Antigenic and genetic characteristics of zoonotic influenza viruses and development of candidate vaccine viruses for pandemic preparedness

February 2013

The development of representative candidate influenza vaccine viruses, coordinated by the World Health Organization (WHO), remains an essential component of the overall global strategy for pandemic preparedness. Comparisons of the candidate vaccine viruses with respect to antigenicity and their relationship to newly emerging viruses are ongoing and will be reported periodically by WHO.

Influenza A(H5N1)

Since their re-emergence in 2003, highly pathogenic avian influenza A(H5N1) viruses have become enzootic in some countries and continue to cause outbreaks in poultry as well as sporadic human infections. The A(H5N1) viruses have diversified both genetically and antigenically leading to the need for multiple candidate vaccine viruses for pandemic preparedness purposes. This summary provides updates on the characterization of A(H5N1) viruses isolated from birds and humans, and the current status of the development of influenza A(H5N1) candidate vaccine viruses.

Influenza A(H5N1) activity from 19 September 2012 to 18 February 2013

A(H5N1) viruses have been detected in birds in Africa and Asia. Human infections have been reported to the WHO by Cambodia, China, Egypt and Indonesia, countries in which infections have also been detected in birds (Table 1).

Table 1. Recent A(H5N1) activity reported to international agencies

Country, area or territory	Host/Source	Genetic clade
Bangladesh	Poultry	2.3.2.1
Bhutan	Poultry	2.3.2.1
Cambodia	Poultry	1.1
	Human (7)#	1.1
China	Human (2)	2.3.4.2
	Environmental	2.3.2.1/2.3.4.2
China Hong Kong SAR	Wild bird	2.3.2.1
Egypt	Poultry	2.2.1
	Human (2)	2.2.1
India	Poultry	2.3.2.1
Indonesia	Poultry	2.3.2.1
	Human (1)	unknown
Nepal	Poultry	2.3.2.1
Viet Nam	Poultry	1.1/2.3.2.1

# denotes number of human cases

Antigenic and genetic characteristics of A(H5N1) viruses

The nomenclature for phylogenetic relationships among the haemagglutinin (HA) genes of A(H5N1) viruses is defined in consultation with representatives of the WHO, the Food and Agriculture Organization of the United Nations (FAO), the World Organisation for Animal Health (OIE) and academic institutions. The updated nomenclature report can be found at http://www.who.int/influenza/gisrs_laboratory/h5n1_nomenclature/en/.

Viruses circulating and characterized from 19 September 2012 to 18 February 2013 belonged to the following clades.

Clade 1.1 viruses were detected in poultry and humans in Cambodia and in poultry in Viet Nam. Genetic characterization of the HA genes showed that these viruses were closely related to viruses detected previously in these countries (Figure 1) and which had reduced HI titres to post-infection ferret antisera raised against available candidate vaccine viruses. Antigenic analysis is ongoing and an additional candidate vaccine virus will be selected to provide improved coverage of recent clade 1.1 viruses.

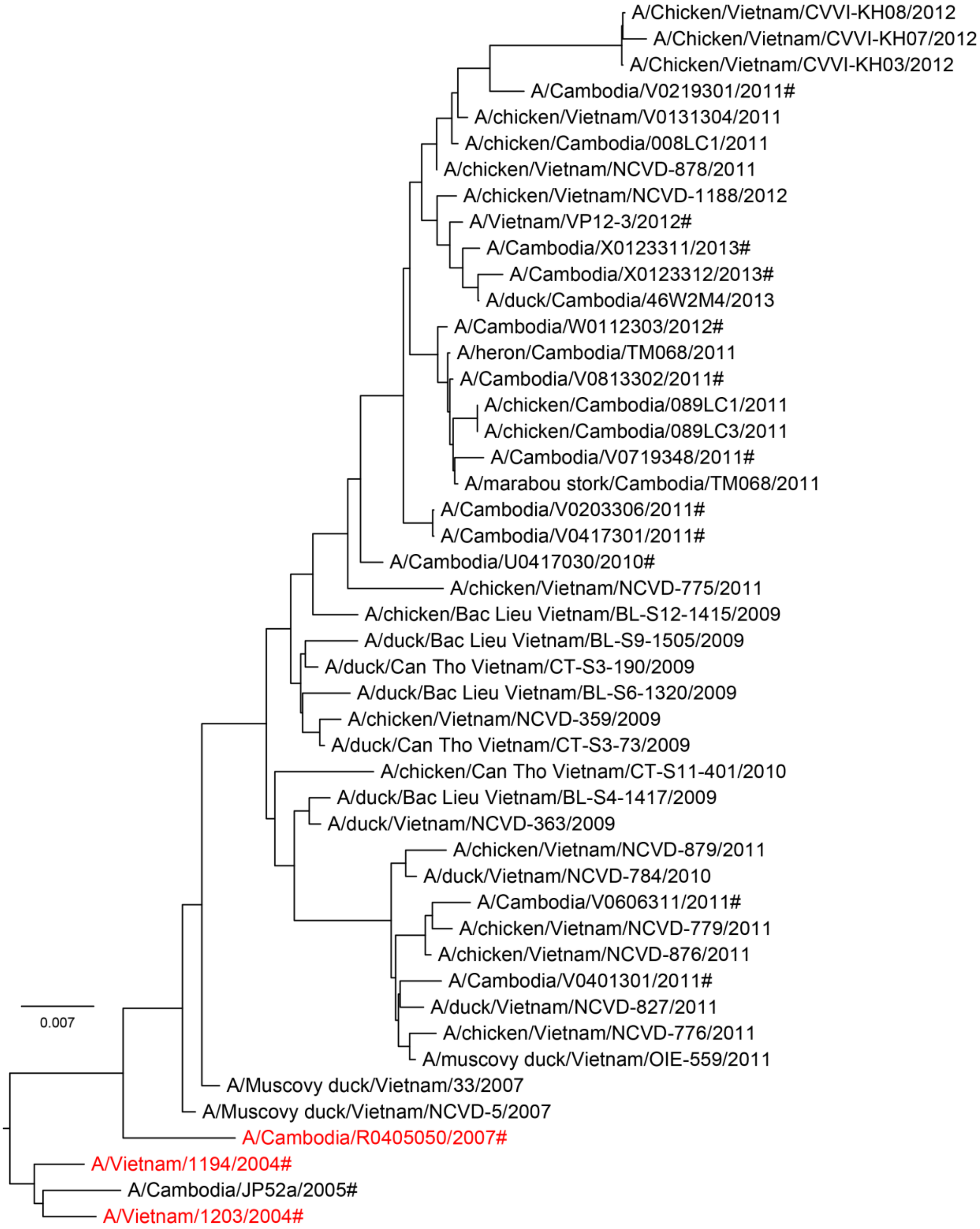

Figure 1. Phylogenetic relationships of A(H5N1) clade 1.1 virus HA genes. The available candidate vaccine viruses are in red. Human viruses are indicated (#). The scale bar represents the number of substitutions per site.

Clade 2.2.1 viruses were detected in poultry and humans in Egypt. While antigenic information on these viruses is unavailable at this time, those genetically analysed to date were shown to be similar to clade 2.2.1 viruses detected in previous years.

Clade 2.3.2.1 viruses were detected in birds and/or environmental samples in Bangladesh, Bhutan, China, India, Indonesia, Nepal, and Viet Nam. This clade continues to diversify genetically. A/barn swallow/Hong Kong/D10-1161/2010-like viruses were detected in Viet Nam and China Hong Kong Special Administrative Region (SAR) and the majority reacted well with post-infection ferret antiserum raised against the A/barn swallow/Hong Kong/D10-1161/2010 candidate vaccine virus. A/Hubei/1/2010-like viruses were detected in Bangladesh, Bhutan, China, India, Nepal, and Viet Nam with the majority reacting well with post-infection ferret antisera raised against available candidate vaccine viruses. Some A/Hubei/1/2010-like viruses from Viet Nam, however, showed significant antigenic divergence from vaccine candidates and further characterization of this group is being conducted. A/Hong Kong/6841/2010-like viruses were detected in Viet Nam and for the first time in Indonesia (Figure 2): these viruses react with post-infection ferret antisera raised against the candidate vaccine virus A/common magpie/Hong Kong/5052/2007 albeit with reduced titres (Table 2).

Table 2. Haemagglutination inhibition reactions of influenza A(H5N1) Clade 2.3.2.1 viruses.

Reference Antigens (genetic cluster)	cm/HK	RG-30	bs/HK	bhg/MG	HK/6841	dk/VN
A/c magpie/Hong Kong/5052/2007	**1280**	80	40	640	640	320
A/Hubei/1/2010 IDCDC RG-30 (HUB)[#]	320	**320**	40	320	640	160
A/b swallow/Hong Kong/1161/2010 SJ003 (BS)	320	80	**80**	80	320	80
A/bh goose/Mongolia/X53/2009 (HK)	640	80	40	**320**	640	320
A/Hong Kong/6841/2010 (HK)	640	80	20	320	**320**	160
A/duck/Viet Nam/NCVD-1584/2012 (HK)	640	160	40	320	640	**320**
Test Antigens						
A/duck/Viet Nam/NCVD-1602/2012 (HK)	640	160	80	640	640	320
A/duck/Viet Nam/NCVD-1902/2012 (HK)	640	80	40	640	640	320
A/duck/Viet Nam/NCVD-1905/2012 (HK)	320	80	40	320	640	160
A/duck/Viet Nam/NCVD-1593/2012 (HK)	320	80	20	320	320	160
A/chicken/Viet Nam/NCVD-1927/2012 (HK)	320	80	20	320	320	160
A/duck/Viet Nam/NCVD-1872/2012 (HK)	320	80	40	320	320	160
A/duck/Viet Nam/NCVD-1869/2012 (HK)	320	40	20	160	320	160
A/duck/Viet Nam/NCVD-1901/2012 (HK)	320	40	20	160	320	160
A/duck/Viet Nam/NCVD-1884/2012 (HK)	160	40	10	160	320	80
A/duck/Viet Nam/NCVD-1878/2012 (HK)	320	40	10	80	160	40

HUB, A/Hubei/1/2010-like; BS, A/barn swallow/Hong Kong/1161/2010-like; HK, A/Hong Kong/6841/2010-like

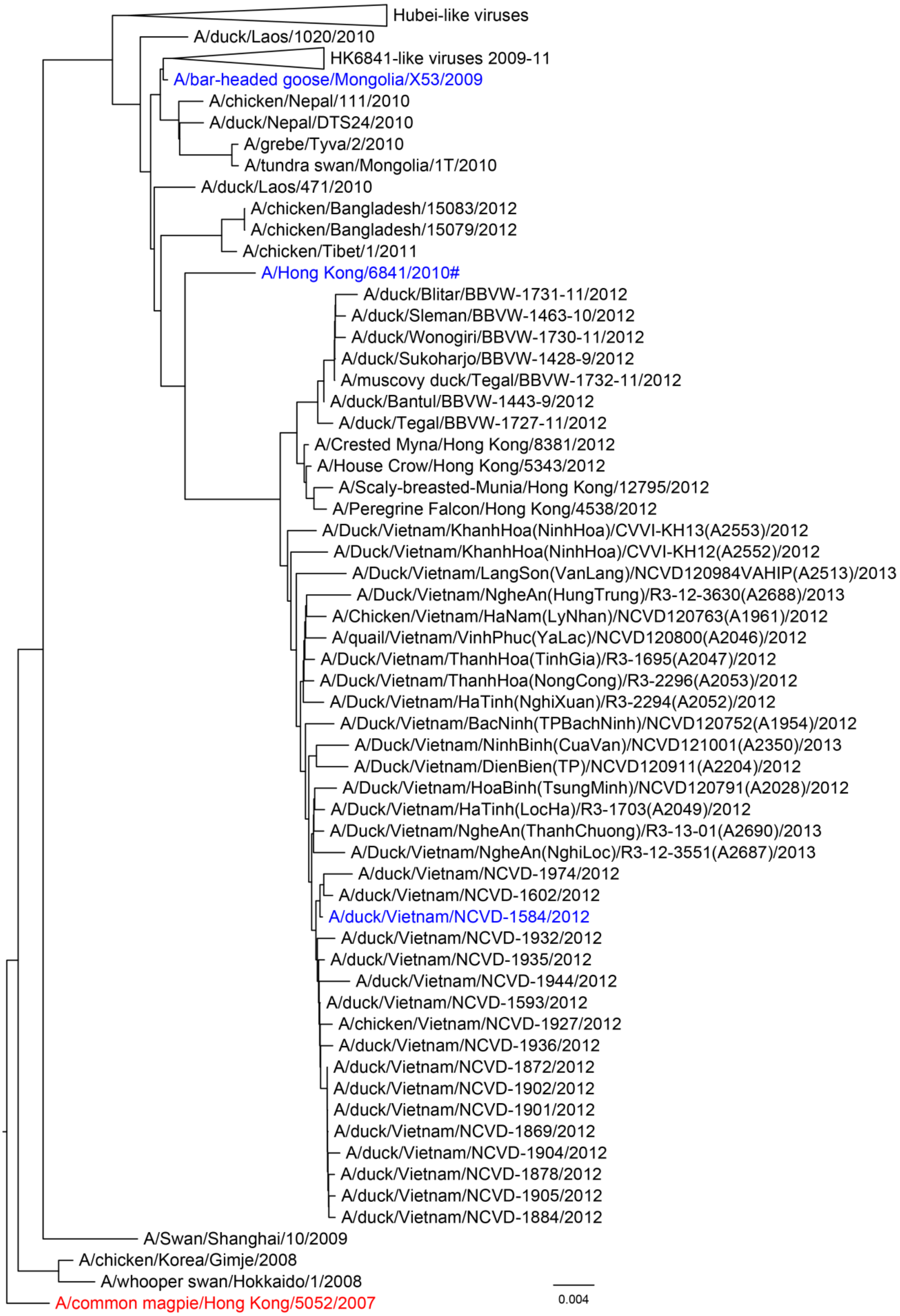

Figure 2. Phylogenetic relationships of A(H5N1) clade 2.3.2.1 A/Hong Kong/6841/2010-like virus HA genes. The available candidate vaccine viruses are in red and the HI reference viruses used in Table 2 are in blue. Human viruses are indicated (#). The scale bar represents the number of substitutions per site.

Clade 2.3.4.2 viruses were isolated from humans in Guizhou province China. These viruses were genetically similar to A/Guizhou/1/2012 (Figure 3) and showed reduced HI titres with post-infection ferret antisera raised against the candidate vaccine viruses A/Anhui/1/2005 and A/chicken/Hong Kong/AP156/2008 (Table 3).

Table 3. Haemagglutination inhibition reactions of influenza A(H5N1) Clade 2.3.4.2 viruses.

Reference antigens	Clade	Anhui/1/2005	ck/HK/AP156/2008
A/Anhui/1/2005	2.3.4	**80**	80
A/chicken/Hong Kong/AP156/2008	2.3.4	NA	**320**
Test antigens			
A/Guizhou/1/2012	2.3.4.2	<40	80
A/Guizhou/1/2013	2.3.4.2	<40	40
A/Guizhou/2/2013	2.3.4.2	<40	40

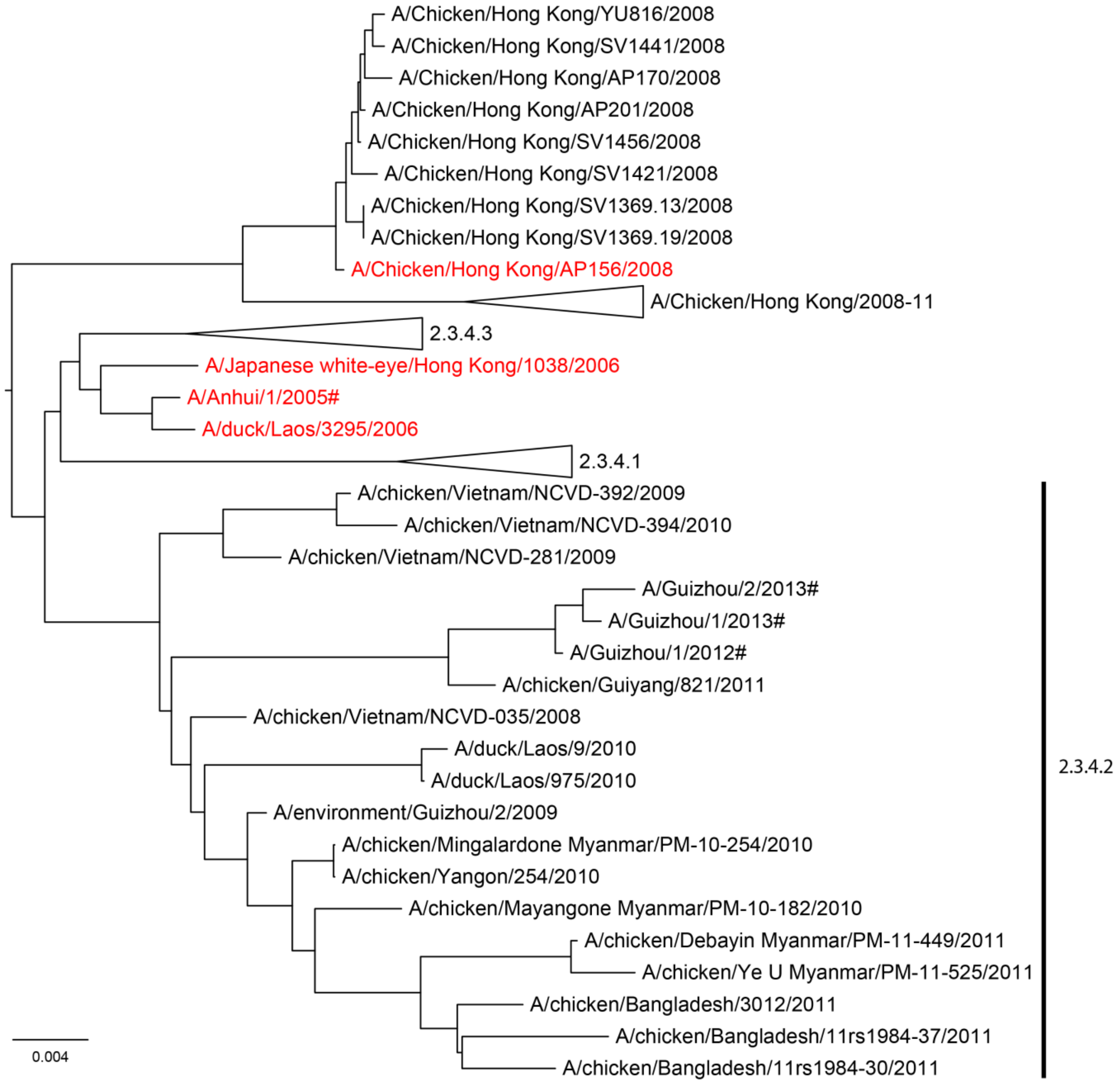

Figure 3. Phylogenetic relationships of A(H5N1) clade 2.3.4.2 HA genes. The available candidate vaccine viruses are in red. Human viruses are indicated (#). The scale bar represents the number of substitutions per site.

Influenza A(H5N1) candidate vaccine viruses

Based on the available antigenic, genetic and epidemiologic data, a new A/Guizhou/1/2013-like clade 2.3.4.2 candidate vaccine virus is proposed. The available and proposed candidate A(H5N1) vaccine viruses are listed in Table 4. On the basis of geographic spread, epidemiology and antigenic and genetic properties of the A(H5N1) viruses in particular locations, national authorities may consider the use of one or more of these candidate vaccine viruses for pilot lot vaccine production, clinical trials and other pandemic preparedness purposes.

As the viruses continue to evolve, new A(H5N1) candidate vaccine viruses will be developed and announced as they become available. Institutions that wish to receive these candidate vaccine viruses should contact WHO at gisrs-whohq@who.int or the institutions listed in announcements published on the WHO website[1].

Table 4. Status of A(H5N1) candidate vaccine virus development (February 2013)

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/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/Indonesia/NIHRD11771/2011-like	2.1.3.2	NIID	Pending
A/Guizhou/1/2013-like	2.3.4.2	CDC/CCDC	Pending

*** Institutions distributing the candidate vaccine viruses:**

CDC - Centers for Disease Control and Prevention, United States of America
CDC/NIV - Centers for Disease Control and Prevention, United States of America/National Institute of Virology, India
CDC/CCDC - Centers for Disease Control and Prevention, United States of America/China Center for Disease Control and Prevention
FDA - Food and Drug Administration, United States of America
NIBSC - National Institute for Biological Standards and Control, Health Protection Agency, United Kingdom of Great Britain and Northern Ireland
NIID- National Institute of Infectious Diseases, Japan
SJCRH - St Jude Children's Research Hospital, United States of America

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[1] http://www.who.int/influenza/vaccines/virus/en/

Influenza A(H9N2)

Influenza A(H9N2) viruses are enzootic in poultry populations in parts of Africa, Asia and the Middle East. The majority of viruses that have been sequenced belong either to the G1 clade or the chicken/Beijing (Y280/G9) clade. Since 1998, when the first human infection was detected, the isolation of A(H9N2) viruses from humans and swine has been reported infrequently. In all human cases the associated disease symptoms have been mild and there has been no evidence of human-to-human transmission.

Influenza A(H9N2) activity from 19 September 2012 to 18 February 2013

No human cases of A(H9N2) infections have been reported in this period. A(H9N2) viruses continue to be isolated from birds in many regions of the world.

Influenza A(H9N2) candidate vaccine viruses

Based on the current antigenic, genetic and epidemiological data, no new A(H9N2) candidate vaccine viruses are proposed. The available A(H9N2) candidate vaccine viruses are listed in Table 5. Institutions that wish to receive candidate vaccine viruses should contact WHO at gisrs-whohq@who.int or the institutions listed in announcements published on the WHO website[2].

Table 5. Status of A(H9N2) candidate vaccine virus development (February 2013)

Candidate vaccine viruses	Type	Clade	Institution*	Available
A/Hong Kong/1073/1999	Wild type	G1	NIBSC	Yes
A/chicken/Hong Kong/G9/1997 (NIBRG-91)	Reverse genetics	Y280/G9	NIBSC	Yes
A/chicken/Hong Kong/G9/1997 (IBCDC-2)	Conventional reassortant	Y280/G9	CDC	Yes
A/Hong Kong/33982/2009 (IDCDC-RG26)	Reverse genetics	G1	CDC	Yes
A/Bangladesh/0994/2011 (IDCDC-RG31)	Reverse genetics	G1	CDC	Yes

* **Institutions distributing the candidate vaccine viruses:**

CDC - Centers for Disease Control and Prevention, United States of America

NIBSC - National Institute for Biological Standards and Control, Health Protection Agency, United Kingdom of Great Britain and Northern Ireland

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[2] http://www.who.int/influenza/vaccines/virus/en/

Influenza A(H7N3)

Influenza A(H7) viruses cause sporadic outbreaks in poultry populations worldwide. Occasionally, during outbreaks in poultry, human cases are documented in those with direct poultry exposure. These infections often cause conjunctivitis with occasional respiratory disease[3,4].

Influenza A(H7N3) activity from 19 September 2012 to 18 February 2013

Highly pathogenic A(H7N3) viruses were detected in poultry in two states in Mexico and in poultry and a wild bird in a third. No human cases have been reported during this period.

Influenza A(H7) candidate vaccine viruses

Based on the current epidemiologic data, no new A(H7) candidate vaccine viruses are proposed. Available A(H7) candidate vaccine viruses are shown in Table 6. Institutions that wish to receive candidate vaccine viruses should contact WHO at gisrs-whohq@who.int or the institutions listed in announcements published on the WHO website[5].

Table 6. Status of A(H7) candidate vaccine virus development (February 2013)

Candidate vaccine viruses	Type	Institution*
A/turkey/Virginia/4529/2002 (H7N2) IBCDC-5	Conventional reassortant	CDC
A/mallard/Netherlands/12/2000 (H7N7) IBCDC-1	Conventional reassortant	CDC
A/mallard/Netherlands/12/2000 (H7N3) NIBRG-60	Reverse genetics	NIBSC
A/mallard/Netherlands/12/2000 (H7N1) NIBRG-63	Reverse genetics	NIBSC
A/Canada/RV444/2004 (H7N3)	Reverse genetics	SJCRH
A/New York/107/2003 (H7N2) NIBRG-109	Reverse genetics	NIBSC

* **Institutions distributing the candidate vaccine virus:**

CDC - Centers for Disease Control and Prevention, United States of America
NIBSC - National Institute for Biological Standards and Control, Health Protection Agency, United Kingdom of Great Britain and Northern Ireland
SJCRH - St Jude Children's Research Hospital, United States of America

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[3] Tweed, SA. et al. Human illness from avian influenza H7N3, British Columbia. 2004. Emerg Infect Dis. 10:2196.

[4] de Jong, MC. et al. Intra- and interspecies transmission of H7N7 highly pathogenic avian influenza virus during the avian influenza epidemic in the Netherlands in 2003. 2009. Rev Sci Tech. 28:333

[5] http://www.who.int/influenza/vaccines/virus/en/

Influenza A(H3N2) variant (v)[6]

Influenza A(H3N2) viruses are enzootic in swine populations in most regions of the world. Depending on geographic location, the genetic and antigenic characteristics of these viruses differ. Human infections with swine A(H3N2) viruses have been documented in Asia, Europe and North America[7].

Influenza A(H3N2)v activity from 19 September 2012 to 18 February 2013

One human case of A(H3N2)v infection was reported in the United States of America[8]. This virus was genetically and antigenically similar to previously characterized A(H3N2)v viruses. Similar viruses continue to be isolated from pigs in the United States of America.

Influenza A(H3N2)v candidate vaccine viruses

Based on the current antigenic, genetic and epidemiologic data, no new A(H3N2)v candidate vaccine viruses are proposed. Available candidate vaccine viruses are shown in Table 7. Institutions that wish to receive candidate vaccine viruses should contact WHO at gisrs-whohq@who.int or the institutions listed in announcements published on the WHO website[9].

Table 7. Status of A(H3N2)v candidate vaccine virus development (February 2013)

Candidate vaccine viruses	Type	Institution*
A/Minnesota/11/2010 (NYMC X-203)	Conventional reassortant	CDC
A/Indiana/10/2011 (NYMC X-213)	Conventional reassortant	CDC

* **Institutions distributing the candidate vaccine virus:**
CDC - Centers for Disease Control and Prevention, United States of America

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[6] http://www.who.int/influenza/gisrs_laboratory/terminology_ah3n2v/en/index.html

[7] Myers, KP. et al. Cases of Swine Influenza in Humans: A Review of the Literature. 2007. Clin Infect Dis. 44:1084.

[8] http://www.cdc.gov/flu/swineflu/h3n2v-situation.htm

[9] http://www.who.int/influenza/vaccines/virus/en/