

Antigenic and genetic characteristics of Influenza A(H5N1) viruses and candidate vaccine viruses developed for potential use in human vaccines

September 2009

Since their reemergence in 2003, influenza A(H5N1) influenza viruses have become endemic in some countries and continue to cause outbreaks in poultry and sporadic human infections. Despite the emergence of the pandemic A(H1N1) 2009 virus, the zoonotic and pandemic threats posed by H5N1 viruses remain. The H5N1 viruses have continued to diversify both genetically and antigenically leading to the need for multiple candidate vaccine viruses. The development of representative H5N1 candidate vaccine viruses, coordinated by the World Health Organization (WHO), remains an essential component of the overall global strategy for pandemic preparedness. This summary provides an update on the characterization of H5N1 viruses isolated from birds and humans, and the current status of the development of candidate H5N1 vaccine viruses.

Comparisons of the candidate H5N1 vaccine viruses with respect to immunogenicity and their relationship to newly emerging H5N1 viruses are ongoing, and will be updated periodically by WHO. An update of current and completed H5N1 vaccine clinical trials can be found at

http://www.who.int/vaccine_research/diseases/influenza/flu_trials_tables/en/index.html

Influenza A(H5N1) activity from February to September 2009

A(H5N1) viruses have continued to be detected in birds in Africa and Asia. Human infections have been reported to WHO from China, Egypt and Viet Nam, countries that have also declared outbreaks in birds (Table 1).

Antigenic and genetic characteristics.

A nomenclature for phylogenetic relationships among the haemagglutinin (HA) genes of H5N1 viruses was devised in consultation with representatives of FAO, OIE and WHO. This nomenclature is updated when novel genetic clades emerge and can be found at http://www.who.int/csr/disease/avian_influenza/guidelines/nomenclature/en/index.html

Viruses characterized during this period fall within the following clades:

Clade 2.2 viruses were detected in chickens in Bangladesh and their genetic characteristics were similar to those of viruses circulating in Bangladesh during 2008 (Figure 1). Data are not available on the antigenic properties of these viruses.

Clade 2.2.1 viruses continue to circulate in poultry in Egypt with sporadic transmission to humans. Viruses isolated during this period were genetically similar to those isolated during 2007 and 2008 (Figure 1). Data are not available on the antigenic properties of the 2009 viruses.

Clade 2.3.2 viruses have continued to be detected in poultry and wild birds in China Hong Kong Special Administrative Region (Hong Kong SAR) and were detected for the first time in wild birds in Southwestern Siberia (Russian Federation) and Mongolia. These viruses were genetically similar to *clade 2.3.2* viruses isolated in previous years (Figure 1). The viruses isolated in Hong Kong SAR were antigenically closely related to previous *clade 2.3.2* viruses.

Clade 2.3.4 viruses were detected in poultry and wild birds in Hong Kong SAR, and in poultry in Viet Nam and Lao People's Democratic Republic. A human case in China was reported in February. The viruses isolated in Hong Kong SAR were genetically similar to viruses isolated in Hong Kong SAR in 2008 (Figure 1) and were antigenically related to the candidate vaccine virus A/chicken/Hong Kong/AP156/2008. Viruses isolated in Viet Nam were genetically diverse. These viruses were antigenically closely related to the candidate vaccine virus A/duck/Laos/3295/2006 (Table 2).

A(H5N1) candidate vaccine viruses

Based on the available data, no new candidate A(H5N1) vaccine viruses are proposed at this time. The available candidate H5N1 vaccine viruses are listed in Table 3. On the basis of the geographical spread, epidemiology, and antigenic and genetic properties of the H5N1 viruses, national authorities may recommend the use of one or more of these for pilot lot vaccine production, clinical trial and subsequent stockpiling of vaccines, should such national policies exist.

Additional H5N1 candidate vaccine viruses may be developed as the viruses continue to evolve and will be announced as they become available. Institutions, companies and others interested in pandemic vaccine development, who wish to receive candidate vaccine viruses, should contact the WHO Global Influenza Program at GISN@who.int or the institutions listed in announcements published at WHO web site http://www.who.int/csr/disease/avian_influenza/guidelinestopics/en/index5.html

Table 1. Influenza A(H5N1) activity reported from February to September 2009		
Country	Host	Genetic clade
Bangladesh	Domestic poultry	2.2
China	Human	2.3.4
	Domestic poultry	unknown
	Wild birds	unknown
China, Hong Kong SAR	Domestic poultry	2.3.2 and 2.3.4
	Wild Birds	2.3.2 and 2.3.4
Egypt	Humans	2.2.1
	Domestic poultry	2.2.1
India	Domestic poultry	unknown
Indonesia	Domestic poultry	2.1 clades
Lao People's Democratic Republic	Domestic poultry	2.3.4
Mongolia	Wild birds	2.3.2
Nepal	Domestic poultry	unknown
Russian Federation	Wild birds	2.3.2
Viet Nam	Humans	unknown
	Domestic poultry	2.3.4

Table 2. Results of haemagglutination inhibition tests of A(H5N1) viruses with postinfection ferret antisera.

	Clade	1 VN/1203	2.1 IND/5	2.2 bhg/Q1	2.2.1 EG/321	2.3.2 ck/KO	2.3.4 ANH/1	2.3.4 jwe/HK	2.3.4 dk/LO	2.3.4 ck/VN/35
Reference antigens										
A/Viet Nam/1203/2004	1	<u>640</u>	5	160	5	5	5	5	10	320
A/Indonesia/5/2005	2.1	5	<u>640</u>	160	160	5	80	5	5	40
A/bh goose/Qinghai/1A/05 X PR8	2.2	20	320	<u>640</u>	320	5	5	80	20	40
A/Egypt/321-NAMRU3/2007	2.2.1	5	320	320	<u>1280</u>	5	5	80	10	40
A/chicken/Korea/GIMJE/08	2.3.2	5	5	80	5	<u>160</u>	5	5	5	80
A/Anhui/1/05	2.3.4	10	80	80	40	5	<u>2560</u>	320	320	640
A/Jap white eye/Hong Kong/1038/06	2.3.4	5	40	640	160	5	2560	<u>1280</u>	640	320
A/duck/Laos/3295/06	2.3.4	5	5	80	5	5	320	80	<u>80</u>	80
A/chicken/Viet Nam/NCVD-35/08	2.3.4	5	20	160	5	5	160	20	160	<u>640</u>
Representative test antigens										
A/chicken/Viet Nam/NCVD-279/09	2.3.4	5	5	80	5	5	320	80	80	160
A/chicken/Viet Nam/NCVD-282/09	2.3.4	5	5	80	40	5	80	20	40	320
A/chicken/Viet Nam/NCVD-283/09	2.3.4	5	5	40	5	5	80	5	80	640

Table 3. Status of H5N1 vaccine virus development (September 2009)			
Reassortants with regulatory approval			
Virus	Clade	Institution*	Availability
A/Cambodia/R0405050/2007	1	NIBSC	Yes
A/Viet Nam/1203/2004	1	CDC and SJ/HKU/NIAID	Yes
A/Viet Nam/1194/2004	1	NIBSC	Yes
A/duck/Hunan/795/2002	2.1	SJ/HKU/NIAID	Yes
A/Indonesia/5/2005	2.1	CDC	Requires Indonesian Government permission
A/bar-headed goose/Qinghai/1A/2005	2.2	SJ/HKU/NIAID	Yes
A/whooper swan/Mongolia/244/2005	2.2	SJ/NIAID	Yes
A/Egypt/2321/2007	2.2.1	CDC	Yes
A/turkey/Turkey/1/2005	2.2.1	NIBSC	Yes
A/Anhui/1/2005	2.3.4	CDC	Yes
A/duck/Laos/3295/2006	2.3.4	FDA	Yes
A/Japanese white-eye/Hong Kong/1038/2006	2.3.4	SJ/HKU/NIAID	Yes
A/goose/Guiyang/337/2006	4	SJ/HKU/NIAID	Yes
Reassortants prepared and awaiting regulatory approval			
Virus	Clade	Institution*	Availability
A/chicken/India/NIV33487/2006	2.2	CDC/NIV	Pending
A/Egypt/3300-NAMRU3/2008	2.2	CDC	Pending
A/common magpie/Hong Kong/5052/2007	2.3.2	SJ/HKU/NIAID	Pending
A/chicken/Viet Nam/NCVD-016/2008-like	7	CDC	Pending
Viruses proposed by WHO for candidate vaccine preparation			
Virus	Clade	Institution*	
A/chicken/Hong Kong/AP156/2008-like	2.3.4	SJ/HKU/NIAID	
A/chicken/Viet Nam/NCVD-03/2008	7	CDC	

* CDC- Centers for Disease Control and Prevention, USA

FDA- Food and Drug Administration, USA

NIAID- National Institute of Allergy and Infectious Disease, NIH, USA

NIBSC- National Institute for Biological Standards and Control, UK

NIV- National Institute of Virology, India

SJ- St Jude Children's Research Hospital, USA

HKU-University of Hong Kong, China Hong Kong SAR

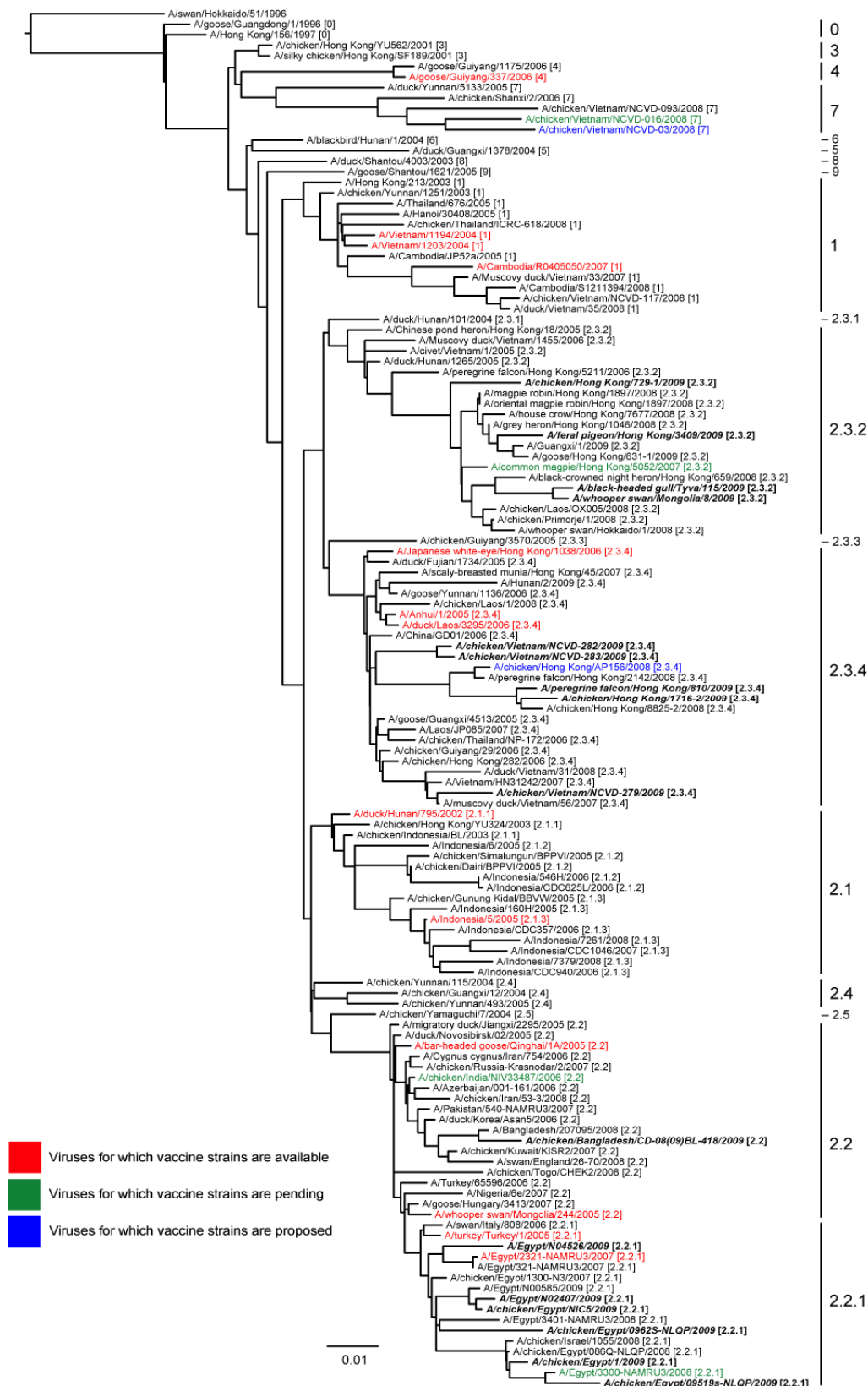


Figure 1. Phylogenetic relationships of H5N1 virus HA genes showing availability of vaccine strains. We gratefully acknowledge the contributions of the originating laboratories and countries that have provided samples and/or submitted sequence data to DDBJ, EMBL-Bank, GenBank, GISAID and other public databases. Sequence has also been provided by the National Influenza Center at the Central Public Health Laboratory, Ministry of Health and the National Laboratory for Veterinary Quality Control on Poultry Production (NLQP), Egypt. Recent viruses (where date of isolation known) are shown in italics.