

Review of Avian Influenza A(H5N1) for WHO SAGE

**SAGE
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SAGE WG on Influenza Vaccines and Immunizations Background for HPAI A(H5N1) vaccine discussions

- HPAI A(H5N1) viruses remain a pandemic threat
- H5N1 vaccines are recognized as a potentially important tool in protecting exposed persons and reducing illness during an H5N1 pandemic
- H5N1 vaccine recommendations depend *in part* on assessment of current/future threat posed by H5N1
 - Changing epidemiology (risk, risk factors)
 - Disease severity
 - Virus evolution
 - Vaccine availability, safety, estimated effectiveness
 - Programmatic issues



SAGE H5N1 Background

EPIDEMIOLOGY

Relevant question:

What is the current / future threat represented by H5N1?



Review of human H5N1 Cases

- May - Dec. 1997, Hong Kong: 18 cases, 6 deaths
- Jan - Feb. 2003, Hong Kong: 2 confirmed cases, 1 death
- November 2003 to October 2013:
 - 641 confirmed cases (15 countries)*
 - 380 deaths (59%)
 - Mostly sporadic cases (children, young adults)
 - Case clusters**
 - Most are due to common poultry exposures
 - Limited human-to-human H5N1 virus transmission
 - 2nd generation (most clusters)
 - Two clusters of 3rd generation transmission (Pakistan, Indonesia)
 - Wintertime seasonality – poultry and human cases
 - Most cases among children and young adults
 - Median age – 18-20y

* WHO, Oct 17, 2013

** Ungchusak et al., NEJM 2005; Kandun et al. NEJM 2006; Wang et al., Lancet 2008; WER 2009; WHO, unpublished data



Cumulative number of confirmed human cases for avian influenza A(H5N1) reported to WHO, 2003-2013

Country	2003-2009*		2010		2011		2012		2013		Total	
	cases	deaths	cases	deaths	cases	deaths	cases	deaths	cases	deaths	cases	deaths
Azerbaijan	8	5	0	0	0	0	0	0	0	0	8	5
Bangladesh	1	0	0	0	2	0	3	0	1	1	7	1
Cambodia	9	7	1	1	8	8	3	3	17	10	38	29
China	38	25	2	1	1	1	2	1	2	2	45	30
Djibouti	1	0	0	0	0	0	0	0	0	0	1	0
Egypt	90	27	29	13	39	15	11	5	4	3	173	63
Indonesia	162	134	9	7	12	10	9	9	1	1	193	161
Iraq	3	2	0	0	0	0	0	0	0	0	3	2
Lao People's Democratic Republic	2	2	0	0	0	0	0	0	0	0	2	2
Myanmar	1	0	0	0	0	0	0	0	0	0	1	0
Nigeria	1	1	0	0	0	0	0	0	0	0	1	1
Pakistan	3	1	0	0	0	0	0	0	0	0	3	1
Thailand	25	17	0	0	0	0	0	0	0	0	25	17
Turkey	12	4	0	0	0	0	0	0	0	0	12	4
Viet Nam	112	57	7	2	0	0	4	2	2	1	125	62
Total	468	282	48	24	62	34	32	20	27	18	637	378

* 2003-2009 total figures. Breakdowns by year available on next table

Total number of cases includes number of deaths
WHO reports only laboratory cases
All dates refer to onset of illness

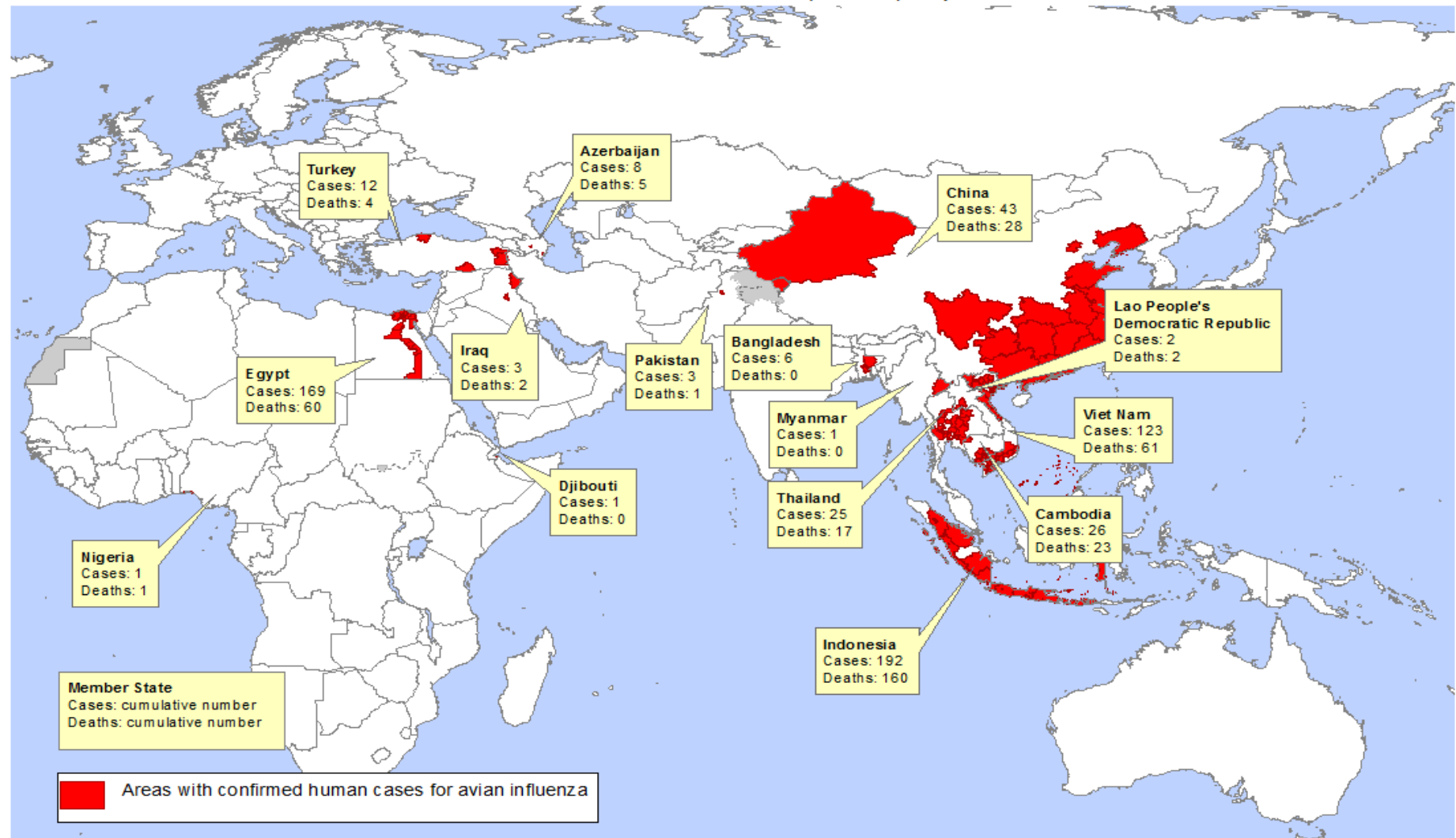
Source: WHO/GIP, data in HQ as of 29 August 2013

- Since 2010, cases confirmed in 6 countries (compared with 15 between 2003-9)
- Fewer cases reported in 2012 and 2013 than any year since emergence

Worldwide H5N1 Outbreak in Humans: 2003 - 2013

Source: WHO (http://gamapserver.who.int/mapLibrary/Files/Maps/2003_AvianInfluenza_GlobalMap_01Feb13.png)

Areas with confirmed human cases for avian influenza A(H5N1) reported to WHO, 2003-2013*

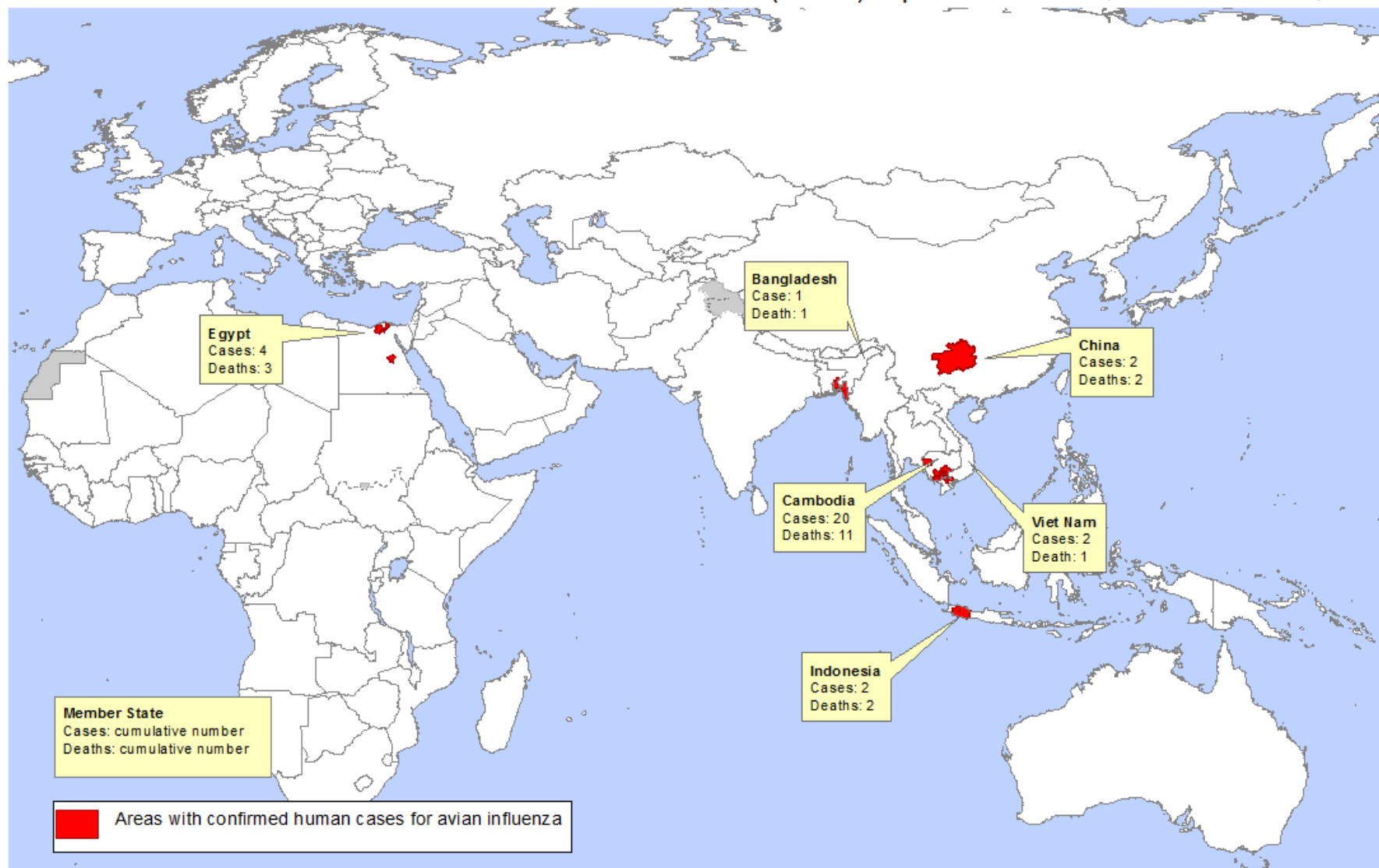


*All dates refer to onset of illness
Data as of 01 February 2013
Source: WHO/HIP

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Areas with confirmed human cases for avian influenza A(H5N1) reported to WHO, 2013- to-date*,

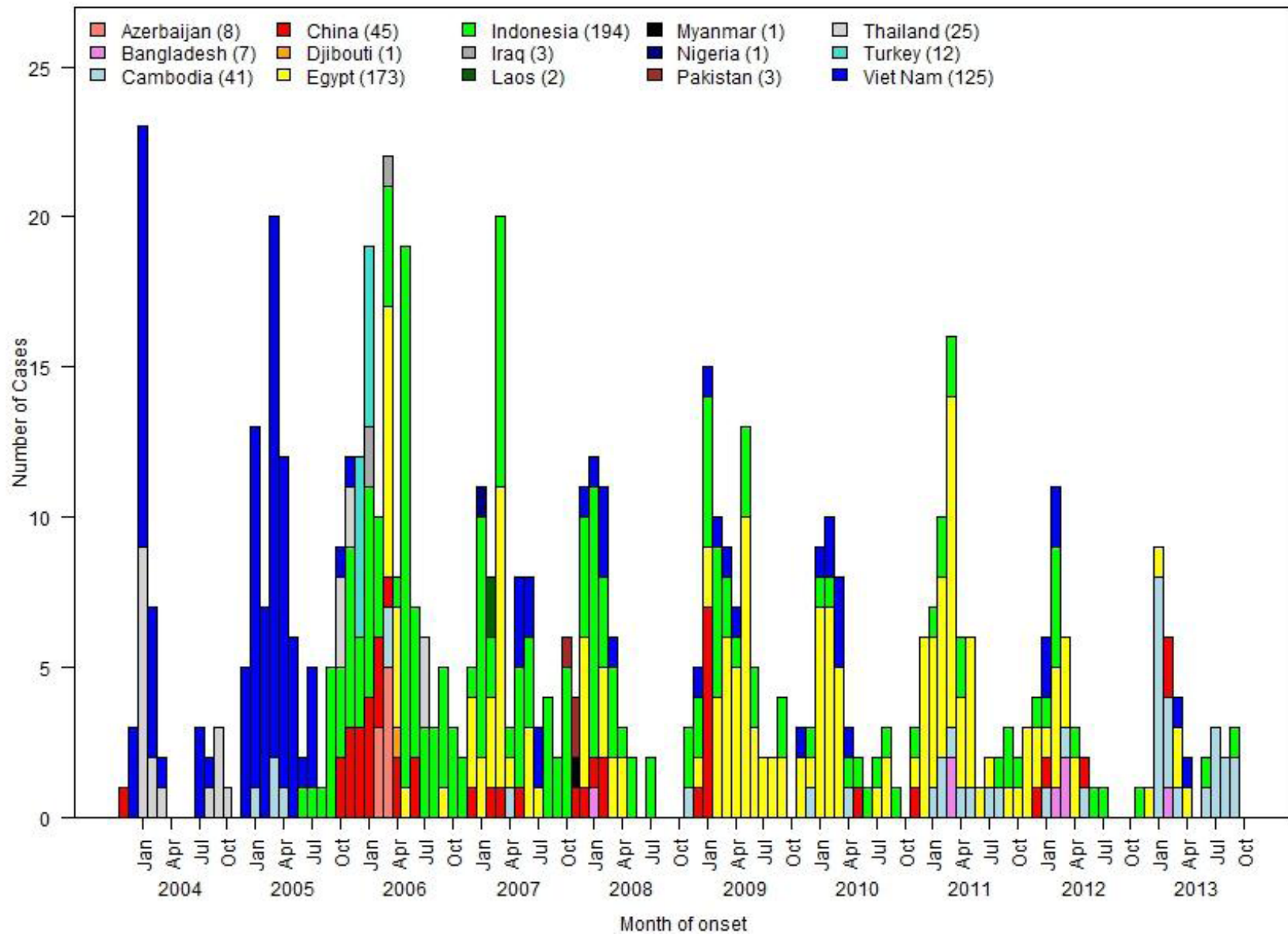


*All dates refer to onset of illness
Data as of 08 October 2013
Source: WHO/GIP

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**Number of Confirmed Human H5N1 Cases
by month of onset as of 2013-10-09**



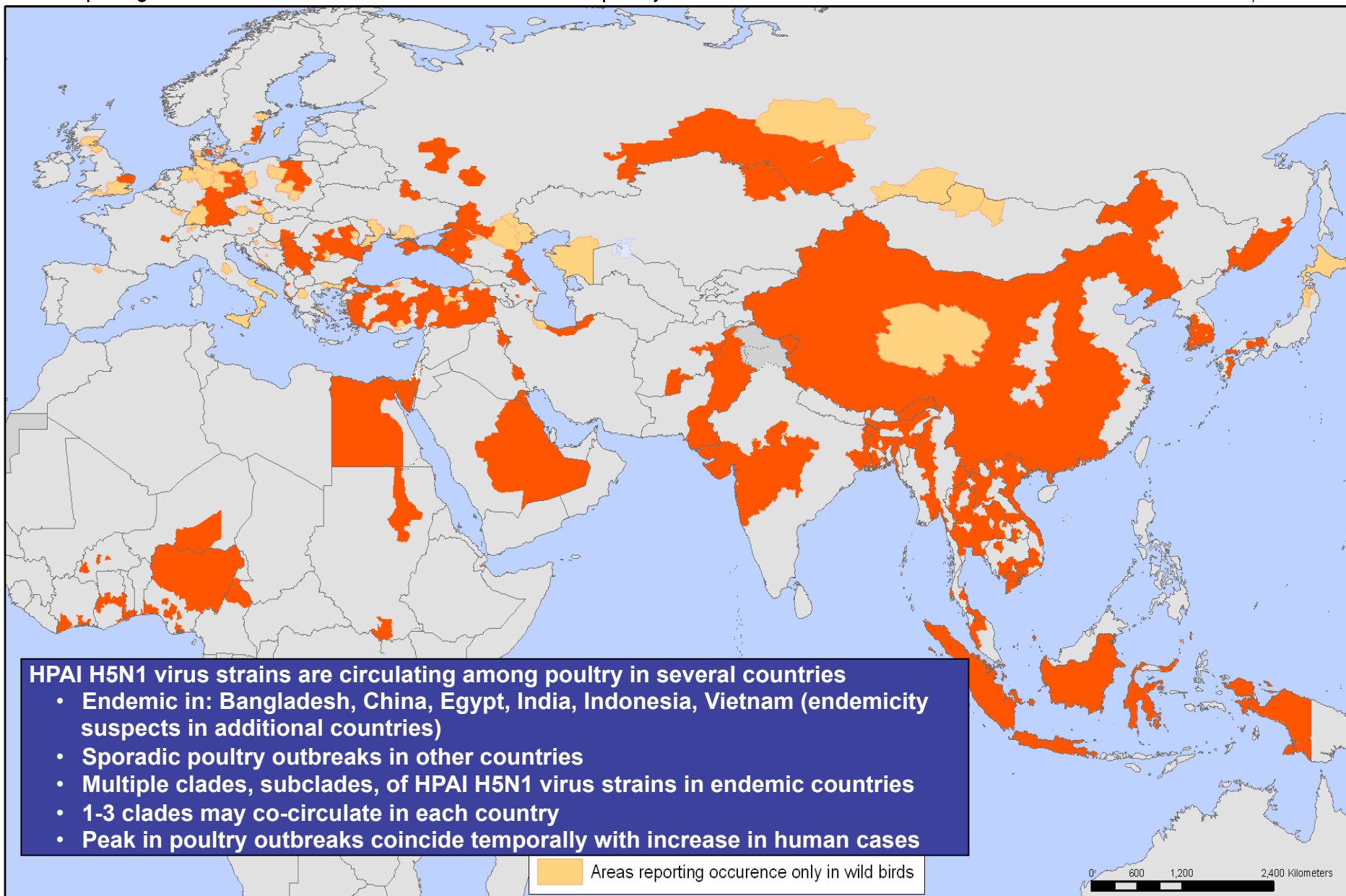
Source: http://www.who.int/influenza/human_animal_interface/Influenza_Summary_IRA_HA_interface_7October13.pdf

Risk factors for human infections with HPAI A(H5N1)

- Direct and close contact with sick or dead poultry
- Exposure to environments contaminated by infected poultry
- Visiting a live poultry market
- Few cases with occupational exposure
- Late presentation/hospitalization/delayed treatment – RF for death

Some cases without identified exposure source





SAGE H5N1 Background

CLINICAL FEATURES

Relevant questions:

How severe is a case? Has case severity changed?



H5N1 in Humans: Clinical Features

- Case fatality proportion: 59% (annual range -)
- Incubation: median = 3 days (2-9 d)
- Presenting symptoms, signs:
 - Fever, cough, shortness of breath, myalgia
 - Diarrhea
 - Leukopenia, lymphopenia, thrombocytopenia
- Pneumonia, acute respiratory disease syndrome, multi-organ failure



- Studies suggest very low rate of mild or asymptomatic infection



Refs: 19-22. 26, 27 in Background document



SAGE H5N1 Background

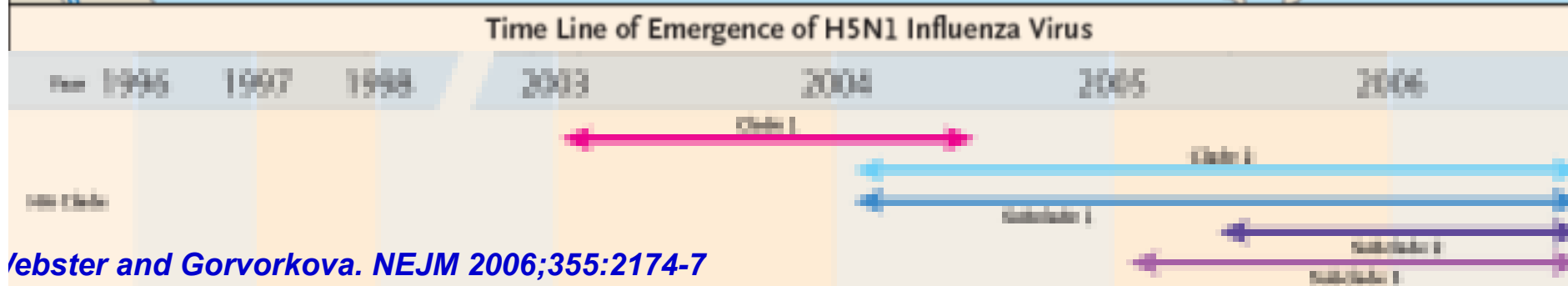
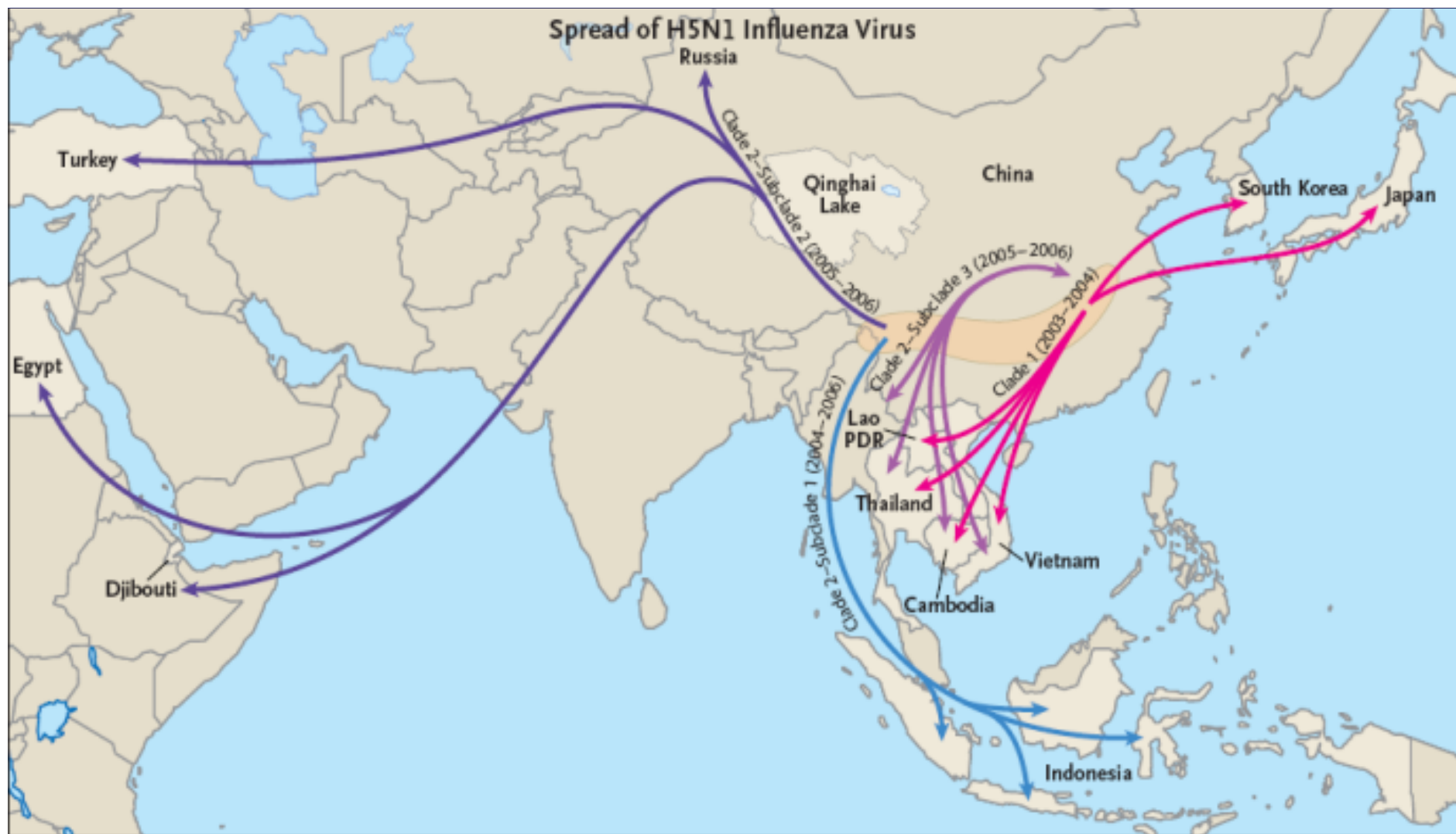
VIROLOGIC FEATURES

Relevant questions:

Are strains evolving?

Are strains becoming more antigenically diverse?

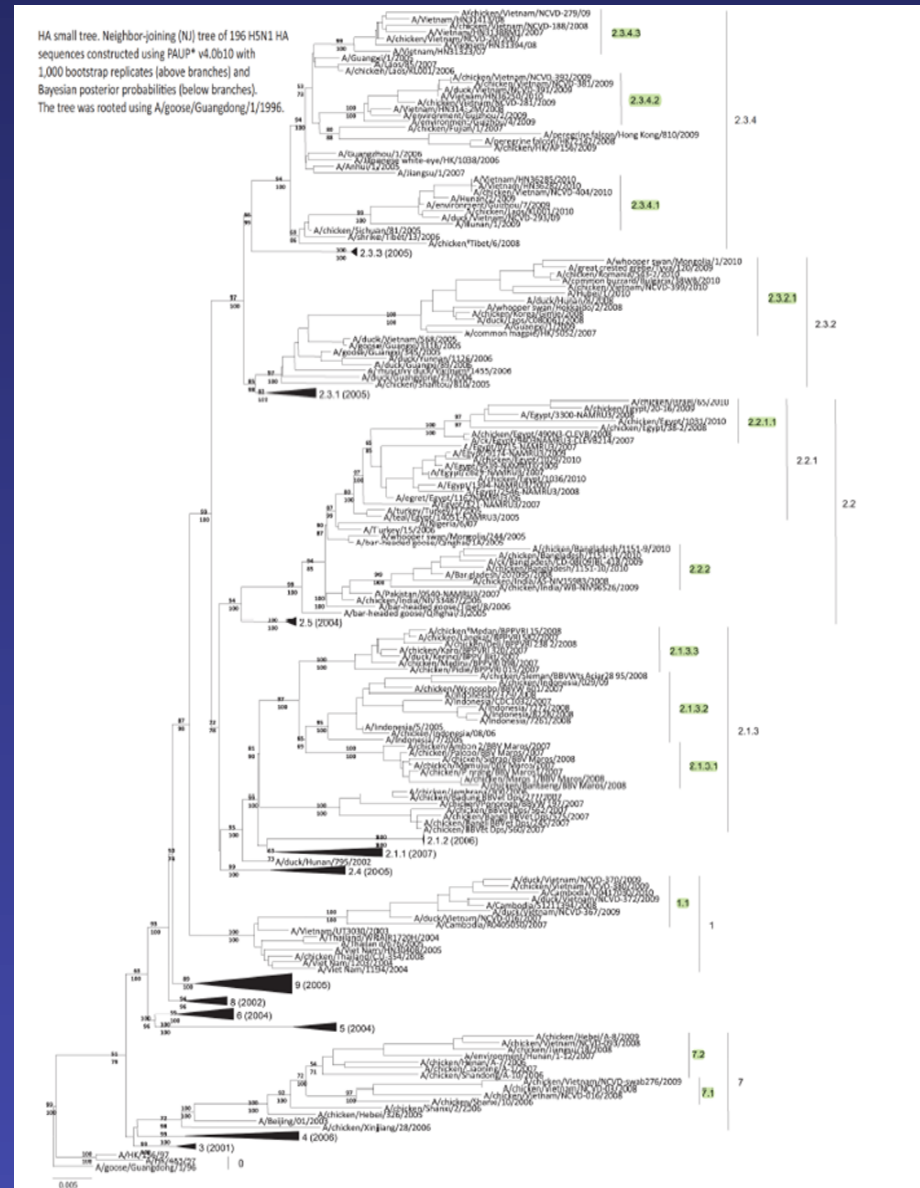




Webster and Gorkovkova. NEJM 2006;355:2174-7

HPAI H5N1 Virus is a Moving Target

- >20 different virus genetic groups (clades) identified in poultry, wild birds since 1997
 - Widespread geographic expansion since 2005
 - Many have not been detected since 2008
 - Continued evolution of viruses



A(H5N1) activity

Country, area or territory	Host (# Cases)	Genetic clade [info]
Bangladesh	Poultry Human (3)	2.3.2.1 2.3.2.1 [3] #
Bhutan	Poultry	2.3.2.1
Cambodia	Poultry Human (2)	1.1 1.1 [2]
China	Poultry	2.3.2.1 & 7.2
China, Hong Kong SAR	Wild birds Human (1)	2.3.2.1 2.3.2.1 [1]
Egypt	Poultry Humans (5)	2.2.1 2.2.1 [2]
India	Poultry Wild birds	2.3.2.1 2.3.2.1
Indonesia	Poultry Humans (5)	unknown 2.1.3.2 [1]
Israel	Poultry Feline	2.2.1 2.2.1
Myanmar	Poultry	2.3.4.2
Nepal	Poultry Wild birds	2.3.2.1 2.3.2.1
Viet Nam	Poultry Humans (1)	1.1 & 2.3.2.1 1.1 [1]



SAGE H5N1 Background

VACCINES

Relevant questions:

Are vaccines available for stockpiling?

How to determine which vaccines to stockpile?



Licensed H5 influenza vaccines

Source: WHO

Type	Producer (country)	Commercial name	Subtype	Strain	Substrate	Adjuvant	Dose (HA content in µg)
Inactivated whole virion	Baxter (Austria)	Pandemic Influenza Vaccine H5N1 Baxter	H5N1	A/Vietnam/1203/2004	Vero cells	None	7.5
	Baxter Innovations GmbH (Austria)	Vepacel	H5N1	A/Vietnam/1203/2004	Vero cells	None	7.5
	Biken (Japan)	Adsorbed Influenza Vaccine (H5N1) "BIKEN"	H5N1	A/Vietnam/1194/2004	Eggs	Al(OH) ₃	3, 30
	Denka Seiken (Japan)	Adsorbed Influenza Vaccine (H5N1) "Seiken"	H5N1	A/Vietnam/1194/2004	Eggs	Al(OH) ₃	
	Kitasato Institute (Japan)	Adsorbed Pandemic Influenza Vaccine (H5N1) "Hokken"	H5N1	A/Viet Nam/1194/2004	Eggs	Al(OH) ₃	30
	Kaketsuken (Japan)	Adsorbed Pandemic Influenza Vaccine (H5N1)"Kaketsuken"	H5N1		Eggs	Al(OH) ₃	
	Valneva (France), Kaketsuken (Japan) & GSK (Belgium)		H5N1		EB66® cell line	ASO ₃	
	Omninvest (Hungary)	Fluval H5N1	H5N1	A/Vietnam/1194/2004	Eggs	AlPO ₄	6
	Sinovac Biotech (China)	Panflu	H5N1	A/Vietnam/1194/2003	Eggs	Al(OH) ₃	15
	RIBSP (Kazakhstan)	Kazfluvac®	H5N1	A/Astana RG/6:2/2009	Eggs	Al(OH) ₃	
Inactivated split virion	GSK Biologicals (Belgium)	Adjupanrix / Qpan	H5N1	A/Vietnam/1194/2004	Eggs	ASO ₃	3.75
	GSK Biologicals (Belgium)	Prepandrix	H5N1	A/Indonesia/05/2005	Eggs	ASO ₃	3.75
	GSK Biologicals (Belgium)	Pumarix	H5N1	A/Indonesia/05/2005	Eggs	ASO ₃	3.75
	CSL Ltd (Australia)	Panvax	H5N1	A/Vietnam/1194/2004	Eggs	Al(OH) ₃	30
	Sanofi Pasteur (France)		H5N1		Eggs		
	Sanofi Pasteur (USA)	Sanofi pasteur Influenza Virus Vaccine, H5N1	H5N1	A/Vietnam/1203/2004	Eggs	None	90
Inactivated subunit	Microgen (Russia)	OrniFlu®	H5N1	A/Vietnam/1194/2004	Eggs	Al(OH) ₃	2 x 15
	Novartis V&D (Italy)	Prepandemic influenza vaccine (H5N1)	H5N1	A/Vietnam/1194/2004	Eggs	MF59C.1	7.5
	Novartis V&D (Italy)	Foclivia	H5N1	A/Vietnam/1194/2004	Eggs	MF59C.1	7.5
Inactivated surface antigen	Novartis V&D (Italy)	Aflunov	H5N1	A/turkey/Turkey/1/05		MF59C.1	7.5
Live-attenuated	Microgen (Russia), Institute of Experimental Medicine (Russia)	Ultragrivak®	H5N2	A/17/Duck/Potsdam/88/92 (H5N2) x Len 17 (H2N2)	Eggs	None	10 ^{8.3} TCID ₅₀

A(H5N1) Candidate Vaccine Viruses

Status of A(H5N1) candidate vaccine virus development

Candidate vaccine viruses	Clade	Institution*	Available
A/Viet Nam/1203/2004 (CDC-RG; SJRG-161052)	1	CDC and SJCRH	Yes
A/Viet Nam/1194/2004 (NIBRG-14)	1	NIBSC	Yes
A/Cambodia/R0405050/2007 (NIBRG-88)	1.1	NIBSC	Yes
A/duck/Hunan/795/2002 (SJRG-166614)	2.1	SJCRH	Yes
A/Indonesia/5/2005 (CDC-RG2)	2.1.3.2	CDC	Yes
A/Indonesia/NIHRD11771/2011 (NIIDRG-9)	2.1.3.2	NIID	Yes
A/bar-headed goose/Qinghai/1A/2005 (SJRG-163222)	2.2	SJCRH	Yes
A/chicken/India/NIV33487/2006 (IBCDC-RG7)	2.2	CDC/NIV	Yes
A/whooper swan/Mongolia/244/2005 (SJRG-163243)	2.2	SJCRH	Yes
A/Egypt/2321-NAMRU3/2007 (IDCDC-RG11)	2.2.1	CDC	Yes
A/turkey/Turkey/1/2005 (NIBRG-23)	2.2.1	NIBSC	Yes
A/Egypt/N03072/2010 (IDCDC-RG29)	2.2.1	CDC	Yes
A/Egypt/3300-NAMRU3/2008 (IDCDC-RG13)	2.2.1.1	CDC	Yes
A/common magpie/Hong Kong/5052/2007 (SJRG-166615)	2.3.2.1	SJCRH	Yes
A/Hubei/1/2010 (IDCDC-RG30)	2.3.2.1	CDC	Yes
A/barn swallow/Hong Kong/D10-1161/2010 (SJ-003)	2.3.2.1	SJCRH	Yes
A/chicken/Hong Kong/AP156/2008 (SJ-002)	2.3.4	SJCRH	Yes
A/Anhui/1/2005 (IBCDC-RG6)	2.3.4	CDC	Yes
A/duck/Laos/3295/2006 (CBER-RG1)	2.3.4	FDA	Yes
A/Japanese white eye/Hong Kong/1038/2006 (SJRG-164281)	2.3.4	SJCRH	Yes
A/goose/Guiyang/337/2006 (SJRG-165396)	4	SJCRH	Yes
A/chicken/Viet Nam/NCVD-016/2008 (IDCDC-RG12)	7.1	CDC	Yes
A/chicken/Viet Nam/NCDV-03/2008 (IDCDC-RG25A)	7.1	CDC	Yes
Candidate vaccine viruses in preparation	Clade	Institution	Availability
A/chicken/Bangladesh/11RS1984-30/2011-like	2.3.4.2	CDC	Pending
A/Guizhou/1/2013-like	2.3.4.2	CDC/CCDC	Pending
A/duck/Bangladesh/19097/2013-like	2.3.2.1	SJCRH	Pending
A/duck/Viet Nam/NCVD-1584/2012-like	2.3.2.1	NIBSC	Pending
A/Cambodia/W0526301/2012-like	1.1	CDC	Pending

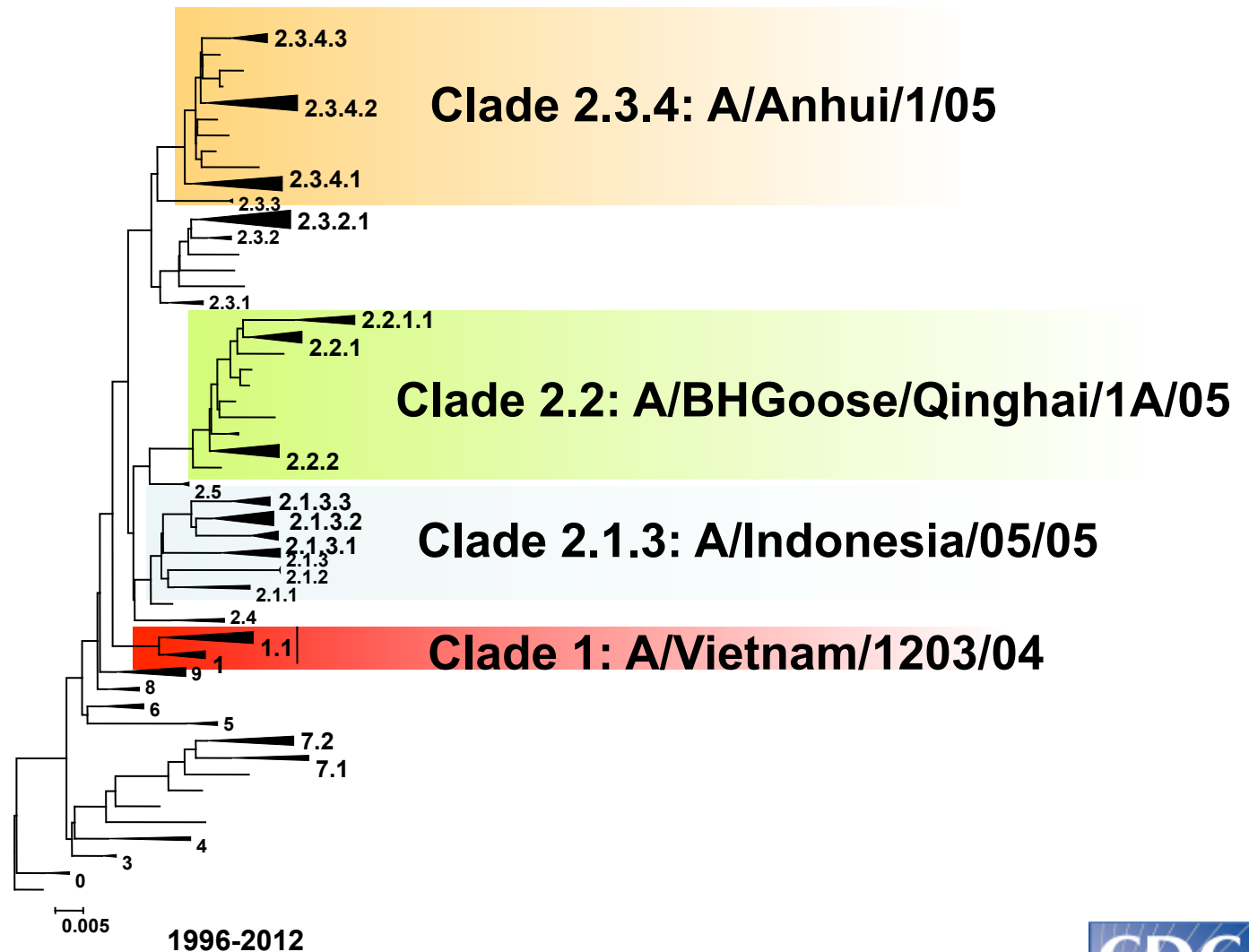
H5N1 vaccines

- Safety
 - Similar safety profiles to comparable seasonal influenza vaccines.
 - Association of adjuvanted pandemic H1N1 vaccine (Pandemrix, GSK) highlights the need for vigorous pre and post-licensure safety assessments
- Efficacy
 - No efficacy / effectiveness data available

H5N1 vaccines - immunogenicity

- H5 HA less immunogenic compared with seasonal influenza virus HA
 - Reduces the vaccine doses available for response
- Strategies to improve immune response
 - Two-dose schedule of high doses vaccines (e.g. 90mcg)
 - Adjuvants
 - Enhance, broaden and increase duration of immune response
 - Allows for lower Ag content in vaccine
 - Oil-in-water adjuvants can reliably increase response
 - Prime - boost
 - Can produce more robust, rapid and durable response
 - Can boost with heterologous vaccine to achieve heterotypic immune response

US HHS H5N1 Pandemic Vaccine Stockpile



Summary

- **Epidemiology and clinical characteristics largely unchanged in recent years**
 - Sporadic human illness caused by infection with HPAI H5N1 virus continues to occur and be identified
 - Children, young adults
 - Exposure to sick/dead poultry continues to be major risk factor
 - Seasonality continues (colder periods)
- **Relatively fewer cases in recent 2 years compared with previous years**
- **Risk remains**
 - Humans exposed, especially in endemic countries
 - Viruses continue to evolve

Summary (2)

- **Several vaccine licensed**
 - Although not currently produced
- **Vaccine seed strains produced against several clades**
- **H5 HA Ags poorly immunogenic in naïve hosts**
 - Requires multiple doses, higher Ag content, adjuvants to produce acceptable immune responses
 - Limited heterotypic immune response
 - Adjuvants, prime-boost strategies required for cross protection