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

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The development of representative candidate influenza vaccine viruses (CVV), coordinated by the World Health Organization (WHO), remains an essential component of the overall global strategy for pandemic preparedness.

Zoonotic influenza viruses continue to be identified and often evolve both genetically and antigenically, leading to the need for update of CVVs for pandemic preparedness purposes. Evaluation of the genetic and antigenic characteristics of these viruses, their relationship to existing CVVs, and their potential risks to public health, justify the need to select and develop new CVVs.

Selection and development of a CVV represents a first step only towards timely vaccine production and does not imply a recommendation for initiating manufacture. National authorities may consider the use of one or more of these CVVs for pilot lot vaccine production, clinical trials and other pandemic preparedness purposes based on their assessment of public health risk and need.

This document summarizes the genetic and antigenic characteristics of recent zoonotic influenza viruses and related viruses circulating in animals and updates the availability of CVVs. Institutions that wish to receive these CVVs should contact WHO at gisrs-whohq@who.int or the institutions listed in announcements published on the WHO website[1].

Influenza A(H5)

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 genetically and antigenically leading to the need for multiple CVVs. Recently viruses have been detected with N6 or N8 genes substituted for the N1 gene. This summary provides updates on the characterization of A(H5) viruses and the current status of the development of influenza A(H5) CVVs.

Influenza A(H5) activity from 18 February 2014 to 23 September 2014

A(H5N1) viruses have been detected in birds in Africa and Asia. A(H5) human infections have been reported to the WHO by Cambodia, China, Egypt and Indonesia, countries in which infections have been detected in birds (Table 1). One of the human infections in China was caused by an A(H5N6) virus. A(H5N1) viruses were detected in birds in Bangladesh, Cambodia, China, Egypt, India, Indonesia, Libya and Viet Nam. A(H5N6) and/or A(H5N8) outbreaks were reported in birds in China, Japan, Lao People's Democratic Republic, Republic of Korea and Viet Nam.

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

Table 1. Recent influenza A(H5) activity reported to international agencies

Reporting country, area or territory	Host/source	Genetic clade*
Bangladesh	Poultry	2.3.2.1a
Cambodia	Poultry	1.1.2
	Human (7)#	1.1.2, 2.3.2.1
China	Poultry/environmental	2.3.2.1c, 2.3.4.6† (H5N1/N6/N8)
	Human (2)	2.3.4.6† (H5N6), unknown
Democratic People's Republic of Korea	Poultry	unknown
Egypt	Poultry	2.2.1
	Human (4)	2.2.1
India	Wild birds	2.3.2.1a
Indonesia	Poultry	2.1.3.2a, 2.3.2.1c
	Human (2)	2.1.3.2a, unknown
Japan	Poultry	2.3.4.6† (H5N8)
Lao People's Democratic Republic	Poultry	2.3.2.1c, 2.3.4.6† (H5N6)
Libya	Poultry	2.2.1
Republic of Korea	Poultry, wild birds	2.3.4.6† (H5N8)
Viet Nam	Poultry	1.1.2, 2.3.2.1c, 2.3.4.6† (H5N6/N1)

* based on available sequences

# denotes number of human cases with illness onset dates falling within reporting period

†provisional, pending formal designation by the WHO/OIE/FAO A(H5N1) evolution working group

Antigenic and genetic characteristics of influenza A(H5) viruses

The nomenclature for phylogenetic relationships among the haemagglutinin (HA) genes of A(H5) 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[2].

Viruses circulating and characterized from 18 February 2014 to 23 September 2014 belonged to the following clades.

Clade 1.1.2 viruses were detected in poultry in Viet Nam and in poultry and humans in Cambodia. Genetic characterization of the HA genes showed that these viruses were closely related to viruses detected previously in these countries. The one human virus from Cambodia available for testing reacted well to ferret antisera raised against the CVV developed from A/Cambodia/X0810301/2013.

Clade 2.1.3.2a viruses continue to circulate in poultry in Indonesia and cause human infections. The HA gene sequence of a 2014 human virus was similar to that of A/Indonesia/NIHRD11771/2011 for which a CVV has been derived. No antigenic information for recent viruses of this clade is available.

Clade 2.2.1 viruses were detected in poultry in Libya and in poultry and humans in Egypt. As compared to the CVVs produced from A/Egypt/N03072/2010 and A/Egypt/2321-NAMRU3/2007, the HA proteins of recent clade 2.2.1 viruses have accumulated a number of amino acid substitutions. These viruses showed reduced reactivity to ferret antisera raised against the CVVs. Further virus characterization is underway.

Clade 2.3.2.1a viruses were detected in birds in Bangladesh and India. The HA genes of these viruses were similar to those of viruses detected previously. The majority of viruses reacted well with ferret antiserum raised against A/duck/Bangladesh/19097/2013 for which a CVV is available. A smaller number of viruses showed reduced reactivity to this antiserum.

Clade 2.3.2.1c viruses were detected in birds and/or environmental samples in Cambodia, China, Indonesia, Lao People's Democratic Republic and Viet Nam. The HA genes of the bird and

[2] WHO/OIE/FAO H5N1 Evolution Working Group. Revised and updated nomenclature for highly pathogenic avian influenza A(H5N1) viruses. John Wiley & Sons Ltd. 2014 (http://onlinelibrary.wiley.com/doi/10.1111/irv.12230/full#irv12230)

environmental viruses were similar to those of viruses detected previously. Antigenic analysis showed that many of these viruses reacted well with ferret antiserum raised against A/duck/Viet Nam/NCVD-1584/2012 or A/barn swallow/Hong Kong/1161/2010 for which CVVs have been prepared.

Clade 2.3.4.6[3] viruses were detected in bird and/or environmental samples in China, Japan, Lao People's Democratic Republic, Republic of Korea and Viet Nam and a human in China. The HA genes of these viruses have evolved into distinct genetic groups (Figure 1). The NA genes of these viruses belonged to the N1, N6, or N8 subtypes. Antigenic information from viruses of this clade showed that they reacted poorly to ferret antisera raised against available CVVs and an A/Sichuan/26221/2014-like CVV is proposed.

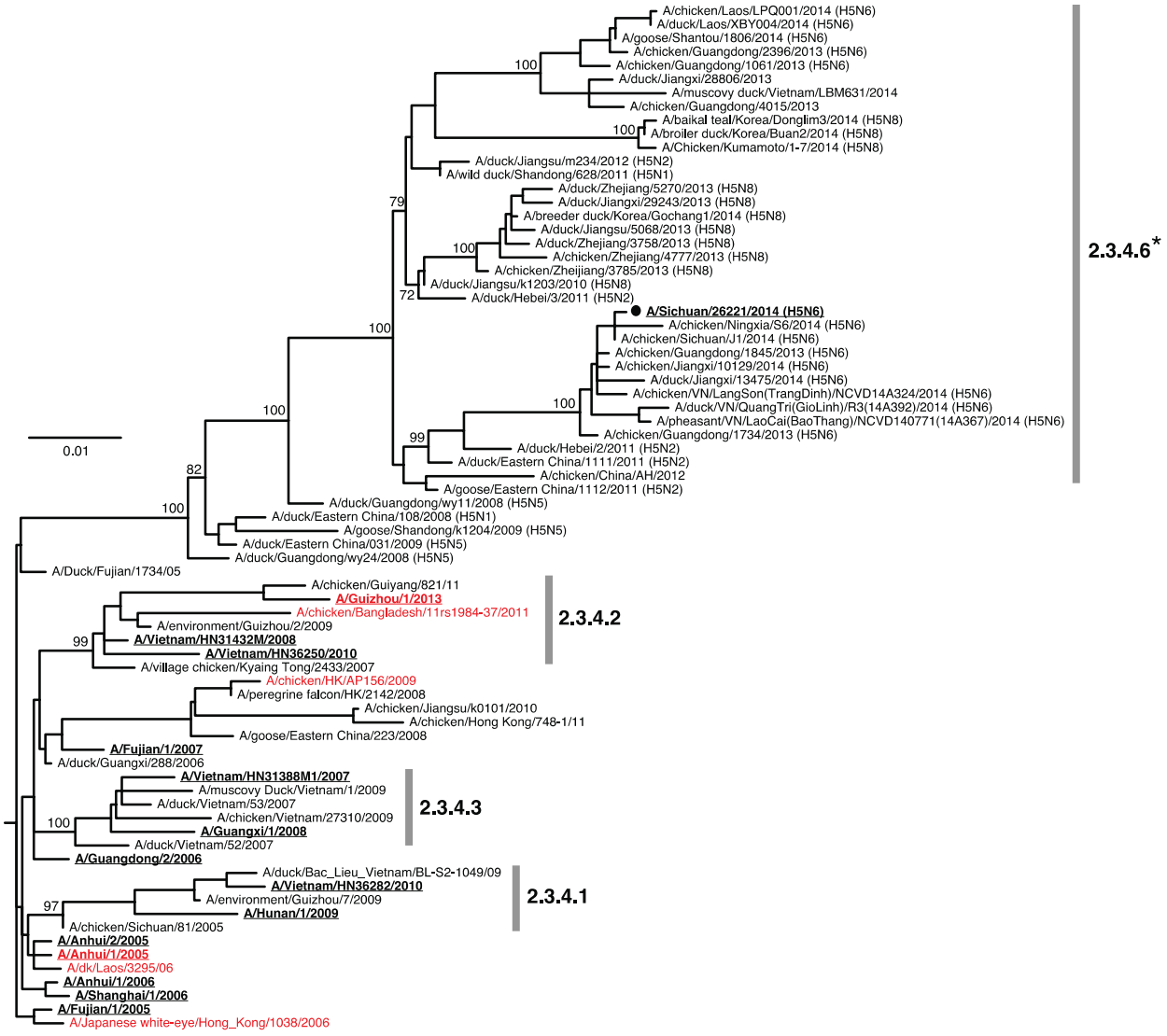

Figure 1. Phylogenetic relationships of A(H5) clade 2.3.4 HA genes. The available CVVs are in red. The proposed CVV is indicated by a circle. Human viruses are underlined and in bold font. The scale bar represents the number of substitutions per site. NA subtypes other than N1 are specified. Bootstrap supports of topology are shown above selected nodes. *refer to footnote 3.

[3] While the HA genes from viruses in this emerging virus group meet the criteria for novel clade designation, a formal nomenclature has not yet been adopted. 2.3.4.6 is used as a provisional nomenclature only.

Influenza A(H5) candidate vaccine viruses

Based on the available antigenic, genetic and epidemiologic data, an A/Sichuan/26221/2014-like (clade 2.3.4.6[3]) CVV is proposed. The available and pending A(H5) CVVs are listed in Table 2. National authorities may consider the use of one or more of these A(H5) CVVs for pilot lot vaccine production, clinical trials and other pandemic preparedness purposes based on their assessment of public health risk and need. As the viruses continue to evolve, new A(H5) CVVs may be developed.

Table 2. Status of influenza A(H5) candidate vaccine virus development

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/Cambodia/X0810301/2013 (IDCDC-RG34B)	1.1.2	CDC	Yes
A/duck/Hunan/795/2002 (SJRG-166614)	2.1.1	SJCRH	Yes
A/Indonesia/5/2005 (CDC-RG2)	2.1.3.2	CDC	Yes
A/Indonesia/NIHRD11771/2011 (NIIDRG-9)	2.1.3.2a	NIID	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)	2.3.2.1a	CDC	Yes
A/duck/Bangladesh/19097/2013 (SJ007)	2.3.2.1a	SJCRH	Yes
A/barn swallow/Hong Kong/D10-1161/2010 (SJ-003)	2.3.2.1b	SJCRH	Yes
A/chicken/Hong Kong/AP156/2008 (SJ002)	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/chicken/Bangladesh/11rs1984-30/2011 (IDCDC-RG36)	2.3.4.2	CDC	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/Guizhou/1/2013-like	2.3.4.2	CDC/CCDC	Pending
A/duck/Viet Nam/NCVD-1584/2012-like	2.3.2.1c	NIBSC	Pending
A/environment/Hubei/950/2013-like	7.2	CDC/CCDC	Pending
A/Sichuan/26221/2014-like	2.3.4.6[3]	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, a centre of the Medicines and Healthcare products Regulatory Agency (MHRA), 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

Influenza A(H7N9)

Influenza A(H7) viruses have been detected in poultry populations worldwide with the associated disease ranging from mild to severe. Human infections with avian influenza A(H7N9) viruses were first reported to WHO on 31 March 2013.

Influenza A(H7N9) activity from 18 February 2014 to 23 September 2014

During this period, 99 human cases of avian influenza A(H7N9) virus infection were reported to WHO, bringing the total number of cases to 454 with at least 171 deaths reported.[4] Comparison of avian influenza A(H7N9) viruses isolated from humans, poultry and environmental samples using haemagglutination inhibition assays shows that limited antigenic diversity exists among this group of viruses and the majority remain antigenically similar to the CVV derived from A/Anhui/1/2013-like viruses.

Influenza A(H7N9) candidate vaccine viruses

Based on the current epidemiologic and virologic data, no new A(H7N9) CVVs have been proposed. Available A(H7N9) CVVs are shown in Table 3. National authorities may consider the use of one or more of these A(H7N9) CVVs for pilot lot vaccine production, clinical trials and other pandemic preparedness purposes based on their assessment of public health risk and need. As the viruses continue to evolve, new A(H7N9) CVVs may be developed.

Table 3. Status of influenza A(H7N9) candidate vaccine virus development

Candidate vaccine virus	Type	Institution*	Available
A/Anhui/1/2013 (H7N9) IDCDC-RG33A	Reverse Genetics	CDC	Yes
A/Anhui/1/2013 (H7N9) NIBRG-268	Reverse Genetics	NIBSC	Yes
A/Anhui/1/2013 (H7N9) NIIDRG-10.1	Reverse Genetics	NIID	Yes
A/Anhui/1/2013 (H7N9) SJ005	Reverse Genetics	SJCRH	Yes
A/Shanghai/2/2013 (H7N9) NIBRG-267	Reverse Genetics	NIBSC	Yes
A/Shanghai/2/2013 (H7N9) CBER-RG4A	Reverse Genetics	FDA	Yes
A/Shanghai/2/2013 (H7N9) IDCDC-RG32A	Reverse Genetics	CDC	Yes
A/Shanghai/2/2013 (H7N9) IDCDC-RG32A.3	Reverse Genetics	CDC	Yes

* **Institutions distributing the candidate vaccine viruses:**
CDC - Centers for Disease Control and Prevention, United States of America
FDA - Food and Drug Administration, United States of America
NIBSC - National Institute for Biological Standards and Control, a centre of the Medicines and Healthcare products Regulatory Agency (MHRA), 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

[4] Communication from Chinese Center for Disease Control and Prevention (CCDC)

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 to the G1, chicken/Beijing (Y280/G9), or Eurasian clades. 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 18 February 2014 to 23 September 2014

No human cases of A(H9N2) infection have been reported in this period. The majority of G1-like viruses tested by haemagglutinin inhibition assay remained antigenically similar to available CVVs. Antigenic heterogeneity exists between viruses of different Y280/G9 sublineages circulating in China with some recent avian viruses reacting less well to ferret antisera raised against CVVs.

Influenza A(H9N2) candidate vaccine viruses

Based on the current antigenic, genetic and epidemiologic data, no new CVVs are proposed. The available A(H9N2) CVVs are listed in Table 4. National authorities may consider the use of one or more of these A(H9N2) CVVs for pilot lot vaccine production, clinical trials and other pandemic preparedness purposes based on their assessment of public health risk and need. As the viruses continue to evolve, new A(H9N2) CVVs may be developed.

Table 4. Status of influenza A(H9N2) candidate vaccine virus development

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	Y280/G9	CDC	Yes
A/Hong Kong/33982/2009 (IDCDC-RG26)	Reverse genetics	G1	CDC	Yes
A/Bangladesh/994/2011 (IDCDC-RG31)	Reverse genetics	G1	CDC	Yes
Candidate vaccine viruses in preparation				
A/Hong Kong/308/2014-like	Reverse genetics	Y280/G9	SJCRH	Pending

* **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, a centre of the Medicines and Healthcare products Regulatory Agency (MHRA), United Kingdom of Great Britain and Northern Ireland
SJCRH - St Jude Children's Research Hospital, United States of America

Influenza A(H3N2) variant (v)[5]

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[6].

Influenza A(H3N2)v activity from 18 February 2014 to 23 September 2014

Two human cases of A(H3N2)v infection were reported in the United States of America during this reporting period[7]. These viruses were genetically distinct from previously characterized A(H3N2)v viruses. Antigenic information is pending. Both cases were in children that had known exposure to swine. Similar viruses continue to be isolated from pigs in the United States of America.

Influenza A(H3N2)v candidate vaccine viruses

Based on the available antigenic, genetic and epidemiologic data, no new A(H3N2)v CVVs are proposed. Available CVVs are shown in Table 5. Institutions that wish to receive CVVs should contact WHO at gisrs-whohq@who.int or Centers for Disease Control and Prevention, United States of America.

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

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

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

5 http://www.who.int/influenza/gisrs_laboratory/terminology_ah3n2v/en/
6 Myers, KP. et al. Cases of Swine Influenza in Humans: A Review of the Literature. Clin Infect Dis. 44:1084. 2007
7 http://www.cdc.gov/flu/swineflu/h3n2v-cases.htm