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

September 2012

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 candidate A(H5N1) vaccine viruses.

Influenza A(H5N1) activity from 23 February to 18 September 2012

A(H5N1) viruses have been detected in birds in Africa, Asia and the Middle East, and from a cat in Israel. Human infections have been reported to the WHO by Bangladesh, Cambodia, China Hong Kong Special Administrative Region (China Hong Kong SAR), Egypt, Indonesia and Viet Nam, countries in which infections have also been detected in birds (Table 1).

Antigenic and genetic characteristics of influenza 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 23 February to 18 September 2012 belonged to the following clades.

Clade 1.1 viruses were detected in poultry and humans in Cambodia and Viet Nam. Genetic characterization of the HA genes showed that the human and poultry viruses were closely related to each other and to viruses detected previously in these countries. The recent avian viruses reacted well with post-infection ferret antisera raised against the clade 1 virus A/Viet Nam/1203/2004 from which candidate vaccine viruses have been developed.

Clade 2.1.3.2 viruses were detected in humans in Indonesia during this period. Genetic characterization of the HA genes of these viruses and recently circulating viruses from poultry showed that they were similar to previously reported clade 2.1.3.2 viruses but are divergent from A/Indonesia/5/2005, from which a candidate vaccine virus has been developed (Figure 1). Viruses isolated from humans during 2011 and 2012 showed reduced titres to post-infection ferret antiserum raised against the candidate vaccine virus developed from A/Indonesia/5/2005 (Table 2).

Clade 2.2.1 viruses were detected in poultry and humans in Egypt, and in poultry and a cat in Israel. Viruses detected during the period were genetically similar to those isolated previously from poultry and humans in the region. Three human viruses isolated in 2012 reacted well with post-infection ferret antiserum raised against A/Egypt/N03072/2010, a virus from which a candidate vaccine virus has been developed.

Clade 2.3.2.1 viruses were detected in wild birds in China Hong Kong SAR, India and Nepal, and in poultry in Bangladesh, Bhutan, China, India, Nepal and Viet Nam. Human cases were reported in Bangladesh and China Hong Kong SAR. Increased genetic heterogeneity in HA gene sequences was observed within recent viruses from this clade. Two genetic groups, A/Hubei/1/2010-like (Figure 2) and A/barn swallow/Hong Kong/D10-1161/2010-like (Figure 3), were previously identified. A third group, A/Hong Kong/6841/2010-like (Figure 4), is spreading in Southeast Asia. The human virus from China Hong Kong SAR and the majority of recent clade 2.3.2.1 avian viruses in the A/barn swallow/Hong Kong/D10-1161/2010-like genetic group reacted well with post-infection ferret antiserum raised against the candidate vaccine virus developed from A/barn swallow/Hong Kong/D10-1161/2010. The majority of recent avian viruses from the A/Hubei/1/2010-like genetic group reacted well with post-infection ferret antiserum raised against the candidate vaccine virus developed from A/Hubei/1/2010. No viruses were isolated from the human cases in Bangladesh. Recent avian viruses from the A/Hong Kong/6841/2010-like genetic group reacted well with post-infection ferret antiserum raised against the candidate vaccine virus developed from the clade 2.3.2.1 virus A/common magpie/Hong Kong/5052/2007.

Clade 2.3.4.2 viruses were isolated from poultry in Myanmar. Genetically these viruses were similar to A/chicken/Bangladesh/11RS1984-30/2011, from which the development of a candidate vaccine virus has been proposed.

A *Clade 7.2* virus was isolated from poultry in China. No antigenic data for this virus are yet available.

Influenza A(H5N1) candidate vaccine viruses

Based on the available antigenic, genetic and epidemiologic data, a new A/Indonesia/NIHRD11771/2011-like clade 2.1.3.2 candidate vaccine virus is proposed. The available and proposed candidate A(H5N1) vaccine viruses are listed in Table 3. 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, for 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].

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

Table 1. Influenza A(H5N1) activity from 23 February to 18 September 2012

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

*number in parentheses denotes number of reported cases during this period
#number in brackets denotes the number of viruses for which genetic information is available

Table 2. Antigenic properties of influenza A(H5N1) 2.1.3.2 viruses

		Reference ferret antiserum			
Reference antigens	**Clade**	**IND/5**	**RG2**	**NIHRD1177/11**	**IND/6**
A/Indonesia/5/2005	2.1.3.2	**640**	640	160	160
A/Indonesia/5/2005 (IBCDC-RG2)	2.1.3.2	640	**640**	80	320
A/Indonesia/NIHRD11771/2011	2.1.3.2	320	80	**1280**	40
A/Indonesia/6/2005	2.1.3.3	1280	640	320	**640**
Test antigens					
A/Indonesia/NIHRD11931/2011	2.1.3.2	80	40	640	10
A/Indonesia/NIHRD11949/2012	2.1.3.2	80	40	640	10
A/Indonesia/NIHRD12379/2012	2.1.3.2	80	40	640	10

Table 3. Status of influenza A(H5N1) candidate vaccine virus development (September 2012)

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

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

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

CDC/NIV - Centres for Disease Control and Prevention, United States of America/National Institute of Virology, India

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

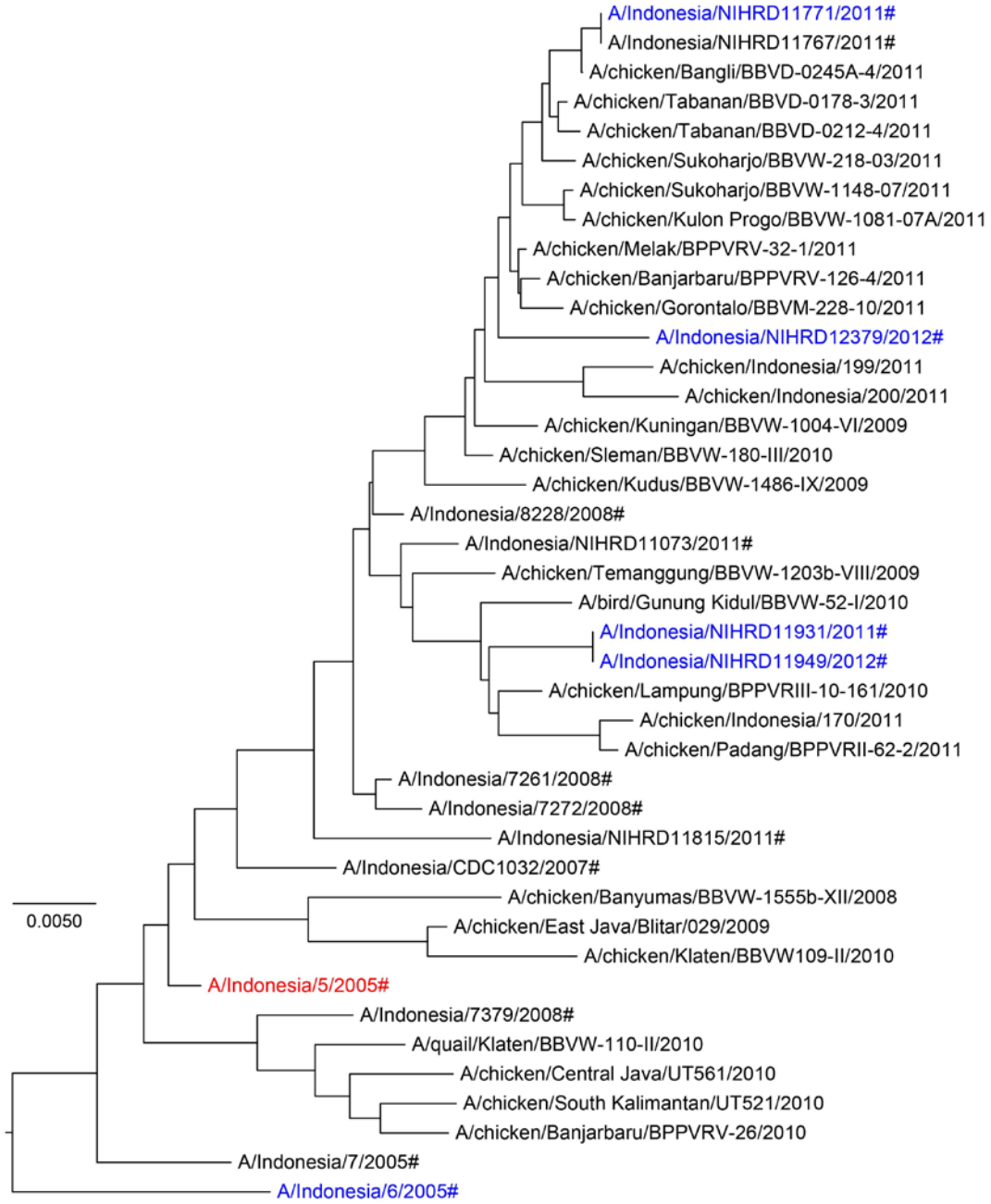

Figure 1. Phylogenetic relationships of influenza A(H5N1) clade 2.1.3.2 virus HA genes. Viruses represented in blue are included in the antigenic analysis as presented in Table 2. The available candidate vaccine virus is in red. Human viruses are indicated (#). The scale bar represents the number of substitutions per site.

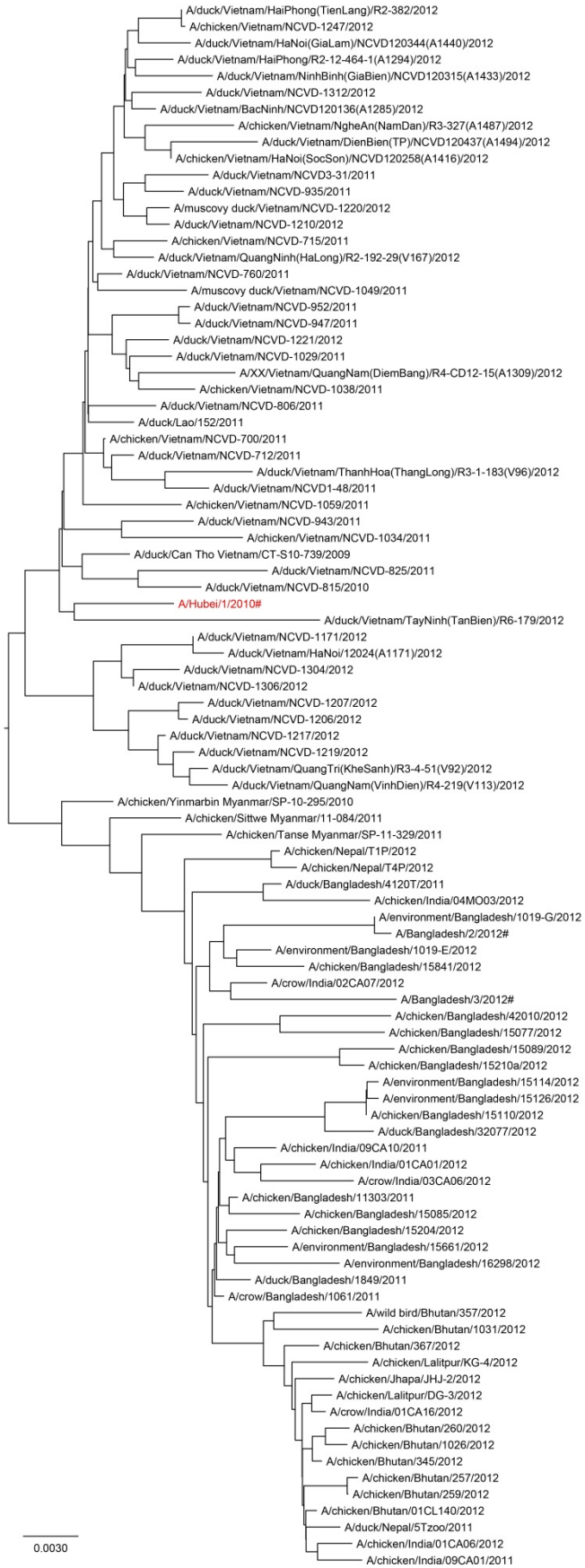

Figure 2. Phylogenetic relationships of influenza A(H5N1) clade 2.3.2.1 A/Hubei/1/2010-like virus HA genes. The available candidate vaccine virus is in red. Human viruses are indicated (#). The scale bar represents the number of substitutions per site.

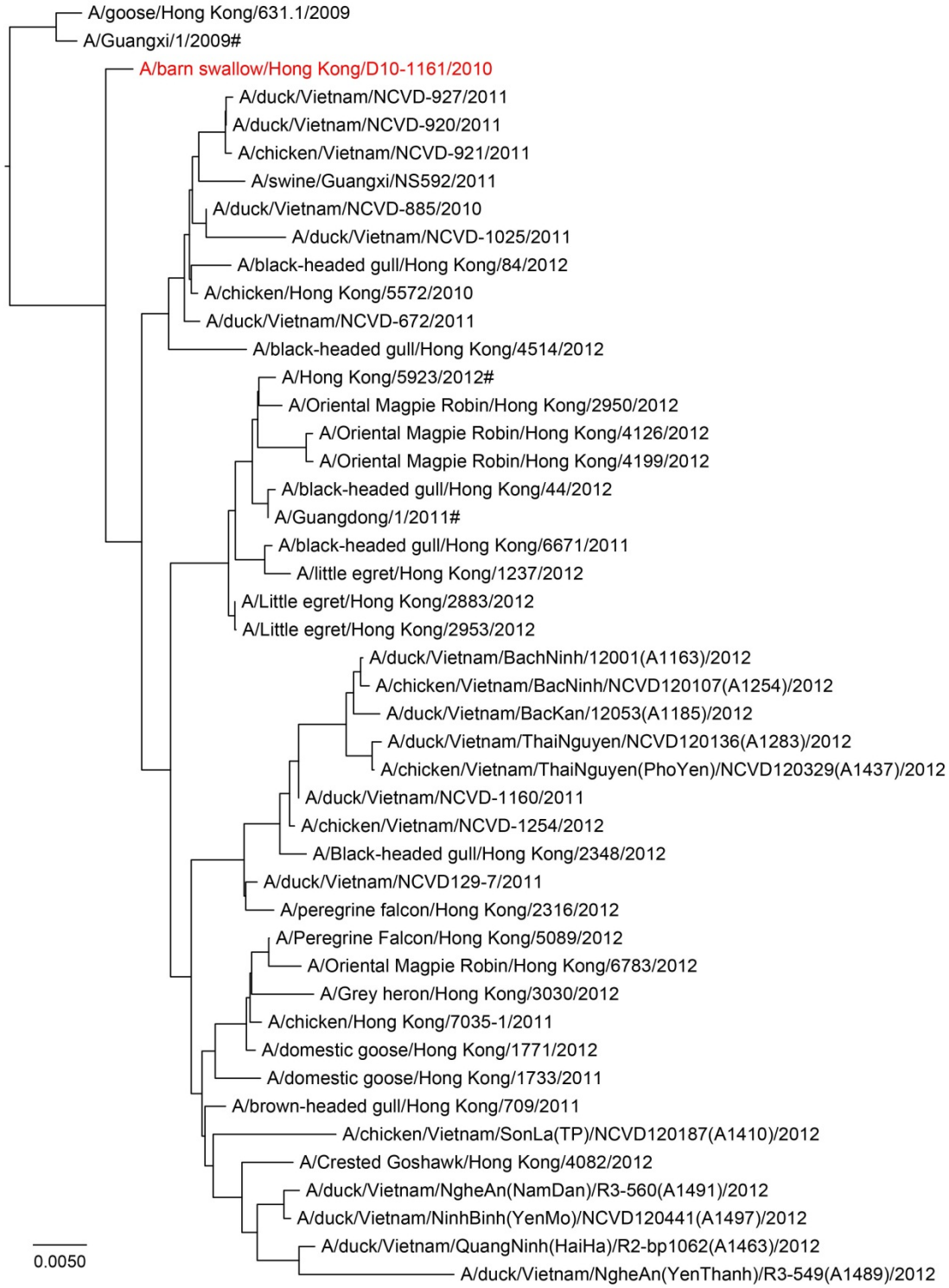

Figure 3. Phylogenetic relationships of influenza A(H5N1) clade 2.3.2.1 A/barn swallow/Hong Kong/D10-1161/2010-like virus HA genes. The aavailable candidate vaccine virus is in red. Human viruses are indicated (#). The scale bar represents the number of substitutions per site.

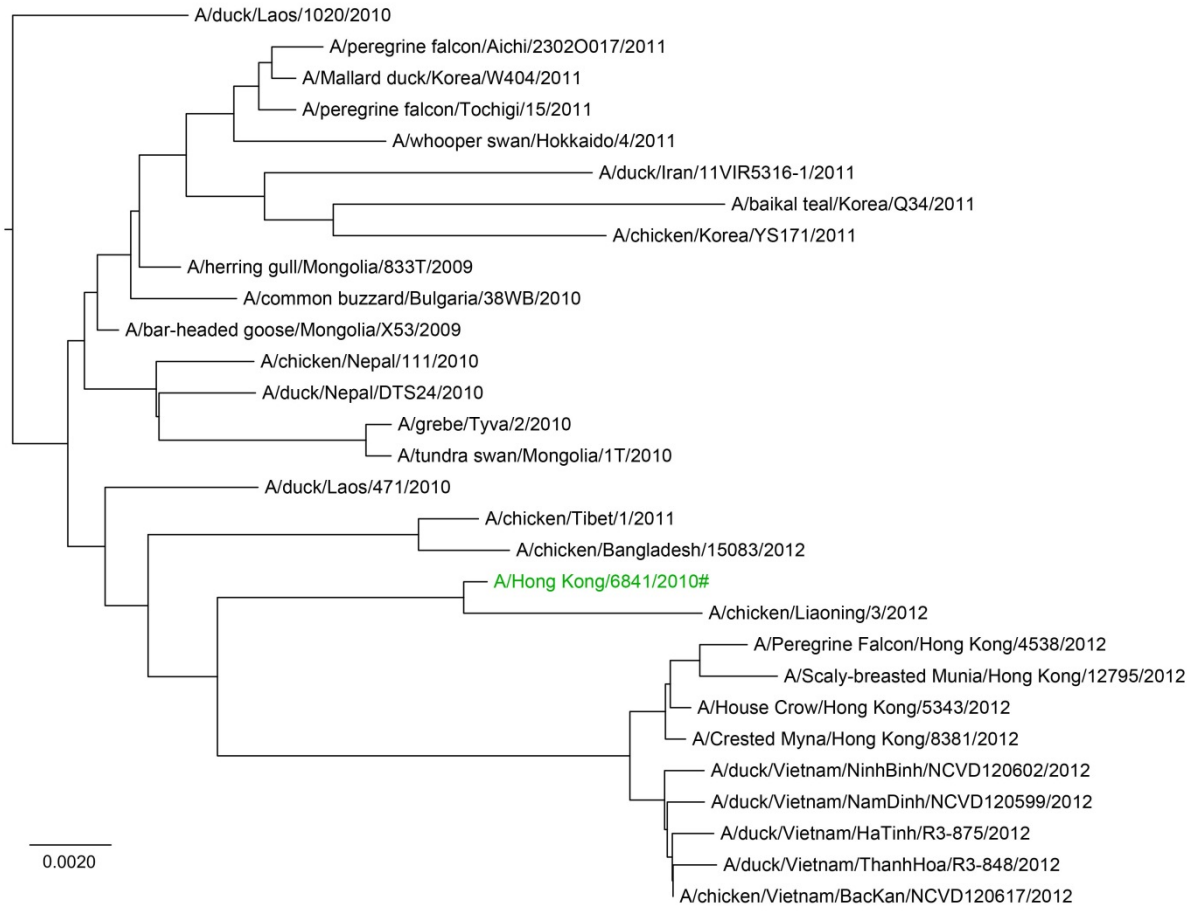

Figure 4. Phylogenetic relationships of influenza A(H5N1) clade 2.3.2.1 A/Hong Kong/6841/2010-like virus HA genes. The A/Hong Kong/6841/2010 virus is indicated in green. Human viruses are indicated (#). The scale bar represents the number of substitutions per site.

Influenza A(H9N2)

Influenza A(H9N2) viruses are enzootic in poultry populations in parts of 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 23 February to 18 September 2012

No human cases of A(H9N2) infections have been reported in the 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 4. 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 4. Status of influenza A(H9N2) candidate vaccine virus development (September 2012)

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

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

Influenza A(H3N2) variant (v)[3]

Influenza A(H3N2) viruses are endemic in swine populations in many 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[4].

Influenza A(H3N2)v activity from 23 February to 18 September 2012

Three hundred and five human infections of A(H3N2)v in multiple states of the United States of America have been detected since July 2012. Limited human-to-human transmission has been detected.

Characteristics of A(H3N2)v viruses

Genetically, the A(H3N2)v viruses were similar to viruses that circulate in swine in the United States of America and also to the previously reported A(H3N2)v viruses[5]. These viruses reacted well with post-infection ferret antisera raised against A/Minnesota/11/2010 and A/Indiana/10/2011 viruses, from which candidate vaccine viruses (NYMC X-203 and NYMC X-213, respectively) have been prepared. The A(H3N2)v viruses tested so far were susceptible to neuraminidase inhibitors and resistant to the adamantanes.

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 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[6].

Table 5. Status of A(H3N2)v candidate vaccine virus development (September 2012)

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

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

[3] http://www.who.int/influenza/gisrs_laboratory/terminology_ah3n2v/en/index.html
[4] Myers, KP. et al. Cases of Swine Influenza in Humans: A Review of the Literature. 2007. Clin Infect Dis. 44:1084.
[5] http://www.who.int/influenza/vaccines/virus/recommendations/2012_13_north/en/index.html
[6] http://www.who.int/influenza/vaccines/virus/en/

Influenza A(H1N1)v and A(H1N2)v

Influenza A(H1N1) and A(H1N2) viruses circulate in swine populations in many regions of the world. Depending on geographic location, the genetic and antigenic characteristics of these viruses differ. Human infections with swine A(H1) viruses have been documented for many years[7].

Influenza A(H1N1)v and A(H1N2)v activity from 23 February to 18 September 2012

Human infections with A(H1N1)v (one case) and A(H1N2)v (three cases) viruses have been detected in the United States of America in the reporting period.

Characteristics of influenza A(H1N1)v and A(H1N2)v viruses

The A(H1N1)v virus, which is similar to viruses that circulate in swine in the United States of America, contains an HA gene genetically and antigenically related to the A(H1N1)pdm09 viruses. The A(H1N2)v viruses are also similar to viruses known to circulate in swine in the United States of America and have HA genes similar to A(H1N1) viruses that circulated in humans until 2007. The A(H1N1)v and A(H1N2)v viruses were susceptible to oseltamivir and zanamivir and resistant to the adamantanes.

Influenza A(H1N1)v and A(H1N2)v candidate vaccine viruses

Based on the risk assessment of the antigenic and genetic characteristics of the A(H1N1)v and A(H1N2)v viruses, candidate vaccine viruses are not proposed at this time.

[7] Shu, B. et al. Genetic analysis and antigenic characterization of swine origin influenza viruses isolated from humans in the United States, 1990-2010. 2012. Virology. 422:151.

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[8,9].

Influenza A(H7N3) activity from 23 February to 18 September 2012

Two human cases of conjunctivitis due to A(H7N3) viruses were reported by Mexico during the period. Both individuals were occupationally exposed to poultry associated with the ongoing highly pathogenic A(H7N3) outbreak in birds in the region. Fever and respiratory illness were absent in both cases.

Characteristics of influenza A(H7N3) viruses

A(H7N3) viruses isolated from infected poultry and humans in Mexico were genetically closely related (Figure 5). These viruses reacted well with post-infection ferret antiserum raised against A/Canada/RV444/2004, a virus from which a candidate vaccine virus has been developed (Table 6). The one human virus tested for susceptibility to antiviral drugs was sensitive to oseltamivir, zanamivir and the adamantanes.

Influenza A(H7) candidate vaccine viruses

Based on the current antigenic, genetic and epidemiologic data, no new A(H7) candidate vaccine viruses are proposed. Available A(H7) 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[10].

Table 6. Antigenic properties of influenza A(H7) viruses

		Reference ferret antiserum			
Reference antigens	**Subtype**	NY/107	CN/RV444	CN/RV504	ck/AR/10
A/New York/107/2003	H7N2	1280	160	320	10
A/Canada/RV444/2004	H7N3	80	80	160	10
A/Canada/RV504/2004	H7N3	80	160	320	10
A/chicken/Arkansas/10/2008	H7N3	80	80	320	80
Test antigens					
A/turkey/Virginia/4529/2002	H7N2	1280	160	320	160
A/goose/Nebraska/17097-4/2011	H7N9	80	160	320	10
A/Mexico/InDRE7218/2012	H7N3	80	160	320	10

[8] Tweed, SA. et al. Human illness from avian influenza H7N3, British Columbia. 2004. Emerg Infect Dis. 10:2196.
[9] 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
[10] http://www.who.int/influenza/vaccines/virus/en/

Table 7. Status of influenza A(H7) candidate vaccine virus development (September 2012)

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

* **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

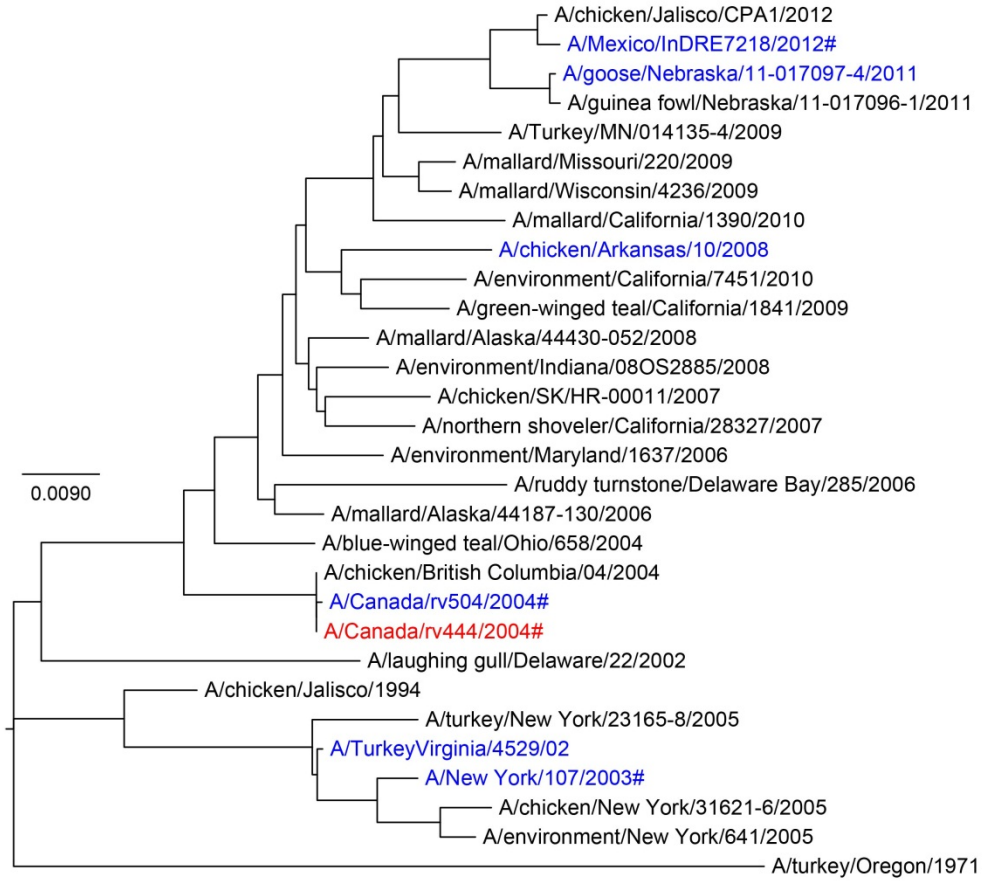

Figure 5. Phylogenetic relationships of influenza A(H7) virus HA genes. Viruses represented in blue are included in the antigenic analysis as presented in Table 6. An available A(H7N3) candidate vaccine virus is in red. Human viruses are indicated (#). The scale bar represents the number of substitutions per site.