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

March 2021

The development of influenza candidate vaccine viruses (CVVs), coordinated by 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 summarises 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, leading to the need for multiple CVVs. Notably, H5 viruses have been detected paired with a variety of neuraminidase (NA) gene segments (N1, N2, N3, N4, N5, N6, N8 or N9). This summary provides updates on the characterisation of A/goose/Guangdong/1/96-lineage A(H5) viruses and the status of the development of influenza A(H5) CVVs.

Influenza A(H5) activity from 1 October 2020 to 3 March 2021

Fourteen human infections with A/goose/Guangdong/1/96-lineage viruses were reported in this period. Since 2003, there have been 7 A(H5N8), 30 A(H5N6) and 862 A(H5N1) human infections reported. A/goose/Guangdong/1/96-lineage A(H5) viruses were detected in domestic and wild birds in many countries since September 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. H5 activity reported to international agencies since September 2020

Country, area or territory	Host	Genetic clade (subtype)*
Afghanistan	Poultry	unknown (H5N8)
Algeria	Poultry	unknown (H5N8)
Austria	Wild Birds	unknown (H5N8)
Bangladesh	Poultry	2.3.2.1a (H5N1)
Belgium	Wild bird Poultry	unknown (H5) 2.3.4.4b (H5N8) 2.3.4.4b (H5N8) unknown (H5N5)
Bulgaria	Poultry	unknown (H5N8)
Cambodia	Poultry	2.3.2.1c (H5N1)
China	Human (6)† Poultry/environmental Wild birds	2.3.4.4h, unknown (H5N6) 2.3.4.4h (H5N6), 2.3.2.1f (H5N1) unknown (H5N6/N8), 2.3.4.4b (H5N8)
China, Hong Kong SAR	Wild birds	unknown (H5N8)
Taiwan, China	Poultry Wild Birds	unknown (H5N2/5) unknown (H5)
Croatia	Poultry	2.3.4.4b (H5N8)
Czechia	Poultry Wild Birds	2.3.4.4b (H5N8) 2.3.4.4b (H5N8)
Denmark	Wild birds Poultry	2.3.4.4b (H5N5/N8) 2.3.4.4b (H5N8)
Estonia	Wild Birds	unknown (H5N8)
Finland	Wild Birds	unknown (H5N8)
France	Wild birds Poultry	2.3.4.4b (H5N8) unknown (H5N3) 2.3.4.4b (H5N5/8)
Georgia	Wild birds	unknown (H5N8)
Germany	Wild bird Poultry	unknown (H5N/x/1/3/4), 2.3.4.4b (H5N5/8) 2.3.4.4b (H5N5/8)
Hungary	Wild birds Poultry	unknown (H5N8) unknown (H5N8)
India	Poultry Wild Birds	unknown (H5N1/8) 2.3.4.4b (H5N8) 2.3.4.4b (H5N1)
Iran (Islamic Republic of)	Wild bird Poultry	unknown (H5N8) unknown (H5N8)
Iraq	Poultry	2.3.4.4b (H5N8)
Ireland	Wild birds Poultry	unknown (H5N3), 2.3.4.4b (H5N8) 2.3.4.4b (H5N8)
Israel	Wild birds Poultry	unknown (H5N8) unknown (H5N8)
Italy	Wild birds Poultry	2.3.4.4b (H5N1/5/8) unknown (H5N8)
Japan	Wild birds Poultry	2.3.4.4b (H5N8) 2.3.4.4b (H5N8)
Kazakhstan	Wild birds Poultry	2.3.4.4b (H5N8) 2.3.4.4b (H5N8)
Kuwait	Poultry	2.3.4.4b (H5N8)
Lao People's Democratic Republic	Human (1) Poultry	2.3.2.1c (H5N1) unknown (H5N1)
Latvia	Wild Birds	unknown (H5N8)
Lithuania	Wild birds Poultry	unknown (H5N8) unknown (H5N8)
Nepal	Poultry	unknown (H5N8)
Netherlands	Wild birds Poultry	2.3.4.4b (H5N1/5/8) 2.3.4.4b (H5N1/8)

Nigeria	Poultry	unknown (H5N1)
Norway	Wild birds	2.3.4.4b (H5N8)
	Poultry	2.3.4.4b (H5N8)
Poland	Poultry	2.3.4.4b (H5N8)
	Wild birds	2.3.4.4b (H5N5/8)
Republic of Korea	Wild birds	2.3.4.4b (H5N8)
	Poultry	2.3.4.4b (H5N8)
Romania	Poultry	unknown (H5N8)
	Wild birds	unknown (H5N8)
Russian Federation	Wild bird	2.3.4.4b (H5N8)
	Poultry	2.3.4.4b (H5N5/8)
	Human (7)	2.3.4.4b (H5Nx/N8)‡
Saudi Arabia	Poultry	unknown (H5N8)
Senegal	Poultry	unknown (H5N1)
	Wild birds	unknown (H5N1)
Slovakia	Poultry	unknown (H5N5/8)
	Wild birds	unknown (H5N8)
Slovenia	Wild birds	unknown (H5N5/8)
Spain	Wild birds	unknown (H5N8)
Sweden	Wild birds	2.3.4.4b (H5N5/8)
	Poultry	2.3.4.4b (H5N5/8)
Switzerland	Wild Birds	unknown (H5N4)
Ukraine	Poultry	2.3.4.4b (H5N8)
United Kingdom of Great Britain and Northern Ireland	Wild birds	2.3.4.4b (H5N1/2/3/5/8)
	Poultry	2.3.4.4b (H5N1/8)
Viet Nam	Poultry	unknown (H5N1) 2.3.4.4h (H5N6)

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

† Number of reported human cases

‡ Final confirmation of clade designation is pending for 6 of the 7 reported cases

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/or characterized from 1 October 2020 to 3 March 2021 belong to the following clades:

Clade 2.3.2.1a viruses were detected in poultry in Bangladesh. Viruses tested were similar genetically to A/duck/Bangladesh/17D1012/2018, for which a CVV is in development, but reacted poorly with a post-infection ferret antiserum raised against this virus. Analyses of further viruses from Bangladesh is underway to determine the need for additional CVVs.

Clade 2.3.2.1c viruses were detected in poultry in Cambodia and in poultry and a human in Lao People's Democratic Republic. The human virus was similar genetically to viruses detected in poultry in the region in recent years and reacted well with post-infection ferret antiserum raised against the A/duck/Vietnam/NCVD-1584/2012 CVV. The antigenic characterisation of recent viruses from Cambodia is ongoing.

Clade 2.3.2.1f viruses were detected in environmental samples collected in live poultry markets in China. These viruses had HAs showing greatest similarity to those of viruses detected in China in 2015 and had 7 HA1 amino acid substitutions compared to A/chicken/Ghana/20/2015, the clade 2.3.2.1f recommended CVV.

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

Clade 2.3.4.4b viruses were detected in poultry and/or wild birds in Belgium, Croatia, Czechia, Denmark, France, Germany, India, Iraq, Ireland, Italy, Japan, Kazakhstan, Republic of Korea, Kuwait, the Netherlands, Norway, Poland, the Russian Federation, Sweden and the United Kingdom of Great Britain and Northern Ireland. The majority of clade 2.3.4.4b virus HAs belonged to one of two phylogenetic groups (Figure 1) consisting of one group of viruses detected in Europe in early 2020 and viruses detected in Asia in late 2020, and the other consisting of viruses from the Middle East, Kazakhstan and the Russian Federation, together with European strains from the last quarter of 2020. These two phylogenetic groups were also antigenically distinct

Table 2. Haemagglutination inhibition* assay of clade 2.3.4.4 viruses

	Subtype	Clade	A/gyrfalcon/Washington/41088/2014 RG43A	A/chicken/Sergiyev Posad/38/ 2017	A/chicken/Kostroma/1718/2017	A/goose/Omsk/0114/2020	A/chicken/Dong Nai/25437VTC/2019	A/chicken/Nghe An/27VTC/2018
Reference antigens								
A/gyrfalcon/Washington/41088/2014 RG43A	H5N8	2.3.4.4c	**10**	<10	<10	<10	<10	<10
A/wigeon/Sakha/1/2014	H5N8	2.3.4.4c	320	40	80	80	20	<10
A/chicken/Sergiyev Posad/38/ 2017	H5N8	2.3.4.4b	40	**20**	40	40	<10	<10
A/chicken/Kostroma/1718/2017	H5N2	2.3.4.4b	10	<10	**80**	<10	<10	<10
A/goose/Omsk/0002/2020	H5N8	2.3.4.4b	20	20	<10	20	<10	<10
A/goose/Omsk/0114/2020	H5N8	2.3.4.4b	10	10	<10	**20**	<10	<10
A/chicken/Dong Nai/25437VTC/2019	H5N6	2.3.4.4g	160	10	20	20	**<10**	<10
A/chicken/Nghe An/27VTC/2018	H5N6	2.3.4.4h	<10	<10	<10	<10	<10	**<10**
Test antigens								
A/Astrakhan/3212/2020	H5N8	2.3.4.4b	<10	10	<10	<10	<10	<10
A/chicken/Tyumen/302-01/2020	H5N8	2.3.4.4b	10	10	<10	<10	<10	<10
A/chicken/Rostov-on-Don/308-02/2020	H5N8	2.3.4.4b	80	10	20	20	<10	<10
A/chicken/Rostov-on-Don/308-03/2020	H5N8	2.3.4.4b	20	10	10	<10	<10	<10
A/turkey/Stavropol/320-03/2020	H5N8	2.3.4.4b	20	<10	<10	<10	<10	<10
A/chicken/Astrakhan/321-05/2020	H5N8	2.3.4.4b	20	10	10	<10	<10	<10
A/turkey/Rostov-on-Don/332-08/2021	H5N8	2.3.4.4b	80	20	10	10	<10	<10
A/turkey/Rostov-on-Don/332-10/2021	H5N8	2.3.4.4b	80	20	10	20	<10	<10
A/chicken/Krasnodar/334-02/2021	H5N8	2.3.4.4b	20	<10	<10	<10	<10	<10
A/chicken/Krasnodar/334-03/2021	H5N8	2.3.4.4b	20	10	10	<10	<10	<10

* Haemagglutination inhibition assay was conducted using turkey red blood cells.

demonstrating antigenic diversity when representative avian viruses were tested with post-infection ferret antisera raised against the A(H5N6) A/Fujian-Sanyuan/21099/2017 CVV (Tables 2 and 3). Although A(H5N1), A(H5N2), A(H5N3), A(H5N4), and A(H5N5) 2.3.4.4b viruses were detected in this period, most of the viruses identified in poultry were of the A(H5N8) subtype. Seven human cases of A(H5) virus infection in workers on a farm in the Russian Federation are under investigation following an A(H5N8) virus poultry outbreak. To date, for the investigated human cases, one virus (A/Astrakhan/3212/2020) has been confirmed as A(H5N8) clade 2.3.4.4b. This virus and those from poultry were nearly identical and were closely related to other clade 2.3.4.4b viruses detected in poultry and wild birds in other parts of Eurasia during this reporting period (Figure 1). The HA of A/Astrakhan/3212/2020 differed by no more than 3 amino acids from that of viruses detected in the Russian Federation, during 2016, 2017 and 2018, which reacted well with post-infection ferret antisera raised against the A(H5N6) A/Fujian-Sanyuan/21099/2017 CVV (Tables 2 and 3). To provide a clade 2.3.4.4b CVV with an NA more representative of currently circulating viruses, an A/Astrakhan/3212/2020 A(H5N8) CVV is proposed.

Table 3. Haemagglutination inhibition* assay of clade 2.3.4.4b viruses

	Subtype	Fujian-Sanyuan/21099	Ghg/Uganda/200144	Ck/Egypt/N13732A	Tufted dk/Drk/2016
Reference antigen					
A/Fujian-Sanyuan/21099/2017 (CNIC-21099)	H5N6	**80**	40	40	40
A/Grey-headed Gull/Uganda/200144/2017	H5N8	80	**160**	80	80
A/chicken/Egypt/N13732A/2017	H5N8	160	160	**160**	160
A/tufted duck/Denmark/17740-1wp1/2016	H5N8	80	80	80	**80**
Test antigen					
A/environment/Kamchatka/18/2016	H5N5	80	80	80	40
A/chicken/Sergiyev Posad/38/2017	H5N8	80	160	160	160
A/chicken/Rostov-on-Don/766/2018	H5N8	160	160	160	160
A/chicken/Kostroma/1718/2017	H5N2	40	40	20	20
A/great crested grebe/Tyva/34/2016	H5N8	40	80	80	40

* Haemagglutination inhibition assay was conducted using chicken red blood cells.

Clade 2.3.4.4h viruses were detected in poultry in Viet Nam and in 5 humans and in poultry/environmental samples in China (Figure 1). These viruses were similar genetically to viruses previously detected in these countries. Representative viruses, including those isolated from humans, reacted well with post-infection ferret antisera raised against the A/Guangdong/18SF020/2018 CVV.

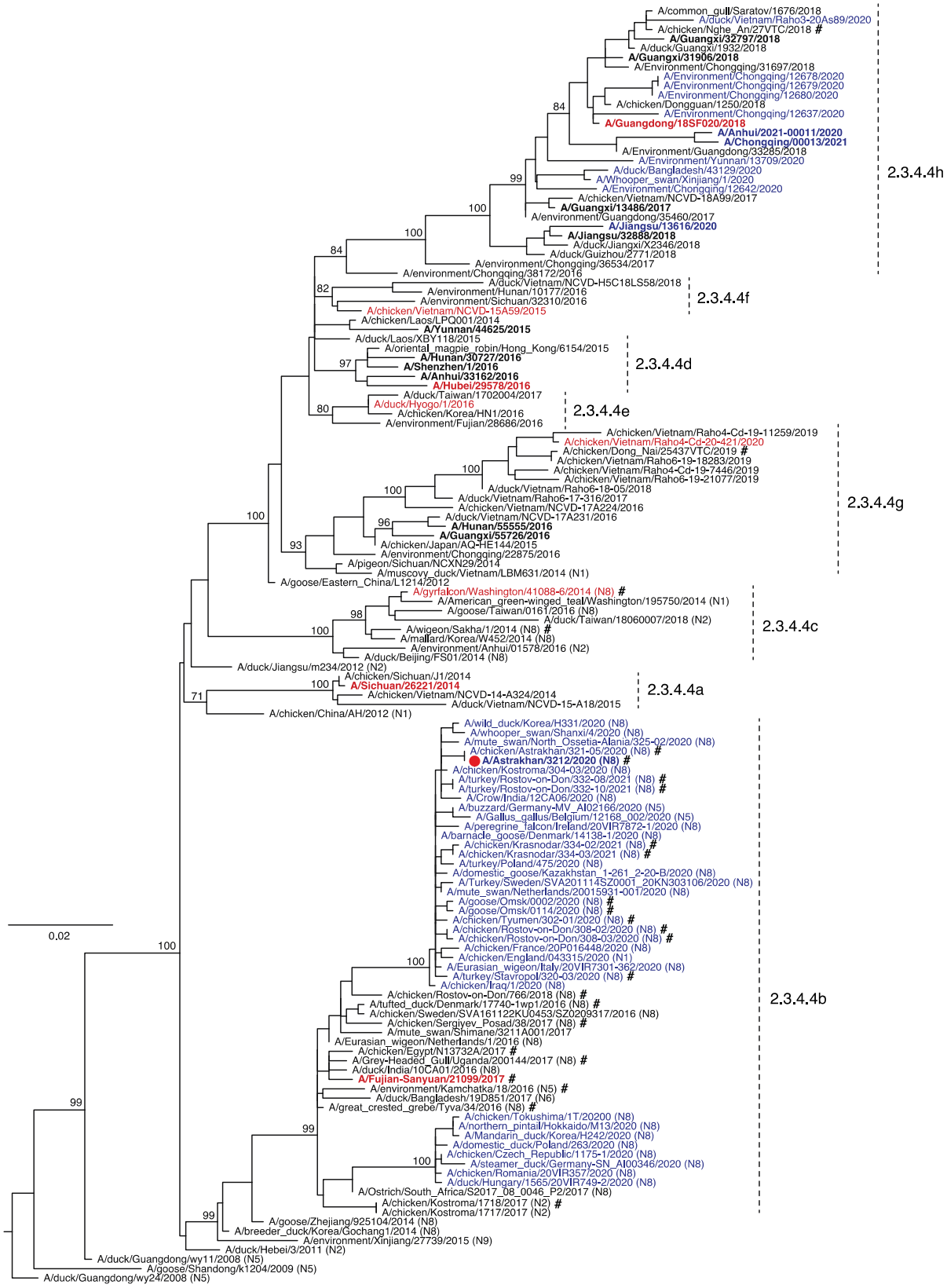

Figure 1. Phylogenetic relationships of A(H5) clade 2.3.4.4 HA genes. The available CVVs are in red. The proposed CVV is indicated by a red dot(●). Human viruses are in bold font. Viruses collected in years 2020 and 2021 are in blue. The viruses tested in haemagglutination inhibition assays are indicated by hashes (#). NA subtypes other than N6 are specified. The tree was built from the nucleotide sequences coding for the mature HA1 protein. 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

Based on current antigenic, genetic and epidemiologic data, a new A(H5N8) clade 2.3.4.4b CVV antigenically like A/Astrakhan/3212/2020 is proposed. The available and pending A(H5) CVVs are listed in Table 4.

Table 4. 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/Vietnam/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/Vietnam/NCVD-016/2008)	7.1	CDC	Yes
IDCDC-RG25A (A/chicken/Vietnam/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/Vietnam/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/Hubei/29578/2016 (H5N6)-like	2.3.4.4d	CCDC	Pending
A/Astrakhan/3212/2020 (H5N8)-like	2.3.4.4b	FDA	Pending
A/Fujian-Sanyuan/21099/2017 (H5N6)-like	2.3.4.4b	CCDC	Pending
A/chicken/Vietnam/RAHO4-CD-20-421/2020 (H5N6)-like	2.3.4.4g	CDC	Pending

* All listed CVVs have been produced using reverse genetics

† Where not indicated, the virus subtype is H5N1

‡ 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

Influenza A(H7)

Human infections with A/Anhui/1/2013 HA lineage avian influenza A(H7N9) viruses were first reported to WHO on 31 March 2013. Other lineages of A(H7) viruses have also caused zoonotic infections in previous years. This summary provides updates on the characterisation of A(H7) viruses related to these zoonotic viruses and the status of the development of corresponding CVVs.

Influenza A(H7) activity from 1 October 2020 to 3 March 2021

No human infections with A(H7), including A/Anhui/1/2013-lineage A(H7N9) viruses, have been detected in this period. In October 2020, fourteen chicken samples tested positive for A(H7N9) virus in Shandong province, China. No information was available on whether these viruses were of low pathogenicity or were highly pathogenic. Low pathogenicity A(H7N7) viruses were detected in domestic geese in Italy and in poultry in South Africa in this period. LPAI (H7) viruses were also detected in wild bird droppings in China and the Republic of Korea.

Influenza A(H7) candidate vaccine viruses

Based on the current epidemiologic data, no new CVVs are proposed. The available and pending CVVs for A(H7) viruses including A(H7N9) are listed in Table 5.

Table 5. Status of influenza A(H7) candidate vaccine virus development

Candidate vaccine virus (like virus)	Lineage (subtype)	Type	Institution*	Available
IDCDC-RG33A (A/Anhui/1/2013)	A/Anhui/1/2013 (H7N9)	Reverse genetics	CDC	Yes
NIBRG-268 (A/Anhui/1/2013)	A/Anhui/1/2013 (H7N9)	Reverse genetics	NIBSC	Yes
NIIDRG-10.1 (A/Anhui/1/2013)	A/Anhui/1/2013 (H7N9)	Reverse genetics	NIID	Yes
SJ005 (A/Anhui/1/2013)	A/Anhui/1/2013 (H7N9)	Reverse genetics	SJCRH	Yes
NIBRG-267 (A/Shanghai/2/2013)	A/Anhui/1/2013 (H7N9)	Reverse genetics	NIBSC	Yes
CBER-RG4A (A/Shanghai/2/2013)	A/Anhui/1/2013 (H7N9)	Reverse genetics	FDA	Yes
IDCDC-RG32A (A/Shanghai/2/2013)	A/Anhui/1/2013 (H7N9)	Reverse genetics	CDC	Yes
IDCDC-RG32A.3 (A/Shanghai/2/2013)	A/Anhui/1/2013 (H7N9)	Reverse genetics	CDC	Yes
IDCDC-RG56B (A/Hong Kong/125/2017)	A/Anhui/1/2013 (H7N9)	Reverse genetics	CDC	Yes
IDCDC-RG56N (A/Guangdong/17SF003/2016)	A/Anhui/1/2013 (H7N9)	Reverse genetics	CDC	Yes
NIBRG-375 (A/Guangdong/17SF003/2016)	A/Anhui/1/2013 (H7N9)	Reverse genetics	NIBSC	Yes
CBER-RG7C (A/Guangdong/17SF003/2016)	A/Anhui/1/2013 (H7N9)	Reverse genetics	FDA	Yes
CBER-RG7D (A/Guangdong/17SF003/2016)	A/Anhui/1/2013 (H7N9)	Reverse genetics	FDA	Yes
IDCDC-RG64A (A/Gansu/23277/2019-like)	A/Anhui/1/2013 (H7N9)	Reverse genetics	CDC	Yes
IBCDC-5 (A/turkey/Virginia/4529/2002)	American (H7N2)	Conventional	CDC	Yes
SJRG-161984-B (A/Canada/rv444/2004)	American (H7N3)	Reverse genetics	SJCRH	Yes
NIBRG-109 (A/New York/107/2003)	American (H7N2)	Conventional	NIBSC	Yes
IBCDC-1 (A/mallard/Netherlands/12/2000)	Eurasian (H7N7)	Conventional	CDC	Yes
NIBRG-60 (A/mallard/Netherlands/12/2000)	Eurasian (H7N3)	Reverse genetics	NIBSC	Yes
NIBRG-63 (A/mallard/Netherlands/12/2000)	Eurasian (H7N1)	Reverse genetics	NIBSC	Yes
Candidate vaccine virus in preparation	**Lineage (subtype)**	**Type**	**Institution***	**Available**
A/chicken/Jiangsu/1/2018-like	Eurasian (H7N4)	Reverse genetics	CCDC	Pending
A/Hunan/02650/2016-like	A/Anhui/1/2013 (H7N9)	Reverse genetics	CCDC	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
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 in parts of Africa, Asia and the Middle East with the majority of viruses belonging to either the A/quail/Hong Kong/G1/97 (G1) or A/chicken/Beijing/1/94 (Y280/G9) lineage. Since the late 1990s, when the first human infection was identified, the detection of A(H9N2) viruses in human and swine specimens has been reported sporadically with associated mild disease in most human cases and no evidence for human-to-human transmission. Since 1998 a total of 74 A(H9N2) human infections have been documented.

Influenza A(H9N2) activity from 1 October 2020 to 3 March 2021

Seventeen human cases of A(H9N2) virus infection were reported by China in this period, 5 with illness onset dates prior to October 2020. The majority of these infections were in children. In all but one of the 17 cases disease severity was mild, and all recovered from infection.

Y280/G9-lineage viruses continue to predominate in environmental and poultry samples in China and Lao People's Democratic Republic. G1-lineage viruses were detected in poultry in some countries of Africa, Asia and the Middle East.

Antigenic and genetic characteristics of influenza A(H9N2) viruses

All recent A(H9N2) human and poultry infections in China, and poultry infections in Lao People's Democratic Republic, were caused by viruses of the Y280/G9-lineage. Seven of the viruses detected in humans in this reporting period were sequenced; two had HA genes showing greatest similarity to the A/Anhui-Lujiang/39/2018 CVV, while the others were most similar to the A/Hong Kong/308/2014 CVV (Figure 2). The viruses from humans reacted well with post-infection ferret antiserum raised against either A/Anhui-Lujiang/39/2018 or A/Hong Kong/308/2014. Poultry viruses collected in Lao People's Democratic Republic were antigenically related to the A/chicken/Hong Kong/G9/97 CVV. In addition, currently available CVVs were antigenically representative of the G1-lineage viruses detected in birds in Bangladesh, despite some genetic divergence.

Influenza A(H9N2) candidate vaccine viruses

Based on the available antigenic, genetic and epidemiologic data, no new CVVs are proposed. The available and pending A(H9N2) CVVs are listed in Table 6.

Table 6. Status of influenza A(H9N2) candidate vaccine virus development

Candidate vaccine viruses (like virus)	Clade	Type	Institution*	Available
A/Hong Kong/1073/99	G1	Wild type	NIBSC	Yes
NIBRG-91 (A/chicken/Hong Kong/G9/97)	Y280/G9	Reverse genetics	NIBSC	Yes
IBCDC-2 (A/chicken/Hong Kong/G9/97)	Y280/G9	Conventional	CDC	Yes
IDCDC-RG26 (A/Hong Kong/33982/2009)	G1	Reverse genetics	CDC	Yes
IDCDC-RG31 (A/Bangladesh/994/2011)	G1	Reverse genetics	CDC	Yes
SJ008 (A/Hong Kong/308/2014)	Y280/G9	Reverse genetics	SJCRH	Yes
IDCDC-RG61A (A/Anhui-Lujiang/39/2018)	Y280/G9	Reverse genetics	CDC/CCDC	Yes

Candidate vaccine viruses in preparation	Type	Clade	Institution	Availability
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

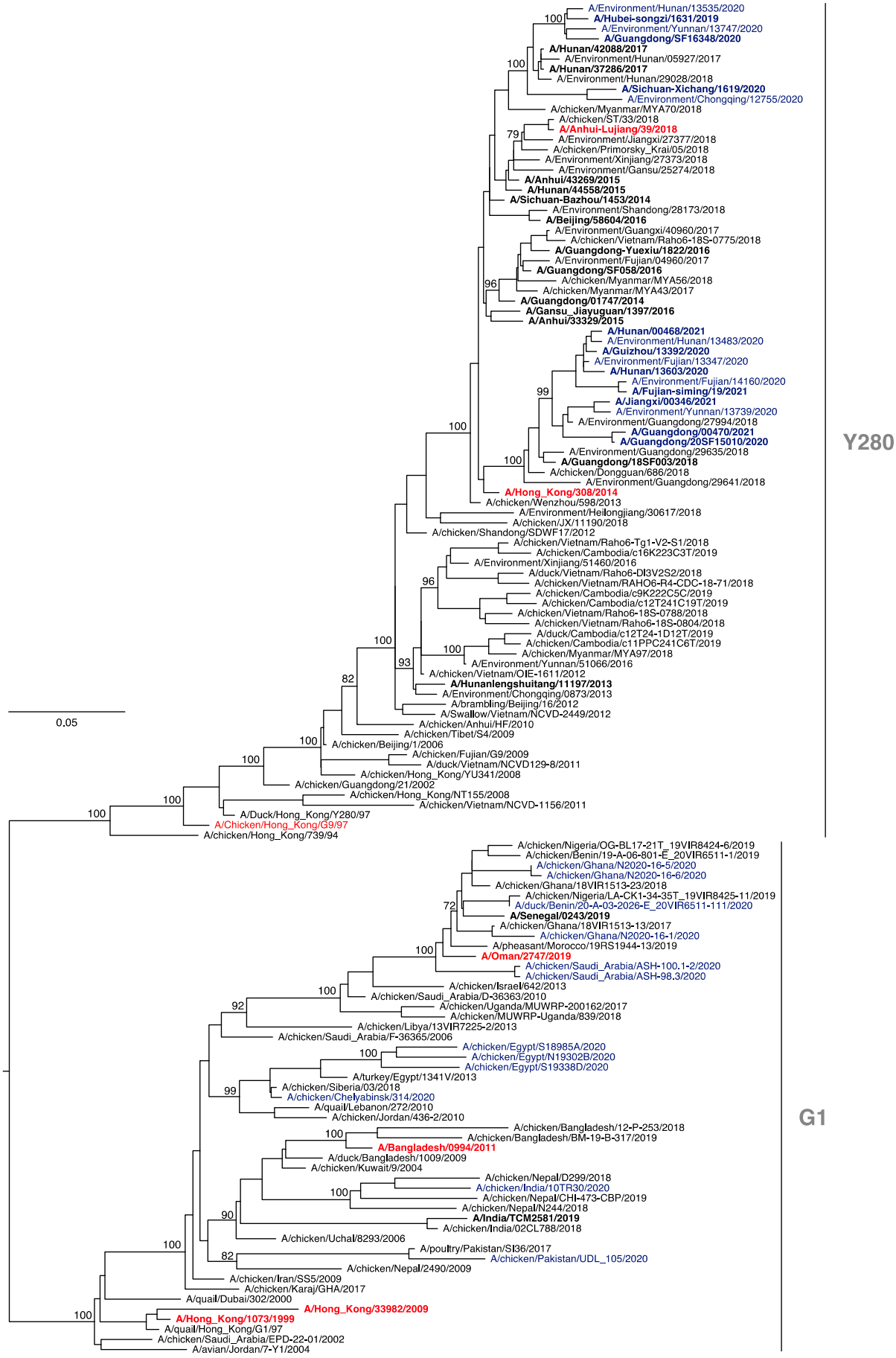

Figure 2. Phylogenetic relationships of A(H9) Y280-like and G1-like HA genes. CVVs that are available or in preparation are in red. Human viruses are in bold font. Viruses collected in years 2020 and 2021 are in blue. The scale bar represents the number of substitutions per site. Bootstrap supports of topology are shown above selected nodes.

Influenza A(H1)v[4]

Influenza A(H1) viruses are enzootic in swine populations in most regions of the world. The genetic and antigenic characteristics of these viruses are highly diverse, notably when viruses in swine populations in different regions/countries are compared. Human infections with swine influenza A(H1) viruses (designated as A(H1)variant (A(H1)v) viruses) have been, and continue to be, documented in the Americas, Asia and Europe.

Influenza A(H1)v activity from 1 October 2020 to 3 March 2021

A(H1N1)v virus infections were identified in China (n=6), Denmark (n=1) and the Netherlands (n=1). One of the cases from China had an illness onset date in August 2020. Single human cases of A(H1N2)v virus infection were reported by Brazil and Canada. All these variant viruses were similar to viruses known to be enzootic in swine populations in the respective regions/countries.

Antigenic and genetic characteristics of influenza A(H1)v viruses

The A(H1N1)v virus infections in China were caused by viruses from the 1C.2.3 swine influenza virus HA lineage[5] (Figure 3). Although there was some variation, a majority of the viruses tested reacted well with post-infection ferret antiserum raised against the A/Hunan/42443/2015 CVV. The virus from Denmark, A/Denmark/1/2021, had an HA belonging to the 1A.3.3.2 lineage (A(H1N1)pdm09 lineage), but it did not react well with post-infection ferret antisera raised against human A(H1N1)pdm09 vaccine viruses. There is considerable global and local heterogeneity in the antigenic properties of 1A.3.3.2 viruses circulating in swine, and additional investigations are underway to identify the most appropriate 1A.3.3.2 lineage viruses, including A/Denmark/1/2021-like, for CVV consideration. The A(H1N1)v virus infection in the Netherlands was caused by a virus with an HA of the 1C.2.1 lineage (Figure 3). The virus was poorly recognized by post-infection ferret antisera raised against lineage 1C.2.1 and 1C.2.2 viruses under development as CVVs including A/Netherlands/3315/2016 and A/Hessen/47/2020 (Table 7).

Table 7. Haemagglutination inhibition* assay of swine and variant A(H1) viruses

	Lineage	A/Sw/CA/1095/05	A/Sw/Switz/7492/05	A/Neth/3315/16	A/Sw/CA/324/2007	A/Hessen/47/20	A/Hessen/47/20
Reference antigens							
A/Sw/Côtes d'Armor/1095/2005	1C.2.1	**80**	<40	<40	<40	<40	<40
A/Sw/Switzerland/7492/2005	1C.2.1	80	**160**	<40	<40	<40	<40
A/Netherlands/3315/2016	1C.2.1	80	80	**400**	40	<40	<40
A/Sw/Côtes d'Armor/324/2007	1C.2.1	320	<40	<40	**640**	320	160
A/Hessen/47/2020 (MDCK)	1C.2.2	320	80	<40	320	**1280**	1280
A/Hessen/47/2020 (egg)	1C.2.2	320	40	<40	320	1280	**2560**
Test antigens							
A/Netherlands/10370-1b/2020	1C.2.1	320	40	<40	160	<40	80

* Haemagglutination inhibition assay was conducted using turkey red blood cells.

The A(H1N2)v virus from Brazil was closely related to reassortant swine influenza viruses circulating in that country with HAs of the 1A.3.3.2 lineage (A(H1N1)pdm09 lineage). No virus was available for antigenic analysis. The virus from Canada, A/Alberta/1/2020, belonged to the 1A.1.1 HA lineage but was antigenically and genetically distinct from the 1A.1.1 CVV derived from A/Ohio/24/2017. Viruses showing similarity to A/Alberta/1/2020 have been detected in pigs in the region and will continue to be monitored for relative distribution in swine populations and assessed for zoonotic risk.

[4] http://www.who.int/influenza/gisrs_laboratory/terminology_variant/en/
[5] https://msphere.asm.org/content/1/6/e00275-16

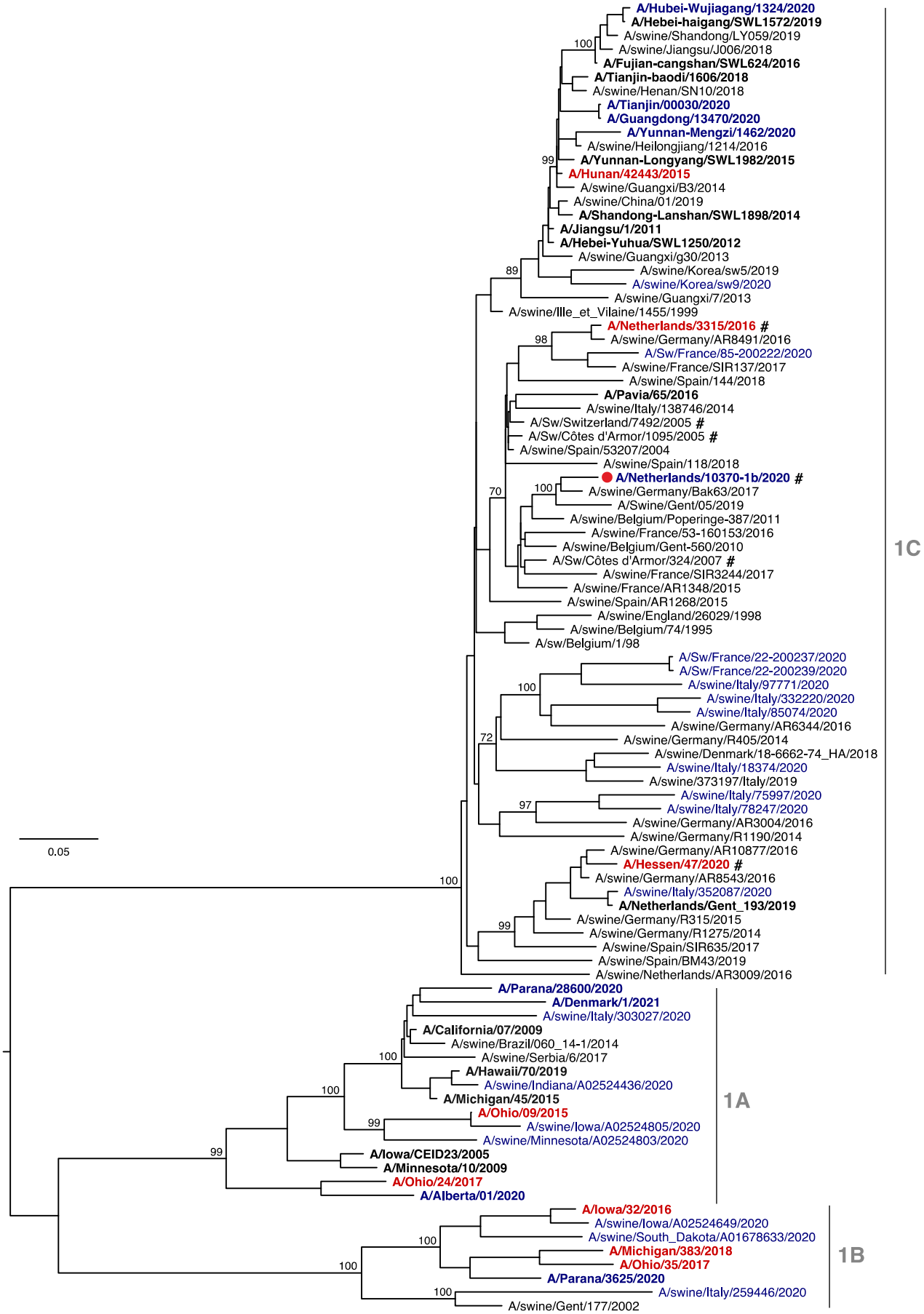

Figure 3. Phylogenetic relationships of influenza A(H1)v HA genes. CVVs that are available or in preparation are in red. Proposed CVV is indicated by a red dot(●). Human viruses are in bold font. Viruses collected in years 2020 and 2021 are in blue. The viruses tested in haemagglutination inhibition assay are indicated by hashes (#). The tree was built from the nucleotide sequences coding for the mature HA1 protein. The scale bar represents the number of substitutions per site. Bootstrap supports of topology are shown above selected nodes.

Influenza A(H1)v candidate vaccine viruses

Based on the current antigenic, genetic and epidemiologic data, a new lineage 1C.2.1 CVV antigenically like A/Netherlands/10370-1b/2020 is proposed. The available and pending A(H1)v CVVs are listed in Table 8.

Table 8. Status of influenza A(H1)v candidate vaccine virus development

Candidate vaccine viruses (like viruses)	Lineage	Type	Institution*	Available
CNIC-1601 (A/Hunan/42443/2015) (H1N1)v	1C.2.3	Conventional	CCDC	Yes
IDCDC-RG48A (A/Ohio/9/2015) (H1N1)v	1A.3.3.3	Reverse genetics	CDC	Yes
IDCDC-RG58A (A/Michigan/383/2018) (H1N2) v	1B.2.1	Reverse genetics	CDC	Yes
IDCDC-RG59 (A/Ohio/24/2017) (H1N2)v	1A.1.1	Reverse genetics	CDC	Yes
Candidate vaccine viruses in preparation		**Type**	**Institution**	**Availability**
A/Iowa/32/2016-like (H1N2)v	1B.2.2.1	Reverse genetics	CDC	Pending
A/Netherlands/3315/2016-like (H1N1)v	1C.2.1	Conventional	NIBSC	Pending
A/Ohio/35/2017-like (H1N2)v	1B.2.1	Conventional	NIBSC	Pending
A/Hessen/47/2020-like (H1N1)v	1C.2.2	Conventional	NIBSC	Pending
A/Netherlands/10370-1b/2020 (H1N1)v	1C.2.1	Conventional	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

Influenza A(H3N2)v

Influenza A(H3N2) viruses are enzootic in swine populations in most regions of the world. The genetic and antigenic characteristics of these viruses are highly diverse, notably when viruses in swine populations in different regions/countries are compared. Human infections with swine influenza A(H3N2)v viruses have been documented in Asia, Australia, Europe, North America.

Influenza A(H3N2)v activity from 1 October 2020 to 3 March 2021

A human case of A(H3N2)v virus infection was reported in the United States of America. The case reported exposure to swine, had mild illness and recovered. A total of 439 human infections with A(H3N2)v viruses have been reported in the United States of America since 2005 when human infections with a novel influenza A virus became nationally notifiable.

Antigenic and genetic characteristics of influenza A(H3N2)v viruses

The human A(H3N2)v virus had an HA gene showing greatest similarity to those of viruses in the human-like 2010.1 lineage, which are currently circulating in pigs in the United States of America. Seventy-nine A(H3N2)v infections with 2010.1 lineage viruses in the United States of America, including this case, have been reported. The A(H3N2)v virus, A/Wisconsin/01/2021, reacted well to post-infection ferret antisera raised against the wild type A/Ohio/13/2017 virus and the A/Ohio/13/2017-like CVV (IDCDC-RG60A).

Influenza A(H3N2)v candidate vaccine viruses

Based on the available antigenic, genetic and epidemiologic data, no new CVVs are proposed. The available A(H3N2)v CVVs are listed in Table 9.

Table 9. Status of influenza A(H3N2)v candidate vaccine virus development

Candidate vaccine viruses	Lineage	Type	Institution*	Available
A/Minnesota/11/2010 (NYMC X-203)	3.1990.4.A	Conventional	CDC	Yes
A/Indiana/10/2011 (NYMC X-213)	3.1990.4.A	Conventional	CDC	Yes
IDCDC-RG55C (A/Ohio/28/2016-like)	3.2010.1	Reverse Genetics	CDC	Yes
Candidate vaccine viruses in preparation		**Type**	**Institution**	**Availability**
A/Ohio/13/2017-like	3.2010.1	Reverse Genetics	CDC	Pending
A/Ohio/28/2016-like	3.2010.1	Conventional	NIBSC	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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