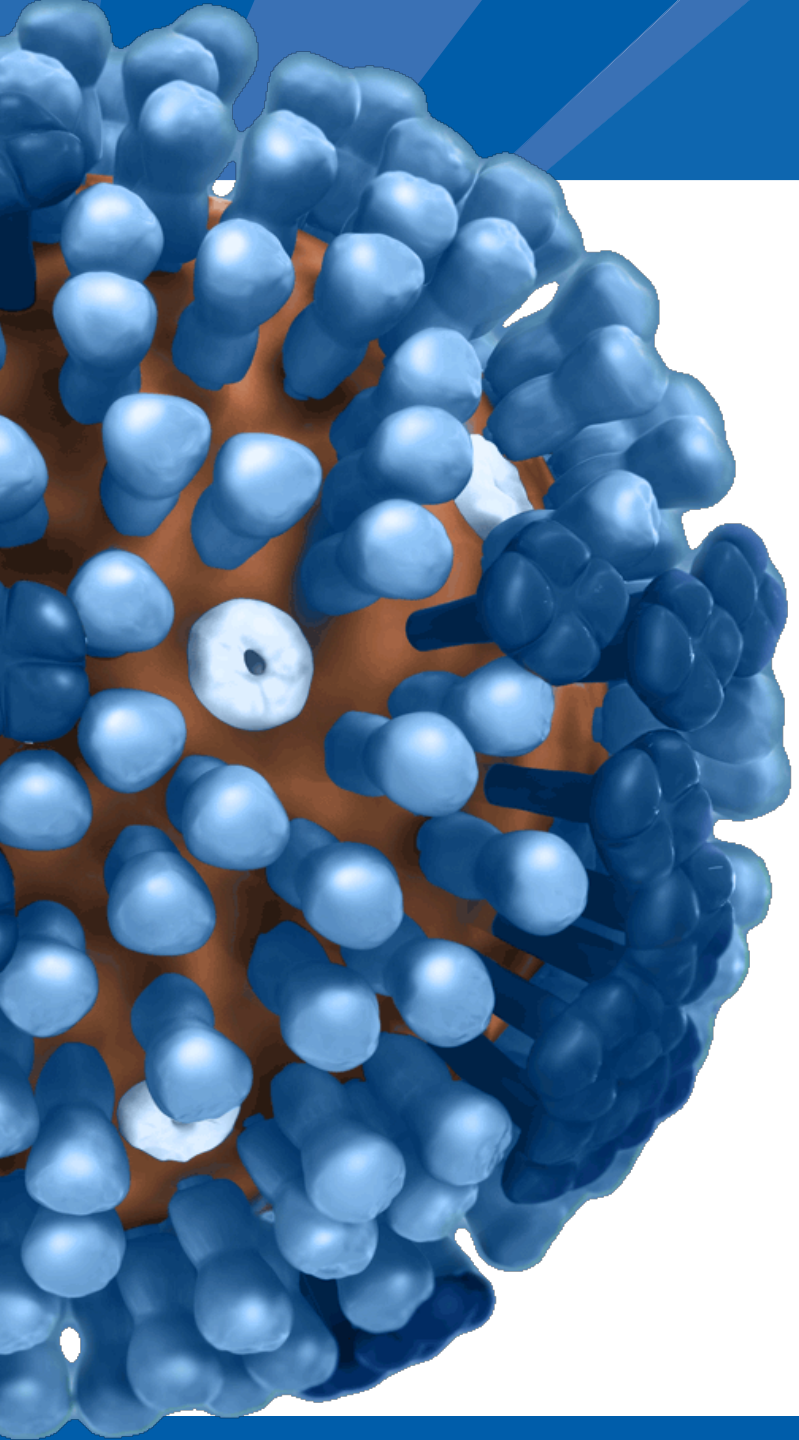


New Approaches for the Characterization of A(H1N1)pdm09 viruses in support of the 2017 SH season vaccine update

Jacqueline Katz

Influenza Division

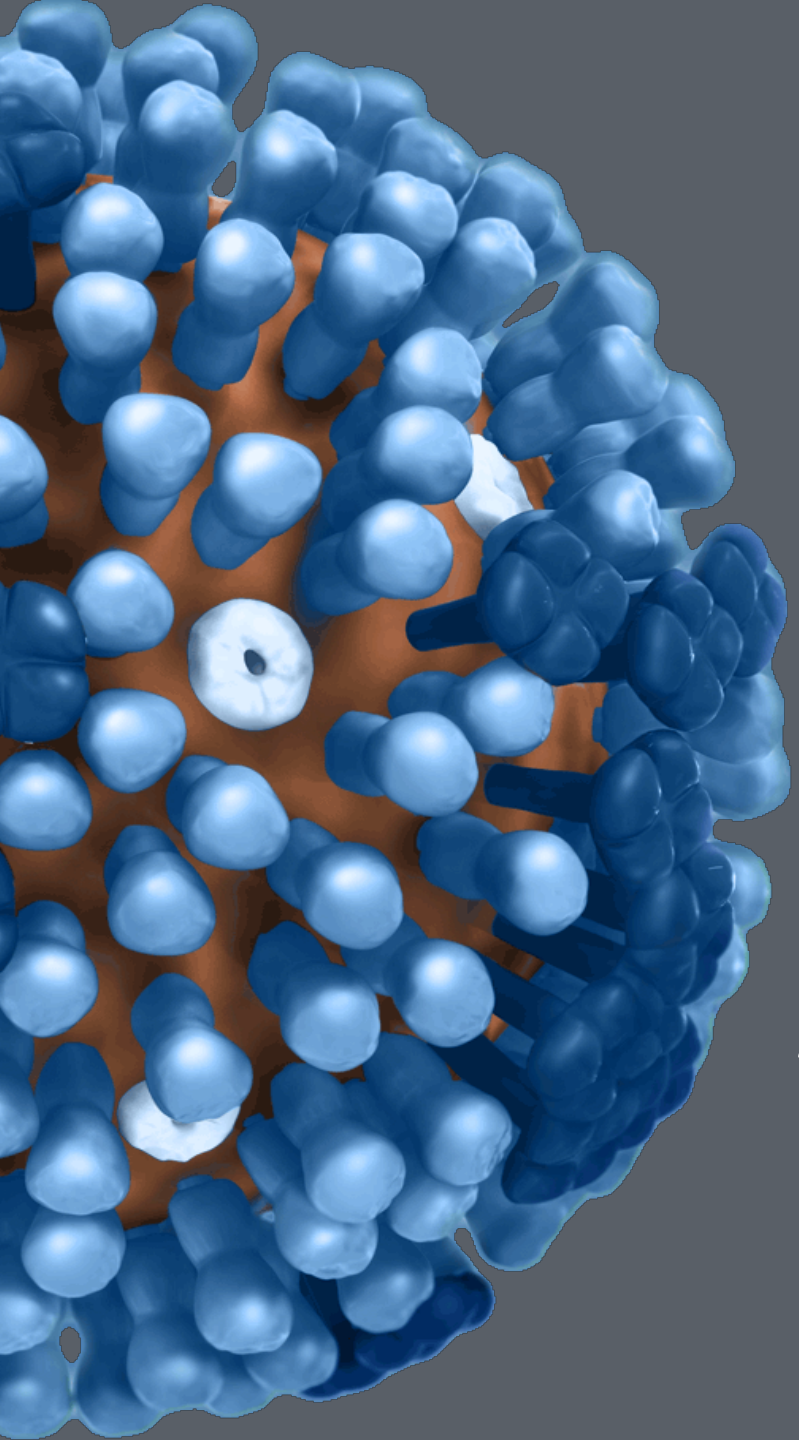
Centers for Disease Control and Prevention

Influenza Specialist Group

Melbourne, Feb 6, 2017

Considerations for New Vaccine Recommendations

- Are there new antigenic variants?
  - Antigenic (HAI and VNT) with post-infection ferret antisera and genetic characterization
    - Detection of signature amino acid changes associated with antigenic change
- Are new variants spreading?
  - Monitoring influenza disease activity and virus spread
- Are current vaccines able to induce antibodies to the new variants?
  - Serological evaluation of vaccinated individuals - pediatric, adult and elderly
- Are any new variants useful for vaccine production?
  - One or more egg isolates are available
  - High growth reassortant candidate vaccine virus that is antigenically similar to parental virus

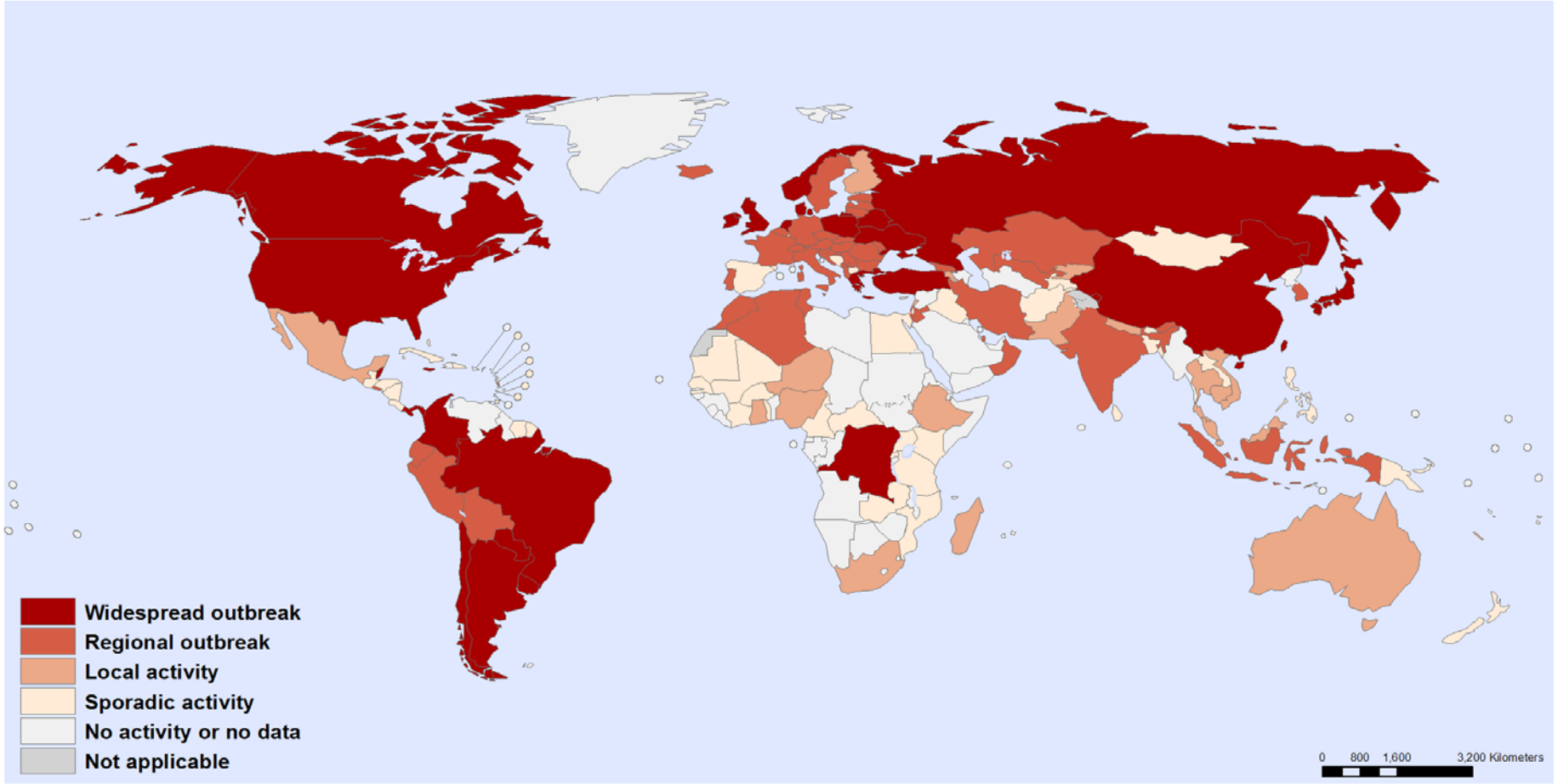


Composition of Influenza Virus Vaccines for Use in the 2017 Southern Hemisphere Season

A(H1N1)pdm09 viruses
February – September 2016

Influenza A(H1N1)pdm09, February to September 2016, maximum

27 September 2016



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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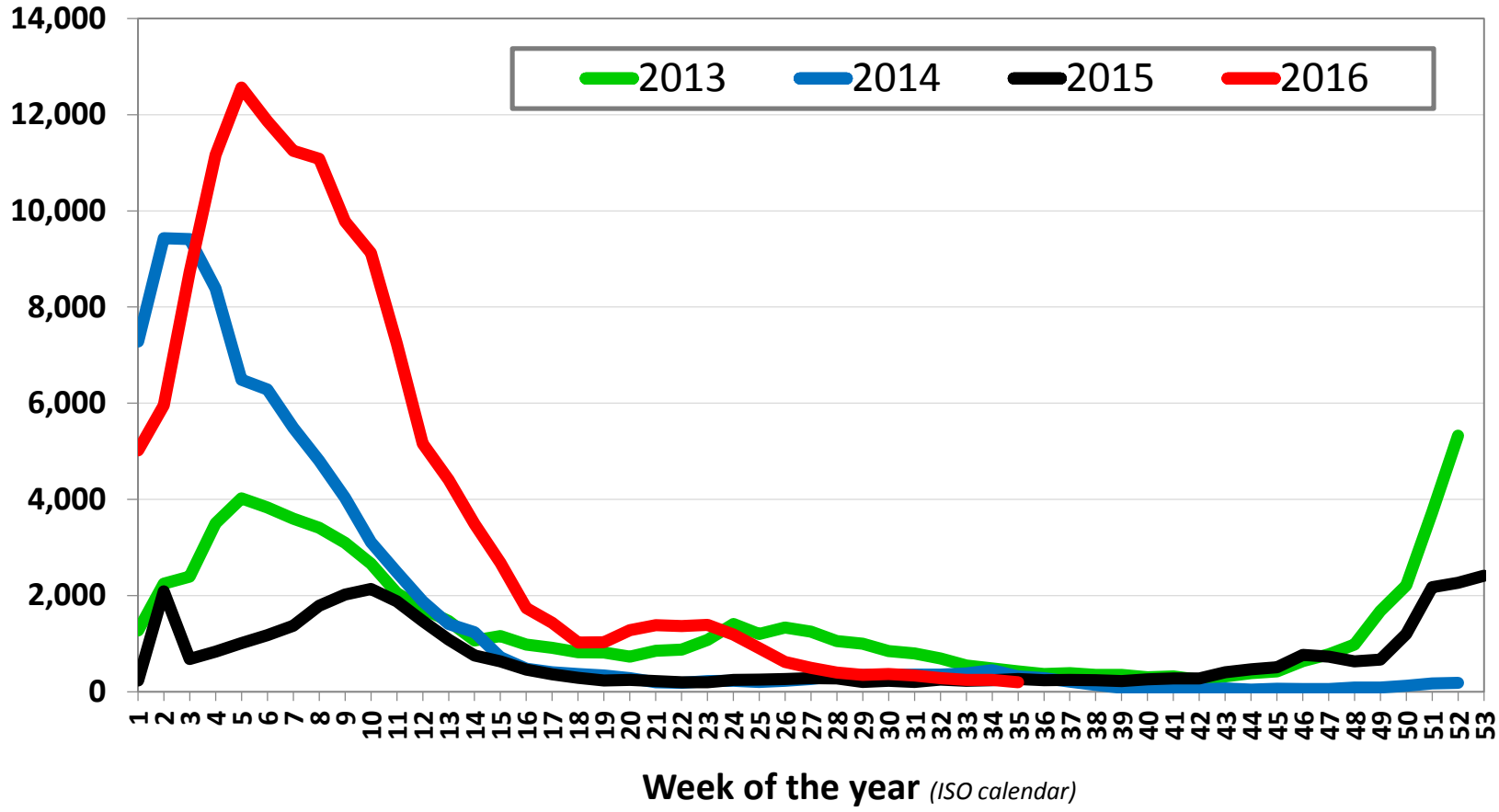
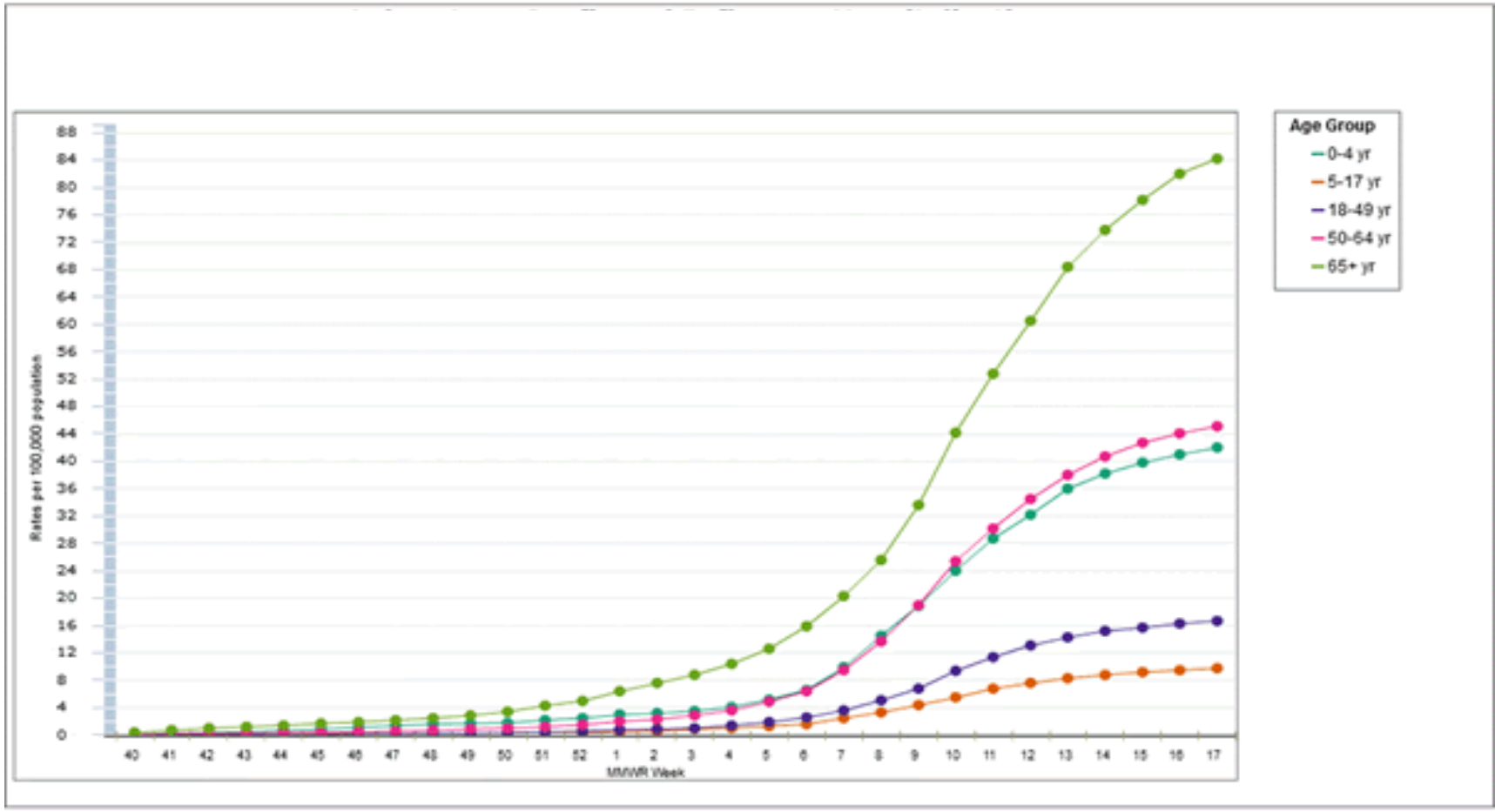
CDC

Number of A(H1N1)pdm09 viruses detected by GISRS

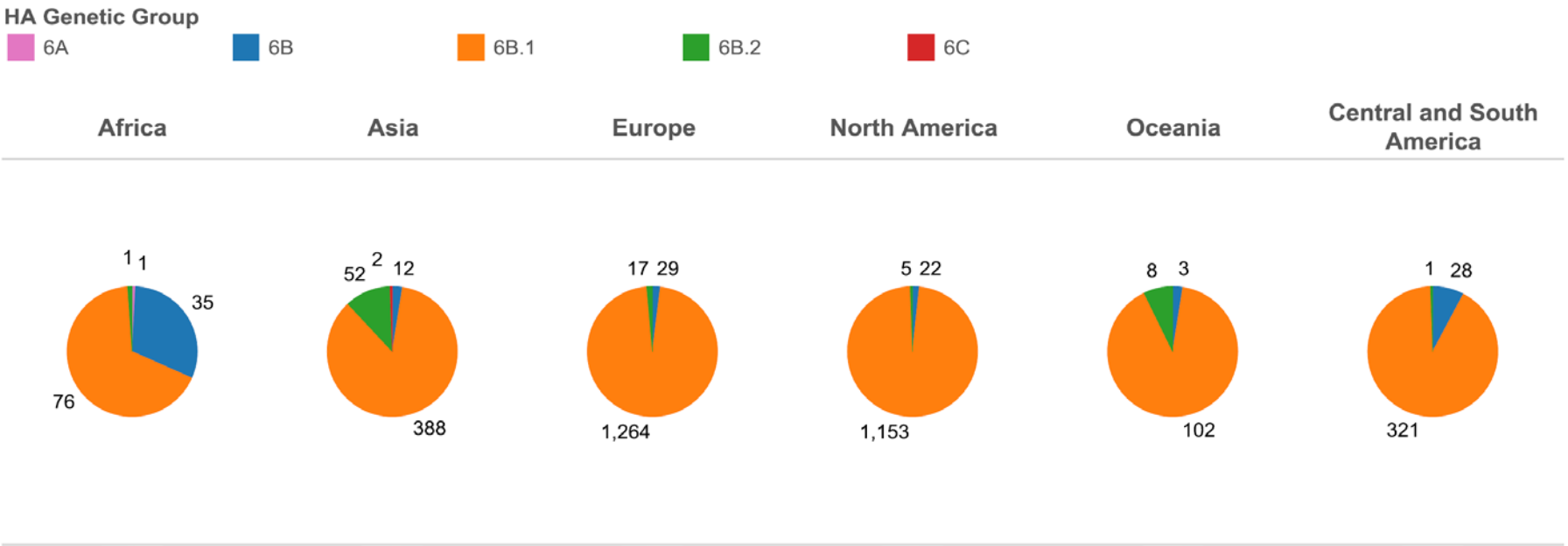


Data source: FluNet, (www.who.int/flunet), Global Influenza Surveillance and Response System (22 September 2016)

U.S. Laboratory-Confirmed Influenza Hospitalizations by Age Group - Week 20, 2015-16 Season



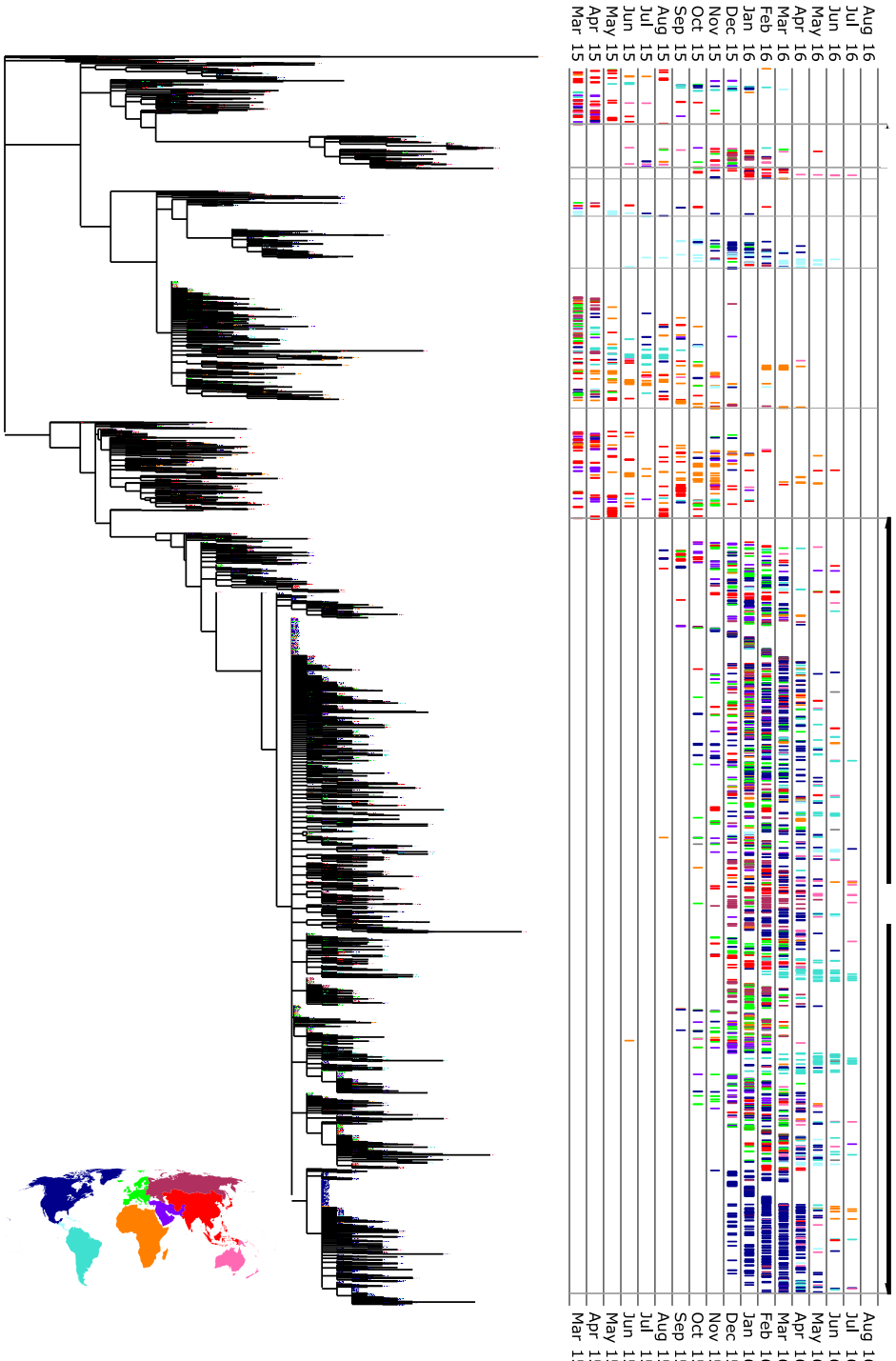
H1N1pdm HA Genetic Groups Since February 1st 2016, Based on Sequence Availability



A/H1N1pdm09 HA Gene Phylogenetic Tree
(University of Cambridge)

Emergence of 6B.1 group in
Aug-Sept 2015

Dark Blue = North America
Light Blue = South America
Green = Europe
Orange = Africa
Purple = Middle East
Maroon = Russia
Red = E/SE Asia
Pink = Oceania
Grey = unknown.



Evolutionary Relationships Among Influenza A(H1N1)pdm09 Hemagglutinin (HA) Genes, 2016

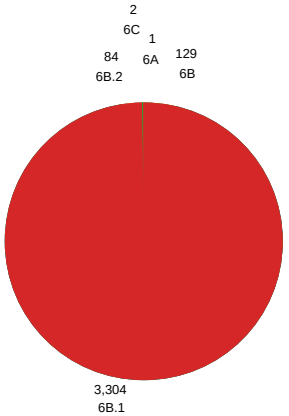
Current Southern Hemisphere Vaccine Strain

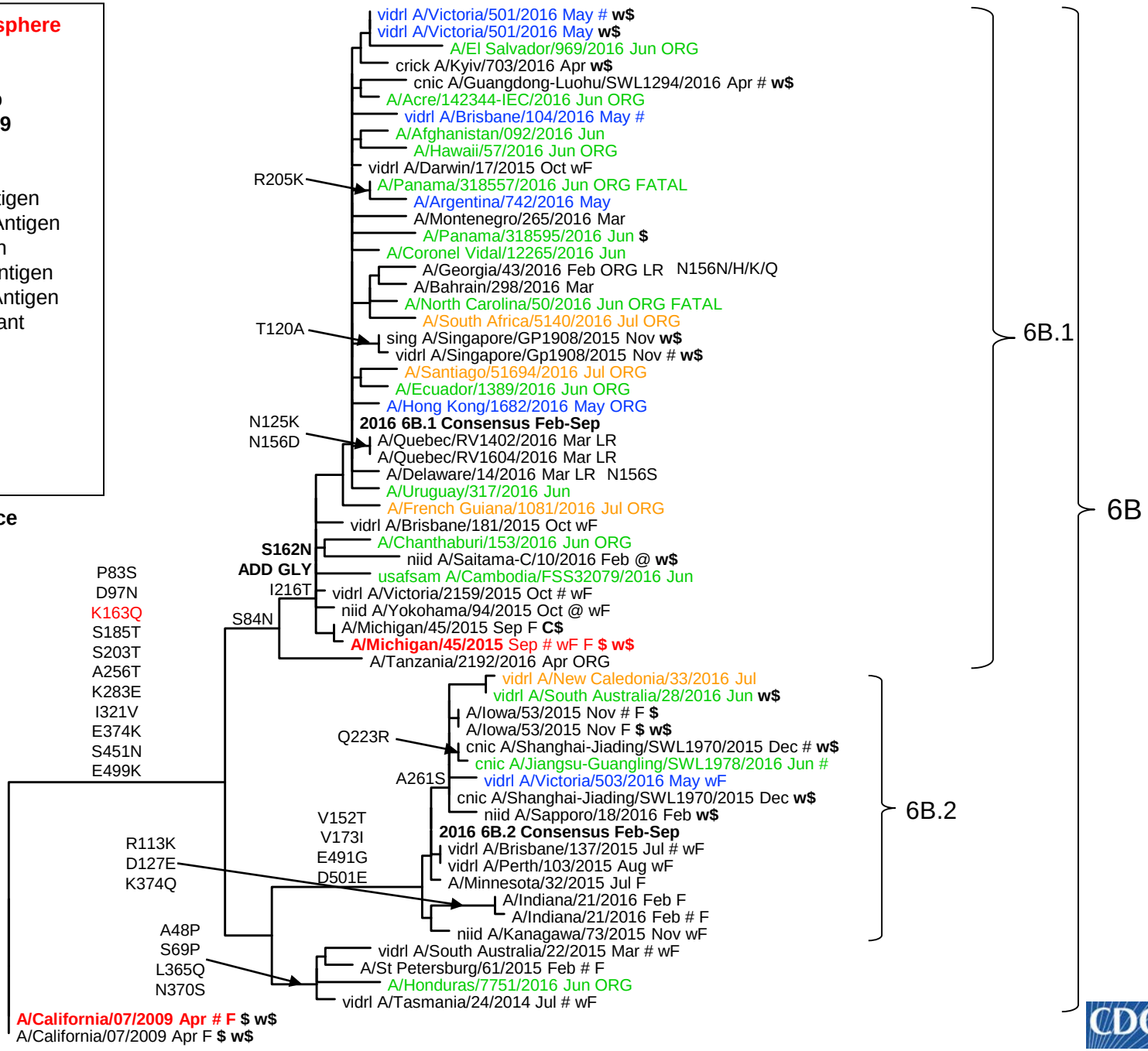
LR- Low Reactor to
A/California/07/2009
(≥ 8 fold)

F - CDC Reference Antigen
wF - WHOcc Reference Antigen
$ - Serology Antigen
w$ - WHOcc Serology Antigen
C$ - Common Serology Antigen
@ Oseltamivir Resistant
# #gg Isolate

May 2016
June 2016
July 2016
August 2016

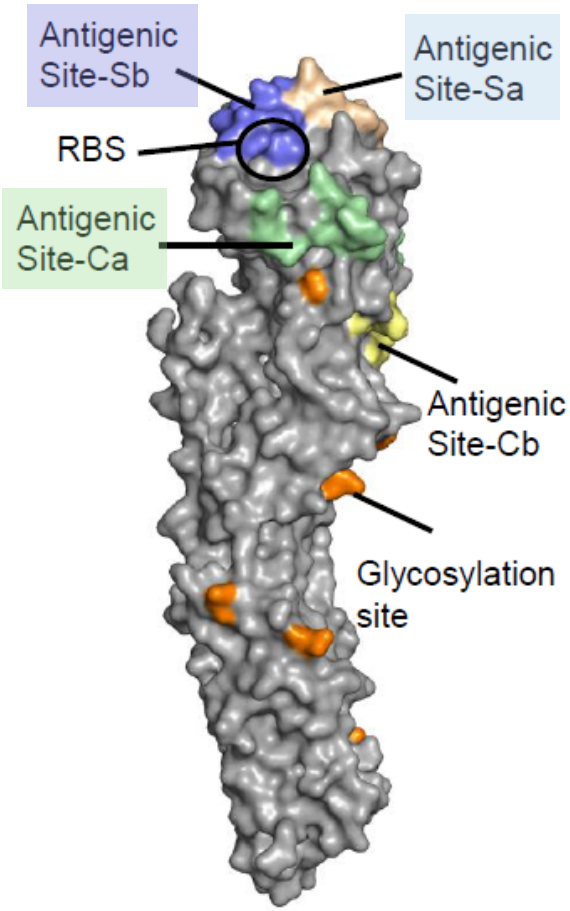
HA Genetic Groups Since February 1st 2016



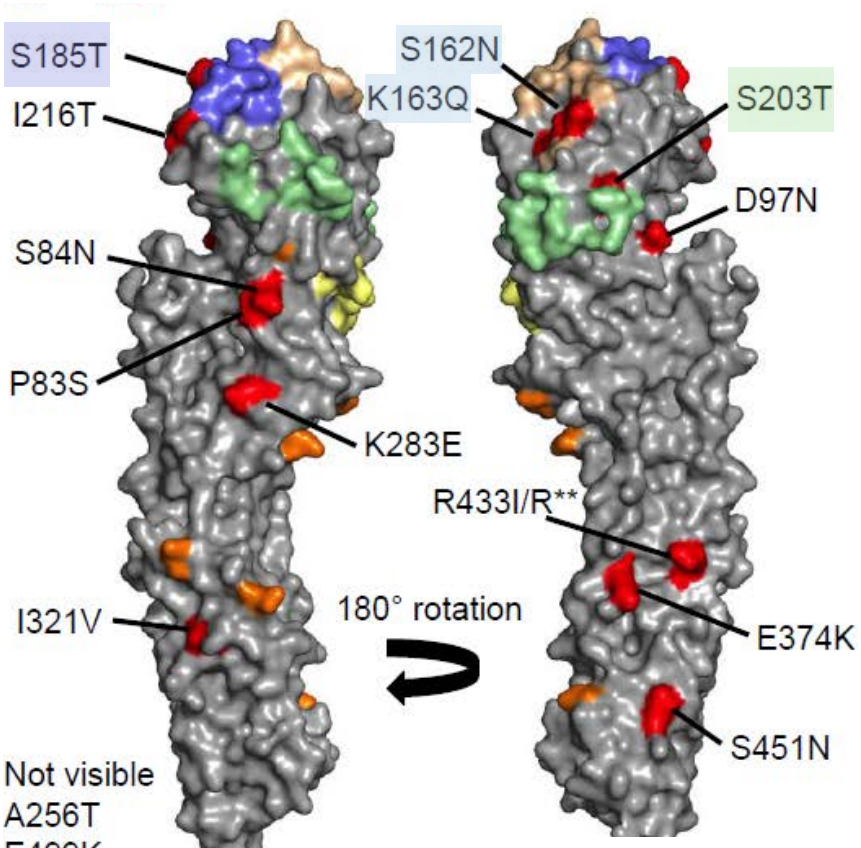


Amino Acid Substitutions in H1N1pdm09 compared to A/California/7/2009

A/California/7/2009



A/Michigan/45/2015 (6B.1)

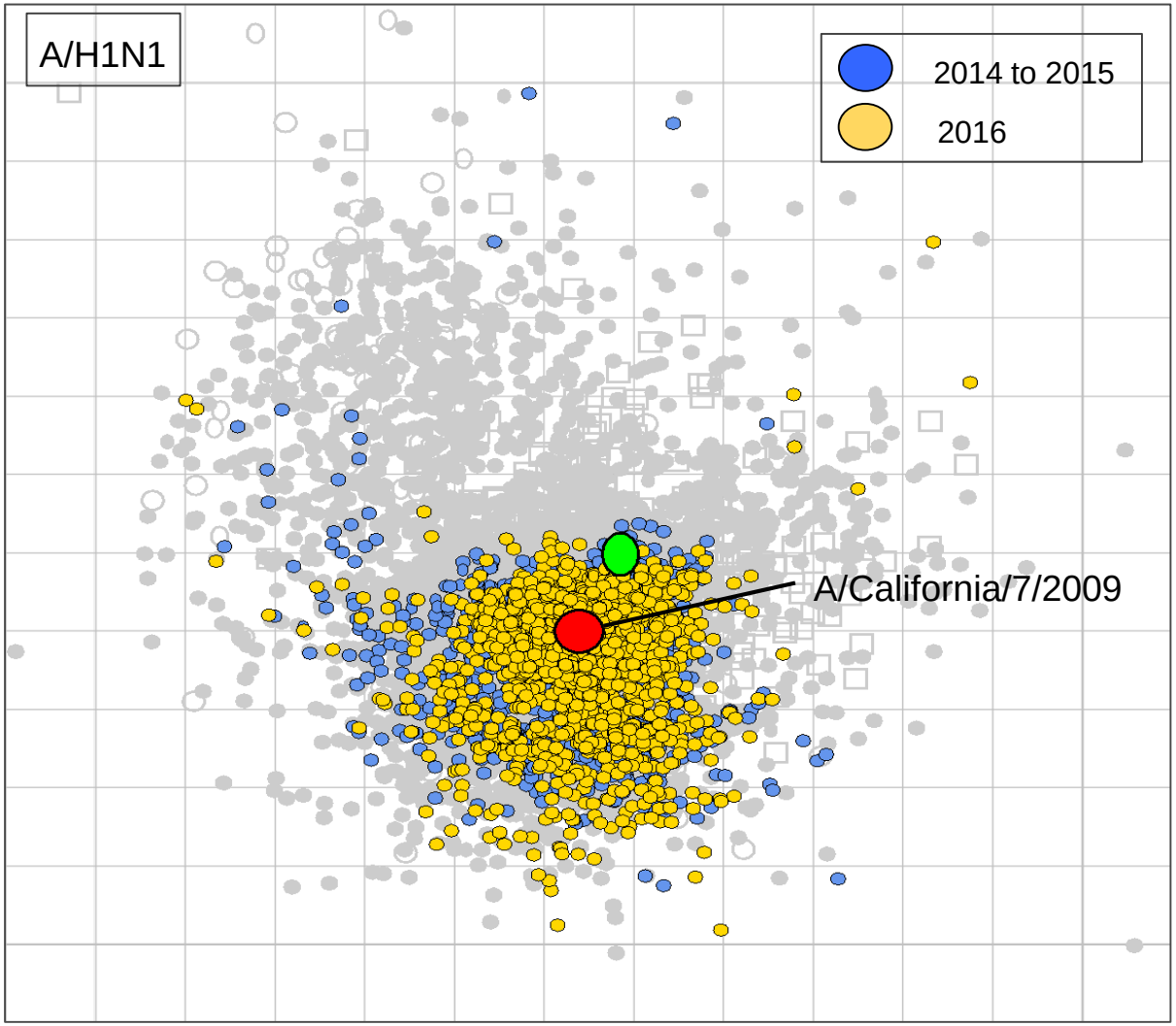


Sites of amino acid changes indicated in red

Antigenic Analysis of A(H1N1)pdm09 Viruses by Hemagglutination Inhibition (HI)

		REFERENCE FERRET ANTISERA													
				6B	6B.1		6B.2								
							R113K, D127E,K374Q								
	REFERENCE ANTIGENS	EGG CA/7	MDCK CA/7	EGG UR/61	EGG MI/45	MDCK MI/45	MDCK MN/32	EGG IN/21	MDCK IN/21	EGG IA/53	MDCK IA/53	HUMAN POOL	HA GROUP	DATE COLL.	PASS.
1	A/CALIFORNIA/7/2009	2560	2560	320	1280	2560	1280	2560	2560	2560	1280	320		2009/04/09	E3
2	A/CALIFORNIA/7/2009	1280	2560	160	640	1280	640	1280	640	1280	1280	160		2009/04/09	C3
3	A/ ST PETERSBURG/61/2015	320	320	640	320	640	320	320	320	320	160	20	6B	2015/02/20	E2/E2
4	A/MICHIGAN/45/2015	2560	5120	320	2560	2560	1280	2560	2560	2560	2560	160	6B.1	2015/09/07	E3
5	A/MICHIGAN/45/2015	2560	2560	160	1280	2560	1280	1280	1280	2560	1280	160	6B.1	2015/09/07	M1/C3
6	A/MINNESOTA/32/2015	1280	1280	160	1280	1280	640	1280	1280	2560	640	80	6B.2	2015/07/09	C3
7	A/INDIANA/21/2016	1280	1280	160	1280	1280	640	1280	1280	1280	640	80	6B.2	2016/02/04	E4
8	A/INDIANA/21/2016	1280	1280	160	1280	1280	640	1280	1280	1280	640	80	6B.2	2016/02/04	C2
9	A/IOWA/53/2015	1280	1280	160	1280	1280	640	1280	1280	1280	1280	80	6B.2	2015/11/04	E4
10	A/IOWA/53/2015	1280	1280	160	1280	1280	640	1280	1280	1280	640	80	6B.2	2015/11/04	C3
	TEST ANTIGENS														
11	A/MICHIGAN/73/2016	2560	2560	320	2560	5120	2560	5120	2560	2560	2560	160	6B.1	2016/04/18	C2
12	A/PENNSYLVANIA/53/2016	2560	2560	320	2560	5120	2560	5120	2560	2560	2560	160	6B.1	2016/03/03	C1
13	A/PERU/46/2016	2560	2560	320	2560	2560	1280	2560	1280	2560	1280	160	6B.1	2016/04/11	C2/C1
14	A/PERU/47/2016	2560	2560	320	1280	2560	1280	2560	2560	2560	2560	160	6B.1	2016/04/07	C2/C1
15	A/PERU/50/2016	2560	2560	320	1280	2560	1280	2560	2560	2560	1280	160	6B.1	2016/04/12	C2/C1
16	A/PERU/51/2016	2560	2560	160	2560	2560	1280	2560	1280	2560	2560	160	6B.1	2016/04/27	C2/C1
17	A/PERU/48/2016	1280	2560	160	1280	1280	1280	1280	1280	2560	1280	160	6B.1	2016/04/18	C2/C1
18	A/KHMELNITSKY/667/2016	2560	2560	320	1280	2560	1280	2560	1280	2560	2560	160	6B.1	2016/02/03	S2/C1
19	A/ODESSA/686/2016	2560	2560	320	1280	2560	1280	1280	1280	2560	2560	160	6B.2	2016/02/04	S2/C1
20	A/ODESSA/692/2016	2560	2560	320	1280	2560	1280	1280	1280	2560	2560	160	6B.1	2016/02/01	S2/C1
21	A/ODESSA/694/2016	2560	2560	320	1280	2560	1280	2560	1280	2560	1280	160	6B.1	2016/02/10	S2/C1
22	A/KHMELNITSKY/662/2016	1280	1280	160	1280	1280	640	1280	1280	2560	1280	160	6B.1	2016/02/27	S2/C1
23	A/KHMELNITSKY/671/2016	1280	1280	160	1280	1280	640	1280	1280	2560	1280	160	6B.1	2016/03/14	S2/C1
24	A/ODESSA/691/2016	1280	1280	320	1280	2560	1280	1280	1280	2560	1280	160	6B.1	2016/02/06	S2/C1
25	A/ODESSA/701/2016	1280	1280	160	1280	1280	1280	2560	1280	2560	1280	160	6B.2	2016/02/27	S2/C1
26	A/ODESSA/688/2016	640	640	80	640	640	640	1280	640	1280	640	160	6B.2	2016/02/05	S2/C1
27	A/UGANDA/1744/2016	1280	1280	160	640	1280	640	1280	640	2560	1280	320	6A	2016/02/11	C2
28	A/AFGHANISTAN/1243/2016	1280	2560	320	2560	2560	1280	2560	1280	2560	1280	160	6B.1	2016/01/03	C2/C1
29	A/AFGHANISTAN/1325/2016	1280	2560	320	1280	2560	1280	2560	1280	2560	1280	160	6B.1	2016/01/03	C2/C1
30	A/AFGHANISTAN/861/2016	1280	2560	160	1280	2560	1280	1280	1280	2560	1280	160	6B.1	2016/01/09	C2/C1

Antigenic Cartography of A/H1N1pdm09 Viruses (University of Cambridge)



US VE Network Data, 2015-2016

Adjusted vaccine effectiveness against medically attended influenza A/H1N1pdm09 by age group

	Influenza Positive		Influenza Negative		Vaccine effectiveness Fully adjusted*	
Age group	**No. vaccinated/ Total**	**(%)**	**No. vaccinated/ Total**	**(%)**	**VE %**	**95% CI**
Overall	308/768	40.1	2902/5570	52.1	**44%**	**(34 to 53)**
6 months – 8 years	58/160	36.3	630/1272	49.5	**49%**	**(26 to 65)**
9–17 years	11/51	21.6	277/694	39.9	**61%**	**(18 to 82)**
18–49 years	98/311	31.5	841/1957	43.0	**43%**	**(24 to 57)**
50–64 years	110/194	56.7	562/918	61.2	**9%**	**(-30 to 36)**
≥65 years	31/52	59.6	592/729	81.2	**64%**	**(32 to 81)**

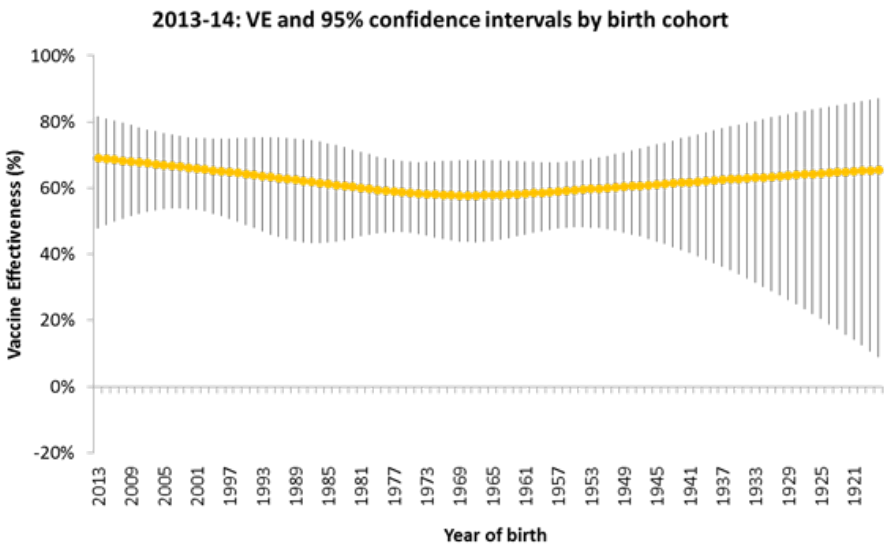
*Adjusted model includes site, age (spline for all ages, years for age groups), race/Hispanic ethnicity, interval from onset to enrollment, sex, general self-rated health status, calendar time (2-week intervals), any high-risk code in the year prior to enrollment

US Flu VE Network Data for Two Recent A/H1N1pdm09 Predominant Seasons

VE Against H1N1pdm09 by Year of Birth

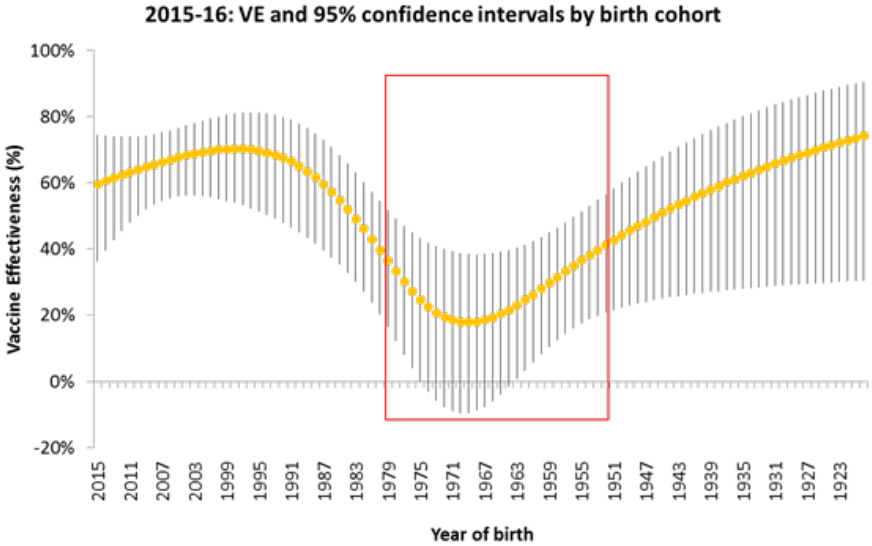
Clade 6B

2013-14



Clade 6B.1

2015-16



Flannery et. al., Options IX, 2016, Poster P-70

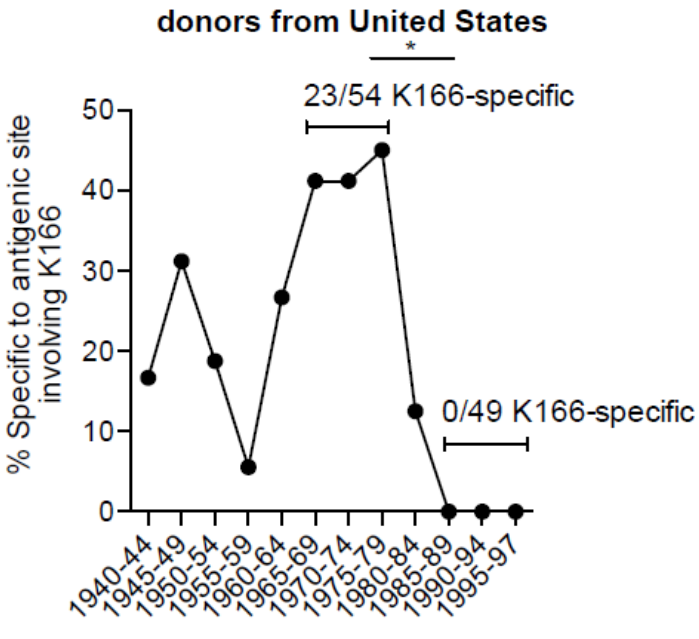
Hensley Group Observations on Effect of K163Q

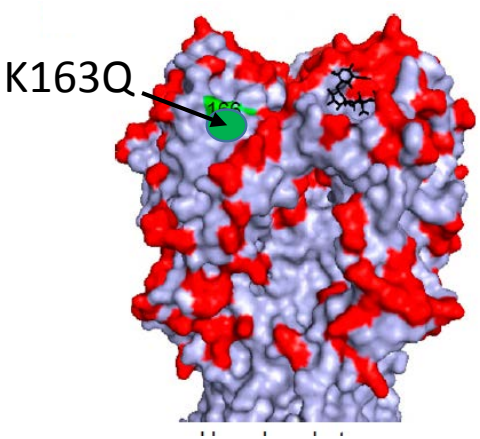
PNAS

Potential antigenic explanation for atypical H1N1 infections among middle-aged adults during the 2013–2014 influenza season

Susanne L. Linderman[a,b,1], Benjamin S. Chambers[a,c,1], Seth J. Zost[a,c,1], Kaela Parkhouse[a], Yang Li[a,c], Christin Herrmann[a,c], Ali H. Ellebedy[d,e], Donald M. Carter[f], Sarah F. Andrews[g], Nai-Ying Zheng[g], Min Huang[g], Yunping Huang[g], Donna Strauss[h], Beth H. Shaz[h], Richard L. Hodinka[i,j], Gustavo Reyes-Terán[k], Ted M. Ross[f], Patrick C. Wilson[g], Rafi Ahmed[d,e], Jesse D. Bloom[l], and Scott E. Hensley[a,b,c,2]

- Single sera collected in 2013-14 from 195 people of different birth cohorts
- Tested by HI with rg viruses with A/CA/07/2009 HA with 163K or 163Q
  - ≥2-fold reductions between 163K and 163Q considered significant
  - 42% of adults born from 1965 to 1979 had 163K-specific antibodies
  - Adults born after 1985 did not have 163K-specific antibodies





Linderman et al., PNAS 2014

US VE Network Data, 2015-2016

Adjusted vaccine effectiveness against medically attended influenza A/H1N1pdm09 by "Hensley" age groups for H1N1 exposure group

	Influenza Positive		Influenza Negative		Vaccine effectiveness Fully adjusted*	
Age group	No. vaccinated/ Total	(%)	No. vaccinated/ Total	(%)	VE %	95% CI
Overall	308/768	40.1	2902/5570	52.1	**44%**	**(34 to 53)**
9–29 years	25/138	18.1	527/1399	37.7	**63%**	**(41 to 77)**
30–64 years	194/418	46.4	1153/2170	53.1	**23%**	**(2 to 39)**
≥65 years	31/52	59.6	592/729	81.2	**64%**	**(32 to 81)**

*Adjusted model includes site, age (spline for all ages, years for age groups), race/Hispanic ethnicity, interval from onset to enrollment, sex, general self-rated health status, calendar time (2-week intervals), any high-risk code in the year prior to enrollment

A/H1N1pdm09 Human Serological Study

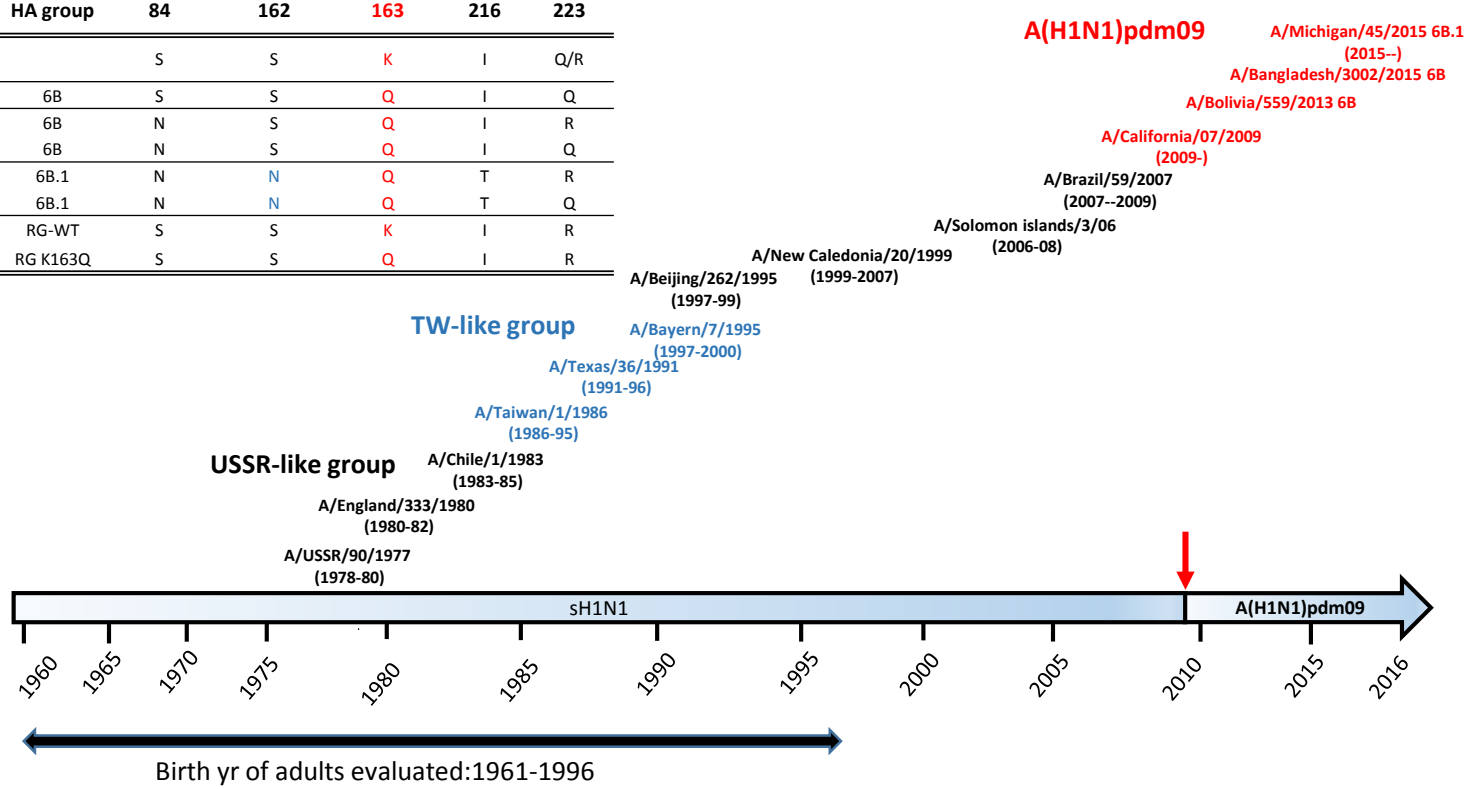
Paired sera collected from US adults pre and post IIV vaccination from 5 influenza seasons post 2009 (2010-2016) ~~were~~ used in the study

Seasons	Study	Pairs (N)	Seroconverted (N)	Age range (yrs)	Median age (yrs)	Birth years
2010-2011	Accelevance	61	43	19-49	32	1961-1991
2011-2012	Accelevance	62	40	21-49	34	1962-1990
2013-2014	Accelevance	51	36	18-49	34	1964-1995
2014-2015	KAI	64	44	18-49	30	1965-1996
2015-2016	KAI	65	26	19-46	33	1969-1996
	Total pairs:	303	189	18-49	33	1961-1996

A/H1N1pdm09 Human Serological Study

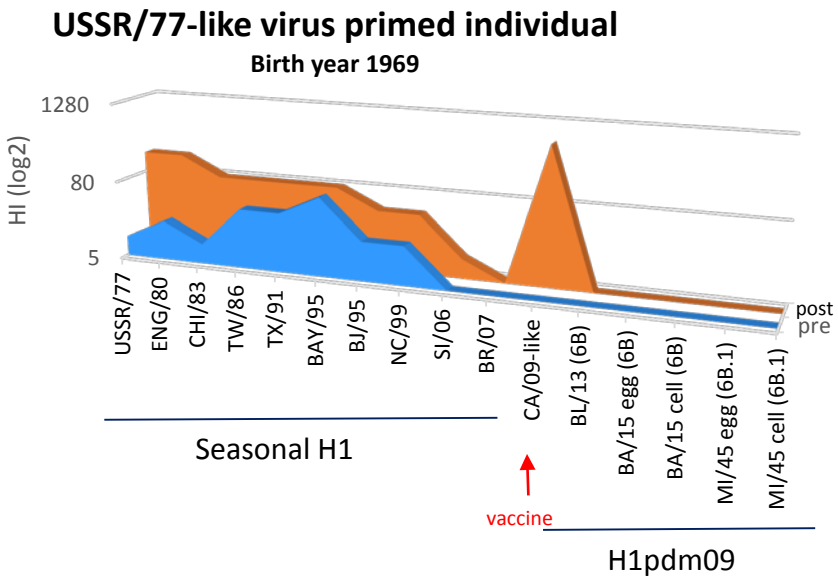
A(H1N1) pdm09, pre-2009 seasonal H1N1 and RG viruses used in the study

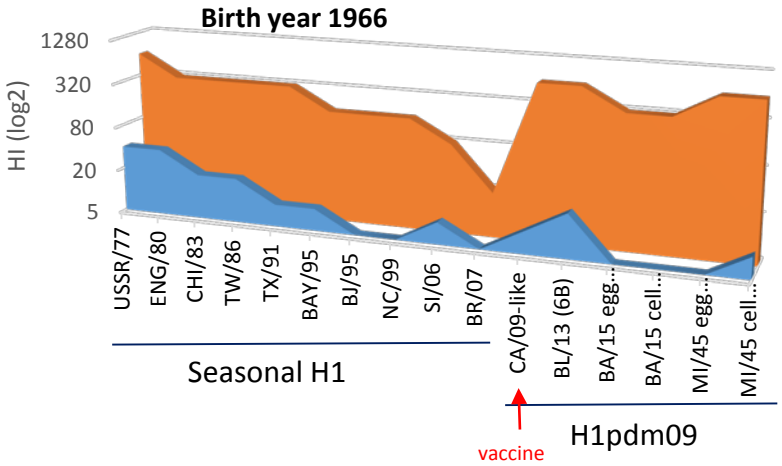
	A(H1N1)pdm09 viruses		HA group	84	162	163	216	223
1	A/CA/07/09-like (A/MX/4108/09)	egg		S	S	K	I	Q/R
2	A/BL/559/13	cell	6B	S	S	Q	I	Q
3	A/BA/3002/15	egg	6B	N	S	Q	I	R
4		cell	6B	N	S	Q	I	Q
5	A/MI/45/15	egg	6B.1	N	N	Q	T	R
6		cell	6B.1	N	N	Q	T	Q
7	RG -CA/09 WT	egg	RG-WT	S	S	K	I	R
8	RG-CA/09 K163Q	egg	RG K163Q	S	S	Q	I	R



A/H1N1pdm09 Human Serological Study

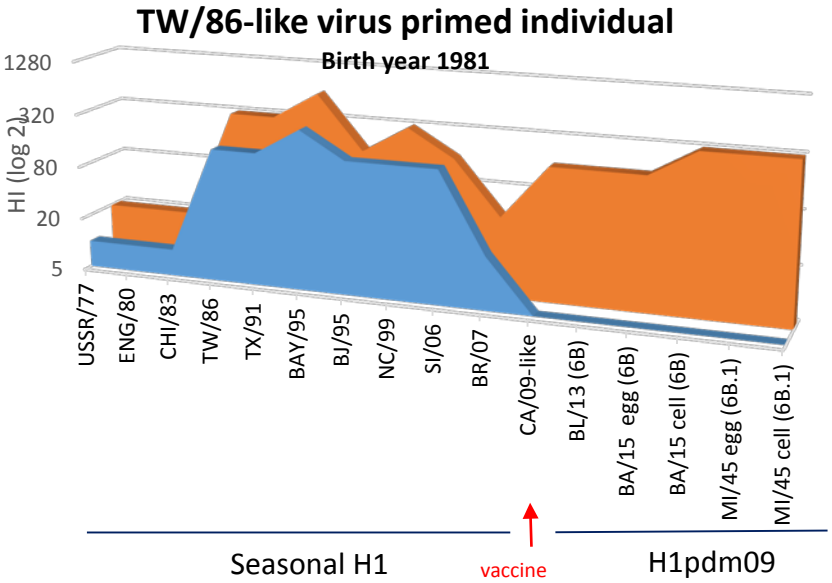
Human Antibody Specificity to A(H1N1)pdm09 Vaccine is Influenced by Priming History





Pre-vaccination

Post-vaccination



Antigenic Analysis of A(H1N1)pdm09 Viruses with Ferret and Human Sera

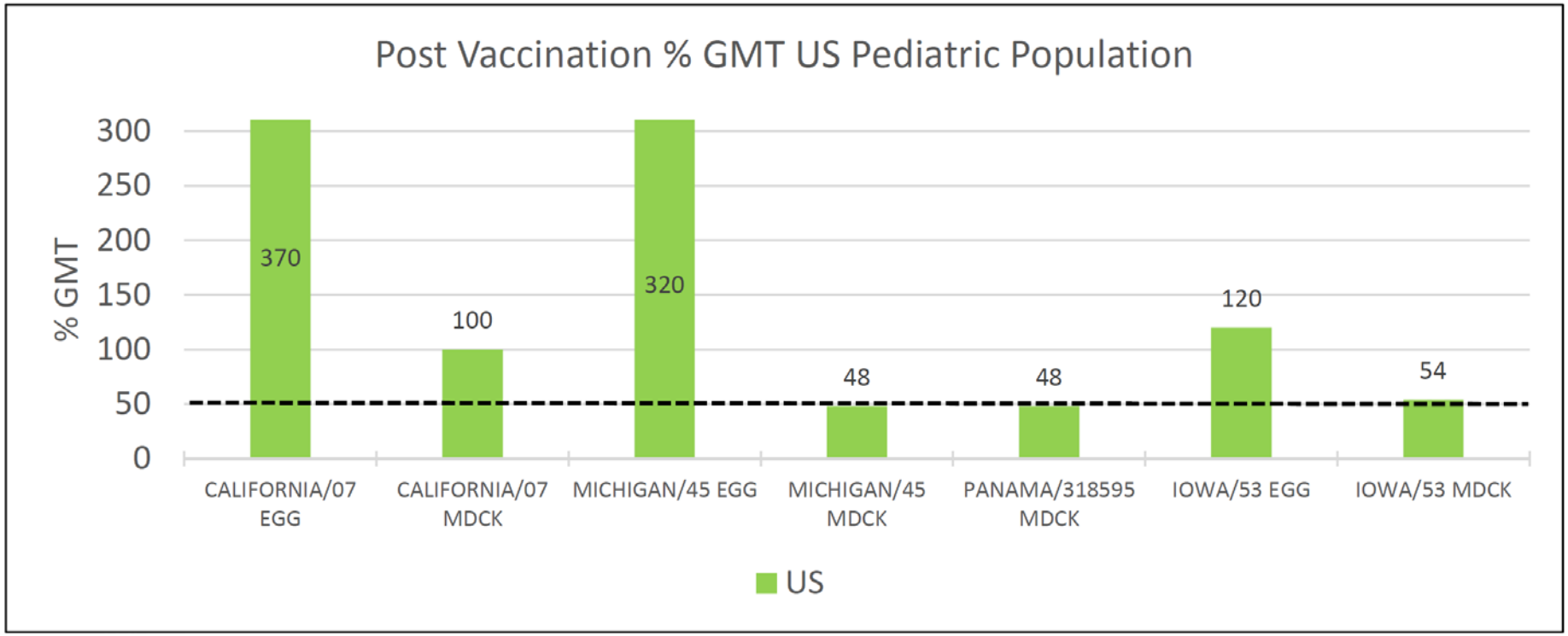
Table 1: Haemagglutination inhibition reactions of A(H1N1)pdm09 viruses

			POST-INFECTION FERRET SERA							POST VACCINATION HUMAN SERA*					
			EGG	MDCK	MDCK	MDCK	MDCK	MDCK	MDCK	2011/12	2013/14	2014/15		2015/16	
STRAIN DESIGNATION	**Genetic Clade**	**Passage history**	**CA/7**	**CA/7**	**MD/13**	**DR/7293**	**BL/559**	**MI/45**	**IA/53**	**A**	**B**	**C**	**D**	**E**	**F**
A/CALIFORNIA/7/2009	H1pdm09	E3	**2560**	2560	2560	2560	2560	2560	1280	640	640	320	640	160	640
A/CALIFORNIA/7/2009	H1pdm09	C3	2560	**2560**	2560	1280	1280	2560	1280	320	640	320	320	320	640
A/MARYLAND/13/2012	6A	M1/C2	5120	2560	**2560**	1280	1280	2560	1280	320	640	160	160	160	640
A/DOMINICAN REP./7293/2013	6C	C2	2560	2560	2560	**2560**	1280	2560	1280	320	1280	320	320	320	640
A/BOLIVIA/559/2013	6B	E5	2560	2560	2560	1280	1280	2560	1280	20	20	40	40	20	640
A/BOLIVIA/559/2013	6B	C2	5120	5120	5120	2560	**2560**	5120	1280	10	10	40	20	20	640
A/MICHIGAN/45/2015	6B.1	E3	2560	5120	5120	2560	2560	5120	2560	80	40	80	640	10	1280
A/MICHIGAN/45/2015	6B.1	M1/C3	2560	2560	2560	2560	2560	**5120**	2560	10	10	40	40	40	1280
A/PANAMA/318595/2016	6B.1	C2	1280	1280	2560	2560	1280	5120	1280	10	10	40	20	20	640
A/IOWA/53/2015	6B.2	E4	1280	1280	1280	1280	640	2560	1280	10	10	20	40	20	320
A/IOWA/53/2015	6B.2	C3	1280	1280	640	1280	640	2560	**1280**	10	10	20	10	20	160
A/MINNESOTA/32/2015	6B.2	C3	640	640	1280	1280	640	1280	1280	10	10	20	10	20	320

* Post vaccination pooled sera (A-D, F) or a single serum (E) from adults (birth years, 1961-83) vaccinated with TIV or QIV from the indicated seasons

HI Antibody Response to the A(H1N1)pdm09 Component in U.S. Children Vaccinated with N. Hemisphere 2015-16 QIV:

Compared with MDCK cell-propagated A/California/7/2009



Summary of A(H1N1)pdm09 viruses

- The vast majority of viruses fell into the phylogenetic HA clade 6B
  - Subclade 6B.1 viruses predominated globally
  - Subclade 6B.2 viruses were most frequently detected in China
- U.S. vaccine effectiveness (VE) studies demonstrated reduced VE against A(H1N1)pdm09 viruses in a subset of adults in the 2015-16 season
- The majority of recent A(H1N1)pdm09 viruses were antigenically indistinguishable from the vaccine virus A/California/07/2009 using post-infection ferret antisera and HI tests
- However, representative 6B.1 and 6B.2 viruses were poorly inhibited by some post-vaccination adult human serum pools
- Pediatric geometric mean post-vaccination HI titers against some 6B.1 and 6B.2 viruses were significantly reduced compared to titers to A/California/07/2009 vaccine virus
  - Not consistently observed for adult and older adult serum panels

WHO Recommendation

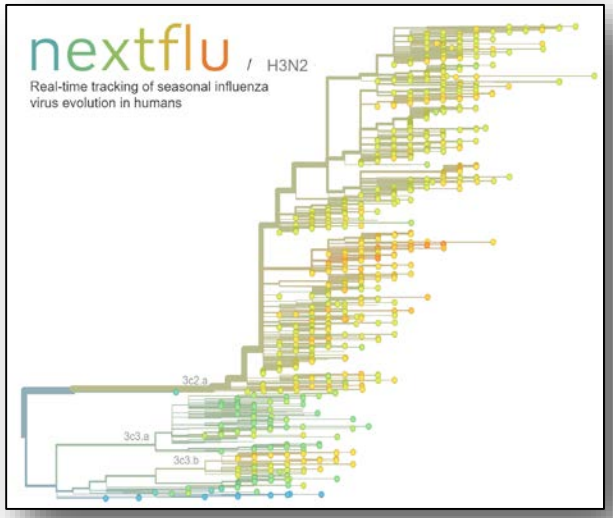
- It is recommended that the following viruses be used for trivalent influenza vaccines in the 2017 southern hemisphere influenza season:
  - an A/Michigan/45/2015 (H1N1)pdm09-like virus;
  - an A/Hong Kong/4801/2014 (H3N2)-like virus; and
  - a B/Brisbane/60/2008-like virus.
- For quadrivalent vaccines containing two B components:
  - Above 3, plus
  - A B/Phuket/3073/2013-like virus

New Approaches to the Vaccine Virus Selection

- Human serological studies can augment antigenic characterization with ferret antisera
  - Birth cohorts matter: need to evaluate all age groups

- Global Influenza Vaccine Effectiveness report now supplied at each Vaccine Consultation Meeting
  - Yearly VE data becoming an important consideration for Vaccine virus selection

- Virus fitness forecasting methods
  - Analyses from different modelling groups



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