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

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

Selection and development of CVVs are the first steps towards timely vaccine production and do 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.

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

This document summarizes the genetic and antigenic characteristics of recent zoonotic influenza viruses and related viruses circulating in animals[1] that are relevant to CVV updates. Institutions interested in receiving these CVVs should contact WHO at gisrs-whohq@who.int or the institutions listed in announcements published on the WHO website[2].

Influenza A(H5)

Since their emergence in 1997, highly pathogenic avian influenza (HPAI) A(H5) viruses of the A/goose/Guangdong/1/96 haemagglutinin (HA) lineage have become enzootic in some countries, have infected wild birds and continue to cause outbreaks in poultry and sporadic human infections. These viruses have diversified genetically and antigenically, including the emergence of viruses with replacement of the N1 gene segment by N2, N3, N5, N6, N8 or N9 gene segments, leading to the need for multiple CVVs. This summary provides updates on the characterization of A/goose/Guangdong/1/96-lineage A(H5) viruses and the current status of the development of influenza A(H5) CVVs.

Influenza A(H5) activity from 23 February 2016 to 26 September 2016

A(H5) human infections have been reported to the WHO by China (4 cases) and Egypt (10 cases -the date of disease onset for two of these fell outside of the reporting period) where A(H5) infections have also been detected in birds. The human infections in Egypt were caused by A(H5N1) viruses, whilst the human infections in China were caused by A(H5N6) viruses. A/goose/Guangdong/1/96-lineage A(H5) viruses were detected in birds in Bangladesh, Cambodia, Cameroon, China, Côte d'Ivoire, Egypt, Ghana, India, Indonesia, Iraq, Lebanon, Myanmar, Nigeria, the Republic of Korea, the Russian Federation, Togo, the United States of America and Viet Nam (Table 1).

[1] For information relevant to other notifiable influenza virus infections in animals refer to http://www.oie.int/wahis_2/public/wahid.php/Wahidhome/Home

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

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

Country, area or territory	Host	Genetic clade
Bangladesh	Poultry	2.3.2.1a
Cambodia	Poultry	2.3.2.1c
Cameroon	Poultry	2.3.2.1c
China	Poultry/environmental	2.3.2.1c, 2.3.4.4 (H5N2/N3/N6/N8/N9)
	Human (4)[#]	2.3.4.4 (H5N6)
Côte d'Ivoire	Poultry	2.3.2.1c
Egypt	Poultry	2.2.1.2
	Human (8)	2.2.1.2
Ghana	Poultry	2.3.2.1c
India	Poultry	2.3.2.1a
Indonesia	Poultry	unknown
Iraq	Poultry	2.3.2.1c
Lebanon	Poultry	2.3.2.1c
Myanmar	Poultry	unknown
Nigeria	Poultry	2.3.2.1c
Republic of Korea	Poultry	2.3.4.4 (H5N8)
Russian Federation	Wild birds	2.3.4.4 (H5N8)
Togo	Poultry	2.3.2.1c
United States of America	Wild bird	2.3.4.4 (H5N2)
Viet Nam	Poultry	2.3.2.1c/2.3.4.4 (H5N6)

# denotes number of human cases reported to WHO within reporting period

Antigenic and genetic characteristics of influenza A(H5) viruses

The nomenclature for phylogenetic relationships among the HA genes of A/goose/Guangdong/1/96-lineage 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[3].

Viruses circulating and characterized from 23 February 2016 to 26 September 2016 belong to the following clades:

Clade 2.2.1.2 viruses were detected in poultry and eight human infections in Egypt. Although the HAs of the 2016 viruses have accumulated a number of amino acid substitutions relative to A/Egypt/N04915/2014, from which a CVV has been developed, they remain antigenically similar to the CVV.

Clade 2.3.2.1a viruses were detected in birds in Bangladesh and India. The HA genes of these viruses are similar to viruses detected in the region in previous periods. While recent viruses isolated from quail in Bangladesh have diversified antigenically, the 2016 clade 2.3.2.1a viruses generally reacted well with post-infection ferret antiserum raised against the A/duck/Bangladesh/19097/2013 CVV.

Clade 2.3.2.1c viruses were detected in birds in Cambodia, Cameroon, China, Côte d'Ivoire, Ghana, Iraq, Lebanon, Nigeria, Togo and Viet Nam. Viruses of this clade have continued to evolve, leading to significant genetic and antigenic diversity. Viruses detected from poultry and the environment in China were genetically and antigenically distinct from A/duck/Viet Nam/NCVD-1584/2012, from which a CVV has been developed (Figure 1 and Table 2) and therefore development of a new CVV derived from an A/chicken/Guiyang/1153/2016-like virus is proposed. Clade 2.3.2.1c viruses from South-East Asia, the Middle-East and West Africa have accumulated a number of amino acid substitutions relative to A/duck/Viet Nam/NCVD-1584/2012. Viruses from several West African countries, in particular, reacted poorly with post-infection ferret antisera raised to available CVVs (Table 3) and the development of a new CVV derived from an A/chicken/Ghana/20/2015-like virus is proposed.

[3] http://onlinelibrary.wiley.com/doi/10.1111/irv.12324/epdf

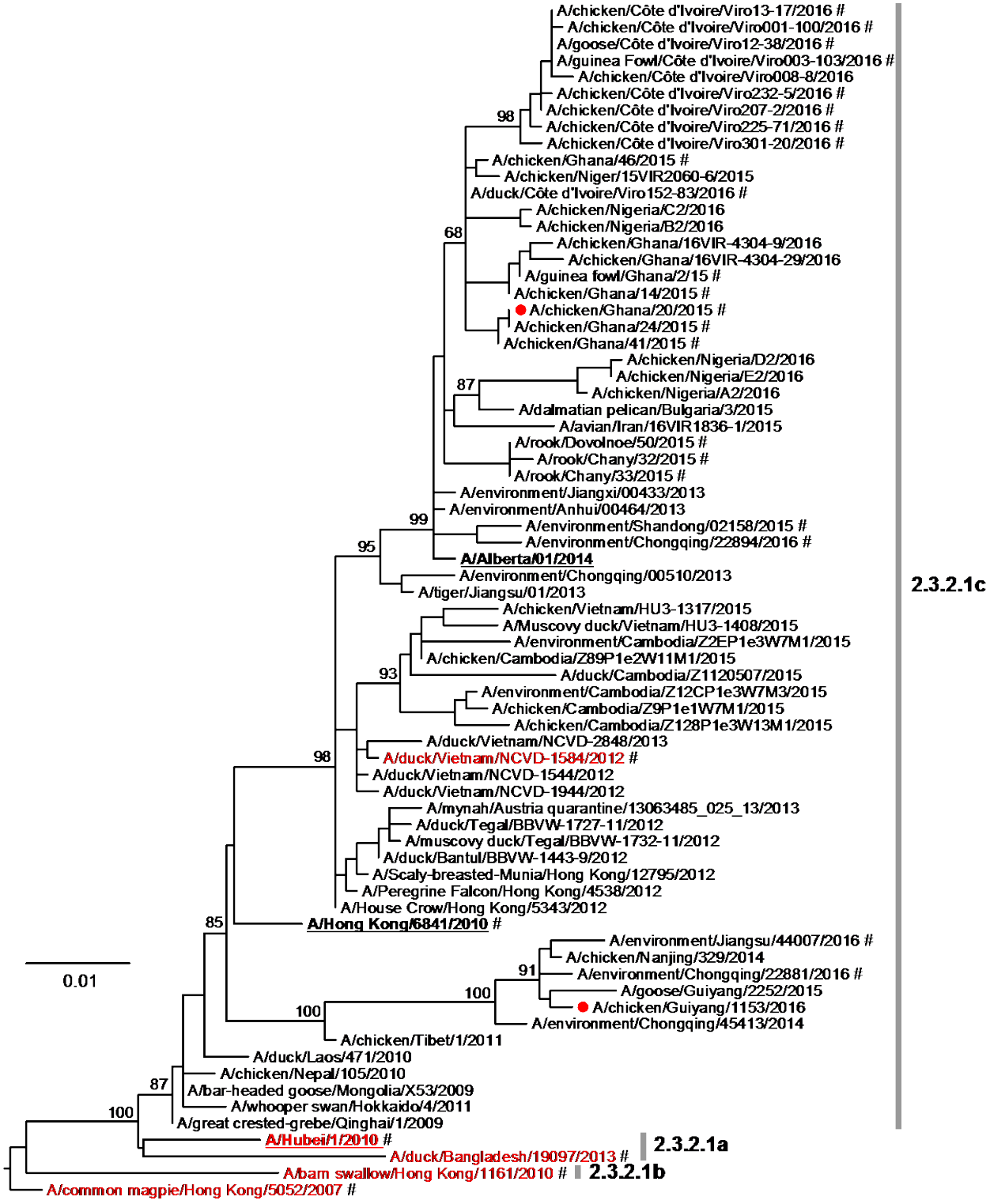

Figure 1. Phylogenetic relationships of A(H5) clade 2.3.2.1 HA genes. The available CVVs are in red. The proposed CVV is indicated by a red dot(●). Human viruses are underlined and in bold font. The viruses tested in haemagglutination inhibition assay are indicated by hashes (#). The scale bar represents the number of substitutions per site. Bootstrap supports of topology are shown above selected nodes.

Table 2. Haemagglutination inhibition assays of clade 2.3.2.1c influenza A(H5N1) viruses.

REFERENCE ANTIGENS	Clade	NIBRG-23	HK/5052	Hubei/10	BA/19097	HK/D10-1161	dk/VN/1584
A/turkey/Turkey/1/2005 NIBRG-23	2.2.1	**80**	320	40	160	1280	160
A/common magpie/Hong Kong/5052/2007 (SJRG-166615)	2.3.2.1	<#	**320**	20	80	640	160
A/Hubei/1/2010 (IDCDC-RG30)	2.3.2.1a	<	640	**160**	160	1280	160
A/duck/Bangladesh/19097/2013 (SJ007)	2.3.2.1a	<	640	<	**640**	640	160
A/barn swallow/Hong Kong/D10-1161/2010 (SJ003)	2.3.2.1b	<	320	<	80	**640**	80
TEST ANTIGENS							
A/Environment/Jiangsu/44007/2016	2.3.2.1c	<	<	<	<	20	<
A/Environment/Chongqing/22881/2016	2.3.2.1c	<	<	<	<	<	<
A/Environment/Chongqing/22894/2016	2.3.2.1c	<	<	<	20	40	20
A/Environment/Shandong/02158/2015	2.3.2.1c	<	<	<	40	80	40

represents a haemagglutination inhibition titre of <20

Table 3. Haemagglutination inhibition assays of clade 2.3.2.1c influenza A(H5N1) viruses.

REFERENCE ANTIGENS	Clade	RG30	BS/HK/1161	dk/VN/1584	HK/6841	CM/HK/5052
A/Hubei/1/2010 (IDCDC-RG30)	2.3.2.1a	**80**	320	160	320	80
A/barn swallow/Hong Kong/1161/2010 (SJ003)	2.3.2.1b	<#	**320**	40	160	40
A/duck/Viet Nam/NCVD-1584/2012 (NIBRG-	2.3.2.1c	160	320	**320**	320	80
A/Hong Kong/6841/2010	2.3.2.1c	10	160	80	**160**	40
A/common magpie/Hong Kong/5052/2007 (SJRG-166615)	2.3.2.1	10	320	40	160	**160**
TEST ANTIGENS						
A/guinea fowl/Côte d'Ivoire/Viro13-17/2016	2.3.2.1c	<	10	40	40	<
A/goose/Côte d'Ivoire/Viro12-38/2016	2.3.2.1c	<	20	160	160	10
A/chicken/Côte d'Ivoire/Viro232-5/2015	2.3.2.1c	<	10	40	40	10
A/chicken/Côte d'Ivoire/Viro225-71/2015	2.3.2.1c	<	<	40	40	<
A/chicken/Côte d'Ivoire/Viro152-83/2015	2.3.2.1c	<	<	20	10	<
A/guinea fowl/Ghana/2/2015	2.3.2.1c	<	20	80	80	10
A/chicken/Ghana/14/2015	2.3.2.1c	<	<	20	10	<
A/chicken/Ghana/20/2015	2.3.2.1c	<	<	<	10	10
A/chicken/Ghana/24/2015	2.3.2.1c	<	<	10	20	20
A/chicken/Ghana/46/2015	2.3.2.1c	<	10	80	40	<
A/rook/Chany/32/2015	2.3.2.1c	<	10	80	80	<
A/rook/Dovolnoe/50/2015	2.3.2.1c	<	<	40	20	<

represents a haemagglutination inhibition titre of <10

Clade 2.3.4.4 viruses were detected in birds in the Republic of Korea, the Russian Federation, the United States of America and Viet Nam and in birds, environmental samples and humans in China. Phylogenetic analysis of the HA gene segment of viruses from the Republic of Korea, the Russian Federation, the United States of America, Viet Nam and some of the viruses from China indicated that they were very similar to those of viruses characterized in previous periods (Figure 2). Correspondingly, these viruses reacted well with post-infection ferret antisera raised to available CVVs. An increasing number of recent viruses from China, including those from human cases, had HA gene sequences that clustered together and had accumulated up to 13 amino acid substitutions relative to A/chicken/Viet Nam/NCVD-15A59/2015, for which a CVV has been proposed. These viruses also reacted poorly with post-infection ferret antisera raised against A/chicken/Viet Nam/NCVD-15A59/2015-like viruses, including A/Guangdong/99710/2014 and A/chicken Shenzhen/433/2013 (Table 4 and 5), and a new CVV based on an A/Hubei/29578/2016-like A(H5N6) virus is proposed.

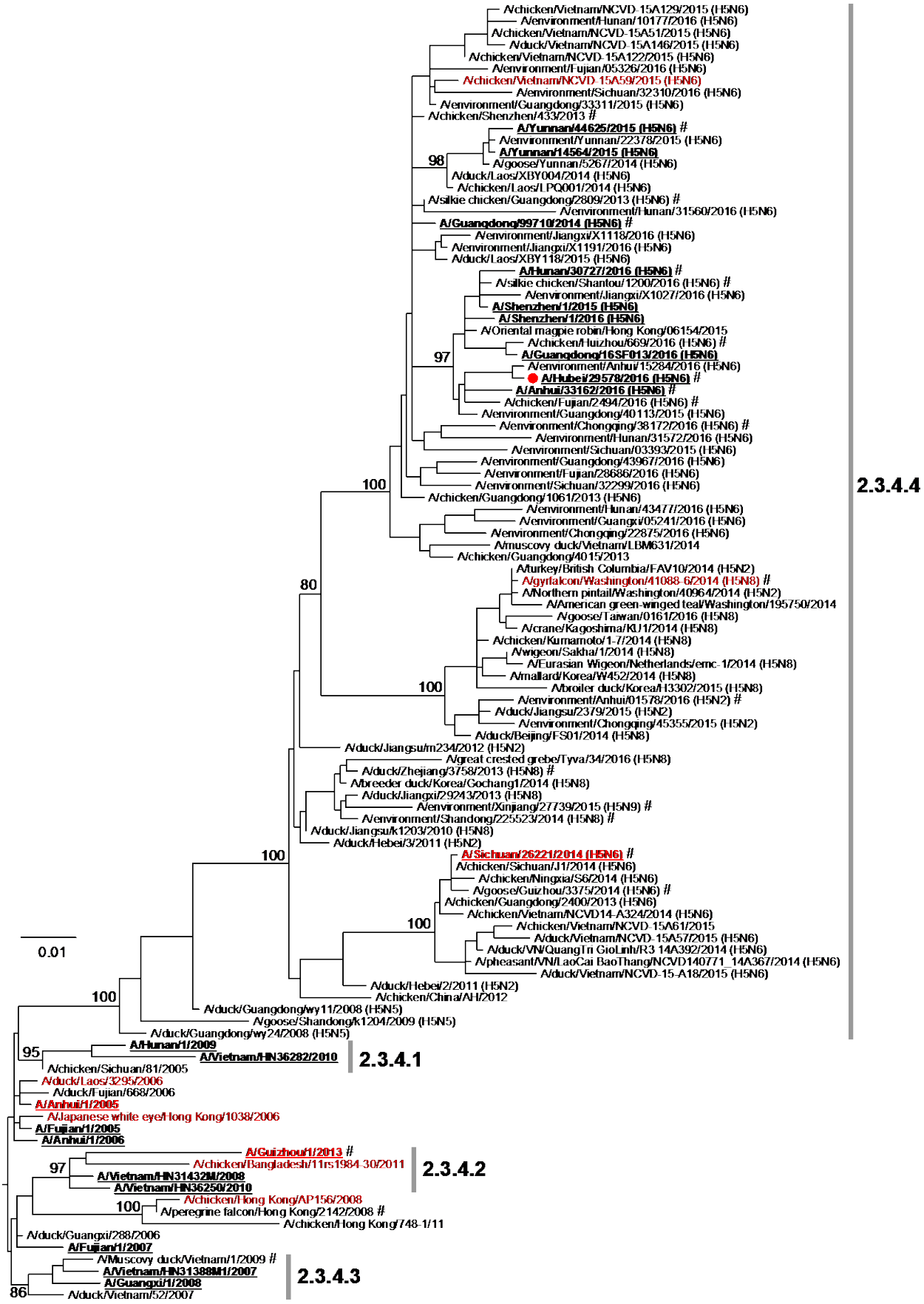

Figure 2. Phylogenetic relationships of A(H5) clade 2.3.4 HA genes. The available CVVs (and those in preparation) are in red. The proposed CVV is indicated by a red dot(●). Human viruses are underlined and in bold font. The viruses tested in haemagglutination inhibition assay are indicated by hashes (#). 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.

Table 4. Haemagglutination inhibition assays of clade 2.3.4.4 influenza A(H5) viruses.

REFERENCE ANTIGENS	Clade	GZ1	SC/ 26221	GD/ 99170	GYR/ 41088-6
A/Guizhou/1/2013 RG35 (H5N1)	2.3.4.2	**320**	<#	<	<
A/Sichuan/26221/2014 RG42A (H5N6)	2.3.4.4	20	**160**	1280	40
A/Guangdong/99710/2014 (H5N6)	2.3.4.4	20	320	**1280**	<
A/gyrfalcon/Washington/41088-6/2014 RG43A (H5N8)	2.3.4.4	<	160	160	**80**
TEST ANTIGENS					
A/environment/Anhui/01578/2016 (H5N2)	2.3.4.4	<	<	160	<
A/environment/Chongqing/38172/2016 (H5N6)	2.3.4.4	<	320	1280	<
A/environment/Shandong/225523/14 (H5N8)	2.3.4.4	<	20	80	<
A/environment/Xinjiang/27739/2015 (H5N9)	2.3.4.4	<	40	320	<
A/Hubei/29578/2016 (H5N6)	2.3.4.4	<	<	<	<
A/Yunan/44625/2015 (H5N6)	2.3.4.4	<	<	20	<
A/Anhui/33162/2016 (H5N6)	2.3.4.4	<	<	<	<
A/Hunan/30727/2016 (H5N6)	2.3.4.4	<	80	80	<

represents a haemagglutination inhibition titre of <20

Table 5. Haemagglutination inhibition assays of clade 2.3.4.4 influenza A(H5) viruses.

REFERENCE ANTIGENS	Clade	Pf/HK/ 2142	MDk/ VN/1	Gs/GY /3375	Dk/ZJ /3758	SCk/ GD/2 809	Ck/S Z/433
A/peregrine falcon/Hong Kong/2142/2008 (H5N1)	2.3.4	**640**	160	<#	<	<	<
A/muscovy duck/Viet Nam/1/2009 (H5N1)	2.3.4.3	160	**640**	<	<	<	<
A/goose/Guiyang/3375/2014 (H5N6)	2.3.4.4	20	<	**160**	40	40	10
A/duck/Zhejiang/3758/2013 (H5N8)	2.3.4.4	40	<	80	**320**	20	<
A/silkie chicken/Guangdong/2809/2013 (H5N6)	2.3.4.4	80	<	1280	160	**320**	80
A/chicken/Shenzhen/433/2013 (H5N6)	2.3.4.4	160	<	1280	160	160	**80**
TEST ANTIGENS							
A/chicken/Huizhou/669/2016 (H5N6)	2.3.4.4	40	<	<	<	<	<
A/silkie chicken/Shantou/1200/2016 (H5N6)	2.3.4.4	40	<	10	<	<	<
A/chicken/Fujian/2494/2016 (H5N6)	2.3.4.4	10	<	10	10	<	<

represents a haemagglutination inhibition titre of <10

Influenza A(H5) candidate vaccine viruses

Based on the available antigenic, genetic and epidemiologic data, new A/Hubei/29578/2016-like (2.3.4.4), A/chicken/Guiyang/1153/2016-like (2.3.2.1c) and A/chicken/Ghana/20/2015-like (2.3.2.1c) CVVs are proposed. The available and pending A(H5) CVVs are listed in Table 6. As the viruses continue to evolve, new A(H5) CVVs may be developed.

Table 6. 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/HKU	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/HKU	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/Egypt/N04915/2014 (NIBRG-306)	2.2.1.2	NIBSC	Yes
A/common magpie/Hong Kong/5052/2007 (SJRG-166615)	2.3.2.1	SJCRH/HKU	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 (SJ003)	2.3.2.1b	SJCRH/HKU	Yes
A/duck/Viet Nam/NCVD-1584/2012 (NIBRG-301)	2.3.2.1c	NIBSC	Yes
A/chicken/Hong Kong/AP156/2008 (SJ002)	2.3.4	SJCRH/HKU	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/HKU	Yes
A/chicken/Bangladesh/11rs1984-30/2011 (IDCDC-RG36)	2.3.4.2	CDC	Yes
A/Guizhou/1/2013 (IDCDC-RG35)	2.3.4.2	CDC/CCDC	Yes
A/goose/Guiyang/337/2006 (SJRG-165396)	4	SJCRH/HKU	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
A/Sichuan/26221/2014 (IDCDC-RG42A) (H5N6)	2.3.4.4	CDC/CCDC	Yes
A/gyrfalcon/Washington/41088-6/2014 (IDCDC-RG43A) (H5N8)	2.3.4.4	CDC	Yes
Candidate vaccine viruses in preparation	**Clade**	**Institution**	**Availability**
A/chicken/Guiyang/1153/2016-like	2.3.2.1c	SJCRH/HKU	Pending
A/chicken/Ghana/20/2015-like	2.3.2.1c	CDC	Pending
A/chicken/Viet Nam/NCVD-15A59/2015-like (H5N6)	2.3.4.4	SJCRH	Pending
A/Hubei/29578/2016-like (H5N6)	2.3.4.4	CCDC	Pending
A/environment/Hubei/950/2013	7.2	CDC/CCDC	Pending

* **Institutions developing and/or distributing the candidate vaccine viruses:**
CDC - Centers for Disease Control and Prevention, United States of America
NIV - National Institute of Virology, India
CCDC - Chinese Center for Disease Control and Prevention
FDA - Food and Drug Administration, United States of America
HKU – University of Hong Kong, Hong Kong Special Administrative Region, China.
NIBSC - National Institute for Biological Standards and Control, a centre of the Medicines and Healthcare products Regulatory Agency (MHRA), United Kingdom
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. A(H7N9) viruses are enzootic in poultry in China and reassortment with A(H9N2) viruses has generated multiple genotypes.

Influenza A(H7N9) activity from 23 February 2016 to 26 September 2016

During this period, 77 human cases of avian influenza A(H7N9) virus infection in mainland China and China Hong Kong Special Administrative Region (SAR) were reported to WHO, bringing the total number of cases since 2013 to 798 with 320 deaths. Concomitant with control measures being implemented, including closure of some live poultry markets, human cases and virus detections in poultry were lower in this fourth wave compared to the prior waves. Recent A(H7N9) viruses were genetically similar to those detected previously. Comparison of human and avian viruses using haemagglutination inhibition assays showed that the majority tested remained antigenically similar to A/Anhui/1/2013 and A/Shanghai/2/2013, from which CVVs have been developed.

Influenza A(H7N9) candidate vaccine viruses

Based on the current epidemiologic and virologic data, no new A(H7N9) CVVs are proposed. Available A(H7N9) CVVs are shown in Table 7. As the viruses continue to evolve, new A(H7N9) CVVs may be developed.

Table 7. Status of influenza A(H7N9) candidate vaccine virus development

Candidate vaccine virus	Type	Institution*	Available
A/Anhui/1/2013 (IDCDC-RG33A)	Reverse Genetics	CDC	Yes
A/Anhui/1/2013 (NIBRG-268)	Reverse Genetics	NIBSC	Yes
A/Anhui/1/2013 (NIIDRG-10.1)	Reverse Genetics	NIID	Yes
A/Anhui/1/2013 (SJ005)	Reverse Genetics	SJCRH	Yes
A/Shanghai/2/2013 (NIBRG-267)	Reverse Genetics	NIBSC	Yes
A/Shanghai/2/2013 (CBER-RG4A)	Reverse Genetics	FDA	Yes
A/Shanghai/2/2013 (IDCDC-RG32A)	Reverse Genetics	CDC	Yes
A/Shanghai/2/2013 (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
NIID - National Institute of Infectious Diseases, Japan
SJCRH - St Jude Children's Research Hospital, United States of America

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 A/quail/Hong Kong/G1/97 (G1) and A/chicken/Beijing/1/94 (Y280/G9) lineages. Since 1998, when the first human infection was identified, the detection of A(H9N2) viruses from humans and swine has been reported infrequently. In most human cases the associated influenza-like symptoms have been mild and there has been no evidence of human-to-human transmission.

Influenza A(H9N2) activity from 23 February 2016 to 26 September 2016

Six human cases of A(H9) infection have been identified in this period, five from China and one from Egypt. A further three cases, one with a fatal outcome, were identified from China but had dates of disease onset prior to this reporting period. The A(H9N2) viruses from China were genetically and antigenically similar to Y280-lineage A(H9N2) viruses known to circulate in birds and they reacted well to post-infection ferret antisera raised against available CVVs. No genetic or antigenic data are available for the A(H9) virus detected in Egypt but A(H9N2) viruses isolated from poultry in Egypt react well with post-infection ferret antiserum raised against A/Bangladesh/0994/2011 from which a CVV has been developed. A(H9N2) viruses from birds were characterized from a number of other countries, with most being similar to those detected in previous periods.

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 8. As the viruses continue to evolve, new A(H9N2) CVVs may be developed.

Table 8. 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
A/Hong Kong/308/2014 (SJ008)	Reverse genetics	Y280/G9	SJCRH	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, a centre of the Medicines and Healthcare products Regulatory Agency (MHRA), United Kingdom

SJCRH - St Jude Children's Research Hospital, United States of America

Influenza A(H1N2) variants (v)[4]

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

Influenza A(H1N2)v activity from 23 February 2016 to 26 September 2016

Three non-fatal A(H1N2)v human cases were detected in the United States of America from March to June 2016 in patients with reported exposure to swine. The HA from one virus belonged to the classical swine 'alpha' lineage of swine influenza viruses[5]. The other two viruses had HA gene segments that belonged to the 'delta 1' lineage of swine influenza viruses, which were derived from seasonal A(H1N1) human viruses of the early 2000s. Each of the three variant viruses had genome compositions closely related to those identified in circulating swine viruses.

All three A(H1N2)v viruses reacted poorly to post-infection ferret antisera generated against available CVVs including those derived from A/California/7/2009 [A(H1N1)pdm09] and A/Ohio/09/2015 [A(H1N1)v] and to a post-infection ferret antiserum generated against A/Brisbane/59/2007 [A(H1N1)]. Reactivity to pooled human sera collected post-vaccination with the 2015-2016 Northern Hemisphere vaccine was also reduced for all three viruses and further evaluation of individual serum samples is underway to better determine the level of population immunity to these viruses and, correspondingly, the need for additional CVVs.

One non-fatal A(H1N2)v human case was retrospectively detected in Brazil; the person had onset of disease in November 2015 and had no known exposure to swine. The HA and NA genes of this virus were similar to those of viruses isolated from swine in Brazil in recent years. The remaining genes were all of A(H1N1)pdm09 origin. Viruses with this genomic composition have been detected in swine in Brazil. Virus was not recovered from the clinical specimen.

Influenza A(H1)v candidate vaccine viruses

Based on the available antigenic, genetic and epidemiologic data, no new A(H1)v CVVs are proposed. The available A(H1)v CVVs are listed in Table 9. As the viruses continue to evolve and as new data are generated, new A(H1)v CVVs may be developed.

Table 9. Status of A(H1N1)v candidate vaccine virus development.

Candidate vaccine viruses	Type	Institution*
A/Ohio/9/2015 (IDCDC-RG48A)	Reverse genetics	CDC
A/Hunan/42443/2015 (CNIC-1601)	Conventional reassortant	CCDC
Candidate vaccine viruses in preparation	**Type**	**Institution**
A/Hunan/42443/2015-like	Conventional reassortant	NIBSC

***Institution distributing the candidate vaccine virus:**
CDC - Centers for Disease Control and Prevention, United States of America
CCDC - Chinese Center for Disease Control and Prevention, China
NIBSC - National Institute for Biological Standards and Control, a centre of the Medicines and Healthcare products Regulatory Agency (MHRA), United Kingdom

[4] http://www.who.int/influenza/gisrs_laboratory/terminology_variant/en/
[5] http://onlinelibrary.wiley.com/doi/10.1111/zph.12049/pdf

Influenza A(H3N2)v

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 influenza A(H3N2) viruses have been documented in Asia, Europe and North America[6].

Influenza A(H3N2)v activity from 23 February 2016 to 26 September 2016

A total of 18 human cases of A(H3N2)v virus infections were detected in the United States of America in July and August. All cases reported exposure to swine while attending agricultural fairs. No human-to-human transmission was identified. Sixteen of these individuals were less than 18 years old with seven being less than 5 years old. Although one person with an underlying condition was hospitalized for two days, all cases eventually recovered. All A(H3N2)v viruses were closely related to A(H3N2) viruses currently circulating in swine populations in the United States of America. Sixteen of the A(H3N2)v viruses had HA genes belonging to the seasonal human-like lineage of swine influenza virus that was likely introduced into swine in 2010 or 2011. The remaining two A(H3N2)v viruses had HA genes that belonged to the IV-A lineage of swine influenza viruses (Figure 3).

The seasonal human-like A(H3N2)v viruses were poorly inhibited by post-infection antisera raised against earlier IV-A lineage viruses and available CVVs. Post-infection ferret antisera raised against previous seasonal human A(H3N2) viruses also poorly inhibited these viruses. The viruses did, however, react well with pooled adult and, to a lesser extent, paediatric human sera from persons immunized with the 2015-2016 Northern Hemisphere seasonal vaccine. The two A(H3N2)v IV-A lineage viruses were well inhibited with post-infection ferret antisera raised against available CVVs (Table 10).

One non-fatal human case of A(H3N2)v virus infection was retrospectively detected in Viet Nam. The case had onset of disease in June 2015 with unknown exposure history. This virus was genetically related to viruses circulating in Vietnamese swine with HA gene segments being derived from human seasonal A(H3N2) viruses circulating in humans during 2003-2004.

Table 10. Haemagglutination inhibition assays of influenza A(H3N2)v viruses.

REFERENCE ANTIGENS	H3N2 clade	MOS/99	Perth/09	SWITZ	IN/10	MN/11	MN/11 X-203	child pool*	Adult pool*
A/Moscow/10/99	Seasonal	**1280**	10	<#	20	10	<	<	160
A/Perth/16/2009	Seasonal	10	**640**	10	10	10	<	640	640
A/Switzerland/9715293/2013	Seasonal	10	10	**640**	20	10	<	640	320
A/Indiana/10/2011	IV-A	10	<	10	**2560**	2560	1280	80	320
A/Minnesota/11/2010	IV-A	10	<	20	1280	**2560**	1280	80	640
A/Minnesota/11/2010 X-203	IV-A	10	80	<	320	640	**2560**	40	40
TEST ANTIGENS									
A/Ohio/27/2016	human-like	20	80	40	160	40	<	160	1280
A/Ohio/28/2016	human-like	20	80	40	160	10	<	320	1280
A/Ohio/29/2016	human-like	20	40	40	160	10	<	320	1280
A/Ohio/32/2016	human-like	20	40	40	80	10	<	160	640
A/Michigan/83/2016	human-like	20	40	40	80	80	40	160	1280
A/Michigan/87/2016	human-like	20	80	40	320	160	160	160	2560
A/Michigan/90/2016	human-like	20	80	40	160	80	80	160	1280
A/Michigan/93/2016	human-like	10	20	10	80	10	<	160	640
A/Michigan/84/2016	IV-A	20	<	10	1280	1280	640	80	320
A/Michigan/94/2016	IV-A	20	10	10	1280	1280	640	80	320

* post immunization human serum pool

represents a haemagglutination inhibition titre of <10

[6] http://www.eurosurveillance.org/images/dynamic/EE/V19N18/art20793.pdf

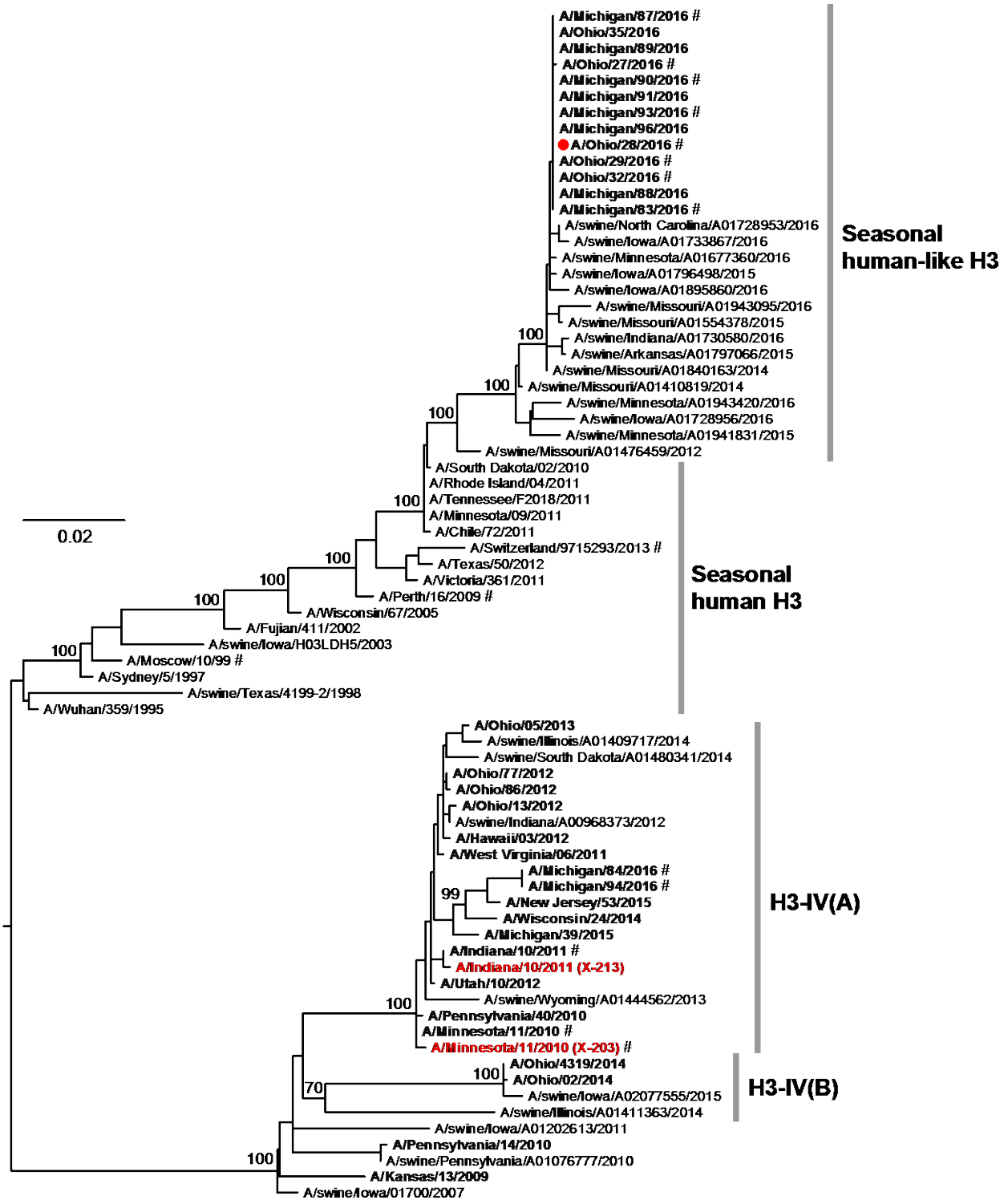

Figure 3. Phylogenetic relationships of A(H3) HA genes. The available CVVs are in red. The proposed CVV is indicated by a red dot(●). The A(H3N2)v viruses are in bold font. The viruses tested in haemagglutination inhibition assay are indicated by hashes (#). The scale bar represents the number of substitutions per site. Bootstrap supports of topology are shown above selected nodes.

Influenza A(H3N2)v candidate vaccine viruses

Based on the available antigenic, genetic and epidemiologic data, a new A/Ohio/28/2016-like A(H3N2)v CVV is proposed. The available A(H3N2)v CVVs are listed in Table 11. As the viruses continue to evolve and as new data are generated, new A(H3N2)v CVVs may be developed.

Table 11. 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
Candidate vaccine viruses in preparation		
A/Ohio/28/2016-like	Conventional reassortant and reverse genetics	NIBSC CDC

* **Institution 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

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