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

March 2017

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 influenza 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 characterisation 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 27 September 2016 to 27 February 2017

A(H5) human infections have been reported to the WHO by China (2 cases) and Egypt (2 cases) where A(H5) infections have also been detected in birds. The human infections in Egypt, of which one was fatal, 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 poultry and wild birds in many countries (Annex 1), 1072 and 644 events, respectively, were reported to the World Organisation for Animal Health (OIE) and by national authorities.

[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/candidates_reagents/home/en/

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), OIE and academic institutions[3].

Viruses circulating and characterised from 27 September 2016 to 27 February 2017 belong to the following clades:

Clade 2.2.1.2 viruses were detected in poultry in Egypt. Although the HAs of the 2016 viruses from birds had accumulated a number of amino acid substitutions relative to A/Egypt/N04915/2014, from which a CVV has been developed, they remained antigenically similar to the CVV. No antigenic or genetic data are available for the human viruses from Egypt.

Clade 2.3.2.1a viruses were detected in birds in Bangladesh, Bhutan and India. The HA genes of these viruses were similar to viruses detected in the region in previous periods. Viruses from Bangladesh were available for antigenic testing and they 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 China, Côte d'Ivoire, Ghana, Lao People's Democratic Republic, Niger, Nigeria, Togo and Viet Nam. The viruses from Africa were genetically and antigenically distinct from those in Asia. The viruses from Africa were genetically and antigenically similar to viruses detected previously, including A/chicken/Ghana/20/2015 from which a CVV is under development. The viruses from Asia were also similar to previously detected viruses and CVVs.

Clade 2.3.4.4 viruses were detected in birds in many countries in Africa, Asia and Europe, in the United States of America and in two humans in China (Annex 1). The clade 2.3.4.4 viruses from Africa and Europe were primarily of the A(H5N8) subtype, those in Asia were primarily A(H5N6) and that in the United States of America was A(H5N2). The HA genes of the human viruses from China fell within the same phylogenetic cluster as A/Hubei/29578/2016, from which a CVV has been developed (Figure 1); antigenic information is not yet available. Clade 2.3.4.4 viruses from birds in Africa and Europe were genetically similar to viruses detected in previous periods (Figure 1). The viruses from Europe reacted well with post-infection ferret antiserum raised against the A/chicken/Viet Nam/NCVD-15A59/2015 CVV (Table 1). The A(H5N6) viruses detected in Japan and the Republic of Korea were genetically similar to each other and did not react well with post-infection ferret antiserum raised against available CVVs (Table 1). A new A/duck/Hyogo/1/2016-like CVV is proposed.

Table 1. Haemagglutination inhibition assays of clade 2.3.4.4 influenza A(H5) viruses.

REFERENCE ANTIGENS	Subtype	np/WA	RG43A	md/Ko	dk/En	ck/ Ku	RG42A	Omr/ HK	ck/ VN	tfdk/ De
A/np/Washington/40964/2014	H5N2	**640**	80	80	20	80	40	< #	160	20
A/gf/Washington/41088-6/2014 RG43A	H5N8	1280	**320**	320	40	320	80	<	640	40
A/mallard/Korea/W452/2014	H5N8	80	80	**80**	10	80	<	<	40	10
A/duck/England/36254/2014	H5N8	1280	160	320	**80**	320	160	<	640	160
A/chicken/Kumamoto/1-7/2014	H5N8	40	20	40	10	**80**	10	<	80	10
A/Sichuan/2622120/2014 RG42A	H5N6	640	80	40	10	160	**80**	10	320	<
A/o.magpie robin/HK/6154/2015	H5N6	<	<	<	<	10	<	**80**	20	<
A/ck/VN/NCVD-15A59/2015	H5N6	80	10	20	<	40	10	<	**160**	<
A/tf.dk/Denmark/11740-1wp1/2016	H5N8	160	80	80	40	80	10	<	160	**80**
TEST ANTIGENS										
A/duck/Hyogo/1/2016	H5N6	20	<	10	<	10	<	20	40	<

represents a haemagglutination inhibition titre of <10

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

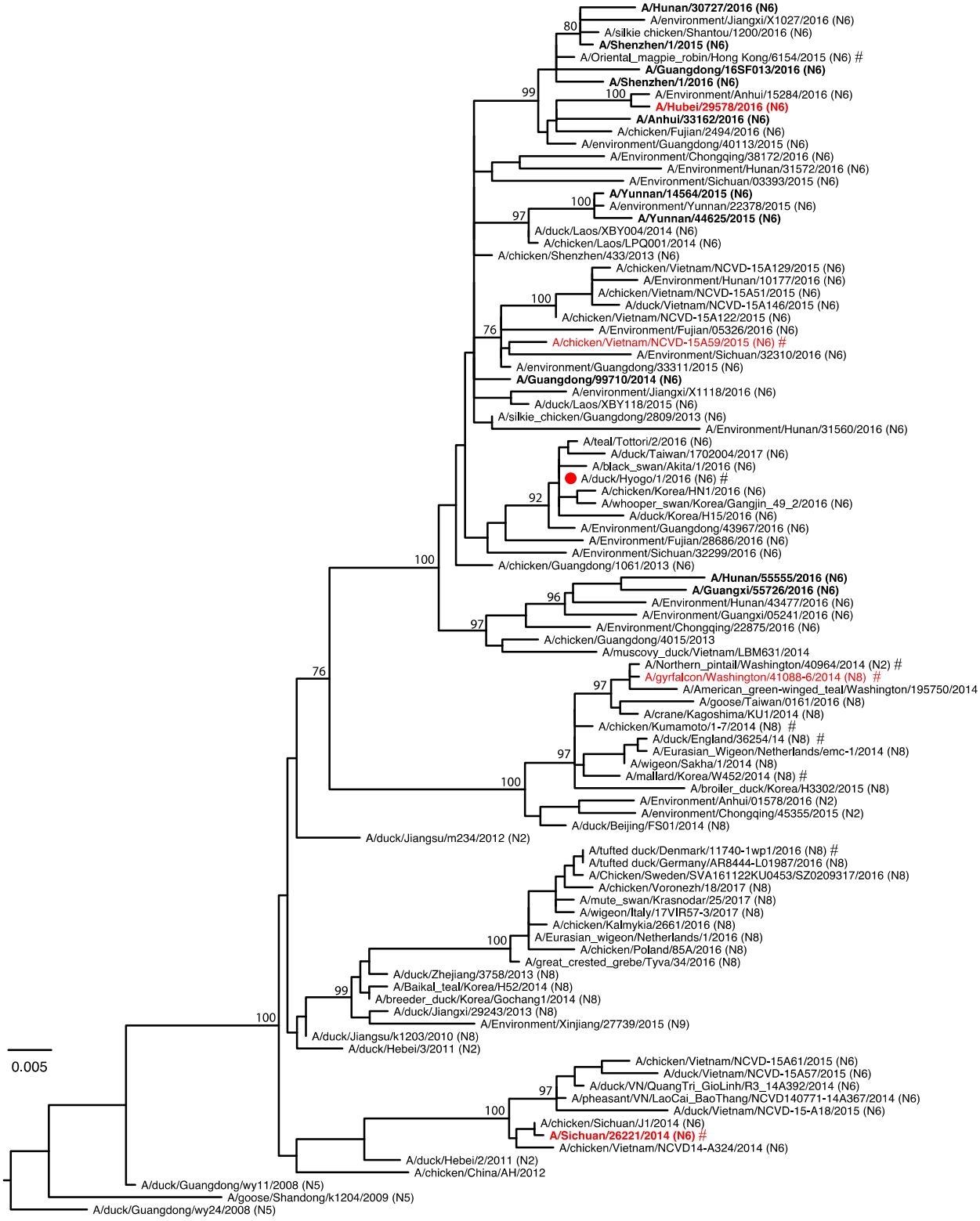

Figure 1. Phylogenetic relationships of A(H5) clade 2.3.4.4 HA genes. The available CVVs are in red. The proposed CVV is indicated by a red dot(●). Human viruses are in bold font. The viruses tested in haemagglutination inhibition assay are indicated by hashes (#). NA subtypes other than N1 are specified. The scale bar represents the number of substitutions per site. Bootstrap supports of topology are shown above selected nodes.

Influenza A(H5) candidate vaccine viruses

The available and pending A(H5) CVVs are listed in Table 2. 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/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/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
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/environment/Hubei/950/2013	7.2	CDC/CCDC	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/duck/Hyogo/1/2016-like (H5N6)	2.3.4.4	NIID	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(H7)

Influenza A(H7N9)

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 continued to generate multiple genotypes.

Influenza A(H7N9) activity from 27 September 2016 to 27 February 2017

During this period, the fifth wave of human infection, 460 cases of A(H7N9) virus infection with 78 deaths were reported in China, China Hong Kong Special Administrative Region and China Macao Special Administrative Region bringing the total number of cases since 2013 to 1258 with 328 deaths. Despite control measures being implemented the number of human cases was higher in this fifth wave compared to the prior waves. Recent A(H7N9) viruses belong to the Yangtze River Delta (YRD) or Pearl River Delta (PRD) HA lineages (Figure 2). Recent viruses of the YRD lineage reacted less well with post-infection ferret antiserum raised against the available A/Anhui/1/2013 and A/Shanghai/2/2013-derived CVVs (Table 3). A new A/Hunan/2650/2016-like CVV is proposed (A/Hong Kong/125/2017 is an A/Hunan/2650/2016-like virus). Additionally, A(H7N9) viruses of the YRD lineage with multiple basic amino acids at the cleavage site have been detected in humans, poultry and environmental samples from live poultry markets. These viruses fulfil the requirements for classification as HPAI viruses. The HPAI A(H7N9) viruses were genetically and antigenically distinct from other A(H7N9) viruses including A/Hunan/2650/2016 and the current CVVs (Figure 2, Table 3 and 4). Therefore, a new CVV derived from an A/Guangdong/17SF003/2016-like virus (HPAI) is proposed.

Table 3. Haemagglutination inhibition assays of influenza A(H7N9) viruses.

REFERENCE ANTIGENS	Epidemic wave / lineage	An/1	An/1-RG	Sh/2	Hu/2650-RG
A/Anhui/1/2013	1st	**160**	80	320	320
A/Anhui/1/2013-RG	1st	320	**160**	640	640
A/Shanghai/2/2013	1st	320	160	**640**	640
A/Shanghai/2/2013-RG	1st	320	160	**640**	640
A/Hunan/2650/2016-RG	4th/YRD#	80	40	80	**640**
A/Hunan/2650/2016	4th/YRD	160	40	160	**640**
TEST ANTIGENS					
A/Fujian/2152/2017	5th/YRD	160	40	160	640
A/Fujian/54840/2016	5th/YRD	160	40	160	640
A/Jiangsu/6463/2017	5th/YRD	320	80	160	1280
A/Jiangsu/6454/2017	5th/YRD	80	40	160	320
A/Anhui/60936/2016	5th/YRD	80	40	80	320
A/Jiangsu/60460/2016	5th/YRD	80	40	80	320
A/Hunan/2287/2017	5th/YRD	160	40	80	640
A/Hunan/6948/2017	5th/YRD	40	<†	80	320
A/Anhui/60933/2016	5th/YRD	<	<	<	<
A/Guangdong/60060/2016	5th/PRD‡	320	160	640	320
A/Guangdong/17SF004/2017	5th/PRD	320	160	640	640
A/Guangdong/60061/2016	5th/PRD	160	80	320	320
A/Guangdong/17SF003/2016§	5th/ YRD	<	<	<	80
A/Guangdong/17SF006/2017§	5th/ YRD	40	<	40	160

Yangtze River Delta lineage; † represents a haemagglutination inhibition titre of <40; ‡ Pearl River Delta lineage; § HPAI viruses

Table 4. Haemagglutination inhibition assays of influenza A(H7N9) viruses.

REFERENCE ANTIGENS	Epidemic period / lineage	An/1	Sh/2	HK/5942	Gd/17SF003
A/Anhui/1/2013	1st	**640**	640	160	320
A/Shanghai/2/2013	1st	1280	**1280**	640	640
A/Hong Kong/5942/2013	2nd	1280	1280	**640**	640
A/Guangdong/17SF003/2016#	5th/YRD†	40	80	40	**320**
TEST ANTIGENS					
A/chicken/Shaoxing/5201/2013	2nd	1280	1280	640	640
A/chicken/Jiangxi/18482/2014	2nd/YRD	1280	1280	640	640
A/chicken/Wenzhou/201/2014	3rd	640	640	640	320
A/chicken/Jiangxi/14879/2015	3rd/YRD	640	640	640	640
A/Shenzen/SP195/2015	3rd/PRD‡	320	640	640	320
A/chicken/Guangzhou/108320/2016	4th/PRD	1280	1280	1280	640
A/chicken/Fujian/11089/2016	5th/YRD	320	320	320	640
A/chicken/Fujian/11766/2016	5th/YRD	320	320	320	640
A/silkie chicken/Shantou/9473/2016	5th/YRD	640	640	640	640
A/chicken/Guangzhou/4954/2016	5th/YRD	320	320	320	640

HPAI virus; †Yangtze River Delta lineage; ‡ Pearl River Delta lineage

Influenza A(H7N9) candidate vaccine viruses

The available and pending A(H7N9) CVVs are listed in Table 5. As the viruses continue to evolve new A(H7N9) CVVs may be developed.

Table 5. 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
Candidate vaccine viruses in preparation	**Type**	**Institution**	**Availability**
A/Guangdong/17SF003/2016-like	Reverse genetics	CCDC and NIBSC	Pending
A/Hunan/2650/2016-like	Reverse genetics	CCDC	Pending
A/Hong Kong/125/2017 (A/Hunan/2650/2016-like)	Reverse genetics	CDC and FDA	Pending

* **Institutions distributing the candidate vaccine viruses:**
CDC - Centers for Disease Control and Prevention, United States of America
CCDC - Chinese 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
NIID - National Institute of Infectious Diseases, Japan
SJCRH - St Jude Children's Research Hospital, United States of America

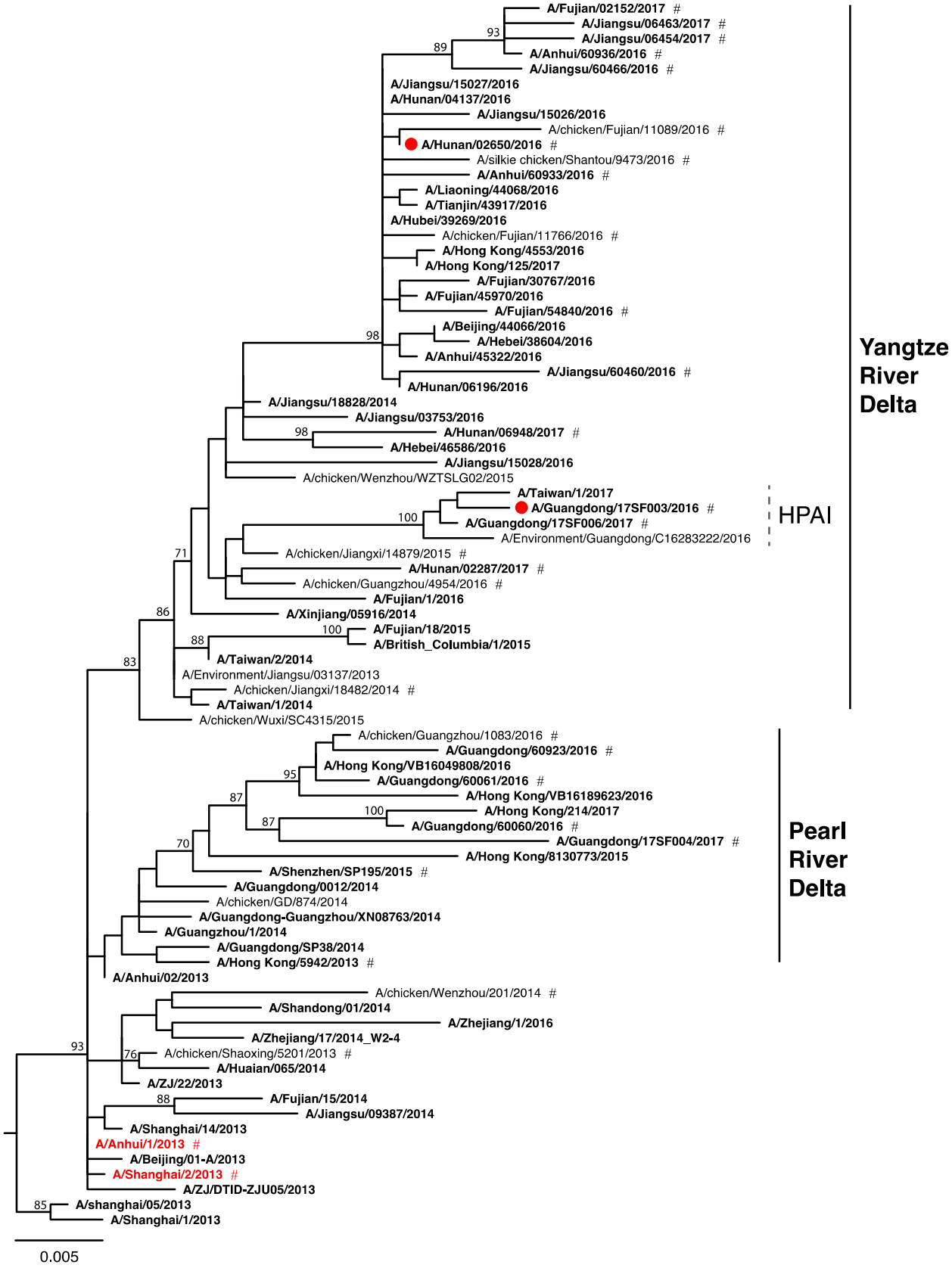

Figure 2. Phylogenetic relationships of A(H7N9) HA genes. The available CVVs are in red. The proposed CVV is indicated by a red dot(●). Human viruses are in bold font. The viruses tested in haemagglutination inhibition assay are indicated by hashes (#). The scale bar represents the number of substitutions per site. Bootstrap supports of topology are shown above selected nodes.

Influenza A(H7N2)

Influenza A(H7N2) viruses have been detected in poultry populations worldwide with rare human infections.

Influenza A(H7N2) activity from 27 September 2016 to 27 February 2017

A(H7N2) viruses were detected in cats in animal shelters in New York, United States of America. A veterinarian with prolonged exposure to infected cats was confirmed infected with a virus very similar to those in the cats. The individual presented with mild illness, was placed on oseltamivir treatment and recovered. The virus was genetically similar to previously identified A(H7N2) viruses in live poultry markets, commercial flocks and a 2003 human case in the United States of America and reacted well with post-infection ferret antiserum raised against the A/turkey/Virginia/4529/2002 CVV.

Influenza A(H7) candidate vaccine viruses

Based on the current antigenic, genetic and epidemiologic data, no new CVVs are proposed. The available A(H7) CVVs, excluding A(H7N9) CVVs listed above, are listed in Table 6. As the viruses continue to evolve, new A(H7) CVVs may be developed.

Table 6. Status of influenza A(H7) candidate vaccine virus development (excluding A(H7N9))

Candidate vaccine virus	Subtype	Type	Institution*	Available
A/mallard/Netherlands/12/2000 NIBRG-63	H7N1	Reverse genetics	NIBSC	Yes
A/turkey/Italy/3889/99	H7N1	Wild type	NIBSC	Yes
A/turkey/Virginia/4529/2002 (H7N2) IBCDC-5	H7N2	Reverse genetics	CDC	Yes
A/New York/107/2003 (H7N2) NIBRG-109	H7N2	Reverse genetics	NIBSC	Yes
A/Canada/rv444/2004 (H7N3) SJRG-161984	H7N3	Reverse genetics	SJCRH	Yes
A/mallard/Netherlands/12/2000 NIBRG-60	H7N3	Reverse genetics	NIBSC	Yes
A/mallard/Netherlands/12/2000 IBCDC-1	H7N7	Conventional	CDC	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(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 27 September 2016 to 27 February 2017

Three human cases of A(H9N2) infections have been identified in China in this period. Sequence information could be generated from samples for only one of these cases. The HA gene of this virus was similar to Y280-lineage A(H9N2) viruses known to circulate in birds in China. Antigenic information for this virus is pending. A(H9N2) viruses from birds were characterised from a small 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 7. As the viruses continue to evolve, new A(H9N2) CVVs may be developed.

Table 7. Status of influenza A(H9N2) candidate vaccine virus development

Candidate vaccine viruses	Type	Clade	Institution*	Available
A/Hong Kong/1073/99	Wild type	G1	NIBSC	Yes
A/chicken/Hong Kong/G9/97 (NIBRG-91)	Reverse genetics	Y280/G9	NIBSC	Yes
A/chicken/Hong Kong/G9/97 (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(H1) variants (v)[4]

Influenza A(H1) 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(H1)v activity from 27 September 2016 to 27 February 2017

Four non-fatal A(H1)v human cases were detected in this reporting period. One case of A(H1N2)v infection was identified in the United States of America in November 2016 in an individual with reported exposure to swine. The HA from this virus, A/Iowa/32/2016, belonged to the delta 1 lineage of swine influenza viruses (Figure 3). The Netherlands detected an influenza A(H1N1)v case in October 2016. The individual developed a severe infection following exposure to infected pigs but recovered. Another case of influenza A(H1N1)v virus was detected in Italy in October 2016. The individual developed acute respiratory distress syndrome following exposure to swine and was hospitalised with pneumonia, but recovered following oseltamivir treatment. In December 2016, an A(H1N1)v case was detected in Switzerland following swine exposure. The three A(H1N1)v viruses detected in Europe were Eurasian avian-like A(H1N1)v influenza viruses related to viruses known to circulate in swine (Figure 3). Antigenic testing demonstrated that ferret antisera raised against current CVVs reacted poorly with the A(H1)v viruses available for testing (Table 8). New CVVs generated from A/Iowa/32/2016 and A/Netherlands/3315/2016-like viruses are proposed.

Table 8. Haemagglutination inhibition assays of influenza A(H1) variant viruses.

REFERENCE ANTIGENS	Lineage	CA/ 7	X-179	RG 48A	Br/59	WI/ 71	sw/ HK	sw/Bg	Hu / 42443	CNIC 1601	pooled human sera
A/California/7/2009	pdm09	**2560**	1280	10	< #	<	1280	640	1280	1280	160
A/California/7/2009 X-179	pdm09	320	**160**	20	<	<	<	20	<	<	80
A/Ohio/9/2015 RG48A	classical γ	<	<	**1280**	<	<	40	160	20	<	20
A/Brisbane/59/2007	pre-2009 H1N1	<	<	10	**640**	10	<	<	<	<	80
A/Wisconsin/71/2016	H1N2v δ	<	<	<	<	**5120**	<	<	<	<	10
A/swine/HK/201/2010	EA† avian	1280	640	10	<	<	**2560**	640	1280	2560	20
A/swine/Belgium/1/98	EA avian	1280	640	20	<	<	640	**2560**	320	640	40
A/Hunan/42443/2015	EA avian	1280	320	<	<	<	1280	640	**1280**	1280	40
A/Hunan/42443/2015 CNIC 1601	EA avian	640	320	<	<	<	1280	640	640	**1280**	<
TEST ANTIGENS											
A/Iowa/32/2016	H1N2v δ	<	<	<	<	1280	<	<	<	<	10
A/Netherlands/3315/2016	EA avian	10	<	10	<	<	160	160	160	10	40

represents a haemagglutination inhibition titre of <10; † Eurasian avian

[4] http://www.who.int/influenza/gisrs_laboratory/terminology_variant/en/

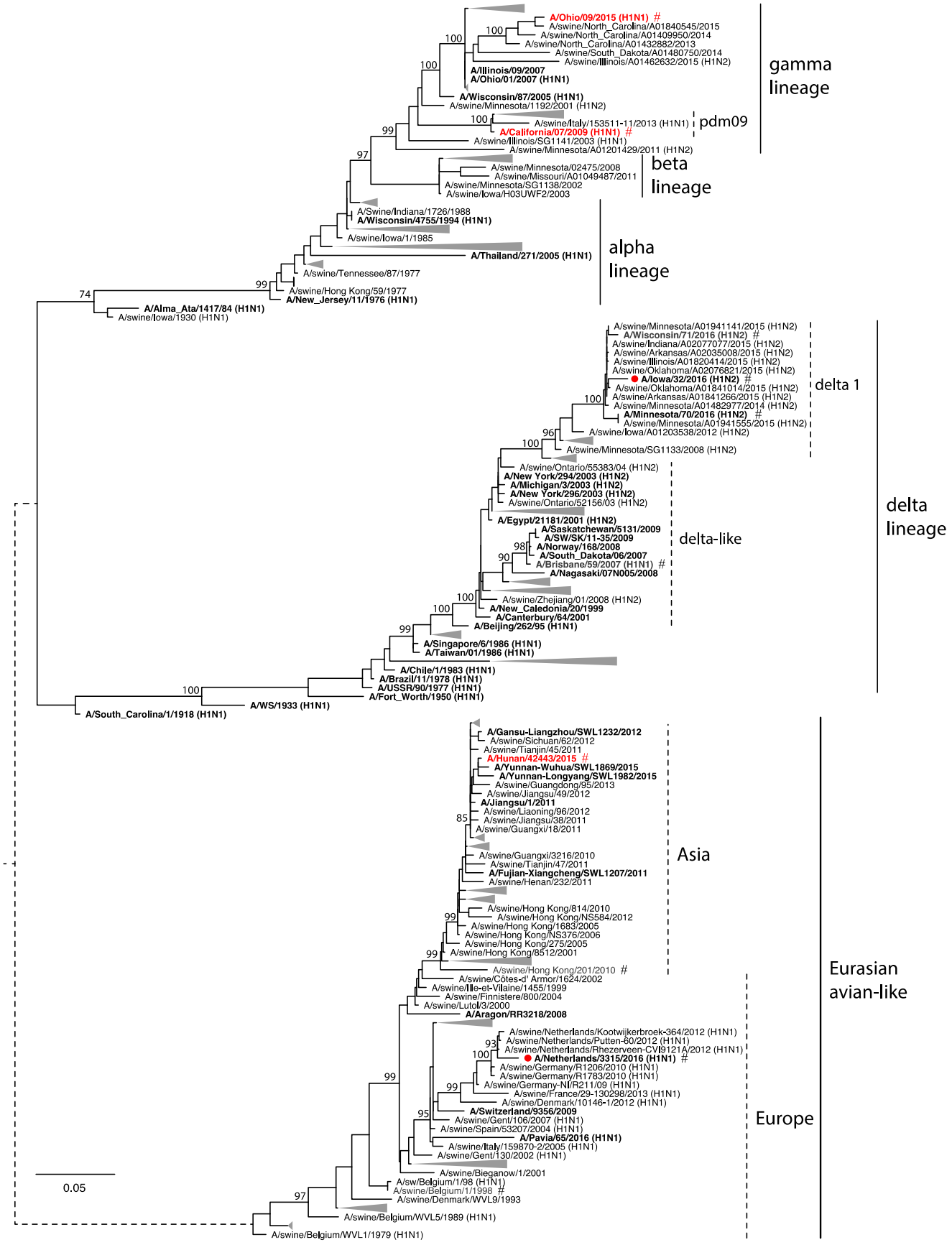

Figure 3. Phylogenetic relationships of A(H1) HA genes. The available CVVs are in red. The proposed CVV is indicated by a red dot(●). Human viruses are in bold font. The viruses tested in haemagglutination inhibition assay are indicated by hashes (#). The scale bar represents the number of substitutions per site. Bootstrap supports of topology are shown above selected nodes. Some branches of virus strains are collapsed into grey triangles for clarity.

Influenza A(H1)v candidate vaccine viruses

The available A(H1)v CVVs are listed in Table 9. As the viruses continue to evolve, new A(H1)v CVVs may be developed.

Table 9. Status of A(H1)v candidate vaccine virus development

Candidate vaccine viruses	**Type**	**Institution***	**Available**
A/Ohio/9/2015 (IDCDC-RG48A)	Reverse genetics	CDC	Yes
A/Hunan/42443/2015 (CNIC-1601)	Conventional	CCDC	Yes
Candidate vaccine viruses in preparation	**Type**	**Institution**	**Availability**
A/Hunan/42443/2015-like	Conventional	NIBSC	Pending
A/Iowa/32/2016-like	Reverse genetics	CDC	Pending
A/Netherlands/3315/2016-like	Reverse genetics/conventional	NIBSC	Pending

***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

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[5].

Influenza A(H3N2)v activity from 27 September 2016 to 27 February 2017
One case of A(H3N2)v infection was identified in Canada. The individual developed symptoms of respiratory infection in October 2016, was hospitalised with pneumonia and recovered. The individual had confirmed exposure to ill swine. The HA gene of the virus isolated from the case, A/Ontario/RV3236/2016, was similar to cluster IV-B A(H3N2) viruses currently circulating in swine populations in the United States of America and Canada.

Antigenic testing of A/Ontario/RV3236/2016 revealed that ferret antisera raised against existing cluster IV-A wild type viruses and CVVs (A/Minnesota/11/2010 and A/Indiana/10/2011) reacted well with this virus.

Influenza A(H3N2)v candidate vaccine viruses
Based on the available antigenic, genetic and epidemiologic data, no new A(H3N2)v CVVs are proposed. The available A(H3N2)v CVVs are listed in Table 10. As the viruses continue to evolve and as new data are generated, new A(H3N2)v CVVs may be developed.

Table 10. Status of A(H3N2)v candidate vaccine virus development

Candidate vaccine viruses	Type	Institution*	Available
A/Minnesota/11/2010 (NYMC X-203)	Conventional	CDC	Yes
A/Indiana/10/2011 (NYMC X-213)	Conventional	CDC	Yes
Candidate vaccine viruses in preparation	**Type**	**Institution**	**Availability**
A/Ohio/28/2016-like	Conventional and reverse genetics	NIBSC CDC	Pending

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

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

Country, area or territory	Host	Genetic clade
Austria	Wild birds	2.3.4.4 (H5N8)
	Poultry	2.3.4.4 (H5N8)
Bangladesh	Wild birds	2.3.2.1a (H5N1)
	Poultry	2.3.2.1a (H5N1)
Belgium	Poultry	2.3.4.4 (H5N8)
Bhutan	Poultry	2.3.2.1a (H5N1)
Bosnia and Herzegovina	Poultry	2.3.4.4 (H5N8)
Bulgaria	Wild birds	2.3.4.4 (H5N8)
	Poultry	2.3.4.4 (H5N8)
Cambodia	Poultry	H5N1
Cameroon	Poultry	2.3.4.4 (H5N8)
China	Wild birds	2.3.4.4 (H5N2/N6/N8/N9)
	Poultry	2.3.2.1c (H5N1), 2.3.4.4 (H5N6/N8)
	Human (2)[#]	2.3.4.4 (H5N6)
China, Hong Kong SAR	Wild birds	2.3.4.4 (H5N6)
Côte d'Ivoire	Poultry	2.3.2.1c (H5N1)
Croatia	Wild birds	2.3.4.4 (H5N8)
	Poultry	2.3.4.4 (H5N8)
Czechia	Wild birds	2.3.4.4 (H5N5/N8)
	Poultry	2.3.4.4 (H5N8)
Denmark	Wild birds	2.3.4.4 (H5N8)
	Poultry	2.3.4.4 (H5N8)
Egypt	Wild birds	2.3.4.4 (H5N8)
	Poultry	2.2.1.2 (H5N1), 2.3.4.4 (H5N8)
	Human (2)[#]	H5N1
Finland	Wild birds	2.3.4.4 (H5N8)
	Poultry	2.3.4.4 (H5N8)
France	Wild birds	2.3.4.4 (H5N8)
	Poultry	2.3.4.4 (H5N8)
Germany	Wild birds	2.3.4.4 (H5N5/N8)
	Poultry	2.3.4.4 (H5N8)
Ghana	Poultry	2.3.2.1c (H5N1)
Greece	Wild birds	2.3.4.4 (H5N5/N8)
	Poultry	2.3.4.4 (H5N8)
Hungary	Wild birds	2.3.4.4 (H5N8)
	Poultry	2.3.4.4 (H5N8)
India	Wild birds	H5N1, 2.3.4.4 (H5N8)
	Poultry	2.3.2.1a (H5N1)
Indonesia	Poultry	H5N1
Iran (Islamic Republic of)	Wild birds	2.3.4.4 (H5N8)
	Poultry	2.3.4.4 (H5N8)
Ireland	Wild birds	2.3.4.4 (H5N8)
	Poultry	2.3.4.4 (H5N8)
Israel	Wild birds	2.3.4.4 (H5N8)
	Poultry	2.3.4.4 (H5N8)

Country, area or territory	Host	Genetic clade
Italy	Wild birds	2.3.4.4 (H5N5/N8)
	Poultry	2.3.4.4 (H5N8)
Japan	Wild birds	2.3.4.4 (H5N6)
	Poultry	2.3.4.4 (H5N6)
Kazakhstan	Wild birds	2.3.4.4 (H5N8)
Kuwait	Poultry	2.3.4.4 (H5N8)
Lao People's Democratic Republic	Poultry	2.3.2.1c (H5N1)
Montenegro	Wild birds	2.3.4.4 (H5N5)
Myanmar	Poultry	2.3.4.4 (H5N6)
Netherlands	Wild birds	2.3.4.4 (H5N5/N8)
	Poultry	2.3.4.4 (H5N8)
Niger	Poultry	2.3.2.1c (H5N1), 2.3.4.4 (H5N8)
Nigeria	Poultry	2.3.2.1c (H5N1), 2.3.4.4 (H5N8)
Poland	Wild birds	2.3.4.4 (H5N5/N8)
	Poultry	2.3.4.4 (H5N8)
Portugal	Wild birds	2.3.4.4 (H5N8)
Republic of Korea	Wild birds	2.3.4.4 (H5N6/N8)
	Poultry	2.3.4.4 (H5N6)
Romania	Wild birds	2.3.4.4 (H5N8)
	Poultry	2.3.4.4 (H5N8)
Russian Federation	Wild birds	2.3.4.4 (H5N8)
	Poultry	2.3.4.4 (H5N8)
Serbia	Wild birds	2.3.4.4 (H5N8)
	Poultry	2.3.4.4 (H5N8)
Slovakia	Wild birds	2.3.4.4 (H5N8)
	Poultry	2.3.4.4 (H5N8)
Slovenia	Wild birds	2.3.4.4 (H5N8)
Spain	Wild birds	2.3.4.4 (H5N8)
Sweden	Wild birds	2.3.4.4 (H5N8)
	Poultry	2.3.4.4 (H5N8)
Switzerland	Wild birds	2.3.4.4 (H5N8)
The former Yugoslav Republic of Macedonia	Wild birds	H5Nx
	Poultry	2.3.4.4 (H5N8)
Togo	Poultry	2.3.2.1c (H5N1)
Tunisia	Wild birds	2.3.4.4 (H5N8)
Uganda	Wild birds	2.3.4.4 (H5N8)
	Poultry	2.3.4.4 (H5N8)
Ukraine	Wild birds	2.3.4.4 (H5N8)
	Poultry	2.3.4.4 (H5N8)
United Kingdom	Wild birds	2.3.4.4 (H5N8)
	Poultry	2.3.4.4 (H5N8)
United States of America	Wild birds	2.3.4.4 (H5N2)
Viet Nam	Poultry	2.3.2.1c (H5N1), 2.3.4.4 (H5N6)

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