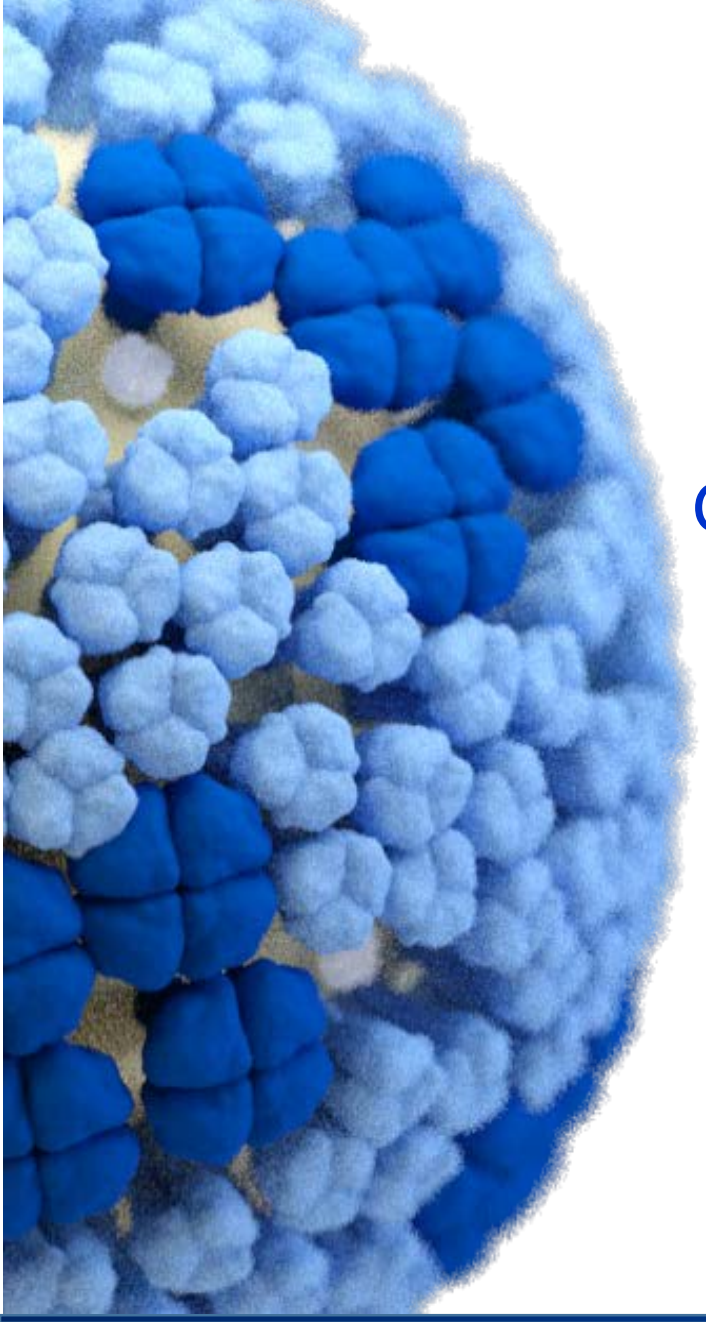


Information For The Vaccine And Related Biological Products Advisory Committee CBER, FDA

Global Influenza Virus Surveillance and Characterization March 5, 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
- Influenza Virus Activity
- A(H1N1)pdm09, describe major highlights
  - Was covered in depth at Sept. 2020 VRBPAC
  - While recommendation is an update for the NH 2021-2022 season, it is the same as the SH 2021 recommendation.
- A(H3N2), will be discussed in detail
  - Update to the recommendation
- B/Victoria lineage viruses
  - Vaccine recommendation remains same as NH 2021-2022 and SH 2021
    - Expansion of previously small group
- B/Yamagata lineage, will be brief as there has been very little circulation of this lineage

WHO Influenza Vaccine Consultation Meeting

- **Year around surveillance conducted by GISRS**
  - WHO Collaborating Centers (WHO CC), National Influenza Centers, WHO Essential Regulatory Laboratories, WHO H5 Reference Laboratories
  - Supported by many countries and partners including GISAID
- **WHO consultation meeting held from Feb 17 – 25, 2021**
  - A virtual meeting – 17 hours' time difference among participants
  - Chaired by Drs David Wentworth and John McCauley
  - 8 Advisers: Directors of WHOCCs and ERLs
    - In their capacity as representative of their corresponding WHO CCs and ERLs
  - 57 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 vaccines for use in the 2021-2022 northern hemisphere influenza season contain the following:

Quadrivalent: Egg-based Vaccines

- an A/Victoria/2570/2019 (H1N1)pdm09-like virus*;
- an A/Cambodia/e0826360/2020 (H3N2)-like virus*;
- a B/Washington/02/2019 (B/Victoria lineage)-like virus; and

→ **Trivalent**

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

Quadrivalent: Cell- or recombinant-based Vaccines

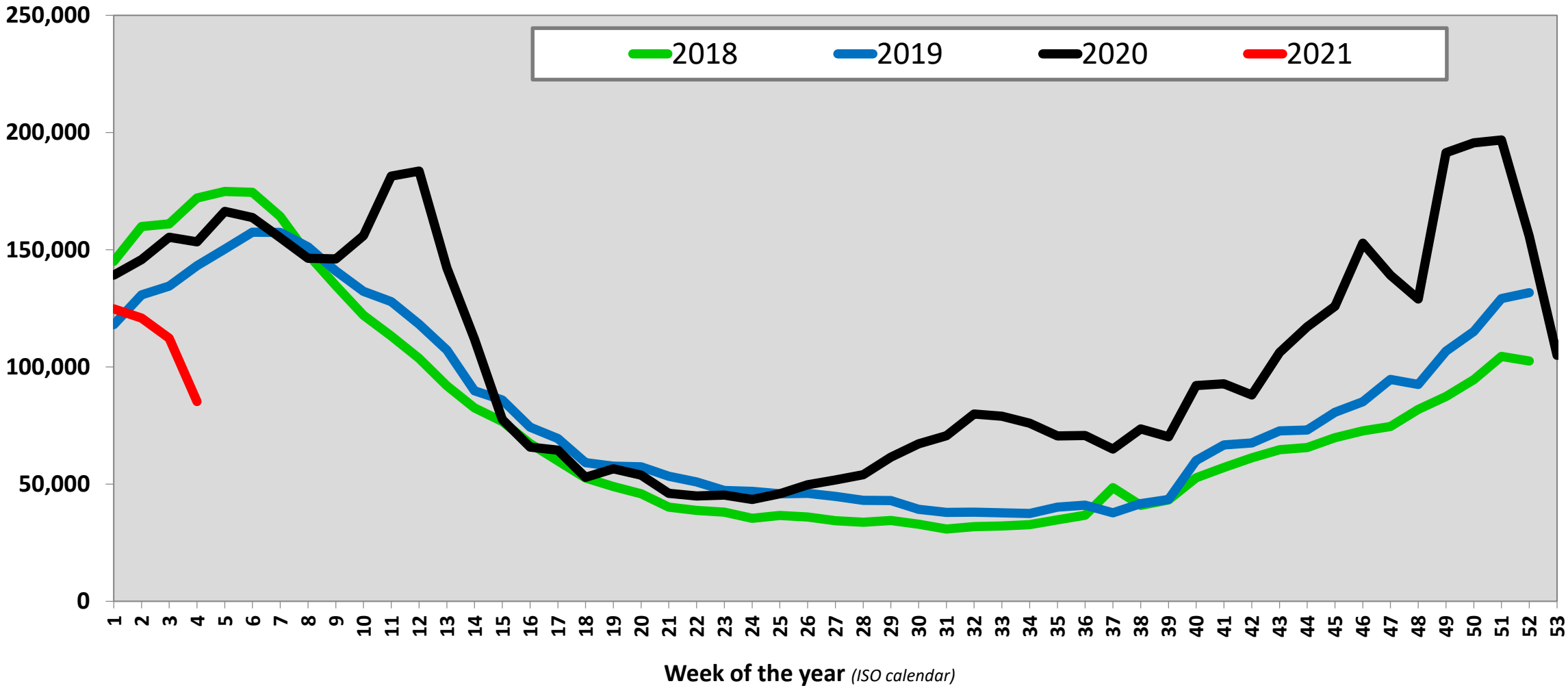
- an A/Wisconsin/588/2019 (H1N1)pdm09-like virus*;
- an A/Cambodia/e0826360/2020 (H3N2)-like virus*;
- a B/Washington/02/2019 (B/Victoria lineage)-like virus; and

→ **Trivalent**

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

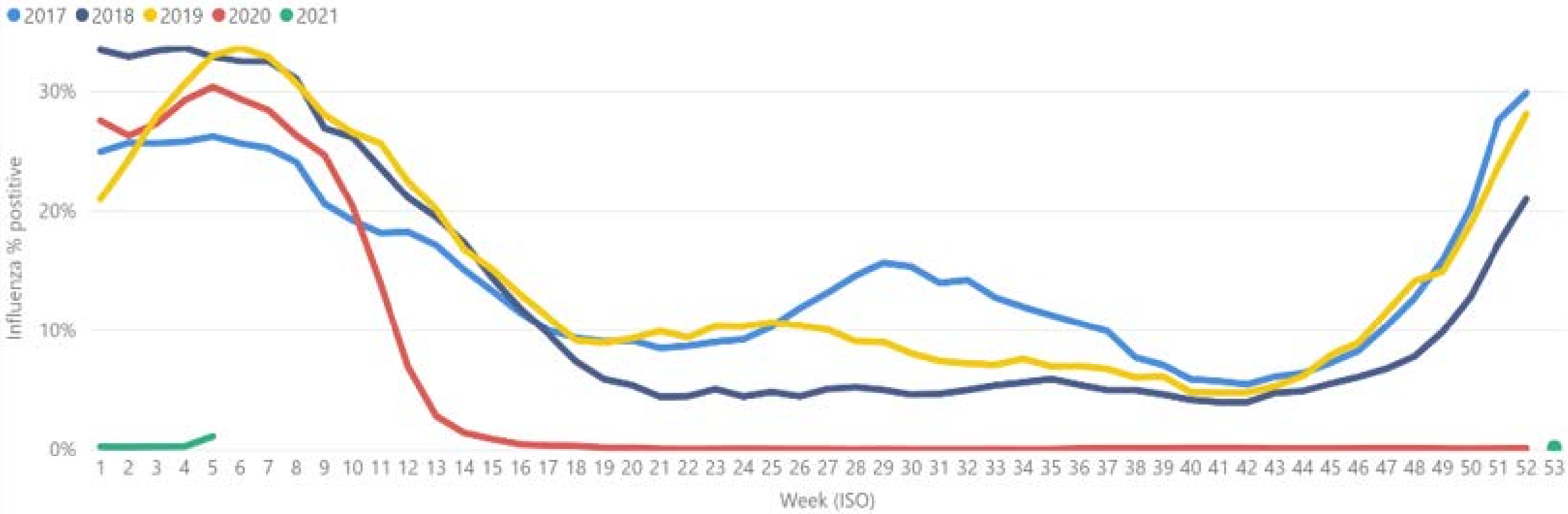
* Different from that recommended for the northern hemisphere 2020-2021 season

Number of Specimens Processed by GISRS



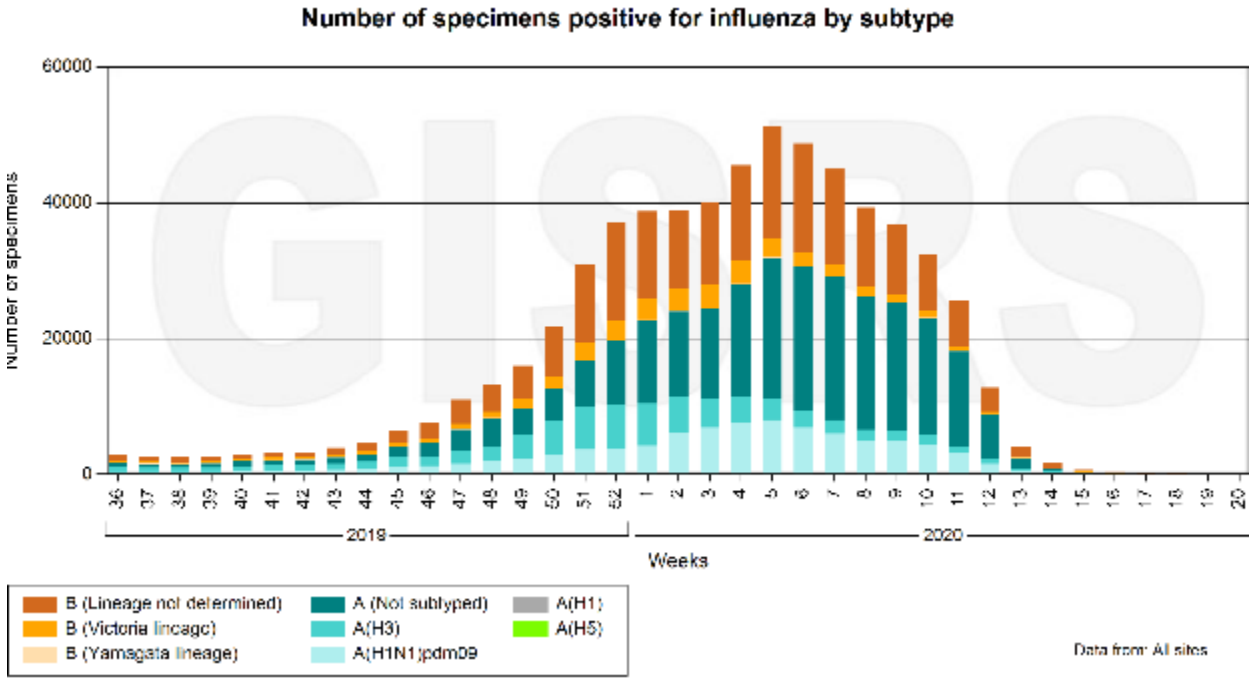
Data source: FluNet, (www.who.int/flunet), Global Influenza Surveillance and Response System (10 February 2021)

Percent Influenza Positive by Calendar Week and Year

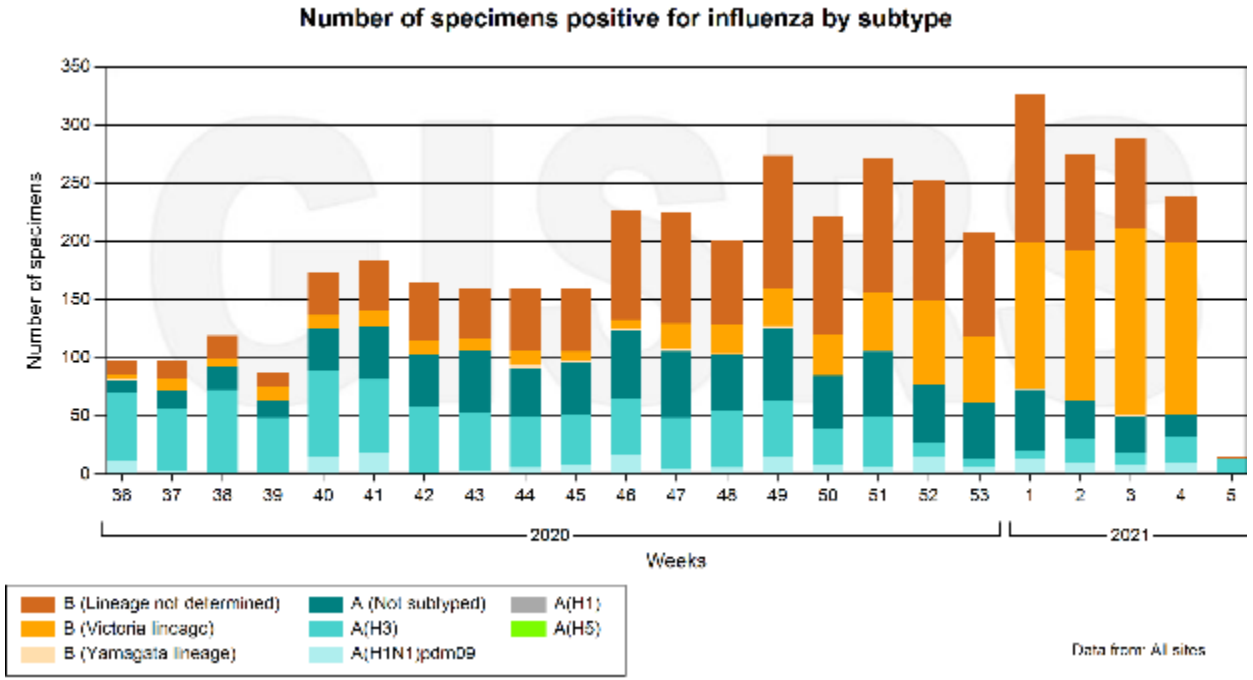


Global Circulation of Influenza Viruses

2019 - 2020

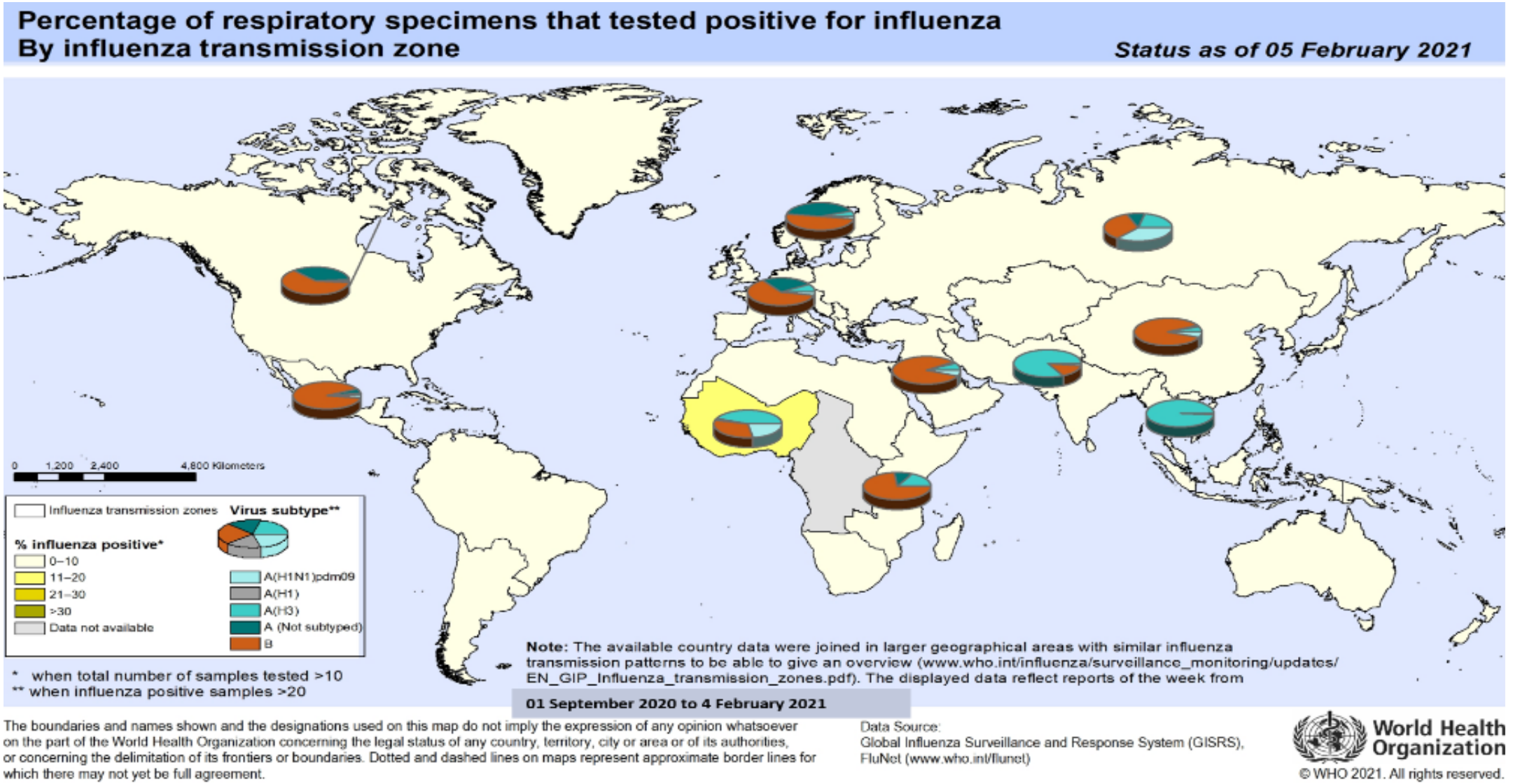


2020 - 2021



Influenza Laboratory Surveillance Information by the Global Influenza Surveillance and Response System (GISRS)

Influenza Activity – Sep 2020 to Jan 2021

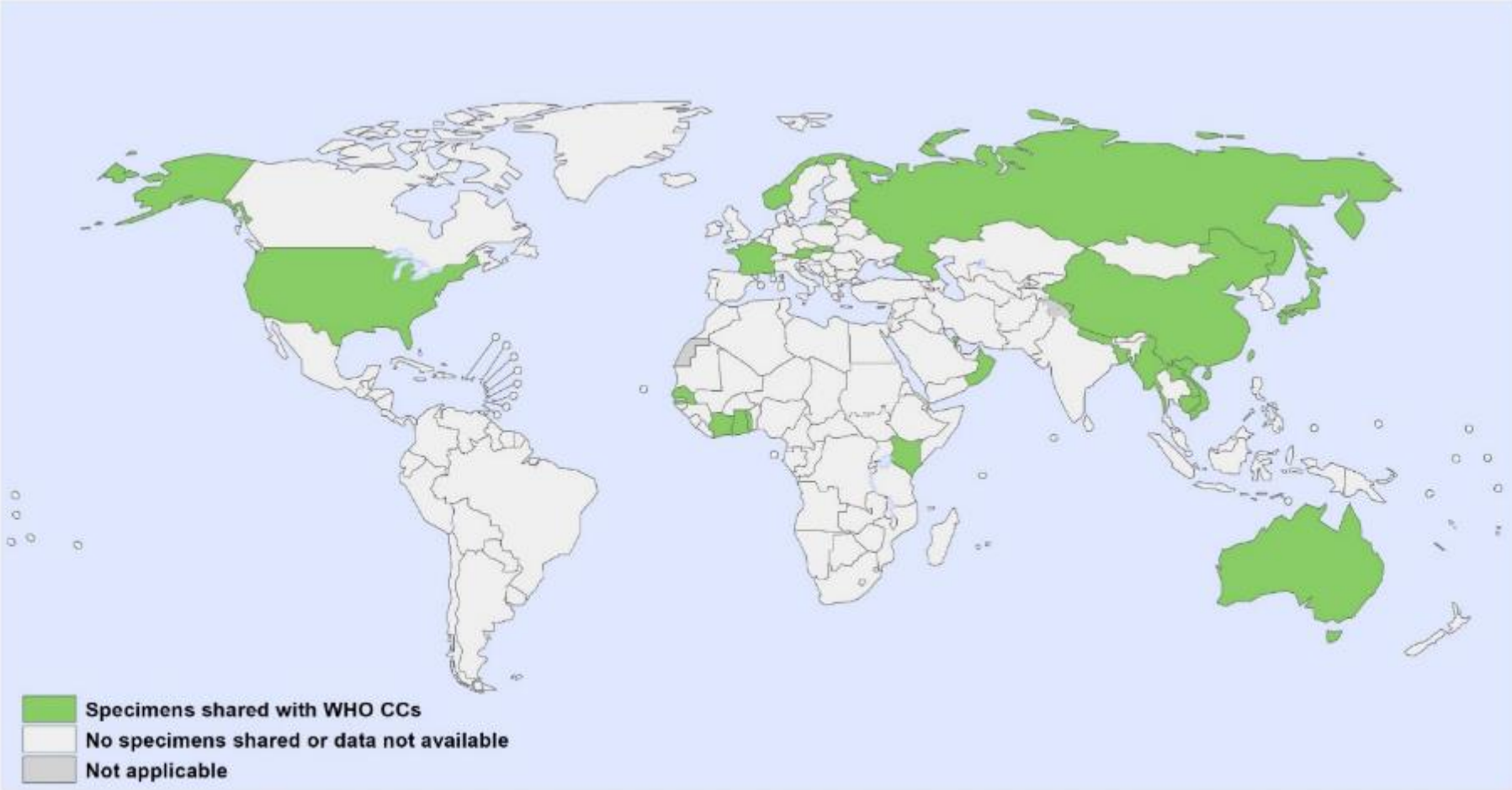


The boundaries and names shown and the designations used on this map do not imply the expression of any opinion whatsoever on the part of the World Health Organization concerning the legal status of any country, territory, city or area or of its authorities, or concerning the delimitation of its frontiers or boundaries. Dotted and dashed lines on maps represent approximate border lines for which there may not yet be full agreement.

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

World Health Organization

Countries, Areas And Territories That Shared Viruses With WHO CCs (Sep 2020 – Jan 2021)

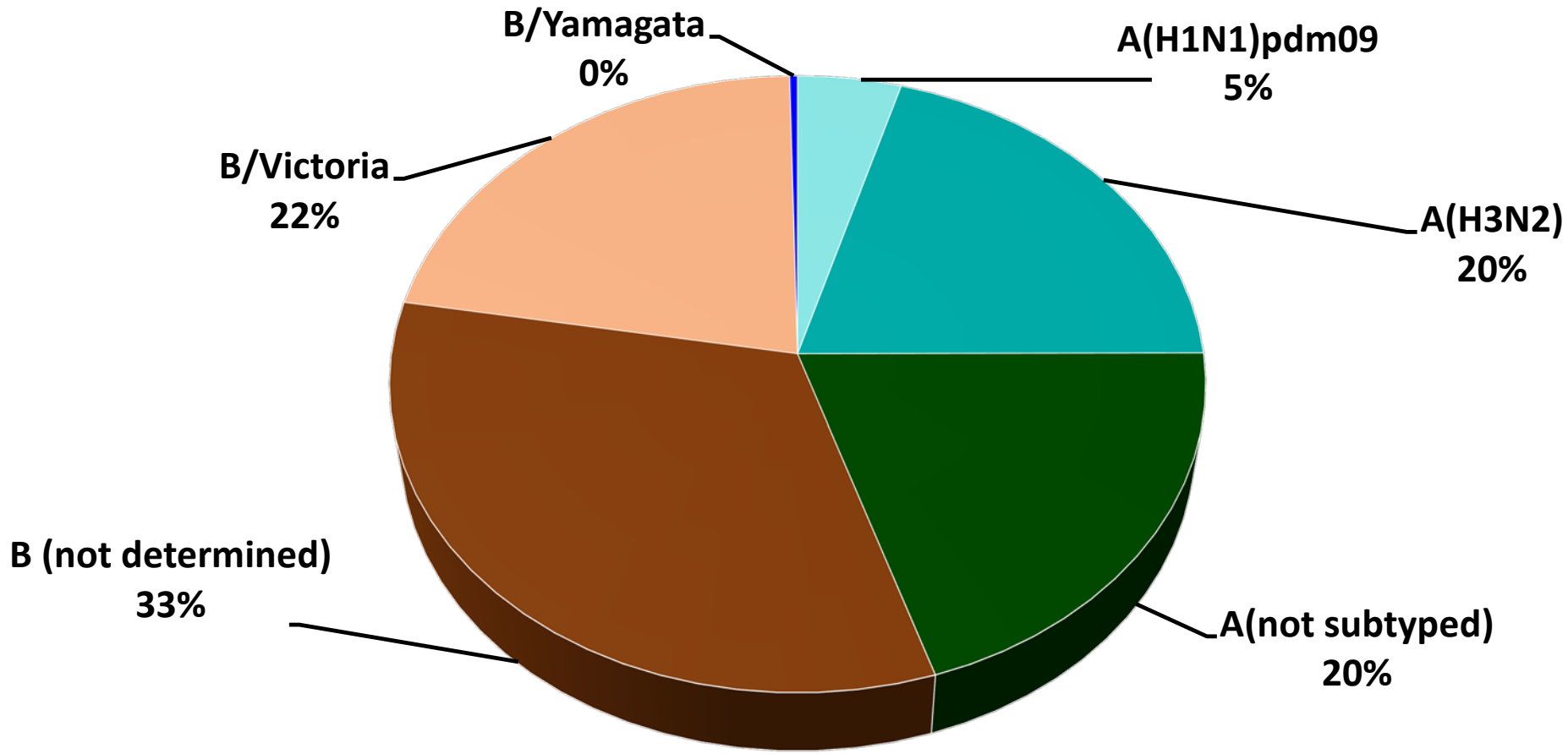


The boundaries and names shown and the designations used on this map do not imply the expression of any opinion whatsoever on the part of the World Health Organization concerning the legal status of any country, territory, city or area or of its authorities, or concerning the delimitation of its frontiers or boundaries. Dotted and dashed lines on maps represent approximate border lines for which there may not yet be full agreement.

Data Source: WHO CC reports for the WHO influenza vaccine composition consultation in February 2021
Map Production: WHO Global Influenza Programme
World Health Organization

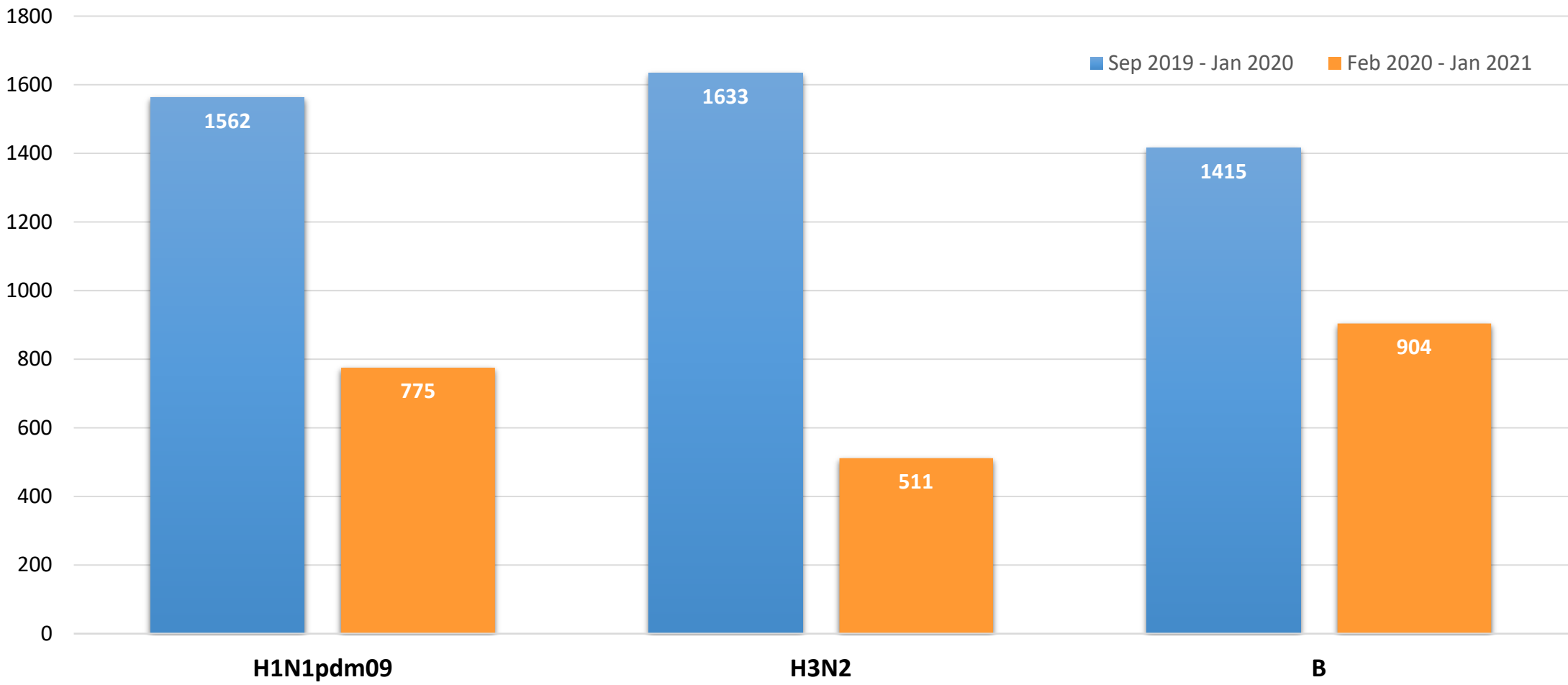
World Health Organization

Percentage of Influenza Viruses by Type/Subtype (Sep 2020– Jan 2021)



Data source: FluNet (www.who.int/flunet), Global Influenza Surveillance and Response System (14 February 2021)

Influenza Viruses Genetically Characterized By WHO CCs



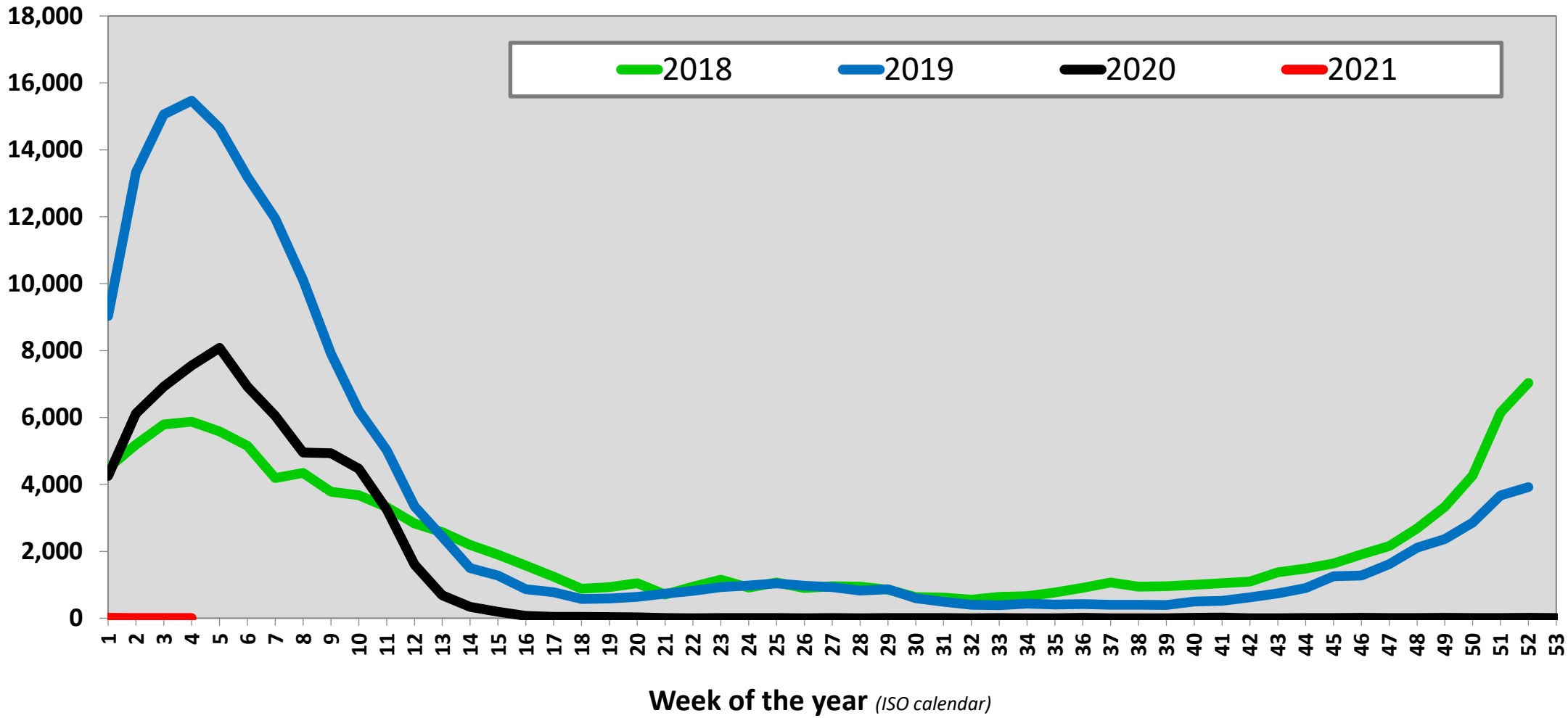
A(H1N1)pdm09 Viruses

September 2020 – February 2021

Influenza A(H1N1)pdm09 Virus Activity Geographic Distribution

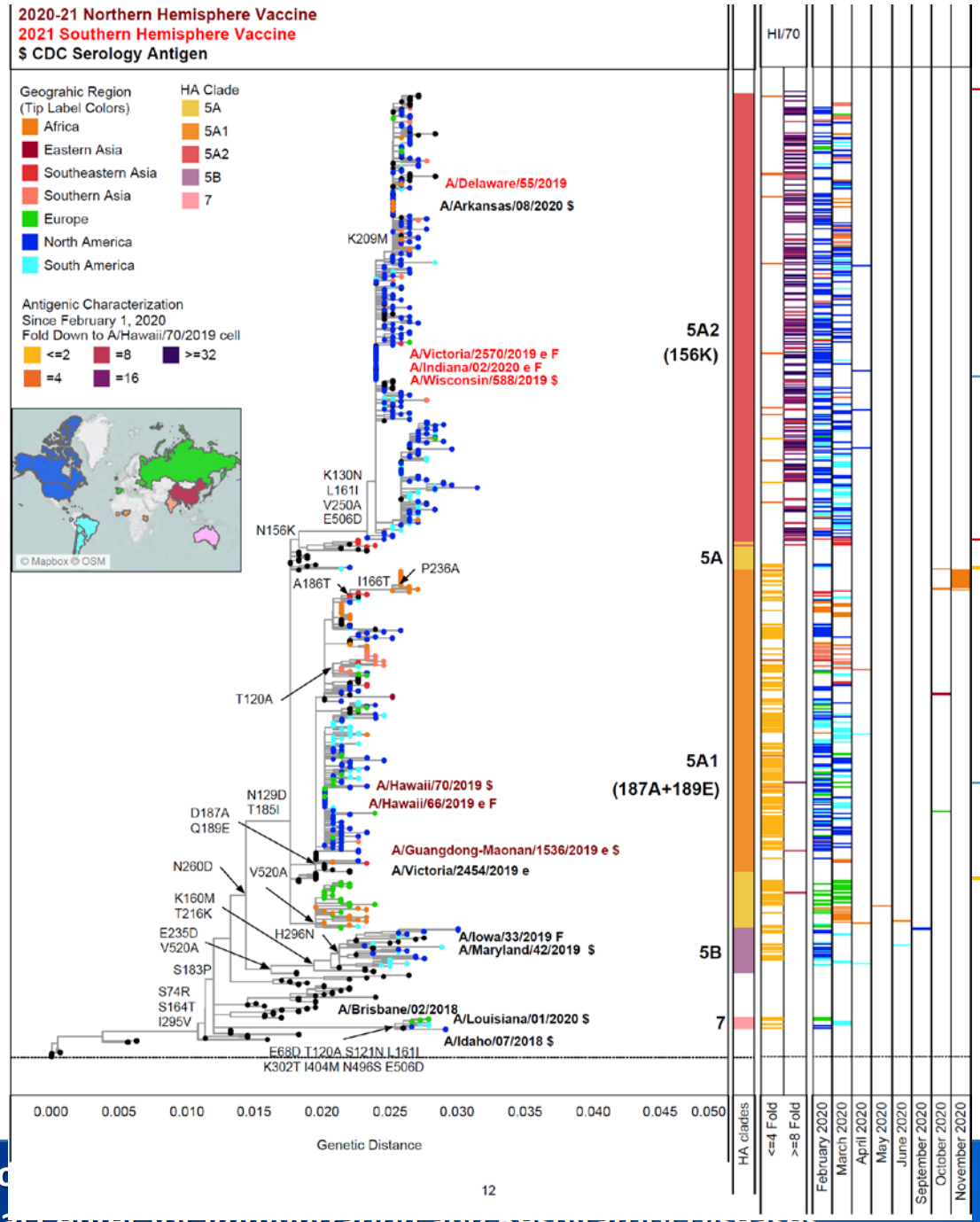
Influenza A(H1N1)pdm09, September 2020 to January 2021, percent of all samples tested

Number of A(H1N1)pdm09 Viruses Detected By GISRS



Data source: FluNet, (www.who.int/flunet), Global Influenza Surveillance and Response System (10 February 2021)

Phylogenetics of A(H1N1)pdm09 HA Gene

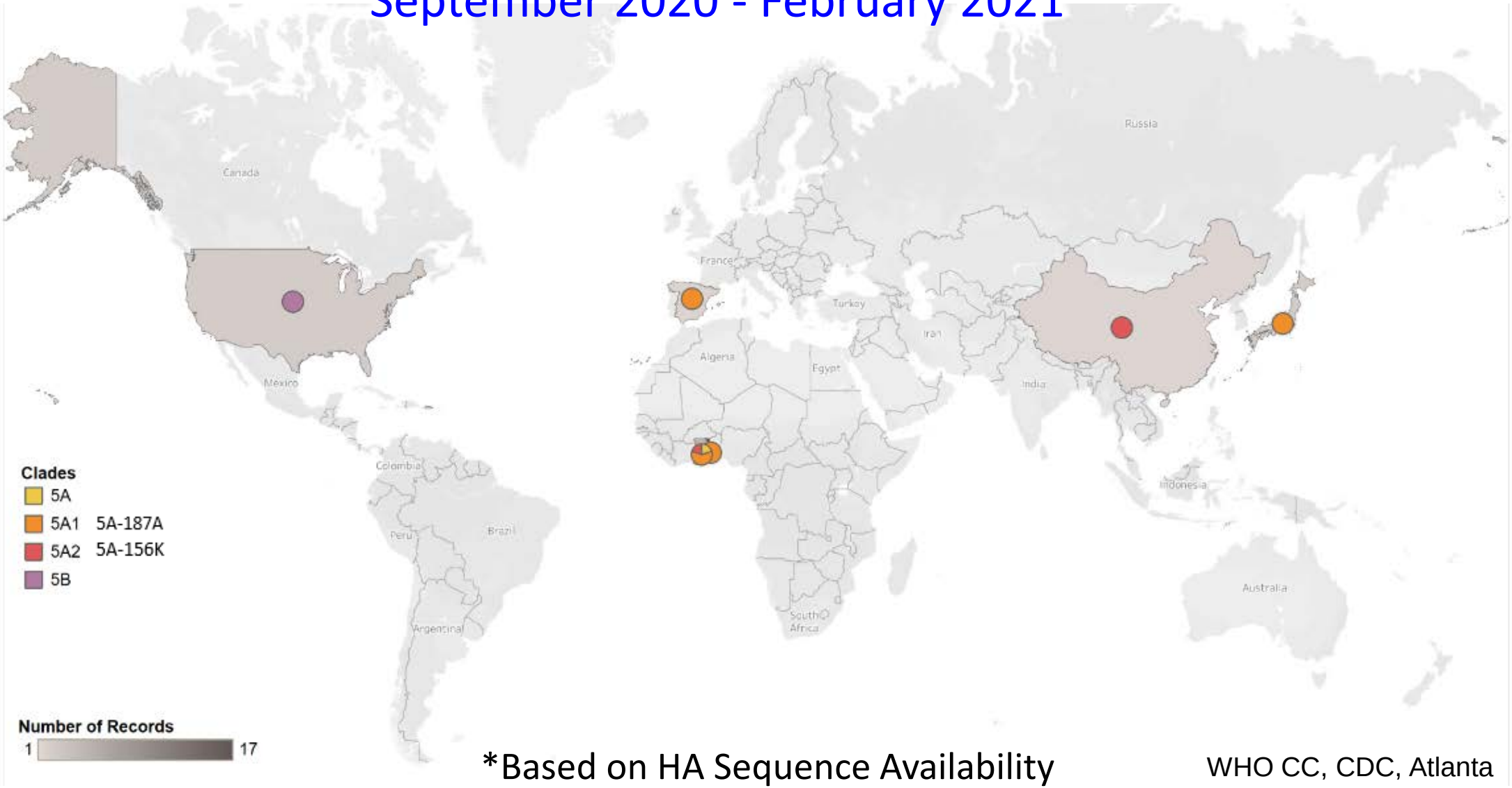


Recommended cell prototype

Current cell prototype

A(H1N1)pdm09 HA 6B.1A Clade Distribution

September 2020 - February 2021*



*Based on HA Sequence Availability

WHO CC, CDC, Atlanta

Reactivity of A(H1N1)pdm09 Viruses With Ferret Antisera To Antigens Recommended For NH 2020-21

Ferret antisera to vaccine reference viruses in clade 6B.1A **5A1**

A/Hawaii/70/2019-like (cell)

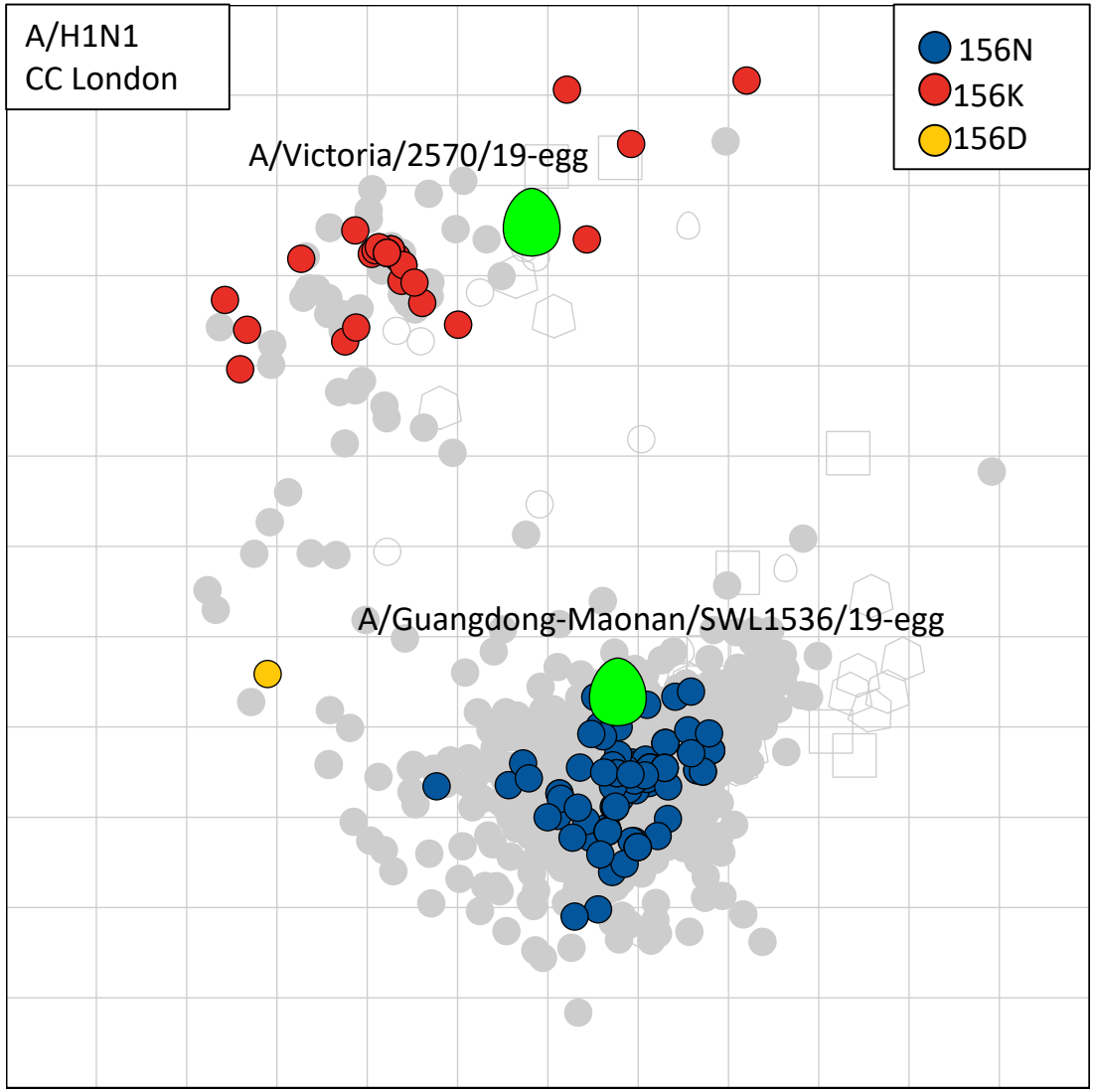
WHO CC	Like (2-4 fold)	Low (≥ 8 fold)
CDC	8 (100%)	0 (0%)
CNIC	0 (0%)	1 (100%)
FCI	2 (100%)	0 (0%)
NIID	1 (100%)	0 (0%)
TOTAL	11 (92%)	1 (8%)

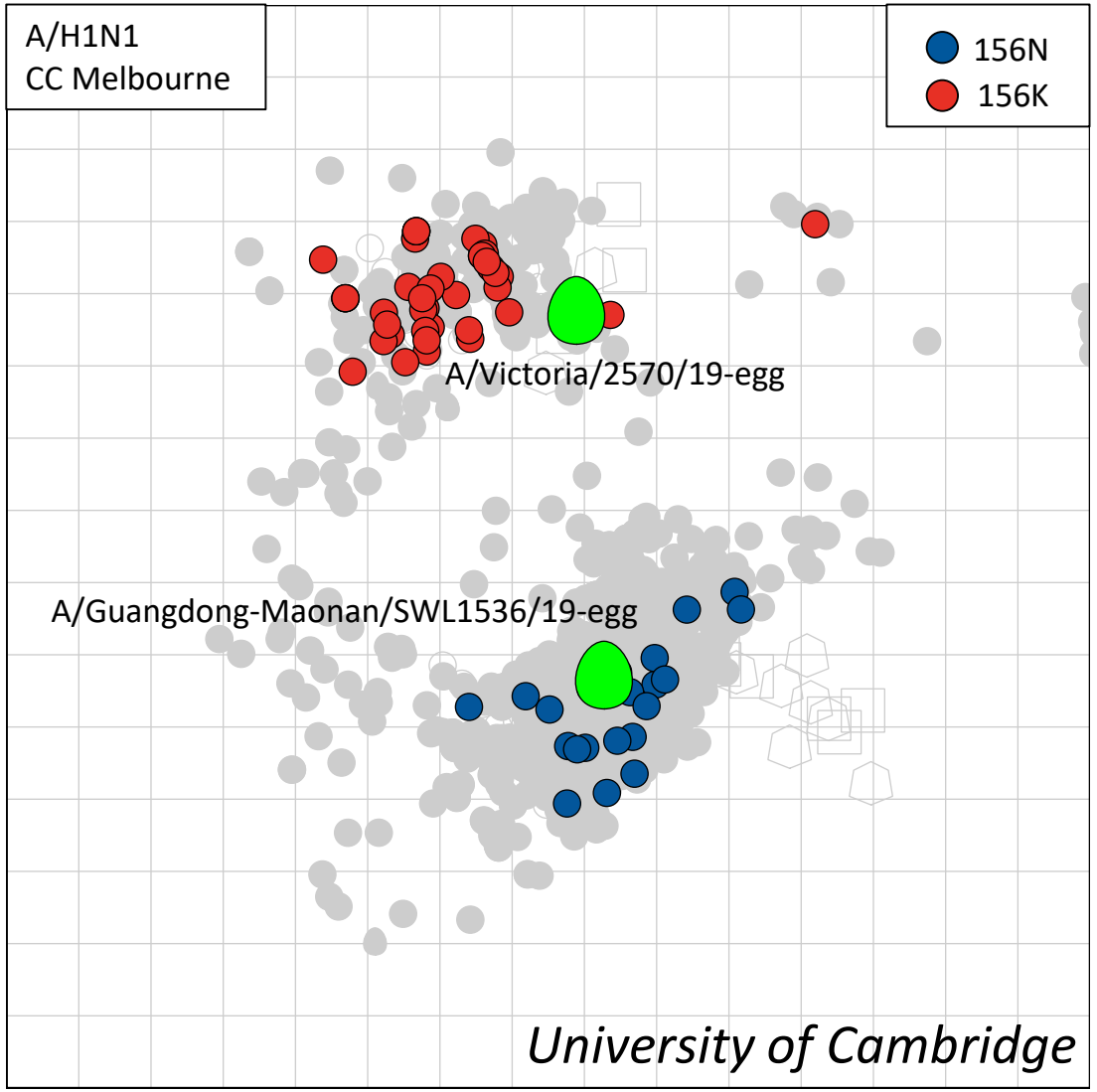
A/Guangdong-Maonan/1536/2019-like (egg)

WHO CC	Like (2-4 fold)	Low (≥ 8 fold)
CDC	8 (100%)	0 (0%)
CNIC	0 (0%)	1 (100%)
FCI	2 (100%)	0 (0%)
NIID	1 (100%)	0 (0%)
TOTAL	11 (92%)	1 (8%)

Data from hemagglutination inhibition assays using viruses isolated from specimens with collection dates from September 1, 2020 to January 31, 2021.

A(H1N1)pdm09 Antigenic Cartography





Past 12 months (older viruses in grey)

Human Post-vaccination Sera Analysis With H1N1 Viruses (1)

GMTs relative to CELL-propagated A/Haw

Clade or Subclade (+ additional substitutions)

				5A1	5A1 +A187V	5A2 (N156K)	5A2 (N156K) +K209M	5B (K130N +K160M)	3	7
				*HI/70 SIat	GUAN/1536 Egg	WI/588 SIat	AR/08 SIat	MD/42 SIat	ID/07 SIat	LA/01 SIat
A/HAWAII/70/2019 SIat	6-35mo Pediatric	USA	IIV4	80	51	10	11	16	16	18
	3-8yr Pediatric	USA	ccIIV4 (Flucelvax)	788	331	166	381	√	√	√
			IIV4	485	190	83	190	√	√	√
	9-17yr Pediatric	USA	ccIIV4 (Flucelvax)	422	219	83	√	√	√	√
			IIV4	618	309	86	251	√	√	√
	Adult	USA	ccIIV4 (Flucelvax)	816	453	166	355	√	437	√
			RIV4 (Flublok)	381	184	43	166	√	√	√
			IIV4	394	√	49	106	260	211	√
		Japan	IIV4	113	√	31	40	√	√	√
		UK/NIBSC	IIV4	60	35	9	18	28	√	√
	50-64yr Older Adult	USA	IIV4	171	√	35	65	121	√	√
	Elderly	Japan	IIV4	127	71	38	48	√	√	√
	≥65yr Elderly	USA	IIV4-HD	394	226	53	98	184	211	211

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/ARKANSAS/08/2020 (AR/08); A/GUANGDONG-MAONAN/1536/2019 (GUAN/1536); A/HAWAII/70/2019 (HI/70); A/IDAHO/07/2018 (ID/07); A/LOUISIANA/01/2020 (LA/01); A/MARYLAND/42/2019 (MD/42); A/WISCONSIN/588/2019 (WI/588).

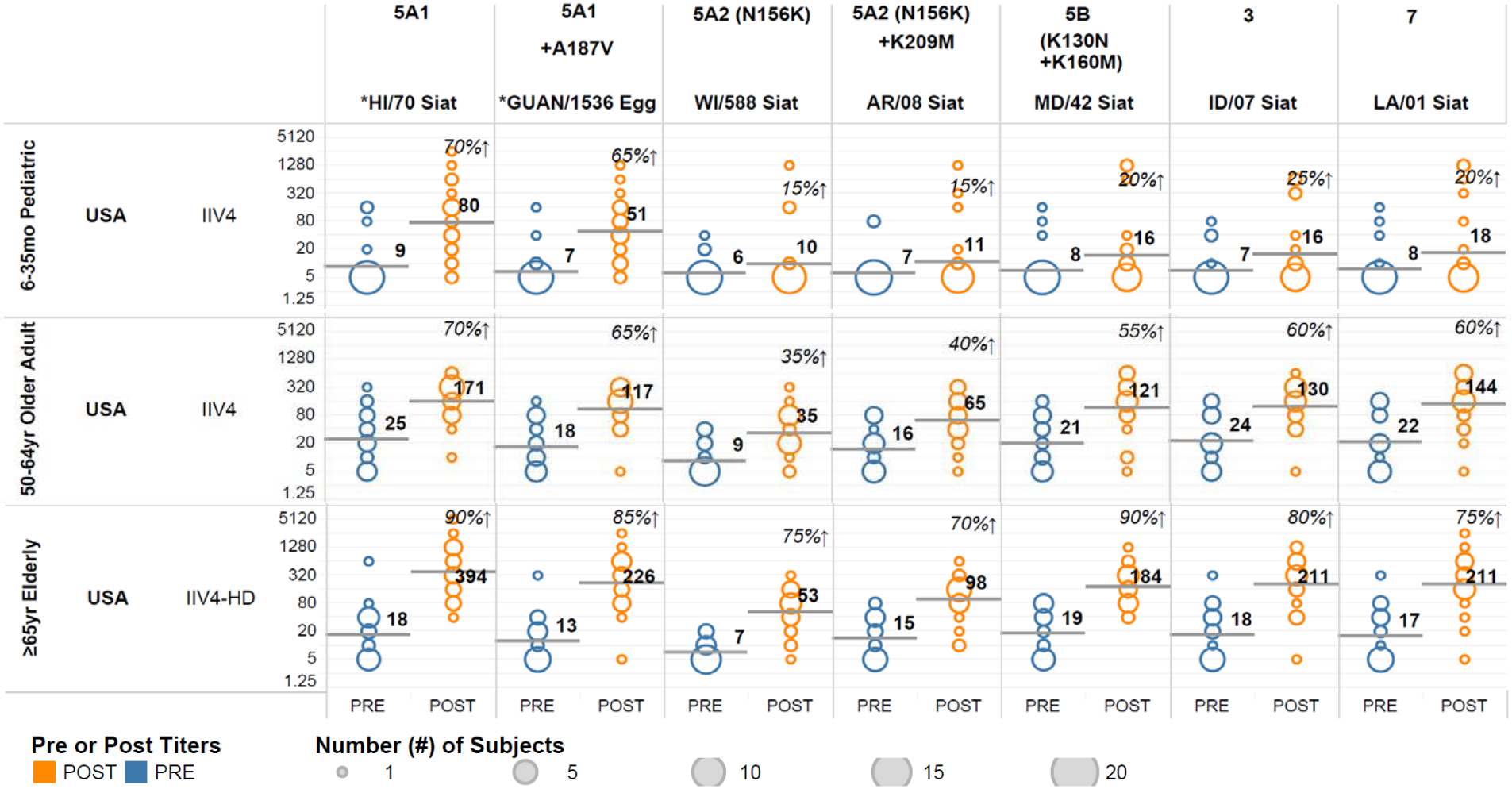
Statistically non-inferior = √
Statistically non-inferior but reference virus GMT < 40 = X

GMT ratio lowerbound (90% CI)
0.0 — 1.0

Human post-vaccination sera analysis with H1N1 viruses (2)

Pre (Bl.)
(Or.) Vac
Tite

Clade or Subclade (+ additional substitutions)



Arrow (↑) represents percent (%) seroconversion: ≥4-fold rise from pre- to post-vaccination with post-vaccination titer ≥ 40

Summary of A(H1N1)pdm09 Viruses (1)

- A(H1N1)pdm09 viruses predominated in some countries in northern hemisphere
  - Africa(Egypt, Niger and Togo), Asia(the Democratic People's Republic of Korea) and Europe(Ukraine).
- HA gene sequences belong to clade 6B.1A, with subclades 5A, 5B co-circulating
  - Majority belong to subclade 5A, which has further diversified
    - 5A1 HA proteins have D187A and Q189E substitutions (site Sb)
    - 5A2 HA proteins have N156K and L161I, K130N, V250A in HA1, as well as E179D in HA2
- Ferret antisera to reference A(H1N1)pdm09 viruses (e.g., A/Guangdong-Maonan/SWL1536/2019-like (5A1) well recognized many circulating viruses, except HA subclade 5A2 (156K) viruses

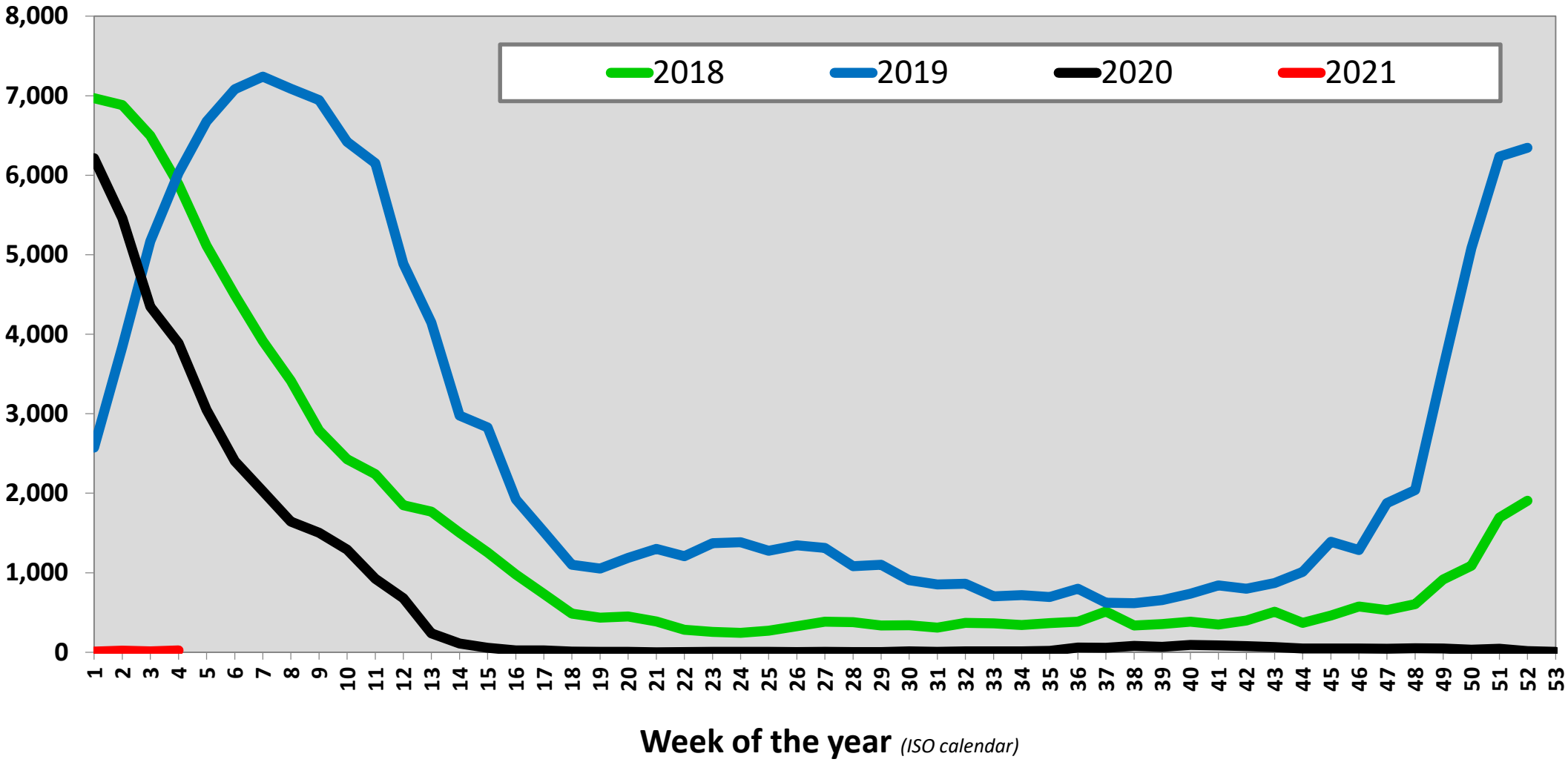
Summary of A(H1N1)pdm09 Viruses (2)

- Post vaccination sera collected from humans vaccinated with NH 2020-2021 vaccines
  - GMTs against viruses representing HA group 5A2 (156K) were significantly reduced
- Of 20 viruses analyzed, none showed reduced susceptibility to one or more of the neuraminidase inhibitors.
- Genetic analysis of 20 viruses indicated that all should be susceptible to baloxavir.

Influenza A(H3N2) viruses

September 2020 - February 2021

Number of A(H3N2) viruses detected by GISRS

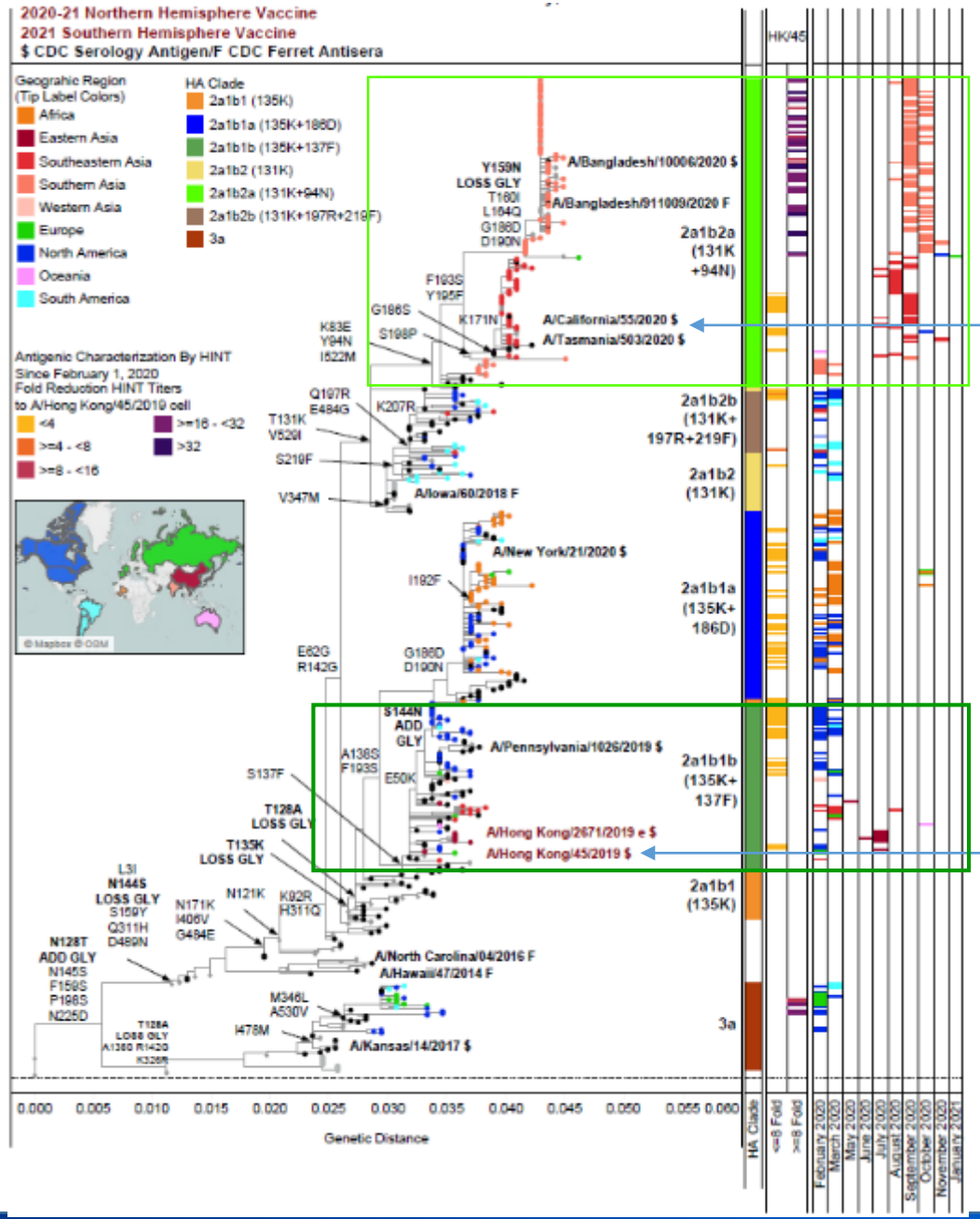


Data source: FluNet, (www.who.int/flunet), Global Influenza Surveillance and Response System (10 February 2021)

Influenza A(H3N2) Virus Activity Global Distribution

Influenza A(H3N2), September 2020 to January 2021, percent of all samples tested

Phylogeography of A(H3N2) HA and Integrated Antigenic Data

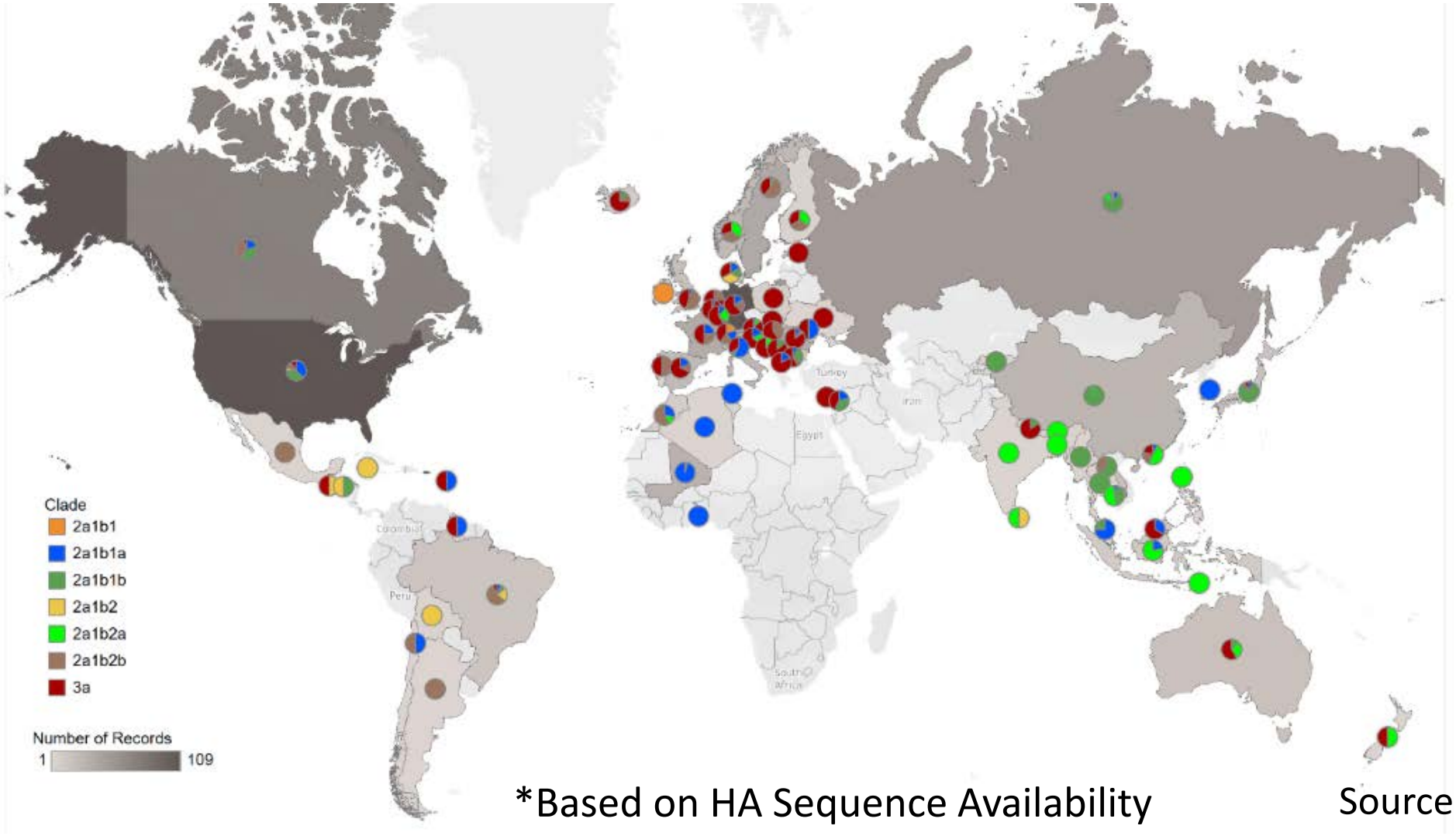


2021-22 vaccine recommendation in this subclade

Current cell prototype

A(H3N2)HA 3C clade distribution

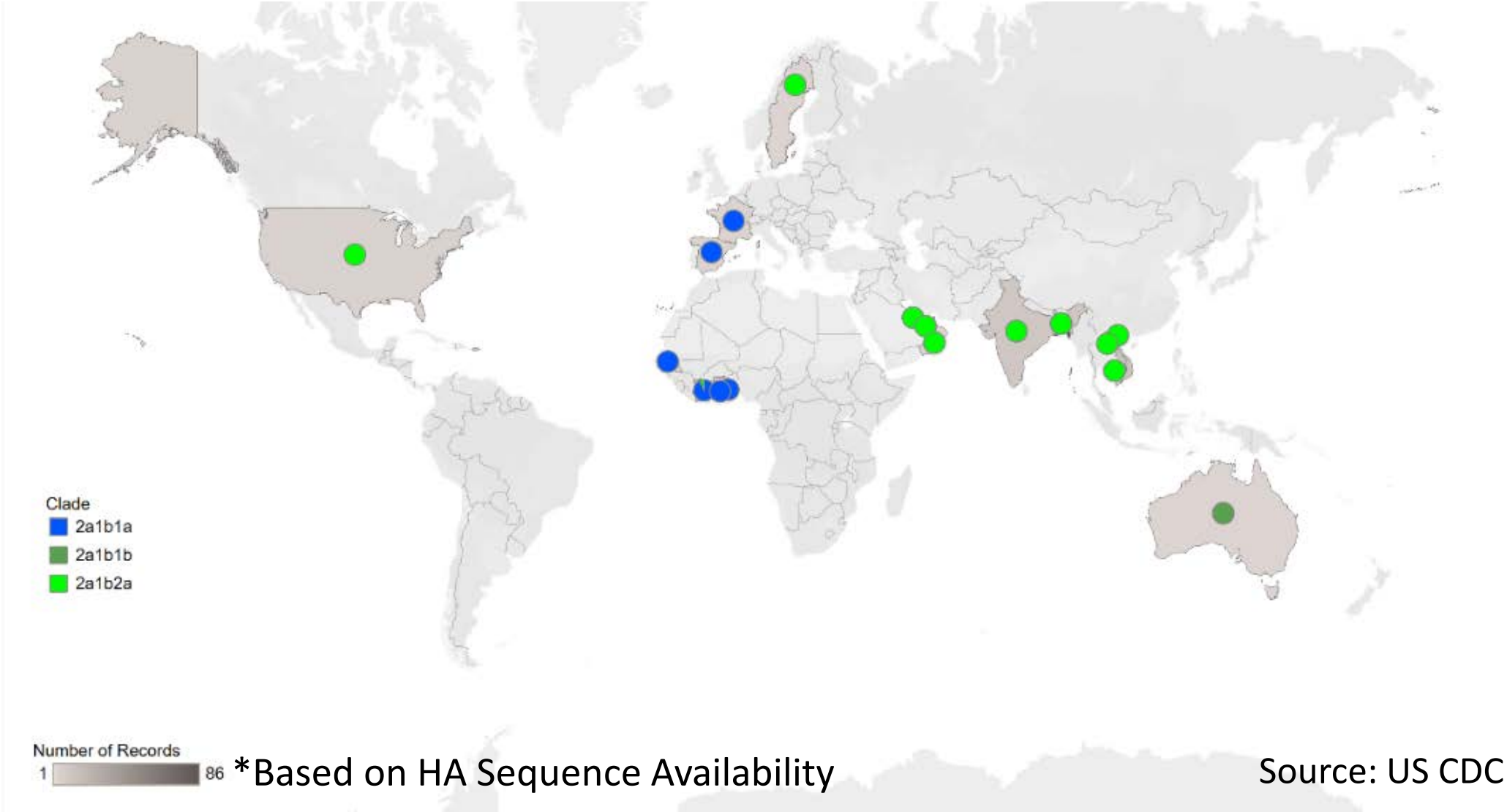
February 2020 to September 2020*



*Based on HA Sequence Availability

Source: US CDC

A(H3N2)HA 3C clade distribution
September - February 2021*



*Based on HA Sequence Availability

Source: US CDC

Reactivity of Recent A(H3N2) Viruses with Antisera to Antigens Recommended for NH 2020-21 and SH 2021

Ferret antisera to vaccine reference viruses in subclade 3C.2a1b.1b

A/Hong Kong/45/2019-Cell

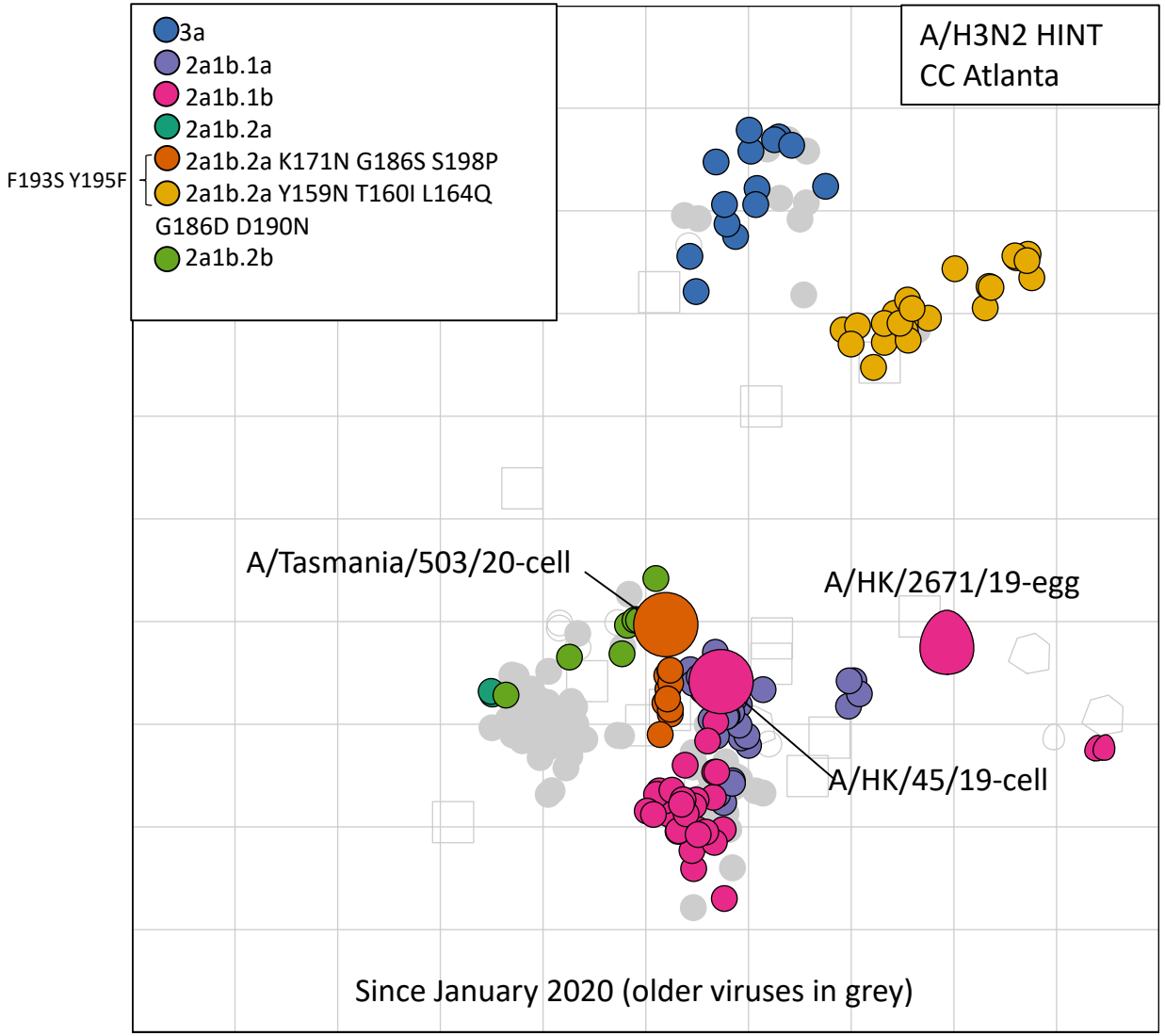
WHO CC	Like (2-4 fold)	Low (≥ 8 fold)
CDC	12 (38%)	20 (63%)
FCI	10 (67%)	5 (33%)
VIDRL	0	3 (100%)
TOTAL	22 (44%)	28 (56%)

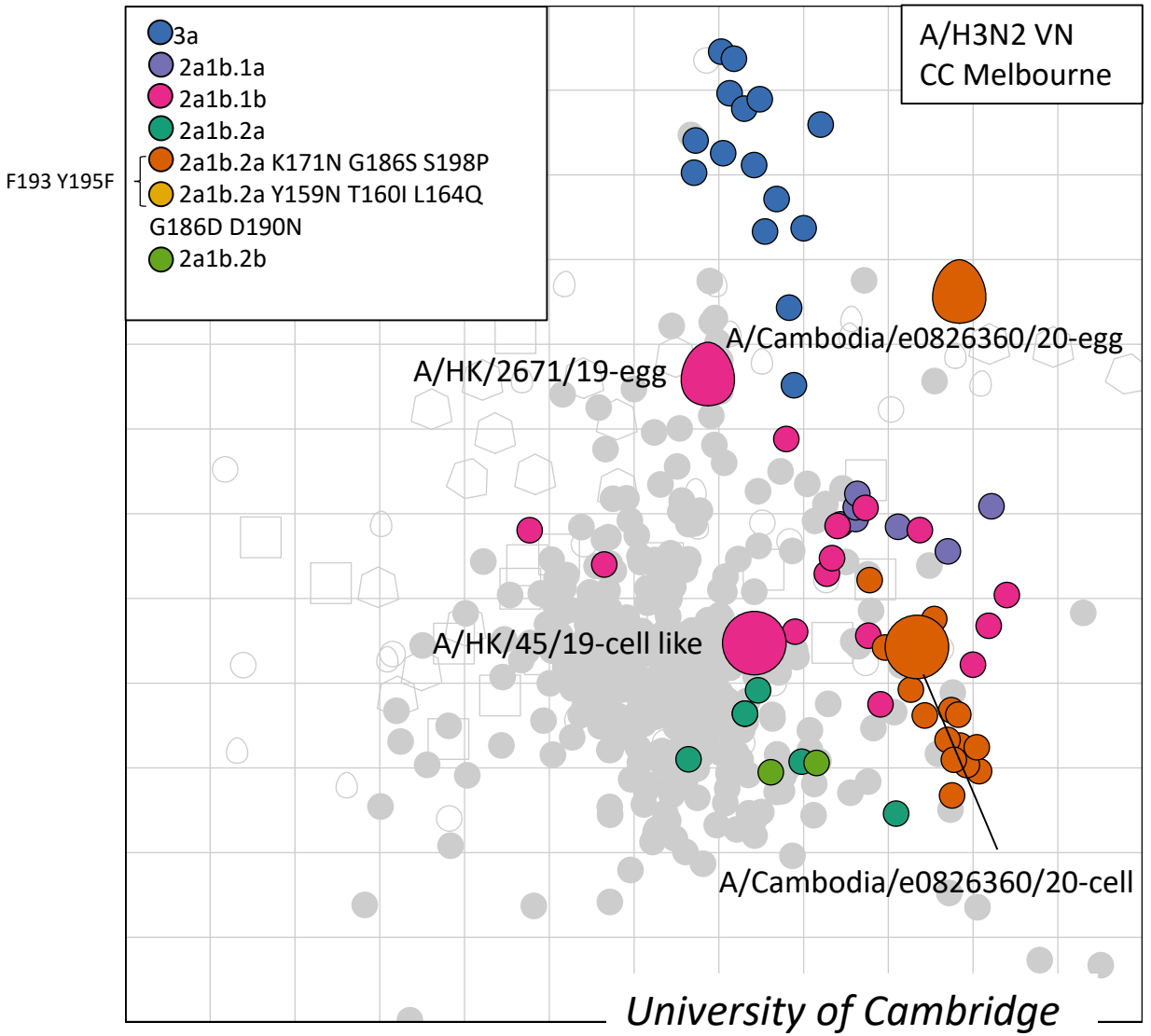
A/Hong Kong/2671/2019-Egg

WHO CC	Like (2-4 fold)	Low (≥ 8 fold)
CDC	0 (0%)	32 (100%)
FCI	0 (0%)	15 (100%)
VIDRL	0 (0%)	3 (100%)
TOTAL	0 (0%)	50 (100%)

Data from virus neutralization assays using viruses isolated from specimens with collection dates from September 1, 2020 to January 31, 2021.

A(H3N2) Antigenic Cartography of VN Data





Antigenic analysis of Recently Circulating A(H3N2) Viruses

Reference viruses for:		Current Vaccine				Recommended Vaccine				
		Cell	Egg			Cell	Egg			
	S3 STHAUST34 A8659 A1b/131K	S1 DAR726 A8831 A1b/137F	E8 HK2671 A8839 A1b/137F	S3 BANG10006 2021–009 A1b/94N	S2 BANG10009 2021–008 A1b/94N	S2 CAMe0826360 A9050 A1b/94N 186S	E5 CAMe0826360 A9049 A1b/94N 186S	S2 TAS503 A8941 A1b/94N 186S	2020 Aust human sera	Clade
REFERENCE ANTIGENS										
A/South Australia/34/2019	**320**	160	40	320	320	320	160	320	**160**	A1b/131K
A/Darwin/726/2019	40	**1280**	80	40	80	320	20	160	40	A1b/137F
A/Hong Kong/2671/2019	80	1280	**1280**	80	320	80	40	80	160	A1b/137F
A/Bangladesh/10006/2020	40	80	40	**320**	320	160	160	80	20	A1b/94N+186D
A/Bangladesh/10009/2020	80	80	40	320	**320**	320	160	80	20	A1b/94N+186D
A/Cambodia/E0826360/2020	80	40	20	160	160	**320**	80	160	10	A1b/94N+186S
A/Cambodia/E0826360/2020.1	40	20	40	80	80	80	**320**	80	10	A1b/94N+186S
A/Tasmania/503/2020	40	40	20	80	80	320	40	**160**	10	A1b/94N+186S
TEST ANTIGENS										
A/Bangladesh/3011/2020	80	160	80	640	640	160	320	80	40	A1b/94N+186D
A/Bangladesh/4002/2020	80	160	80	640	640	320	320	160	40	A1b/94N+186D
A/Bangladesh/3005/2020	80	80	80	640	640	160	320	80	40	A1b/94N+186D
A/Bangladesh/911009/2020	40	80	40	640	640	160	320	80	40	A1b/94N+186D
A/Timor-Leste/17/2020	160	160	40	320	320	640	160	640	20	A1b/94N+186S
A/Cambodia/E0826361/2020	80	80	40	160	160	640	80	320	20	A1b/94N+186S
A/Cambodia/E0908371/2020	80	80	40	160	320	640	80	320	20	A1b/94N+186S
A/Cambodia/E0826362/2020	80	40	40	160	320	640	80	320	20	A1b/94N+186S
A/Cambodia/E1009251/2020	160	80	20	160	160	640	160	320	20	A1b/94N+186S
A/Timor-Leste/2/2020	80	80	20	160	160	320	80	320	10	A1b/94N+186S
A/Cambodia/E0826363/2020	80	40	20	160	160	640	80	320	20	A1b/94N+186S
A/Cambodia/E0908364/2020	80	40	20	160	160	320	80	160	10	A1b/94N+186S
A/Cambodia/E0925253/2020	80	40	20	160	160	320	80	320	10	A1b/94N+186S
A/Cambodia/E0925256/2020	80	40	20	160	160	640	80	320	20	A1b/94N+186S
A/California/55/2020	40	20	20	80	80	320	40	160	10	A1b/94N+186S

Fold difference

- <4−fold
- 4−fold
- 8−fold
- >8−fold

Hemagglutination Inhibition Assay

Source: VIDRL

Human Post-vaccination Sera Analysis With A(H3N2) Viruses (1)

GMTs relative to CELL-propagated A/Hong Kong/45/2019 (2a1b.**1b**)

Recent …**2a** subclade viruses

A/HONG KONG/45/2019 Siat				2a1b1b *HK/45 Siat	2a1b1b +T160I (CHO-) +G186V +D225N +N312S HK/2671 Egg	2a1b1b +E50K +S144N (CHO+) PA/1026 Siat	2a1b1a +G186D +D190N NY/21 Siat	2a1b2a +A128T (CHO+) +K135T (CHO+) +G186S TAS/503 Siat	2a1b2a +A128T (CHO+) +K135T (CHO+) +K171N +G186S CA/55 Siat	2a1b2a +A128T (CHO+) +K135T (CHO+) +Y159N+T160I (CHO-) +L164Q+G186D +D190N BGD/10006 Siat	3a KS/14 Siat
6-35mo Pediatric	USA	IIV4	23	X	10	X	11	10	9	14
3-8yr Pediatric	USA	ccIIV4 (Flucelvax)	640	√	171	√	331	260	155	320
		IIV4	144	√	21	89	46	29	30	√
9-17yr Pediatric	USA	ccIIV4 (Flucelvax)	597	√	149	√	160	166	83	309
		IIV4	171	√	44	121	70	41	25	√
65yr or older	USA	ccIIV4 (Flucelvax)	485	√	126	234	126	92	57	279
		RIV4 (Flublok)	453	√	155	√	144	95	61	√
		IIV4	152	√	65	√	56	31	25	71
	Japan	IIV4	44	√	22	√	15	15	25	√
	UK/NIBSC	IIV4	44	√	18	√	17	15	13	√
50-64yr Older Adult	USA	IIV4	121	√	37	√	65	43	29	80
Elderly	USA	IIV4-HD	113	√	61	√	65	37	15	√

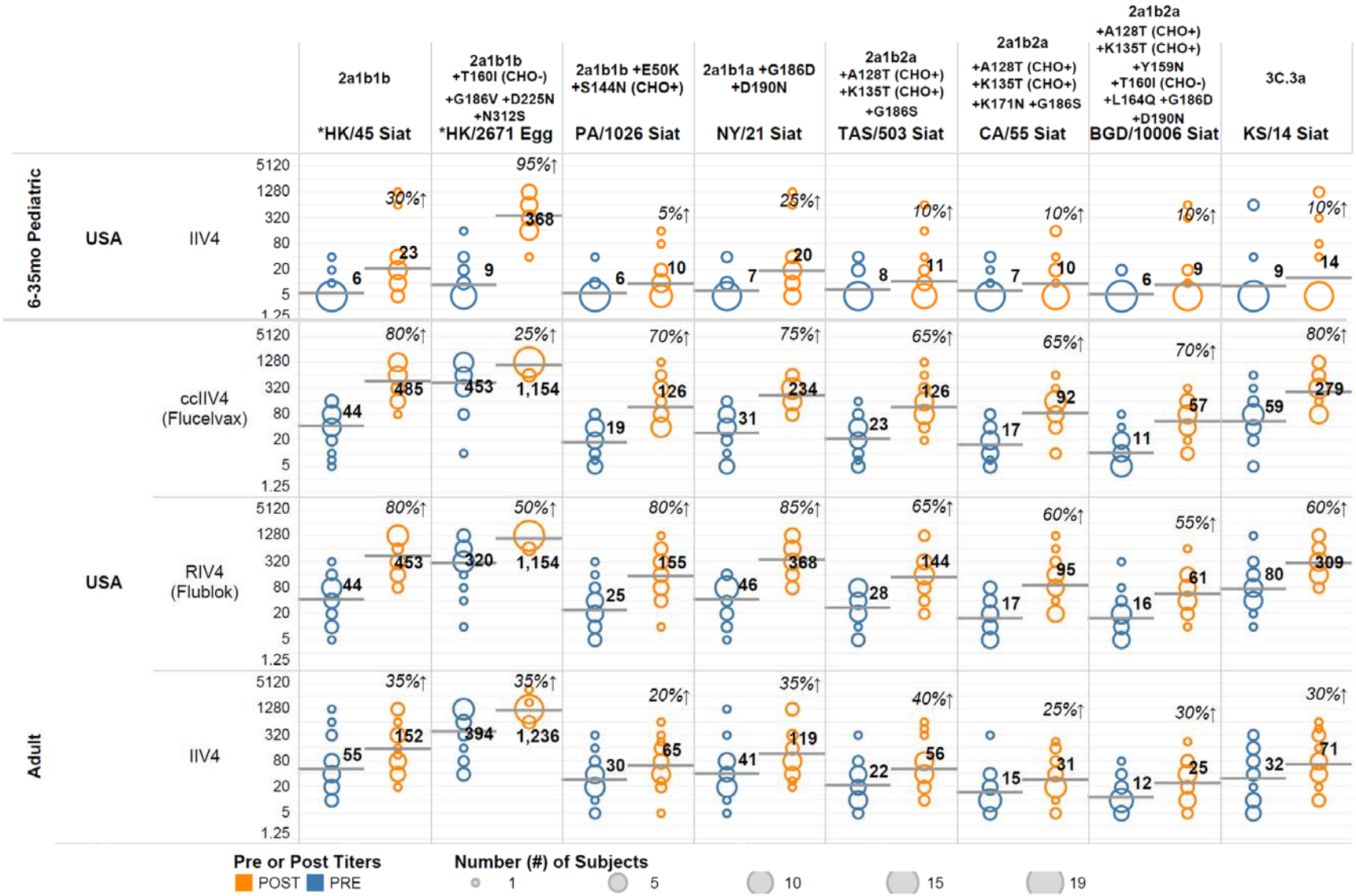
Geometric Mean Titer (GMT) ratios between reference and test antigens are calculated with 90% (CI) confidence intervals for each cohort and panel location. Unadjusted model results are shown. If the CI lower bound is greater than 50%, it is statistically non-inferior (95% confidence level), otherwise 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/10006/2020 (BGD/10006); A/CALIFORNIA/55/2020 (CA/55); A/HONG KONG/2671/2019 (HK/2671); A/HONG KONG/45/2019 (HK/45); A/KANSAS/14/2017 (KS/14); A/NEW YORK/21/2020 (NY/21); A/PENNSYLVANIA/1026/2019 (PA/1026); A/TASMANIA/503/2020 (TAS/503).

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

GMT ratio lowerbound (90% CI)
0.0 — 1.0

Human post-vaccination sera analysis with A(H3N2) viruses (2)

Pre (Bl.) vs Post (Or.) Vaccination Titers



Arrow (↑) represents percent (%) seroconversion: ≥4-fold rise from pre- to post-vaccination with post-vaccination titer ≥ 40

Summary of A(H3N2) Viruses (1)

- In most countries, areas and territories reporting influenza A viruses, both A(H1N1)pdm09 and A(H3N2) subtypes were detected.
- HA phylogenetics: Circulating A(H3N2) viruses in this period belonged to 3C.2a1b subclades with the following shared HA1 substitutions
  - 1a (also called T135K-A), with T135K, A138S, G186D, D190N, F193S & S198P
  - 1b (also called T135K-B) withT135K, S137F, A138S & F193S
    - 2020-21 vaccine virus in this group
  - 2a (also called T131K-A) with K83E, Y94N & T131K
    - New vaccine virus recommendations are in this group
    - Two subgroups that share F193S and Y195F formed these have:
      - K171N, G186S & S198P
      - Y159N, T160I (resulting in the loss of a glycosylation site), L164Q, G186D & D190N
    - Both groups shared D463N and N465S substitutions in the NA, which creates a potential N-linked glycosylation motif.
  - Viruses with HA genes belonging to 3C.2a1b subclade 2b (also called T131K-B) with T131K, Q197R and S219F, or clade 3C.3a were not detected in this period.

Summary of A(H3N2) Viruses (2)

- Ferret antisera raised against cell culture-propagated A/Hong Kong/45/2019-like viruses (3C.2a1b.**1b**) recognized
  - subclade 3C.2a1b.**1a** viruses well
  - the group within subclade 3C.2a1b.**2a** with HA1 substitutions K171N, G186S and S198P less well
  - the group within subclade 3C.2a1b.**2a** with HA1 substitutions Y159N, T160I, L164Q, G186D and D190N poorly
- Ferret antisera raised against egg-propagated A/Hong Kong/2671/2019-like viruses (3C.2a1b.**1b**) recognized all recent viruses poorly.

Summary of A(H3N2) Viruses (3)

- Ferret antisera to cell culture-propagated A/Cambodia/e0826360/2020 and A/Tasmania/503/2020 (3C.2a1b.**2a**) recognized viruses from
  - Subclade 3C.2a1b.**1a** and subclade 3C.2a1b.**2a** with additional HA1 substitutions K171N, G186S and S198P well
  - Subclade 3C.2a1b.**2a** with additional HA1 substitutions Y159N, T160I, L164Q, G186D and D190N less well
- Neither group of 3C.2a1b.**2a** viruses was recognized as well by antisera to egg-propagated A/Cambodia/e0826360/2020-like viruses in HI and VN assays.

Summary of A(H3N2) Viruses (4)

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 subclade 3C.2a1b.**1b** and 3C.2a1b.**2a** viruses but not against either 3C.2a1b.**1a** or 3C.2a1b.**2b** subclades or the 3C.3a HA clade.
- When compared to titres against egg-propagated A/Hong Kong/2671/2019-like reference viruses, significant reductions in GMTs were observed against cell culture-propagated viruses from all HA subclades.

Antiviral Susceptibility

- Of 140 A(H3N2) viruses collected and tested after August 2020, none showed reduced inhibition to neuraminidase inhibitors.
- Of 147 A(H3N2) viruses collected and tested after August 2020, none showed genetic or phenotypic evidence of reduced susceptibility to baloxavir.

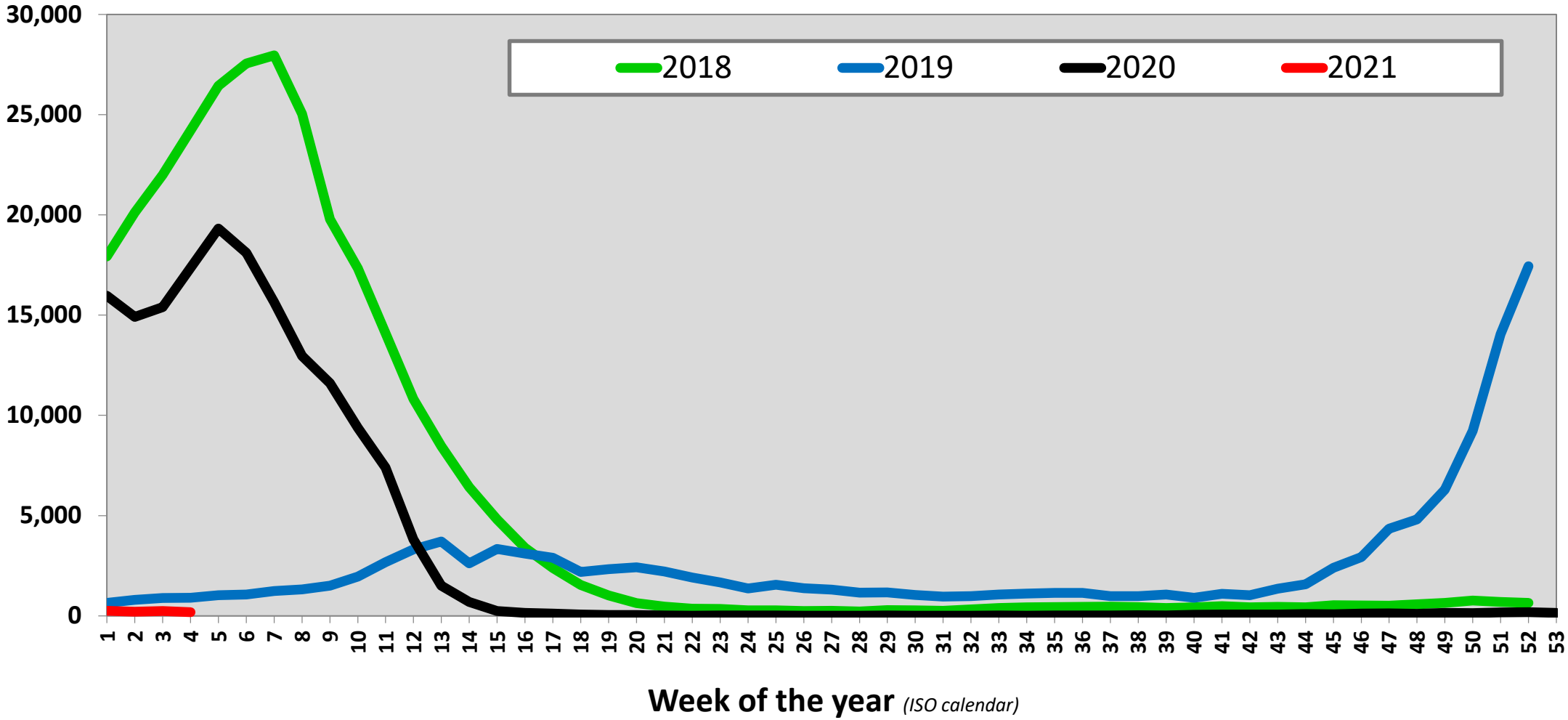
Influenza B viruses

September 2020 - February 2021

Influenza B Virus Activity Geographic Distribution

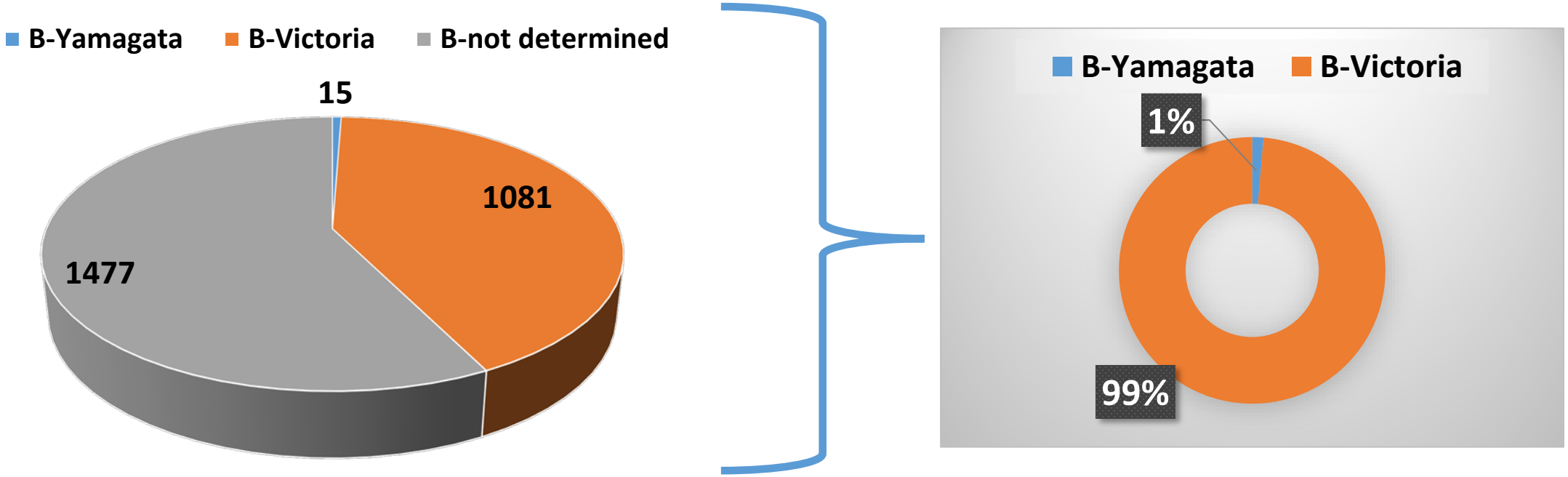
Influenza B, September 2020 to January 2021, percent of all samples tested

Number of B viruses detected by GISRS



Data source: FluNet, (www.who.int/flunet) Global Influenza Surveillance and Response System (10 February 2021)

Influenza B virus lineages %
(Sep 2020 – Jan 2021)

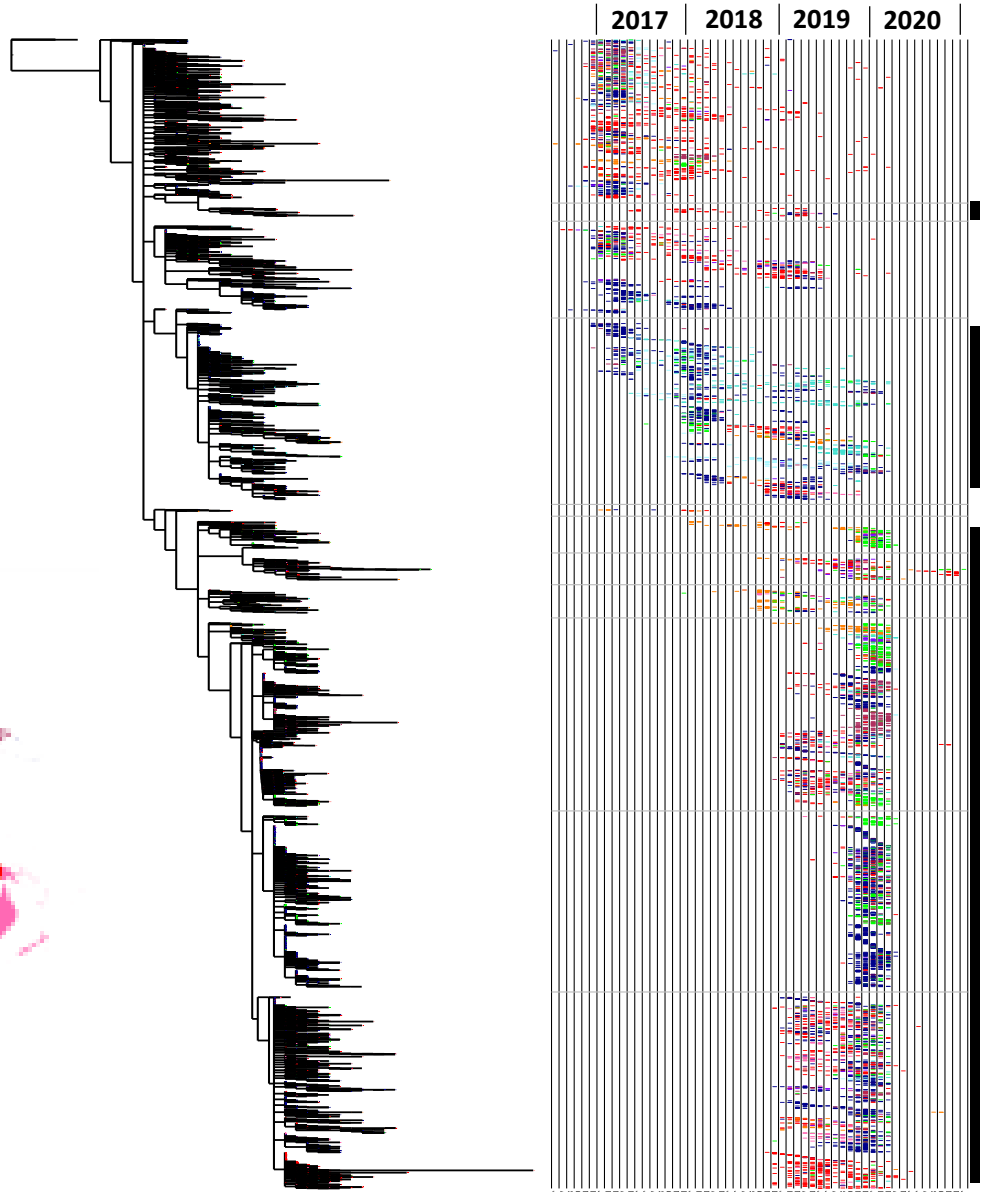


Data source: FluNet, (www.who.int/flunet) Global Influenza Surveillance and Response System (10 February 2021)

Influenza B/Victoria lineage viruses

B/Victoria HA phylogenetic tree

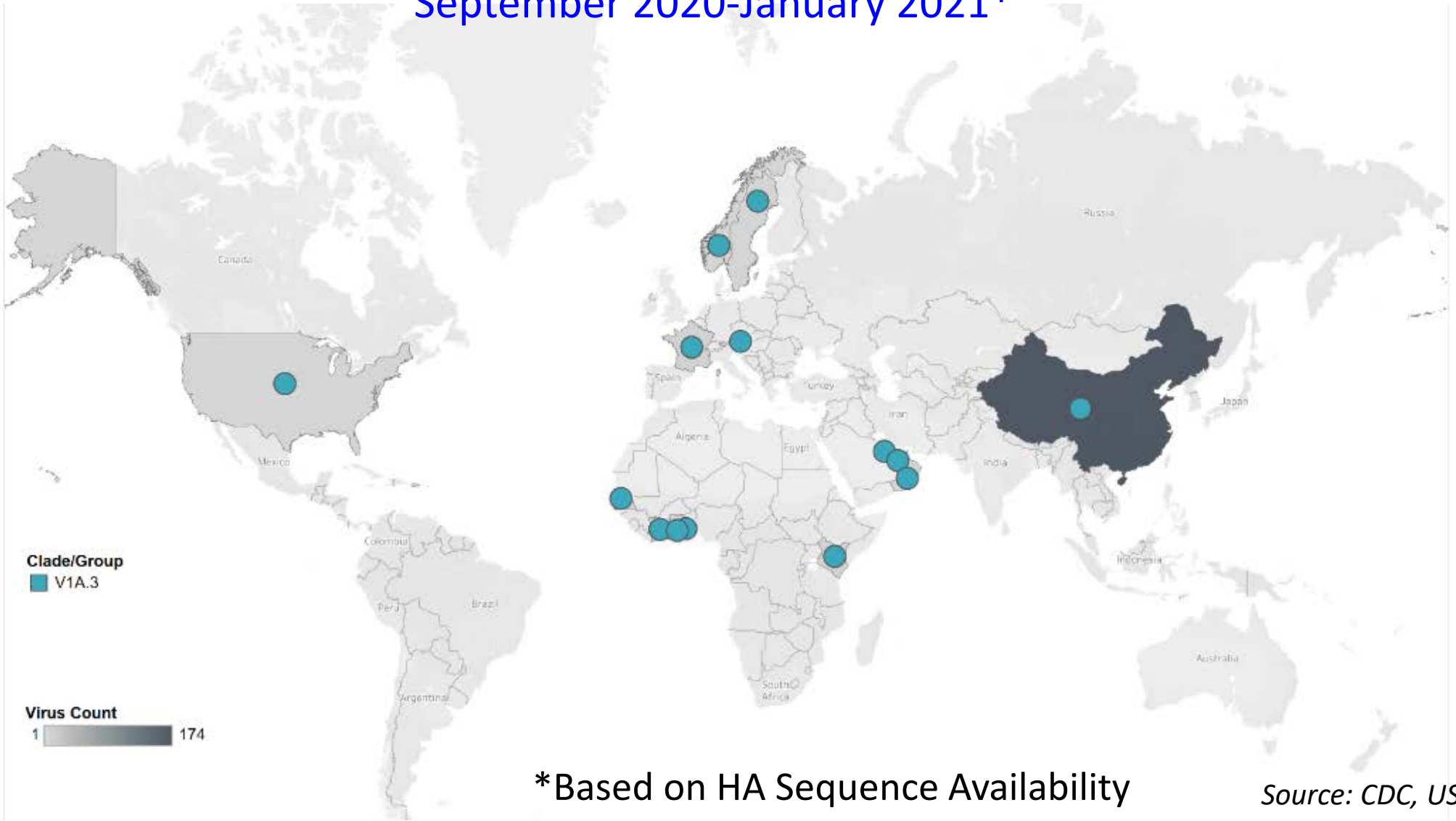
North America
South America
Europe
Africa
Middle East
Russia
E SE Asia
Oceania



Source: University of Cambridge

B/Victoria HA clade distribution

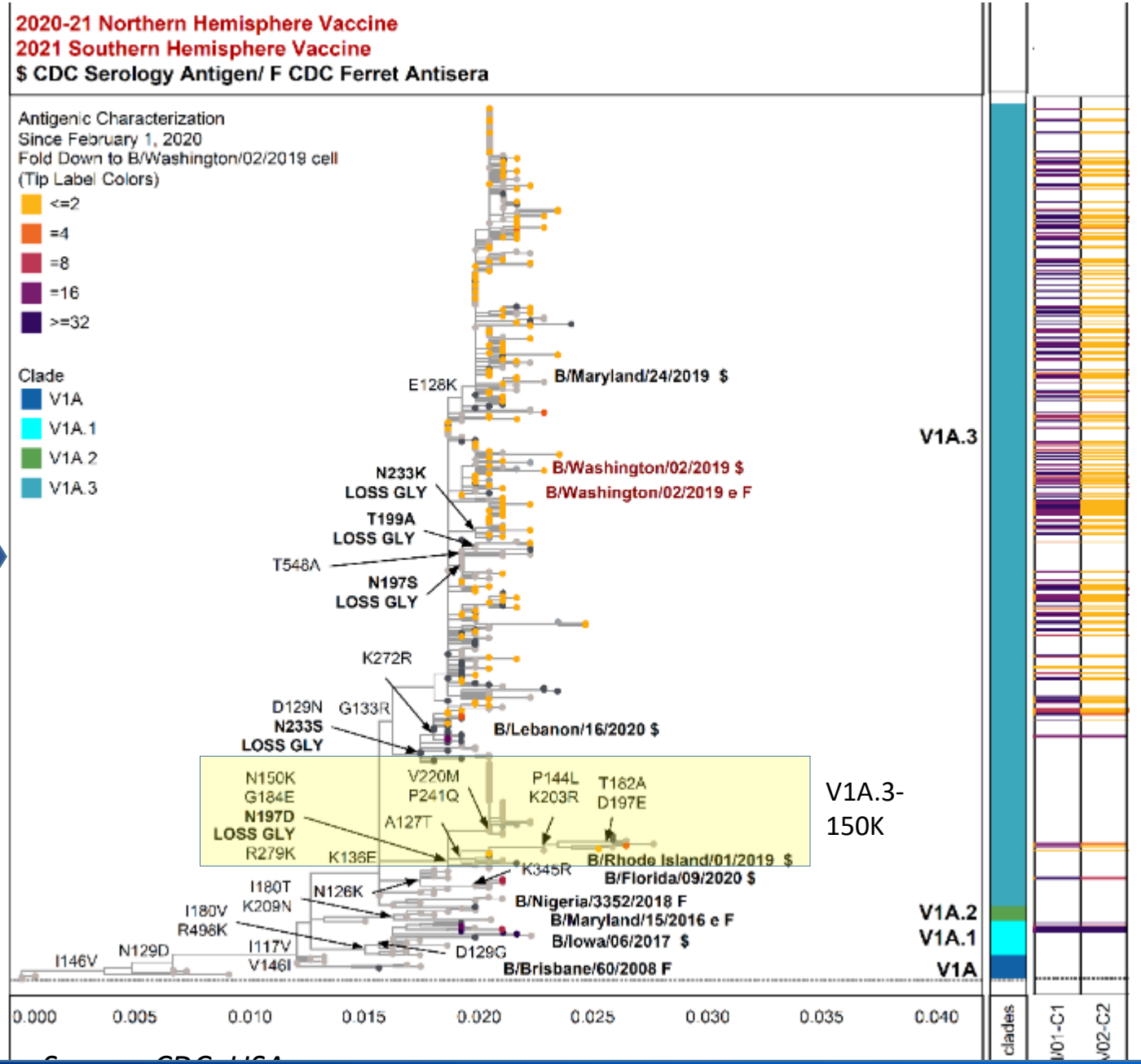
September 2020-January 2021*



*Based on HA Sequence Availability

Source: CDC, USA

B/Victoria lineage phylogenetic and antigenic integration



Reactivity of B/Victoria viruses with ferret antisera to antigens recommended for NH 2020-21 and SH 2021 by HI Assay

Feb. 2020 -Jan. 2021

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

WHO CC	Like (2-4 fold)	Low (≥ 8 fold)
CDC	144 (95%)	7 (5%)
CNIC	93 (38%)	149 (62%)
FCI	176 (81%)	41 (19%)
NIID	59 (98%)	1 (2%)
VIDRL	32 (100%)	0 (0%)
TOTAL	504 (72%)	198 (28%)

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

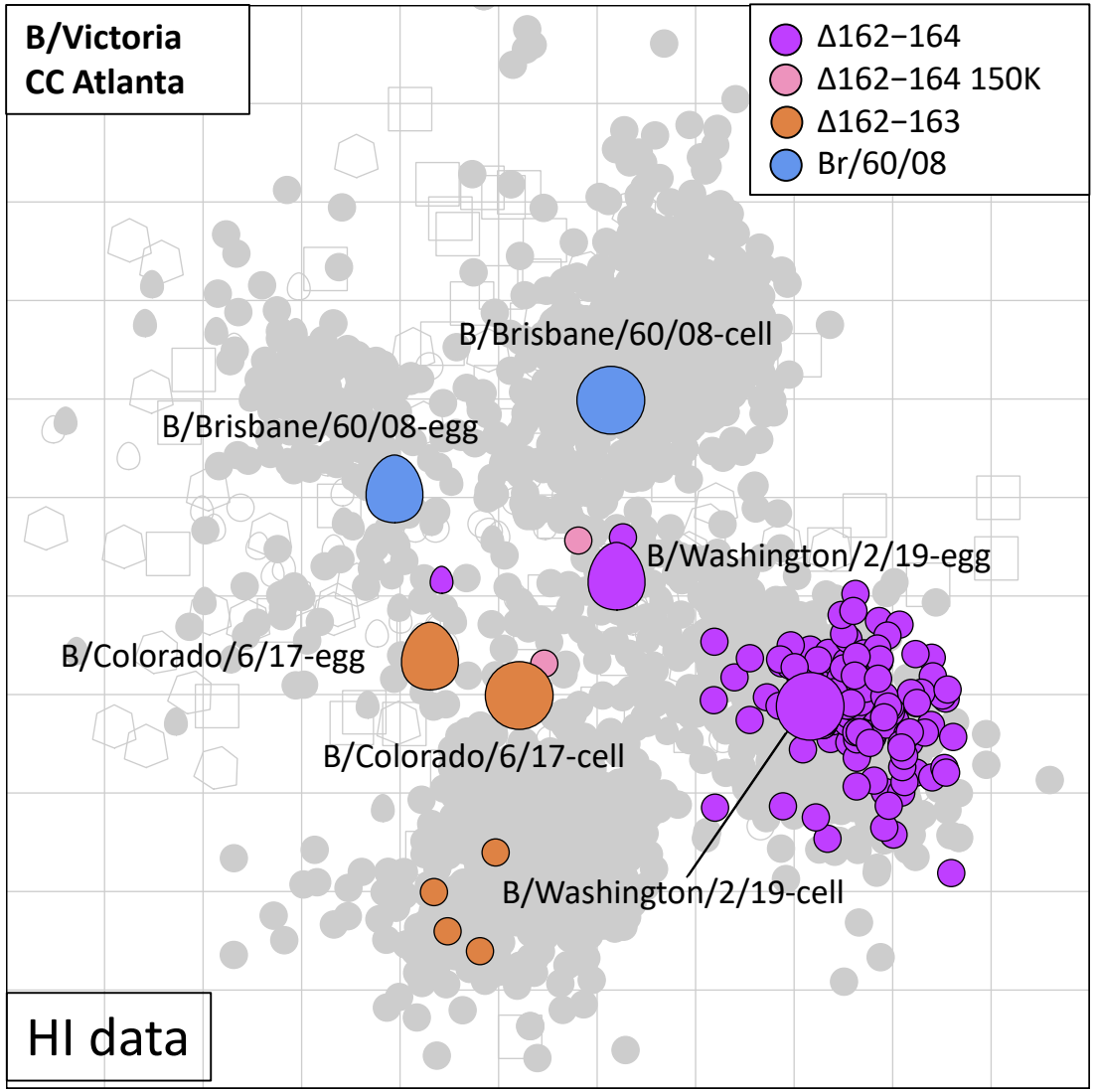
WHO CC	Like (2-4 fold)	Low (≥ 8 fold)
CDC	141 (93%)	10 (7%)
CNIC	107 (43%)	144 (57%)
FCI	172 (79%)	45 (21%)
NIID	60 (100%)	0 (0%)
VIDRL	26 (81%)	6 (19%)
TOTAL	506 (71%)	205 (29%)

Sept. 2020 -Jan. 2021

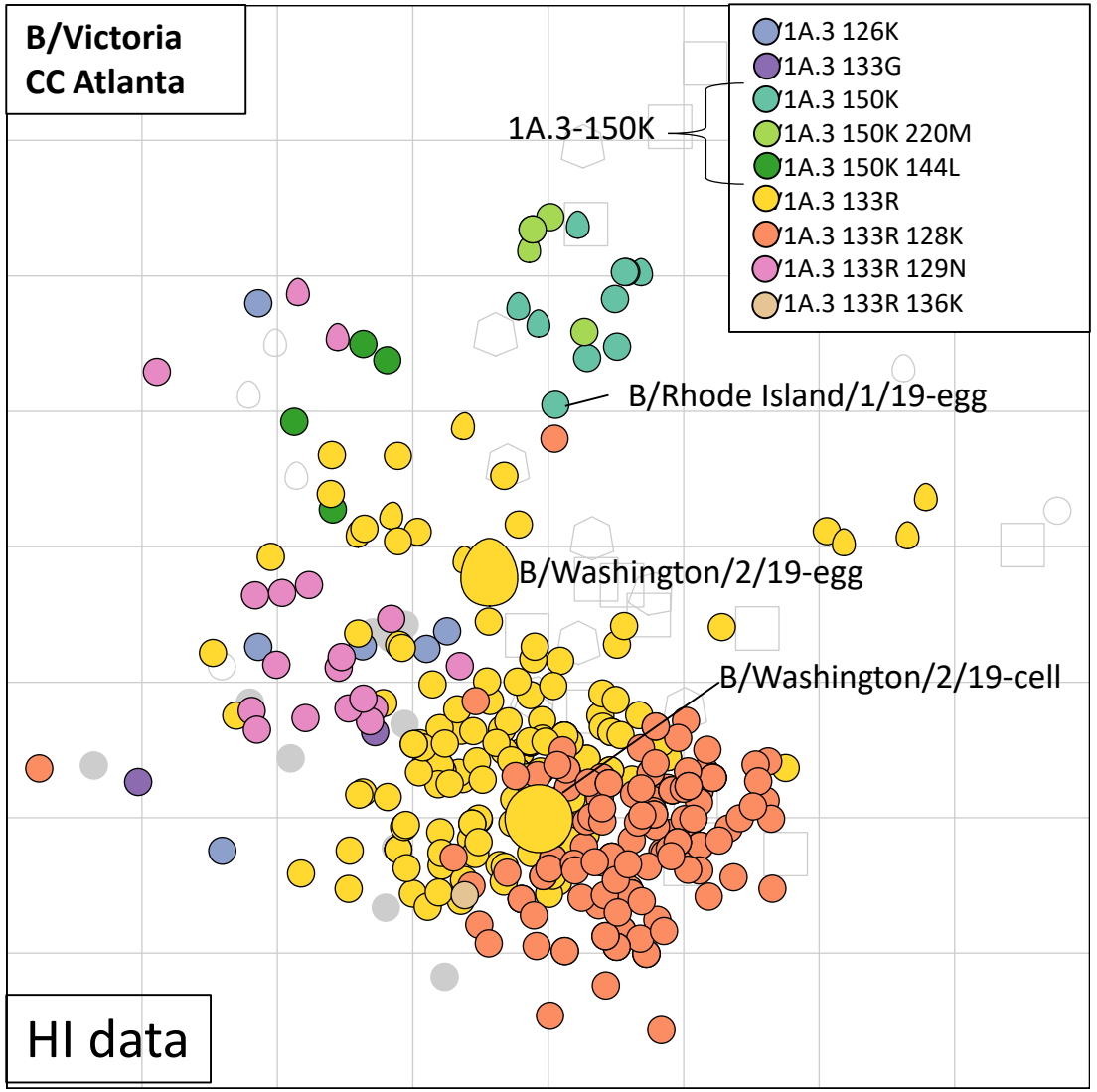
WHO CC	Like (2-4 fold)	Low (≥ 8 fold)
CDC	2 (100%)	0 (0%)
CNIC	32 (18%)	149 (82%)
FCI	1 (20%)	4 (80%)
TOTAL	35 (19%)	153 (81%)

WHO CC	Like (2-4 fold)	Low (≥ 8 fold)
CDC	2 (100%)	0 (0%)
CNIC	48 (27%)	133 (73%)
FCI	0 (0%)	5 (100%)
TOTAL	50 (27%)	138 (73%)

B/Victoria Antigenic Cartography



Past 12 months (older viruses in grey)

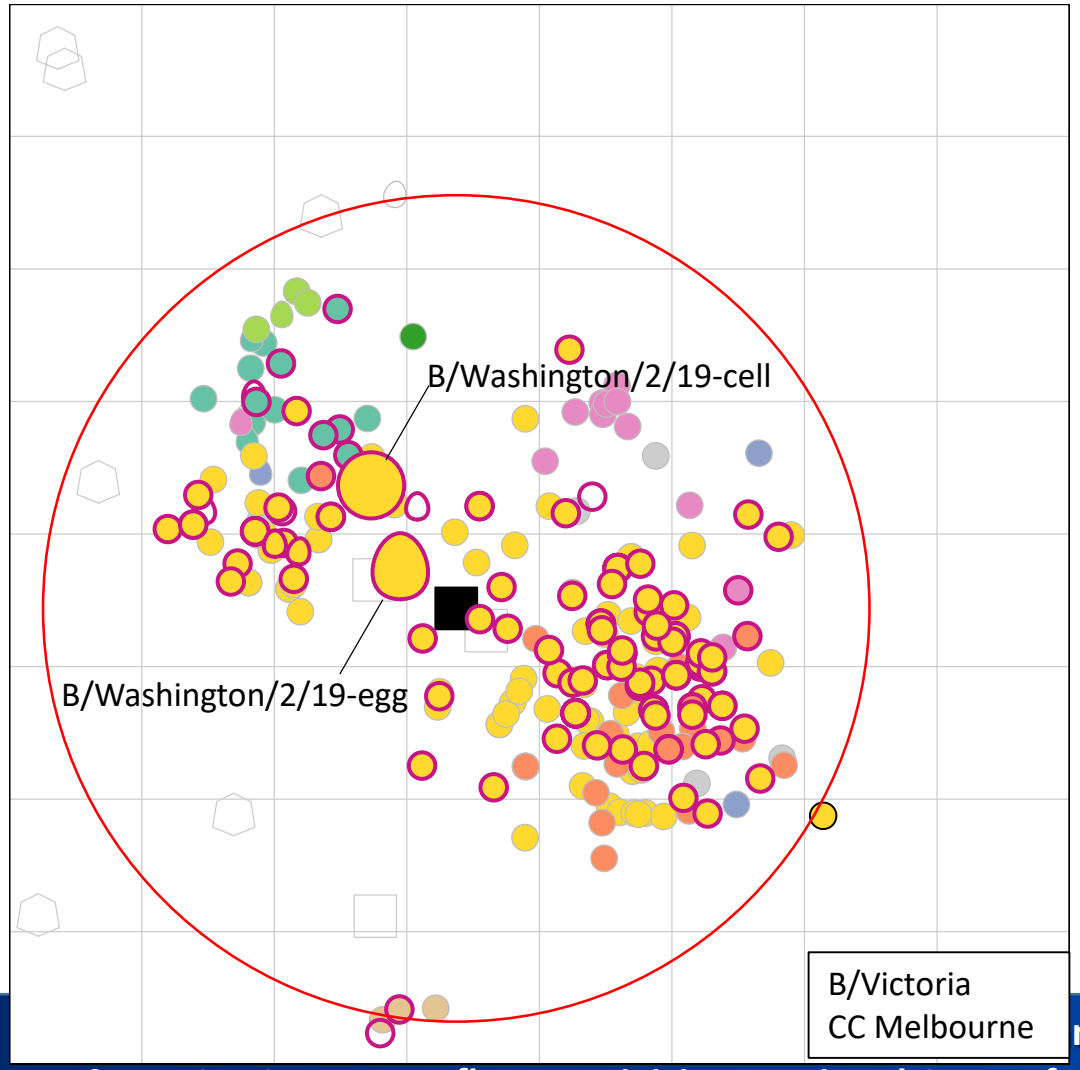


University of Cambridge

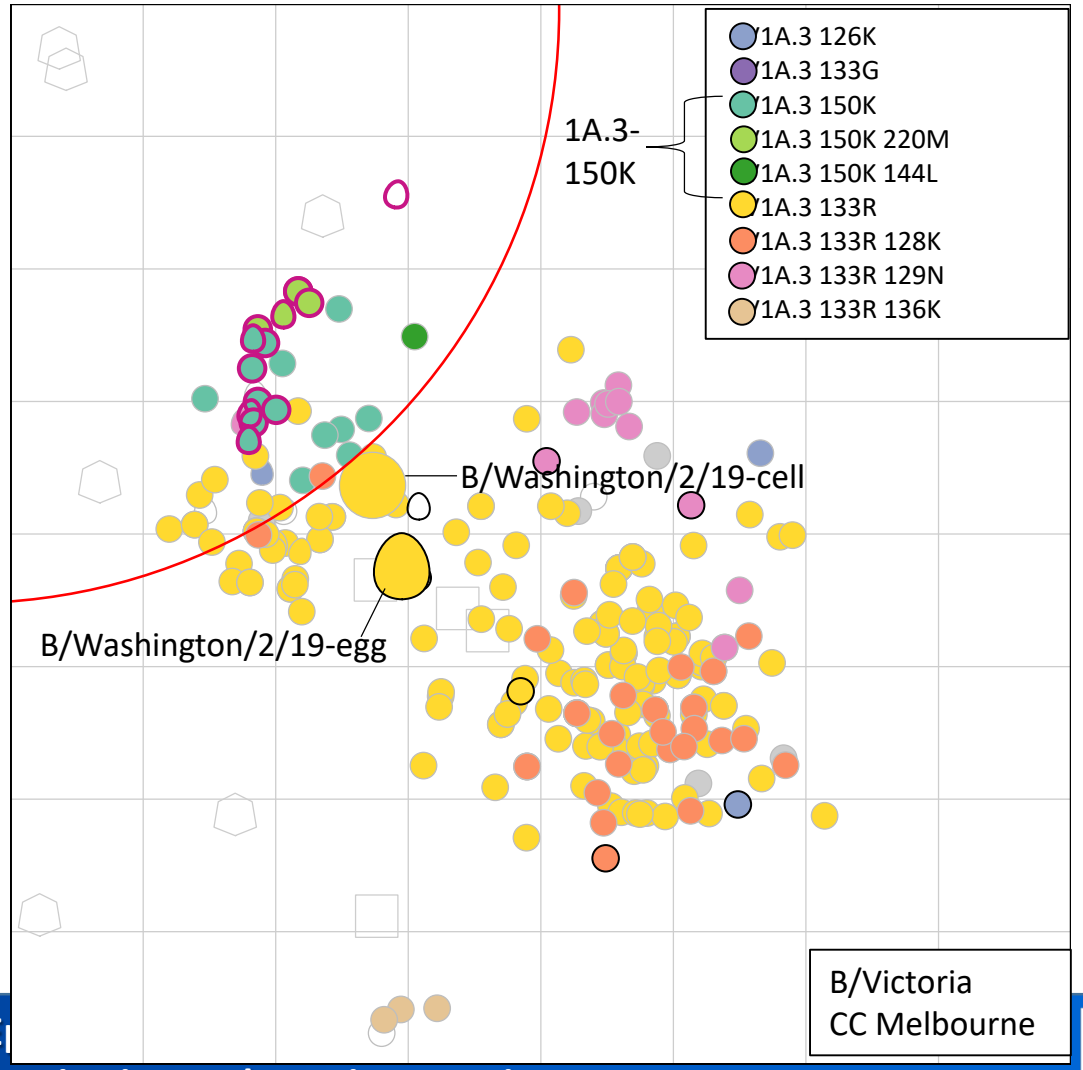
Reactivity patterns of various antisera

Antisera circles (within 4-fold of homologous titer) using antisera to:

B/Victoria/705/2018-cell



B/Sichuan Jingyang/12048/2019-cell



Human post-vaccination sera analysis with B/Victoria Viruses (1)

HI GMTs relative to CELL-propagated B/Washington/02/2019 (V1A.3)

				V1A.3	V1A.3 +N197S (CHO-)	V1A.3 +E128K	V1A.3 +N150K +N197D (CHO-)	V1A.3 +D129G +N233S (CHO-)	V1A.3 +N126K	V1A.1
				*WA/02 MDCK	WA/02 Egg	MD/24 MDCK	RI/01 MDCK	LBN/16 MDCK	FL/09 MDCK	IA/06 MDCK
B/WASHINGTON/02/2019 MDCK	6-35mo Pediatric	USA	IIV4	18	X	X	X	X	X	X
	3-8yr Pediatric	USA	ccIIV4 (Flucelvax)	92	√	√	√	√	√	51
			IIV4	61	√	√	√	√	√	√
	9-17yr Pediatric	USA	ccIIV4 (Flucelvax)	70	√	√	√	√	√	√
			IIV4	117	√	65	√	√	57	√
	Adult	USA	ccIIV4 (Flucelvax)	106	√	√	63	√	√	√
			RIV4 (Flublok)	135	√	√	√	√	√	√
			IIV4	46	√	25	√	√	√	29
		Japan	IIV4	30	X	X	X	X	X	X
		UK/NIBSC	IIV4	45	√	√	√	√	√	√
	50-64yr Older Adult	USA	IIV4	32	X	17	X	20	X	X
	Elderly	USA	IIV4-HD	46	√	√	√	√	31	24
		Japan	IIV4	27	X	X	X	X	X	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: B/FLORIDA/09/2020 (FL/09); B/IOWA/06/2017 (IA/06); B/LEBANON/16/2020 (LBN/16); B/MARYLAND/24/2019 (MD/24); B/RHODE ISLAND/01/2019 (RI/01); B/WASHINGTON/02/2019 (WA/02).

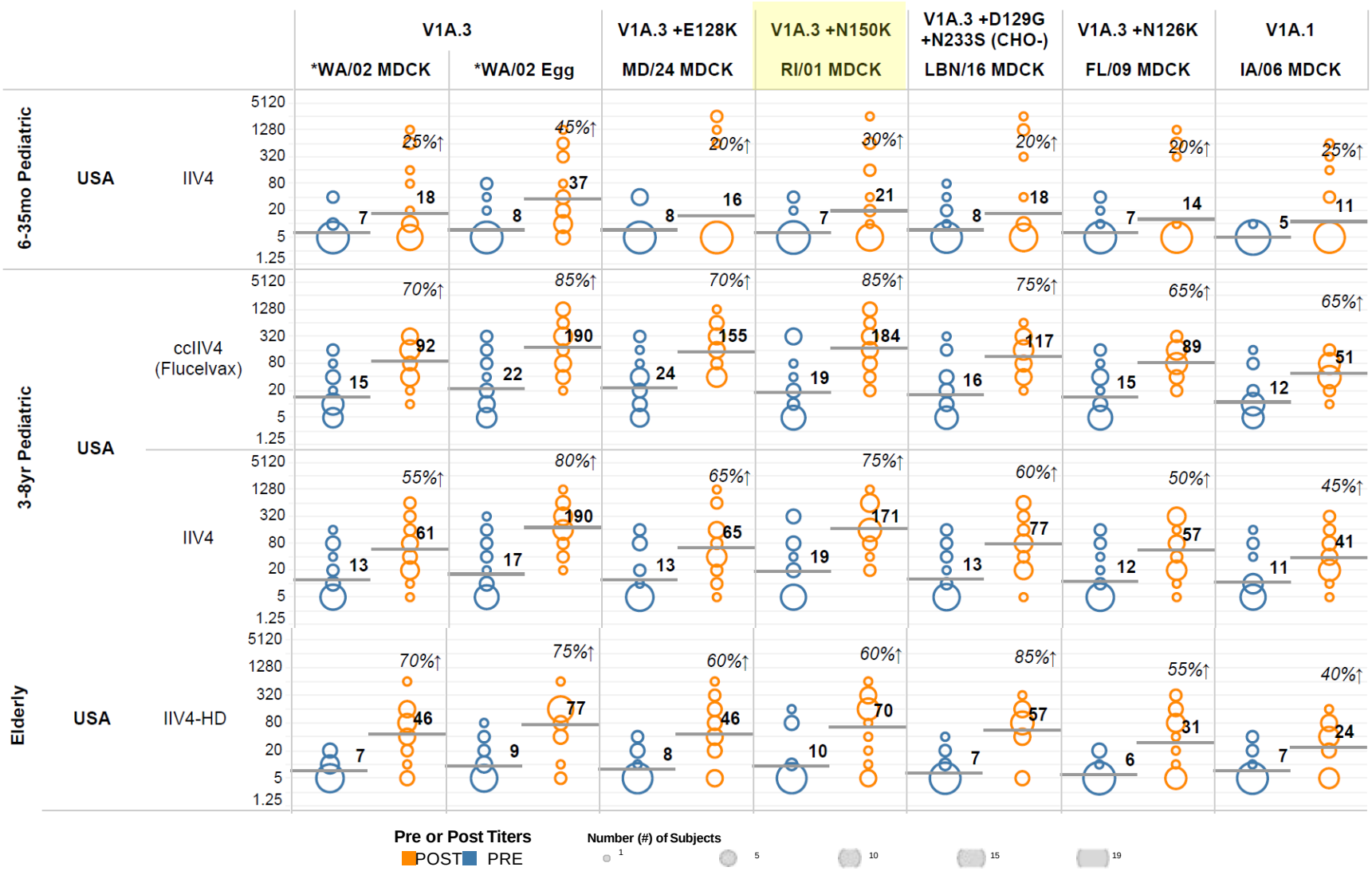
Source: CDC, USA

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

GMT ratio lowerbound (90% CI)
0.0 — 1.0

Human post-vaccination sera analysis with B/Victoria Viruses (2)

Pre (Bl.) vs Post (Or.) Vaccination Titers



Arrow (↑) represents percent (%) seroconversion: ≥4-fold rise from pre- to post-vaccination with post-vaccination titer ≥ 40

Summary of B/Victoria Lineage Viruses (1)

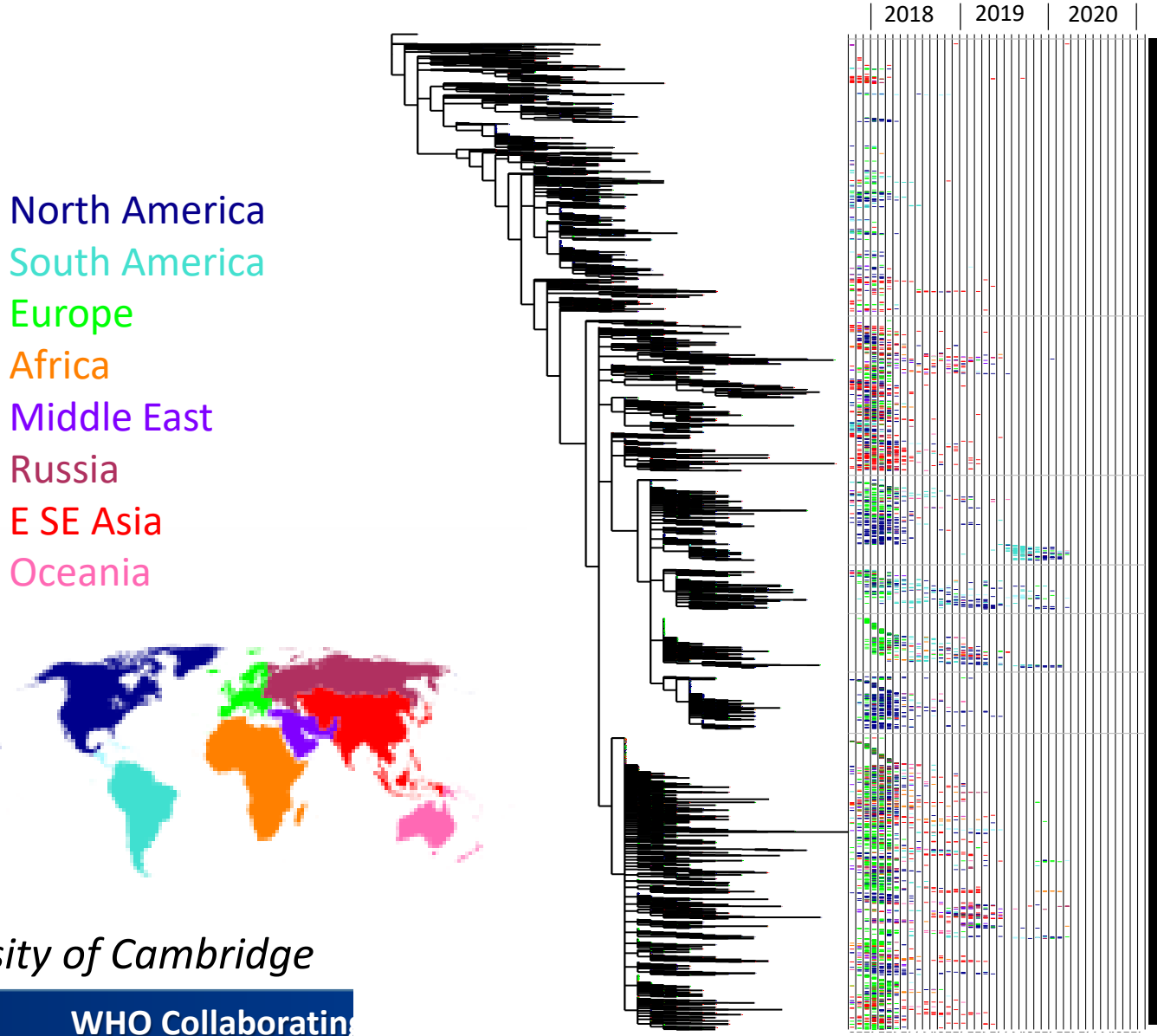
- Influenza B Victoria lineage viruses greatly predominated over those of the B/Yamagata lineage
  - Majority of viruses from this period were identified in China
- HA phylogenetics
  - All HA genes belonged to subclade 1A.3. These have a deletion of residues 162-164 and a K136E substitution in HA1.
    - Many also share G133R
  - The HA of most recently collected viruses are in subclade 1A.3 and form a subgroup sharing N150K, G184E, N197D (CHO loss) and R279K, but lack G133R (1A.3-150K)
    - Two recent subgroups that have either V220M and P241Q (China and West Africa), or A127T, P144L and K203R (Europe, West Africa and Oman)

Summary of B/Victoria Lineage Viruses (2)

- Antigenic characteristics
  - Most viruses tested since February 2020 were recognized well by ferret antisera raised against cell-propagated or egg-propagated B/Washington/02/2019
  - 1A.3-150K HA subgroup of viruses predominated since September 2020
    - Showed reduced inhibition by ferret antisera to cell- or egg-propagated B/Washington/02/2019-like viruses
  - Ferret antisera to cell-propagated HA subgroup 1A.3-150K reference viruses
    - well inhibited closely related 1A.3-150K HA subgroup viruses
    - poorly inhibited most other viruses that have 1A.3 HA genes
- Post vaccination human sera generally well inhibited all test viruses including 1A.3-150K HA subgroup viruses
- Antiviral susceptibility
  - Of 144 viruses analyzed, all were susceptible to oseltamivir, 1 showed reduced inhibition by zanamivir
  - All 16 viruses tested were susceptible to laninamivir and peramivir
  - None of the 41 viruses analyzed showed evidence of reduced susceptibility to baloxavir

B/Yamagata lineage viruses

B/Yamagata phylogenetic tree



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

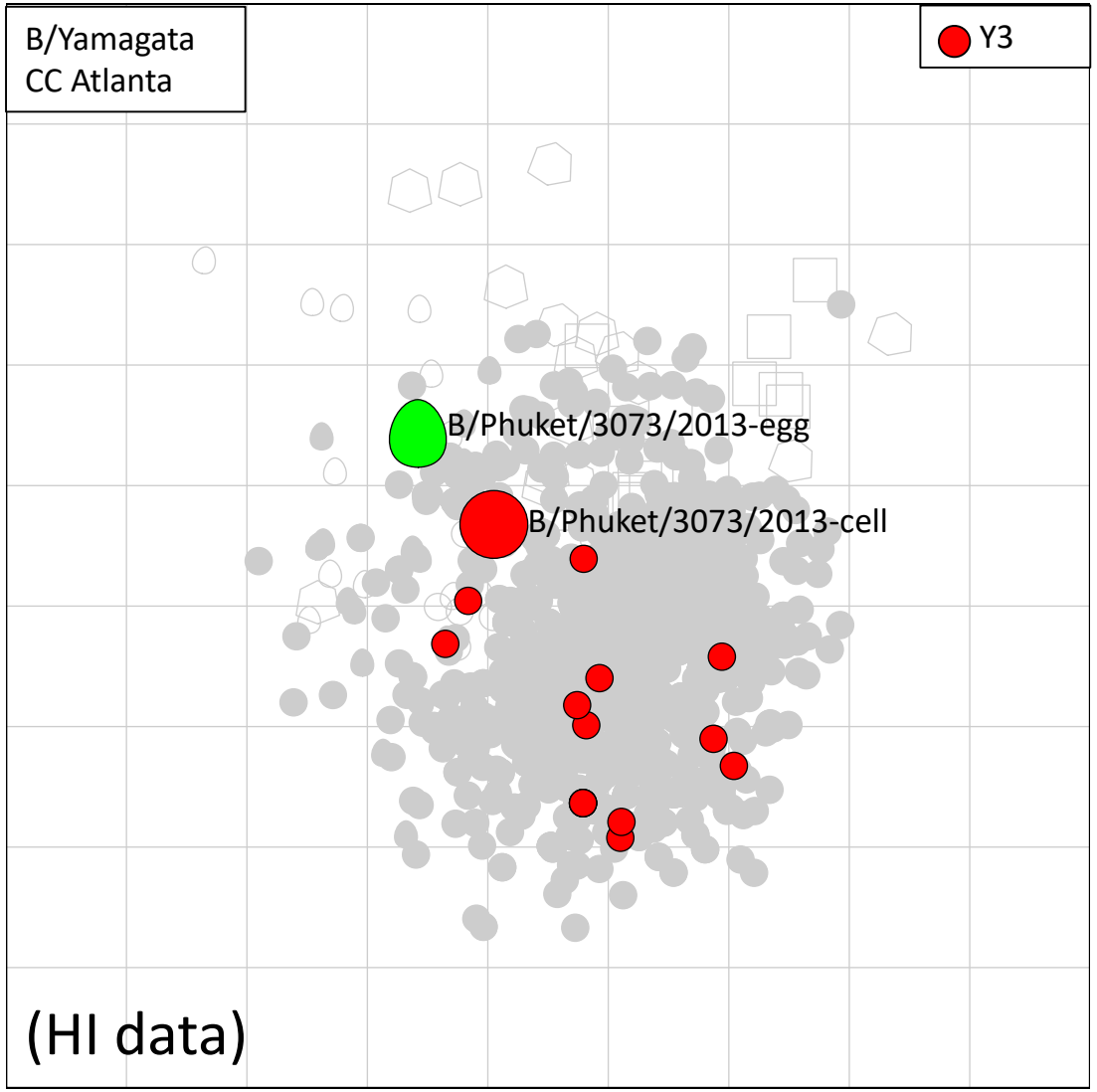
Clade 3
A/Phuket/3073/2013

University of Cambridge

Reactivity of recent B/Yamagata viruses with antisera to antigens recommended for NH 2020-21 and SH 2021

- No B/Yamagata lineage viruses with collection dates after August 2020 were available for antigenic analysis
- The few viruses available with collection dates earlier in 2020 were antigenically similar to B/Phuket/3073/2013

B/Yamagata Antigenic Cartography



Past 12 months (older viruses in grey)

University of Cambridge

Summary of B/Yamagata Lineage Viruses

- Influenza B viruses of the B/Yamagata lineage were rarely detected
  - No viruses were available with collection dates after August 2020
- All viruses from 2020 had HA genes in clade 3 (e.g. B/Phuket/3073/2013)
- Most recent viruses were well recognized by ferret antisera to cell culture-propagated or egg-propagated B/Phuket/3073/2019
- Post vaccination human sera well recognized viruses representative of those most recently circulating

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

Candidate vaccine viruses

- The WHO recommended candidate viruses for vaccine development and production for NH 2021-2022 available: http://www.who.int/influenza/vaccines/virus/en/
- Guidance to tropical and subtropical countries: which formulation (northern hemisphere vs. southern hemisphere) and when to start vaccination:
  - http://www.who.int/influenza/vaccines/tropics/en/
- FAQ – vaccine composition recommendation: http://www.who.int/influenza/
- Candidate vaccine viruses and reagents
  - http://www.who.int/influenza/vaccines/virus/candidates_reagents/home/en/
- Zoonotic influenza summary reports and candidate vaccine viruses on H5/H7/H9 vaccine viruses:
  - WHO GISRS website: http://www.who.int/influenza/gisrs_laboratory/en/
    - http://www.who.int/influenza/vaccines/virus/en/

Publications

- Guidance to tropical and subtropical countries: which formulation (northern hemisphere vs. southern hemisphere) and when to start vaccination:
  - http://www.who.int/influenza/vaccines/tropics/en/
- Vaccine composition recommendation report and summary report on H5/H7/H9 vaccine viruses:
  - WHO GlSRS website: http://www.who.int/influenza/gisrs_laboratory/en/
    - http://www.who.int/influenza/vaccines/virus/en/
  - WHO Weekly Epidemiological Record: http://www.who.int/wer/en/
- FAQ – vaccine composition recommendation: http://www.who.int/influenza/
- Candidate vaccine viruses and reagents
  - http://www.who.int/influenza/vaccines/virus/candidates_reagents/home/en/

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