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

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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, recently detected H5 viruses have been 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 March through September 2021

Twenty-three human infections with A/goose/Guangdong/1/96-lineage viruses were reported in this period. Since 2003, there have been 3 A(H5), 7 A(H5N8), 49 A(H5N6) and 863 A(H5N1) human infections reported. A/goose/Guangdong/1/96-lineage A(H5) viruses were detected in domestic and wild birds in many countries after February 2021 (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] https://www.who.int/teams/global-influenza-programme/vaccines/who-recommendations/candidate-vaccine-viruses

Table 1. H5 activity reported to international agencies after February 2021

Country, area or territory	Host	Genetic clade*
Afghanistan	Poultry	2.3.4.4b (H5N8)
Albania	Poultry	unknown (H5N8)
Algeria	Poultry	unknown (H5N8)
	Wild Birds	unknown (H5N8)
Austria	Poultry	2.3.4.4b (H5N8)
	Wild Birds	2.3.4.4b (H5N5/8)
Bangladesh	Poultry	2.3.2.1a (H5N1)
Belgium	Poultry	unknown (H5)
	Wild Birds	unknown (H5N8)
Bulgaria	Poultry	2.3.4.4b (H5N8)
	Wild Birds	2.3.4.4b (H5N5)
Botswana	Poultry	2.3.4.4b (H5N1)
Burkina Faso	Poultry	2.3.4.4b (H5N8)
China	Human (18) †	2.3.4.4b (H5N6); unknown (H5N6)
	Poultry	2.3.4.4b (H5N6/8); 2.3.4.4h (H5N6)
	Wild Birds	2.3.4.4b (H5N6/8)
Taiwan, China	Poultry	unknown (H5N2/5)
Côte d'Ivoire	Poultry	unknown (H5N1)
Croatia	Wild Birds	2.3.4.4b (H5N8)
Czechia	Poultry	2.3.4.4b (H5N8)
	Wild Birds	2.3.4.4b (H5N8)
Denmark	Wild Birds	unknown (H5N1/5/8)
Estonia	Poultry	unknown (H5N8)
	Wild Birds	unknown (H5N8)
Finland	Poultry	unknown (H5N8)
	Wild Birds	unknown (H5N1/8)
France	Poultry	2.3.4.4b (H5N8)
	Wild Birds	2.3.4.4b (H5N1/8)
Germany	Poultry	2.3.4.4b (H5N1/5/8)
	Wild Birds	2.3.4.4b (H5N1/3/4/8)
Ghana	Poultry	unknown (H5)
Greece	Wild Birds	2.3.4.4b (H5N8)
Hungary	Wild Birds	unknown (H5N1/8)
India	Human (1)	2.3.2.1a (H5N1)
	Wild Birds	2.3.2.1a (H5N1)
Iran (Islamic Republic of)	Poultry	unknown (H5N8)
Iraq	Poultry	unknown (H5N8)
Ireland	Wild Birds	2.3.4.4b (H5N3)
Israel	Wild Birds	unknown (H5N8)
Italy	Poultry	unknown (H5N8)
	Wild Birds	2.3.4.4b (H5N8)
Japan	Poultry	2.3.4.4b (H5N8)
	Wild Birds	2.3.4.4b (H5N8)
Kosovo	Poultry	2.3.4.4b (H5N8)
	Wild Birds	2.3.4.4b (H5N8)
Kuwait	Wild Birds	unknown (H5N8)
Lao People's Democratic Republic	Human (1)	unknown (H5N6)
	Poultry	2.3.4.4h (H5N6)
Latvia	Wild Birds	unknown (H5N1)
Lesotho	Poultry	unknown (H5)
Lithuania	Poultry	2.3.4.4b (H5N8)
	Wild Birds	2.3.4.4b (H5N8)
Mali	Avian	2.3.4.4b (H5N1)
Nepal	Poultry	unknown (H5N8)

Netherlands	Wild Birds	unknown (H5N1/8)
Niger	Poultry	2.3.4.4b (H5N1)
Nigeria	Human (3) ‡	2.3.4.4b (H5)
	Poultry	2.3.4.4b (H5N1/8)
Norway	Poultry	2.3.4.4b (H5N8)
	Wild Birds	2.3.4.4b (H5N8)
Pakistan	Poultry	unknown (H5N8)
Poland	Poultry	2.3.4.4b (H5N8)
	Wild Birds	2.3.4.4b (H5N1/8)
Republic of Korea	Poultry	unknown (H5N8)
Romania	Poultry	2.3.4.4b (H5N5/8)
	Wild Birds	2.3.4.4b (H5N5/8)
Russian Federation	Poultry	2.3.4.4b (H5N1)
	Wild Birds	2.3.4.4b (H5N1/5)
Senegal	Poultry	2.3.4.4b (H5N1)
	Wild Birds	2.3.4.4b (H5N1)
Serbia	Wild Birds	unknown (H5N8)
South Africa	Poultry	2.3.4.4b (H5N1)
	Wild Birds	2.3.4.4b (H5N1)
Spain	Wild Birds	2.3.4.4b (H5N8)
Sweden	Wild Birds	unknown H5N4/5/8
	Poultry	unknown (H5N8)
Switzerland	Wild Birds	2.3.4.4b (H5N4)
Togo	Avian	2.3.4.4b (H5N1)
Ukraine	Poultry	2.3.4.4b (H5N8)
United Kingdom of Great Britain and Northern Ireland	Poultry	2.3.4.4b (H5N8)
	Wild Birds	2.3.4.4b (H5N8)
Viet Nam	Poultry	2.3.4.4b (H5N8); 2.3.4.4g, 2.3.4.4h (H5N6)

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

† Number of reported human cases

‡ A total of 7 cases were reported but only 3 were confirmed as A(H5)

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 characterised from March through September 2021 belong to the following clades:

Clade 2.3.2.1a viruses were detected in a human and poultry in India, and in poultry in Bangladesh. No antigenic data were available for the human virus. The HA of an A(H5N1) virus detected in a crow in India in March had accumulated 12 amino acid changes relative to the A/duck/Bangladesh/19097/2013 2.3.2.1a CVV. In general, avian viruses 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 2.3.4.4b viruses of the A(H5N1/N3/N5/N6/N8) subtypes were detected in birds in many countries in Africa, Asia and Europe and in humans in China and Nigeria. Seven human infections with non-seasonal influenza A viruses were reported in Nigeria, three were confirmed as being caused by A(H5) 2.3.4.4b viruses. An additional 18 A(H5N6) human infections were reported in China, one of which had an illness onset date prior to this reporting period. At least ten of these infections were caused by 2.3.4.4b viruses that had, at most, four HA substitutions relative to the A/Astrakhan/3212/2020 2.3.4.4b CVV.

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

The 2.3.4.4b viruses detected in this reporting period belonged to one of three major genetic groups, two represented by the A/Astrakhan/3212/2020 and A/Fujian-Sanyuan/21099/2017 CVVs and the third by viruses most recently detected in Japan. An increasing number of countries reported detection of clade 2.3.4.4b viruses in birds with HAs that grouped with the A/Astrakhan/3212/2020 CVV. This included detections of A(H5N1) and A(H5N8) viruses in poultry in Nigeria that were temporally and spatially related to the human infections and had only one or two HA substitutions relative to A/Astrakhan/3212/2020. While there is an accumulating genetic diversity of 2.3.4.4b viruses, most of those tested reacted well to post-infection ferret antisera raised against existing CVVs or their parental viruses.

Clade 2.3.4.4g viruses were detected in poultry in Viet Nam. These A(H5N6) viruses were genetically similar to viruses detected in recent years including the proposed A/chicken/Vietnam/Raho4-Cd-20-421/2020 2.3.4.4g CVV.

Clade 2.3.4.4h viruses were detected in birds in China, Lao People's Democratic Republic (PDR) and Viet Nam. These viruses were genetically similar to viruses previously detected in these countries. The HAs of the viruses from China had accumulated up to 14 amino acid substitutions relative to the A/Guangdong/18SF020/2018 2.3.4.4h CVV and a subset of these viruses were poorly recognized by post-infection ferret antiserum raised against this CVV. Other viruses from China and representative viruses from Lao PDR and Viet Nam reacted well.

Influenza A(H5) candidate vaccine viruses

Based on current antigenic, genetic and epidemiologic data, no new CVVs are proposed. The available and pending A(H5) CVVs are 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/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/CDC	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 A(H7) viruses have also caused zoonotic infections in previous and subsequent 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 March through September 2021

No human infections with A(H7), including A/Anhui/1/2013-lineage A(H7N9) viruses, have been detected in this reporting period.

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 3.

Table 3. 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, sporadic detections of A(H9N2) viruses in human and swine specimens have been reported with associated mild disease in most human cases and no evidence for human-to-human transmission.

Influenza A(H9N2) activity from March through September 2021
Eight A(H9N2) human infections with Y280/G9-lineage viruses were reported in this period, two with illness onset dates prior to March 2021. All recovered from their infections. Since 1998, a total of 82 A(H9N2) human infections have been documented.

Y280/G9-lineage viruses continue to predominate in environmental and poultry samples in Cambodia, China, Lao PDR and Viet Nam. G1-lineage viruses were detected in poultry in some countries of Africa, Asia and the Middle East, notably Bangladesh, Egypt, India and Niger.

Antigenic and genetic characteristics of influenza A(H9N2) viruses
Seven of the eight human infections were detected in China and sequence data were generated from four. The HAs of these viruses had accumulated a number of amino acid substitutions but still belonged to one of two Y280/G9 lineages represented by A/Anhui-Lujiang/39/2018 and A/Hong Kong/308/2014, respectively. The first A(H9N2) human infection ever detected in Cambodia, the eighth reported in this period, was caused by a virus that was genetically and antigenically similar to the A/Anhui-Lujiang/39/2018 CVV. The recent Y280/G9-lineage poultry infections in Cambodia, China, Lao PDR and Viet Nam, and G1-lineage outbreaks in Bangladesh, Egypt, India and Niger were caused by viruses genetically and/or antigenically similar to those seen in recent years.

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 4.

Table 4. 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	**Clade**	**Type**	**Institution**	**Availability**
A/Oman/2747/2019-like	G1	Reverse genetics	CDC	Pending
A/Anhui-Lujiang/39/2018-like	Y280/G9	Conventional	NIBSC	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

Influenza A(H10)

A(H10) viruses are frequently detected in birds in many regions of the world with rare human infections reported. Since 2013, three A(H10N8) human infections had been detected.

Influenza A(H10) activity from March through September 2021
A single case of A(H10N3) human infection was identified in China. The illness was severe, but the patient recovered.

Investigations relating to the human infection identified genetically similar A(H10N3) viruses in environmental samples collected in local live poultry markets.

Antigenic and genetic characteristics of influenza A(H10N3) viruses. The HA and NA of the human virus were genetically similar to viruses recently detected in poultry in several provinces of China with its HA being phylogenetically distinct from those of the A(H10N8) human viruses from 2013/14. The remaining gene segments of the virus were derived from A(H9N2) viruses. No antigenic data were available.

Influenza A(H10) candidate vaccine viruses
Based on the available epidemiologic data, no CVVs are proposed.

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 the viruses circulating in different regions are diverse. 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 March through September 2021

Eighteen cases of A(H1)v virus infection were identified in Austria (1), Canada (2), China (4), Taiwan, China (1) , France (1), Germany (1), and USA (8). Seven cases resulted from A(H1N2)v infections and 11 were due to A(H1N1)v infection. Most individuals reported exposure to swine prior to illness onset and all recovered. The A(H1)v 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

A/Mecklenburg-Vorpommern/1/2021, the A(H1N1)v virus detected in Germany, had an HA gene similar to the clade 1C.2.1 recommended CVV A/Netherlands/10370-1b/2020 and was recognised well by antisera raised against this CVV. The A(H1N2)v virus from France, A/Bretagne/24241/2021, belongs to clade 1C.2.4 and is genetically distinct from recommended CVVs (Figure 1). Four influenza A(H1N1)v viruses from clade 1C.2.3 were detected in China and had multiple HA amino acid substitutions compared to the closest CVV, CNIC-42443 (A/Hunan/42443/2015-like). Detailed antigenic testing of the A(H1)v viruses from Austria (no virus isolate currently), France and China is pending.

The A(H1N2)v virus detected in Manitoba, Canada belonged to clade 1A.1.1 and was related to swine influenza viruses circulating in the region. Ferret antisera raised against the North American alpha (1A.1.1) lineage A/Ohio/24/2017-like CVV, reacted poorly with A/Manitoba/1/2021. Pools of antisera from children and adults who received seasonal influenza vaccine also showed poor cross-reactivity with this virus. Two A(H1N2)v viruses from the USA belonged to clade 1B.2.1 and were genetically and antigenically related to the A/Michigan/383/2018-like CVV.

Two A(H1N1)v viruses from Canada and the USA belonged to clade 1.A.3.3.2 and were related to circulating A(H1N1)pdm09-like swine influenza viruses. Both were poorly recognised by ferret antisera raised against recent seasonal vaccine viruses but showed better recognition by serum pools from vaccinated children and adults. Four A(H1N1)v viruses identified in the USA belonged to the 1A.3.3.3 clade and were related to circulating swine viruses. Three of the four were genetically divergent from the A/Ohio/09/2015-like CVV (Figure 2) and were poorly recognized by ferret antisera raised against this CVV, as were most of the 1A.3.3.3 swine viruses tested. Post-infection ferret antiserum raised against a recent 1A.3.3.3 virus, A/Wisconsin/03/2021, recognised most of these viruses well (Table 5).

Table 5. Haemagglutination inhibition* assay of A(H1N1)v and swine viruses

Reference antigens	Lineage	OH/ 09	RG48A	WI/03
A/Ohio/09/2015	1A.3.3.3	**2560**	1280	80
IDCDC-RG48A (A/Ohio/9/2015)	1A.3.3.3	2560	**1280**	80
A/Wisconsin/03/2021	1A.3.3.3	160	40	**640**
Test antigens				
A/North Carolina/15/2020	1A.3.3.3	640	320	80
A/Minnesota/33/2014	1A.3.3.3	320	20	80
A/Iowa/39/2015	1A.3.3.3	320	80	320
A/Wisconsin/04/2021	1A.3.3.3	320	40	320
A/swine/Iowa 19SW2680/2019	1A.3.3.3	160	10	320
A/swine/Iowa 19SW2683/2019	1A.3.3.3	160	10	160
A/swine/Iowa 19SW2874/2019	1A.3.3.3	160	10	320

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

[4] standardization_of_terminology_influenza_virus_variants_update.pdf (who.int)

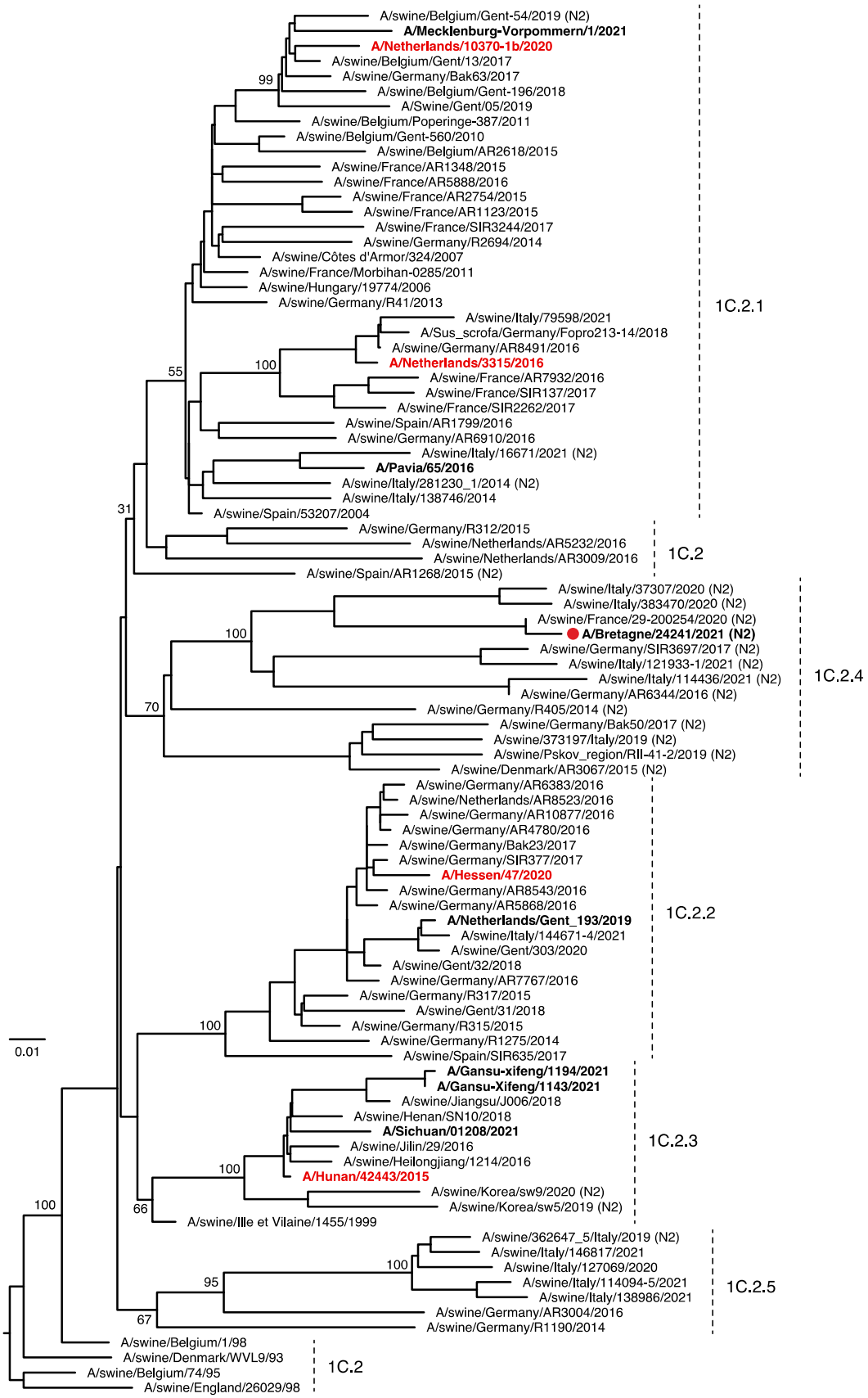

Figure 1. Phylogenetic relationships of influenza A(H1)v HA genes of 1C clades. CVVs that are available or in preparation are in red. Proposed CVV is indicated by a red dot(●). Human viruses are in bold font. The tree was built from the nucleotide sequences coding for the mature HA1 protein. The scale bar represents the number of substitutions per site. Bootstrap supports of topology are shown above selected nodes.

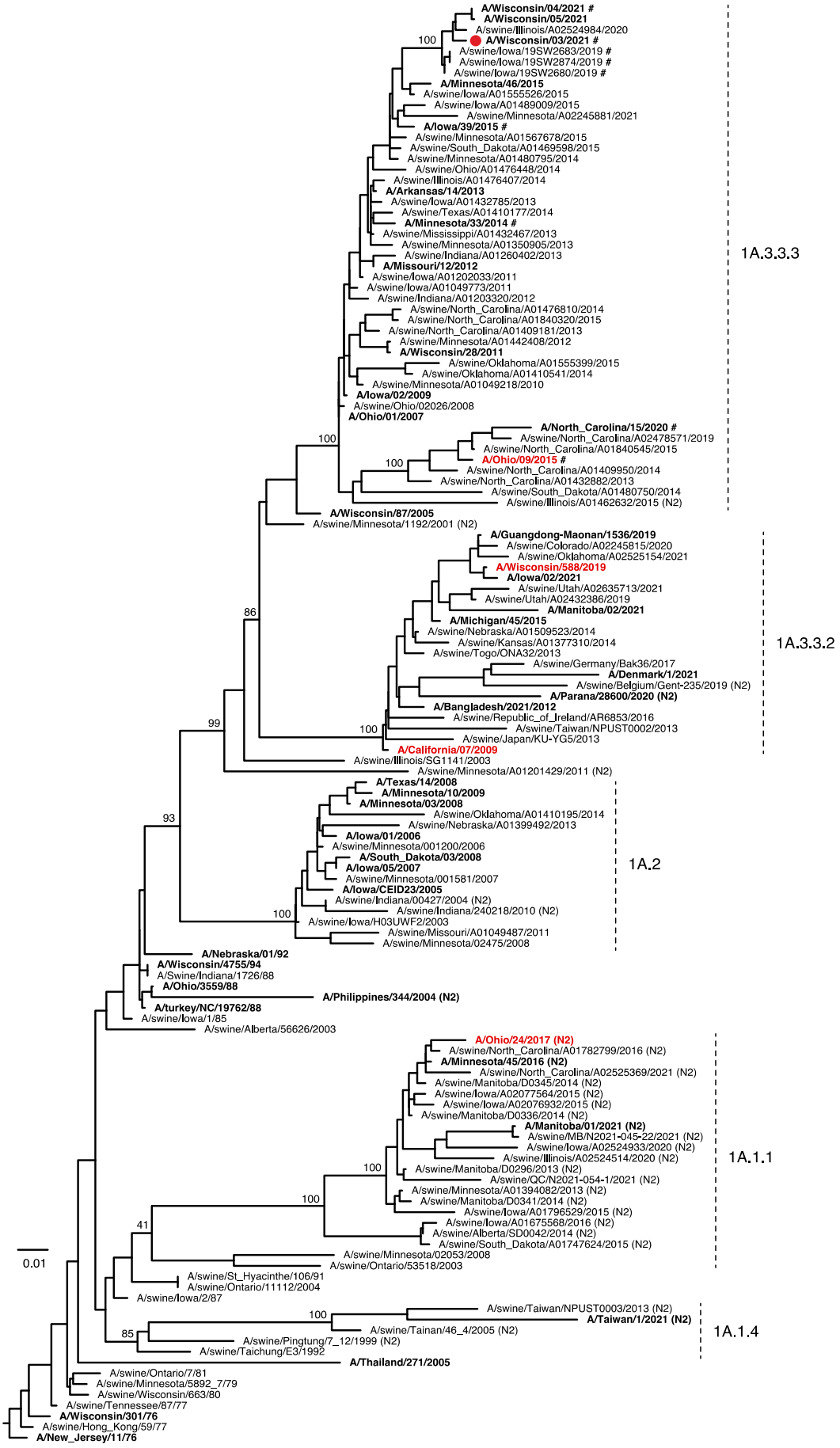

Figure 2. Phylogenetic relationships of influenza A(H1)v HA genes of 1A clades. CVVs that are available or in preparation are in red. Proposed CVV is indicated by a red dot(●). Human viruses are in bold font. The viruses tested in haemagglutination inhibition assay are indicated by hashes (#). The tree 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 clade 1C.2.4 CVV antigenically like A/Bretagne/24241/2021 and a new clade 1A.3.3.3 CVV antigenically like A/Wisconsin/03/2021 are proposed. The available and pending A(H1)v CVVs are listed in Table 6.

Table 6. 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	Reverse genetics	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
A/Bretagne/24241/2021 (H1N2)v	1C.2.4	Reverse genetics	SJCRH	Pending
A/Wisconsin/03/2021 (H1N1)v	1A.3.3.3	Reverse genetics	CDC	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
SJCRH – St Jude Children's Research Hospital, United States of America

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 the viruses circulating in different regions are diverse. Human infections with swine influenza A(H3N2)v viruses have been documented in Asia, Australia, Europe and North America.

Influenza A(H3N2)v activity from March through September 2021

Two human cases of A(H3N2)v virus infection were reported, one each in Canada and the USA. An additional A(H3N2)v case with an illness onset date in January 2021 was detected in Australia. None of the cases reported exposure to swine and all recovered following mild illness. The majority of A(H3N2)v infections have been detected in the USA where a total of 440 cases have been reported since 2005, when human infections with a novel influenza A virus became nationally notifiable.

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

A/Iowa/03/2021 showed a close genetic relationship to clade 3.1990.4 A(H3N2) swine influenza viruses detected in the USA during 2020-2021 and the recommended A/Minnesota/11/2010-like CVV. Ferret antisera raised against A/Minnesota/11/2010 reacted with A/Iowa/03/2021 and related swine viruses at titers within 4-fold of the homologous virus titer in haemagglutination inhibition assays. A/Manitoba/03/2021 had more than 20 HA amino acid substitutions relative to A/Minnesota/11/2010 and was not well recognised by ferret antisera raised against A/Minnesota/11/2010 or the corresponding CVV. Sera from recently vaccinated adults recognised A/Iowa/03/2021 and A/Manitoba/03/2021 well, whereas post-vaccination sera from children aged 6 months to 3 years recognised the viruses less well. The HA gene of the A(H3N2)v virus from Australia was similar to that of an A(H3N2)v virus detected in South Australia in 2018. Both HAs were most likely derived from an A(H3N2) virus that circulated in the Australian human population around 1997.

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 7.

Table 7. Status of influenza A(H3N2)v candidate vaccine virus development

Candidate vaccine viruses (like 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)	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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