Vaccines and Related Biological Products Advisory Committee Meeting

July 23, 2009

Pandemic Influenza A (H1N1) Virology Update

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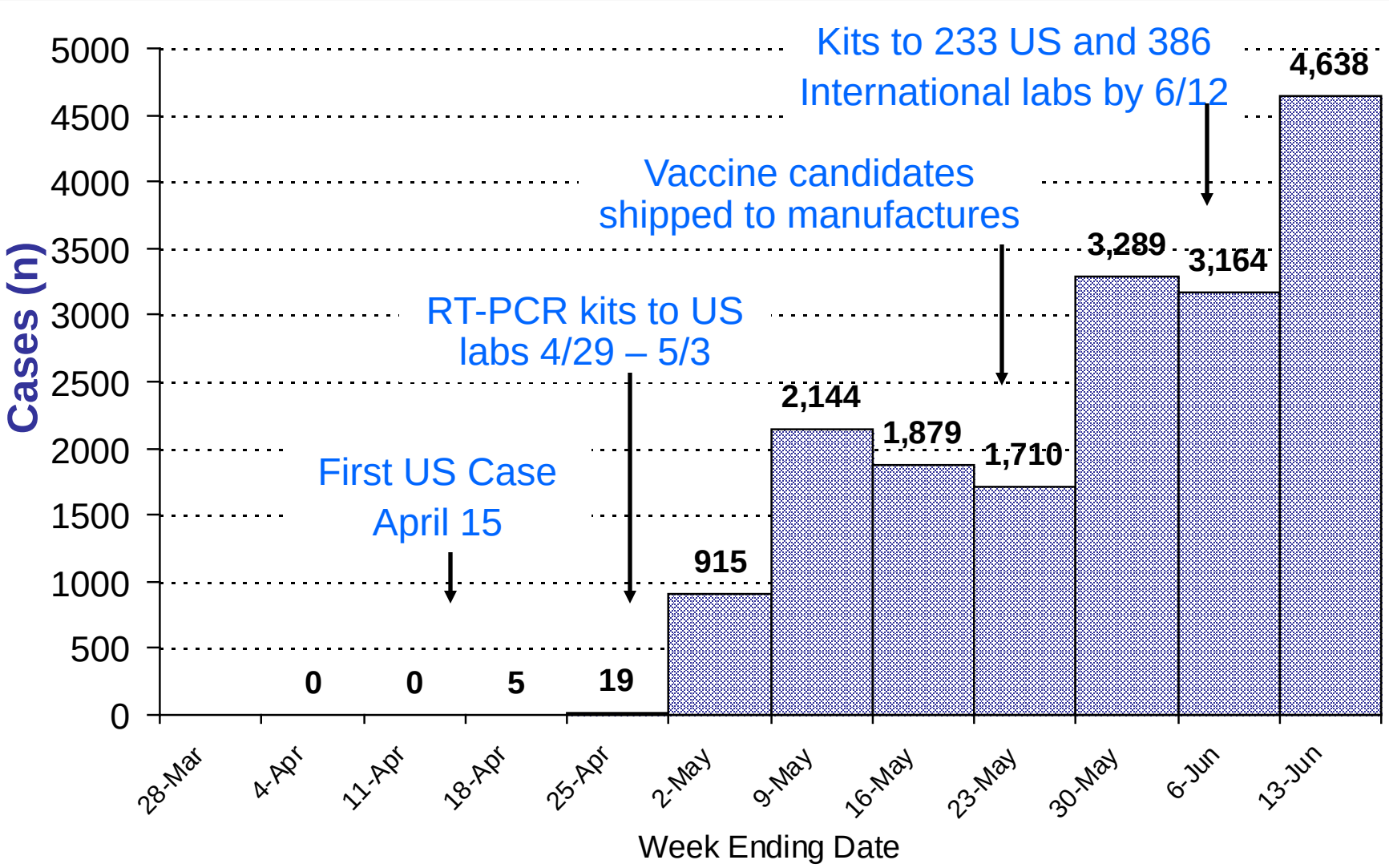
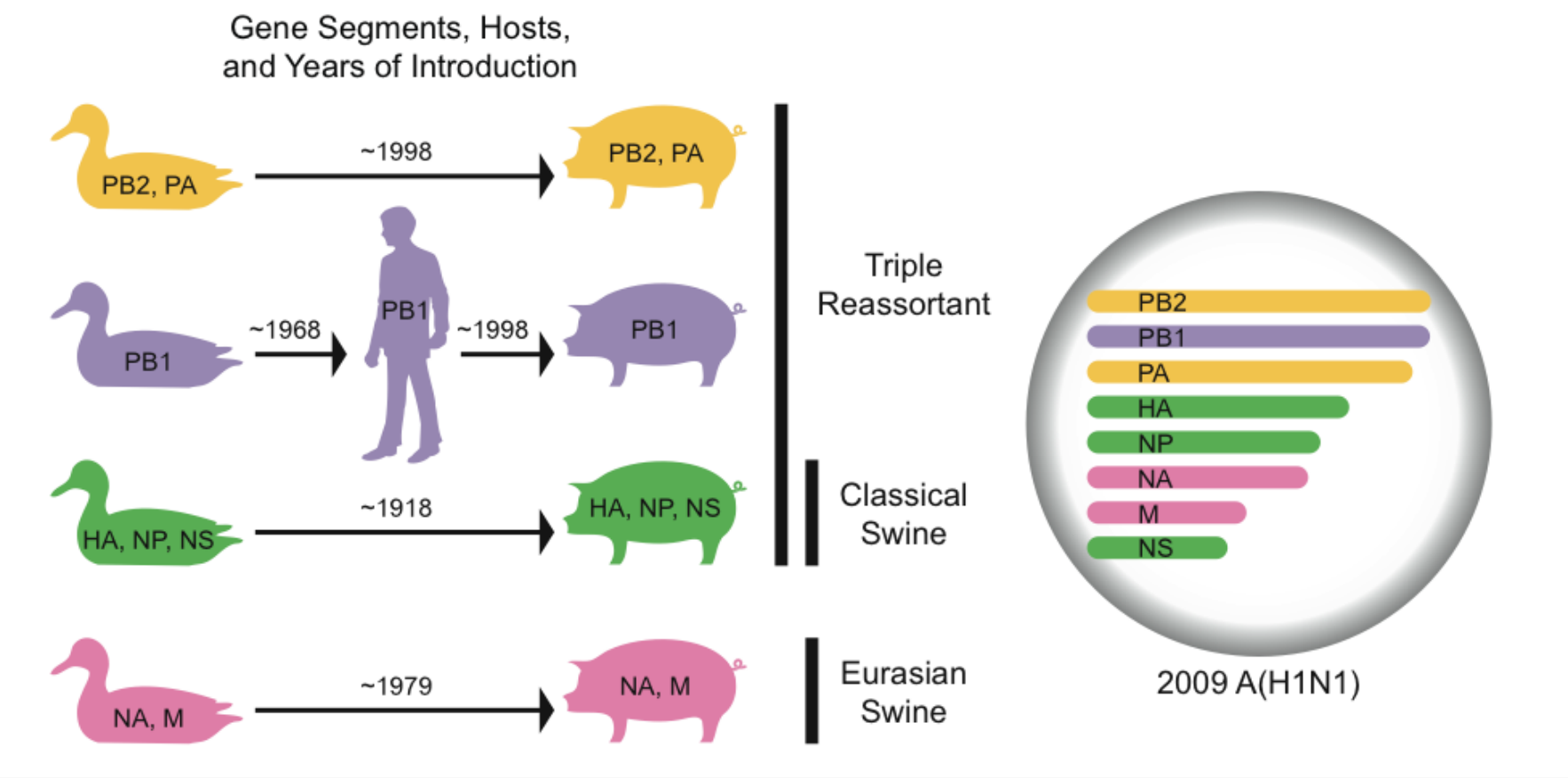
BEGINNING OF THE 2009 H1N1 PANDEMIC

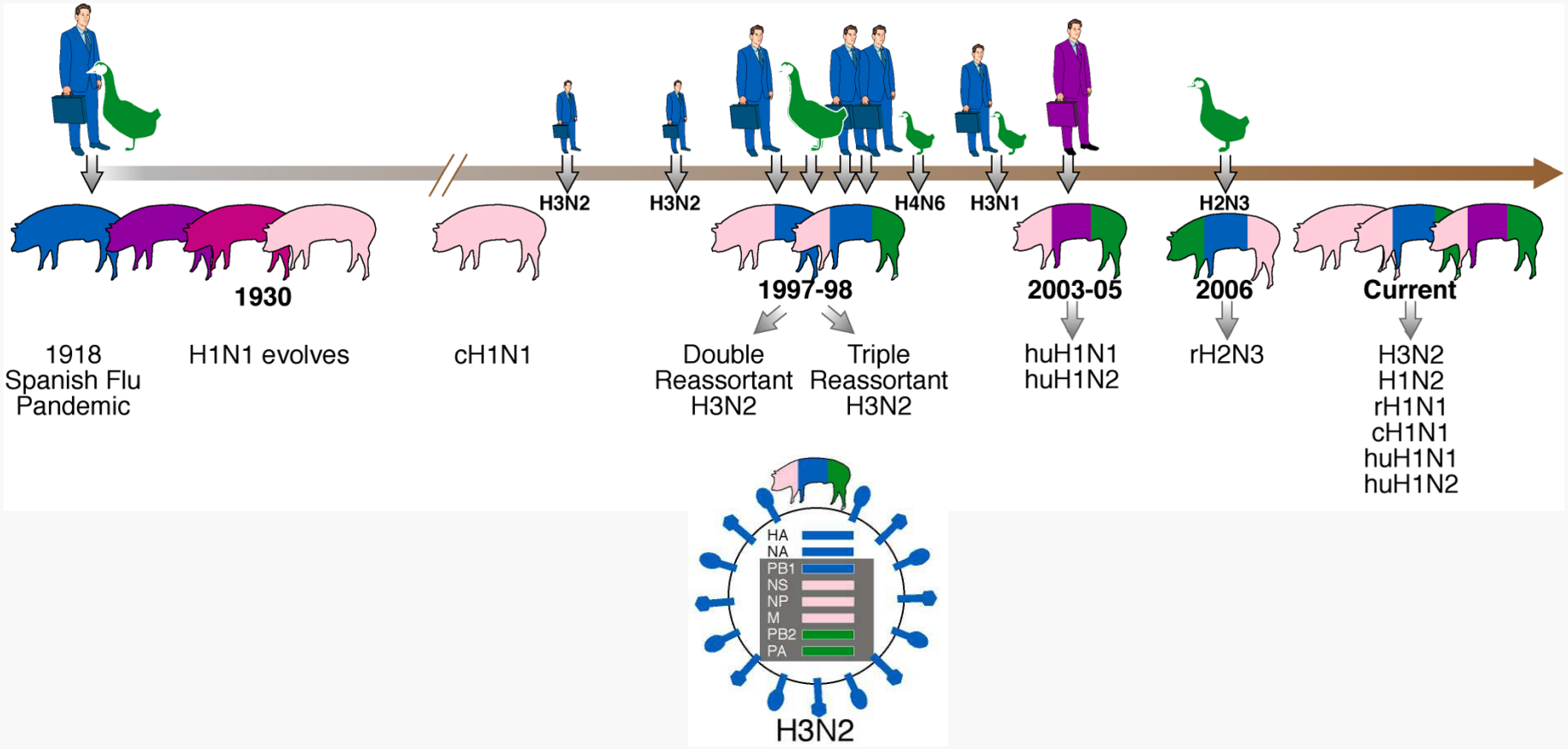


HOST AND LINEAGE ORIGINS FOR THE GENE SEGMENTS OF THE 2009 A(H1N1) VIRUS



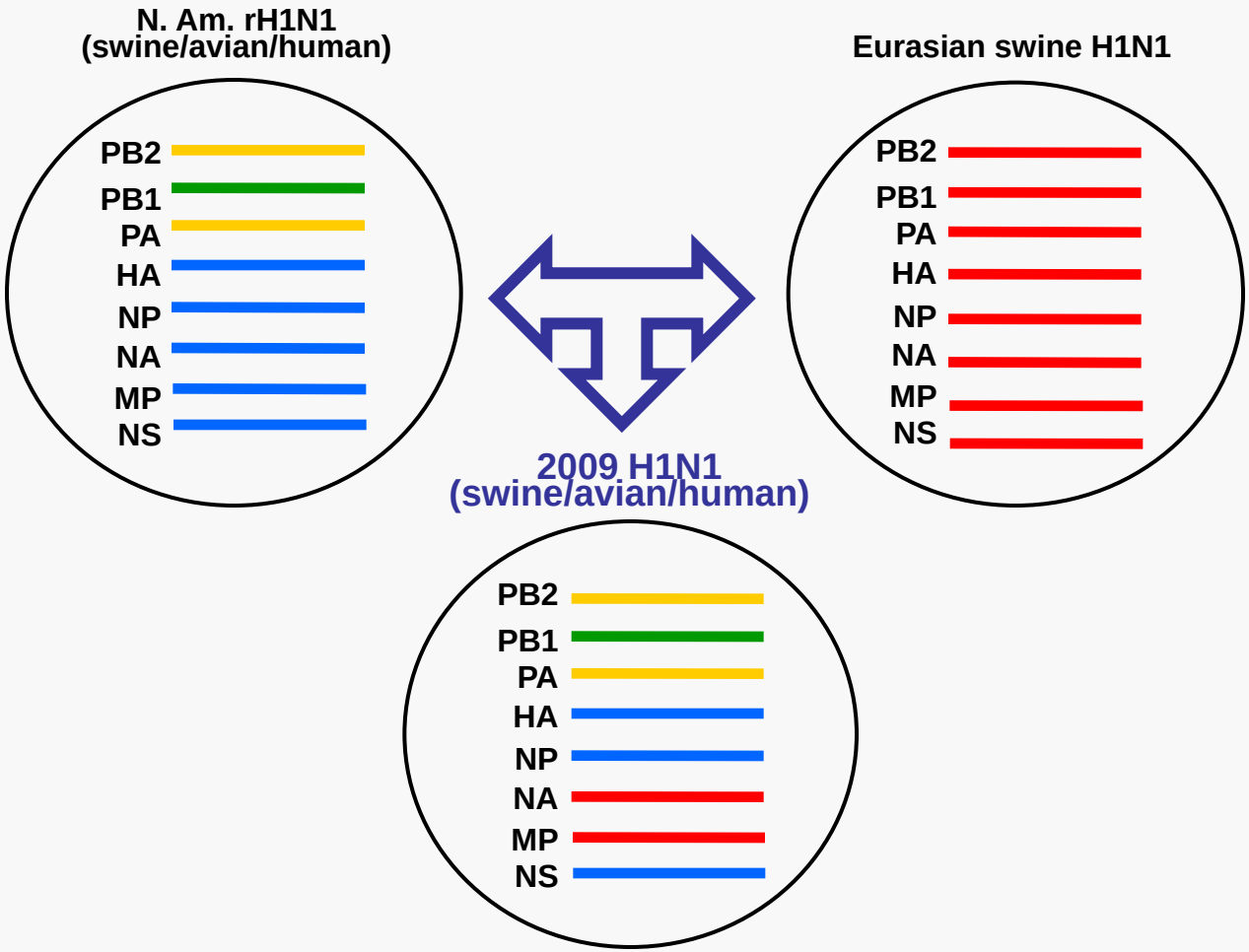
Garten, et al. Science Express 2009

REASSORTANT EVENTS AMONG SWINE INFLUENZA VIRUSES (SIV) IN NORTH AMERICA



Slide courtesy of Dr. Amy Vincent, NADC, USDA

ORIGIN OF THE 2009 PANDEMIC H1N1 VIRUS



Evolutionary Relationships Among 2009 Pandemic Influenza A (H1N1) Neuraminidase Genes

07/21/09

#: Egg Isolate

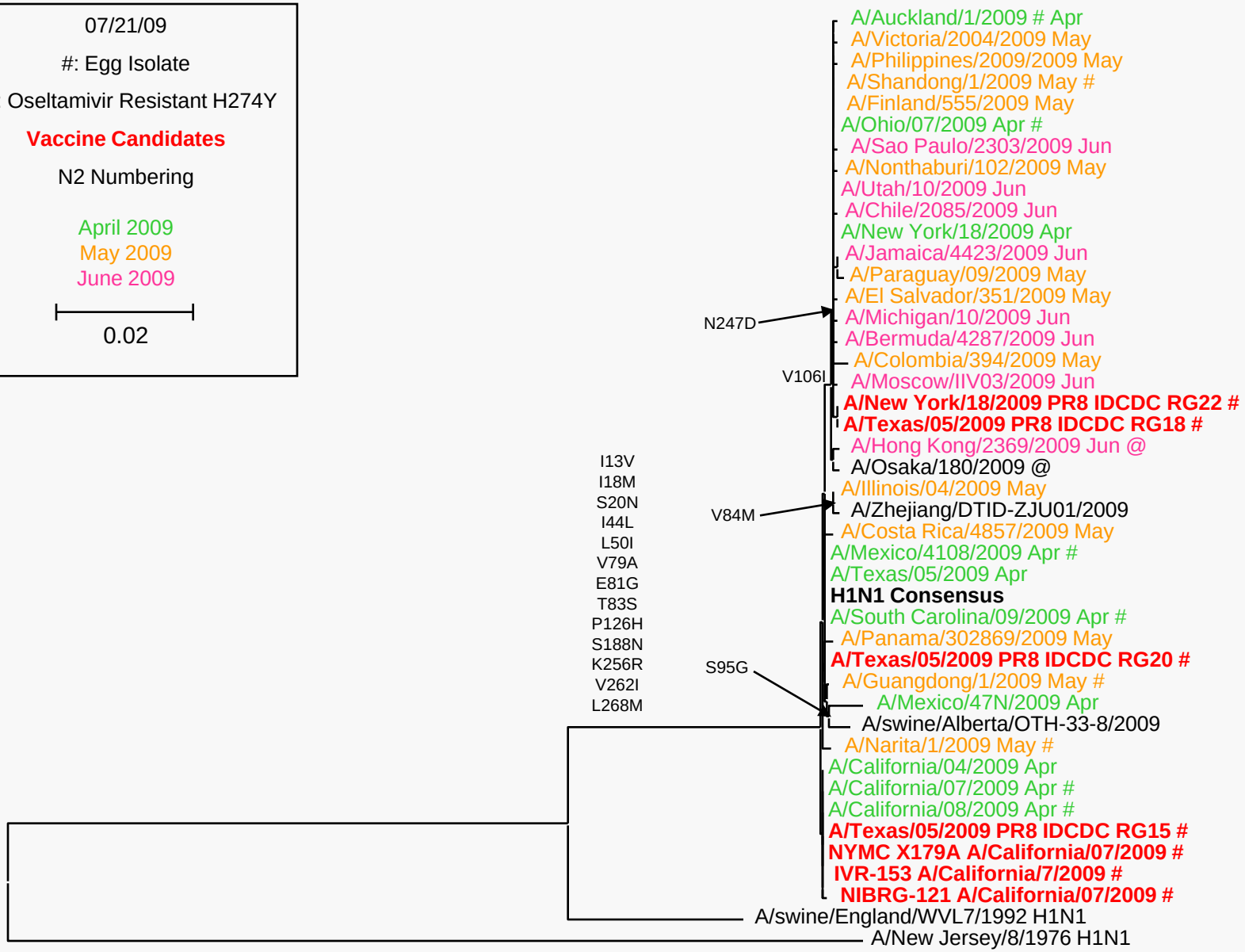
@: Oseltamivir Resistant H274Y

Vaccine Candidates

N2 Numbering

April 2009
May 2009
June 2009

0.02



GENETIC DISTANCE BETWEEN A/NEW JERSEY/8/1976 AND A/TEXAS/05/2009 COMPARING WITH H3N2 VIRUSES

	HA Number of Nucleotide Differences (%)	HA Number of Amino Acid Differences (%)	NA Number of Nucleotide Differences (%)	NA Number of Amino Acid Differences (%)
A/New Jersey/8/1976 vs A/California/7/2009 (H1N1)	184 (11%)	44 (8%)	282 (20%)	82 (18%)
A/Victoria/3/1975 vs A/Brisbane/10/2007 (H3N2)	185 (11%)	57 (10%)	120 (9%)	47 (10%)

HI REACTIONS OF PANDEMIC INFLUENZA H1N1v VIRUSES (CDC)

		REFERENCE FERRET ANTISERA												Date
	STRAIN DESIGNATION	SW/IA/3	NJ/8/76	WI/10	TX/14	IL/9	IA/09	CA/07	MX/410	NY/18	TX/15	AS/59	Passage	collected
1	A/SWINE/IOWA/1930	320	160	5	10	5	5	5	5	5	5	5	XEXE3	UNKN
2	A/NEWJERSEY/8/1976	160	640	10	20	10	10	5	5	5	5	5	SpfE7	UNKN
3	A/WISCONSIN/10/1998	5	80	1280	1280	1280	640	640	640	640	640	5	C3/C3E2	12/31/98
4	A/TEXAS/14/2008	80	160	320	2560	1280	1280	1280	1280	640	2560	5	M1/C2	10/15/08
5	A/ILLINOIS/9(33304)/2007	80	160	1280	2560	5120	5120	2560	2560	1280	1280	5	C2	09/01/07
6	A/IOWA/02/2009	40	160	1280	5120	5120	5120	2560	2560	2560	2560	5	E2	02/13/09
7	A/CALIFORNIA/07/2009	40	10	320	2560	1280	1280	2560	1280	1280	1280	5	E3	04/09/09
8	A/MEXICO/4108/2009	40	10	320	2560	1280	1280	2560	640	640	640	5	C1/E2	04/03/09
9	A/NEW YORK/18/2009	10	5	320	1280	640	1280	1280	640	640	640	5	E2	UNKN
10	A/TEXAS/15/2009	20	10	640	5120	2560	2560	5120	2560	1280	1280	5	C2	
11	A/BRISBANE/59/07	5	5	5	5	5	5	5	5	5	5	160	E2/E2	07/01/07
	TEST ANTIGENS													
	Fatal cases													
12	A/UTAH/03/2009	20	5	160	2560	1280	1280	2560	1280	1280	1280	5	C1	05/15/09
13	A/WASHINGTON/14/2009	5	5	160	2560	1280	1280	1280	640	640	640	5	C2	05/07/09
14	A/ARIZONA/07/2009	20	5	320	2560	1280	1280	2560	2560	2560	2560	5	C1	05/07/09
	MDCK and EGG pairs													
15	A/NEW YORK/04/2009	5	5	320	2560	640	1280	2560	1280	640	1280	5	C1	UNKN
16	A/NEW YORK/04/2009	80	20	320	2560	1280	1280	2560	640	640	1280	5	E2	UNKN
17	A/NEW YORK/05/2009	40	20	320	2560	1280	1280	2560	1280	1280	1280	5	C1	UNKN
18	A/NEW YORK/05/2009	5	5	320	2560	1280	1280	2560	640	1280	1280	5	E2	UNKN
19	A/NEW YORK/35/2009	160	80	320	5120	2560	2560	5120	2560	2560	5120	5	C1	04/25/09
20	A/NEW YORK/35/2009	20	5	320	2560	1280	1280	2560	2560	2560	5120	5	E2	04/25/09
	MDCK or EGG grown													
21	A/TEXAS/31/2009	10	5	320	2560	1280	1280	2560	2560	1280	1280	5	C1	05/12/09
22	A/ MONTANA/01/2009	20	10	320	2560	1280	1280	1280	1280	1280	1280	5	C1	05/05/09
23	A/FLORIDA/09/2009	5	5	320	2560	1280	1280	2560	1280	1280	1280	5	C1	05/01/09
24	A/CALIFORNIA/18/2009	5	5	160	1280	640	640	1280	1280	640	1280	5	C1	04/30/09
25	A/NEW HAMPSHIRE/03/20	20	10	320	1280	1280	1280	2560	1280	1280	1280	5	C1	04/28/09
26	A/GEORGIA/02/2009	5	5	320	2560	1280	640	1280	1280	1280	1280	5	C1	05/04/09
27	A/IDAHO/03/2009	5	5	320	2560	640	640	1280	1280	1280	1280	5	C1	05/05/09
28	A/MAINE/02/2009	80	10	640	2560	2560	2560	2560	2560	2560	2560	5	C1	05/05/09
29	A/NEVADA/04/2009	40	5	640	2560	1280	1280	2560	1280	1280	1280	5	E2	04/29/09
30	A/NEW YORK/45/2009	80	5	1280	2560	1280	1280	2560	2560	2560	2560	5	E2	04/25/09
31	A/MEXICO/4283/2009	160	40	1280	5120	2560	5120	5120	2560	5120	5120	5	C1/C1	04/15/09
32	A/MEXICO/4575/2009	320	80	1280	5120	5120	5120	5120	5120	5120	5120	5	C1/C1	04/20/09
33	A/GUATEMALA/450/2009	10	5	320	2560	1280	1280	2560	1280	640	1280	5	C1	05/01/09
34	A/COLOMBIA/330/2009	5	5	640	5120	2560	2560	2560	2560	2560	2560	5	C1	05/02/09
35	A/EL SALVADOR/351/2009	20	5	320	2560	1280	1280	2560	1280	1280	1280	5	C1	05/13/09
36	A/NONTHABURI/102/09	40	10	640	5120	2560	2560	2560	2560	1280	2560	5	C1/C1	05/04/09
37	A/AUCKLAND/01/2009	5	5	640	2560	1280	1280	2560	1280	640	1280	5	C2/C1	04/25/09
38	A/AUCKLAND/03/2009	10	5	320	2560	640	1280	2560	640	1280	1280	5	C2/C1	04/25/09
39	A/ENGLAND/195/2009	20	10	640	5120	2560	2560	5120	1280	1280	2560	5	X/C1	UNKN
	Reassortants													
40	A/CALIFORNIA/07/2009 X-	5	5	640	5120	2560	2560	2560	1280	1280	2560	5	EX/E1	REASS
41	A/TEXAS/5/2009xPR8-IDCI	20	5	640	2560	1280	2560	2560	1280	1280	1280	5	VE2/E1	REASS

HI REACTIONS OF PANDEMIC INFLUENZA H1N1v VIRUSES (NIMR)

POST INFECTION FERRET ANTISERA

	Passage	A/sw/Iowa 15/30	A/NJ 8/76	A/Cal 4/09	A/Cal 7/09	X179A	IVR-153	A/Eng 195/09	A/Auck 3/09	A/Narita 1/09	A/Bris 59/07
REFERENCE VIRUSES											
A/Iowa/15/30	Ex	1280	<40	<40	<40	<40	<40	<40	<40	<40	<40
A/New Jersey/8/76	Ex	320	640	320	640	320	160	320	640	640	<40
A/California/4/2009	C1,M1,E1	<40	160	2560	2560	2560	640	2560	2560	2560	<40
A/California/7/2009	E1+1	<40	160	2560	2560	2560	640	2560	2560	2560	<40
X-179A	Ex+1	<40	320	2560	2560	2560	640	2560	2560	5120	<40
IVR153	Ex+1	<40	160	2560	2560	2560	640	2560	2560	2560	<40
A/England/195/2009	MDCK3	<40	80	1280	1280	1280	320	1280	1280	2560	<40
A/Auckland/3/2009	Ex+1	<40	320	2560	2560	2560	640	2560	2560	2560	<40
A/Narita/1/2009	E2+1	<40	320	2560	2560	2560	640	2560	2560	5120	<40
A/Brisbane/59/2007	E9	<40	<40	<40	<40	<40	<40	<40	<40	<40	320
TEST VIRUSES											
A/Clermont-Ferrand/960/20(	MDCK2+1	<40	80	1280	1280	1280	320	1280	1280	2560	<40
A/Perpignan/969/2009	MDCK2+1	<40	80	1280	1280	1280	640	1280	1280	2560	<40
A/Toulouse/1026/2009	MDCK2+1	<40	160	2560	2560	2560	640	2560	2560	2560	<40
A/Lyon/1041/2009	MDCK2+1	<40	160	2560	1280	2560	640	2560	2560	2560	<40
A/Cyprus/S9/2009	MDCK3	<40	80	1280	1280	1280	640	1280	2560	2560	<40
A/Cyprus/S14/2009	MDCK3	<40	160	2560	1280	1280	640	1280	2560	2560	<40
A/Cyprus/S17/2009	MDCK2	<40	80	1280	1280	1280	320	1280	2560	2560	<40
A/Cyprus/S25/2009	MDCK3	<40	160	2560	1280	2560	640	1280	2560	5120	<40
A/Algeria/G594/2009	MDCK3	<40	160	2560	1280	2560	640	1280	2560	2560	<40
A/Singapore/99/2009	MDCK 1+1	<40	160	2560	1280	2560	640	1280	2560	2560	<40
A/Singapore/58/2009	MDCK 1+1	<40	160	1280	2560	2560	640	1280	2560	2560	<40
A/Singapore/100/2009	MDCK 1+1	<40	160	2560	2560	2560	640	2560	2560	5120	<40
A/Singapore/101/2009	MDCK 1+1	<40	160	2560	2560	2560	640	1280	2560	2560	<40
A/Singapore/102/2009	MDCK 1+1	<40	160	2560	2560	2560	640	1280	2560	2560	<40
A/Qatar/84/2009	MDCK4	<40	160	1280	2560	1280	640	1280	2560	2560	<40
A/Mauritius/3/2009JS	MDCK3	<40	160	2560	2560	2560	640	1280	2560	2560	<40

HI REACTIONS OF PANDEMIC INFLUENZA H1N1v VIRUSES (NIID)

	NIID-ID	Antigens	Passage History (E: Egg/C: MDCK)	Sample date	Ferret Antisera			
					Brisbane/59/2007 (H1N1) E No.2	California/07/2009 (H1N1)pdmE2+1 No.1	Narita/1/2009 (H1N1)pdmE1 No.3	Narita/1/2009 (H1N1)pdm C1 No.6
		Refference Antigens						
1	07/08-130	A/Brisbane/59/2007	E4	2007/07/01	640	<10	<10	<10
2	08/09-713	A/California/07/2009	E2+2	2009/04/09	<10	1280	2560	1280
3	08/09-718	A/Narita/1/2009	E2	2009/05/08	<10	1280	2560	1280
4	08/09-721	A/Narita/1/2009	C2	2009/05/08	<10	1280	5120	2560
		Test Antigens						
5	08/09-745	A/Osaka/2/2009	C1	2009/05/17	<10	1280	2560	1280
6	08/09-802	A/Sakai/2/2009	C1		<10	1280	5120	2560
7	08/09-821	A/Fukuoka-C/3/2009	C1		<10	1280	2560	1280
8	08/09-840	A/Fukushima/1/2009	C1		<10	2560	5120	2560
9	08/09-841	A/Iwate/2/2009	C1		<10	1280	5120	2560
10	08/09-842	A/Iwate/1/2009	C1		<10	1280	2560	1280
11	08/09-864	A/Myanmar/60/2009	C1		<10	1280	2560	1280
12	08/09-866	A/Shizuoka-c/97/2009	C1	2009/05/26	<10	1280	2560	1280
13	08/09-867	A/Hiroshima/200/2009	C4	2009/07/01	<10	1280	2560	1280
14	08/09-868	A/Hiroshima/207/2009	C1	2009/06/15	<10	1280	2560	1280
15	08/09-872	A/Niigata/690/2009	C2	2009/06/16	<10	640	2560	1280
16	08/09-873	A/Chiba-c/48/2009	C1	2009/06/02	<10	640	2560	1280
17	08/09-874	A/Chiba-c/51/2009	C1	2009/06/16	<10	1280	5120	1280
18	08/09-875	A/Yamaguchi/21/2009	C2	2009/06/03	<10	1280	2560	1280
19	08/09-876	A/Yamaguchi/23/2009	C1	2009/06/22	<10	2560	5120	2560
20	08/09-877	A/Osaka/180/2009*	C2		<10	1280	2560	1280

*) Oseltamivir resistant virus

COUNTRIES FOR WHICH SEQUENCING OR ANTIGENIC DATA ARE AVAILABLE

North America

Canada	14
Mexico	130
USA	305
TOTAL	**449**

Central and South America

Barbados	1
Bermuda	1
Bolivia	2
Brazil	12
British Virgin Islands	1
CAREC	3
Chile	11
Colombia	6
Costa Rica	2
Dominican Republic	3
Ecuador	1
El Salvador	15
Guatemala	2
Honduras	2
Jamaica	1
Nicaragua	1
Panama	5
Paraguay	8
Trinidad and Tobago	3
TOTAL	**81**

Asia and Oceania

Australia	6
China	26
Hong Kong	1
Japan	28
New Zealand	18
Philippines	4
Singapore	19
South Korea	1
Thailand	3
TOTAL	**106**

Europe

Denmark	1
Finland	3
France	15
Germany	20
Greece	22
Ireland	12
Israel	8
Italy	40
Luxembourg	1
Netherlands	3
Norway	2
Poland	1
Portugal	1
Russia	4
Spain	68
Sweden	18
Switzerland	1
Turkey	2
United Kingdom	3
TOTAL	**225**

TOTAL 861

39 complete genomes sequenced

RESISTANCE OF PANDEMIC INFLUENZA H1N1v VIRUSES TO ADAMANTANES (M2 BLOCKERS)

	Isolates tested (n)	Resistant isolates	% Resistance
US Isolates	305	305	100
Foreign Isolates	78	78	100
Global Isolates	383	383	100

RESISTANCE OF PANDEMIC INFLUENZA H1N1v VIRUSES TO NEURAMINIDASE INHIBITORS

	Isolates tested (n)	Resistant (%)	
		Zanamivir	Oseltamivir
US isolates	267	0 (0)	0 (0)
Foreign isolates	105	0 (0)	0 (0)
Global isolates	372	0 (0)	0 (0)

Five oselatmivir-resistant cases were recently documented:

- Denmark (after oseltamivir treatment)
- Japan (2) (after oseltamivir treatment)
- Canada (after oseltamivir treatment)
- Hong Kong (travel from U.S., no treatment)

SERUM CROSS-REACTIVE ANTIBODY RESPONSE TO A NOVEL INFLUENZA A(H1N1) VIRUS AFTER VACCINATION WITH SEASONAL INFLUENZA VACCINES (MMWR MAY 2009)

TABLE 1. Cross-reactive microneutralization (MN) antibody response to novel influenza A (H1N1) virus* in pediatric recipients (aged 6 months–9 years) of seasonal influenza vaccines

Vaccine	Influenza season	Influenza virus	Age group	No.	% with fourfold or greater increase in antibody titer†	% with MN titer of ≥40§		Geometric mean titer (GMT)¶		
						Prevaccination	Postvaccination	Prevaccination (95% CI**)	Postvaccination (95% CI)	Postvaccination to prevaccination ratio
TIV††	2005–2007§§	A/New Caledonia/20/1999	6 mos–9 yrs	33	67	42	94	31 (21–46)	255 (172–378)	8
		A/California/04/2009			0	0	0	5 (4–6)	6 (6–7)	1
	2007–08	A/Solomon Is/3/2006	5–9 yrs	13	85	54	100	42 (22–80)	575 (303–1093)	14
		A/California/04/2009			0	8	8	10 (7–15)	12 (8–17)	1
	2008–09	A/Brisbane/59/2007	6 mos–3 yrs	9	100	0	100	5 (4–7)	285 (202–402)	57
		A/California/04/2009			0	0	0	5 (—)	5 (—)	1
LAIV¶¶	2005–2007§§	A/New Caledonia/20/1999	6 mos–9 yrs	24	25	46	79	33 (17–63)	73 (38–139)	2
		A/California/04/2009			0	0	4	5 (4–6)	6 (5–7)	1

* A/California/04/2009.
† A fourfold or greater increase in antibody titer indicates seroconversion (a response to the vaccine).
§ A linear regression model was used to predict the MN titer for seasonal H1N1 viruses that corresponded to a hemagglutination inhibition (HI) antibody titer of 40. (Serum HI antibody titers of 40 are associated with at least a 50% decrease in risk for influenza infection or disease [7]). In pediatric populations, an HI titer of 40 corresponds with an MN titer of 40.
¶ A titer of 1280 was used for all samples with a titer of ≥1280. The dilution of sera in the first well is based on the combination of a 1:10 serum dilution with an equal volume of diluted virus for a final serum dilution referred to as 1:10. In the statistical models, study participants were treated as random effects sampled from a larger population of study participants, and duplicate samples were treated as random effects nested within each study participant.
** Confidence interval.
†† Trivalent, inactivated influenza vaccine.
§§ 2005–06 and 2006–07 influenza seasons.
¶¶ Live, attenuated influenza vaccine.

SERUM CROSS-REACTIVE ANTIBODY RESPONSE TO A NOVEL INFLUENZA A(H1N1) VIRUS AFTER VACCINATION WITH SEASONAL INFLUENZA VACCINES (MMWR MAY 2009)

TABLE 2. Cross-reactive microneutralization (MN) antibody response to novel influenza A (H1N1) virus* in adult recipients of seasonal influenza vaccines

Vaccine	Influenza season	Influenza virus	Age group (yrs)	No.	% with fourfold or greater increase in antibody titer†	% with MN titer of ≥160§		Geometric mean titer (GMT)¶		
						Prevaccination	Postvaccination	Prevaccination (95% CI**)	Postvaccination (95% CI)	Postvaccination to prevaccination ratio
TIV††	2007–08	A/Solomon Is/3/2006	18–64	134	74	28	92	48 (40–59)	561 (462–682)	12
		A/California/04/2009			19	9	25	28 (23–34)	53 (43–66)	2
	2008–09	A/Brisbane/59/2007	18–40	83	78	20	88	29 (22–38)	546 (418–713)	19
		A/California/04/2009			12	6	7	11 (9–14)	21 (16–26)	2
	2007–08	A/Solomon Is/3/2006	>60	63	54	14	54	31 (22–42)	143 (105–194)	5
		A/California/04/2009			3	33	43	92 (71–121)	97 (74–127)	1

* A/California/04/2009.
† A fourfold or greater increase in antibody titer indicates seroconversion (a response to the vaccine).
§ A linear regression model was used to predict the MN titer for seasonal H1N1 viruses that corresponded to a hemagglutination inhibition (HI) antibody titer of 40. (Serum HI antibody titers of 40 are associated with at least a 50% decrease in risk for influenza infection or disease [7]). In adult populations, an HI titer of 40 corresponds with an MN titer of ≥160.
¶ A titer of 1280 was used for all samples with a titer of ≥1280. The dilution of sera in the first well is based on the combination of a 1:10 serum dilution with an equal volume of diluted virus for a final serum dilution referred to as 1:10. In the statistical models, study participants were treated as random effects sampled from a larger population of study participants, and duplicate samples were treated as random effects nested within each study participant.
** Confidence interval.
†† Trivalent, inactivated influenza vaccine.

IMMUNITY TO 2009 H1N1 VIRUS RESULTING FROM PRIOR INFLUENZA INFECTION OR VACCINATION WITH SEASONAL INFLUENZA VACCINE IN DIFFERENT AGE GROUPS (NEJM submitted)

- Less than 4% of individuals born during or after 1980 exhibited preexisting, cross-reactive, neutralizing antibody titers of ≥40 to the pandemic virus, whereas 34% of individuals born prior to 1950 had titers of ≥80

- Vaccination with recent seasonal trivalent influenza vaccines (TIV), resulted in a ≥4-fold rises in cross-reactive antibody to the pandemic virus in
  - only ~2% of children aged 6 months to 9 years,
  - 12-22% of adults aged 18-64 years, and
  - ≤5% or less of adults aged >60 years

- Seasonal TIV with adjuvant induced similar cross-reactive antibody responses; no increase in cross-reacting antibody to pandemic H1N1 virus

CONCLUSIONS

- All 2009 pandemic H1N1 viruses are antigenically similar to A/California/7/2009
- Minor genetic variability
- No evidence of reassortment with seasonal or H5N1viruses
- Resistant to M2 blockers
- Sensitive to NI (oseltamivir and zanamavir)
  - Oseltamivir-resistant documented (4 of 5 after treatment or prophylaxis)
- Vaccination with contemporary seasonal influenza vaccines, with or without an adjuvant, induces little or no cross-reactive antibody to the 2009 pandemic H1N1 virus in any age group
  - Individuals <30 years of age are serologically “naïve”
  - A proportion of older adults appear to have pre-existing, cross-reactive antibodies

CONCLUSIONS

- Genetic and antigenic characterization of viruses, serologic assays, animal models, and epidemiologic assessments - all critical components for public health risk assessment
  - Substantial consistency between laboratory and epidemiologic results
  - Suggest novel H1N1 may not be fully adapted to humans
- Epidemiologic and virologic surveillance are important for identification of future changes in
  - Antigenic characteristics
  - Transmission characteristics
  - Severity of disease
  - Antiviral resistance
  - Intensity (surge) in US cases
- Limited understanding of diversity of influenza viruses in pigs globally is a major gap in pandemic preparedness
  - USDA's efforts to initiate surveillance should be supported and encouraged by public health, putting "One Health" concept into action
  - Ensuring virus sharing public health, animal health, academia and industry is a key component of pandemic planning

ACKNOWLEDGEMENTS

- State and Local Health Departments
- WHO's Global Influenza Surveillance Network
  - National Influenza Centers (esp. Mexico and Canada's NICs)
  - WHO CCs
  - WHO RO and HQ
- Influenza Division Staff, CDC
  - Office of the Director
    - Dan Jernigan, Deputy Director
    - Carolyn B. Bridges, Associate Director for Science
    - Michael Shaw, Associate Director for Laboratory Science
  - Epidemiology and Surveillance Branch
    - Joe Bresee, Chief
  - Immunology and Pathogenesis Branch
    - Jackie Katz, Chief
  - Viral Surveillance and Diagnostics Branch
    - Alexander Klimov, Chief
  - Molecular Genetics Branch
    - Ruben Donis, Chief
- CDC Pandemic H1N1 Response Team, Emergency Ops Center

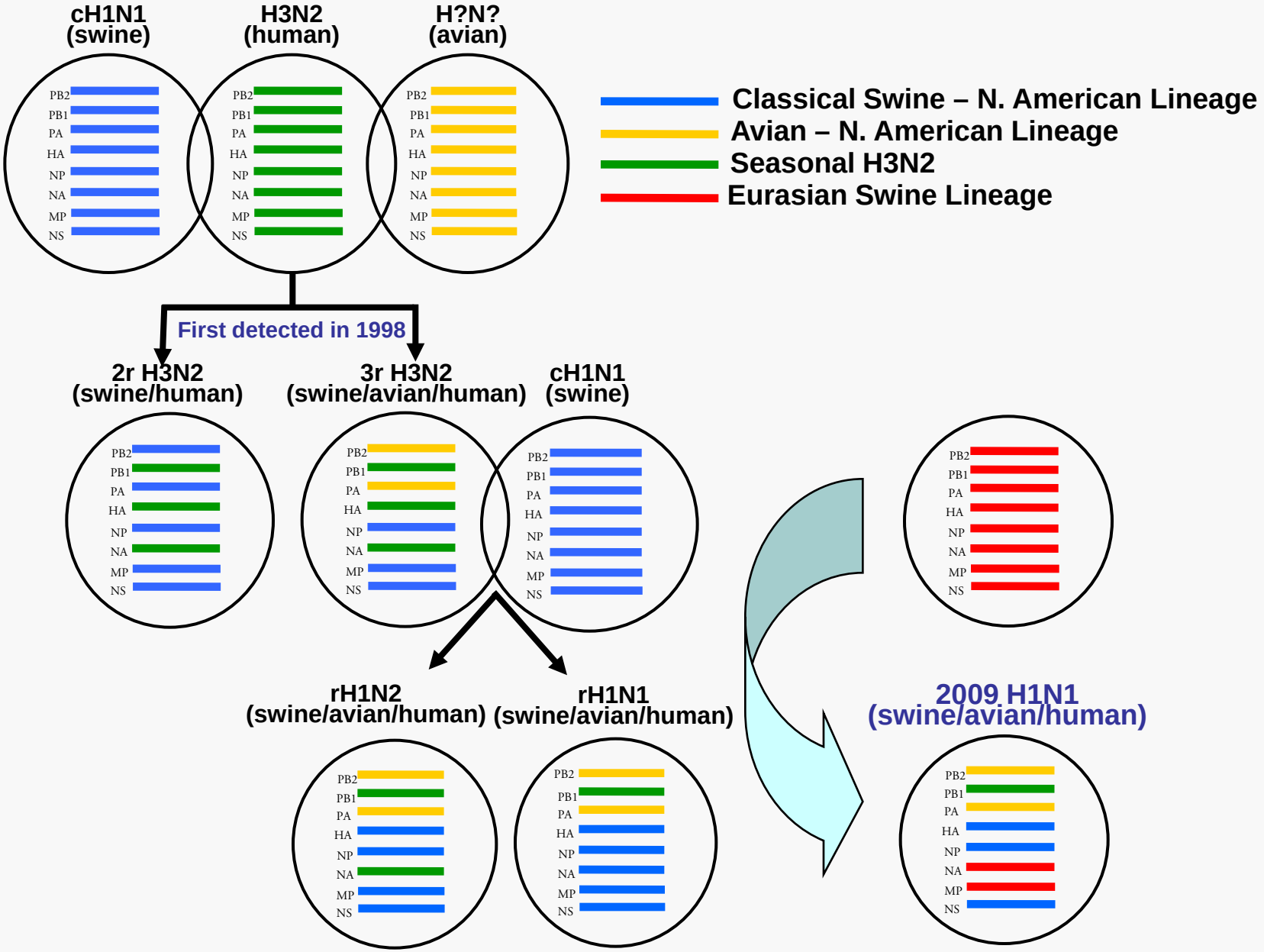
Questions?

CROSS-REACTIVE MN ANTIBODY RESPONSE IN ADULT RECIPIENTS (25-65 y.o.) OF 1976 INFLUENZA VACCINE (1976-77 INFLUENZA SEASON)

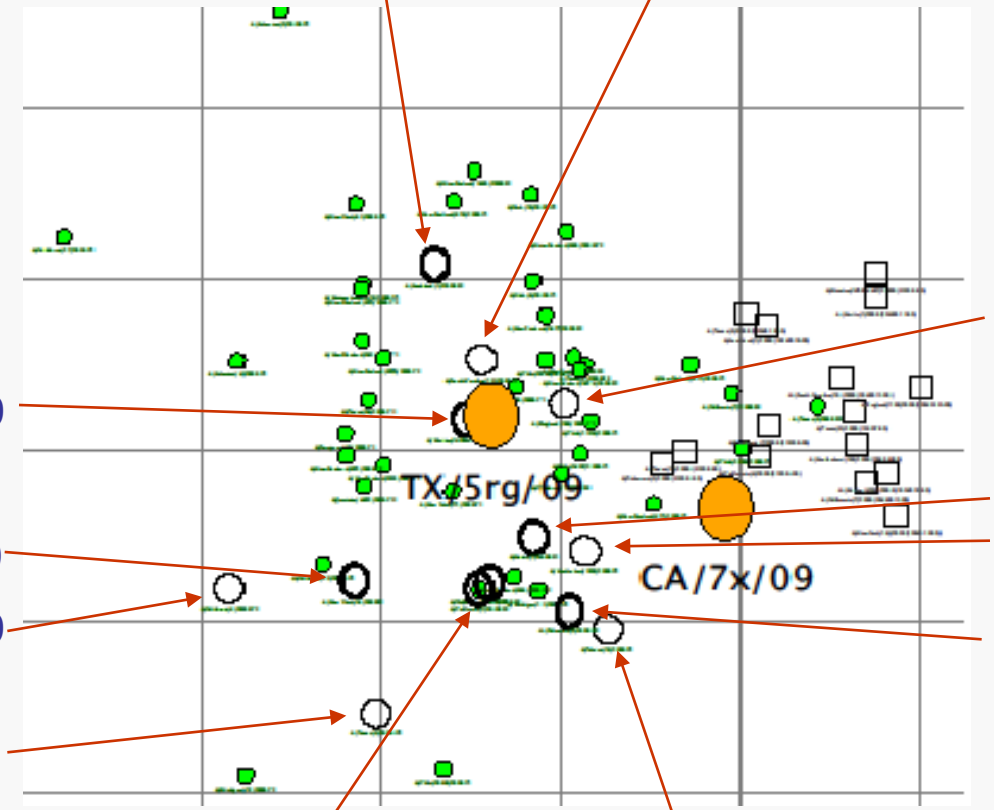
Influenza Virus	No	% with ≥4-fold increase in antibody titer	GMT			% with MN ≥ 80		% with MN ≥ 160	
			Pre-vacc (95% CI)	Post-vacc (95% CI)	Post / pre ratio	Pre-vacc	Post-vacc	Pre-vacc	Post-vacc
A/New Jersey/8/1976	83	81	29 (22-37)	260 (198-341)	9	12	82	5	71
A/California/04/2009		54	58 (46-73)	194 (153-246)	3	35	78	16	63

(NEJM submitted)

ORIGIN OF THE 2009 PANDEMIC H1N1 VIRUS



ANTIGENIC MAPPING
(CDC, 54 antigens; 16 sera)



HI REACTIONS OF PANDEMIC INFLUENZA H1N1v VIRUSES (CDC)

		REFERENCE FERRET ANTISERA											Date
	STRAIN DESIGNATION	CA/04	CA/07	X-179A	MX/4108	NY/18	TH/102	TX/05	RG-15	ENG/ 195	AS/59	Passage	collected
1	A/CALIFORNIA/04/2009	**320**	1280	640	1280	640	320	1280	80	640	5	C2	04/01/09
2	A/CALIFORNIA/07/2009	1280	**2560**	1280	2560	2560	640	2560	320	1280	5	E3	04/09/09
3	A/CALIFORNIA/7/09 NYMC X-179A	5120	20480	**2560**	5120	5120	1280	5120	1280	2560	5	EX/E1	REASS
4	A/MEXICO/4108/2009	2560	5120	1280	**1280**	2560	640	2560	320	1280	5	C1/E2	04/03/09
5	A/NEW YORK/18/2009	1280	2560	1280	1280	**1280**	320	1280	160	640	5	E2	UNKN
6	A/NONTHANBURI/102/2009	2560	10240	2560	2560	2560	**640**	2560	320	2560	5	C1/C2	05/04/09
7	A/TEXAS/05/2009	640	2560	640	1280	1280	320	**1280**	160	640	5	X/C2	04/15/09
8	A/TEXAS/5/2009 XPR8-IDCDC RG15	2560	5120	2560	1280	1280	640	2560	**640**	1280	5	VE2/E1	REASS
9	A/ENGLAND/195/2009	2560	5120	2560	2560	2560	640	5120	320	**2560**	5	X/C1	UNKN
10	A/BRISBANE/59/07	5	5	5	5	5	5	5	5	5	**320**	E2/E2	07/01/07
	TEST ANTIGENS												
11	A/DELAWARE/03/2009	2560	5120	2560	2560	5120	640	2560	320	1280	5	E2	04/28/09
12	A/SOUTH CAROLINA/10/2009	1280	2560	2560	2560	2560	640	5120	160	1280	5	C1	04/15/09
13	A/ARKANSAS/04/2009	640	1280	640	1280	640	320	1280	160	640	5	C2	05/07/09
14	A/MICHIGAN/11/2009	1280	5120	1280	2560	2560	640	2560	320	2560	5	C2	05/04/09
15	A/CALIFORNIA/23/2009	1280	2560	640	1280	640	320	1280	160	1280	5	C2	05/26/09
16	A/MASSACHUSETTS/15/2009	640	2560	1280	1280	1280	320	2560	160	1280	5	C1	05/26/09
17	A/NEW YORK/61/2009	640	2560	640	1280	1280	320	2560	160	1280	5	C2	05/26/09
18	A/NEW YORK/71/2009	1280	5120	1280	1280	1280	640	2560	320	2560	5	C1	05/23/09
19	A/TEXAS/36/2009	1280	5120	1280	1280	1280	320	2560	160	1280	5	C1	04/29/09
20	A/MEXICO/INDRE4487(10)/2009	1280	5120	1280	2560	1280	640	5120	640	1280	5	E2/E1	UNKN
21	A/PARAGUAY/41/2009	1280	2560	1280	1280	1280	320	2560	160	1280	5	C1	06/04/09
22	A/CHILE/2408/2009	1280	5120	2560	2560	2560	640	2560	320	2560	5	C2/C1	06/08/09
23	A/CHILE/2085/2009	640	2560	640	1280	1280	320	1280	160	1280	5	C2/C1	06/05/09
24	A/JAMAICA/4422/2009	1280	2560	1280	1280	1280	320	2560	160	1280	5	C2	06/06/09
25	A/NARITA/1/2009	2560	5120	1280	2560	2560	640	2560	640	1280	5	E2/E1	UNKN
26	A/AUCKLAND/1/2009	1280	5120	1280	1280	1280	320	2560	320	1280	5	E2/E2	04/25/09
27	A/NEW ZEALAND/870/2009	640	2560	1280	1280	1280	640	1280	160	1280	5	C2	06/14/09
28	A/NEW ZEALAND/1680/2009	1280	2560	640	1280	1280	320	2560	320	1280	5	E2	06/19/09
	FATAL CASES												
29	A/TEXAS/15/2009	2560	10240	2560	2560	2560	640	2560	320	2560	5	C2	04/15/09
30	A/UTAH/10/2009	1280	2560	1280	1280	1280	640	5120	320	2560	5	C2	06/05/09
31	A/UTAH/06/2009	1280	5120	1280	2560	1280	640	5120	320	2560	5	C1	06/12/09
	REASSORTANTS-DIRECT TESTING												
32	A/TEXAS/05/2009-PR8-IDCDC RG18	5120	20480	5120	10240	10240	2560	10240	1280	10240	5	V1E3	REASS
33	A/TEXAS/05/2009-PR8-IDCDC RG20	2560	10240	2560	2560	2560	640	5120	640	2560	5	V1E3	REASS
34	A/NEW YORK/18/2009-PR8-IDCDC RG22	2560	5120	2560	2560	2560	1280	5120	320	2560	5	V1E3	REASS
35	A/CALIFORNIA/07/2009 186D MEDIMMUNE	5120	10240	5120	5120	2560	1280	5120	640	5120	5	EX	REASS
36	A/CALIFORNIA/07/2009 395N MEDIMMUNE	2560	5120	2560	2560	2560	1280	5120	320	2560	5	EX	REASS

HI REACTIONS OF PANDEMIC INFLUENZA H1N1v VIRUSES (CDC)

		REFERENCE FERRET ANTISERA													Date
	STRAIN DESIGNATION	CA/04	CA/07	X-179A	IVR-153	RG-20	MX/4108	NY/18	TX/05	RG-15	JP/1	NZ/1	AS/59	Passage	collected
1	A/CALIFORNIA/04/2009	**320**	160	320	320	320	640	320	640	40	320	640	5	C2	04/01/09
2	A/CALIFORNIA/07/2009	1280	**2560**	1280	1280	640	1280	1280	2560	320	2560	1280	5	E3	04/09/09
3	A/CALIFORNIA/7/09 NYMC X-179A	2560	5120	**2560**	2560	1280	2560	2560	5120	1280	5120	2560	5	EX/E1	REASS
4	A/CALIFORNIA/7/2009 IVR-153	2560	5120	2560	**2560**	1280	2560	2560	1280	640	5120	2560	5	EX/E1	REASS
5	A/CALIFORNIA/04/2009 PR8 RG-2(	1280	2560	1280	1280	**640**	1280	1280	2560	160	2560	1280	5	EX/E1	REASS
6	A/MEXICO/4108/2009	1280	2560	1280	1280	640	**2560**	1280	2560	320	5120	1280	5	C1/E2	04/03/09
7	A/NEW YORK/18/2009	640	1280	320	640	320	640	**640**	1280	160	1280	640	5	E2	UNKN
8	A/TEXAS/05/2009	1280	5120	2560	2560	1280	2560	2560	**5120**	1280	5120	5120	5	X/C2	04/15/09
9	A/TEXAS/5/2009 XPR8-IDCDC RG1	1280	2560	1280	1280	640	640	1280	5120	**640**	5120	2560	5	VE2/E1	REASS
10	A/NARITA/1/2009	1280	2560	640	1280	320	1280	1280	5120	320	**5120**	2560	5	E2/E1	UNKN
11	A/AUCKLAND/1/2009	1280	2560	1280	1280	320	640	640	5120	320	5120	**2560**	5	E2/E2	4/25/2009
12	A/BRISBANE/59/07	5	5	5	5	5	5	5	5	5	5	5	**320**	E2/E2	07/01/07
	TEST ANTIGENS														
13	A/CALIFORNIA/22/2009	1280	5120	1280	2560	640	2560	1280	5120	320	5120	2560	5	C2	05/04/09
14	A/MONTANA/07/2009	640	1280	640	1280	320	1280	640	2560	160	2560	1280	5	C1	05/04/09
15	A/WISCONSIN/12/2009	1280	2560	1280	1280	640	1280	1280	5120	160	5120	2560	5	C1	05/07/09
16	A/VIRGINIA/05/2009	1280	2560	1280	1280	640	1280	1280	2560	320	5120	2560	5	C2	05/06/09
17	A/KENTUCKY/07/2009	1280	5120	1280	1280	640	1280	1280	5120	320	5120	2560	5	C1	05/04/09
18	A/WASHINGTON/17/2009	2560	5120	2560	2560	640	2560	2560	5120	320	5120	2560	5	C2	05/04/09
19	A/TENNESSEE/08/2009	1280	2560	1280	1280	640	1280	1280	2560	160	2560	1280	5	C1	05/07/09
20	A/NEW HAMPSHIRE/06/2009	2560	5120	2560	2560	640	2560	2560	5120	320	5120	2560	5	C1	05/17/09
21	A/WEST VIRGINIA/05/2009	1280	5120	1280	1280	640	2560	1280	2560	160	2560	1280	5	C1	05/25/09
22	A/MICHIGAN/09/2009	1280	2560	1280	2560	1280	1280	1280	5120	320	2560	2560	5	C2	05/26/09
23	A/RHODE ISLAND/04/2009	2560	5120	1280	2560	640	1280	1280	2560	160	2560	2560	5	C1	06/01/09
24	A/UTAH/09/2009	1280	2560	1280	1280	640	1280	1280	1280	160	2560	1280	5	C1	05/27/09
25	A/MASSACHUSETTS/14/2009	1280	5120	1280	2560	1280	2560	2560	2560	320	5120	2560	5	C1	05/27/09
26	A/JAMAICA/4423/2009	1280	2560	1280	1280	640	1280	640	2560	320	2560	1280	5	C1	06/06/09
27	A/TRINIDAD/4276/2009	2560	5120	1280	2560	640	2560	1280	2560	320	2560	2560	5	C2	06/04/09
28	A/BERMUDA/4287/2009	1280	2560	1280	1280	640	1280	1280	2560	320	2560	2560	10	C1	06/03/09
29	A/BR. VIRGIN ISL./5437/2009	1280	2560	1280	1280	640	1280	1280	2560	320	2560	2560	5	C1	06/15/09
30	A/BARBADOS/5211/2009	2560	5120	2560	2560	1280	2560	1280	5120	320	5120	2560	5	C1	06/17/09
31	A/CAREC/5160/2009 *	1280	2560	1280	2560	640	2560	2560	5120	320	5120	2560	5	C1	06/14/09
32	A/CAREC/5186/2009 *	1280	2560	1280	1280	640	1280	1280	2560	320	5120	2560	5	C1	06/15/09
33	A/CAREC/5172/2009 *	2560	5120	2560	2560	1280	2560	2560	5120	320	5120	5120	5	C1	06/15/09
34	A/KOBE/1/2009	2560	5120	2560	2560	1280	5120	2560	2560	320	5120	2560	5	C2/C2	UNKN
35	A/OSAKA/1/2009	2560	5120	2560	2560	1280	2560	2560	2560	320	2560	2560	5	C2/C2	UNKN
36	A/OSAKA-C/1/2009	1280	2560	1280	1280	640	1280	1280	1280	160	2560	1280	5	C2/C2	UNKN
37	A/AMAGASAKI/1/2009	1280	5120	1280	1280	640	1280	1280	1280	160	2560	1280	5	C2/C1	UNKN
	FATAL CASES														
38	A/NEW YORK/58/2009	2560	5120	2560	5120	1280	5120	5120	2560	320	5120	2560	5	C1	05/23/09
39	A/MICHIGAN/10/2009	640	2560	1280	1280	640	1280	1280	1280	160	2560	1280	5	C1	06/03/09
40	A/MICHIGAN/10/2009	1280	2560	1280	1280	320	1280	1280	2560	160	2560	1280	5	C1	06/03/09

* CARIBBEAN

HI REACTIONS OF PANDEMIC INFLUENZA H1N1v VIRUSES (NIID)

Antigens	Passage History (E: Egg/C: MDCK)	Ferret Antisera			
		Brisbane/59/2007 (H1N1)	California/07/2009 (H1N1)pdmE2+1 No.1	Narita/1/2009 (H1N1)pdmE1 No.3	Narita/1/2009 (H1N1)pdm C1 No.6
Refference Antigens					
Brisbane/59/2007 (H1N1)	E4	640	<10	<10	<10
California/07/2009 (H1N1)pdm	E2+2	<10	1280	5120	1280
Narita/1/2009 (H1N1)pdm	E2	<10	1280	2560	1280
Narita/1/2009 (H1N1)pdm	C2	<10	1280	5120	2560
Test Antigens					
TN/1-560/2009 (H1N1)pdm	E3	<10	2560	5120	2560
Sapporo/1/2009 (H1N1)pdm	C1	<10	2560	5120	5120
Akita/1/2009 (H1N1)pdm	C1	<10	2560	5120	2560
Niigata-C/1/2009 (H1N1)pdm	C1	<10	2560	5120	2560
Utsunomiya/1/2009 (H1N1)pdm	C1	<10	1280	5120	2560
Utsunomiya/2/2009 (H1N1)pdm	C1	<10	1280	10240	5120
Shizuoka/759/2009 (H1N1)pdm	C1	<10	1280	2560	1280

TRANSMISSION EXPERIMENTAL DESIGN

Respiratory Droplet (RD)

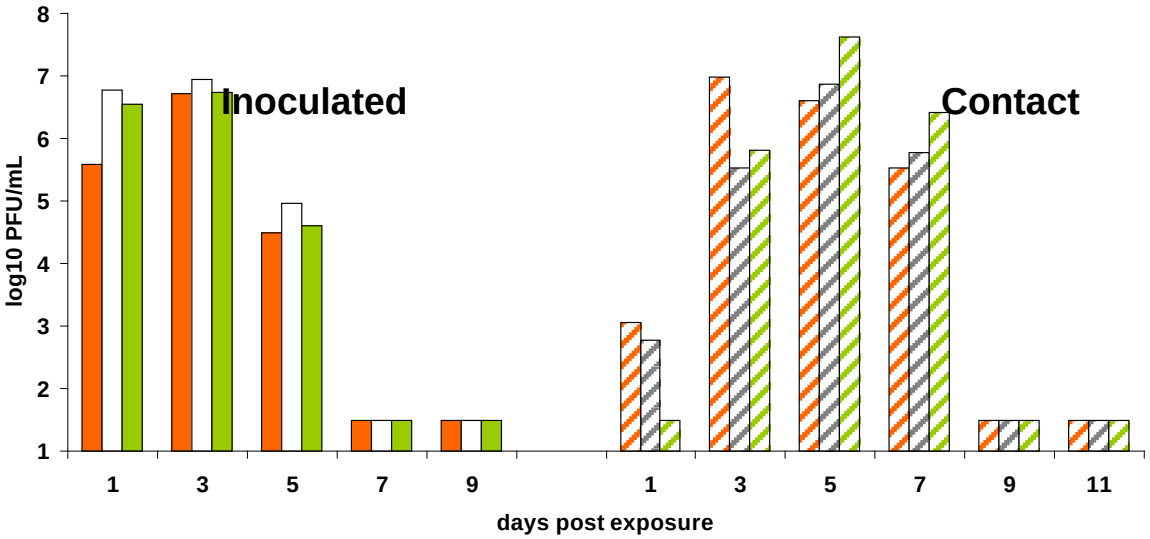
Inoculated	Contact
Inoculated	Contact
Inoculated	Contact

Direct Contact (DC)

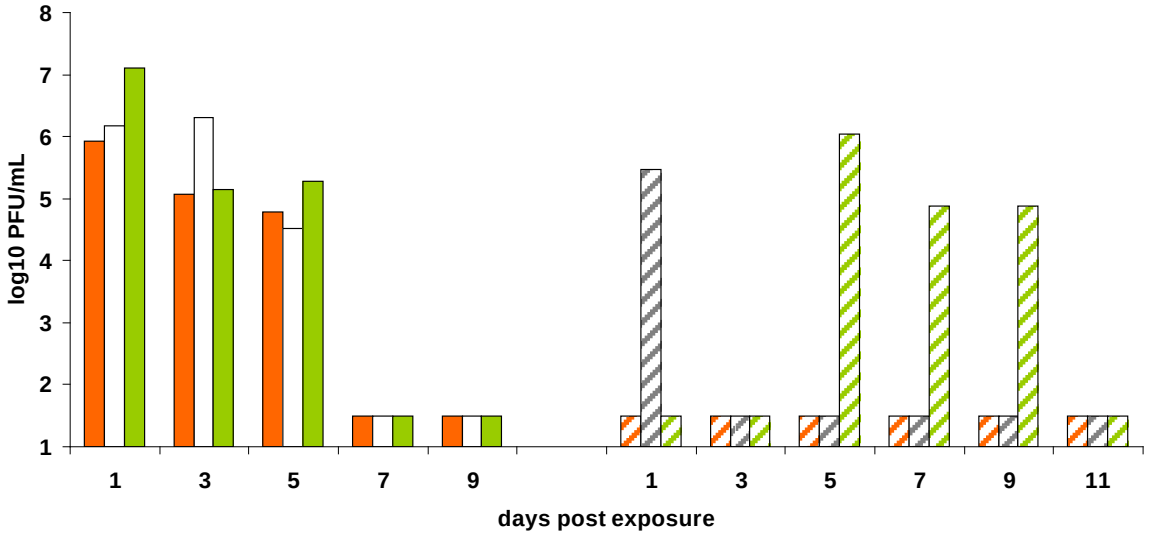
Inoc	Cont
Inoc	Cont
Inoc	Cont

RESPIRATORY DROPLET TRANSMISSION OF 2009 PANDEMIC INFLUENZA A(H1N1)

Seasonal H1N1



Pandemic H1N1



PATHOGENESIS AND TRANSMISSIBILITY OF 2009 PANDEMIC INFLUENZA A(H1N1) VIRUSES IN FERRETS

- Compared with seasonal A(H1N1) influenza, two novel H1N1 viruses caused
  - Increased morbidity
  - Replicated to higher titers in lung tissue
  - Recovered from the intestinal tract of intranasally inoculated ferrets
- Results suggest higher virulence of novel H1N1 compared to seasonal H1N1 in the ferret model

KEY QUESTIONS REMAINING FOR EFFECTIVE 2009 H1N1 RESPONSE

- Timing of expected fall wave of 2009 H1N1 in the NH?
  - Timing and dosing for 2009 H1N1 monovalent vaccine, if recommended, based on clinical trial data?
  - Target populations for 2009 H1N1 vaccine?
  - Will reassortment occur with 0-resistant seasonal influenza viruses or with H5N1 viruses?
  - How will antiviral drugs be used, assuming they are effective?
  - Effectiveness of non-pharmaceutical interventions?