



## **Antigenic and genetic characteristics of H5N1 viruses and candidate H5N1 vaccine viruses developed for potential use as pre-pandemic Vaccines**

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The development of representative pre-pandemic H5N1 candidate vaccine viruses by the WHO Global Influenza Programme<sup>1</sup> is being conducted as one component of the overall global strategy for pandemic preparedness. This summary provides an update on the characterization of H5N1 viruses circulating in birds, those that have caused human infections and on the current status of the development of candidate H5N1 vaccine viruses. This information may be used to guide national authorities as regards decisions on production of pre-pandemic vaccines.

The H5N1 viruses chosen previously for development of pre-pandemic candidate vaccine viruses were representative of antigenically and genetically distinct groups of viruses that infected humans primarily through contact with ill or dead H5N1-infected birds. These representative candidate H5N1 vaccine viruses were prepared by reverse genetics and safety tested prior to release for production of pilot vaccine lots, that may be used for experimental studies and in some instances for stockpiling by governments in advance of a possible H5N1 pandemic.

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 that are described below.

Comparisons of the candidate H5N1 vaccine viruses developed from clade 1 and clade 2 viruses with respect to immunogenicity and cross-reactivity and their relationship to newly emerging H5N1 viruses are ongoing, and will be reported periodically by WHO.

### **Genetic characteristics of recent H5N1 viruses**

The haemagglutinin (HA) sequences of the majority of H5N1 viruses circulating in avian species during the past 4 years separate into two distinct phylogenetic clades (genetic groups)<sup>2</sup>. Clade 1 viruses circulating in Cambodia, Thailand and Viet Nam were responsible for human infections in those countries during 2004 and 2005 and in Thailand during 2006. Clade 2 viruses have circulated in birds in China and Indonesia since 2003 and spread westwards during 2005 and 2006 to the Middle East, Europe and Africa. This latter genetic group of viruses has been principally responsible for human infections since late 2005. Multiple subclades of clade 2 have been distinguished, three of

<sup>1</sup> <http://www.who.int/csr/disease/influenza/en/>

<sup>2</sup> <http://www.cdc.gov/ncidod/EID/vol11no10/05-0644.htm>

which, subclades 1, 2 and 3, (Figure 1) differ in geographical distribution and have so far been largely responsible for human cases.

Between August 2006 and March 2007, the majority of HA sequences of H5N1 viruses which have continued to circulate or have re-emerged in avian species and which have been associated with sporadic human infections in Africa, Asia and Europe fall into the previously designated phylogenetic clades and subclades. Clade 1 viruses were responsible for outbreaks in birds in Viet Nam and Thailand and human infections in Thailand. Clade 2.1 viruses have continued to circulate in poultry and cause human infections in Indonesia. Clade 2.2 viruses have caused outbreaks in birds in some countries in Africa, Asia and Europe and have been associated with human infections in Egypt, Iraq and Nigeria. Clade 2.3 viruses have been isolated sporadically in Asia and have been responsible for human infections in China and Laos.

In addition, a few viruses, which fall outside of this classification, were isolated from domestic poultry during localized outbreaks in Asia and fall into new, seemingly emerging clades, represented by A/goose/Guizhou/337/2006 and A/chicken/Shanxi/2/2006, respectively.

### **Antigenic characteristics of recent H5N1 viruses**

Haemagglutination inhibition tests of human H5N1 isolates within subclades 2.1, 2.2 and 2.3 showed them to be antigenically closely-related to the previously recommended candidate vaccine viruses<sup>3</sup>, A/Indonesia/5/2005, A/bar-headed goose/Qinghai/1A/2005 and A/Anhui/1/2005, respectively. Additional data is required to determine the antigenic relationships among representative viruses from the emerging clades and the previously identified clades.

### **New candidate H5N1 vaccine viruses**

Viruses representative of the newly emerging clades referred to above are being sought for analyses and development of candidate vaccine viruses by reverse genetics.

### **Recommended use of candidate H5N1 vaccine viruses**

Pre-pandemic vaccines are being developed by manufacturers using clade 1 and clade 2 viruses<sup>4</sup>. Clinical trials have been conducted or are under way in several countries and stockpiling of clade 1 vaccines has begun in some countries. Because it is not known if the next influenza pandemic will be caused by H5N1 viruses or which of the clades or subclades of H5N1 would be responsible, should one occur, clinical trials using both clade 1 and clade 2 viruses should continue as an essential element in pandemic preparedness, to maximize data available on priming, cross-reactivity and cross-protection by vaccine viruses from different clades and subclades.

On the basis of the geographical spread, the epidemiology, and the antigenic and genetic properties of the H5N1 viruses isolated from humans, national authorities may recommend the use of one or more of the following H5N1 candidate vaccine viruses for pilot lot vaccine production and subsequent stockpiling of vaccines, should relevant national policies exist:

<sup>3</sup> [http://www.who.int/csr/disease/avian\\_influenza/guidelines/recommendationvaccine.pdf](http://www.who.int/csr/disease/avian_influenza/guidelines/recommendationvaccine.pdf)

<sup>4</sup> <http://www.ifpma.org/Influenza/index.aspx?42>

- An A/Indonesia/5/2005-like virus
- An A/Bar headed goose/Qinghai/1A/2005-like virus<sup>a</sup>
- An A/Anhui/1/2005-like virus

<sup>a</sup>. Candidate vaccine viruses also include A/turkey/Turkey/1/2005 and A/Whooper swan/Mongolia/244/2005

Additional pre-pandemic H5N1 candidate vaccine viruses will be developed as 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 [whoinfluenza@who.int](mailto:whoinfluenza@who.int) or the institutions listed in announcements published at WHO web site [http://www.who.int/csr/disease/avian\\_influenza/guidelinetopics/en/index5.html](http://www.who.int/csr/disease/avian_influenza/guidelinetopics/en/index5.html) .

Fig. 1

## Evolution of the H5N1 Haemagglutinin Gene

