

# **Antigenic and genetic characteristics of H5N1 viruses and candidate H5N1 vaccine viruses developed for potential use in human vaccines**

**September 2008**

It is not known if the next influenza pandemic will be caused by H5N1 viruses or, should one occur, which of the clades of H5N1 viruses would be responsible. However, because an H5N1 pandemic is an important possibility, the development of representative H5N1 candidate vaccine viruses coordinated by the World Health Organization (WHO) is one component of the overall global strategy for pandemic preparedness. This summary provides an update on the characterization of available H5N1 viruses circulating in birds, including those that have caused human infections and the current status of the development of candidate H5N1 vaccine viruses. This information may be used to guide national decisions on procurement of H5N1 vaccines.

H5N1 vaccines continue to be developed by manufacturers using clade 1 and clade 2 viruses. Clinical trials have been conducted or are under way in several countries and stockpiles of clade 1 and clade 2 vaccines are being acquired by a number of countries ([http://www.who.int/vaccine\\_research/diseases/influenza/flu\\_trials\\_tables/en/index.html](http://www.who.int/vaccine_research/diseases/influenza/flu_trials_tables/en/index.html)). Clinical trials using different viruses should continue as an essential element in pandemic preparedness and provide data on priming, vaccination schedules, and induction of cross-reactive immunity by vaccines containing viruses from different clades.

Companies are recommended to consult individual national authorities on the specific H5N1 viruses to be used for preparing experimental pilot lots and stockpiles of H5N1 vaccines. Decisions should be based on the epidemiology and geographical distribution of the circulating H5N1 viruses.

Comparisons of the candidate H5N1 vaccine viruses with respect to immunogenicity and cross-reactivity and their relationship to newly emerging H5N1 viruses are ongoing, and will be updated periodically by WHO.

## **Molecular epidemiology of H5N1 viruses**

A revised nomenclature for phylogenetic relationships among the haemagglutinin (HA) genes of H5N1 viruses was devised by consultation among representatives of OIE, FAO and WHO ([http://www.who.int/csr/disease/avian\\_influenza/guidelines/nomenclature/en/index.html](http://www.who.int/csr/disease/avian_influenza/guidelines/nomenclature/en/index.html)) (Figure 1). The HA sequences of the majority of H5N1 viruses circulating in avian species are separated into a number of distinct clades. Clade 1 viruses have caused human infections in Cambodia, China Hong Kong Special Administrative Region, Thailand and Viet Nam and have been recently detected in poultry in Cambodia, Thailand and Viet Nam. Clade 2.1 viruses have continued to circulate in poultry and caused human infections in Indonesia. Clade 2.2 viruses have the most geographically diverse distribution and have caused outbreaks in birds in over 60 countries in Africa, Asia and Europe with human infections in Azerbaijan, Bangladesh, China, Djibouti, Egypt, Iraq, Nigeria, Pakistan and Turkey. Some recent clade 2.2 viruses have diverged genetically from reference strains. Clade 2.3 viruses are genetically diverse. Clade 2.3.2 and 2.3.4 viruses continue to circulate in birds in Asia; clade 2.3.4 viruses have been responsible for human infections in China, Lao People's Democratic Republic, Myanmar and Viet Nam. Viruses from other clades, including clade 7, have been sporadically detected in birds in Asia.

## **Antigenic characteristics of H5N1 viruses**

Haemagglutination inhibition tests of available H5N1 viruses demonstrate that current vaccine candidates continue to provide good antigenic coverage of most isolates within corresponding clades. However, some viruses within clades 2.2, 2.3.4, and 7 show evidence of antigenic heterogeneity (Table 1). While the majority of available clade 2.2 viruses were antigenically similar to currently available vaccine candidates, some recently characterized clade 2.2 viruses from Egypt show evidence of antigenic heterogeneity. For instance, A/Egypt/3300-NAMRU3/2008 is antigenically distinguishable from previous vaccine candidate viruses and this virus is recommended as a new candidate vaccine virus. Viruses within clade 2.3.2 are antigenically distinguishable from other 2.3 clades. Some recent clade 2.3.4 viruses e.g., A/chicken/Hong Kong/AP156/2008, are antigenically distinguishable from reference strains. Similarly, a recently isolated clade 7 virus, A/chicken/Viet Nam/NCVD-016/2008, is poorly reactive with antisera to current vaccine candidate viruses.

## **Potential H5N1 vaccine viruses**

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 the H5N1 candidate vaccine viruses listed in Table 2 for pilot lot vaccine production and subsequent stockpiling of vaccines, should relevant national policies exist.

Additional H5N1 candidate vaccine viruses are being 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 these prototype viruses, should contact the WHO Global Influenza Programme at [GISN@who.int](mailto: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](http://www.who.int/csr/disease/avian_influenza/guidelinestopics/en/index5.html) .

**Table 1. Antigenic properties of H5N1 viruses**

	REFERENCE FERRET ANTISERA							
	CLADE	1	2.1	2.1	2.2	2.3.2	2.3.4	7
REFERENCE ANTIGENS		VN/1203	IND/5	DK/HU	MG/244	MD/VN	ANH/1	CK/VN
A/Viet Nam/1203/2004 (VN/1203)	1	<u>320</u>	20	40	<10	40	-	<10
A/Indonesia/5/2005 (IND/5)	2.1	10	<u>640</u>	80	80	160	-	80
A/duck/Hunan/795/2002 (DK/HU)	2.1	80	1280	<u>160</u>	-	-	40	-
A/whooper swan/Mongolia/244/2005 (MG/244)	2.2	20	160	160	<u>320</u>	80	-	-
A/muscovy duck/Viet Nam/1455/2006 (MD/VN)	2.3.2	40	160	-	160	<u>320</u>	<10	-
A/Anhui/1/2005 (ANH/1)	2.3.4	40	320	-	<10	-	<u>640</u>	<10
A/chicken/Viet Nam/NCVD-016/2008 (CK/VN)	7	<10	<10	-	-	-	<10	<u>640</u>
<b>TEST ANTIGENS</b>								
A/Thailand/676/2005	1	160	20	-	<10	-	40	-
A/duck/Viet Nam/NCVD16/2007	1	40	<10	-	<10	-	<10	-
A/Indonesia/CDC1031/2007	2.1	<10	640	-	160	-	160	-
A/Indonesia/CDC625L/2006	2.1	40	80	40	20	-	<10	-
A/Turkey/65-596/2006	2.2	160	1280	-	5120	-	320	-
A/egret/Egypt/1162- NAMRU3/2006	2.2	<10	320	-	320	-	<10	-
A/Egypt/3300-NAMRU3/2008	2.2	<10	160	-	80	-	20	-
A/Bangladesh/207095/2008	2.2	<10	320	-	320	-	<10	-
A/common magpie/Hong Kong/5052/2007	2.3.2	80	320	40	-	320	<10	-
A/house crow/Hong Kong/719/2007	2.3.4	<10	80	-	<10	-	320	-
A/chicken/Viet Nam/NCVD74/2007	2.3.4	20	<10	-	<10	-	40	-
A/duck/Viet Nam/NCVD81/2007	2.3.4	<10	<10	-	<10	-	80	-
A/chicken/Hong Kong/AP156/2008	2.3.4	<10	<10	40	<10	40	<10	-
A/chicken/Viet Nam/NCVD-03/2008	7	<10	<10	-	-	-	<10	40

**Table 2. Status of H5N1 vaccine virus development as of 20 September 2008**

<b>Reassortants with completed regulatory approval</b>			
<b>Virus</b>	<b>Clade</b>	<b>Institution*</b>	<b>Availability</b>
A/Viet Nam/1203/2004	1	CDC and SJ/NIAID	Yes
A/Viet Nam/1194/2004	1	NIBSC	Yes
A/Indonesia/5/2005	2.1	CDC	Requires Indonesian Government permission
A/bar-headed goose/Qinghai/1A/2005	2.2	SJ/NIAID	Yes
A/whooper swan/Mongolia/244/2005	2.2	SJ/NIAID	Yes
A/turkey/Turkey/1/2005	2.2	NIBSC	Yes
A/Anhui/1/2005	2.3.4	CDC	Yes
A/Japanese white-eye/Hong Kong/1038/2006	2.3.4	SJ/NIAID	Yes
A/Cambodia/R0405050/2007	1	NIBSC	Yes
A/duck/Laos/3295/2006	2.3.4	FDA	Yes
<b>Reassortants prepared and awaiting regulatory approval</b>			
<b>Virus</b>	<b>Clade</b>	<b>Institution*</b>	<b>Availability</b>
A/chicken/India/NIV33487/2006	2.2	CDC/NIV	Pending
A/goose/Guiyang/337/2006	4	SJ/NIAID	Anticipated Oct 08
A/common magpie/Hong Kong/5052/2007	2.3.2	SJ/NIAID	Pending
A/duck/Hunan/795/2002	2.1	SJ/NIAID	Pending
<b>Viruses proposed by WHO for candidate vaccine preparation</b>			
<b>Virus</b>	<b>Clade</b>	<b>Institution*</b>	
A/Egypt/3300-NAMRU3/2008	2.2	CDC	
A/Egypt/2321/2007-like	2.2	CDC	
A/chicken/Viet Nam/NCVD-016/2008-like	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

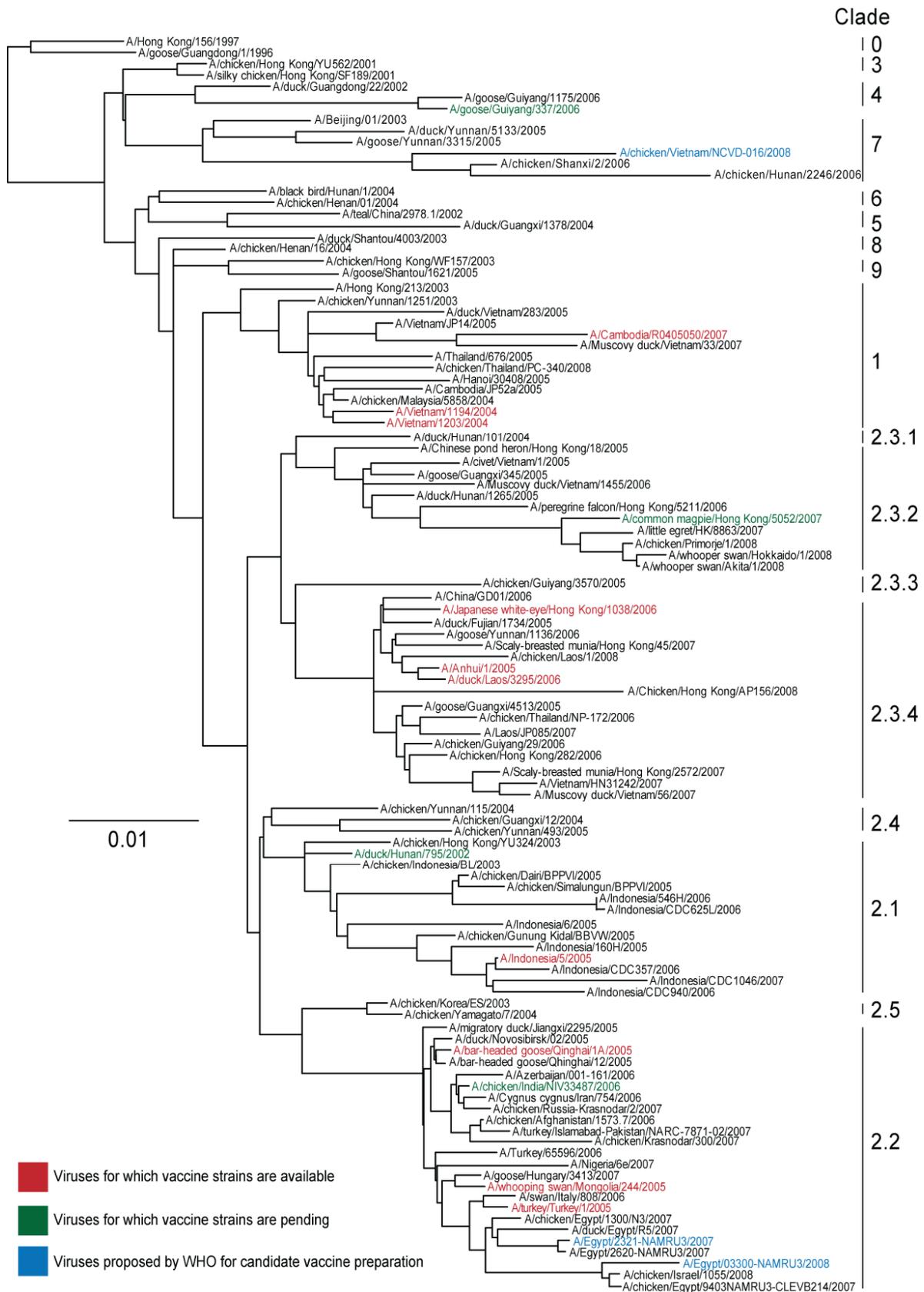


Figure 1. Phylogenetic relationships of H5N1 viruses.