INFORMATION FOR THE VACCINE AND RELATED BIOLOGICAL PRODUCTS ADVISORY COMMITTEE CBER, FDA

Global Surveillance and Virus Characterization

March 4, 2015

Jacqueline Katz, Ph. D.
Deputy Director (acting), Influenza Division
Director, WHO COLLABORATING CENTER FOR SURVEILLANCE, EPIDEMIOLOGY AND CONTROL OF INFLUENZA
Influenza Division
National Center for Immunization and Respiratory Diseases
Centers for Disease Control and Prevention
Atlanta, GA 30333

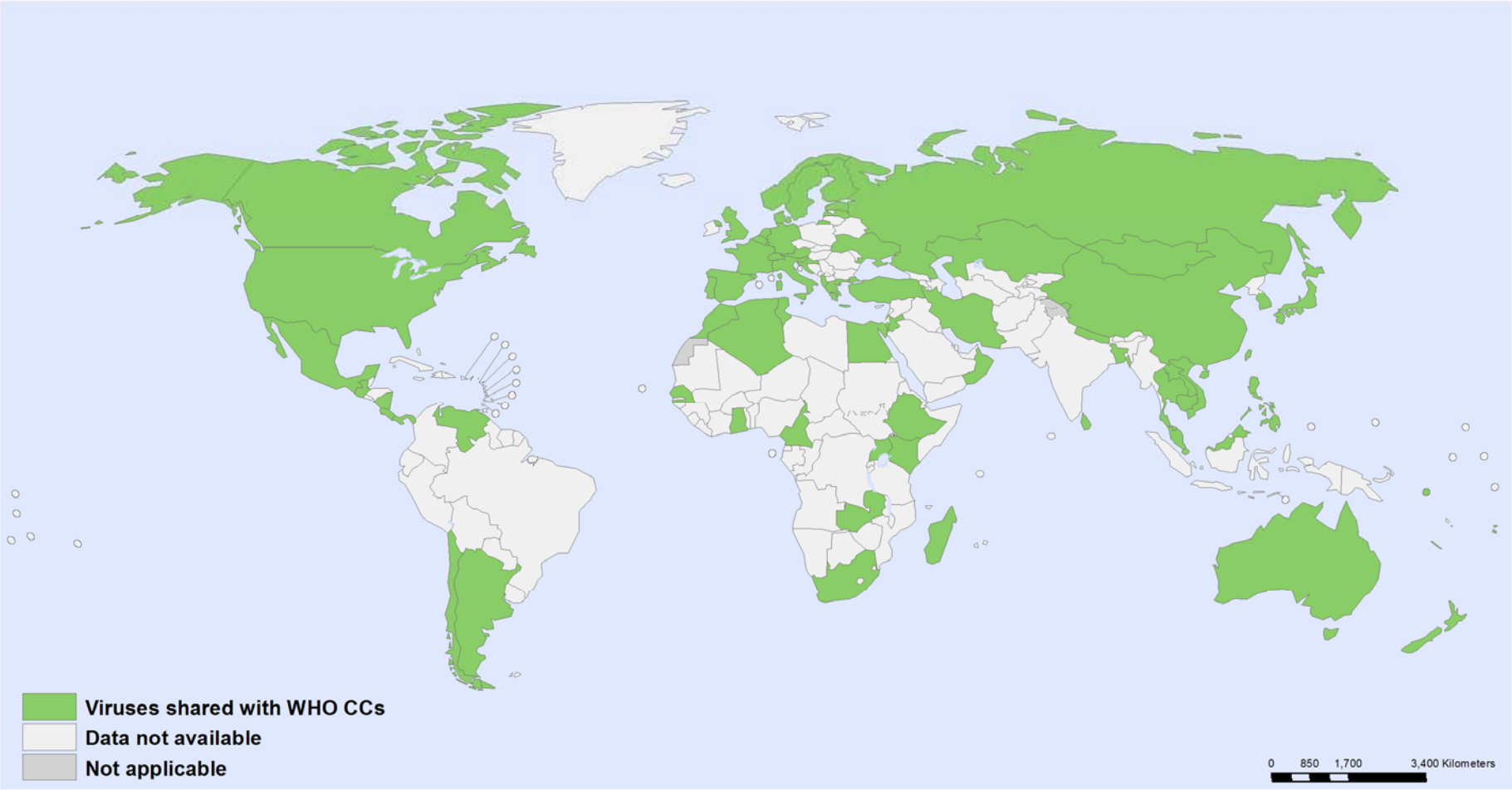
Global Influenza Surveillance and Response System (GISRS)

- Year around surveillance conducted by GISRS
  - 142 National Influenza Centers (NICs) in 112 countries, 6 WHOCCs, WHO Essential Regulatory Labs, H5 Reference Labs
- WHO Vaccine Consultation Meeting, 23-25 Feb 2015: Global data review and analysis followed by writing recommendations for publication for seasonal and pre-pandemic vaccine viruses
- Chaired by Dr. John McCauley, WHOCC, NIMR London
  - 9 Advisers: Directors of WHOCCs and WHO ERLs
  - 26 observers from NICs, H5 Reference Laboratories, WHOCCs, WHO ERLs, academic partners and the veterinary sector

CDC

Countries, areas and territories sharing viruses with WHO CCs from September 2014 to January 2015

19 February 2015



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Data Source: WHO CCs reports for the WHO influenza vaccine composition consultation in February 2015
Map Production: WHO GISRS Team
World Health Organization

World Health Organization

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CDC

World Health Organization

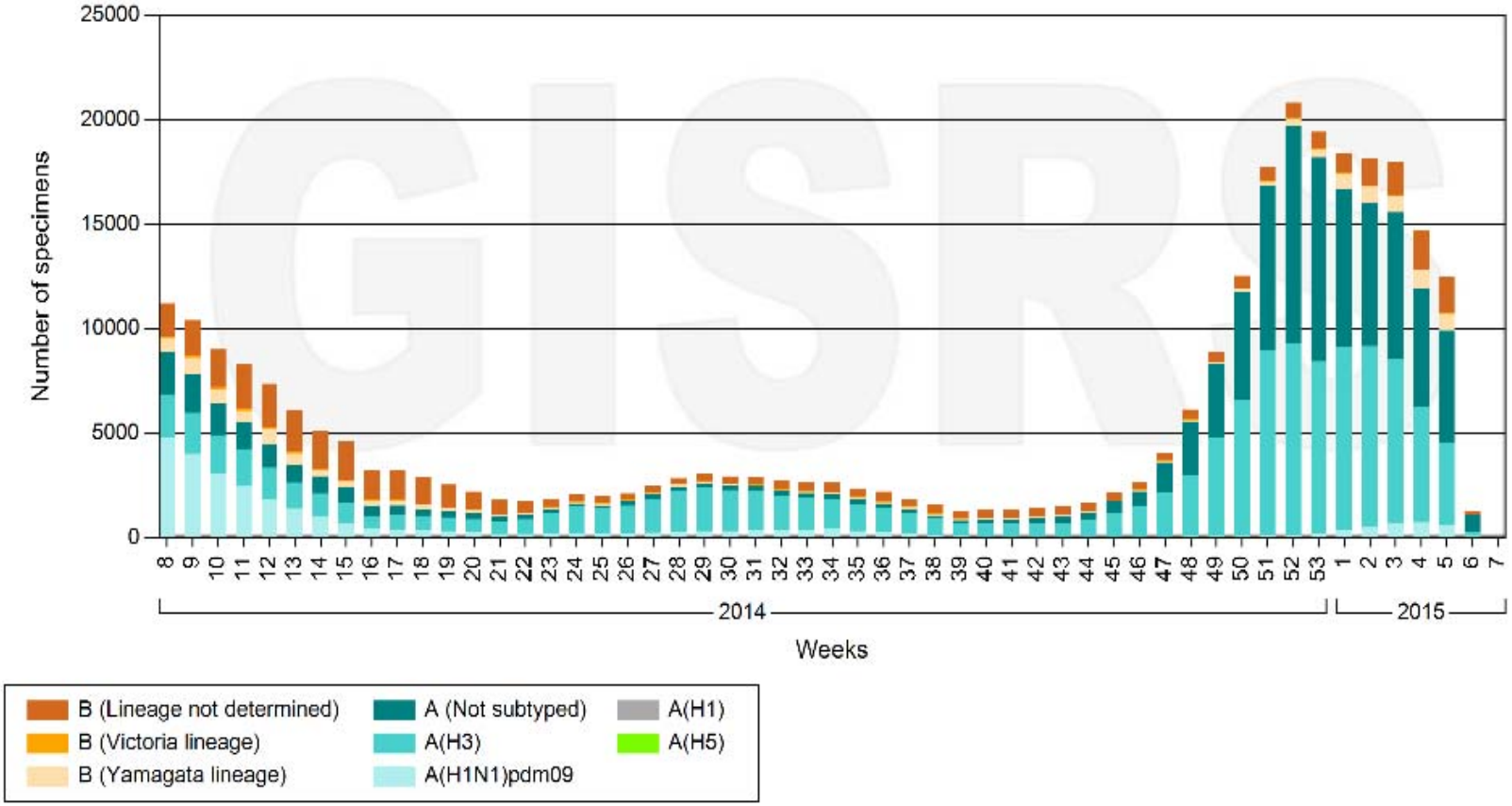
Influenza Laboratory Surveillance Information

by the Global Influenza Surveillance and Response System (GISRS)

generated on 17/02/2015 14:36:40 UTC

Global circulation of influenza viruses

Number of specimens positive for influenza by subtype



Data source: FluNet (www.who.int/flunet), GISRS

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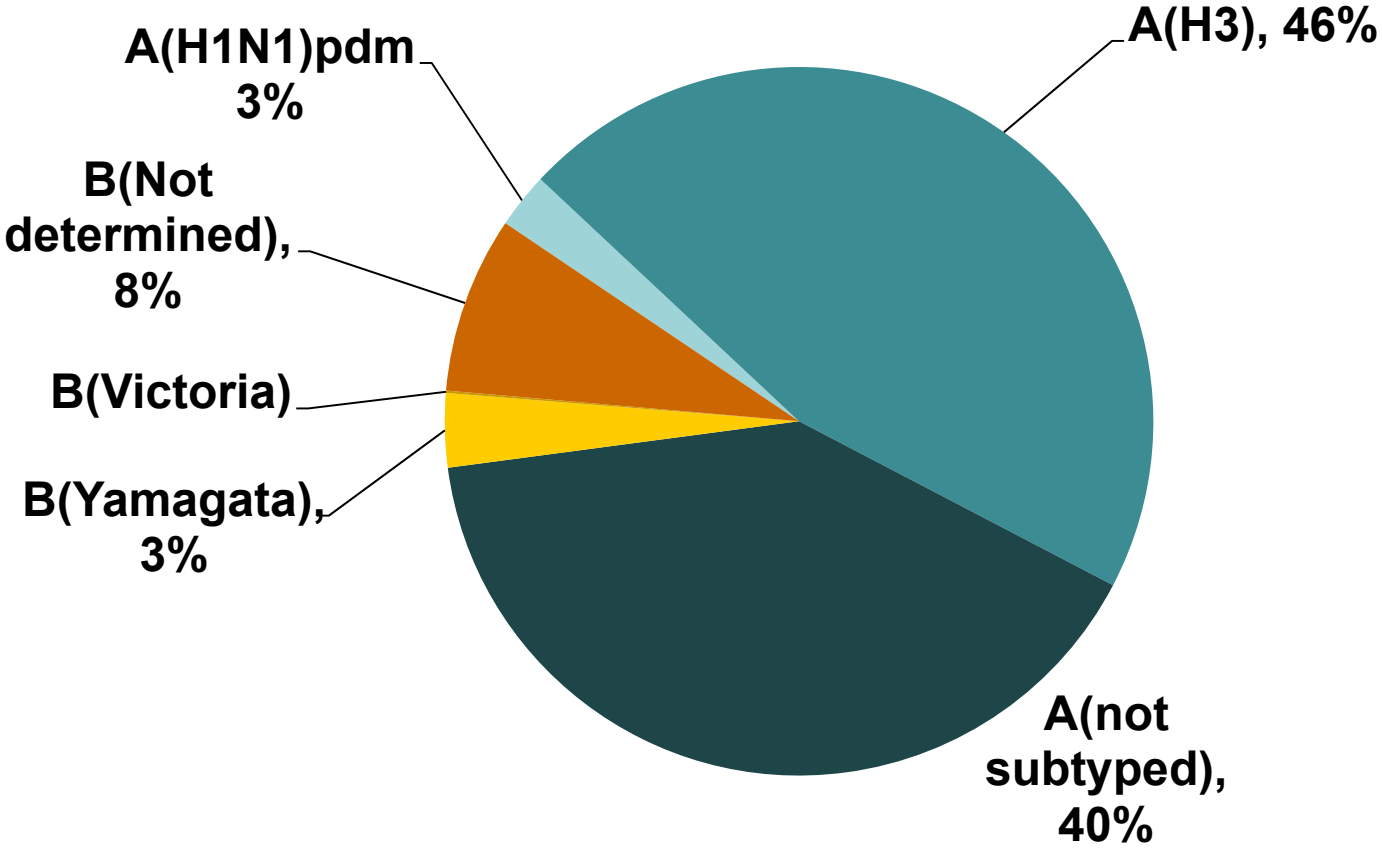
CDC

Percentage of influenza viruses by subtypes
(From 31 August 2014 – 7 February 2015)



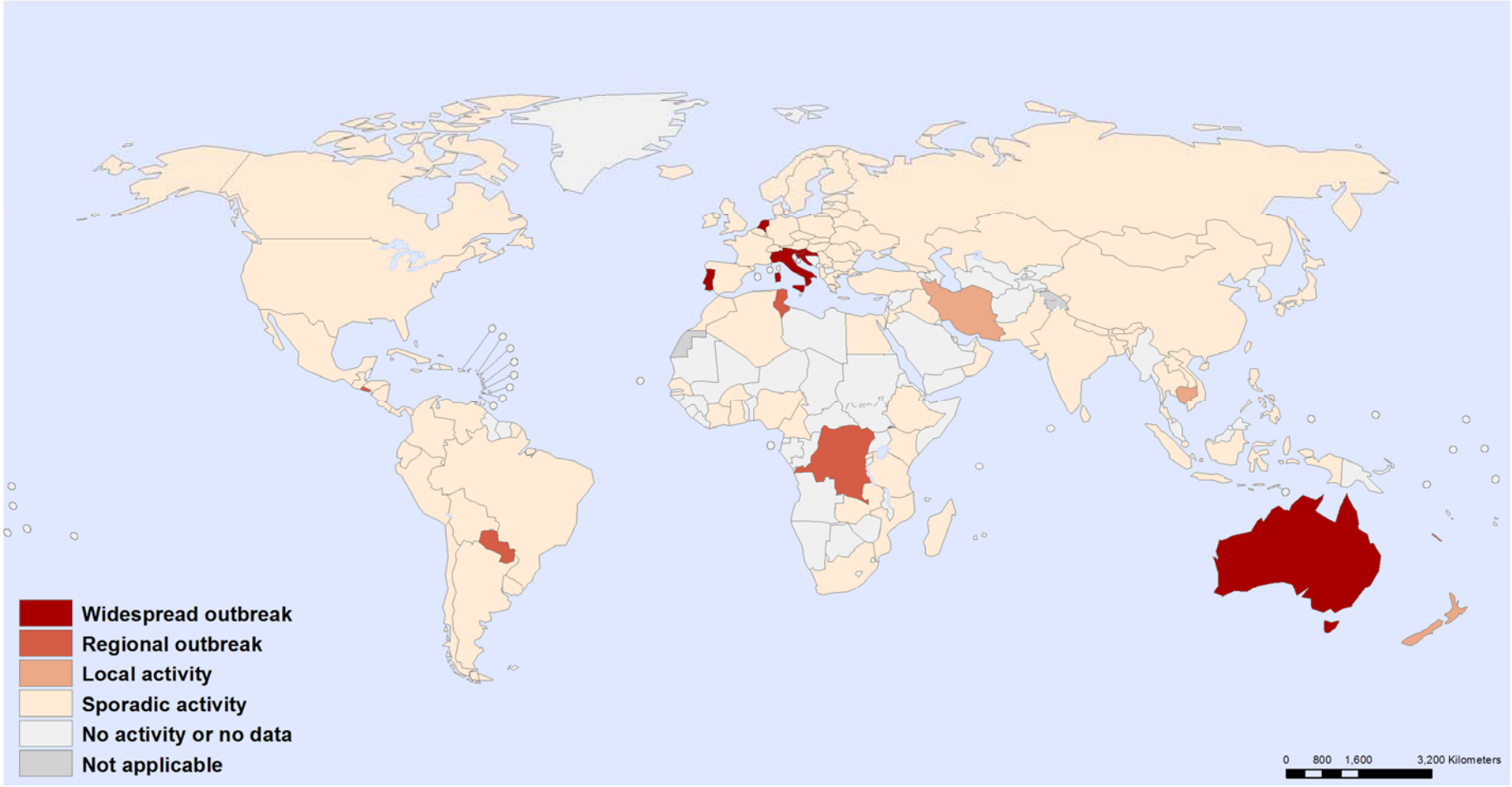
Data source: FluNet, (www.who.int/flunet), Global Influenza Surveillance and Response System (17 February 2015)

A(H1N1)pdm09 viruses

September 2014 – January 2015

Influenza A(H1N1)pdm09, September 2014 to January 2015, maximum

19 February 2015



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Data Source: Global Influenza Surveillance and Response System (GISRS), WHO
Map Production: WHO GISRS Team
World Health Organization

World Health Organization

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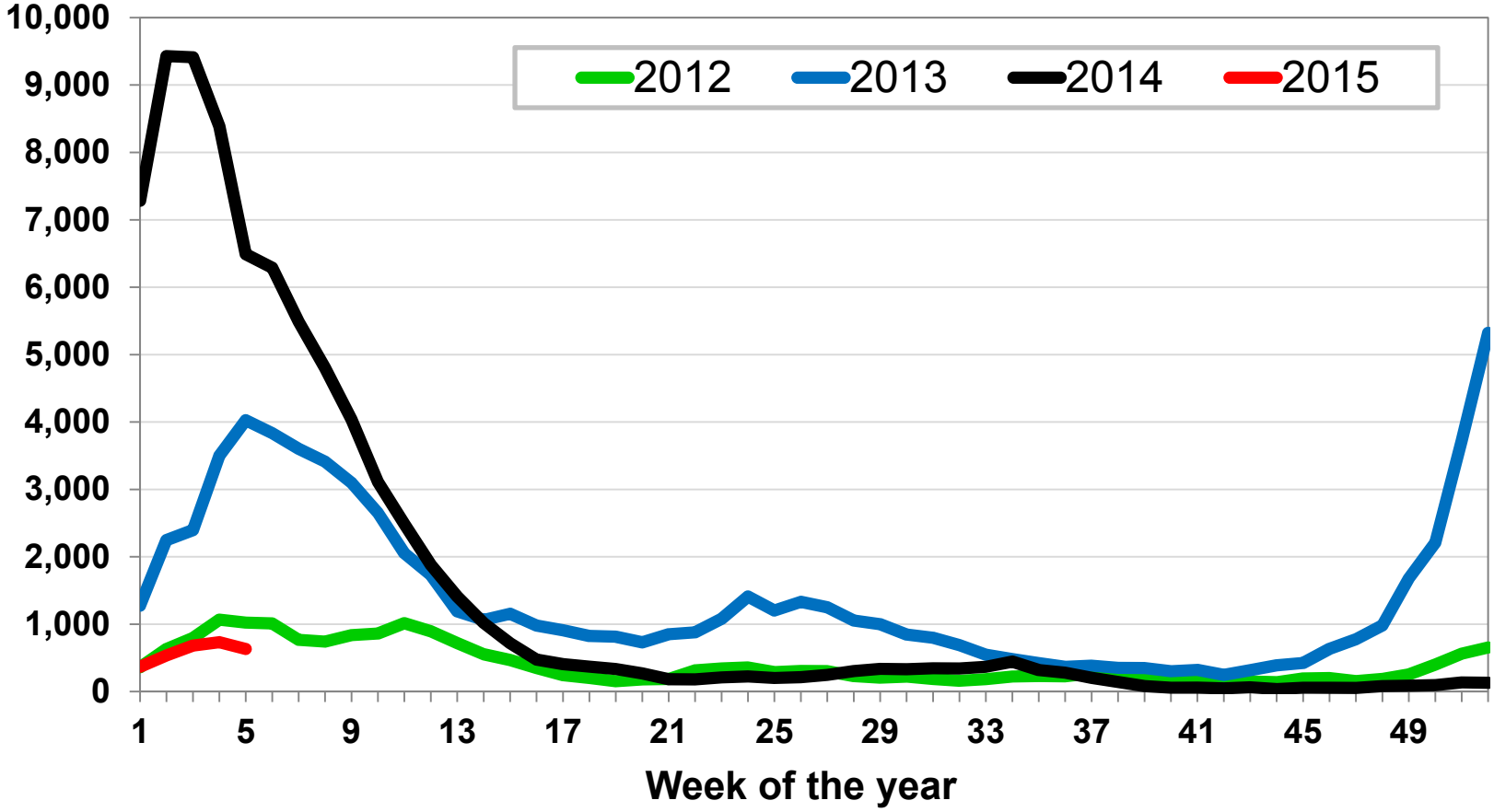
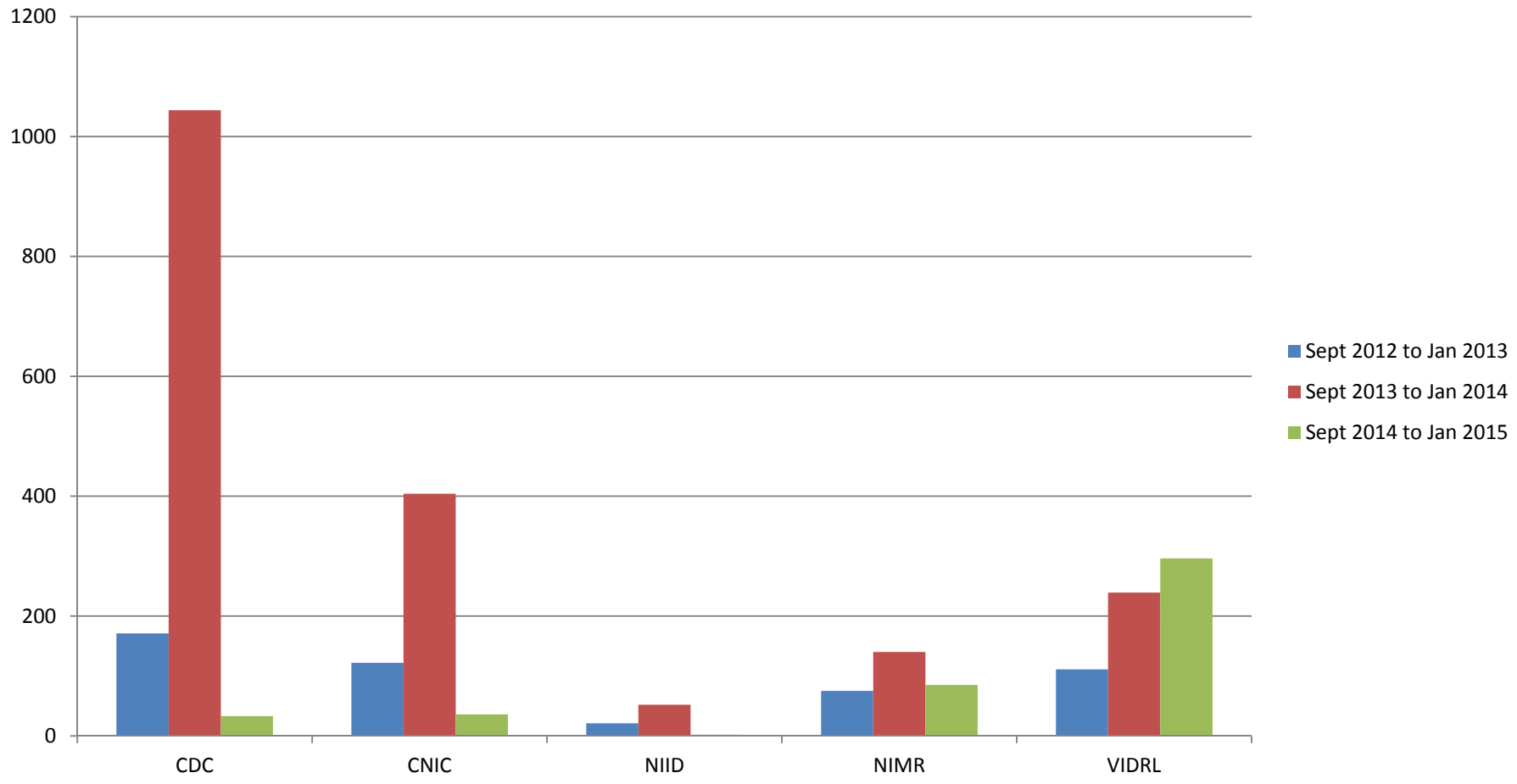
CDC

Number of A(H1N1)pdm09 viruses detected by GISRS



Data source: FluNet, (www.who.int/flunet), Global Influenza Surveillance and Response System (17 February 2015)

(H1N1)pdm09 viruses characterized by HI during the past 3 periods Sept to Jan



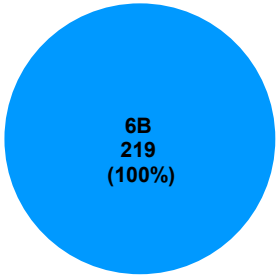
Evolutionary Relationships Among Influenza H1N1pdm09 Hemagglutinin (HA) Genes, 2014-2015

LR- Low Reactor to
A/California/07/2009
(≥ 8 fold)

F - CDC Reference Antigen
wF – WHOcc Reference Antigen
$ – Serology Antigen
w$ - WHOcc Serology Antigen
C$ - Common Serology Antigen

-Egg Isolate
* HA1 only

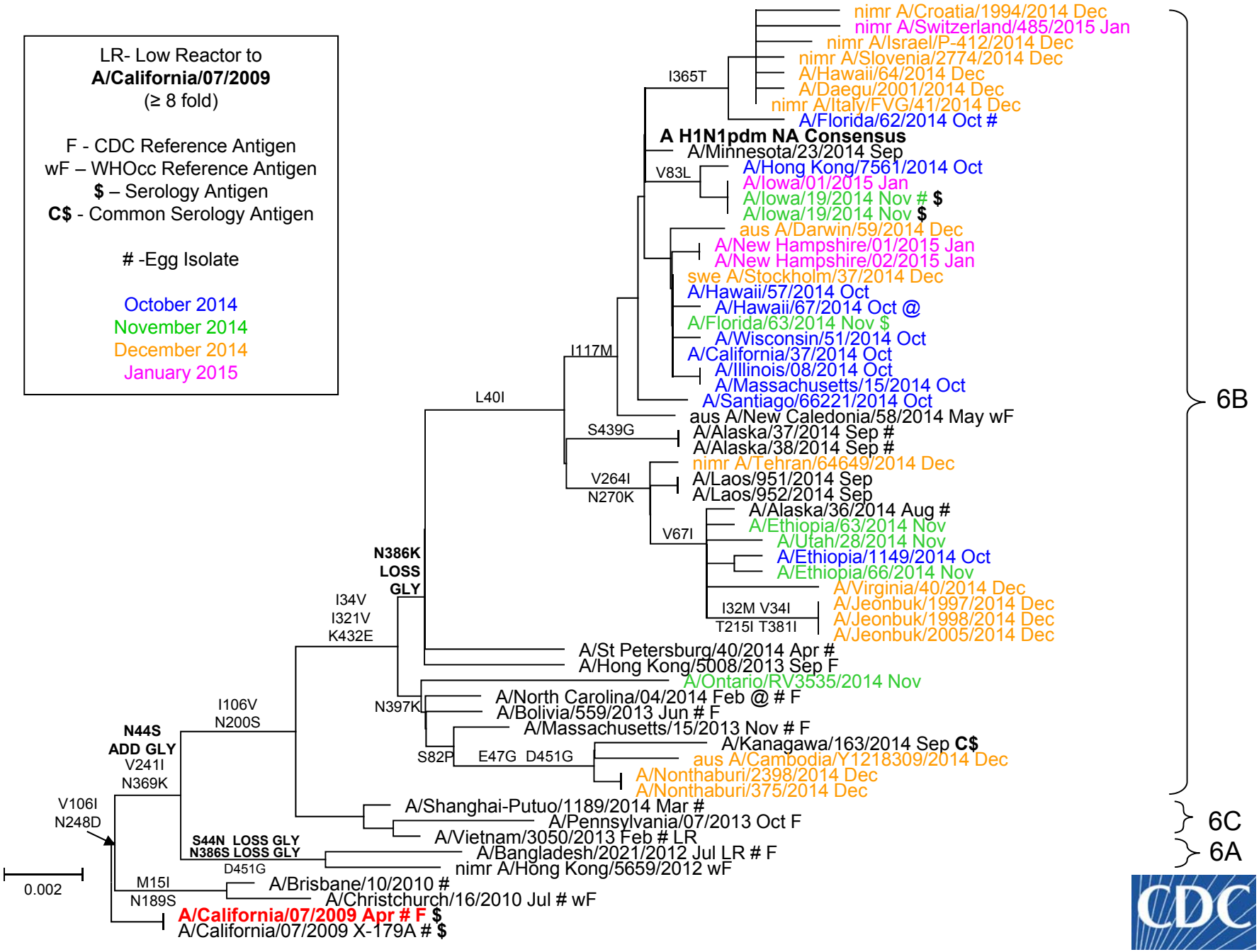
October 2014
November 2014
December 2014
January 2015



HA Genetic Groups
Since September 1st 2014

nimr A/Israel/P-412/2014 Dec
nimr A/Lisboa/EVA60/2015 Jan
nimr A/Slovenia/119/2015 Jan
nimr A/Switzerland/485/2015 Jan
nimr A/Italy/FVG/02/2015 Jan
A/Hawaii/64/2014 Dec
nimr A/Croatia/1994/2014 Dec
A/Daegu/2001/2014 Dec
A/Florida/62/2014 Oct #
A/Florida/63/2014 Nov **$**
A/Iowa/01/2015 Jan
A48P
A/Iowa/19/2014 Nov # **$**
A/Iowa/19/2014 Nov **$**
A/Hong Kong/7561/2014 Oct
A/Massachusetts/15/2014 Oct
A/California/37/2014 Oct
A/Hawaii/57/2014 Oct
A/Minnesota/23/2014 Sep
A/Hawaii/67/2014 Oct @
swe A/Stockholm/37/2014 Dec
A/New Hampshire/01/2015 Jan
A/New Hampshire/02/2015 Jan
A/Wisconsin/51/2014 Oct
A/Idaho/05/2014 Oct
aus A/Darwin/59/2014 Dec
A/Illinois/08/2014 Oct
A H1N1pdm HA Consensus 202
aus A/New Caledonia/58/2014 May wF
A/Alaska/37/2014 Sep #
A/Alaska/38/2014 Sep #
nimr A/Tehran/64649/2014 Dec
A48P
A/Ethiopia/66/2014 Nov
A/Ethiopia/1149/2014 Oct
A/Alaska/36/2014 Aug #
A/Ethiopia/63/2014 Nov I321V/A
A/Laos/952/2014 Sep
A/Virginia/40/2014 Dec
E491G
A139D
A/Jeonbuk/1997/2014 Dec
A/Jeonbuk/1998/2014 Dec
A/Jeonbuk/2005/2014 Dec
A/Utah/28/2014 Nov
A/Laos/951/2014 Sep
A/Santiago/66221/2014 Oct
A/St Petersburg/40/2014 Apr # V321I
A/North Carolina/04/2014 Feb @ # F
A/Ontario/RV3535/2014 Nov
A/Hong Kong/5008/2013 Sep F K283D
K163Q
A256T
A/Bolivia/559/2013 Jun # F
V19I
A/Nonthaburi/2398/2014 Dec
A/Nonthaburi/375/2014 Dec
aus A/Cambodia/Y1218309/2014 Dec
A/Kanagawa/163/2014 Sep **C$** E283K
A/Massachusetts/15/2013 Nov # F
A/Pennsylvania/07/2013 Oct F
A/Vietnam/3050/2013 Feb # LR
A/Shanghai-Putuo/1189/2014 Mar #
A/Bangladesh/2021/2012 Jul LR # F
nimr A/Hong Kong/5659/2012 wF **K119N ADD GLY**
6B
6C
6A
P83S
S203T
I321V
E374K
D97N
S185T
S451N
K283E
E499K
V234I
H138R V249L
N125D
A/Brisbane/10/2010 #
A/Christchurch/16/2010 Jul # wF
A/California/07/2009 X-179A # F **w$**
A/California/07/2009 Apr # F $
0.002

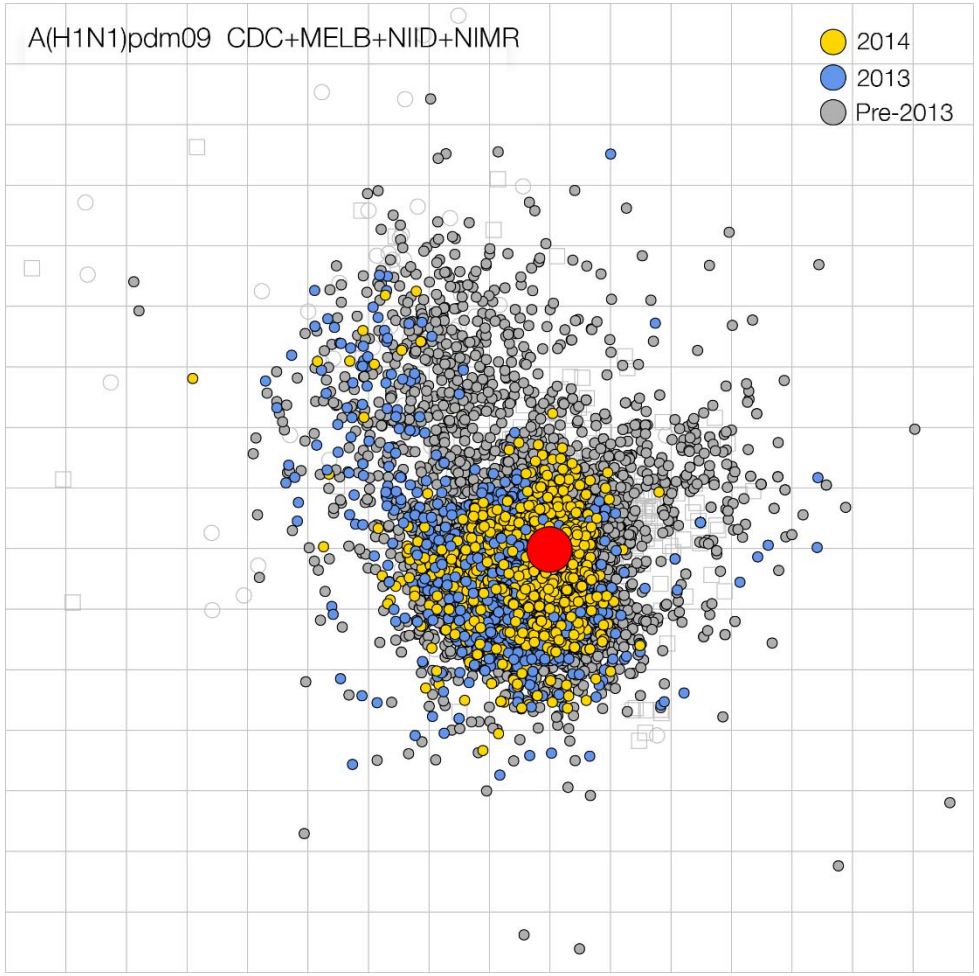
Evolutionary Relationships Among Influenza H1N1pdm09 Neuraminidase (NA) Genes, 2014-2015



HEMAGGLUTINATION INHIBITION REACTIONS OF INFLUENZA A(H1N1)pdm09 VIRUSES (2015/01/26)

	REFERENCE FERRET ANTISERA										
			6A	6B			6C				
REFERENCE ANTIGENS	EGG CA/7	MDCK CA/7	EGG BA/2021	EGG NC/4	MDCK NC/4	MDCK HK/5008	MDCK PA/7	HUMAN POOL	*HA GROUP	DATE COLL.	PASS.
1 A/CALIFORNIA/07/2009	1280	2560	320	640	640	1280	2560	320		2009/04/09	E3
2 A/CALIFORNIA/07/2009	2560	2560	320	1280	1280	2560	2560	160		2009/04/09	C2
3 A/BANGLADESH/2021/2012	80	160	640	160	40	40	160	160	6A	2012/07/21	E4
4 A/NORTH CAROLINA/04/2014	1280	2560	320	1280	1280	1280	2560	160	6B	2014/02/16	E4
5 A/NORTH CAROLINA/04/2014	1280	1280	160	640	640	1280	1280	160	6B	2014/02/16	C2
6 A/HONG KONG/5008/13	2560	2560	320	640	640	1280	2560	160	6B	2013/09/19	CX/C2
7 A/PENNSYLVANIA/07/2013	1280	1280	320	320	320	640	1280	160	6C	2013/10/02	C3
TEST ANTIGENS											
8 A/IOWA/19/2014	2560	2560	320	1280	1280	2560	2560	320	6B	2014/11/05	E2
9 A/CALIFORNIA/37/2014	2560	2560	320	1280	1280	2560	2560	320	6B	2014/10/04	C1
10 A/IOWA/23/2014	2560	2560	320	1280	1280	2560	2560	320		2014/11/23	C1
11 A/HAWAII/64/2014	2560	2560	320	1280	1280	2560	2560	320	6B	2014/12/05	C1
12 A/IOWA/24/2014	2560	2560	320	1280	1280	2560	2560	320		2014/12/02	C1
13 A/IOWA/25/2014	2560	2560	320	1280	1280	2560	2560	320		2014/12/02	C1
14 A/IOWA/26/2014	2560	2560	320	1280	1280	2560	2560	320		2014/12/11	C1
15 A/IOWA/27/2014	2560	2560	320	1280	1280	2560	2560	320		2014/12/09	C1
16 A/IOWA/01/2015	2560	2560	320	1280	1280	2560	2560	320	6B	2015/01/07	C1
17 A/IOWA/02/2015	2560	2560	320	1280	1280	2560	2560	320		2015/01/07	C1
18 A/UTAH/28/2014	2560	2560	320	1280	1280	2560	2560	320	6B	2014/11/25	C1
19 A/NEW HAMPSHIRE/01/2015	1280	1280	320	640	640	1280	1280	160	6B	2015/01/07	C1
20 A/NEW HAMPSHIRE/02/2015	1280	1280	160	640	640	1280	1280	160	6B	2015/01/07	C1
21 A/ONTARIO/RV3535/2014	640	1280	80	640	640	640	1280	160	6B	2014/11/12	X1/C1
22 A/SANTIAGO/66221/2014	1280	1280	160	640	640	1280	1280	160	6B	2014/10/14	C2/C1
23 A/HONG KONG/7561/2014	2560	2560	320	1280	640	1280	2560	160	6B	2014/10/13	C1/C1
24 A/LAOS/951/2014	2560	2560	320	1280	1280	2560	2560	320	6B	2014/09/17	C1/C1
25 A/HONG KONG/7572/2014	1280	1280	160	640	640	1280	1280	160	6B	2014/10/20	C1/C1
26 A/HONG KONG/7573/2014	1280	2560	320	640	640	1280	1280	160	6B	2014/10/23	C1/C1
27 A/LAOS/952/2014	1280	2560	320	1280	1280	1280	2560	320	6B	2014/09/15	C1/C1
28 A/ETHIOPIA/82/2014	2560	2560	320	1280	1280	2560	2560	320		2014/01/30	C1

Antigenic cartography of A(H1N1)pdm09 viruses



Gold: viruses from 2014
Blue: viruses from 2013
Grey: viruses before 2013
Large red dot: A/California/7/2009

(H1N1)pdm09 low reactors in HI assays by WHO CCs

WHO CC	A/Cal/07/09	Low (≥ 8 fold)
CDC	33 (100%)	0 (0%)
CNIC	36 (100%)	0 (0%)
NIID	2 (100%)	0 (0%)
NIMR	85 (100%)	0 (0%)
VIDRL	213 (100%)	0 (0%)
Total	369 (100%)	0

CDC

Summary of A(H1N1)pdm09 Viruses

- A(H1N1)pdm09 activity was generally sporadic in Asia, Africa, the Americas, Europe, and was variable in Oceania.
  - Local to widespread outbreaks occurred in Australia, New Caledonia, and New Zealand in September and October, 2014.
- The majority circulating A(H1N1)pdm09 viruses belonged to genetic clade 6B.
- All of the A(H1N1)pdm09 viruses remained antigenically similar to the recommended vaccine virus A/California/7/2009.
- The majority of A(H1N1)pdm09 viruses were sensitive to NA inhibitor antivirals
  - Two viruses showed highly reduced inhibition by oseltamivir and peramivir, but remained sensitive to zanamivir and laninamivir, due to H275Y mutation in the neuraminidase

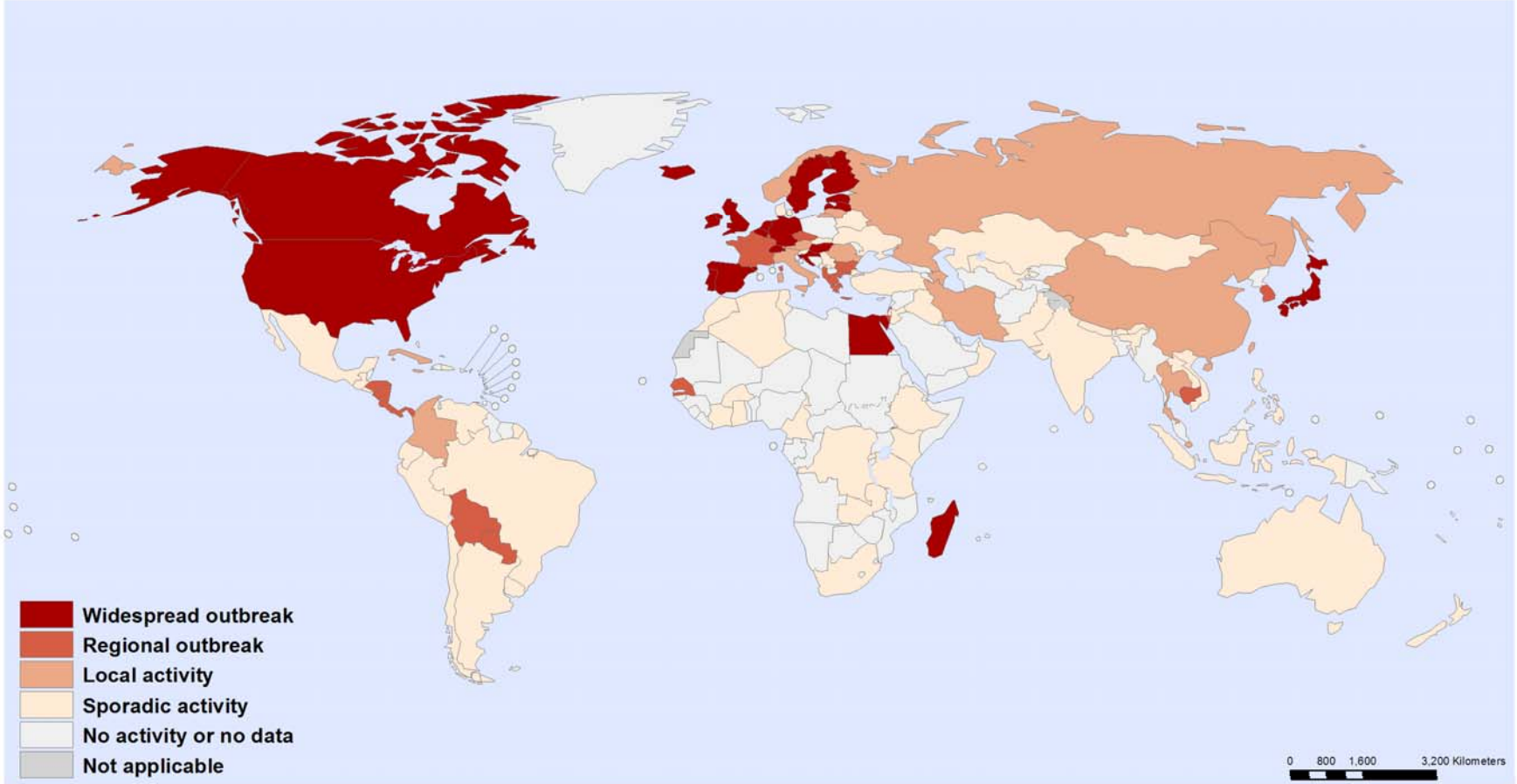
A(H3N2) viruses

Sept 2014 – Jan 2015

CDC

Influenza A(H3N2), September 2014 to January 2015, maximum

19 February 2015



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Map Production: WHO GISRS Team
World Health Organization

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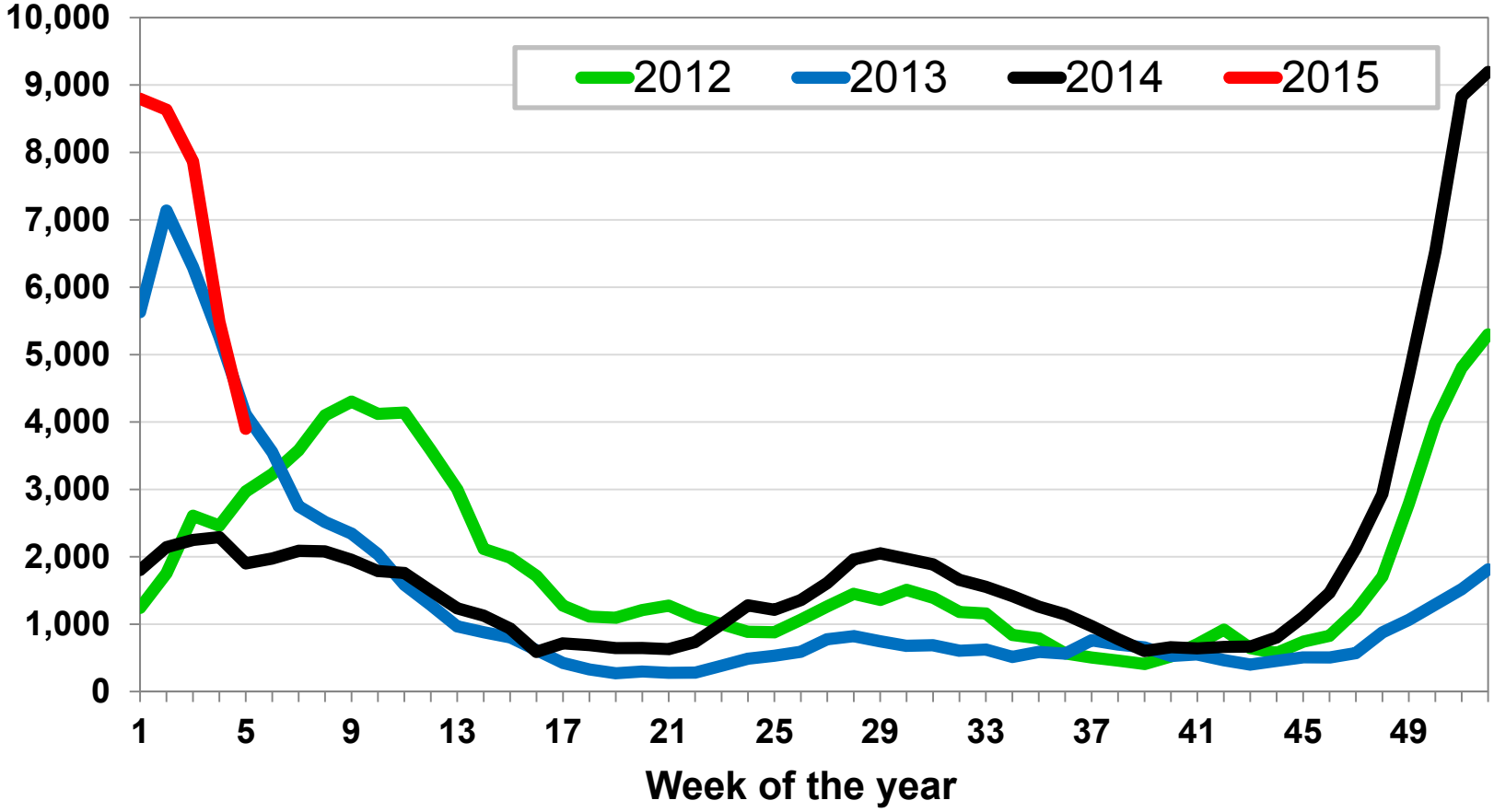
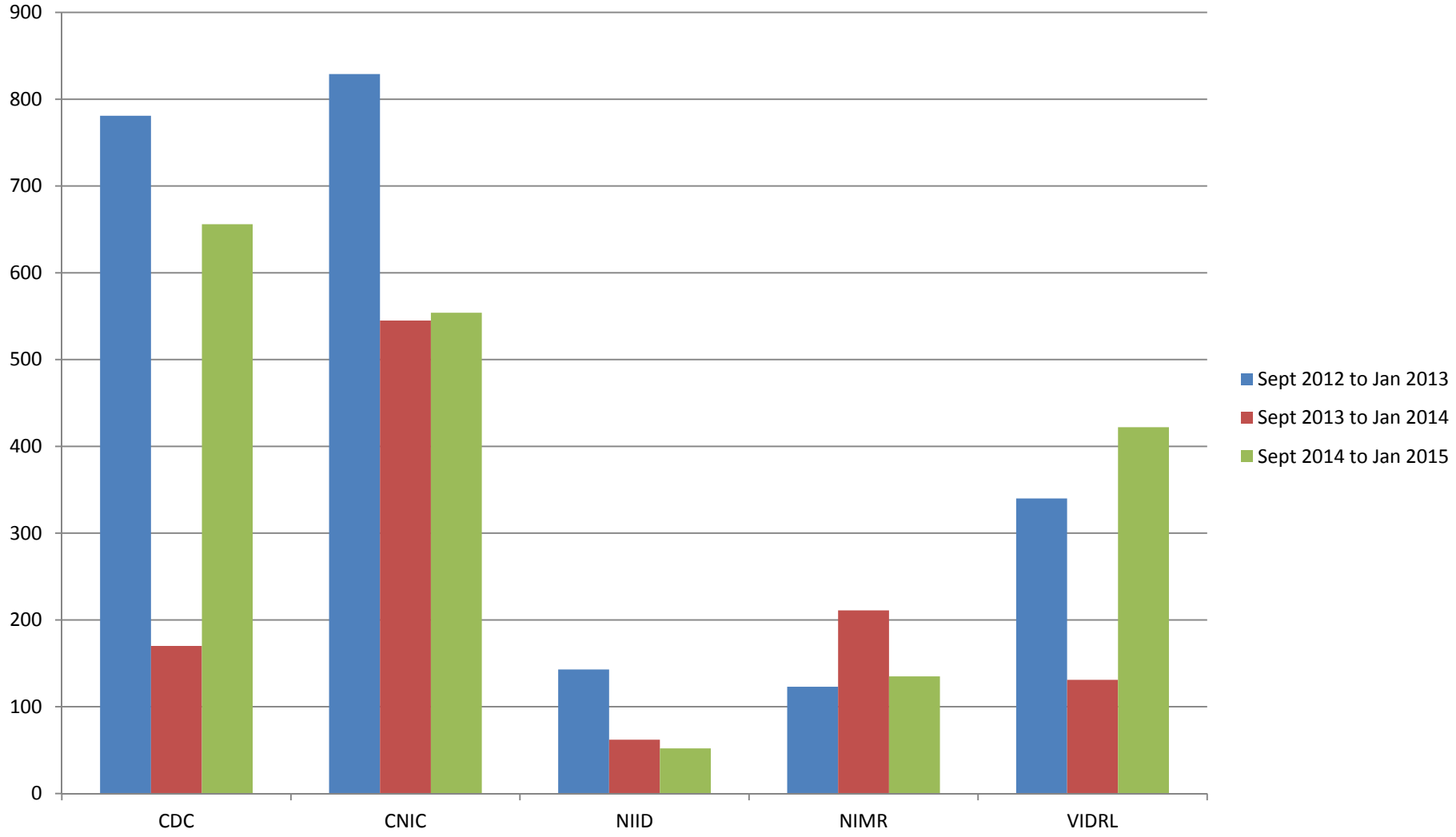
CDC

Number of A(H3N2) viruses detected by GISRS



ıta source: FluNet, (www.who.int/flunet), Global Influenza Surveillance and Response System (17 February 2015)

H3N2 viruses characterized by HI during the past 3 periods Sept to Jan



CDC timeline of detection of H3N2 antigenic drift variant

- Feb 2014: 1% of viruses tested are characterized as “Vaccine-like low”
  - The HA genes belong to phylogenetic clade 3C, with sub-clade 3C.3 and 3C.2 viruses comprising approx. 80 % and 20 % of viruses, respectively
  - WHO recommends A/Texas/50/2012-like virus for the NH 2014-15
- March: 4% of viruses tested are characterized as antigenically distinct from Texas/50/2012 vaccine virus
  - CDC notifies other WHO CCs to look for possible antigenic variants
- April-May: CDC expands genetic analysis to characterize more viruses
  - Begins to isolate viruses in eggs as potential donor for candidate vaccine virus (CVV)
- June- Aug: About one third of viruses characterized are antigenic drift variants
  - CDC sends two egg-grown virus to reassorting lab (NY Medical College)
- Sept: Nearly two third of viruses characterized are drift variants.
  - WHO recommends A/Switzerland/9715293/2013-like virus for the SH 2015

CDC

Evolutionary Relationships Among Influenza A(H3N2) Hemagglutinin (HA) Genes, 2014-2015

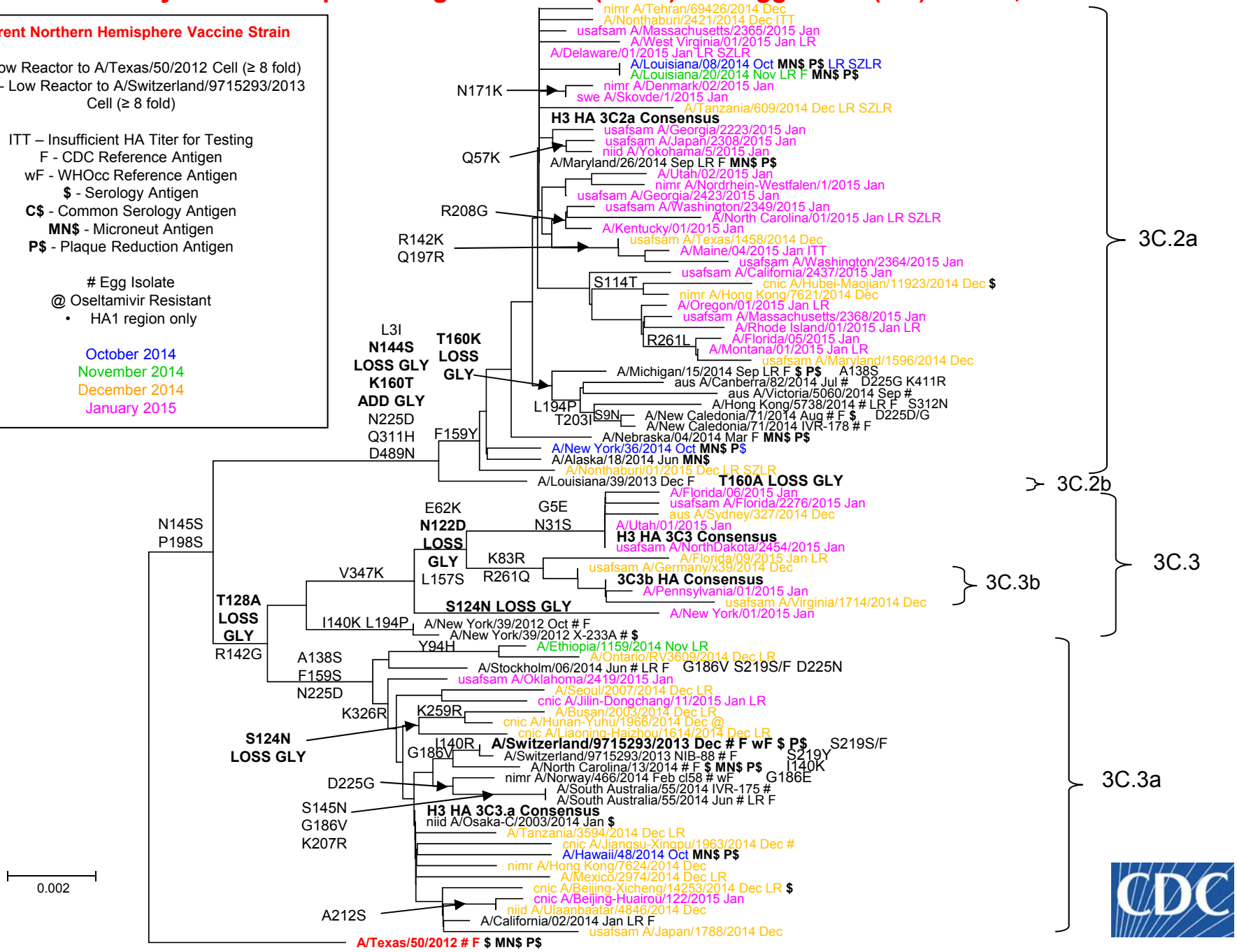
Current Northern Hemisphere Vaccine Strain

LR- Low Reactor to A/Texas/50/2012 Cell (≥ 8 fold)
SZLR - Low Reactor to A/Switzerland/9715293/2013 Cell (≥ 8 fold)

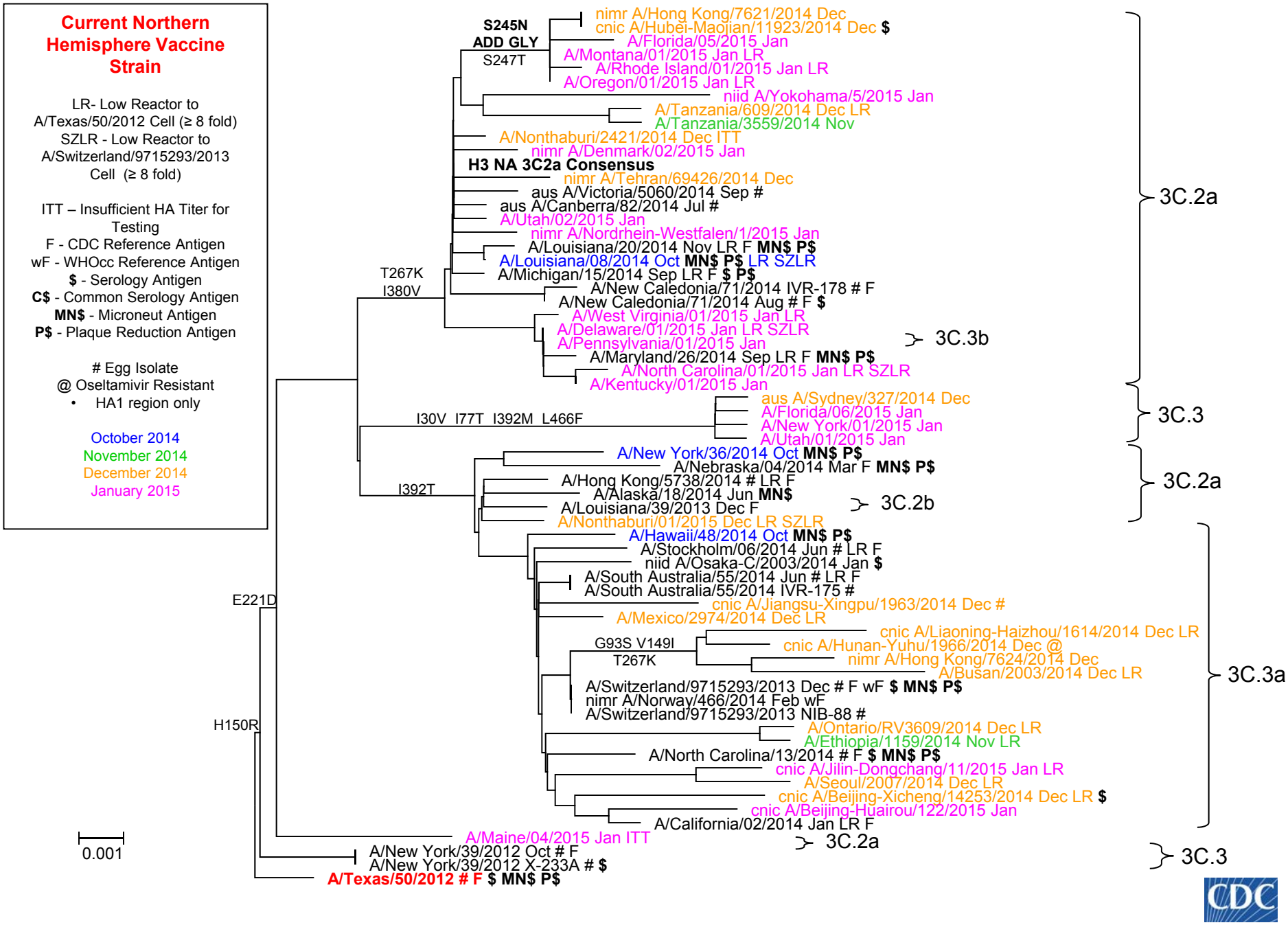
ITT – Insufficient HA Titer for Testing
F - CDC Reference Antigen
wF - WHOcc Reference Antigen
$ - Serology Antigen
C$ - Common Serology Antigen
MN$ - Microneut Antigen
P$ - Plaque Reduction Antigen

Egg Isolate
@ Oseltamivir Resistant
• HA1 region only

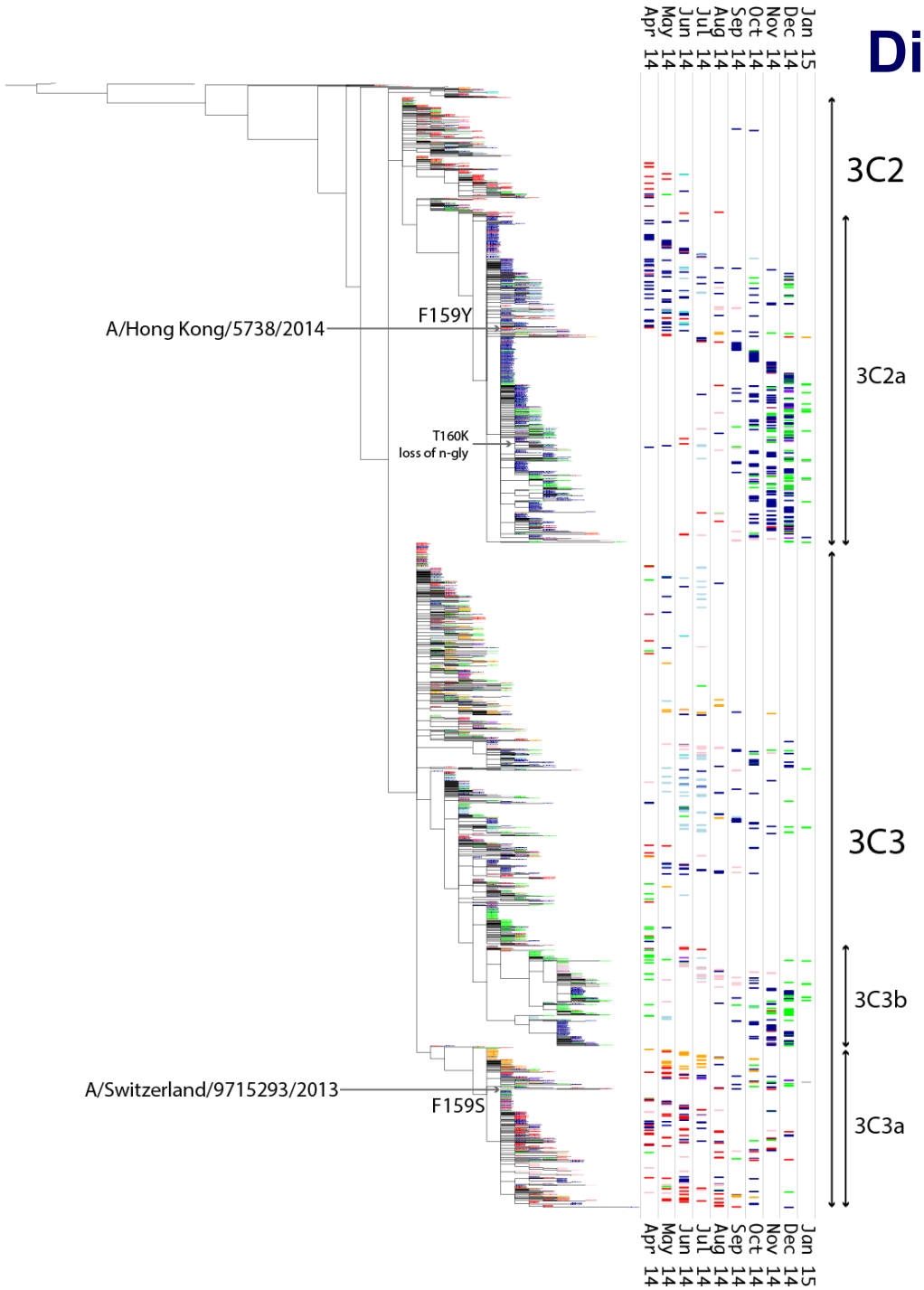
October 2014
November 2014
December 2014
January 2015



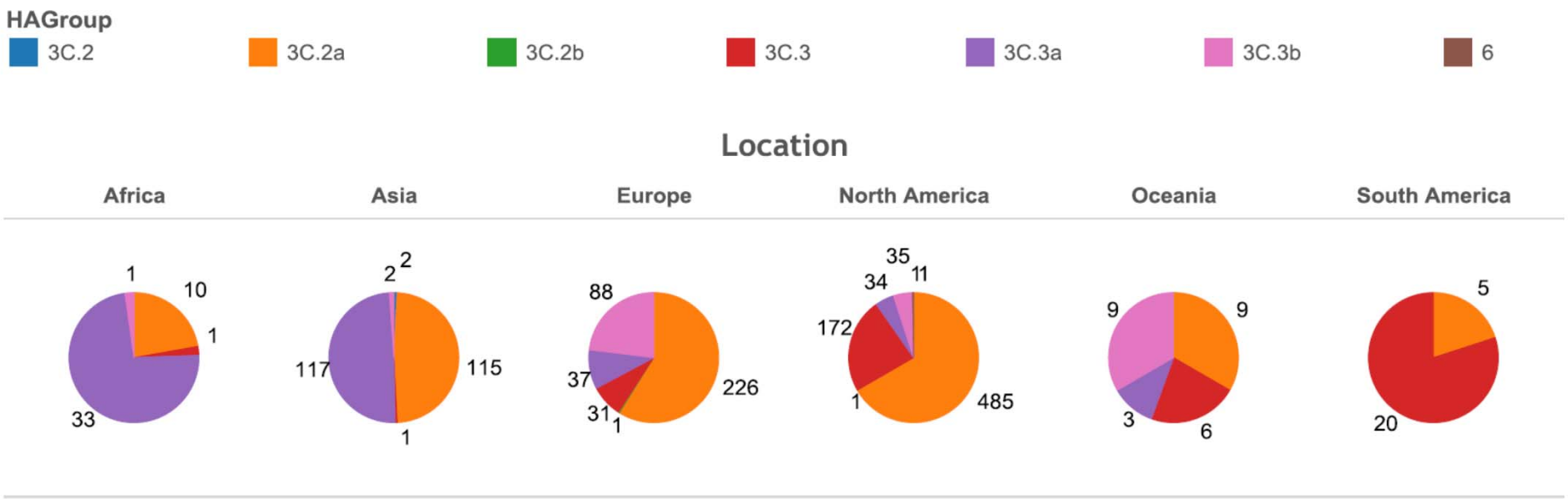
Evolutionary Relationships Among Influenza A(H3N2) Neuraminidase (NA) Genes, 2014-2015



Distribution of H3 HA clades over the last 10 months



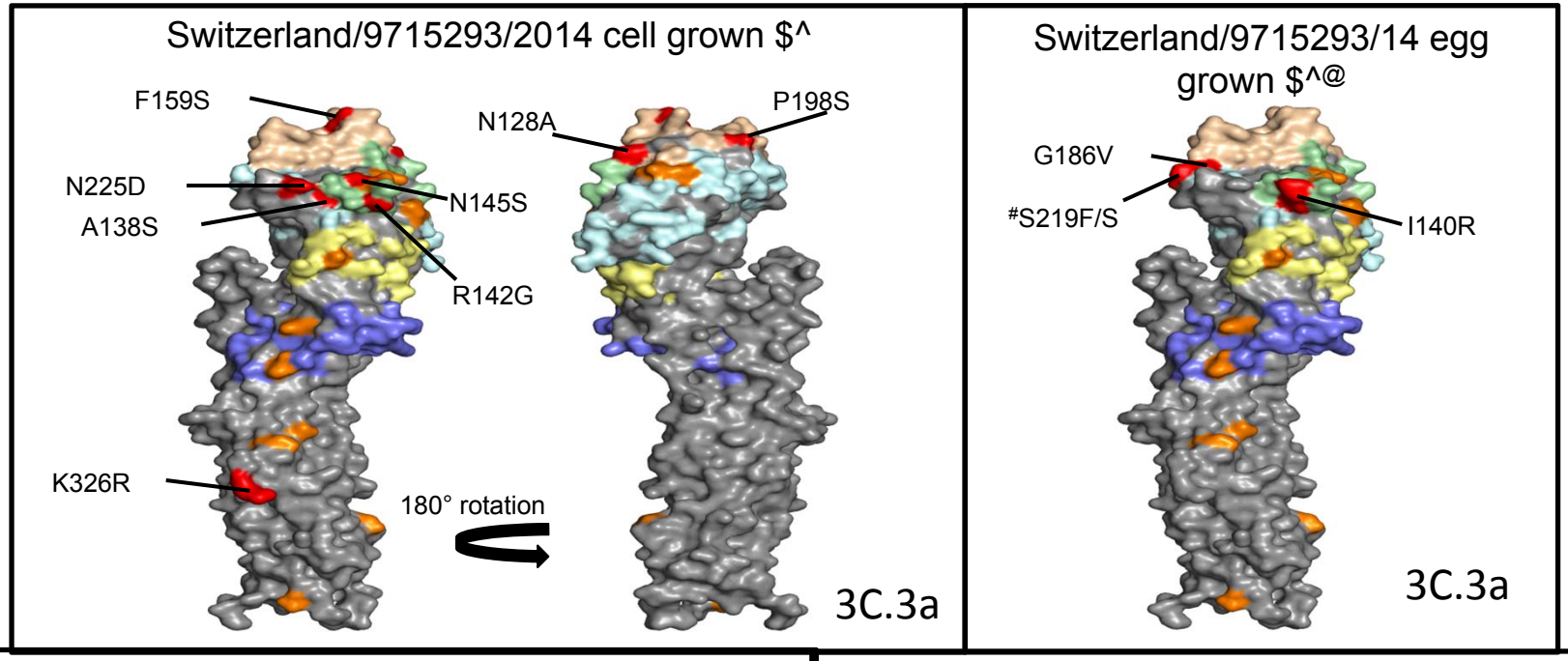
Global Distribution of H3 HA Clades

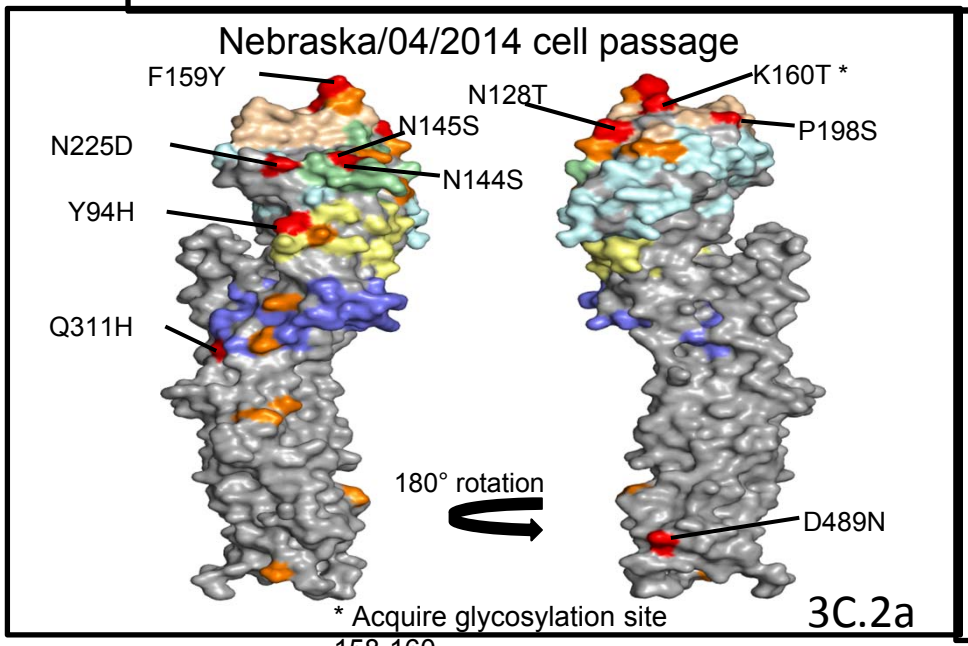


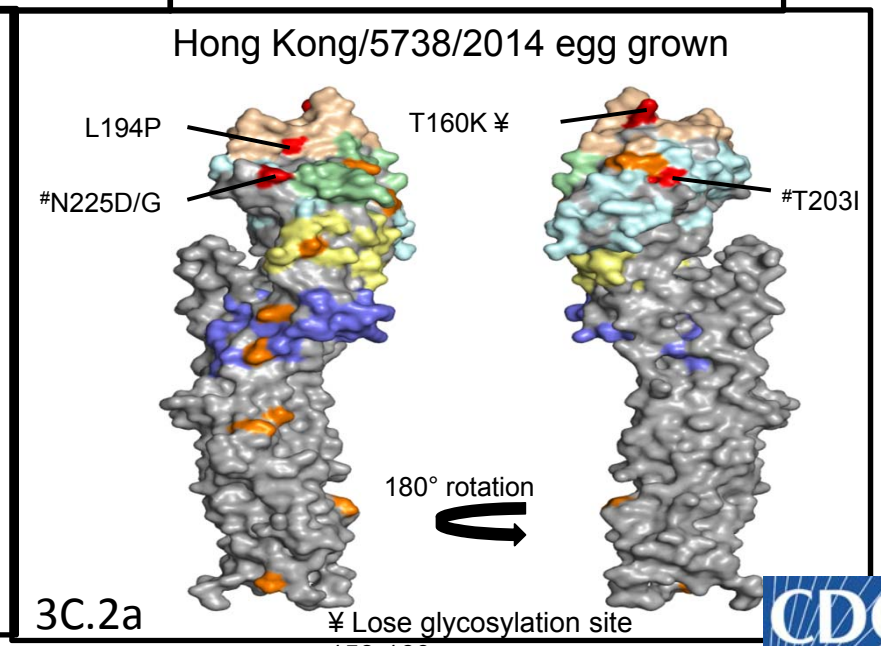
Total Number of Countries with 3C.2a = 47

Total Number of Countries with 3C.3a = 29

H3N2 Hemagglutinin changes compared to A/Texas/50/2012-cell







Challenges for Antigenic Characterisation of H3N2 Viruses

- NA of recent H3N2 viruses grown in MDCK cells exhibited red blood cell binding activity due to acquisition of mutations at residues 151 (or 148) in NA
  - Growth of viruses in MDCK-SIAT1 cells reduced proportion of viruses with NA mutation
  - HI in the presence of NA inhibitor (oseltamivir) eliminated NA RBC binding activity

- Both 3C.2a and 3C.3a have N225D involved in receptor binding

- 3C.2a encode a glycosylation motif at 158-160 in HA1

- Many 3C.2a viruses did not agglutinate red blood cells
  - Could not be characterized antigenically in HI

- The 158-160 motif is lost on egg-adaptation and multiple cell passage

- Antigenic characterization required both HI complemented by virus neutralization assays
  - More extensive genetic characterization for more comprehensive virological surveillance

CDC

HEMAGGLUTINATION INHIBITION REACTIONS OF INFLUENZA H3 VIRUSES WITH 20nM OSELTAMIVIR, 4 HA UNITS/ 50 MICROLITERS (2015/01/27)

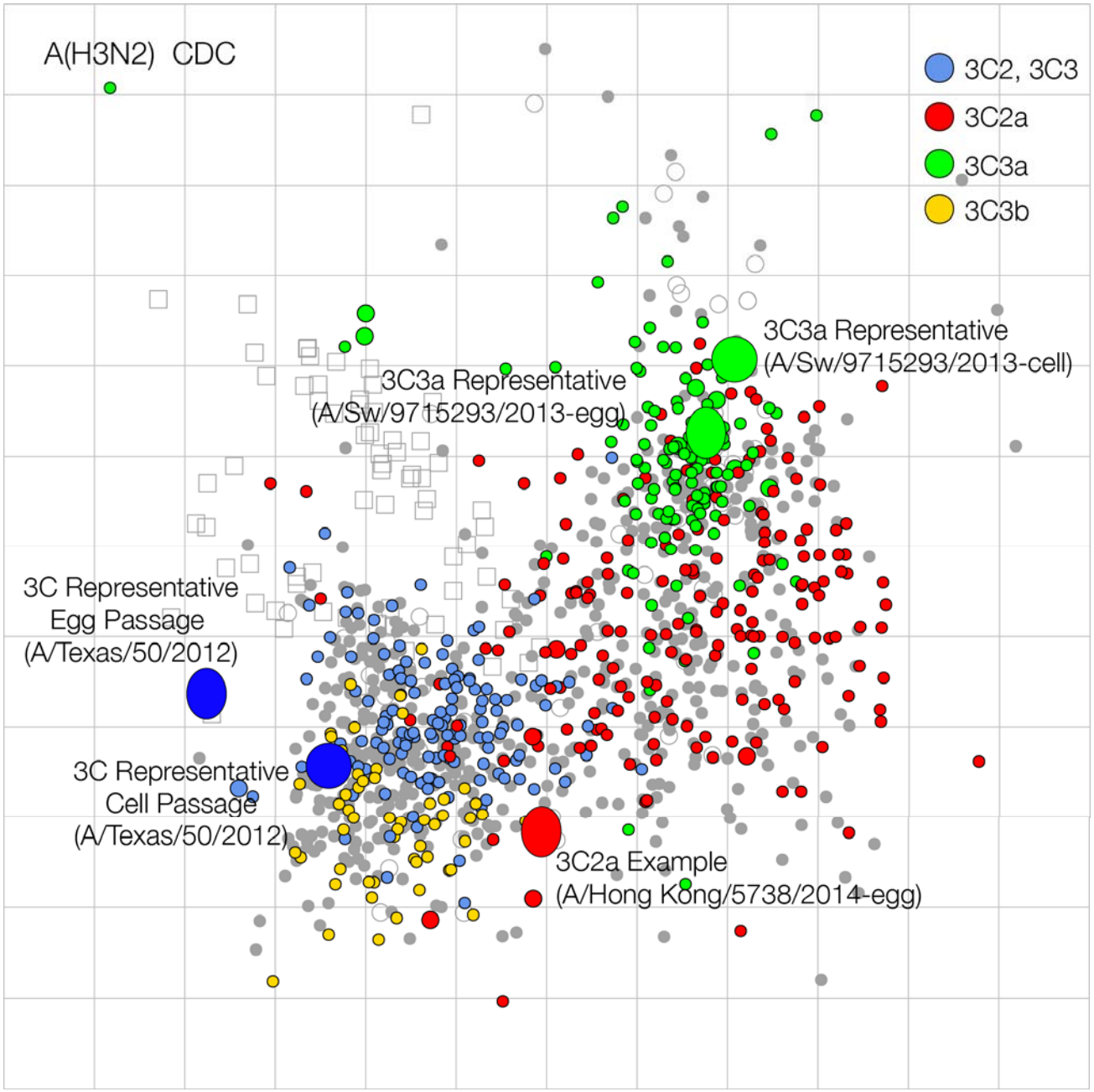
		REFERENCE FERRET ANTISERA								
		3C.1			3C.2a	3C.3a				
		EGG	MDCK	SIAT	SIAT	EGG	SIAT	HA	DATE	
REFERENCE ANTIGENS		TX/50	TX/50	TX/50	MI/15	SZ/13	SZ/13	GROUP	COLL.	PASS.
1	A/TEXAS/50/2012	2560	1280	1280	640	320	160	3C.1	2012/04/15	E5
2	A/TEXAS/50/2012	2560	2560	5120	1280	640	640	3C.1	2012/04/15	M1/C2
3	A/TEXAS/50/2012	640	1280	1280	640	160	320	3C.1	2012/04/15	M1/C1S2
4	A/MICHIGAN/15/2014	160	320	320	1280	80	160	3C.2a	2014/09/24	M1/S1
5	A/SWITZERLAND/9715293/2013	320	80	80	320	320	80	3C.3a	2013/12/06	E4/E2
6	A/SWITZERLAND/9715293/2013	80	80	80	160	160	320	3C.3a	2013/12/06	S1S2/S2
7	A/NORTH CAROLINA/13/2014	320	80	80	320	320	80	3C.3a	2014/04/15	E5
8	A/NORTH CAROLINA/13/2014	80	80	160	160	160	320	3C.3a	2014/04/15	S2
TEST ANTIGENS										
9	A/KANSAS/13/2014	1280	1280	1280	1280	320	640	3C.3	2014/12/20	S1
10	A/TENNESSEE/19/2014	320	640	1280	320	80	160	3C.3	2014/12/17	S1
11	A/KENTUCKY/21/2014	160	640	640	320	80	160	3C.3	2014/12/17	MX/S1
12	A/NORTH CAROLINA/43/2014	320	640	640	320	40	160	3C.3	2014/12/23	M1/S1
13	A/PENNSYLVANIA/60/2014	320	320	640	320	20	160	3C.3b	2014/12/22	S1
14	A/PENNSYLVANIA/61/2014	320	640	640	320	80	320	3C.3b	2014/12/29	S1
15	A/PENNSYLVANIA/62/2014	320	640	640	640	80	320	3C.3b	2014/12/29	S1
16	A/MAINE/02/2015	160	320	320	160	20	80	3C.3b	2015/01/02	S1
17	A/WISCONSIN/69/2014	320	80	160	320	80	160	3C.2a	2014/12/17	S1
18	A/WYOMING/20/2014	160	80	160	320	80	80	3C.2a	2014/12/09	S3
19	A/DISTRICT OF COLUMBIA/05/2014	160	80	160	320	80	160	3C.2a	2014/12/19	S1
20	A/ILLINOIS/15/2014	320	160	160	320	80	160	3C.2a	2014/12/20	S1
21	A/MISSOURI/20/2014	160	160	160	640	80	160	3C.2a	2014/12/26	M1/S1
22	A/NORTH CAROLINA/42/2014	160	160	160	320	80	160	3C.2a	2014/12/19	M1/S1
23	A/NORTH CAROLINA/45/2014	160	160	160	320	80	80	3C.2a	2014/12/25	M1/S1
24	A/COLORADO/36/2014	320	80	80	320	160	320	3C.2a	2014/12/17	S2
25	A/MEXICO/3040/2014	320	160	320	640	160	640	3C.3a	2014/12/17	C1/S1
26	A/MEXICO/2971/2014	80	80	160	320	160	320	3C.3a	2014/12/04	C2/S1
27	A/MEXICO/2974/2014	160	160	160	320	160	320	3C.3a	2014/12/08	

Antigenic analyses of influenza A(H3N2) viruses (Guinea Pig RBC with 20nM Oseltamivir)

Viruses	Genetic group	Collection Date	Passage History	Haemagglutination inhibition titre[1] — Post infection ferret antisera						
				A/Vic 361/11 T/C F09/12	A/Texas 50/12 Egg F42/13	A/Samara 73/13 F24/13	A/Switz 9715293/13 NIB F13/14	A/Switz 9715293/13 F25/14	A/HK 5738/14 T/C F30/14	A/HK 5738/14 NIB F53/14
				3C.1	3C.1	3C.3	3C.3a	3C.3a cl123	3C.2a	3C.2a cl 121
REFERENCE VIRUSES										
A/Victoria/361/2011	3C.1	2011-10-24	MDCK2/SIAT5	320	320	640	160	320	160	80
A/Texas/50/2012	3C.1	2012-04-15	E5/E2	1280	1280	1280	80	640	160	80
A/Samara/73/2013	3C.3	2013-03-12	C1/SIAT4	320	320	1280	160	640	640	80
A/Switzerland/9715293/2013	3C.3a	2013-12-06	SIAT1/SIAT3	40	40	320	160	160	160	40
A/Switzerland/9715293/2013	3C.3a	2013-12-06	E4/E1 clone 123	160	160	320	160	1280	320	40
A/Hong Kong/5738/2014	3C.2a	2014-04-30	MDCK1/MDCK2/SIAT1	80	80	320	160	160	320	80
A/Hong Kong/5738/2014	3C.2a	2014-04-30	E5/E1 clone121	40	80	320	80	40	640	1280
TEST VIRUSES										
A/Rouen/2291/2014	3C.2a	2014-12-09	MDCK1/SIAT1	80	80	160	40	80	80	<
A/Israel/O-6994/2014	3C.2a	2014-12-11	SIATx/SIAT2	40	<	80	<	40	80	<
A/Dakar/20/2014	3C.3a	2014-08-21	C3/MDCK1	40	40	320	160	160	80	<
A/Dakar/23/2014	3C.3a	2014-08-21	C3/MDCK1	40	40	160	80	160	80	<
A/Rouen/2273/2014	3C.3a	2014-12-05	MDCK1/SIAT1	40	40	160	80	80	80	<
A/Picardie/2297/2014	3C.3a	2014-12-13	MDCK2/SIAT1	<	<	80	<	40	80	<
A/Paris/2306/2014	3C.3a	2014-12-13	MDCK2/SIAT1	40	40	80	40	80	80	<
A/Caen/2354/2014	3C.3a	2014-12-14	MDCK2/SIAT1	80	80	320	40	80	80	<
A/Norway/0144/2015	3C.3b	2015-01-03	SIAT1	80	40	160	<	80	40	<
					Vaccine SH2014 NH 2014/15			Vaccine SH2015		

1. < = <40

Cartography of HI Data from CDC



Summary of A(H3N2) isolates collected since September-01-2014 showing reduction in reactivity with ferret antisera raised against reference viruses in HI assays

	HA Genetic Group	Reference Antigen Passage History	LIKE ≤4 fold[a]	LIKE-LOW ≥8 fold[a]	Number Tested	Tested Since
A/Texas/50/2012	3C.1	E5	190 (30%)	441 (70%)	631	Sep-14
		M1/C1S2	272 (43%)	359 (57%)	631	Sep-14
		M1/C2	226 (36%)	405 (64%)	631	Sep-14
A/Switzerland/9715293/2013	3C.3a	E4/E2	449 (71%)	182 (29%)	631	Sep-14
		S1S2/S2	593 (85%)	38 (6%)	631	Sep-14
A/Michigan/15/2014	3C.2a	M1/S1	391 (91%)	40 (9%)	431	Dec-14
A/Hong Kong/5738/2014	3C.2a	E5/E2	12 (8%)	130 (92%)	142	Dec-14

[a]Reduction in HI titer, compared to the homologous titer with post-infection ferret antisera indicated

Antigenic analysis of influenza A(H3N2) viruses
Plaque Reduction Neutralisation (SIAT1)

Viruses		Collection Date	Passage History	Neutralisation titre[1]				
				Post infection ferret sera				
				A/Vic/ 361/11 T/C F09/12	A/Switz/ 9715923/13 cl123 Egg F25/14	A/Switz/ 9715923/13 T/C NIB F13/14	A/HK/ 5738/14 cl121 Egg NIB F53/14	A/HK/ 5738/14 T/C F30/14
Amino acid sequence at the HA1 158-160 glycosylation site				NFK	NSK	NSK	NYK	N/KYT
Genetic group				3C.1	3C.3a	3C.3a	3C.2a	3C.2a
REFERENCE VIRUSES								
A/Victoria/361/2011	3C.1	2011-10-24	MDCK2/SIAT4	320 (255)	320 (200)	80 (100)	ND	40 (26)
A/Switzerland/9715293/2013 cl123	3C.3a	2013-12-06	E5	80 (62)	640 (534)	80 (65)	ND	80 (90)
A/Switzerland/9715293/2013	3C.3a	2013-12-06	SIAT1/SIAT2	40 (45)	80 (79)	160 (138)	ND	40 (33)
A/Hong Kong/5738/2014 cl121	3C.2a	2014-04-30	E6	40 (48)	40 (36)	80 (62)	2560 (2237)	320 (422)
A/Hong Kong/5738/2014	3C.2a	2014-04-30	MDCK1/MDCK2	40 (45)	80 (75)	80 (60)	80 (59)	320 (304)
TEST VIRUSES								
A/England/527/2014	3C.3	2014-11-18	SIAT1/SIAT1	320 (364)	320 (338)	320 (381)	40 (37)	80 (70)
A/Galicia/2084/2014	3C.3	2014-12-02	MDCKx/SIAT1	320 (325)	320 (274)	160 (190)	160 (159)	320 (427)
A/Paris/1971/2014	3C.2a	2014-10-02	MDCK2/SIAT1	160 (145)	160 (224)	320 (349)	320 (302)	320 (315)
A/Belgium/H82/2014	3C.2a	2014-10-23	SIAT1/SIAT1	80 (73)	320 (300)	320 (346)	160 (189)	1280 (1579)
A/Belgium/G604/2014	3C.2a	2014-10-29	SIAT1/SIAT1	160 (155)	320 (450)	160 (137)	320 (272)	1280 (1034)
A/Galicia/2056/2014	3C.2a	2014-11-19	MDCKx/SIAT1	80 (74)	160 (190)	80 (118)	320 (288)	1280 (1046)
A/England/528/2014	3C.2a	2014-11-20	SIAT2/SIAT1	40 (28)	160 (132)	80 (60)	160 (179)	1280 (1227)
A/England/530/2014	3C.2a	2014-11-26	MDCK1/SIAT1	40 (56)	160 (192)	80 (91)	80 (109)	160 (194)
					Vaccine			

1. The titres associated with a 50% reduction in plaque formation are shown based on doubling dilution of antisera closest to the automated reading value (shown in parentheses)

•

H3 low reactors in HI assays conducted by WHO CCs

WHO CC	A/Texas/50/2012 -like	Low (≥ 8 fold)
CDC	243 (37%)	413 (63%)
CNIC	22 (4%)	532 (96%)
NIID	7 (28%)	18 (72%)
NIMR	84 (62%)	51 (38%)
VIDRL	30 (17%)	143 (83%)
Total	386 (27%)	1055 (73%)

A(H3N2) Summary (1)

- Influenza A(H3N2) activity was generally sporadic in Africa and Oceania, but was regional to widespread in the Americas, Asia and Europe.
- A(H3N2) viruses collected from September 2014 to January 2015 fell into the phylogenetic clades 3C.2 and 3C.3.
- Viruses in sub-clade 3C.2a became predominant in many regions, while sub-clade 3C.3a predominated in parts of Asia, Eastern Europe and Africa.
  - In addition, 3C.3 and sub-clade 3C.3b viruses were still in circulation.
- Antigenic characterization of A(H3N2) viruses has become technically difficult
  - Many 3C.2a viruses had low or undetectable haemagglutination activity.
- Modified HI and virus neutralization assays were used to characterize viruses with panels of post-infection ferret antisera.
- The majority of recent A(H3N2) viruses were poorly inhibited by ferret antisera raised against egg- and cell-propagated reference A/Texas/50/2012 (clade 3C.1) viruses.

CDC

A(H3N2) Summary (2)

- Most viruses were well inhibited by ferret antisera raised against cell-propagated A/Switzerland/9715293/2013 (3C.3a) virus and representative cell-propagated 3C.2a viruses
  - 3C.2a and 3C.3a viruses were antigenically related, but distinguishable in some cases
- Ferret antisera raised against egg-propagated A/Switzerland/9715293/2013 reacted well with most recently circulating viruses.
- Initial data obtained with antisera raised against two egg-propagated 3C.2a viruses showed variable reactivity with circulating viruses.
- The vast majority of A(H3N2) viruses tested were susceptible to all four NA inhibitors.

CDC

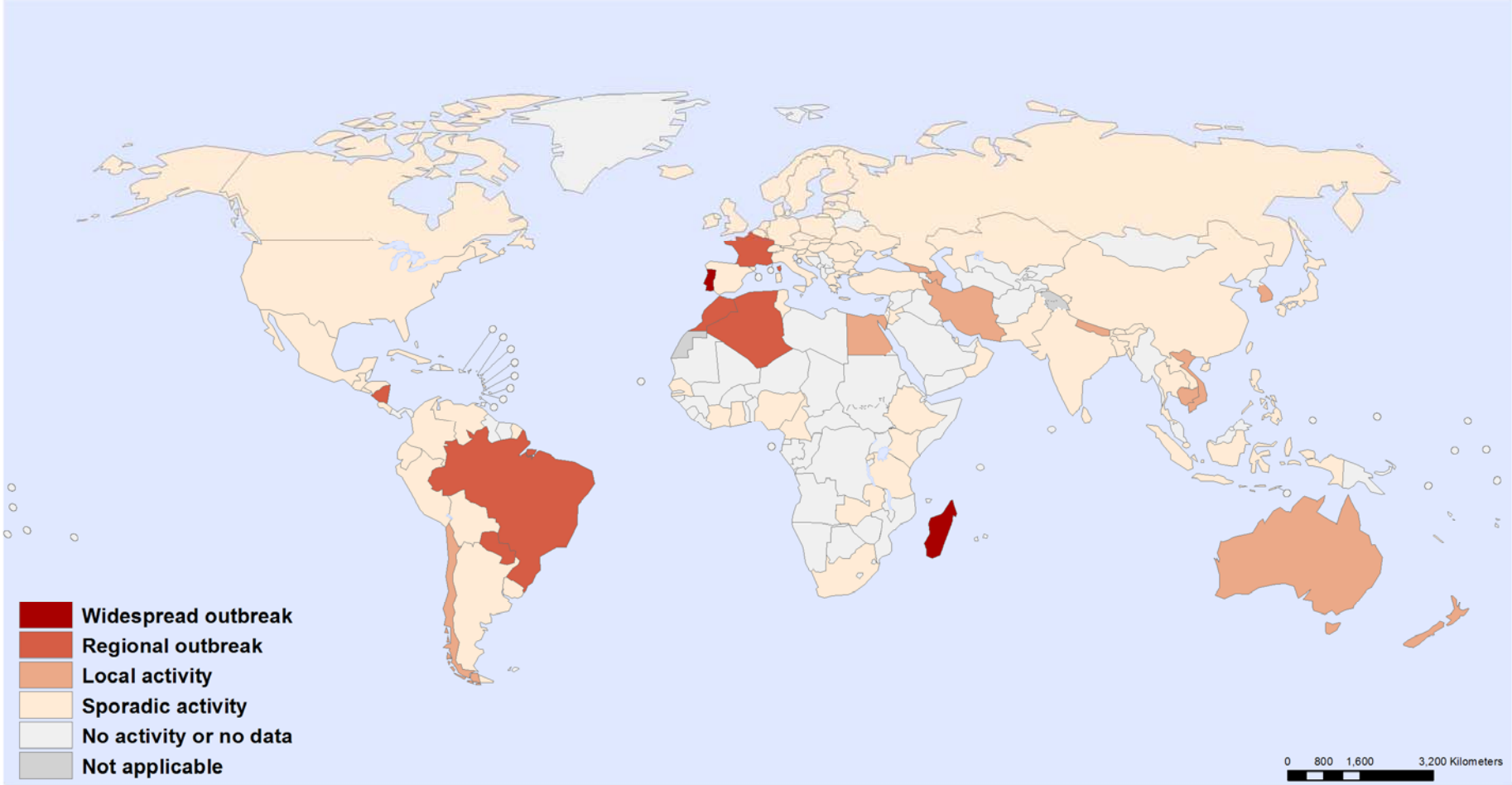
Influenza B viruses

Sept 2013 – Jan 2014

CDC

Influenza B, September 2014 to January 2015, maximum

19 February 2015



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), WHO
Map Production: WHO GISRS Team
World Health Organization

World Health Organization

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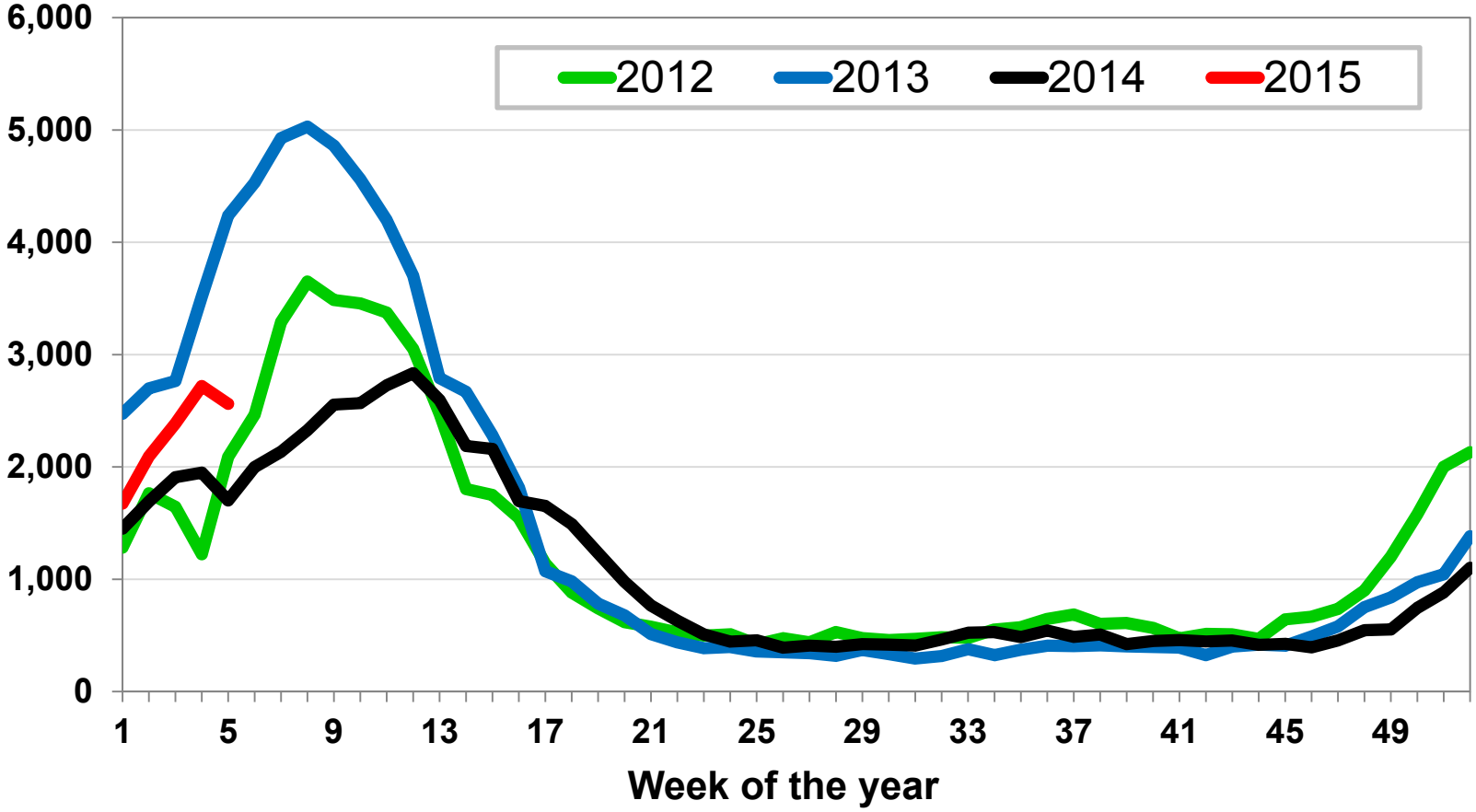
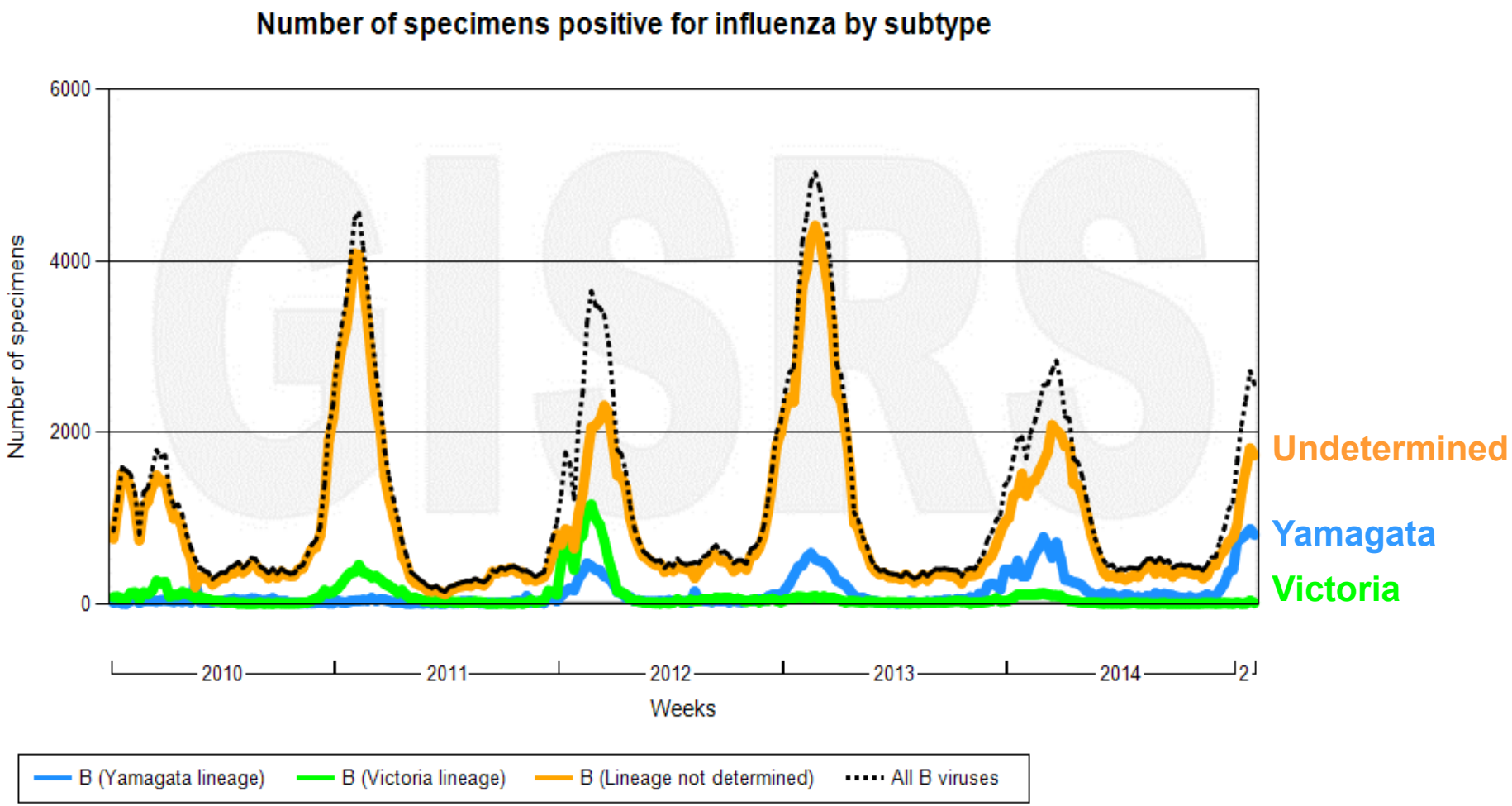
CDC

Number of influenza B viruses detected by GISRS



Data source: FluNet, (www.who.int/flunet), Global Influenza Surveillance and Response System (17 February 2015)

Global circulation of influenza B viruses



Data source: FluNet (www.who.int/flunet), GISRS

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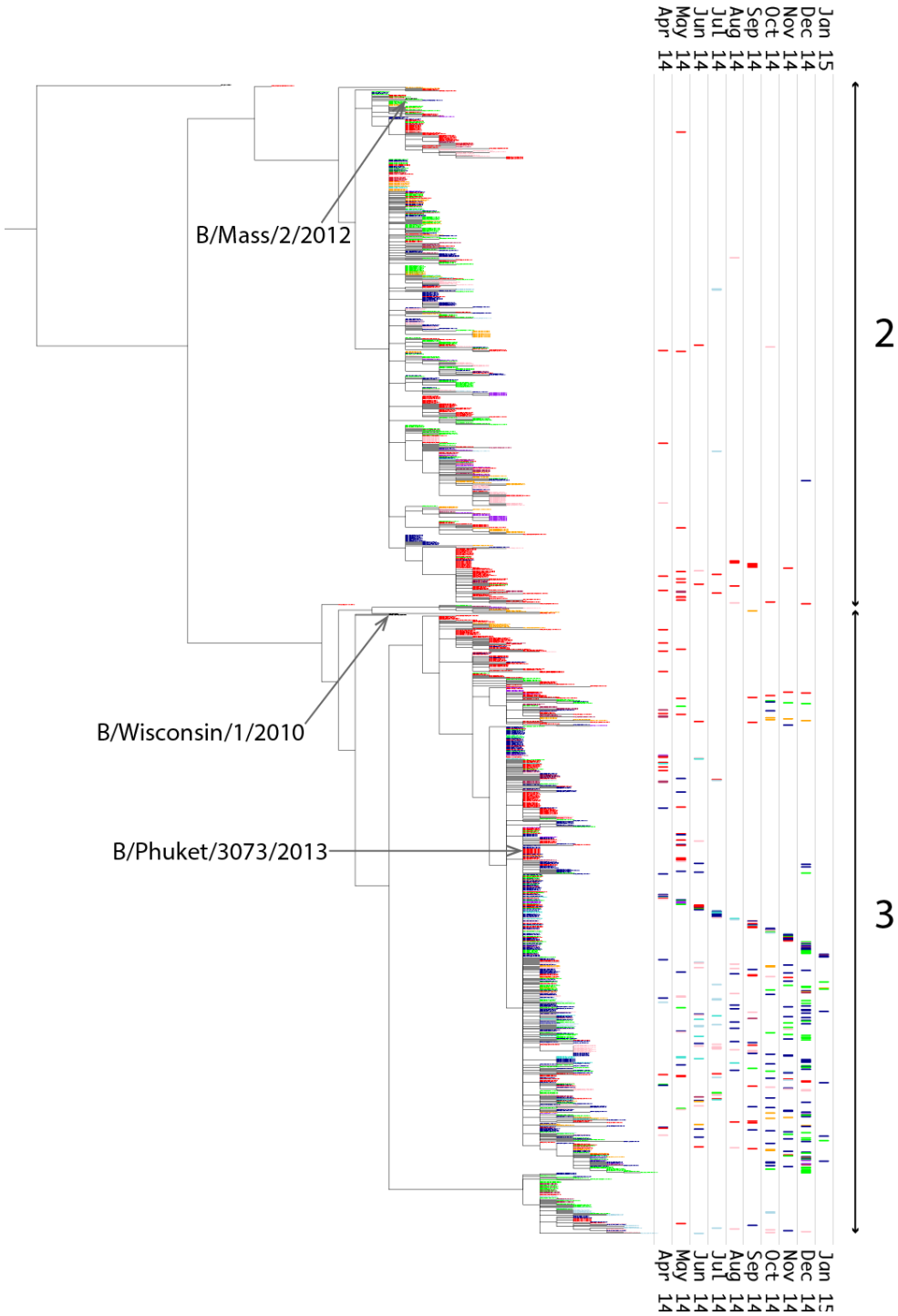
B/Yamagata lineage viruses


Jan 15
Dec 14
Nov 14
Oct 14
Sep 14
Aug 14
Jul 14
Jun 14
May 14
Apr 14
2
3
B/Mass/2/2012
B/Wisconsin/1/2010
B/Phuket/3073/2013
Apr 14
May 14
Jun 14
Jul 14
Aug 14
Sep 14
Oct 14
Nov 14
Dec 14
Jan 15

Evolutionary Relationships Among Influenza B Yamagata Lineage Hemagglutinin (HA) Genes, 2014-2015

Current Northern Hemisphere Vaccine Strain

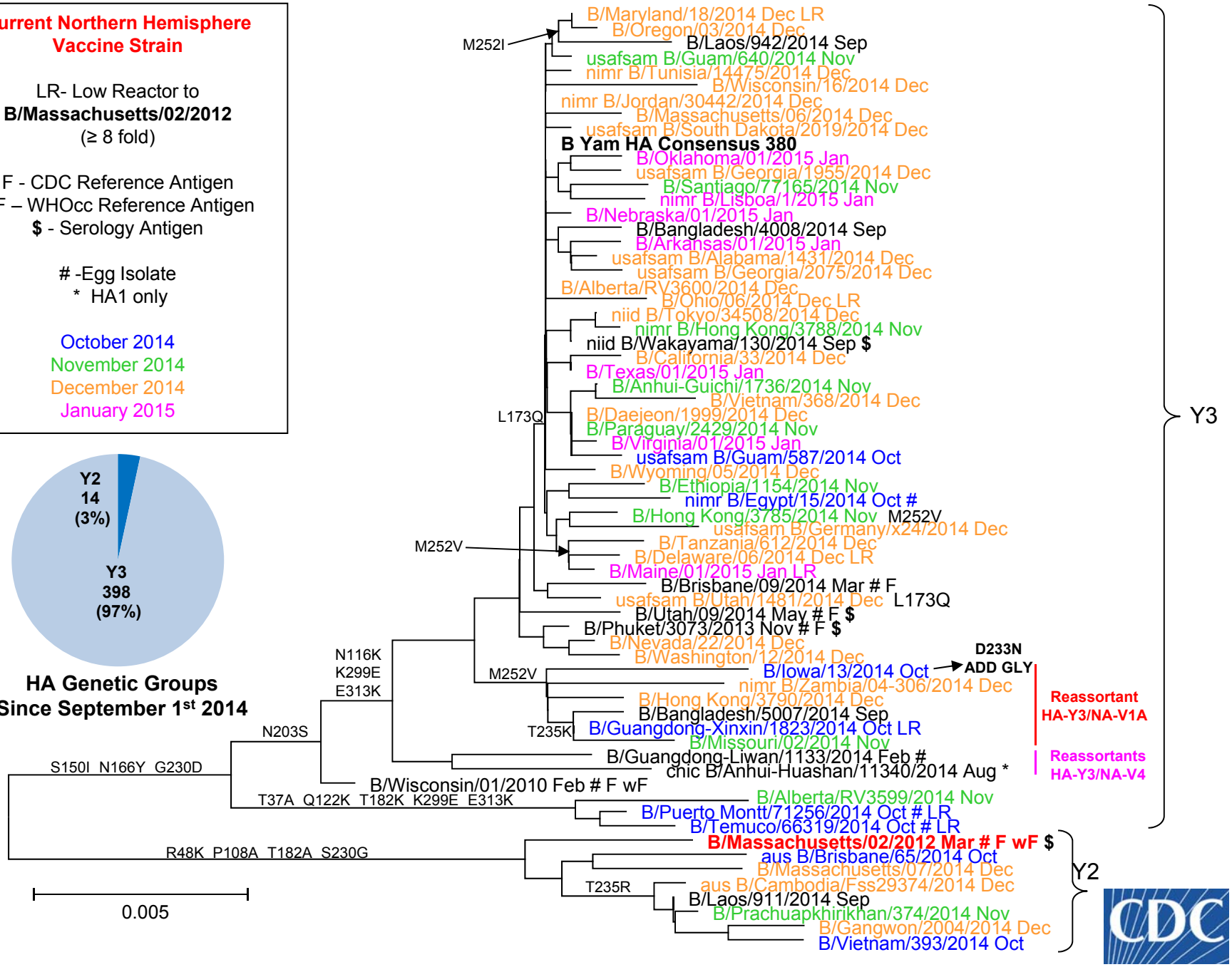
LR- Low Reactor to
B/Massachusetts/02/2012
(≥ 8 fold)

F - CDC Reference Antigen
wF – WHOcc Reference Antigen
$ - Serology Antigen

-Egg Isolate
* HA1 only

October 2014
November 2014
December 2014
January 2015

HA Genetic Groups Since September 1st 2014



Evolutionary Relationships Among Influenza B Yamagata Lineage Neuraminidase (NA) Genes, 2014-2015

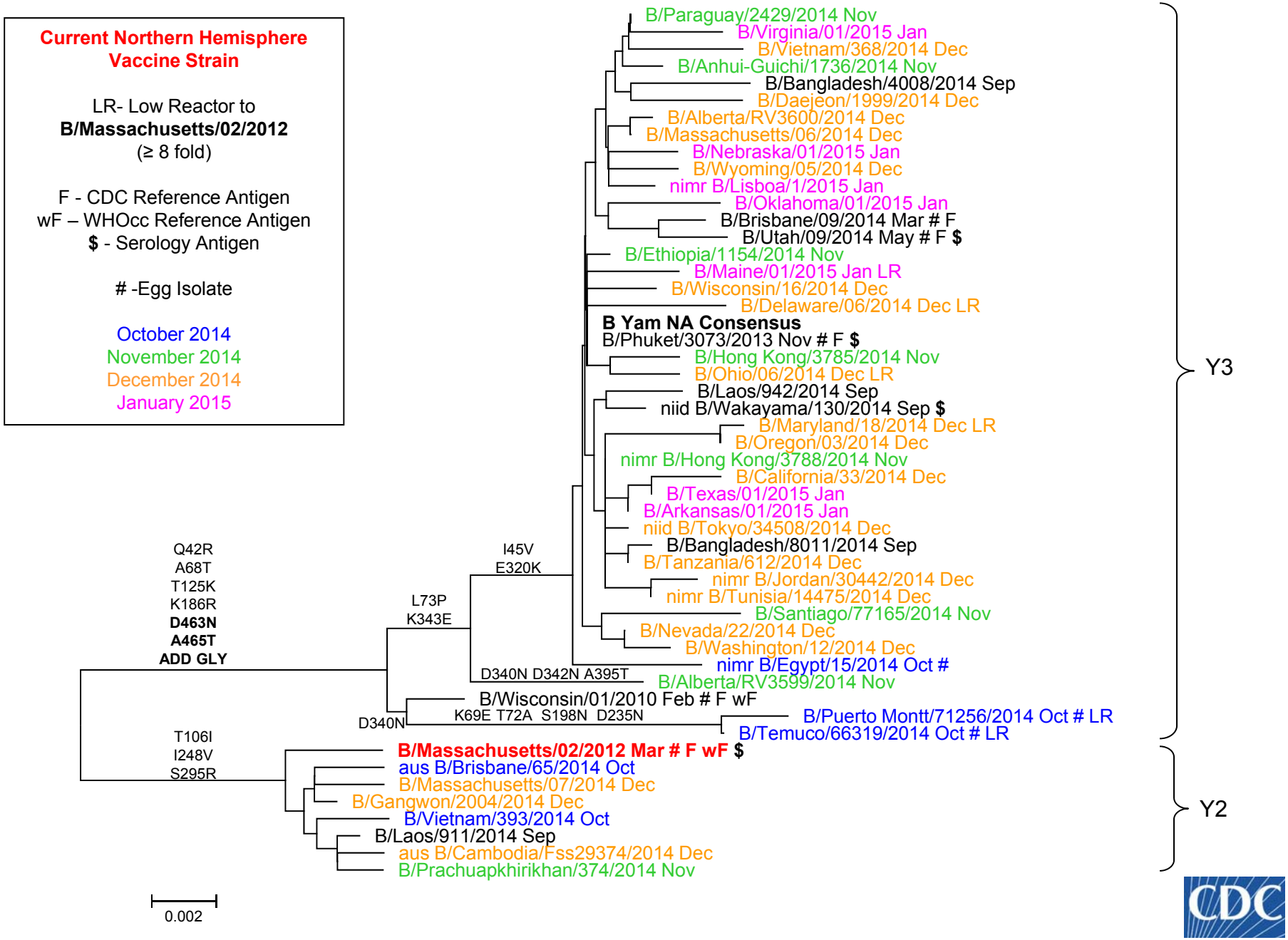


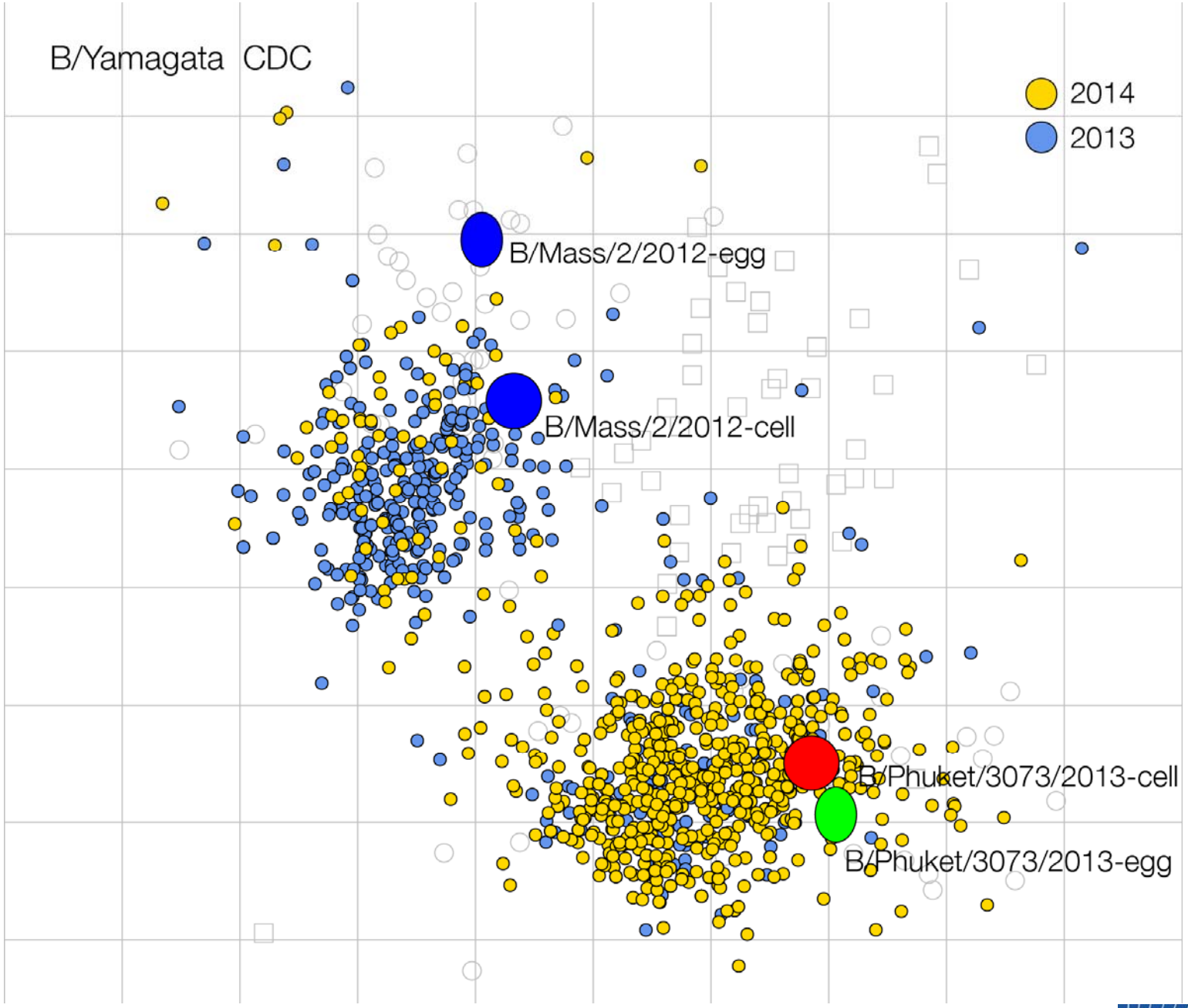
Table 14-7. Antigenic analyses of influenza B viruses (Yamagata lineage) 2015-02-04

Viruses	Genetic Group	Collection date	Passage History	Haemagglutination Inhibition Titre[1] Post-infection ferret antisera					
				B/Estonia 55669/11 F26/11	B/Mass 02/12 Egg F28/13	B/Mass 02/12 T/C F15/13	B/Phuket 3073/13 Egg F36/14	B/Phuket 3073/13 T/C F35/14	B/HK 3417/14 St Judes F715/14
				2	2	2	3	3	3
REFERENCE VIRUSES									
B/Estonia/55669/2011	2	2011-03-14	MDCK1/MDCK1	640	160	640	160	160	320
B/Massachusetts/02/2012	2	2012-03-13	E3/E4	80	1280	160	320	20	320
B/Massachusetts/02/2012	2	2012-03-13	MDCK1/C2/MDCK3	320	640	1280	320	160	640
B/Phuket/3073/2013	3	2013-11-21	E4/E3	40	320	80	160	40	320
B/Phuket/3073/2013	3	2013-11-21	M2/M2	640	640	320	640	1280	320
B/Hong Kong/3417/2014	3	2014-06-04	E5	20	80	40	80	<	160
TEST VIRUSES									
B/Dakar/02/2014	3	2014-09-29	C1/MDCK1	160	320	160	160	320	320
B/Zambia/04-294/2014	3	2014-10-11	MDCK2/MDCK1	80	160	160	320	320	640
B/Madagascar/3124/2014	3	2014-10-22	MDCK2/MDCK1	320	640	640	640	640	640
B/Madagascar/3129/2014	3	2014-10-24	MDCK1/MDCK1	640	640	640	640	1280	640
B/Zambia/06-051/2014	3	2014-10-29	MDCK2/MDCK1	80	160	160	320	160	640
B/Zambia/06-046/2014	2	2014-10-30	MDCK2/MDCK1	160	320	640	80	80	320
B/Zambia/04-309/2014	3	2014-11-15	MDCK2/MDCK1	160	320	320	320	320	320
B/Jordan/30442/2014	3	2014-12-06	MDCK1/MDCK1	80	80	80	160	160	320
B/Finland/470/2014	3	2014-12-10	MDCK1/MDCK1	80	80	160	160	160	320
B/Tunisia/14192/2014	3	2014-12-11	MDCK1	80	160	160	160	160	320
B/Zambia/04-306/2014	3	2014-12-11	MDCK2/MDCK1	160	320	320	320	320	640
B/Finland/471/2014	3	2014-12-15	MDCK1/MDCK1	80	160	160	160	160	320
B/Meknes/32/2014	3	2014-12-16	MDCK1/MDCK1	80	80	160	160	80	320
B/Tunisia/14475/2014	3	2014-12-17	MDCK1	40	80	80	160	80	320
B/Jordan/20555/2014	3	2014-12-17	MDCK1/MDCK1	160	160	320	320	320	640
B/Norway/3238/2014	3	2014-12-19	MDCK1	80	160	160	160	160	320
B/Oujda/96/2014	3	2014-12-23	MDCK1/MDCK1	160	320	160	320	320	320
B/Croatia/1988/2014	3	2014-12-29	MDCKx/MDCK1	80	160	80	160	160	640
B/Croatia/1989/2014	3	2014-12-29	MDCKx/MDCK1	80	320	160	320	320	640
B/Meknes/102/2015	3	2015-01-07	MDCK1/MDCK1	80	320	160	320	320	320
B/Valladolid/1/2015	3	2015-01-08	MDCK1	80	160	160	160	160	320
B/Slovenia/135/2015	3	2015-01-09	MDCKx/MDCK1	80	160	160	160	160	640
					Vaccine NH2013/14 SH 2014 NH 2014/15		Vaccine SH2015		

1. < = <10

TABLE 5.8: B viruses (B/Yamagata lineage) (5)

Haemagglutination Inhibition Assay - WHO Influenza Centre											
Reference Antisera											
	Sequenced		A	B	C	D	E	F	G		
	Oct 14 Part A&B; Nov 20, 2014		F2507	F3061	F2570	F3060	F3064	F3067	F3128		
			E2	**E3/E1**	**MDCK1**	**MDCKX**	**E4**	**MDCK1**	**E4**	**Passage**	**Date**
	Reference Antigens	**Clade**	**BRIS/36**	**MASS/2**	**MASS/2**	**SYD/7**	**PHU/3073**	**PHU/3073**	**BRIS/9**	**History**	
A	B/BRISBANE/36/2012	**2**	**640**	160	320	<20	160	<20	20	E3	
B	B/MASS/02/2012	**2**	640	**320**	640	80	640	40	80	E3.E2	
C	B/MASS/02/2012	**2**	640	640	**1280**	160	160	80	80	MDCK3	
D	B/SYDNEY/7/2014	**3**	320	640	160	**320**	320	160	320	MDCKX	
E	B/PHUKET/3073/2013	**3**	320	320	80	80	**640**	80	160	E5	
F	B/PHUKET/3073/2013	**3**	320	640	160	320	320	**160**	320	MDCK2	
G	B/BRISBANE/9/2014	**3**	320	320	80	80	320	80	**160**	E4	
	Test Antigens										
1	B/VICTORIA/504/2014		160	320	80	160	160	160	160	mdck1	16/08/2014
2	A/VICTORIA/413/2014		320	640	160	320	320	160	320	MDCK1	26/08/2014
3	B/STH AUSTRALIA/25/2014		160	320	80	320	160	160	320	MDCK1	19/08/2014
4	B/STH AUSTRALIA/1025/2014		160	320	80	320	160	160	160	mdck1	23/09/2014
5	B/WELLINGTON/23/2014		320	640	160	320	320	160	320	MDCKX	7/08/2014
6	B/WAIKATO/3/2014	**3**	320	640	160	320	320	160	320	MDCKX	6/08/2014
7	B/CHRISTCHURCH/3/2014	**3**	160	640	160	320	320	160	320	MDCKX	8/08/2014
8	B/BRISBANE/54/2014		320	640	160	320	320	160	320	mdck2	6/09/2014
9	B/STH AUCKLAND/17/2014		160	320	80	160	160	160	160	MDCKX	20/08/2014
10	B/VICTORIA/503/2014		160	320	80	320	160	80	160	mdck1	17/08/2014
11	B/VICTORIA/506/2014		160	320	80	160	320	80	160	mdcl1	20/08/2014
12	B/CANBERRA/10/2014		160	320	80	160	160	80	160	mdck1	25/08/2014
13	B/VICTORIA/804/2014	**3**	160	320	80	160	160	80	160	mdck1	2/09/2014
14	B/WELLINGTON/18/2014		160	320	80	160	160	80	160	SIATX,M1	1/08/2014
15	B/WELLINGTON/19/2014		160	320	80	320	160	80	160	MDCKX	4/08/2014
16	B/STH AUCKLAND/14/2014	**3**	160	320	80	160	160	80	160	SIATX,M1	16/08/2014
17	B/BRISBANE/59/2014		160	320	80	160	160	80	160	mdck2	17/09/2014
18	B/BRISBANE/60/2014		1280	640	1280	160	160	80	160	mdck2	18/09/2014
19	B/TOWNSVILLE/7/2014		640	640	1280	160	160	80	160	mdck2	16/09/2014
20	B/WELLINGTON/47/2014		160	320	80	160	160	80	160	MDCKX	1/09/2014
21	B/WELLINGTON/48/2014	**3**	160	320	160	320	160	80	320	MDCKX	3/09/2014
22	B/WELLINGTON/51/2014		160	320	80	160	160	80	160	MDCKX	10/09/2014
23	B/WELLINGTON/52/2014		160	320	80	160	160	80	160	MDCKX	5/09/2014
24	B/STH AUCKLAND/18/2014		160	320	160	320	160	80	320	MDCKX	23/08/2014
25	B/STH AUCKLAND/24/2014		160	320	80	160	160	80	160	MDCKX	26/08/2014
26	B/STH AUCKLAND/25/2014	**3**	160	320	80	160	80	80	160	MDCKX	8/09/2014
27	B/WELLINGTON/21/2014	**2**	640	320	640	80	40	40	40	SIATX,M1	7/08/2014


B/Yamagata CDC
2014
2013
B/Mass/2/2012-egg
B/Mass/2/2012-cell
B/Phuket/3073/2013-cell
B/Phuket/3073/2013-egg

B/Victoria lineage viruses

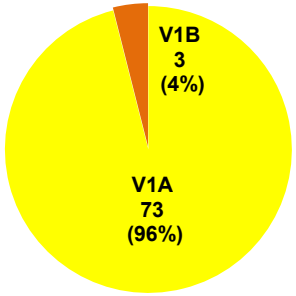
Evolutionary Relationships Among Influenza B Victoria Lineage Hemagglutinin (HA) Genes, 2014-2015

LR- Low Reactor to
B/Brisbane/60/2008
(≥ 8 fold)

F - CDC Reference Antigen
wF – WHOcc Reference Antigen
$ – Serology Antigen

-Egg Isolate
* HA1 only

October 2014
November 2014
December 2014
January 2015



HA Genetic Groups Since September 1st 2014

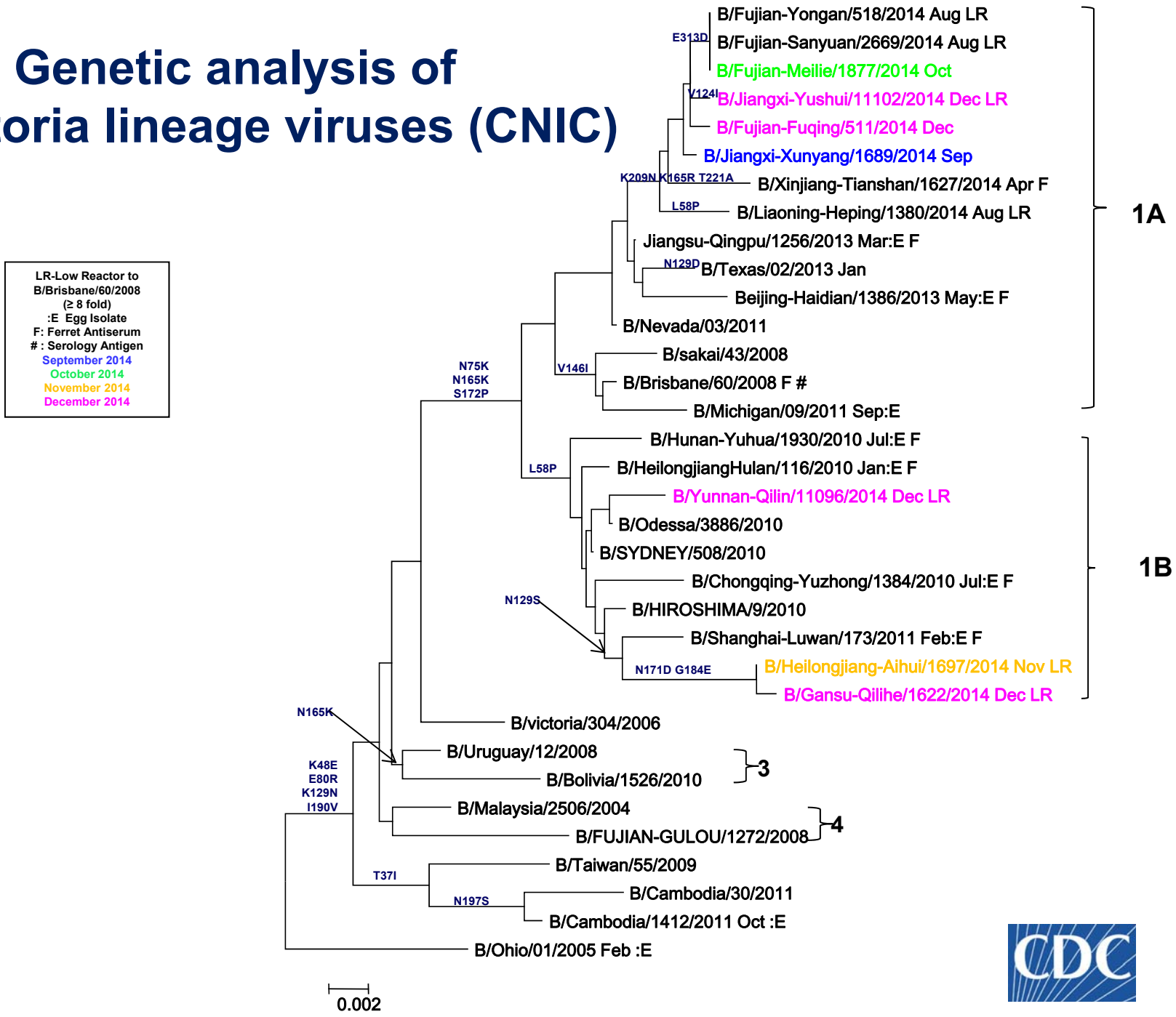
B/Missouri/03/2014 Dec
B/Utah/22/2014 Dec
usafsam B/Oklahoma/1674/2014 Dec
B/Colorado/03/2014 Nov
B/Arkansas/06/2014 Dec
B/North Dakota/03/2014 Dec
B/Texas/42/2014 Dec
swe B/Stockolm/6/2014 Nov
B/Texas/28/2014 Nov LR
B/Florida/01/2015 Jan
usafsam B/Georgia/1089/2014 Dec
usafsam B/Georgia/2024/2014 Dec
B/New Mexico/05/2014 Dec
B/New Mexico/04/2014 Dec
B/Texas/41/2014 Dec
usafsam B/Mississippi/1098/2014 Dec **N531D LOSS GLY**
B/Iowa/15/2014 Dec
B/Nevada/23/2014 Dec
B/Wyoming/06/2014 Dec
B/Arkansas/04/2014 Dec
B/Mexico/2511/2014 Nov
B/Hawaii/24/2014 Jul #
B/Wisconsin/13/2014 Dec
B/Texas/33/2014 Dec
B/California/32/2014 Nov LR
usafsam B/California/M1023/2014 Oct
B/Louisiana/15/2014 Dec
B/Ohio/04/2014 Dec
usafsam B/Kentucky/1797/2014 Dec
B/Florida/43/2014 Oct #
B/Paraguay/4674/2014 Dec
B/Texas/02/2013 Jan # F **$**
B/Maryland/16/2014 Nov LR
B/Texas/02/2013 Jan F
B/Santiago/69223/2014 Oct
B Vic HA Consensus 67
B/Nonthaburi/373/2014 Nov
bra B/Sao Paulo/2513/2015 Jan V146I
B/Paraguay/672/2014 Nov
bra B/Sao Paulo/97623/2014 Dec
aus B/New Caledonia/6/2014 Nov #
aus B/Darwin/43/2014 Dec
aus B/Brisbane/70/2014 Nov
aus B/Brisbane/74/2014 Nov
aus B/Brisbane/63/2014 Oct #
B/Guangdong-Zhongshan/1465/2014 May #
nimr B/Baden-Wurttemberg/3/2014 Oct **N166S LOSS GLY**
nimr B/Ghana/DILI-14-1032/2014 Nov
cnic B/Xinjiang-Hutubi/1291/2014 May LR *
nimr B/Ghana/DILI-14-0878/2014 Nov
niid B/Taiwan/452/2014 Oct
B/Iowa/14/2014 Nov
B/Louisiana/14/2014 Nov LR
nimr B/Cameroon/14V-7839/2014 Oct
usafsam B/Louisiana/1033/2014 Dec
B/Nevada/03/2011 Feb # F
B/Brisbane/60/2008 Aug # F $
nimr B/Rheinland-Pfalz/1/2014 Dec V146I
B/Montana/05/2012 Oct # LR F
cnic B/Guangdong-Xiangqiao/1489/2014 Jun *

I318V
V248I
V146I
I117V
A276T
R118S
N129D
A169E
K56N V124A D526E
E183K
K209N
L58P
L58P N129S N171D

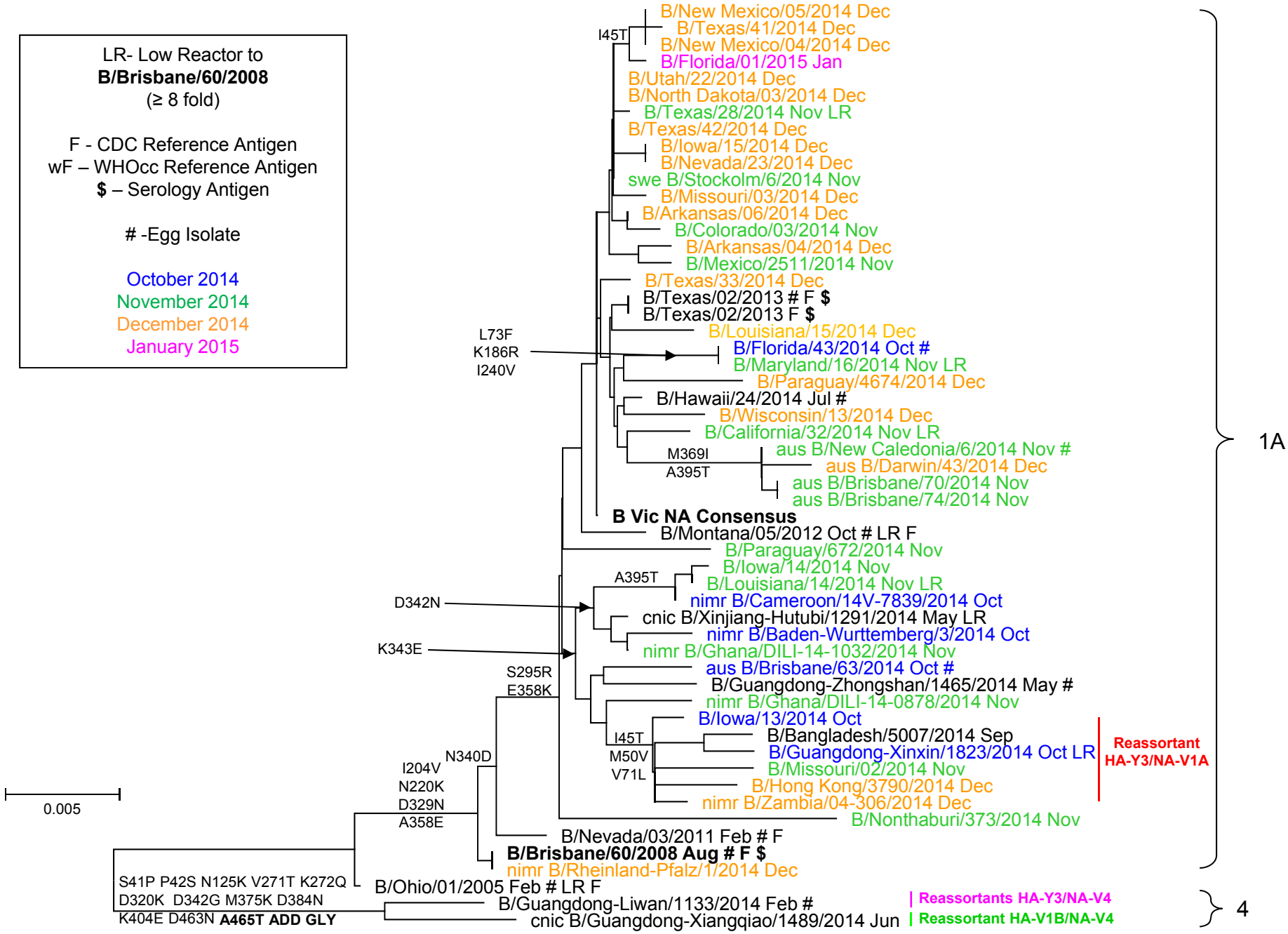
V1A
V1B

0.002

Genetic analysis of B/Victoria lineage viruses (CNIC)



Evolutionary Relationships Among Influenza B Victoria Lineage Neuraminidase (NA) Genes, 2014-2015

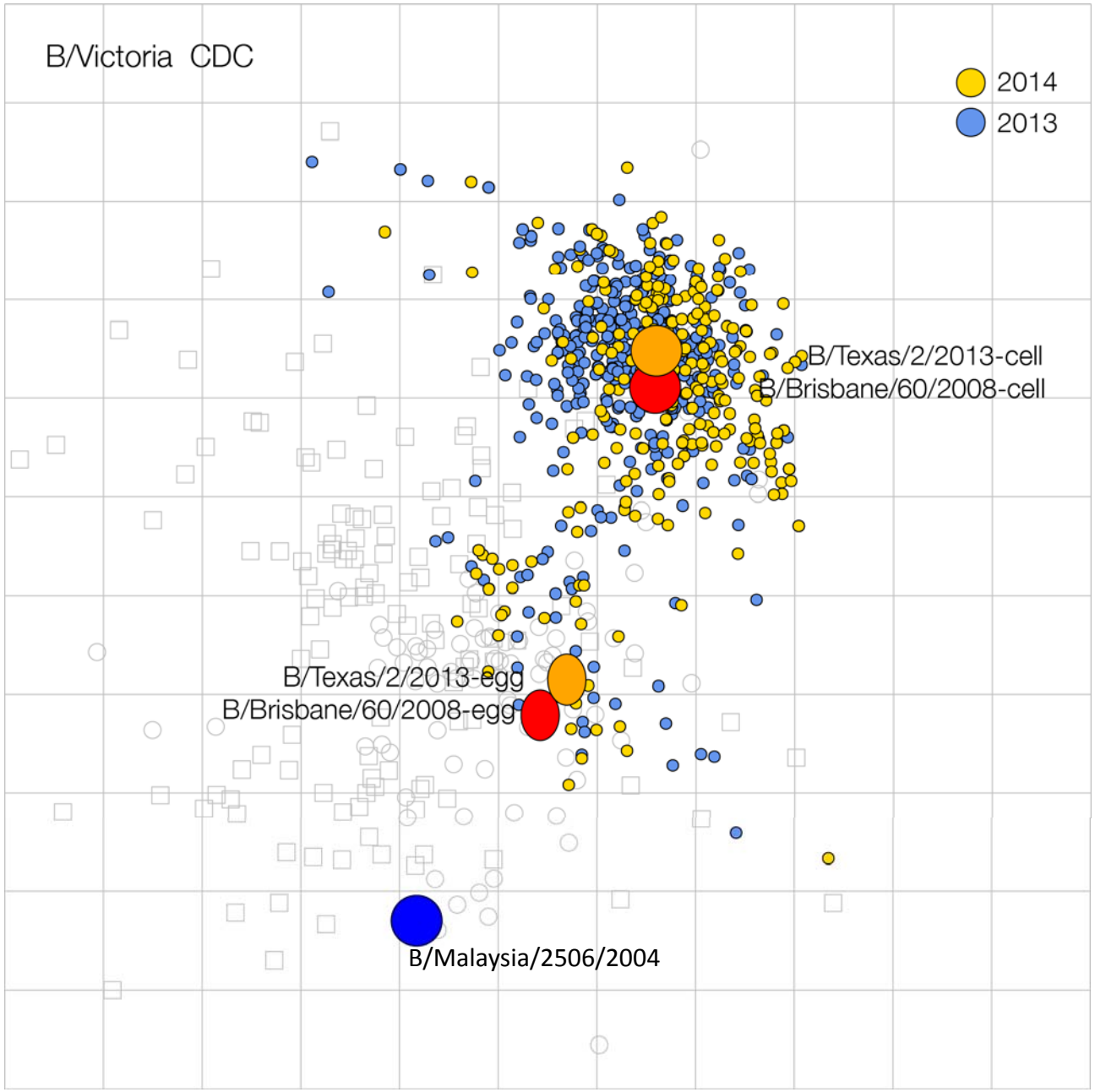


HEMAGGLUTINATION INHIBITION REACTIONS OF INFLUENZA TYPE B VICTORIA LINEAGE VIRUSES (2015/01/29)

		REFERENCE FERRET ANTISERA										
		V1A						V1B				
				A169E, G184E		N129D						
REFERENCE ANTIGENS		EGG BRI/60	MDCK BRI/60	EGG UT/08	MDCK UT/08	EGG TX/02	MDCK TX/02	MDCK MT/05	*HA GROUP	GLY 197-199	DATE COLL.	PASS.
1	B/BRISBANE/60/2008[$]	640	160	320	320	640	160	320	V1A	NO	2008/08/04	E4/E4
2	B/BRISBANE/60/2008	320	320	160	320	640	320	640	V1A	YES	2008/04/08	CX,C4/C2
5	B/UTAH/08/2012	640	640	2560	640	2560	160	640	V1A	NO	2012/10/13	E5
6	B/UTAH/08/2012	640	320	1280	640	1280	320	320	V1A	NO	2012/10/13	C2
7	B/TEXAS/02/2013[$]	320	80	320	160	640	160	160	V1A	NO	2013/01/09	E5
8	B/TEXAS/02/2013	160	160	80	160	320	160	640	V1A	YES	2013/01/09	M1/C2
9	B/MONTANA/05/2012	160	160	160	160	320	160	640	V1B	YES	2012/10/21	C2
TEST ANTIGENS												
10	B/TEXAS/41/2014	640	320	160	160	640	320	640	V1A	YES	2014/12/18	C1
11	B/ARKANSAS/06/2014	320	160	160	320	640	320	1280	V1A	YES	2014/12/30	C1
12	B/IOWA/15/2014	320	320	160	160	320	320	640	V1A	YES	2014/12/26	C1
13	B/NEW MEXICO/05/2014	320	320	320	320	640	320	1280	V1A	YES	2014/12/03	M1/C1
14	B/WYOMING/06/2014	320	160	160	160	640	160	320	V1A	YES	2014/12/08	C1
15	B/FLORIDA/01/2015	160	160	160	160	320	160	320	V1A	YES	2015/01/03	MX/C1
16	B/IOWA/14/2014	160	320	160	160	640	320	640	V1A	YES	2014/11/30	C1
17	B/LOUISIANA/15/2014	160	160	160	320	640	320	1280	V1A	YES	2014/12/09	C1
18	B/LOUISIANA/16/2014	160	320	320	320	640	640	1280			2014/12/09	C1
19	B/OHIO/04/2014	160	160	80	160	320	160	320	V1A	YES	2014/12/21	C1
20	B/TEXAS/42/2014	160	160	160	160	640	320	640	V1A	YES	2014/12/09	M1/C1
21	B/NONTHABURI/373/2014	160	160	160	160	320	320	640	V1A	YES	2014/11/25	C1/C1

*All sequences are available in GISAID

[$] Serology antigen


B/Victoria CDC
2014
2013
B/Texas/2/2013-cell
B/Brisbane/60/2008-cell
B/Texas/2/2013-egg
B/Brisbane/60/2008-egg
B/Malaysia/2506/2004

Influenza B low reactors by lineage in HI assays in WHO CCs

WHO CC	Victoria (B/Brisbane/60/2008)	Yamagata (B/Phuket/3073/2013)
CDC	55 (90%)	170 (92%)
Low Reactors	6 (10%)	13 (8%)
CNIC	3 (15%)	201 (100%)
Low Reactors	17 (85%)	0 (0%)
NIID	1 (100%)	5 (100%)
Low Reactors	0 (0%)	0 (0%)
NIMR	10 (70%)	107 (100%)
Low Reactors	4 (30%)	0 (0%)
VIDRL	16 (100%)	36 (100%)
Low Reactors	0 (0%)	0 (0%)
Total (%)	112 (81%)	519 (98%)
Low Reactors	27 (19%)	13 (2%)

Influenza B Summary

- Influenza B activity was generally low world-wide
- B/Victoria and B/Yamagata lineage viruses co-circulated, with B/Yamagata viruses continuing to predominate.
- **B/Yamagata lineage viruses**:
  - HA genes fell into genetic clades 2 and 3.
  - The great majority of tested viruses belonged to clade 3.
  - Recently circulating viruses were well inhibited by antisera raised against egg-propagated B/Phuket/3073/2013, the virus recommended for use in the 2015 southern hemisphere vaccine.
- **B/Victoria lineage viruses**:
  - Of the low number of viruses tested, most were antigenically and genetically similar to B/Brisbane/60/2008.
- The majority of influenza B viruses tested were sensitive to neuraminidase inhibitors
  - Three B/Yam viruses with D197N substitution in NA showed reduced inhibition by oseltamivir and zanamivir.

Recommendation

- It is recommended that the following viruses be used for influenza vaccines in the 2015-2016 influenza season (northern hemisphere):
  - an A/California/7/2009 (H1N1)pdm09-like virus;
  - an A/Switzerland/9715293/2013 (H3N2)-like virus;
  - a B/Phuket/3073/2013-like virus.
- For quadrivalent vaccines containing 2 B components:
  - Above 3, plus
  - A B/Brisbane/60/2008-like virus

CDC

Acknowledgements

- WHO Collaborating Centers in Beijing, Melbourne, London and Tokyo and WHO Geneva staff
  - National Influenza Centers
  - University of Cambridge partners
- Essential Regulatory Laboratories
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