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

February 2020

The development of influenza candidate vaccine viruses (CVVs), coordinated by 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 domestic birds and sporadic human infections. These viruses have diversified genetically and antigenically, leading to the need for multiple CVVs. Notably, H5 viruses have been detected with the N1 gene segment replaced by N2, N3, N5, N6, N8 or N9 gene segments. 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 24 September 2019 to 24 February 2020

No human infections with A/goose/Guangdong/1/96-lineage viruses have been reported in this period. Since 2003, there have been 24 A(H5N6) and 861 A(H5N1) human infections confirmed. A/goose/Guangdong/1/96-lineage A(H5) viruses were detected in domestic and wild birds in several countries from 24 September 2019 to 24 February 2020 (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/candidates_reagents/home/en/

Table 1. Recent A(H5) activity

Country, area or territory	Host	Genetic clade*
Bangladesh	Poultry	2.3.2.1a (H5N1)
Bulgaria	Poultry	2.3.4.4b (H5N8)
China	Poultry	2.3.2.1d (H5N1); 2.3.4.4h (H5N6)
	Wild bird	2.3.4.4h (H5N6)
Taiwan, China	Poultry	2.3.4.4c (H5N2/N5); Unknown (H5)
Czech Republic	Poultry	2.3.4.4b (H5N8)
Egypt	Poultry	2.3.4.4b (H5N8)
Germany	Poultry	2.3.4.4b (H5N8)
	Wild bird	2.3.4.4b (H5N8)
Hungary	Poultry	2.3.4.4b (H5N8)
India	Poultry	2.3.2.1a (H5N1)
Indonesia	Poultry	Unknown (H5N1)
Iran (Islamic Republic of)	Poultry	2.3.4.4b (H5N3)
Israel	Wild bird	Unknown (H5N8)
Lao People's Democratic Republic	Poultry	2.3.4.4h (H5N6)
Nigeria	Poultry	2.3.4.4b (H5N6/N8)
Poland	Poultry	2.3.4.4b (H5N8)
	Wild bird	2.3.4.4b (H5N8)
Romania	Poultry	2.3.4.4b (H5N8)
Saudi Arabia	Poultry	Unknown (H5N8)
Slovakia	Poultry	2.3.4.4b (H5N8)
	Wild bird	2.3.4.4b (H5N8)
Ukraine	Poultry	2.3.4.4b (H5N8)
Viet Nam	Poultry	2.3.2.1c (H5N1); 2.3.4.4g (H5N6); 2.3.4.4h (H5N6)

* Utilizing proposed update to the unified nomenclature for HPAI A(H5) viruses

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 WHO, the Food and Agriculture Organization of the United Nations (FAO), the World Organisation for Animal Health (OIE) and academic institutions.[3]

A(H5) viruses circulating and characterized from 24 September 2019 to 24 February 2020 belong to the following clades:

Clade 2.3.2.1a viruses were detected in domestic birds in Bangladesh and India. The majority of viruses tested from Bangladesh reacted well with a post-infection ferret antiserum raised against A/duck/Bangladesh/17D1012/2018, for which a CVV is in development.

Clade 2.3.2.1c viruses were detected in domestic birds in Viet Nam. Most viruses reacted well with post-infection ferret antisera raised against A/duck/Vietnam/NCVD-1584/2012 and its corresponding CVV.

Clade 2.3.2.1d viruses were detected in a small number of domestic birds in China in early 2019. While these viruses reacted poorly with post-infection ferret antiserum raised to the CVV developed from A/chicken/Guiyang/1153/2016, the extent of their current circulation in poultry is unclear and no new CVVs are proposed at this time.

Clade 2.3.4.4b viruses were detected in wild birds in Germany, Poland and Slovakia, and in domestic birds in Bulgaria, Czech Republic, Egypt, Germany, Hungary, Iran (Islamic Republic of), Nigeria, Poland, Romania,

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

Slovakia and Ukraine with evidence for multiple separate introductions into some countries. Most recent clade 2.3.4.4b viruses reacted well with post-infection ferret antiserum raised against the CVV developed from A/Fujian-Sanyuan/21099/2017.

Clade 2.3.4.4c viruses were detected in domestic birds in Taiwan, China. Compared with the most closely related CVV, A/gyrfalcon/Washington/41088-6/2014, there were up to 15 amino acid differences in the HA. No antigenic data are available for these viruses.

Clade 2.3.4.4g viruses were detected in domestic birds in Viet Nam. These viruses were genetically similar to viruses detected in Viet Nam in recent years and reacted well with post-infection ferret antiserum raised against the CVV developed from A/Fujian-Sanyuan/21099/2017 (clade 2.3.4.4b), albeit at reduced levels.

Clade 2.3.4.4h viruses were detected in wild and domestic birds in China, and domestic birds in the Lao People's Democratic Republic and Viet Nam. Most of the HAs from these viruses had fewer than 10 amino acid differences relative to that of A/Guangdong/18SF020/2018, the closest virus from which a CVV has been developed. The majority of viruses from China reacted well with post-infection ferret antiserum raised against this CVV.

Influenza A(H5) candidate vaccine viruses

Based on the current antigenic, genetic and epidemiologic data, development of new A(H5) CVVs is not proposed. Availability of A(H5) CVVs is listed in Table 2.

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

Candidate vaccine viruses (like virus)	Clade	Institution*	Available
CDC-RG (A/Viet Nam/1203/2004)	1	CDC	Yes
SJRG-161052 (A/Viet Nam/1203/2004)	1	SJCRH	Yes
NIBRG-14 (A/Viet Nam/1194/2004)	1	NIBSC	Yes
NIBRG-88 (A/Cambodia/R0405050/2007)	1.1	NIBSC	Yes
IDCDC-RG34B (A/Cambodia/X0810301/2013)	1.1.2	CDC	Yes
SJRG-166614 (A/duck/Hunan/795/2002)	2.1.1	SJCRH/HKU	Yes
CDC-RG2 (A/Indonesia/5/2005)	2.1.3.2	CDC	Yes
NIIDRG-9 (A/Indonesia/NIHRD11771/2011)	2.1.3.2a	NIID	Yes
SJRG-163222 (A/bar-headed goose/Qinghai/1A/2005)	2.2	SJCRH/HKU	Yes
IBCDC-RG7 (A/chicken/India/NIV33487/2006)	2.2	CDC/NIV	Yes
SJRG-163243 (A/whooper swan/Mongolia/244/2005)	2.2	SJCRH	Yes
IDCDC-RG11 (A/Egypt/2321-NAMRU3/2007)	2.2.1	CDC	Yes
NIBRG-23 (A/turkey/Turkey/1/2005)	2.2.1	NIBSC	Yes
IDCDC-RG29 (A/Egypt/N03072/2010)	2.2.1	CDC	Yes
IDCDC-RG13 (A/Egypt/3300-NAMRU3/2008)	2.2.1.1	CDC	Yes
NIBRG-306 (A/Egypt/N04915/2014)	2.2.1.2	NIBSC	Yes
SJRG-166615 (A/common magpie/Hong Kong/5052/2007)	2.3.2.1	SJCRH/HKU	Yes
IDCDC-RG30 (A/Hubei/1/2010)	2.3.2.1a	CDC	Yes
SJ007 (A/duck/Bangladesh/19097/2013)	2.3.2.1a	SJCRH	Yes
SJ003 (A/barn swallow/Hong Kong/D10-1161/2010)	2.3.2.1b	SJCRH/HKU	Yes
NIBRG-301 (A/duck/Viet Nam/NCVD-1584/2012)	2.3.2.1c	NIBSC	Yes
SJ002 (A/chicken/Hong Kong/AP156/2008)	2.3.4	SJCRH/HKU	Yes
IBCDC-RG6 (A/Anhui/1/2005)	2.3.4	CDC	Yes
CBER-RG1 (A/duck/Laos/3295/2006)	2.3.4	FDA	Yes
SJRG-164281 (A/Japanese white eye/Hong Kong/1038/2006)	2.3.4	SJCRH/HKU	Yes
IDCDC-RG36 (A/chicken/Bangladesh/11rs1984-30/2011)	2.3.4.2	CDC	Yes
IDCDC-RG35 (A/Guizhou/1/2013)	2.3.4.2	CDC/CCDC	Yes
IDCDC-RG42A (A/Sichuan/26221/2014) (H5N6)	2.3.4.4a	CDC/CCDC	Yes
IDCDC-RG43A (A/gyrfalcon/Washington/41088-6/2014) (H5N8)	2.3.4.4c	CDC	Yes
NIID-001 (A/duck/Hyogo/1/2016) (H5N6)	2.3.4.4e	NIID	Yes
SJRG-165396 (A/goose/Guiyang/337/2006)	4	SJCRH/HKU	Yes
IDCDC-RG12 (A/chicken/Viet Nam/NCVD-016/2008)	7.1	CDC	Yes
IDCDC-RG25A (A/chicken/Viet Nam/NCVD-03/2008)	7.1	CDC	Yes
Candidate vaccine viruses in preparation[†]	**Clade**	**Institution**	**Availability**
A/duck/Bangladesh/17D1012/2018-like	2.3.2.1a	CDC	Pending
A/chicken/Guiyang/1153/2016-like	2.3.2.1d	SJCRH/HKU	Pending
A/chicken/Ghana/20/2015-like	2.3.2.1f	CDC	Pending
A/chicken/Viet Nam/NCVD-15A59/2015 (H5N6)-like	2.3.4.4f	SJCRH	Pending
A/Guangdong/18SF020/2018 (H5N6)-like	2.3.4.4h	CDC/CCDC	Pending
A/Fujian-Sanyuan/21099/2017 (H5N6)-like	2.3.4.4b	CCDC	Pending
A/Hubei/29578/2016	2.3.4.4d	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 – The 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

[†] Development of the A/environment/Hubei/950/2013-like CVV (clade 7.2) has been discontinued.

Influenza A(H7)

Human infections with avian influenza A(H7N9) viruses were first reported to WHO on 31 March 2013. This summary provides updates on the characterisation of A/Anhui/1/2013 HA lineage A(H7) viruses and the current status of the development of corresponding CVVs.

Influenza A(H7) activity from 24 September 2019 to 24 February 2020

A/Anhui/1/2013-lineage A(H7N9) viruses have not been detected in this period.

Influenza A(H7) candidate vaccine viruses

Based on the current antigenic, genetic and epidemiologic data, no new CVVs are proposed. Availability of A(H7N9) CVVs is listed in Table 3.

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

Candidate vaccine virus (like virus)	Type	Institution*	Available
IDCDC-RG33A (A/Anhui/1/2013)	Reverse genetics	CDC	Yes
NIBRG-268 (A/Anhui/1/2013)	Reverse genetics	NIBSC	Yes
NIIDRG-10.1 (A/Anhui/1/2013)	Reverse genetics	NIID	Yes
SJ005 (A/Anhui/1/2013)	Reverse genetics	SJCRH	Yes
NIBRG-267 (A/Shanghai/2/2013)	Reverse genetics	NIBSC	Yes
CBER-RG4A (A/Shanghai/2/2013)	Reverse genetics	FDA	Yes
IDCDC-RG32A (A/Shanghai/2/2013)	Reverse genetics	CDC	Yes
IDCDC-RG32A.3 (A/Shanghai/2/2013)	Reverse genetics	CDC	Yes
IDCDC-RG56B (A/Hong Kong/125/2017)	Reverse genetics	CDC	Yes
IDCDC-RG56N (A/Guangdong/17SF003/2016)	Reverse genetics	CDC	Yes
NIBRG-375 (A/Guangdong/17SF003/2016)	Reverse genetics	NIBSC	Yes
CBER-RG7C (A/Guangdong/17SF003/2016)	Reverse genetics	FDA	Yes
CBER-RG7D (A/Guangdong/17SF003/2016)	Reverse genetics	FDA	Yes
Candidate vaccine virus in preparation	**Type**	**Institution**	**Availability**
A/Guangdong/17SF003/2016-like	Reverse genetics	CCDC	Pending
A/Hunan/02650/2016-like	Reverse genetics	CCDC	Pending
A/Gansu/23277/2019-like	Reverse Genetics	CDC	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
HKU – The 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
SJCRH – St Jude Children's Research Hospital, United States of America

Influenza A(H9N2)

Influenza A(H9N2) viruses are enzootic in poultry in parts of Africa, Asia and the Middle East. The majority of viruses sequenced from these regions belong to either the A/quail/Hong Kong/G1/97 (G1) or A/chicken/Beijing/1/94 (Y280/G9) lineages. Since the late 1990s, 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 illness has been mild and there has been no evidence of human-to-human transmission.

Influenza A(H9N2) activity from 24 September 2019 to 24 February 2020

Five human cases of A(H9N2) virus infections were reported in this period. Two cases, one each from India and Senegal, had illness onset dates from the previous reporting period. These were the first reports of human infections with A(H9N2) viruses from these countries. The three other new cases were reported by China (2) and Hong Kong, Special Administrative Region, China (1) and were from the Y280/G9 lineage. All cases recovered. The Y280/G9 lineage viruses continue to predominate in environmental and poultry samples in China and Viet Nam. G1 lineage viruses were detected in poultry in a number of countries in Africa and Asia.

Antigenic and genetic characteristics of influenza A(H9N2) viruses

All recent A(H9N2) human and poultry infections in China, and all poultry infections in Viet Nam, were caused by viruses of the Y280/G9 lineage. Representatives of these recent viruses reacted well with post-infection ferret antiserum raised against A/Anhui-Lujiang/39/2018, from which a CVV is being developed. A subset of viruses detected in Viet Nam were not well inhibited by this post-infection ferret antiserum, but reacted well with a ferret antiserum raised against the A/chicken/Hong Kong/G9/97 CVV.

HA sequence data obtained from the human cases detected in India and Senegal were related to those of G1 lineage poultry viruses and the previously characterized virus (A/Oman/2747/2019) from a human case in Oman (Figure 1). Viruses were not recovered from these recent cases but genetically related poultry viruses from Ghana, Niger and Nigeria were antigenically characterized and reacted poorly with post-infection ferret antisera raised against the current G1 lineage CVVs (Table 4). Poultry viruses of the G1 lineage detected in Bangladesh were antigenically and/or genetically similar to those detected in previous periods and to available G1lineage CVVs.

Table 4. Haemagglutination inhibition assay of G1-lineage A(H9N2) influenza viruses

Reference Antigens	**Lineage**	**BD/0994**	**HK/33982**
A/Bangladesh/0994/2011	G1	**640**	-
A/Hong Kong/33982/2009	G1	-	**640**
Test Antigens			
A/chicken/Ghana/18VIR1513-23/2018	G1	80	80
A/chicken/Ghana/18VIR1513-13/2017	G1	40	20
A/chicken/Niger/19VIR1322-37/2019	G1	20	40
A/chicken/Nigeria/19VIR8425-11/2019	G1	40	40
A/chicken/Nigeria/19VIR8424-13/2019	G1	<10	<10
A/chicken/Nigeria/19VIR8424-6/2019	G1	160	80
A/chicken/Nigeria/19VIR8424-15/2019	G1	160	80
A/guinea fowl/Nigeria/19VIR8424-18/2019	G1	160	80
A/guinea fowl/Nigeria/19VIR8424-5/2019	G1	80	40

Influenza A(H9N2) candidate vaccine viruses

Based on the available antigenic, genetic and epidemiologic data, an A/Oman/2747/2019-like A(H9N2) CVV is proposed. The available and pending A(H9N2) CVVs are listed in Table 5.

Table 5. Status of influenza A(H9N2) candidate vaccine virus development

Candidate vaccine viruses (like virus)	**Type**	**Clade**	**Institution***	**Available**
A/Hong Kong/1073/99	Wild type	G1	NIBSC	Yes
NIBRG-91 (A/chicken/Hong Kong/G9/97)	Reverse genetics	Y280/G9	NIBSC	Yes
IBCDC-2 (A/chicken/Hong Kong/G9/97)	Conventional	Y280/G9	CDC	Yes
IDCDC-RG26 (A/Hong Kong/33982/2009)	Reverse genetics	G1	CDC	Yes
IDCDC-RG31 (A/Bangladesh/994/2011)	Reverse genetics	G1	CDC	Yes
SJ008 (A/Hong Kong/308/2014)	Reverse genetics	Y280/G9	SJCRH	Yes
Candidate vaccine viruses in preparation	**Type**	**Clade**	**Institution**	**Availability**
A/Anhui-Lujiang/39/2018-like	Reverse genetics	Y280/G9	CDC/CCDC	Pending
	Conventional	Y280/G9	NIBSC	Pending
A/Oman/2747/2019-like	Reverse genetics	G1	CDC	Pending

* **Institutions distributing the candidate vaccine viruses:**

CCDC – Chinese Center for Disease Control and Prevention

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

HKU – The 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

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

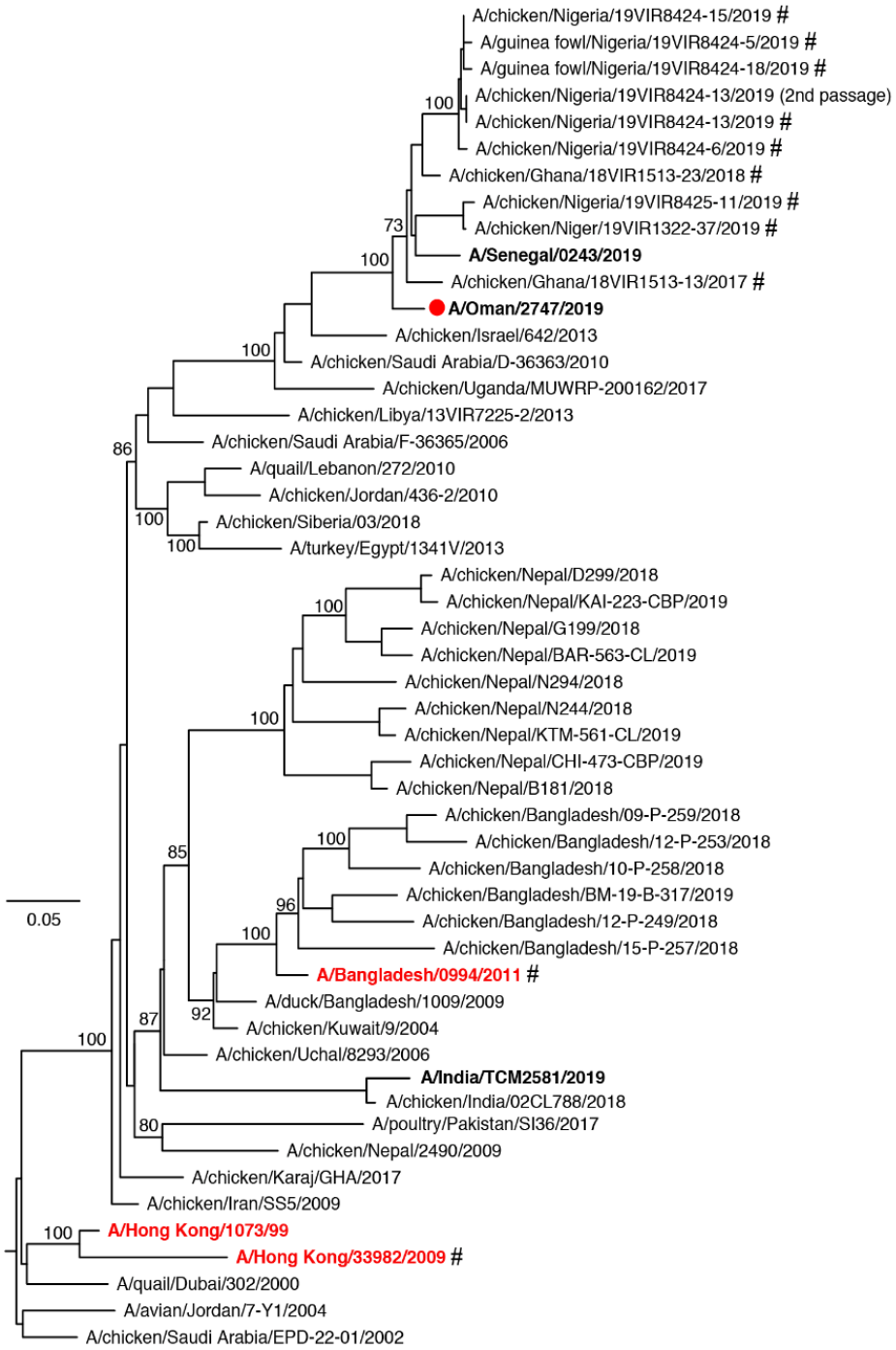

Figure 1. Phylogenetic relationships of A(H9N2) G1-like HA genes. CVVs that are available or in preparation are in red. The proposed CVV is indicated by a red dot(●). Human viruses are in bold font. The viruses tested in haemagglutination inhibition assay are indicated by hashes (#). The scale bar represents the number of substitutions per site. Bootstrap supports of topology are shown at selected nodes.

Influenza A(H1)v

Influenza A(H1) 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(H1) viruses (designated as A(H1)v viruses) have been documented previously in Asia, Europe and the Americas.

Influenza A(H1)v activity from 24 September 2019 to 24 February 2020

One human case of an A(H1N1)v virus infection was identified in China in this period. In addition, a previously unreported A(H1N1)v case from China with an onset date of December 2018 was also identified. These A(H1N1)v cases were caused by viruses from the 1C[4] (Eurasian avian-like) swine influenza virus lineage.

Antigenic and genetic characteristics of the influenza A(H1N1)v virus

The A(H1N1)v virus detected in this period had an HA that differed by 5 amino acids from that of A/Hunan/42443/2015 from which a CVV has been developed. Viruses with similar HA and NAs are known to circulate in swine in the region. No antigenic data are available from these recent viruses. Viruses of the 1C HA genetic lineage, detected in swine in Europe, were genetically and antigenically distinct from the A(H1)v A/Hunan/42443/2015 CVV and A/Netherlands/3315/2016, from which a CVV is being developed. Additional ferret antisera production and antigenic characterization are underway in order to monitor the antigenic diversity of these 1C lineage viruses.

Influenza A(H1)v candidate vaccine viruses

Based on the current antigenic, genetic and epidemiologic data, development of new A(H1)v CVVs is not proposed. Availability of A(H1)v CVVs is listed in Table 6.

Table 6. Status of A(H1)v candidate vaccine virus development

Candidate vaccine viruses (like viruses)	Type	Institution*	Available
CNIC-1601 (A/Hunan/42443/2015) (H1N1)	Conventional	CCDC	Yes
IDCDC-RG48A (A/Ohio/9/2015) (H1N1)	Reverse genetics	CDC	Yes
IDCDC-RG58A (A/Michigan/383/2018) (H1N2)	Reverse genetics	CDC	Yes
Candidate vaccine viruses in preparation	**Type**	**Institution**	**Availability**
A/Iowa/32/2016-like (H1N2)	Reverse genetics	CDC	Pending
A/Netherlands/3315/2016-like (H1N1)	Conventional	NIBSC	Pending
A/Ohio/24/2017-like (H1N2)	Reverse genetics	CDC	Pending
A/Ohio/35/2017-like (H1N2)	Reverse genetics	NIBSC	Pending

* Institution distributing the candidate vaccine viruses:
CDC – Centers for Disease Control and Prevention, United States of America
CCDC – Chinese Center for Disease Control and Prevention
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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[4] https://msphere.asm.org/content/1/6/e00275-16