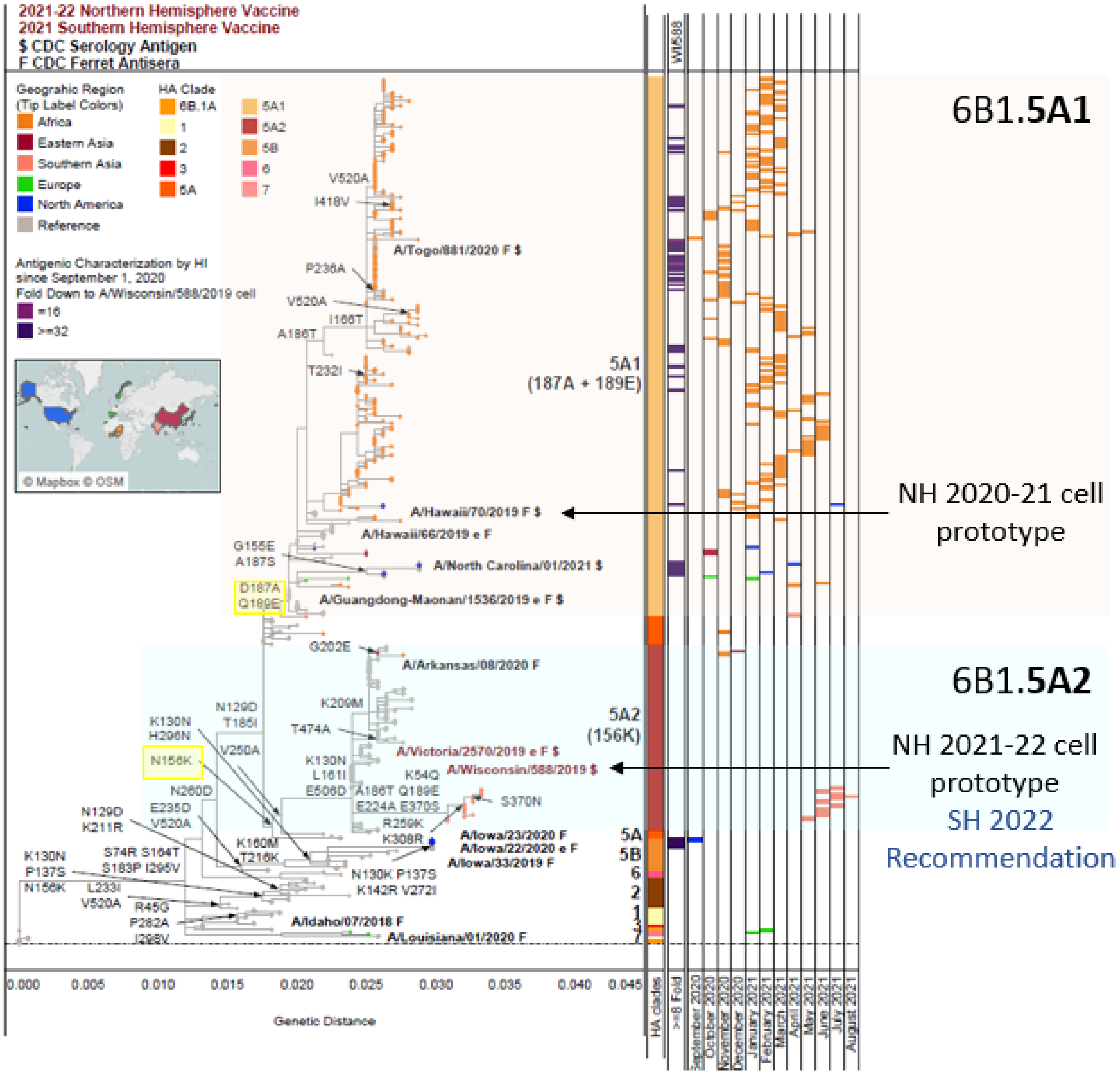
Influenza A(H1N1)pdm09 Activity



Colour intensity shows the proportion of influenza A(H1N1) among all influenza positives during this period per country
Data source: FluNet, (www.who.int/flunet), Global Influenza Surveillance and Response System (9 Sep 2021)

A(H1N1)pdm09 HA Phylogenetics

- Two major 6B.1.5A subclades
  - 5A1 (e.g., HI/70)
    - Often share D187A, Q189E
    - 2020-21 vaccine antigen
    - Recent viruses from West Africa
    - Few with G155E (NC/01)
  - 5A2 HA (e.g., WI/588)
    - Often share N156K
    - NH 2021-2022 vaccine virus
    - SH 2022 recommendation
    - Recent viruses from India



6B1.5A1

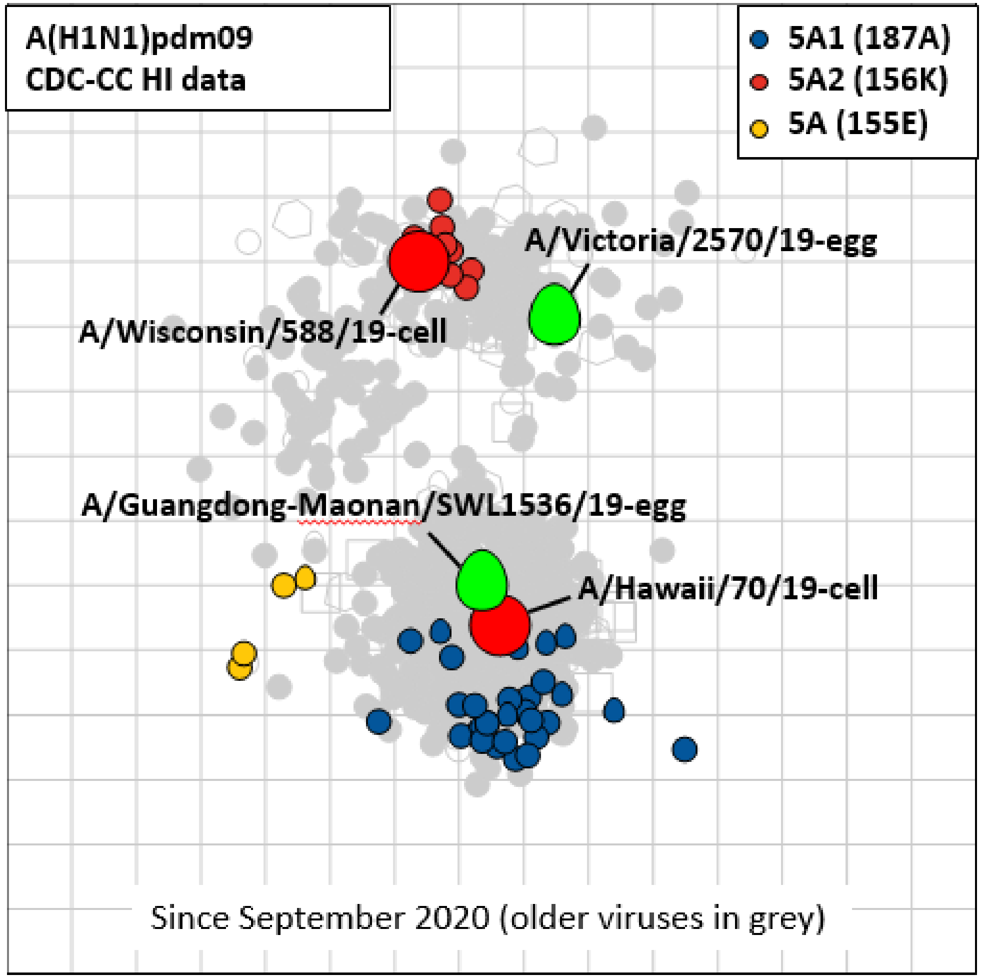
NH 2020-21 cell prototype

6B1.5A2

NH 2021-22 cell prototype

SH 2022 Recommendation

A(H1N1)pdm09 Antigenic Maps

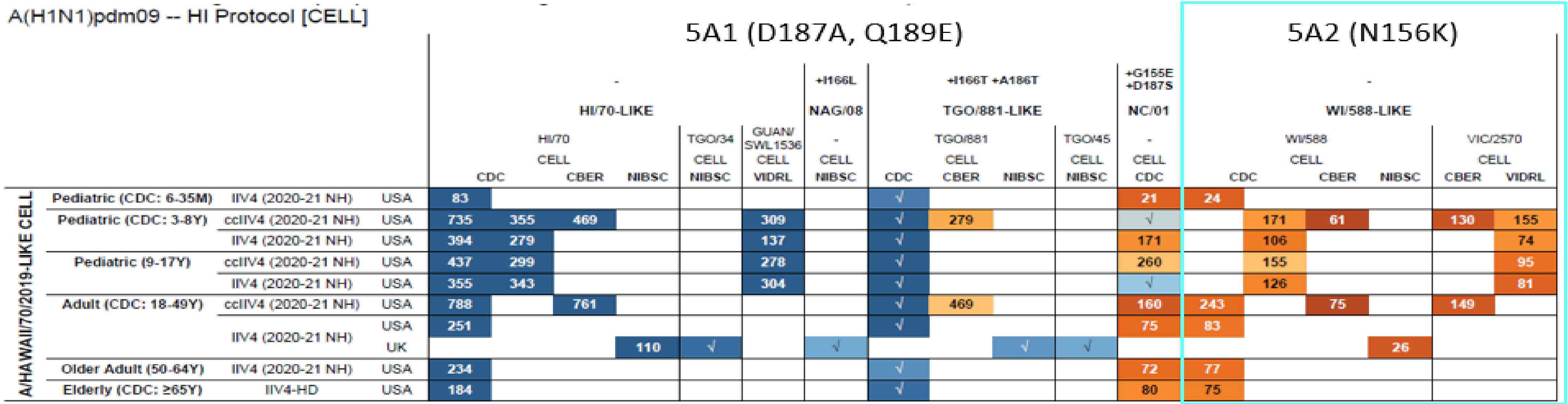


Since September 2020 (older viruses in grey)

University of Cambridge

- The viruses with HA from 6B.1A subclades **5A1** (187A) and **5A2** (156K) form two antigenically distinct groups
  - Virus of each subclade cluster with respective vaccine reference viruses
- Few 5A viruses with G155E are antigenically distinguishable

Human Post-vaccination Sera Analysis of A(H1N1)pdm09 Viruses
(NH 2020-21 Vaccine (5A1))



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

				5A1 (D187A, Q189E)												5A2 (N156K)					
				-						+I166L	+I166T +A186T				+G155E +D187S	-					
				HI/70-LIKE						NAG/08	TGO/881-LIKE				NC/01	WI/588-LIKE					
				HI/70				TGO/34	GUAN/ SWL1536	-	TGO/881			TGO/45	-	WI/588				VIC/2570	
				CELL				CELL	CELL	CELL	CELL			CELL	CELL	CELL				CELL	
				CDC		CBER	NIBSC	NIBSC	VIDRL	NIBSC	CDC	CBER	NIBSC	NIBSC	CDC	CDC		CBER	NIBSC	CBER	VIDRL
A/HAWAII/70/2019-LIKE CELL	Pediatric (CDC: 6-35M)	IIV4 (2020-21 NH)	USA	83							√				21	24					
	Pediatric (CDC: 3-8Y)	ccIIV4 (2020-21 NH)	USA	735	355	469			309		√	279			√		171	61		130	155
		IIV4 (2020-21 NH)	USA	394	279				137		√				171		106				74
	Pediatric (9-17Y)	ccIIV4 (2020-21 NH)	USA	437	299				278		√				260		155				95
		IIV4 (2020-21 NH)	USA	355	343				304		√				√		126				81
	Adult (CDC: 18-49Y)	ccIIV4 (2020-21 NH)	USA	788		761					√	469			160	243		75		149	
		IIV4 (2020-21 NH)	USA	251							√				75	83					
			UK				110	√		√			√	√					26		
	Older Adult (50-64Y)	IIV4 (2020-21 NH)	USA	234							√				72	77					
	Elderly (CDC: ≥65Y)	IIV4-HD	USA	184							√				80	75					

Geometric Mean Titer (GMT) ratios between reference and test antigens are calculated with 90% (CI) confidence intervals for each cohort and panel location. Unadjusted model results are shown. If the CI lower bound is greater than 50%, it is statistically non-inferior (95% confidence level), otherwise it is *possibly* inferior. Heat map cells are colored using the GMT ratio lower bound. Blue indicates statistical non-inferiority and orange denotes *possible* inferiority. Numbers shown are post-vaccination GMTs for the unadjusted model. They are shown for common *reference antigens* and possibly inferior test antigens (consolidated by passage-type). Marks √ or X denote statistically significant non-inferiority when the reference virus GMT is ≥40 or <40, respectively. Number and percent (in parentheses) of *possibly* inferior responses are summarized below the heat map.

Included Strains: A/DARWIN/27/2021 (DAR/27); A/GUANGDONG-MAONAN/SWL1536/2019 (GUAN/SWL1536); A/HAWAII/70/2019 (HI/70); A/INDIA/PUN-NIV319825/2021 (INDIA/PUN-NIV319825); A/NAGASAKI/08/2020 (NAG/08); A/NORTH CAROLINA/01/2021 (NC/01); A/TOGO/34/2021 (TGO/34); A/TOGO/45/2021 (TGO/45); A/TOGO/881/2020 (TGO/881); A/VICTORIA/2570/2019 (VIC/2570); A/WISCONSIN/588/2019 (WI/588).

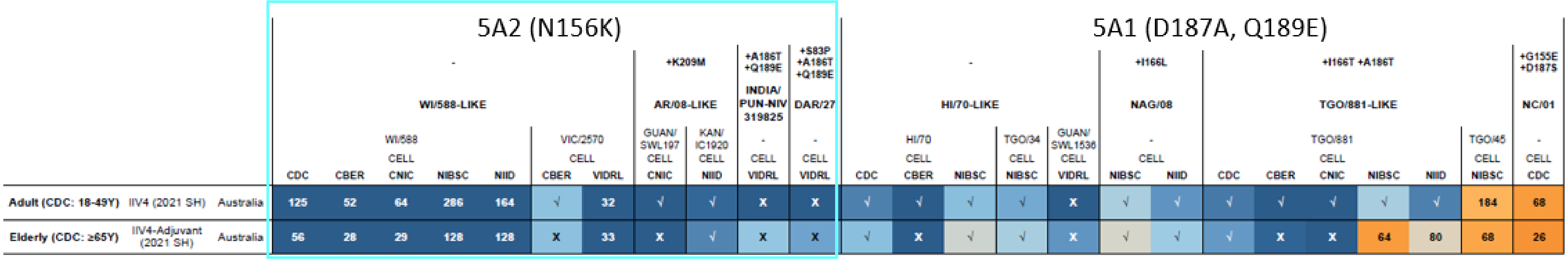
Statistically non-inferior = √
Statistically non-inferior but reference virus GMT < 40 = X

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

- Post vaccination sera from NH 2020-21 (5A1), inhibits 5A1 viruses
  - Except G155E viruses (e.g., NC/01), which were infrequently detected
  - GMTs to HA subclade 5A2 (N156K) viruses were low in all serum panels

Human Post-vaccination Sera Analysis of A(H1N1)pdm09 Viruses
(SH 2021 Vaccine (5A2))

WHO Collaborating Center (CC): Human Serological Panels SH2021 serum panels
A(H1N1)pdm09 -- HI Protocol [CELL]



			5A2 (N156K)										
			-							+K209M		+A186T +Q189E	+S83P +A186T +Q189E
			WI/588-LIKE							AR/08-LIKE		INDIA/ PUN-NIV 319825	DAR/27
			WI/588					VIC/2570		GUAN/ SWL197	KAN/ IC1920	-	-
			CELL					CELL		CELL	CELL	CELL	CELL
			CDC	CBER	CNIC	NIBSC	NIID	CBER	VIDRL	CNIC	NIID	VIDRL	VIDRL
Adult (CDC: 18-49Y)	IIV4 (2021 SH)	Australia	125	52	64	286	164	√	32	√	√	X	X
Elderly (CDC: ≥65Y)	IIV4-Adjuvant (2021 SH)	Australia	56	28	29	128	128	X	33	X	√	X	X

			5A1 (D187A, Q189E)													
			-					+I166L		+I166T +A186T						+G155E +D187S
			HI/70-LIKE					NAG/08		TGO/881-LIKE						NC/01
			HI/70			TGO/34	GUAN/ SWL1536	-		TGO/881					TGO/45	-
			CELL			CELL	CELL	CELL		CELL					CELL	CELL
			CDC	CBER	NIBSC	NIBSC	VIDRL	NIBSC	NIID	CDC	CBER	CNIC	NIBSC	NIID	NIBSC	CDC
Adult (CDC: 18-49Y)	IIV4 (2021 SH)	Australia	√	√	√	√	X	√	√	√	√	√	√	√	184	68
Elderly (CDC: ≥65Y)	IIV4-Adjuvant (2021 SH)	Australia	√	X	√	√	X	√	√	√	X	X	64	80	68	26

Geometric Mean Titer (GMT) ratios between reference and test antigens are calculated with 90% (CI) confidence intervals for each cohort and panel location. Unadjusted model results are shown. If the CI lower bound is greater than 50%, it is statistically non-inferior (95% confidence level), otherwise it is *possibly* inferior. Heat map cells are colored using the GMT ratio lower bound. Blue indicates statistical non-inferiority and orange denotes *possible* inferiority. Numbers shown are post-vaccination GMTs for the unadjusted model. They are shown for common *reference antigens* and possibly inferior test antigens (consolidated by passage-type). Marks √ or X denote statistically significant non-inferiority when the reference virus GMT is ≥40 or <40, respectively. Number and percent (in parentheses) of *possibly* inferior responses are summarized below the heat map.

Included Strains: A/DARWIN/27/2021 (DAR/27); A/GUANGDONG-MAONAN/SWL1536/2019 (GUAN/SWL1536); A/GUANGDONG-MAONAN/SWL197/2020 (GUAN/SWL197); A/HAWAII/70/2019 (HI/70); A/INDIA/PUN-NIV319825/2021 (INDIA/PUN-NIV319825); A/KANAGAWA/IC1920/2020 (KAN/IC1920); A/NAGASAKI/08/2020 (NAG/08); A/NORTH CAROLINA/01/2021 (NC/01); A/TOGO/34/2021 (TGO/34); A/TOGO/45/2021 (TGO/45); A/TOGO/881/2020 (TGO/881); A/VICTORIA/2570/2019 (VIC/2570); A/WISCONSIN/588/2019 (WI/588).

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

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

- Post vaccination sera from SH 2021 (5A2), inhibits 5A2 and most 5A1 viruses
  - Exception G155E virus (e.g., NC/01), which were infrequently detected

A(H1N1)pdm09 Summary (I)

- Low circulation but, A(H1N1)pdm09 viruses were detected in West Africa and India, and sporadically in a few other regions
- The great majority of HA gene sequences belonged to clade 6B.1A5A, subclades;
  - **5A1** (HA1 **D187A**, Q189E) HA proteins predominant in West Africa with additional HA1 substitutions I166T and A186T;
  - **5A2** (HA1 K130N, **N156K**, L161I, V250A and HA2 E179D) HA proteins were seen in recent viruses from India with additional HA1 substitutions K54Q, A186T, Q189E and E224A in HA1 and N43S in HA2;
- Characterization with ferret antisera showed **5A1 and 5A2 viruses were antigenically distinct**
  - Antisera 5A1 viruses (e.g., A/Hawaii/70/2019) well recognized most recent 5A1 viruses, but not 5A2 viruses
  - Antisera to 5A2 viruses (e.g. A/Wisconsin/588/2019) well recognized recently circulating 5A2 viruses, but not HA subclade 5A1 viruses

A(H1N1)pdm09 Summary (II)

Post vaccination sera collected from humans vaccinated with:

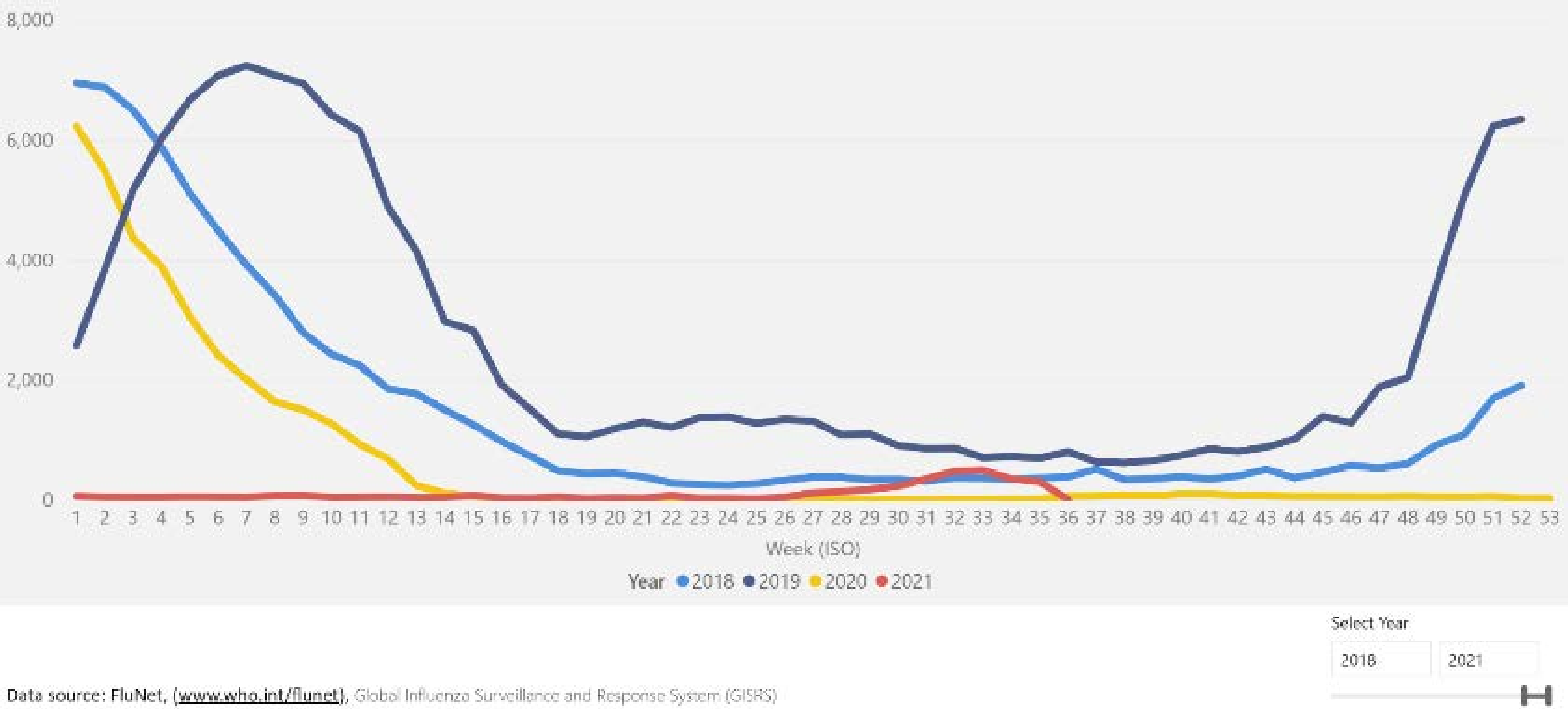
- NH 2020-21 vaccines (5A1 antigens) inhibited reference viruses representing most 5A1 viruses, but not 5A2 viruses
- SH 2021 vaccines (5A2 antigens) had sera that inhibited 5A2 viruses and well recognized viruses representing most 5A1 viruses

Antiviral susceptibility

- All A(H1N1)pdm09 viruses analyzed showed normal susceptibility to the neuraminidase inhibitors.
- Genetic analysis revealed a single virus with reduced susceptibility to baloxavir.

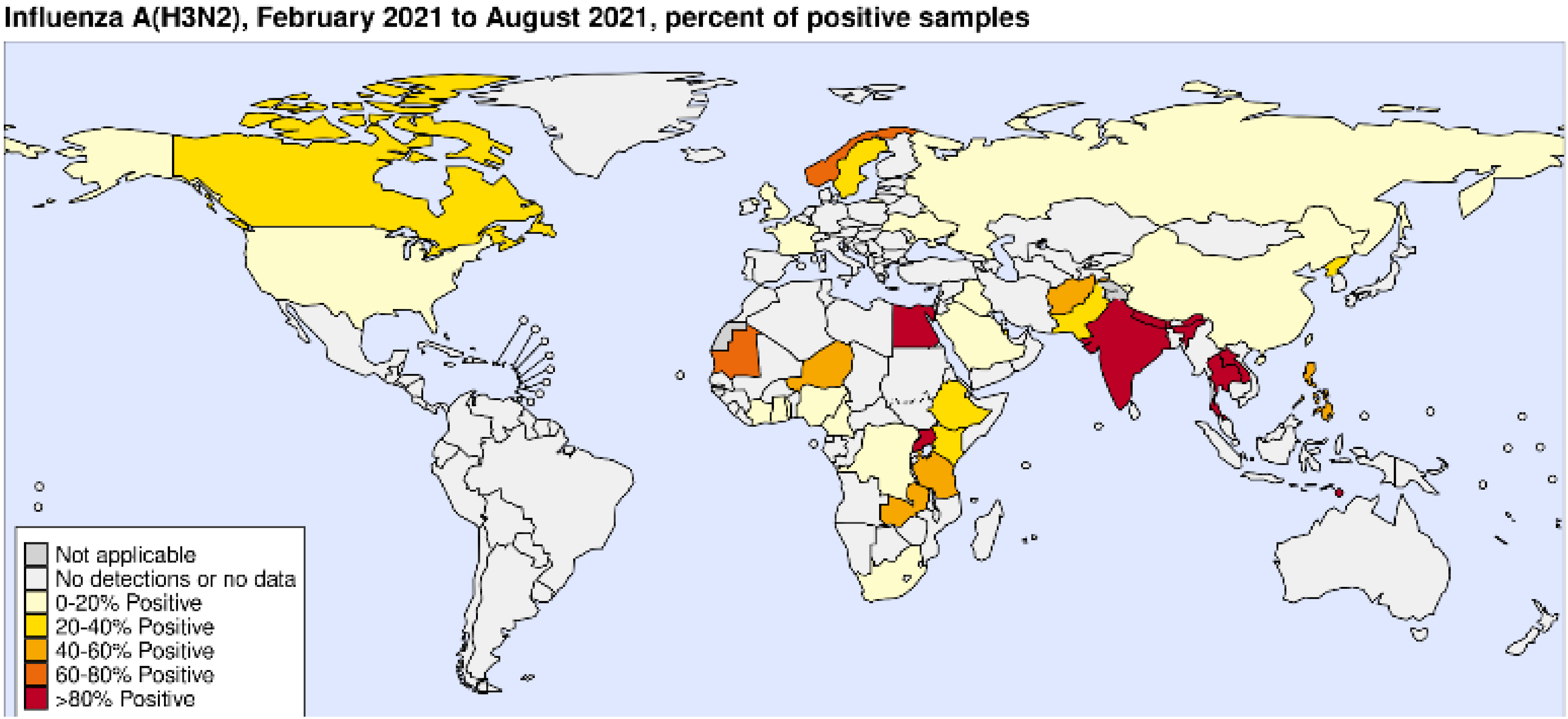
Influenza A(H3N2) Viruses

Number of A(H3N2) Viruses Detected by GISRS (2018-2021)



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

Influenza A(H3N2) Activity

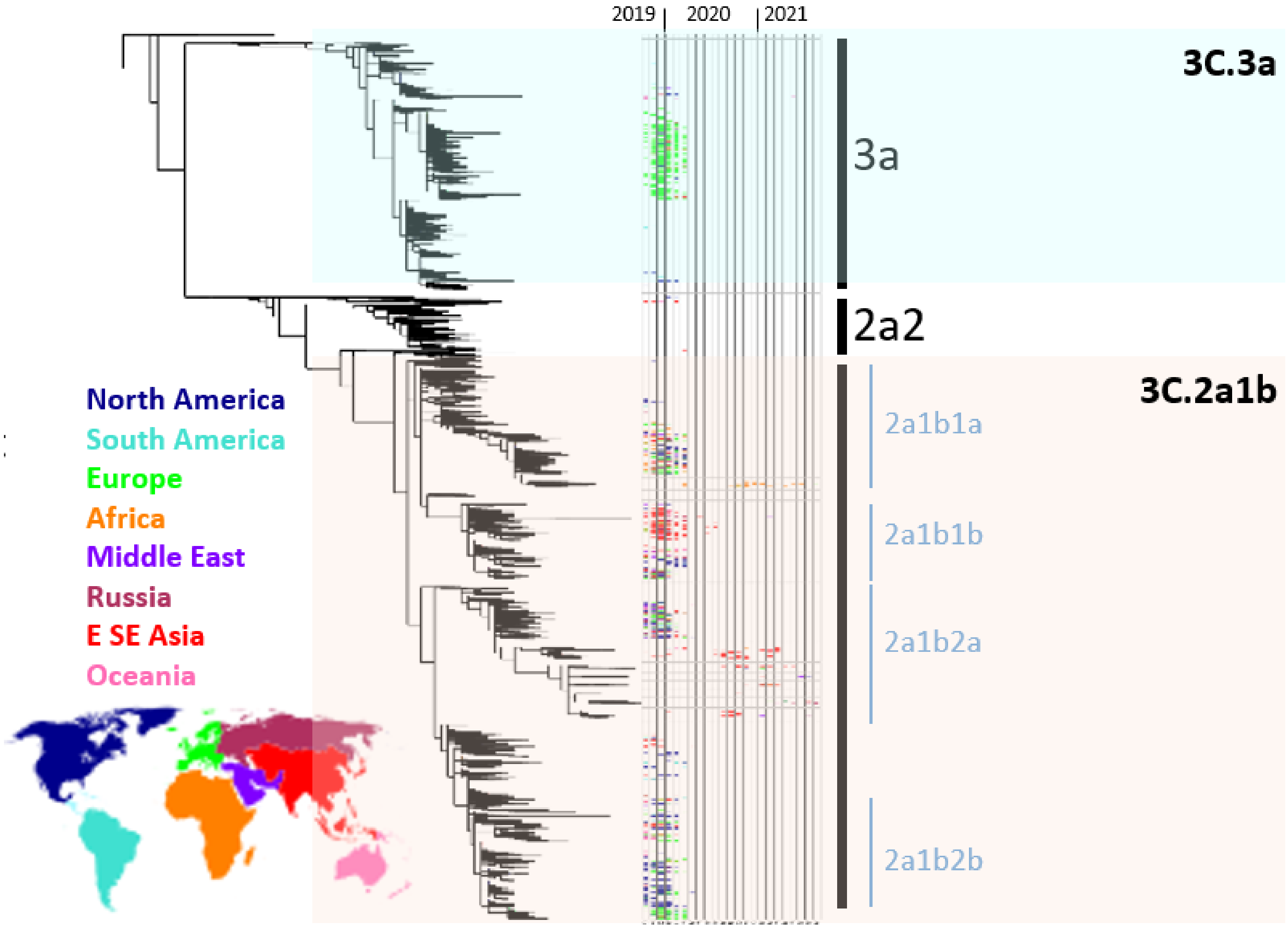


Colour intensity shows the proportion of influenza A(H3N2) among all influenza positives during this period per country

Data source: FluNet, (www.who.int/flunet), Global Influenza Surveillance and Response System (9 Sep 2021)

Phylogenetics of A(H3N2) HA Gene

- Many clades co-circulate
- Major clades
    - 3C.3a
    - 3C.2a
        - Many 2a1b subclades
- 2a1b1a subclades 1a and 2a represent most recent circulating viruses

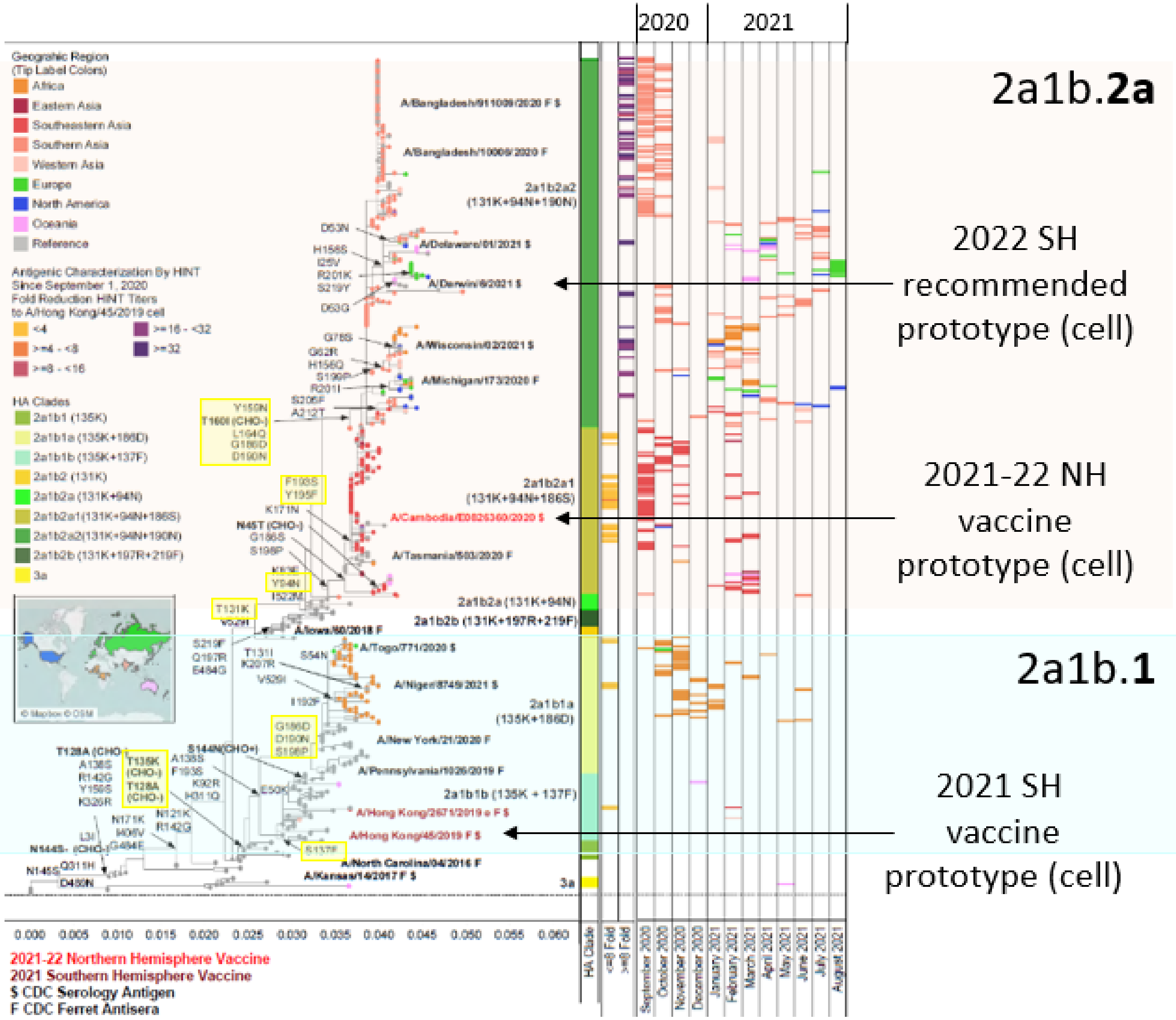


Source: University of Cambridge

Integrated Analysis of A(H3N2) HA Gene

Nearly all viruses have clade 3C.2a1b HA gene which continues to diversify

- 2a1b.**1b** (e.g., A/Hong Kong/45/2019)
  - Often share T135K, S137F
- 2a1b.**1a** (e.g., A/New York/21/2020)
  - Typically share T135K, G186D, S198P
    - Further diversified
      - I192F (e.g., A/Togo/771/2020)
      - T131I & I192F (e.g., A/Niger/8749/2021)
- 2a1b.**2a** (most of the recent viruses)
  - Usually share T131K, Y94N, F193S, Y195F
  - Evolved into two subclades
    - **2a1** (e.g., A/Cambodia/E0826360/2020)
      - Often have K171N, G186S, S198P
    - **2a2** (e.g., A/Bangladesh/10006/2020)
      - Often have Y159N, T160I, L164Q, G186D, D190N



2022 SH recommended prototype (cell)

2021-22 NH vaccine prototype (cell)

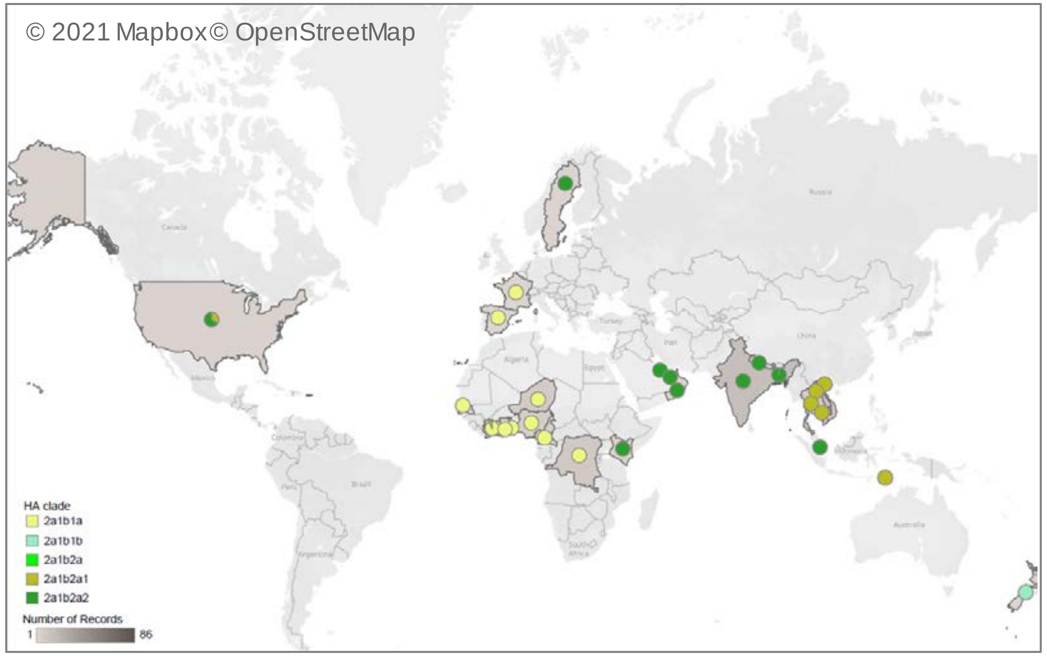
2021 SH vaccine prototype (cell)

2021-22 Northern Hemisphere Vaccine
2021 Southern Hemisphere Vaccine
$ CDC Serology Antigen
F CDC Ferret Antisera

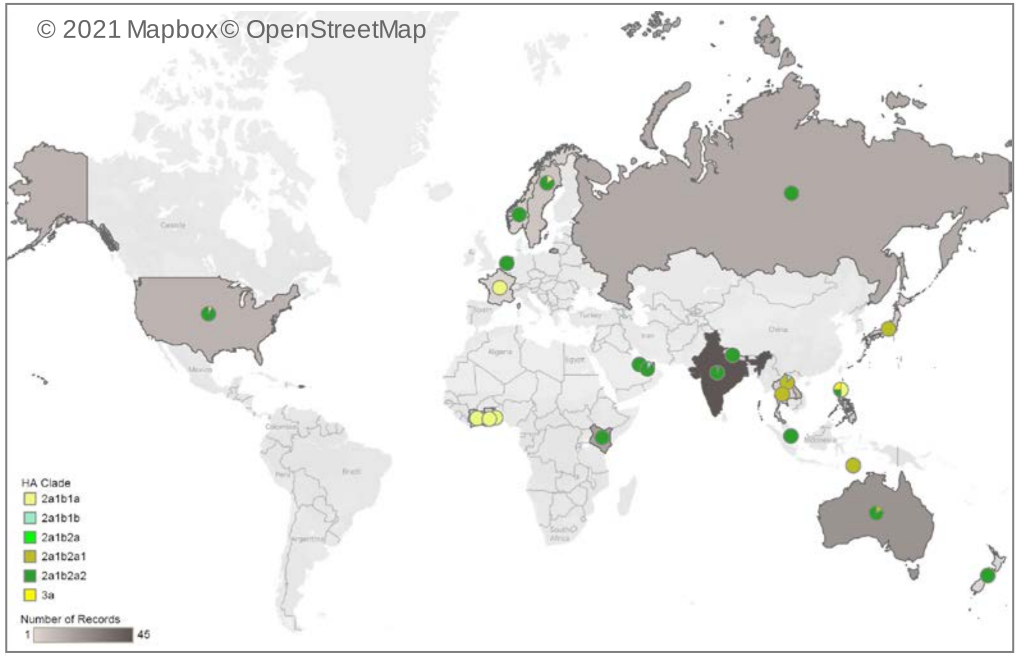
Source: U.S. CDC: Based on HA Sequence Availability on 09/13/2021

Global Circulation of A(H3N2) Viruses

September 2020 – January 2021



February 2021 – August 2021

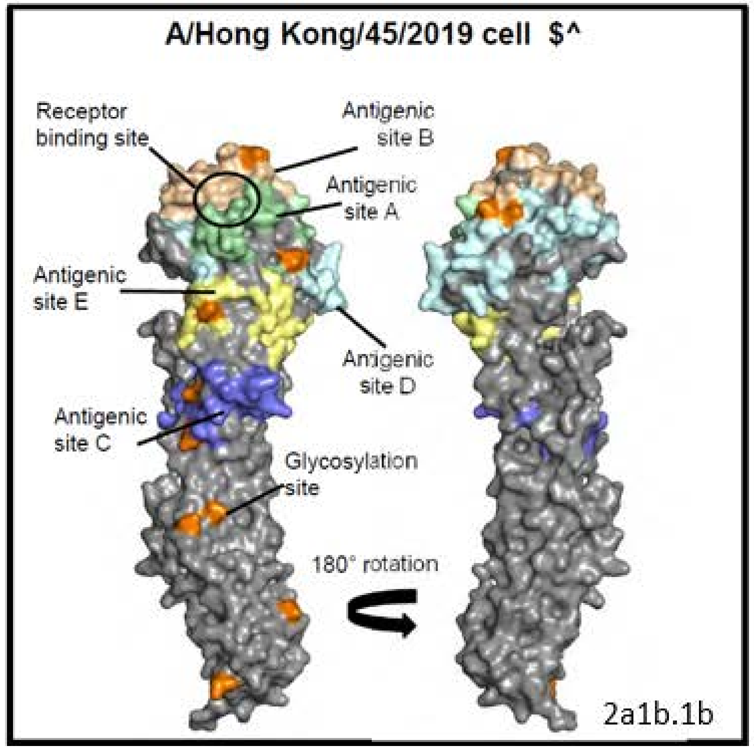


Source: U.S. CDC: Based on HA Sequence Availability on 09/13/2021

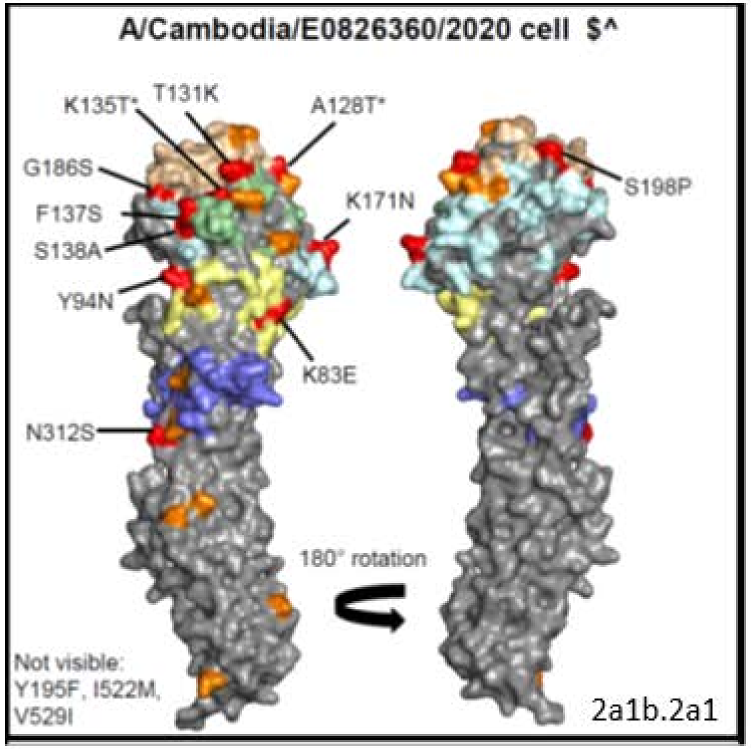
- ❑ Phylogeography of the HA gene shows transition of 2a1b subclades
  - Global distribution of 1a and 1b decreased (yellow/aqua)
  - Global distribution of 2a2 (forest green) increased and 2a1 continued to circulate

Location of Substitutions on H3 HA Monomer

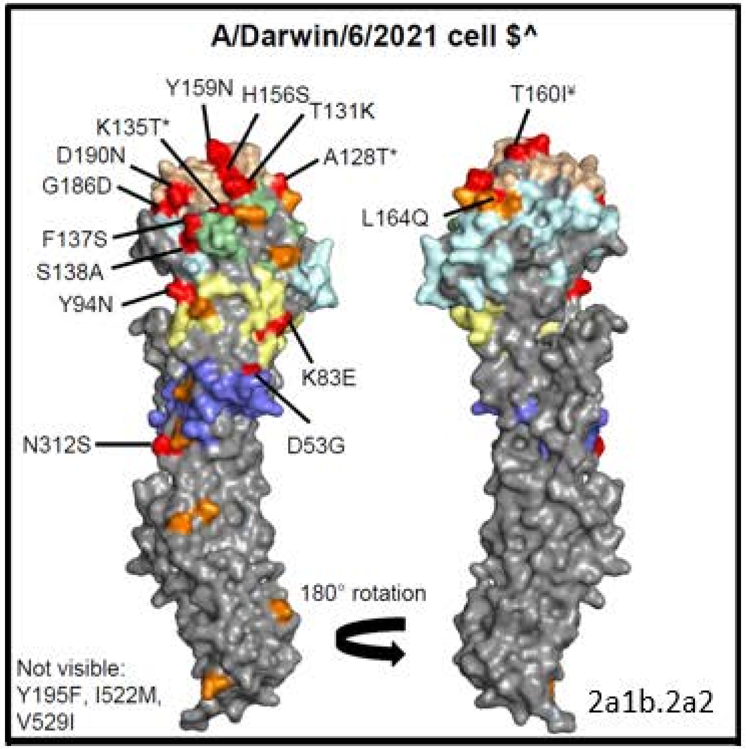
SH 2021 Vaccine Prototype



NH 2021-22 Vaccine Prototype



SH 2022 Recommendation



Source: U.S. CDC

- HA Clade 2a1b.**2A** viruses have mutations in many epitopes compared to SH 2021 vaccine prototype (2a1b.**1b**)
  - **2a1** and **2a2** share many changes (e.g., Y94N, S138A, F137S, G186S/D, K135T, T131K, A128T)
  - Compared to **2a1**, emerging **2a2** have a few additional substitutions (e.g., Y159N, D190N)

Neutralization of A(H3N2) Viruses By Antisera To Antigens Recommended For The 2021 Southern Hemisphere

A/Hong Kong/45/2019-like (cell)*

WHO CC	Like (2-4 fold)	Low (≥ 8 fold)
CDC	0 (0%)	20 (100%)
FCI	6 (21%)	22 (79%)
NIID	0 (0%)	14 (100%)
VIDRL	1 (4%)	26 (96%)
TOTAL	7 (8%)	82 (92%)

A/Hong Kong/2671/2019-like (egg)*

WHO CC	Like (2-4 fold)	Low (≥ 8 fold)
CDC	0 (0%)	20 (100%)
NIID	0 (0%)	14 (100%)
VIDRL	0 (0%)	12 (100%)
TOTAL	0 (0%)	46 (100%)

*Reference viruses are in HA clade 3C.2a1b.**1b**

Showing data from viruses isolated from swabs collected from February through August 2021

Neutralization of A(H3N2) Viruses By Antisera To Antigens Recommended for Northern Hemisphere 2021-2022

A/Cambodia/E0826360/2020-like (cell)*

WHO CC	Like (2-4 fold)	Low (≥ 8 fold)
CDC	8 (40%)	12 (60%)
FCI	14 (50%)	14 (50%)
NIID	13 (80%)	1 (20%)
VIDRL	22 (81%)	5 (19%)
TOTAL	57 (64%)	32 (36%)

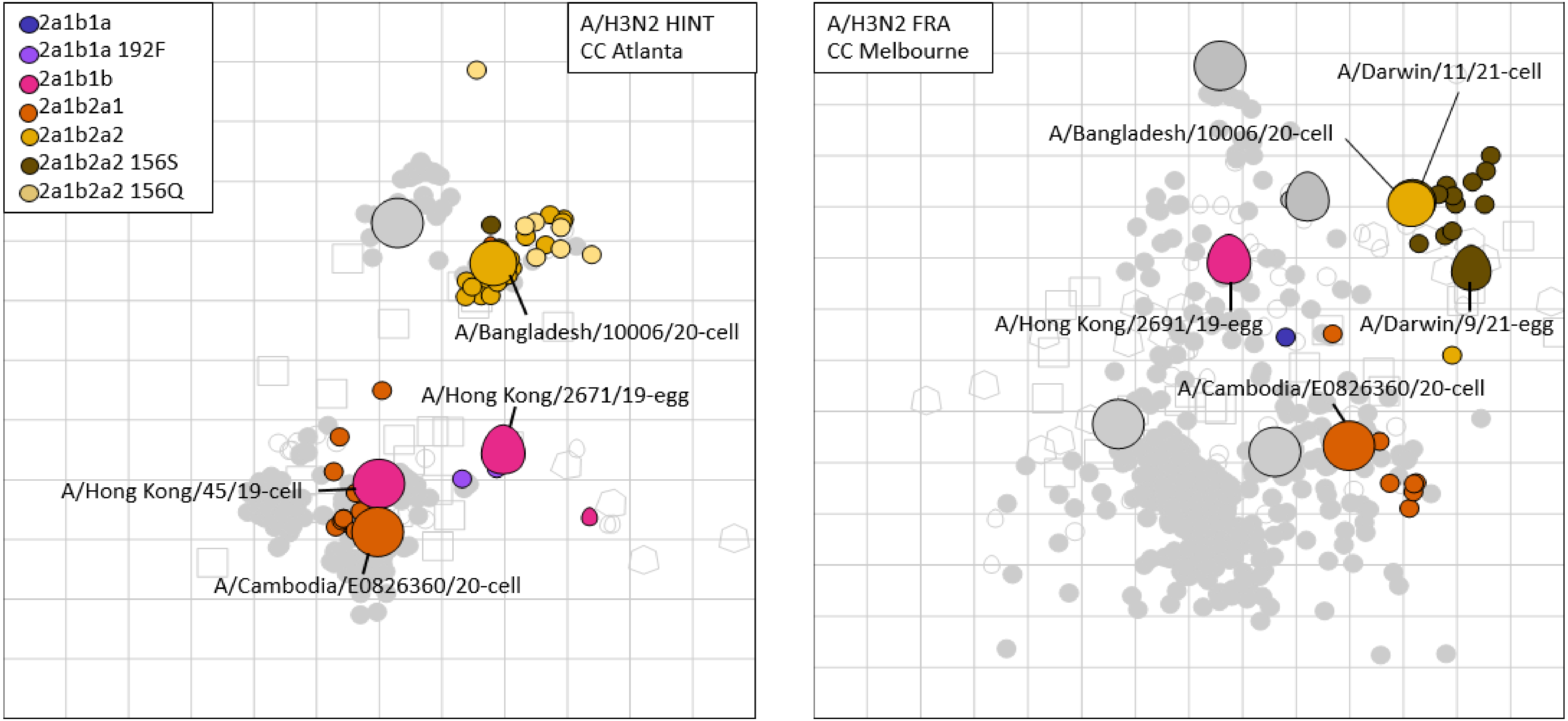
A/Cambodia/E0826360/2020-like (egg)

WHO CC	Like (2-4 fold)	Low (≥ 8 fold)
FCI	9 (32%)	19 (68%)
NIID	0 (0%)	14 (100%)
VIDRL	0 (0%)	12 (100%)
TOTAL	9 (17%)	45 (83%)

*Reference viruses are in HA clade 3C.2a1b.**2a1**

Showing data from viruses isolated from swabs collected from February through August 2021

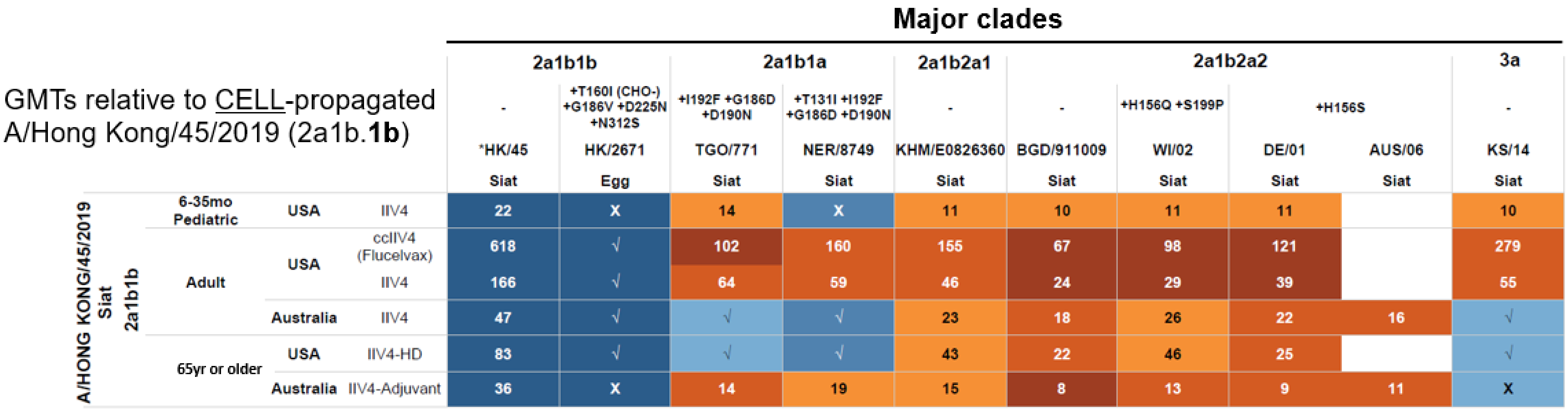
A(H3N2) Antigenic Cartography



Source: University of Cambridge

Since September 2020 (older viruses in grey)

Human Post-vaccination Sera Analysis of A(H3N2) Viruses



Major clades

GMTs relative to CELL-propagated A/Hong Kong/45/2019 (2a1b.**1b**)				2a1b1b		2a1b1a		2a1b2a1	2a1b2a2				3a
				-	+T160I (CHO-) +G186V +D225N +N312S	+I192F +G186D +D190N	+T131I +I192F +G186D +D190N	-	-	+H156Q +S199P	+H156S		-
				*HK/45	HK/2671	TGO/771	NER/8749	KHM/E0826360	BGD/911009	WI/02	DE/01	AUS/06	KS/14
				Siat	Egg	Siat	Siat	Siat	Siat	Siat	Siat	Siat	Siat
A/HONG KONG/45/2019 Siat 2a1b1b	6-35mo Pediatric	USA	IIV4	22	X	14	X	11	10	11	11		10
	Adult	USA	ccIIV4 (Flucelvax)	618	√	102	160	155	67	98	121		279
			IIV4	166	√	64	59	46	24	29	39		55
		Australia	IIV4	47	√	√	√	23	18	26	22	16	√
	65yr or older	USA	IIV4-HD	83	√	√	√	43	22	46	25		√
		Australia	IIV4-Adjuvant	36	X	14	19	15	8	13	9	11	X

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. Green indicates statistical non-inferiority and red denotes possible inferiority. Numbers shown are post-vaccination GMTs for the unadjusted model. They are shown for reference antigens* and possibly inferior test antigens. Marks √ or X denote statistically significant non-inferiority when the reference virus GMT is ≥40 or <40 respectively. Strain abbreviations: A/BANGLADESH/911009/2020 (BGD/911009); A/CAMBODIA/E0826360/2020 (KHM/E0826360); A/DARWIN/06/2021 (AUS/06); A/DELAWARE/01/2021 (DE/01); A/HONG KONG/2671/2019 (HK/2671); A/HONG KONG/45/2019 (HK/45); A/KANSAS/14/2017 (KS/14); A/NIGER/8749/2021 (NER/8749); A/TOGO/771/2020 (TGO/771); A/WISCONSIN/02/2021 (WI/02).

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

GMT ratio lowerbound (90% CI)
0.0 1.0

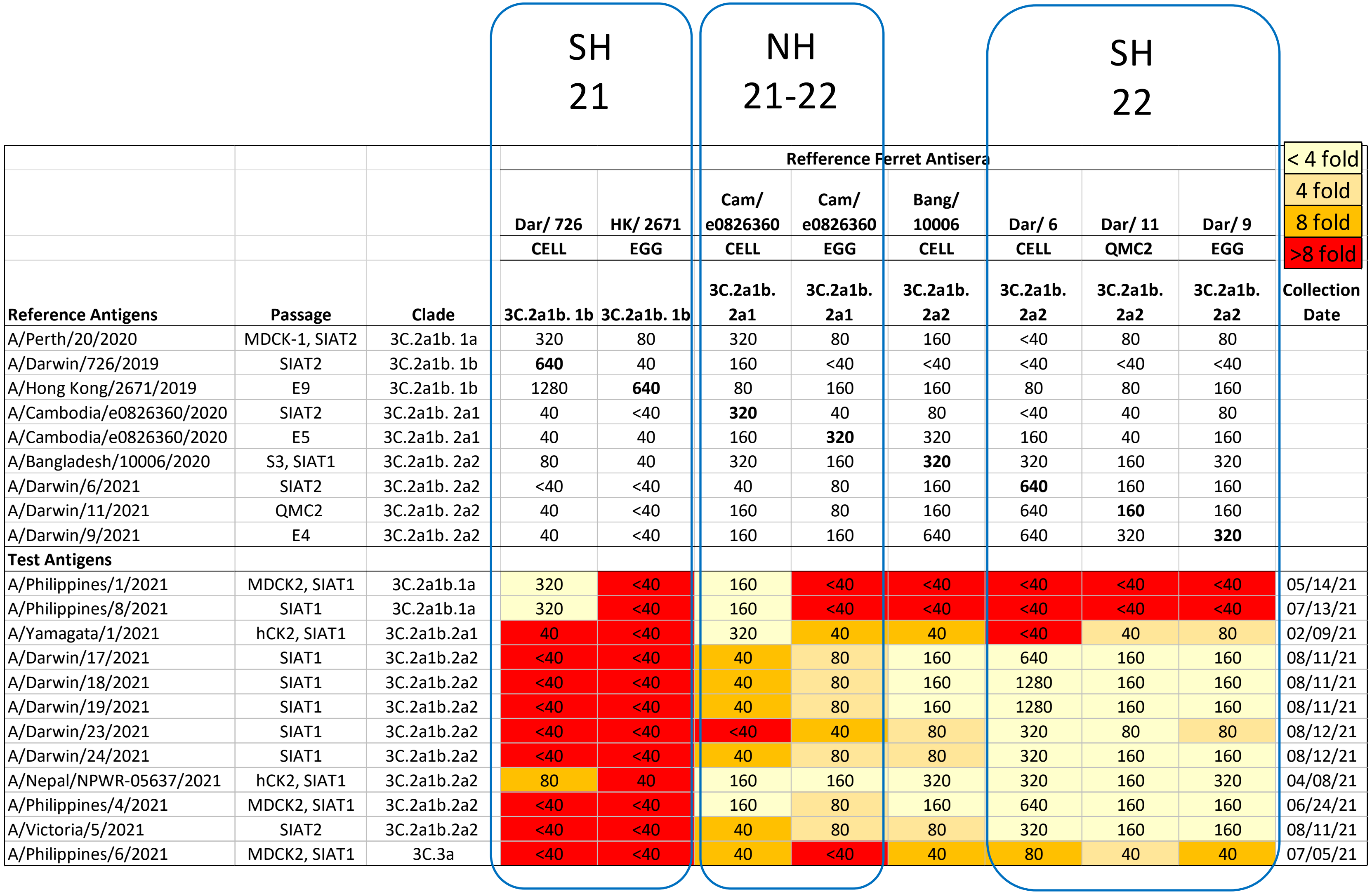
Source: U.S. CDC

- Multiple serum panels show the clade 2a1b.**2a** viruses escaped neutralization
    - GMTs to **2a2** viruses were typically the lowest

Antigenic Analysis of Reference Viruses & Candidate Vaccine Viruses (CVVs)

Ferret antisera to:

- SH 2021 reference viruses
  - Inhibit clade 1a and 1b
  - Poorly inhibited clade 2a1 and 2a2 viruses
- NH 2021-22 reference viruses
  - Inhibited 1a, 1b and 2a1 viruses
  - Reduced inhibition of clade 2a2 viruses
- 2a2 reference viruses
  - SH 2022 recommendation
  - Well inhibited 2a2
  - Reduced inhibition of 2a1
  - Poor inhibition of 1a and 1b viruses



			SH 21		NH 21-22			SH 22			
			Refference Ferret Antisera								
			Dar/ 726	HK/ 2671	Cam/ e0826360	Cam/ e0826360	Bang/ 10006	Dar/ 6	Dar/ 11	Dar/ 9	
			CELL	EGG	CELL	EGG	CELL	CELL	QMC2	EGG	
Reference Antigens	**Passage**	**Clade**	**3C.2a1b. 1b**	**3C.2a1b. 1b**	**3C.2a1b. 2a1**	**3C.2a1b. 2a1**	**3C.2a1b. 2a2**	**3C.2a1b. 2a2**	**3C.2a1b. 2a2**	**3C.2a1b. 2a2**	**Collection Date**
A/Perth/20/2020	MDCK-1, SIAT2	3C.2a1b. 1a	320	80	320	80	160	<40	80	80	
A/Darwin/726/2019	SIAT2	3C.2a1b. 1b	**640**	40	160	<40	<40	<40	<40	<40	
A/Hong Kong/2671/2019	E9	3C.2a1b. 1b	1280	**640**	80	160	160	80	80	160	
A/Cambodia/e0826360/2020	SIAT2	3C.2a1b. 2a1	40	<40	**320**	40	80	<40	40	80	
A/Cambodia/e0826360/2020	E5	3C.2a1b. 2a1	40	40	160	**320**	320	160	40	160	
A/Bangladesh/10006/2020	S3, SIAT1	3C.2a1b. 2a2	80	40	320	160	**320**	320	160	320	
A/Darwin/6/2021	SIAT2	3C.2a1b. 2a2	<40	<40	40	80	160	**640**	160	160	
A/Darwin/11/2021	QMC2	3C.2a1b. 2a2	40	<40	160	80	160	640	**160**	160	
A/Darwin/9/2021	E4	3C.2a1b. 2a2	40	<40	160	160	640	640	320	**320**	
Test Antigens											
A/Philippines/1/2021	MDCK2, SIAT1	3C.2a1b.1a	320	<40	160	<40	<40	<40	<40	<40	05/14/21
A/Philippines/8/2021	SIAT1	3C.2a1b.1a	320	<40	160	<40	<40	<40	<40	<40	07/13/21
A/Yamagata/1/2021	hCK2, SIAT1	3C.2a1b.2a1	40	<40	320	40	40	<40	40	80	02/09/21
A/Darwin/17/2021	SIAT1	3C.2a1b.2a2	<40	<40	40	80	160	640	160	160	08/11/21
A/Darwin/18/2021	SIAT1	3C.2a1b.2a2	<40	<40	40	80	160	1280	160	160	08/11/21
A/Darwin/19/2021	SIAT1	3C.2a1b.2a2	<40	<40	40	80	160	1280	160	160	08/11/21
A/Darwin/23/2021	SIAT1	3C.2a1b.2a2	<40	<40	<40	40	80	320	80	80	08/12/21
A/Darwin/24/2021	SIAT1	3C.2a1b.2a2	<40	<40	40	80	80	320	160	160	08/12/21
A/Nepal/NPWR-05637/2021	hCK2, SIAT1	3C.2a1b.2a2	80	40	160	160	320	320	160	320	04/08/21
A/Philippines/4/2021	MDCK2, SIAT1	3C.2a1b.2a2	<40	<40	160	80	160	640	160	160	06/24/21
A/Victoria/5/2021	SIAT2	3C.2a1b.2a2	<40	<40	40	80	80	320	160	160	08/11/21
A/Philippines/6/2021	MDCK2, SIAT1	3C.3a	<40	<40	40	<40	40	80	40	40	07/05/21

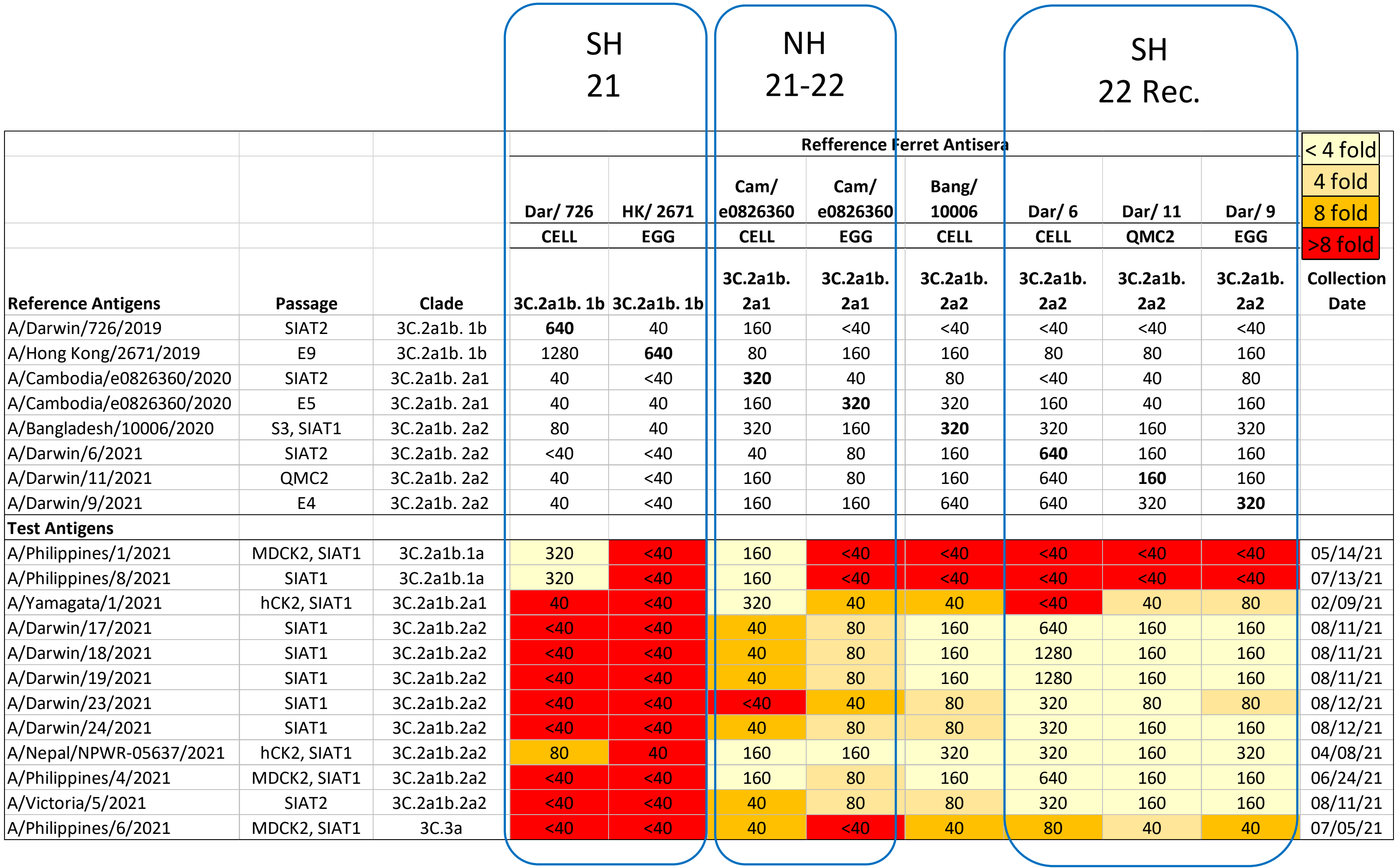
< 4 fold
4 fold
8 fold
>8 fold

Source: VIDRL HI test

Antigenic Analysis of Reference Viruses & Candidate Vaccine Viruses (CVVs)

Ferret antisera to:

- SH 2021 reference viruses
    - Inhibit clade 1a and 1b
    - Poorly inhibited clade 2a1 and 2a2 viruses
- NH 2021-22 reference viruses
    - Inhibited 1a, 1b and 2a1 viruses
    - Reduced inhibition of clade 2a2 viruses
- 2a2 reference viruses
    - SH 2022 recommendation
    - Well inhibited 2a2
    - Reduced inhibition of 2a1
    - Poor inhibition of 1a and 1b viruses

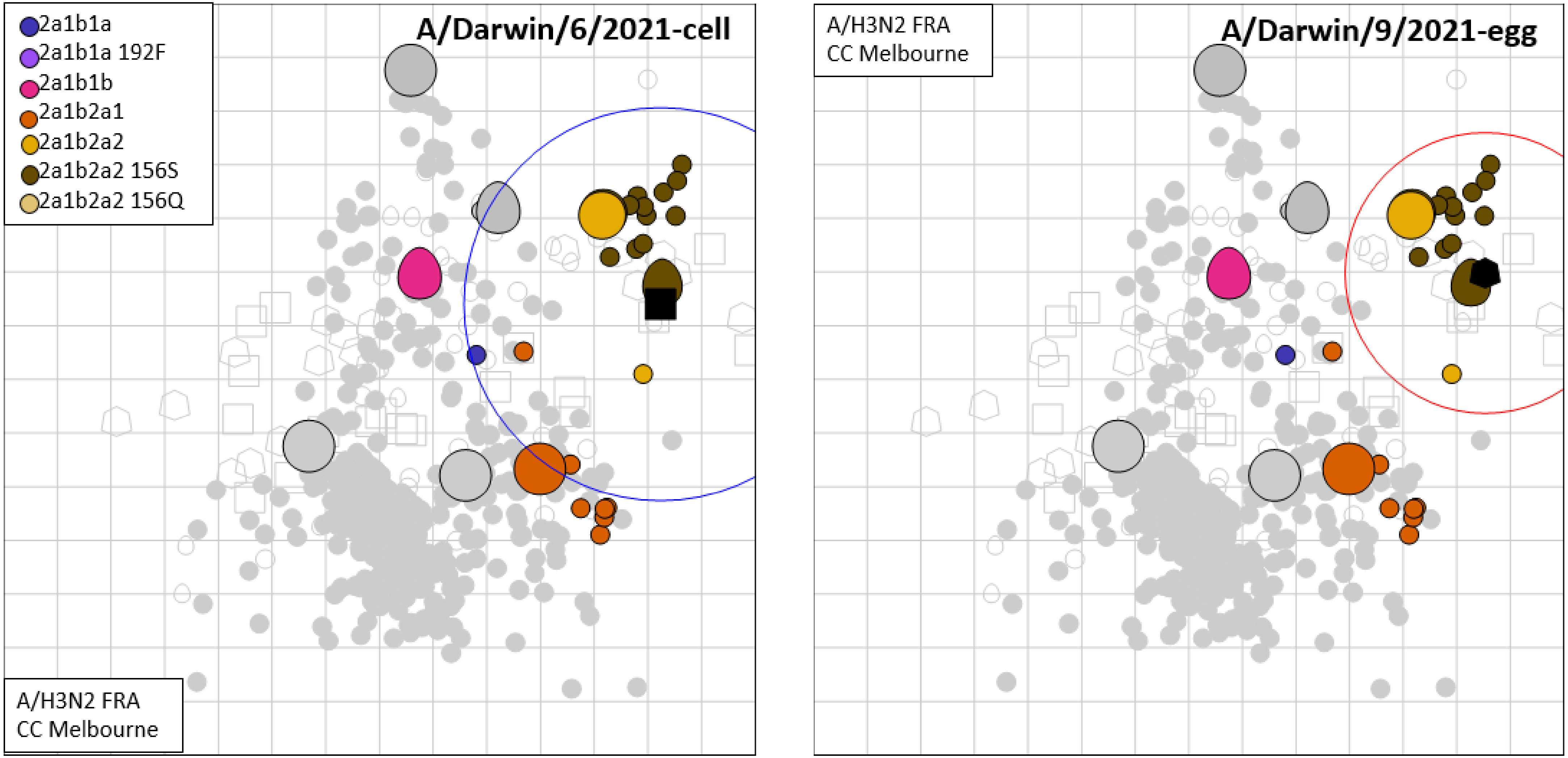


			SH 21		NH 21-22			SH 22 Rec.			
			Refference Ferret Antisera								
			Dar/ 726 CELL	HK/ 2671 EGG	Cam/ e0826360 CELL	Cam/ e0826360 EGG	Bang/ 10006 CELL	Dar/ 6 CELL	Dar/ 11 QMC2	Dar/ 9 EGG	
Reference Antigens	**Passage**	**Clade**	**3C.2a1b. 1b**	**3C.2a1b. 1b**	**3C.2a1b. 2a1**	**3C.2a1b. 2a1**	**3C.2a1b. 2a2**	**3C.2a1b. 2a2**	**3C.2a1b. 2a2**	**3C.2a1b. 2a2**	**Collection Date**
A/Darwin/726/2019	SIAT2	3C.2a1b. 1b	**640**	40	160	<40	<40	<40	<40	<40	
A/Hong Kong/2671/2019	E9	3C.2a1b. 1b	1280	**640**	80	160	160	80	80	160	
A/Cambodia/e0826360/2020	SIAT2	3C.2a1b. 2a1	40	<40	**320**	40	80	<40	40	80	
A/Cambodia/e0826360/2020	E5	3C.2a1b. 2a1	40	40	160	**320**	320	160	40	160	
A/Bangladesh/10006/2020	S3, SIAT1	3C.2a1b. 2a2	80	40	320	160	**320**	320	160	320	
A/Darwin/6/2021	SIAT2	3C.2a1b. 2a2	<40	<40	40	80	160	**640**	160	160	
A/Darwin/11/2021	QMC2	3C.2a1b. 2a2	40	<40	160	80	160	640	**160**	160	
A/Darwin/9/2021	E4	3C.2a1b. 2a2	40	<40	160	160	640	640	320	**320**	
Test Antigens											
A/Philippines/1/2021	MDCK2, SIAT1	3C.2a1b.1a	320	<40	160	<40	<40	<40	<40	<40	05/14/21
A/Philippines/8/2021	SIAT1	3C.2a1b.1a	320	<40	160	<40	<40	<40	<40	<40	07/13/21
A/Yamagata/1/2021	hCK2, SIAT1	3C.2a1b.2a1	40	<40	320	40	40	<40	40	80	02/09/21
A/Darwin/17/2021	SIAT1	3C.2a1b.2a2	<40	<40	40	80	160	640	160	160	08/11/21
A/Darwin/18/2021	SIAT1	3C.2a1b.2a2	<40	<40	40	80	160	1280	160	160	08/11/21
A/Darwin/19/2021	SIAT1	3C.2a1b.2a2	<40	<40	40	80	160	1280	160	160	08/11/21
A/Darwin/23/2021	SIAT1	3C.2a1b.2a2	<40	<40	<40	40	80	320	80	80	08/12/21
A/Darwin/24/2021	SIAT1	3C.2a1b.2a2	<40	<40	40	80	80	320	160	160	08/12/21
A/Nepal/NPWR-05637/2021	hCK2, SIAT1	3C.2a1b.2a2	80	40	160	160	320	320	160	320	04/08/21
A/Philippines/4/2021	MDCK2, SIAT1	3C.2a1b.2a2	<40	<40	160	80	160	640	160	160	06/24/21
A/Victoria/5/2021	SIAT2	3C.2a1b.2a2	<40	<40	40	80	80	320	160	160	08/11/21
A/Philippines/6/2021	MDCK2, SIAT1	3C.3a	<40	<40	40	<40	40	80	40	40	07/05/21

< 4 fold
4 fold
8 fold
>8 fold

Source: VIDRL HI test

A(H3N2) Cartography: Antisera Reactivity



Source: University of Cambridge

Since September 2020 (older viruses in grey)

A(H3N2) Summary (I): Global Circulation

- In many countries, areas and territories reporting influenza A viruses, A(H3N2) subtypes were detected.
  - Included countries in Southeast Asia, South Asia, Middle East, Africa, Oceania, North America and Europe
- HA phylogenetics: circulating A(H3N2) viruses in this period belonged to 3C.2a1b subclades that typically have HA1 substitutions indicated:
  - 1a (T135K (-CHO), A138S, G186D, D190N, F193S and S198P)
  - 1b (T135K (-CHO), S137F, A138S and F193S)
  - **2a (K83E, Y94N and T131K)**
    - 2a1 (G186S, F193S, Y195F and S198P)
    - 2a2 (Y159N, T160I (-CHO), L164Q, G186D, D190N, F193S and Y195F)
  - Viruses in the 2a2 group represented increasing proportion
    - 2a2>2a1>1a>1b

A(H3N2) Summary (II): Antigenic Characteristics

- 2a2 viruses are antigenically distinct
  - Ferret antisera to:
    - A/Hong Kong/45/2019-like viruses (SH 21: Cell, 3C.2a1b.**1b**)
      - Neutralized 1a, 1b viruses well, 2a1 viruses less well, and 2a2 viruses poorly
    - A/Cambodia/e0826360/2020 (NH 21-22: Cell 3C.2a1b.**2a1**)
      - Reacted well with 1a, 1b and 2a1 viruses but 2a2 viruses were reduced
    - A/Darwin/6/2021 (SH 22 rec: Cell 3c2a1b.**2a2**)
      - Well recognized 2a2 viruses, showed reduced recognition of 2a1 and poorly reacted 1a, and 1b viruses

A(H3N2) Summary (III)

Human serology studies with serum panels from individuals vaccinated with A/Hong Kong/2671/2019-like or A/Hong Kong/45/2019-like (3C.2a1b.**1b**) viruses:

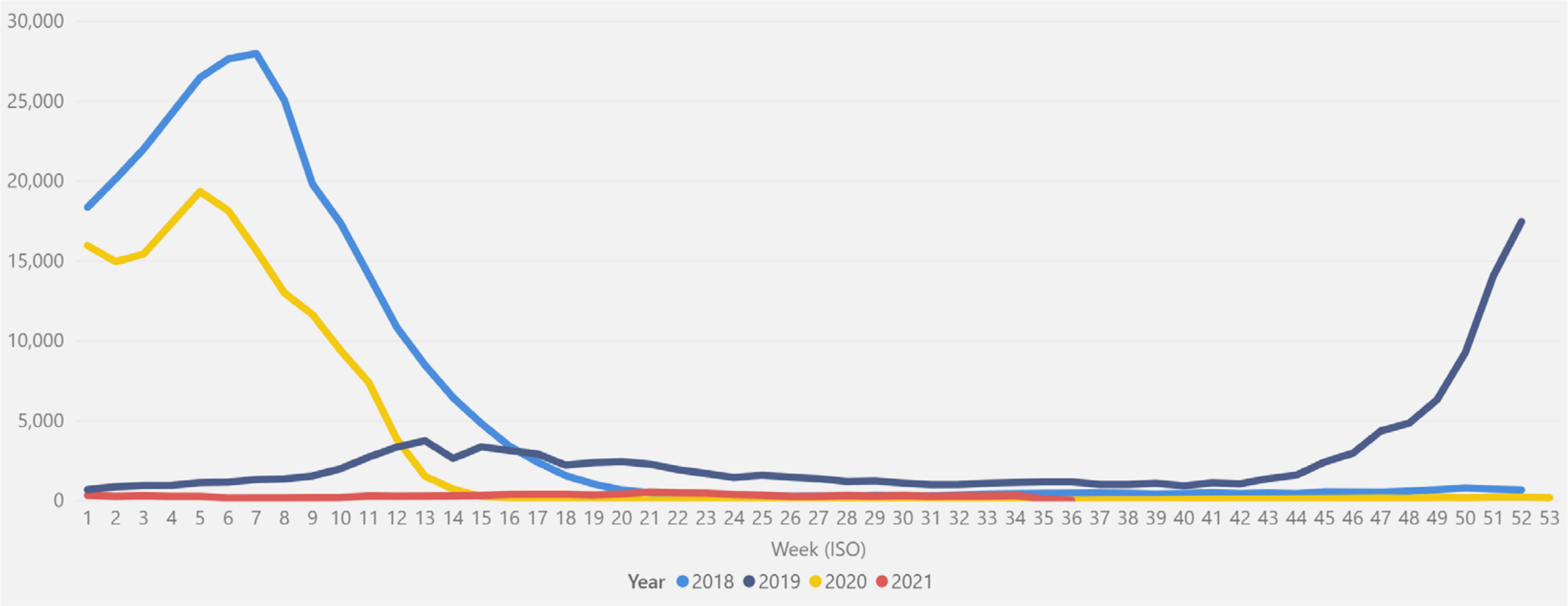
- Post-vaccination GMTs were significantly reduced against cell culture-propagated 3C.2a1b.**2a1** and 3C.2a1b.**2a2**

Antiviral Susceptibility

- Of 105 A(H3N2) viruses collected and tested after January 2021, none showed reduced inhibition to neuraminidase inhibitors.
- Of 125 A(H3N2) viruses collected and tested after January 2021, none showed genetic or phenotypic evidence of reduced susceptibility to baloxavir.

Influenza B Viruses

Number of B Viruses Detected by GISRS



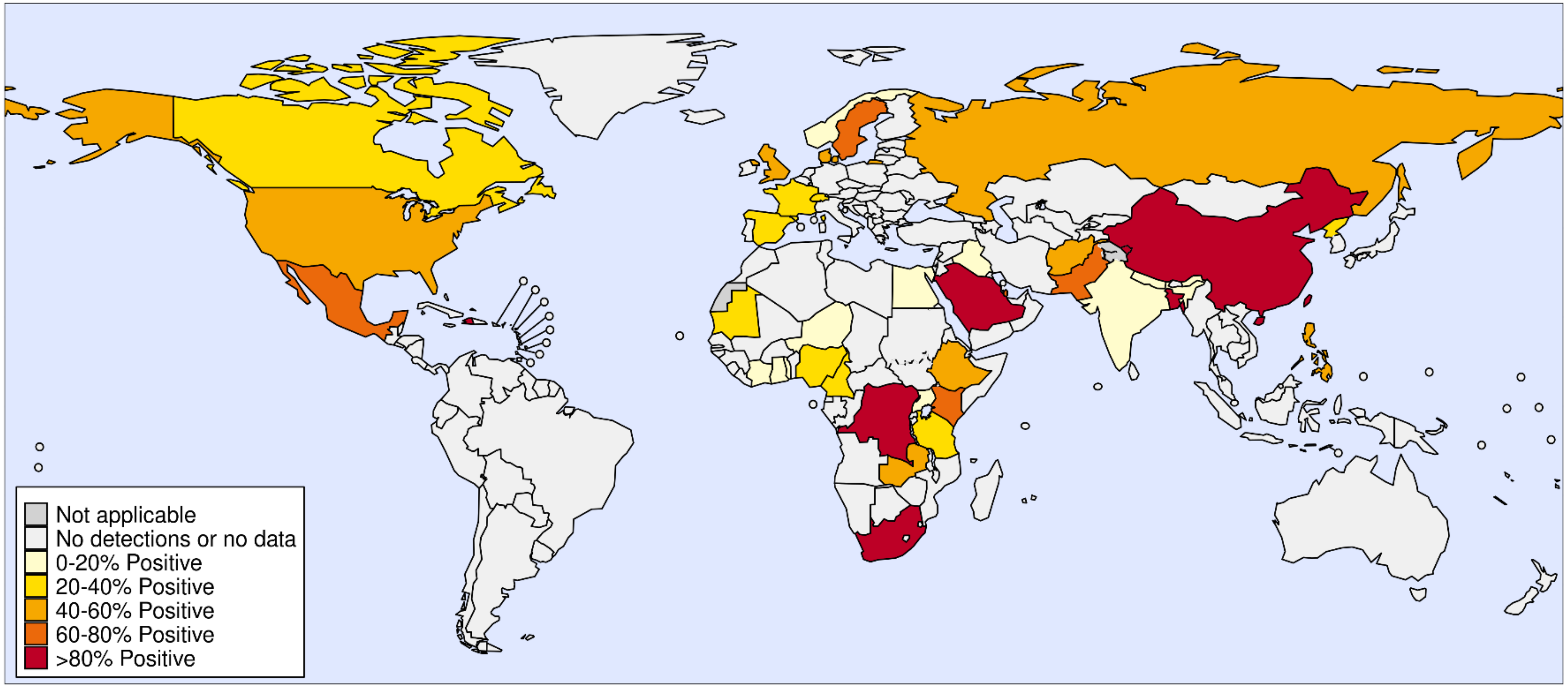
Select Year

2018 2021

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

Influenza B Virus Activity

Influenza B, February 2021 to August 2021, percent of positive samples



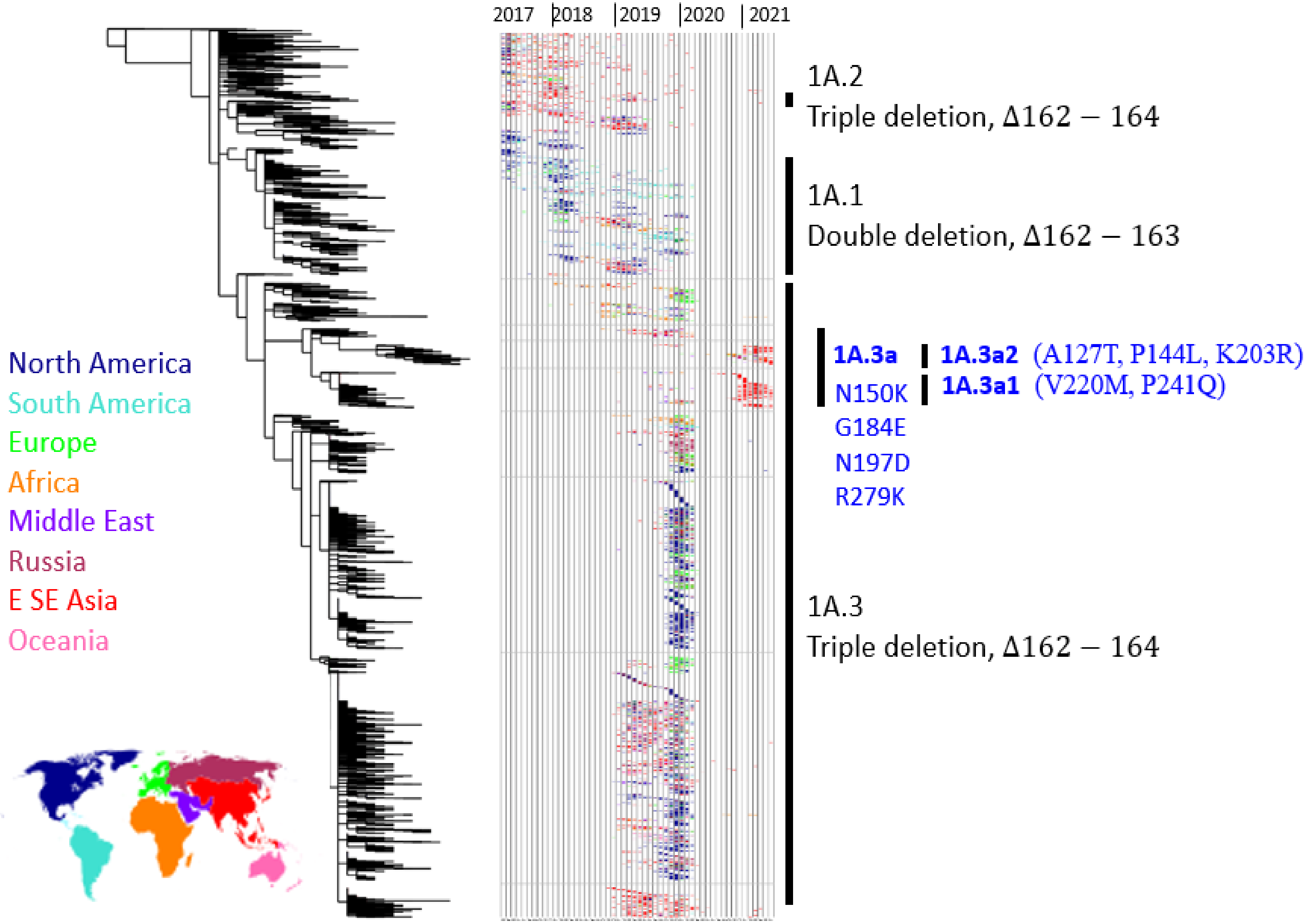
Colour intensity shows the proportion of influenza B among all influenza positives during this period per country
Data source: FluNet, (www.who.int/flunet), Global Influenza Surveillance and Response System (9 Sep 2021)

Influenza B/Victoria Lineage Viruses

B/Victoria HA Phylogenetic Tree

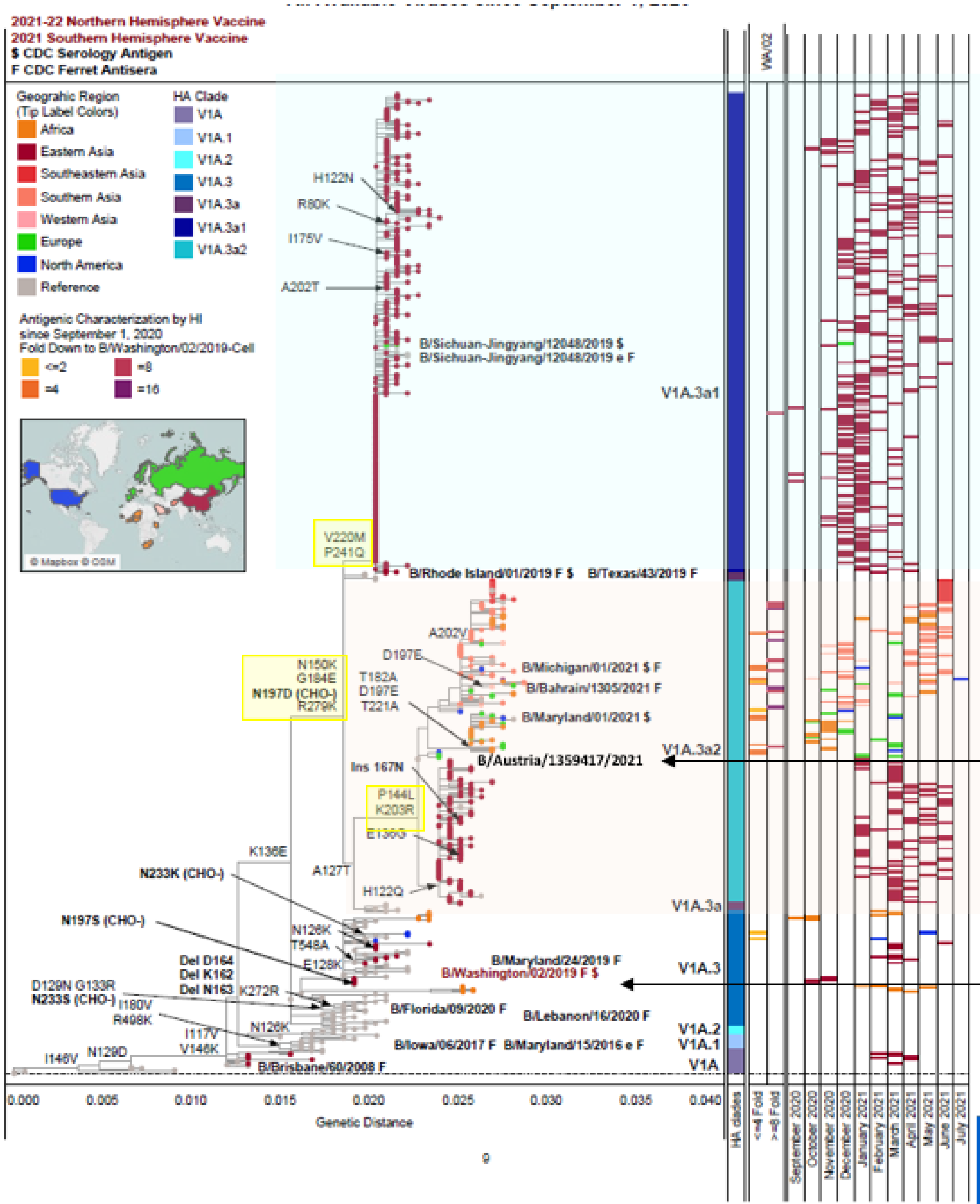
- Clade 1A.3
  - Predominated prior to COVID-19
- Clade 1A.3a (N150K)
  - re-emerged & diversified
    - 1A.3a1
    - 1A.3a2

University of Cambridge



Integrated B/Victoria HA Phylogenetics

- Clade 1A.3
  - Predominated prior to COVID-19
  - SH 2021 vaccine virus (e.g., B/Washington/02/2019)
- Clade 1A.3a (N150K) evolved further
  - Represent most recent viruses
  - 3a1 (V220M, P241Q)
    - Predominated in China early in 2021
    - B/Sichuan-Jingyang/12048/2019
  - 3a2 (A127T, P144L, K203R)
    - Increased steadily in recent months
    - B/Austria/1359417/2021
    - B/MI/01/2021



1A.3a1

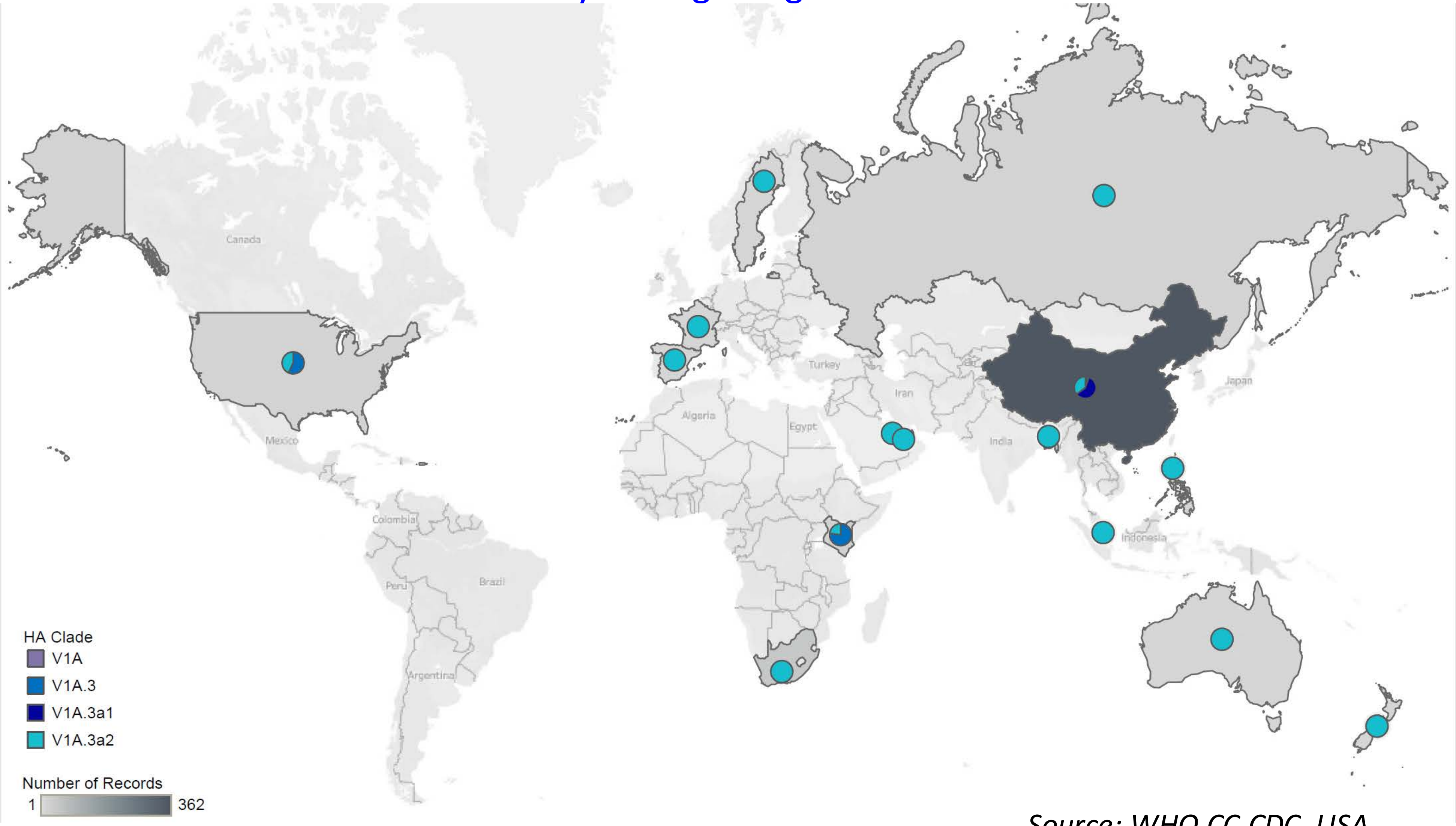
1A.3a2

SH 2022 Recommendation

SH 2021
NH 2021-22 cell
prototype

B/Victoria HA Clade Distribution

February through August 2021



Source: WHO CC CDC, USA

Neutralization of B/Victoria Viruses By Antisera To Antigens Recommended For The 2021 Southern Hemisphere

B/Washington/02/2019-like (cell)*

WHO CC	Like (2-4 fold)	Low (≥ 8 fold)
CDC	12 (60%)	8 (40%)
CNIC	251 (17%)	1224 (83%)
FCI	0 (0%)	10 (100%)
VIDRL	15 (50%)	15 (50%)
TOTAL	278 (18%)	1257 (82%)

B/Washington/02/2019-like (egg)*

WHO CC	Like (2-4 fold)	Low (≥ 8 fold)
CDC	15 (75%)	5 (25%)
CNIC	548 (37%)	927 (63%)
FCI	0 (0%)	10 (100%)
VIDRL	0 (0%)	25 (100%)
TOTAL	563 (37%)	967 (63%)

*Reference viruses are in HA clade 1A.3

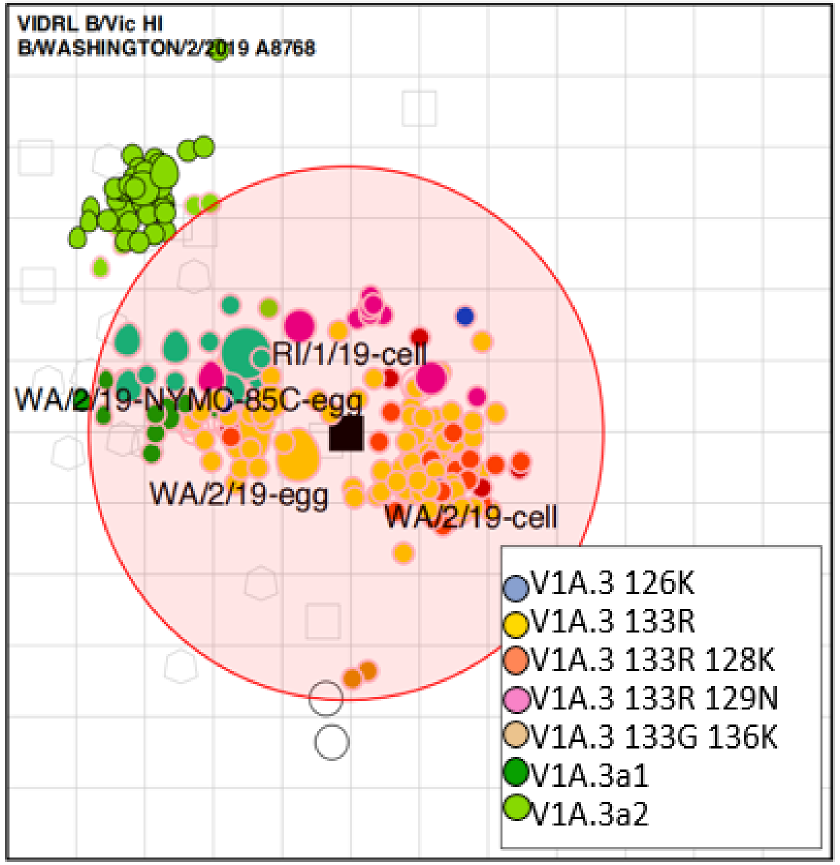
Showing data from viruses isolated from swabs collected from February through August 2021

Reactivity Patterns of Various Antisera

Antiserum circles (within 4-fold of homologous titers) using antisera raised against:

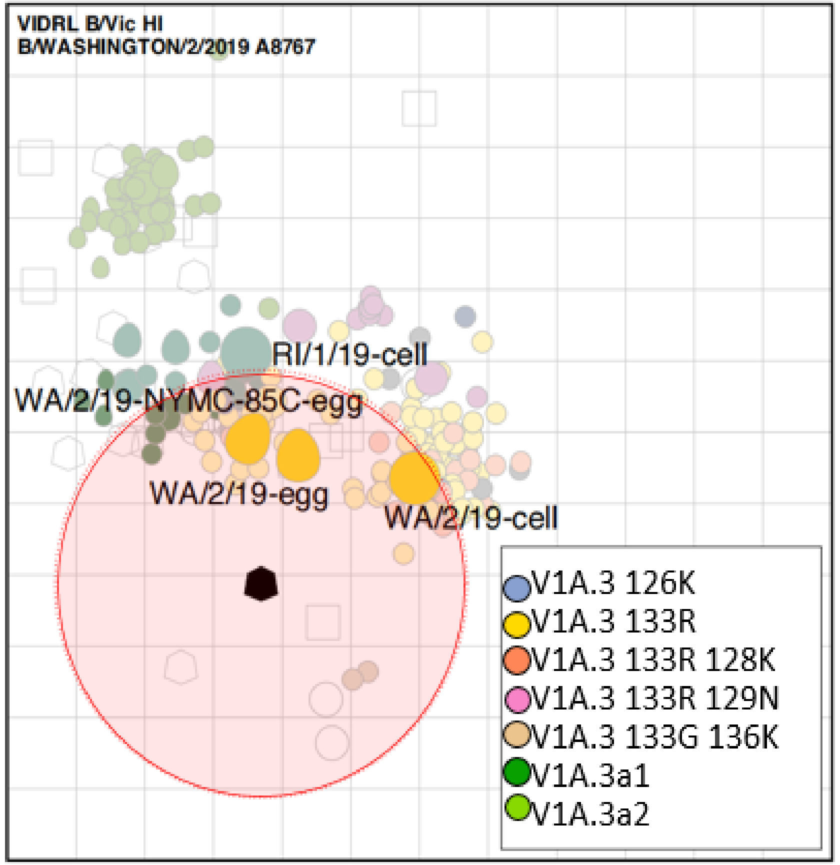
1A. 3

B/Washington/02/2019-cell



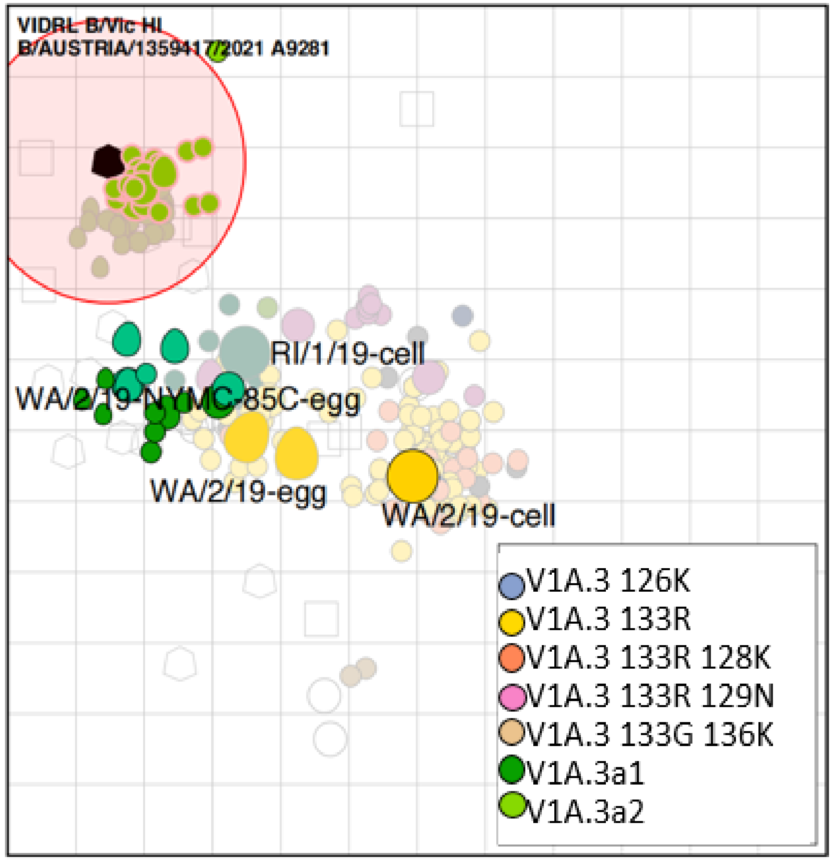
1A. 3

B/Washington/02/2019-egg



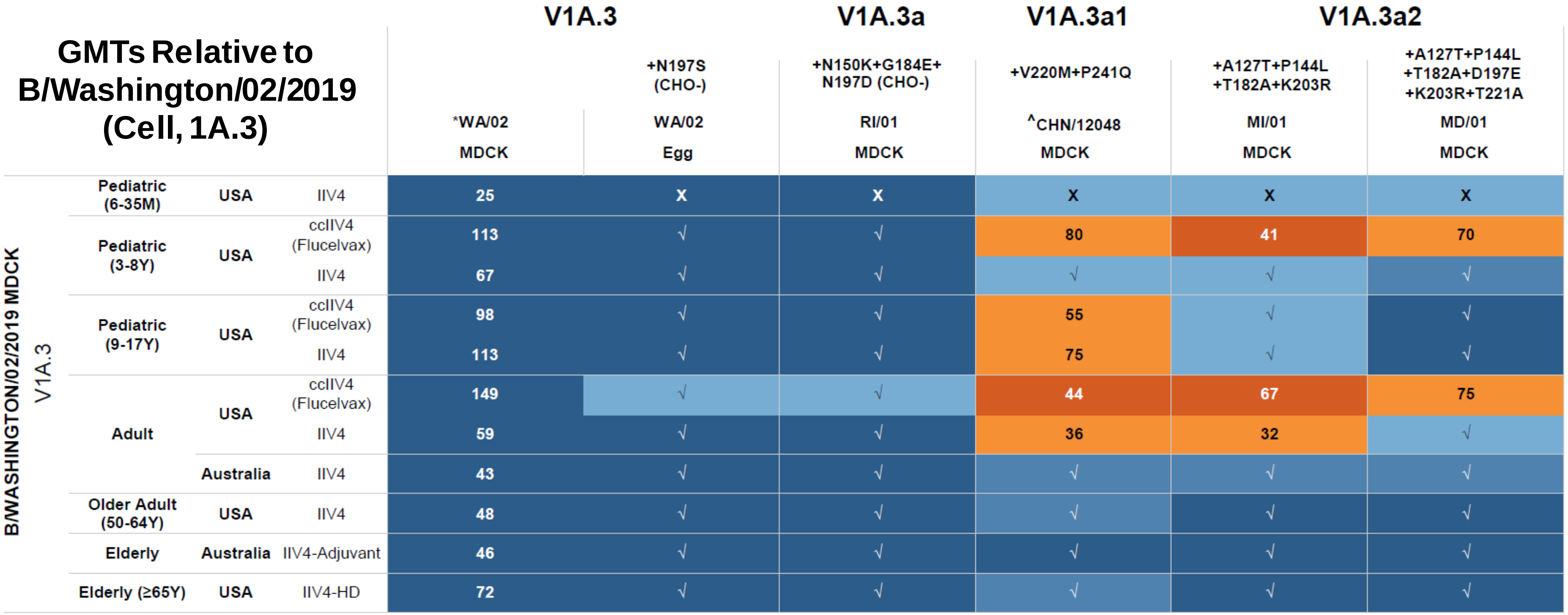
1A. 3a2

B/Austria/1359417/2021-egg



Cambridge Cartography of VIDRL, Australia HI data

Human Post-vaccination Sera Analysis of B/Victoria Viruses



GMTs Relative to B/Washington/02/2019 (Cell, 1A.3)

B/WASHINGTON/02/2019 MDCK V1A.3

			V1A.3		V1A.3a	V1A.3a1	V1A.3a2	
				+N197S (CHO-)	+N150K+G184E+ N197D (CHO-)	+V220M+P241Q	+A127T+P144L +T182A+K203R	+A127T+P144L +T182A+D197E +K203R+T221A
			*WA/02	WA/02	RI/01	^CHN/12048	MI/01	MD/01
			MDCK	Egg	MDCK	MDCK	MDCK	MDCK
Pediatric (6-35M)	USA	IIV4	25	X	X	X	X	X
Pediatric (3-8Y)	USA	ccIIV4 (Flucelvax)	113	√	√	80	41	70
		IIV4	67	√	√	√	√	√
Pediatric (9-17Y)	USA	ccIIV4 (Flucelvax)	98	√	√	55	√	√
		IIV4	113	√	√	75	√	√
Adult	USA	ccIIV4 (Flucelvax)	149	√	√	44	67	75
		IIV4	59	√	√	36	32	√
	Australia	IIV4	43	√	√	√	√	√
Older Adult (50-64Y)	USA	IIV4	48	√	√	√	√	√
Elderly	Australia	IIV4-Adjuvant	46	√	√	√	√	√
Elderly (≥65Y)	USA	IIV4-HD	72	√	√	√	√	√

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. Green indicates statistical non-inferiority and red denotes possible inferiority. Numbers shown are post-vaccination GMTs for the unadjusted model. They are shown for reference antigens* and possibly inferior test antigens. Marks √ or X denote statistically significant non-inferiority when the reference virus GMT is ≥40 or <40 respectively.
Strain abbreviations: B/MARYLAND/01/2021 (MD/01); B/MICHIGAN/01/2021 (MI/01); B/RHODE ISLAND/01/2019 (RI/01); B/SICHUAN-JINGYANG/12048/2019 (CHN/12048); B/WASHINGTON/02/2019 (WA/02).
†This virus stock has amino acid polymorphisms K203K/R, W141G/W and Q241Q/K

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

GMT ratio lowerbound (90% CI)
0.0 1.0

- Geometric mean titers of some serum panels were reduced to the 1A.**3a1** and 1A.**3a2** viruses

Antigenic Analysis of Reference Viruses & Candidate Vaccine Viruses (CVVs)

			SH 21			Recomendation		
			Reference Ferret Antisera					
			CELL	**CELL**	**EGG**	**CELL**	**EGG**	
			B/Washington/02/2019	**B/Sichuan-Jingyang/12048/2019**		**B/Austria/1359417/2021**		
Reference Antigens	**Passage**	**Clade/Subgroup**	1A.3	1A.3a1		1A.3a2		**Collection Dates**
B/Washington/02/2019	MDCK4	1A.3	**160**	160	80	40	20	
B/Sichuan-Jingyang/12048/2019	MDCK3	1A.3a1	80	**1280**	1280	160	160	
B/Sichuan-Jingyang/12048/2019	E3	1A.3a1	80	>2560	**>2560**	160	320	
B/Austria/1359417/2021	MDCK7	1A.3a2	80	640	640	**1280**	>2560	
B/Austria/1359417/2021	E3	1A.3a2	80	320	640	1280	**>2560**	
Test Antigens								
B/Hubei-Wujiagang/1299/2021	MDCK3	1A.3a1	80	>2560	1280	160	160	2021-03-18
B/Henan-Shanyang/37/2021	MDCK3	1A.3a1	80	>2560	1280	160	320	2021-03-29
B/Fujian-Zhangpu/34/2021	MDCK3	1A.3a1	80	>2560	1280	160	320	2021-03-22
B/Cote d'Ivoire/1063/2020	MDCK5	1A.3a2	40	640	320	640	1280	2021-01-25
B/Singapore/WUH4855/2021	MDCK1	1A.3a2	40	320	640	640	1280	2021-06-20
B/Gansu-Baiyin/1281/2021	MDCK3	1A.3a2	<20	320	640	640	1280	2021-04-13
B/Henan-Xigong/1118/2021	MDCK3	1A.3a2	40	640	640	1280	>2560	2021-02-17
B/Gansu-Chengguan/1515/2021	MDCK3	1A.3a2	<20	320	640	1280	640	2021-03-30
B/Singapore/WUH4618/2021	MDCK1	1A.3a2	40	640	640	1280	>2560	2021-06-18
B/Victoria/2/2021	MDCK1	1A.3a2	80	640	640	1280	>2560	2021-07-08
B/Philippines/6/2021	MDCK1	1A.3a2	40	640	640	1280	>2560	2021-06-14
B/Philippines/8/2021	MDCK1	1A.3a2	80	640	320	1280	1280	2021-07-05

Source: WHO CC VIDRL, Australia

B/Yamagata Lineage Viruses

Sporadic B/Yamagata/16/88 lineage viruses have been reported in 2021 but none have been confirmed by WHO Collaborating Centres and no viruses with collection dates after March 2020 were available for characterization.

Summary of Influenza B Viruses (I)

- Influenza B/Victoria lineage viruses predominated by a huge margin and no B/Yamagata lineage viruses were available for analysis
- HA phylogenetics of B/Victoria lineage viruses
  - Nearly all HA genes belonged to subclade 1A.3
    - These have a deletion of residues 162-164 and a K136E substitution in HA1
  - Group 1A.3a viruses with HA genes encoding further substitutions of N150K, G184E, N197D and R279K in HA1 have predominated and two subgroups have emerged:
    - 1A.3a1 has additional HA1 substitutions V220M and P241Q, seen almost exclusively in China
    - 1A.3a2 with A127T, P144L and K203R seen in Asia, Africa, Oceania, Europe and North America
  - The number and the proportion of 1A.3a2 viruses have increased steadily over recent months, and they are geographically dispersed

Summary of Influenza B Viruses (II)

Antigenic characteristics of B/Victoria lineage viruses using ferret antisera

- Subgroup 1A.3a1 and 1A.3a2 viruses are antigenically drifted from B/Washington/02/2019-like (1A.3) viruses
  - 3a1 and 3a2 viruses are antigenically distinguishable from each other
- Antisera to B/Austria/1359417/2021-like viruses (1A.3a2) well inhibited circulating viruses from the 3a2 subclade

Human post vaccination sera

- GMTs of some serum panels were significantly reduced against 3a1 and 3a2 viruses

Antiviral susceptibility

- All viruses analyzed showed normal susceptibility to the neuraminidase inhibitors and endonuclease inhibitors

Acknowledgements

- WHO Collaborating Centers in Beijing, Melbourne, London and Tokyo and WHO Geneva staff
  - GISRS; National Influenza Centers
  - University of Cambridge partners
- Essential Regulatory Laboratories
- US partners:
  - Association of Public Health Laboratories
  - United States Air Force School of Aerospace Medicine (USAFSAM)
  - Naval Health Research Center (NHRC)
- Fitness forecasting partners in Europe and US
  - M. Lässig, M. Łuksza
  - T. Bedford, R. Neher
- CDC Influenza Division staff
  - Special thanks to Rebecca Kondor, Min Levine, Larisa Gubareva and John Steel

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).

CDC

Biomedical Advanced Research & Development Authority
Assistant Secretary for Preparedness & Response
U.S. Department of Health & Human Services

National Institute of Allergy and Infectious Diseases
Leading research to understand, treat, and prevent infectious, immunologic, and allergic diseases.