Genetic and antigenic 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 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 across a wide geographic area. These viruses have diversified genetically and antigenically, leading to the need for multiple CVVs. H5 HA gene segments have paired with a variety of neuraminidase (NA) subtypes (N1, N2, N3, N4, N5, N6, N8 or N9). This summary provides updates on the characterization 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 20 September 2022 to 20 February 2023

Nine human infections with A/goose/Guangdong/1/96-lineage viruses have been reported in this period. Since 2003, there have been 3 A(H5), 7 A(H5N8), 84 A(H5N6) and 871 A(H5N1) human infections reported. Since September 2022, A/goose/Guangdong/1/96-lineage A(H5) viruses have been detected in both domestic and wild birds in many countries, with sporadic detections in mammals (Table 1).

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 (WOAH) and academic institutions.[3]

[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

[3] Smith GJ, Donis RO, World Health Organization, World Organisation for Animal Health, Food Agriculture Organization, H5 Evolution Working Group. Nomenclature updates resulting from the evolution of avian influenza A(H5) virus clades 2.1.3.2a, 2.2.1, and 2.3.4 during 2013-2014. Influenza Other Respir Viruses 2015;9(5):271-6. Available at: http://onlinelibrary.wiley.com/doi/10.1111/irv.12324/epdf

Table 1. H5 activity reported to international agencies since September 2022

Country, area or territory	Host	Genetic clade
Algeria	Poultry	unknown* (H5N1)
Argentina	Poultry	unknown (H5)
	Wild Birds	unknown (H5)
Austria	Poultry	2.3.4.4b (H5N1)
	Wild Birds	2.3.4.4b (H5N1)
Bangladesh	Poultry	2.3.2.1a (H5N1)
Belgium	Poultry	2.3.4.4b (H5N1)
	Mammals (ferret, fox)	2.3.4.4b (H5N1)
	Wild Birds	2.3.4.4b (H5N1)
Bolivia	Poultry	2.3.4.4b (H5N1)
	Wild Birds	unknown (H5N1)
Canada	Poultry	2.3.4.4b (H5N1)
	Mammals (dolphin, fox, Racoon, skunk)	2.3.4.4b (H5N1)
	Wild Birds	2.3.4.4b (H5N1)
Chile	Poultry	unknown (H5N1)
	Mammal (sea lion)	unknown (H5N1)
	Wild Birds	2.3.4.4b (H5N1)
China	Human (5)†	2.3.4.4b (H5N1/N6); unknown (H5N6)
	Poultry	2.3.4.4b (H5N1/N6)
China, Hong Kong SAR	Environment	2.3.4.4b (H5N1)
	Wild Birds	2.3.4.4b (H5N1)
Taiwan, China	Poultry	2.3.4.4b (H5N1); unknown (H5N2/5)
	Wild Birds	unknown (H5N1)
Croatia	Poultry	2.3.4.4b (H5N1)
	Wild Birds	2.3.4.4b (H5N1)
Colombia	Poultry	2.3.4.4b (H5N1)
	Wild Birds	2.3.4.4b (H5N1)
Costa Rica	Wild Birds	unknown (H5)
Cuba	Wild Birds	unknown (H5N1)
Cyprus	Poultry	2.3.4.4b (H5N1)
	Wild Birds	2.3.4.4b (H5N1)
Czech Republic	Poultry	2.3.4.4b (H5N1)
	Wild Birds	2.3.4.4b (H5N1)
Denmark	Poultry	2.3.4.4b (H5N1)
	Mammal (fox)	2.3.4.4b (H5N1)
	Wild Birds	2.3.4.4b (H5N1)
Ecuador	Human (1)	2.3.4.4b (H5N1)
	Poultry	2.3.4.4b (H5N1)
	Wild Birds	unknown (H5)
Egypt	Poultry	2.3.4.4b (H5N8); 2.3.4.4b (H5N1)
Faroe Islands	Poultry	unknown (H5N1)
	Wild Birds	unknown (H5N1)
France	Poultry	2.3.4.4b (H5N1)
	Mammal (cat)	2.3.4.4b (H5N1)
	Wild Birds	2.3.4.4b (H5N1)
Guatemala	Wild Birds	2.3.4.4b (H5N1)
Germany	Poultry	2.3.4.4b (H5N1)
	Mammal (coati)	2.3.4.4b (H5N1)
	Wild Birds	2.3.4.4b (H5N1)
Honduras	Wild Birds	2.3.4.4b (H5N1)
Hungary	Poultry	2.3.4.4b (H5N1)
Iceland	Wild Birds	2.3.4.4b (H5N1)
India	Poultry	2.3.4.4b (H5N1)

	Wild Birds	unknown (H5N1)
Indonesia	Poultry	unknown (H5N1)
Ireland	Poultry	2.3.4.4b (H5N1)
	Mammal (fox)	2.3.4.4b (H5N1)
	Wild Birds	2.3.4.4b (H5N1)
Isle of Man	Poultry	unknown (H5N1)
	Wild Birds	unknown (H5N1)
Israel	Wild Birds	2.3.4.4b (H5N1)
Italy	Poultry	2.3.4.4b (H5N1)
	Wild Birds	2.3.4.4b (H5N1)
Japan	Poultry	2.3.4.4b (H5N1/2)
	Wild Birds	2.3.4.4b (H5N1/N2)
Lao People's Democratic Republic	Poultry	2.3.4.4b (H5N1/N6); 2.3.2.1c (H5N1)
Mexico	Poultry	2.3.4.4b (H5N1)
	Wild Birds	2.3.4.4b (H5N1)
Moldova, Republic of	Poultry	2.3.4.4b (H5N1)
Nepal	Poultry	2.3.4.4b (H5N1)
Netherlands	Poultry	2.3.4.4b (H5N1)
	Wild Birds	2.3.4.4b (H5N1)
Niger	Poultry	unknown (H5N1)
Nigeria	Poultry	2.3.4.4b (H5N1)
	Wild Birds	unknown (H5N1)
North Macedonia	Poultry	2.3.4.4b (H5N1)
Norway	Poultry	2.3.4.4b (H5N1/N5)
	Wild Birds	2.3.4.4b (H5N1)
Panama	Poultry	2.3.4.4b (H5N1)
	Wild Birds	2.3.4.4b (H5N1)
Peru	Poultry	2.3.4.4b (H5N1)
	Mammals (dolphin, seal, sea lion)	unknown (H5N1)
	Wild Birds	2.3.4.4b (H5N1)
Philippines	Poultry	unknown (H5N1)
Poland	Poultry	2.3.4.4b (H5N1)
	Wild Birds	2.3.4.4b (H5N1)
Portugal	Poultry	2.3.4.4b (H5N1)
	Wild Birds	2.3.4.4b (H5N1)
Republic of Korea	Poultry	2.3.4.4b (H5N1)
	Wild birds	2.3.4.4b (H5N1/8)
Reunion	Poultry	unknown (H5N1)
Romania	Wild Birds	2.3.4.4b (H5N1)
Russian Federation	Poultry	2.3.4.4b (H5N1)
	Wild Birds	2.3.4.4b (H5N1)
Serbia	Wild Birds	2.3.4.4b (H5N1)
Slovakia	Poultry	2.3.4.4b (H5N1)
	Wild Birds	2.3.4.4b (H5N1)
Slovenia	Wild Birds	2.3.4.4b (H5N1)
South Africa	Poultry	unknown (H5N1/N2)
Spain	Human (2)	2.3.4.4b (H5N1)
	Poultry	2.3.4.4b (H5N1)
	Mammal (mink)	2.3.4.4b (H5N1)
	Wild Birds	2.3.4.4b (H5N1)
Sweden	Wild Birds	2.3.4.4b (H5N1)
Switzerland	Wild Birds	2.3.4.4b (H5N1)
Timor-Leste	Poultry	2.3.2.1e (H5N1)

United Kingdom of Great Britain and Northern Ireland	Poultry	2.3.4.4b (H5N1)
	Mammals (otter, fox)	2.3.4.4b (H5N1)
	Wild Birds	2.3.4.4b (H5N1)
United States of America	Poultry	2.3.4.4b (H5N1/N4)
	Mammals (bear, bobcat, cat, dolphin, fox, leopard, lion, opossum, racoon, skunk)	2.3.4.4b (H5N1)
	Wild Bird	2.3.4.4b (H5N1)
Uruguay	Wild Birds	unknown (H5)
Venezuela	Wild Birds	2.3.4.4b (H5N1)
Viet Nam	Human (1)	unknown (H5N1)
	Poultry	2.3.4.4b (H5N1/N8); 2.3.2.1c (H5N1);

*Uknown: denotes instances where specific lineage designations were not available
†Number of reported human cases

Genetic and antigenic characteristics of influenza A(H5) viruses

Three A(H5N6) and two A(H5N1) infections were identified in China, one A(H5N1) infection in Ecuador, two A(H5N1) detections in Spain, and one A(H5N1) infection in Viet Nam. The majority of cases reported exposure to poultry. Two of the A(H5N6) cases were fatal, the third was severe. One of the A(H5N1) cases was fatal, three more were severe, and two were asymptomatic. All cases from which sequence information is available (n=6) were caused by clade 2.3.4.4b viruses. The HAs of the sequenced viruses had 2 to 7 amino acid substitutions compared with the HA of A/Astrakhan/3212/2020, from which a clade 2.3.4.4b CVV has been developed.

A(H5) viruses from birds and non-human mammals characterized from September 2022 to February 2023 belonged to the following clades:

Clade 2.3.2.1a viruses were detected in poultry in Bangladesh. There were up to 10 amino acid substitutions in the HA of recent viruses compared to the HA of A/duck/Bangladesh/17D1012/2018, from which a CVV has been developed. Some of the recent viruses did not react well to a post-infection ferret antiserum raised against the A/duck/Bangladesh/17D1012/2018 CVV but instead reacted well with a post-infection ferret antiserum raised against the A/duck/Bangladesh/19097/2013 CVV.

Clade 2.3.2.1c viruses were detected in birds in Viet Nam and Lao People's Democratic Republic. Viruses from Viet Nam reacted well with a post-infection ferret antiserum raised against the A/duck/Vietnam/NCVD-1584/2012 CVV, despite recent strains having up to 9 amino acid substitutions in the HA.

Clade 2.3.2.1e viruses were detected in Timor-Leste. The HAs of these viruses were most closely related to viruses previously detected in Indonesia. There are no CVVs representative of this HA clade and the viruses from Timor-Leste reacted poorly with post-infection ferret antisera raised against clade 2.3.2.1a and 2.3.2.1c CVVs. No human infections have been associated with viruses of this clade and the extent of their circulation is uncertain.

Clade 2.3.4.4b viruses were detected in birds in many countries in Africa, Asia, Europe, North America and, for the first time, in Central and South America. An increasing number of infections in wild and captive mammals has been reported, with mink-to-mink transmission suspected on a farm in Spain. Viruses from this clade have been associated with several different NA subtypes with N1 now predominating. The high levels of infection in birds with these viruses and increased geographic distribution have been accompanied by genetic diversification. Some A(H5N1) viruses from Europe, the United States of America (USA) and Viet Nam show reduced reactivity with post-infection ferret antisera raised against the A/Astrakhan/3212/2020 CVV. All viruses from Europe reacted well with post-infection ferret antiserum raised against A/chicken/Ghana/AVL-763_21VIR7050-39/2021; a representative CVV is being developed. Many viruses from the USA that had reduced reactivity with antisera raised against the A/Astrakhan/3212/2020 CVV showed better reactivity with post-infection ferret antisera raised against A/American wigeon/South Carolina/22-000345-001/2021 (Table 2).

Table 2. Haemagglutination inhibition assay* of clade 2.3.4.4b A(H5) viruses

Reference antigens	Clade	Subtype	SJRG-161052	CNIC-FJ21099	IDCDC-RG71A	Am wg/2021
SJRG-161052 (A/Vietnam/1203/2004-like)	1	H5N1	**2560**	<10	<10	<10
CNIC-FJ21099 (A/Fujian-Sanyuan/21099/2017-like)	2.3.4.4b	H5N6	10	**80**	160	<10
IDCDC-RG71A (A/Astrakhan/3212/2020-like)	2.3.4.4b	H5N8	<10	<10	**320**	<10
A/American wigeon/South Carolina/22-000345-001/2021	2.3.4.4b	H5N1	<10	<10	80	**80**
Test antigens						
A/red-shouldered hawk/Minnesota/22-012000-004/2022	2.3.4.4b	H5N1	<10	40	320	160
A/black vulture/Florida/22-010358-001/2022	2.3.4.4b	H5N1	<10	<10	160	80
A/chicken/Pennsylvania/22-012092-006/2022	2.3.4.4b	H5N1	<10	<10	160	160
A/black vulture/Florida/22-012331-001/2022	2.3.4.4b	H5N1	<10	<10	160	160
A/bald eagle/Wyoming/22-013015-001/2022	2.3.4.4b	H5N1	<10	<10	160	80
A/chicken/Pennsylvania/22-012092-010/2022	2.3.4.4b	H5N1	<10	<10	160	80
A/Canada goose/Wyoming/22-011671-001/2022	2.3.4.4b	H5N1	<10	<10	80	80
A/turkey/Iowa/22-012098-001/2022	2.3.4.4b	H5N1	<10	<10	80	80
A/black vulture/Florida/22-012333-001/2022	2.3.4.4b	H5N1	<10	<10	80	320
A/black vulture/Maryland/22-012407-001/2022	2.3.4.4b	H5N1	<10	<10	80	80
A/Cooper's hawk/Minnesota/22-012931-001/2022	2.3.4.4b	H5N1	<10	<10	40	40

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

Figure 1. Phylogenetic relationships of A(H5) clade 2.3.4.4 HA genes. The available CVVs are in red. The proposed CVV is indicate by a red dot (●). Human viruses are in bold font. The viruses tested in haemagglutination inhibition assays are indicated by hashes (#). NA subtypes other than N1 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 clade 2.3.4.4b CVV that is antigenically like A/American wigeon/South Carolina/22-000345-001/2021 is proposed. The available and pending A(H5) CVVs are listed in Table 3.

Table 3. 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	MHRA	Yes
NIBRG-88 (A/Cambodia/R0405050/2007)	1.1	MHRA	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	MHRA	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	MHRA	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	MHRA	Yes
SJ009 (A/chicken/Guiyang/1153/2016)	2.3.2.1d	SJCRH/HKU	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-RG71A (A/Astrakhan/3212/2020) (H5N8)	2.3.4.4b	CDC	Yes
CBER-RG8A (A/Astrakhan/3212/2020) (H5N8)	2.3.4.4b	FDA	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
IDCDC-RG65A (A/Guangdong/18SF020/2018) (H5N6)	2.3.4.4h	CDC	Yes
Candidate vaccine viruses in preparation	**Clade**	**Institution**	**Availability**
IDCDC-RG63A (A/duck/Bangladesh/17D1012/2018-like)	2.3.2.1a	CDC	Pending
IDCDC-RG75A (A/chicken/Ghana/20/2015-like)	2.3.2.1f	CDC	Pending
A/Guangdong/18SF020/2018-like (H5N6)	2.3.4.4h	CCDC	Pending
CNIC-HB29578 (A/Hubei/29578/2016-like) (H5N6)	2.3.4.4d	CCDC	Pending
CNIC-FJ21099 (A/Fujian-Sanyuan/21099/2017-like) (H5N6)	2.3.4.4b	CCDC	Pending
SJ010 (A/chicken/Vietnam/NCVD-15A59/2015) (H5N6)	2.3.4.4f	SJCRH	Pending
IDCDC-RG69A (A/ck/Vietnam/RAHO4-CD-20-421/2020-like) (H5N6)	2.3.4.4g	CDC	Pending
A/chicken/Ghana/AVL-763_21VIR7050-39/2021-like	2.3.4.4b	CDC	Pending
A/American Wigeon/South Carolina/22-000345-001/2021	2.3.4.4b	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
MHRA – Medicines and Healthcare products Regulatory Agency (previously known as NIBSC), 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 many 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 humans and pigs have been reported, with associated mild disease in most human cases and no evidence for human-to-human transmission.

Influenza A(H9N2) activity from 20 September 2022 to 20 February 2023

Eight A(H9N2) human infections have been identified in China in this period. One of these infections was severe, five were mild and no information was available for the other two. Four infected individuals reported exposure to poultry, two reported no exposure and two had unknown exposures.

Genetic and antigenic characteristics of influenza A(H9N2) viruses

Sequence information was available for three of the eight viruses detected in humans. All belonged to the Y280/G9 lineage. Of these three viruses, one had 24 and two had 25 HA amino acid substitutions compared to both the A/Anhui-Lujiang/39/2018 and A/Hong Kong/308/2014 CVVs. Recent A(H9N2) viruses detected in humans in China reacted with a post-infection ferret antiserum raised against A/Anhui-Lujiang/39/2018, albeit with reduced titers.

A(H9N2) viruses from birds characterized from September 2022 to February 2023 belonged to the following lineages:

Y280/G9 lineage A(H9N2) viruses were frequently detected in poultry in China and in Viet Nam. Although viruses from this lineage were genetically diverse, post-infection ferret antisera raised against the A/Anhui-Lujiang/39/2018 CVV reacted well with many of the viruses tested. Some viruses from Viet Nam reacted better with post-infection ferret antisera raised against an older Y280/G9 lineage CVV. Other viruses from China had reduced reactivity with post-infection ferret antisera raised against existing CVVs. Further antigenic characterization is underway.

G1 lineage A(H9N2) viruses were detected in birds in Bangladesh, Egypt, Mali and Morocco. Post-infection ferret antisera raised against the A/Bangladesh/994/2011 and A/Oman/2747/2019 CVVs reacted well with most of the viruses from Bangladesh. Antigenic data for the viruses from Egypt, Mali and Morocco were not available.

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	MHRA	Yes
NIBRG-91 (A/chicken/Hong Kong/G9/97)	Y280/G9	Reverse genetics	MHRA	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	MHRA	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
MHRA – Medicines and Health care products Regulatory Agency (previously known as NIBSC), United Kingdom
SJCRH – St Jude Children's Research Hospital, United States of America

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 are designated as A(H1)variant ((H1)v) viruses and continue to be documented in the Americas, Asia and Europe.

Influenza A(H1)v activity from 20 September 2022 to 20 February 2023

Three A(H1N1)v virus infections were identified, one in Brazil (clade 1A.3.3.2[5]) and two in China (one was clade 1C.2.3 and one is sequence pending). Two cases of A(H1N2)v virus were reported, one each in the Netherlands (clade 1C.2.2) and Taiwan, China (clade 1C.2.5). Swine exposure prior to illness, which in each instance was mild, was reported for the cases in Brazil and the Netherlands and unknown for the other cases.

Genetic and antigenic characteristics of influenza A(H1)v viruses

The A(H1N1)v virus from Brazil belonged to clade 1A.3.3.2 and was related to circulating A(H1N1)pdm09-like influenza viruses reported globally in swine, including previous detections in swine in Brazil. Antigenic testing is pending for the 1A.3.3.2 A(H1N1)v virus from Brazil. The 1C.2.3 A(H1N1)v virus identified in China was genetically related to previous viruses detected in humans and swine in China but had 16 amino acid substitutions in the HA compared to the clade 1C.2.3 A/Hunan/42443/2015 CVV. No antigenic data was available.

The A(H1N2)v virus from the Netherlands was related to clade 1C.2.2 viruses previously reported in swine from Europe, but no contemporaneous swine surveillance data were available from the Netherlands. This virus had 19 HA amino acid substitutions compared to the A/Hessen/47/2020 CVV, but reacted well with a post-infection ferret antiserum raised against this CVV, as well as a post-infection ferret antiserum raised against A/Netherlands/10370-1b/2020 for which a CVV has been proposed. 1C.2.5 viruses were reported previously in swine in Europe, but the Taiwan, China, A(H1N2)v virus is the first report of this swine influenza clade in the region, and there were no new swine data. The Taiwan, China A(H1N2)v virus was genetically distinct from recommended CVVs and antigenic testing is pending. The A(H1)v viruses detected in swine clade 1C.2.5 represented the first human case in this clade (Fig. 2).

Influenza A(H1)v candidate vaccine viruses

Based on the current antigenic, genetic and epidemiologic data, no new A(H1)v CVVs are proposed. The available and pending A(H1)v CVVs are listed in Table 5.

Table 5. 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
NIB-124 (A/Hessen/47/2020) (H1N1)v	1C.2.2	Conventional	MHRA	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	MHRA	Pending
A/Ohio/35/2017-like (H1N2)v	1B.2.1	Reverse genetics	MHRA	Pending
A/Netherlands/10370-1b/2020 (H1N1)v	1C.2.1	Conventional	MHRA	Pending
A/Bretagne/24241/2021 (H1N2)v	1C.2.4	Reverse genetics	SJCRH	Pending
		Conventional	MHRA	Pending
A/Wisconsin/03/2021 (H1N1)v	1A.3.3.3	Reverse genetics	CDC	Pending

[4] Standardization of terminology for the influenza virus variants infecting humans: Update https://cdn.who.int/media/docs/default-source/influenza/global-influenza-surveillance-and-response-system/nomenclature/standardization_of_terminology_influenza_virus_variants_update.pdf?sfvrsn=d201f1d5_6

[5] Anderson TK, Macken CA, Lewis NS, Scheuermann RH, Van Reeth K, Brown IH, et al. A Phylogeny-Based Global Nomenclature System and Automated Annotation Tool for H1 Hemagglutinin Genes from Swine Influenza A Viruses. mSphere 2016;1(6). Available at: A Phylogeny-Based Global Nomenclature System and Automated Annotation Tool for H1 Hemagglutinin Genes from Swine Influenza A Viruses - PubMed (nih.gov)

A/California/71/2021 (H1N2)v	1A.1.1	Reverse genetics	CDC	Pending

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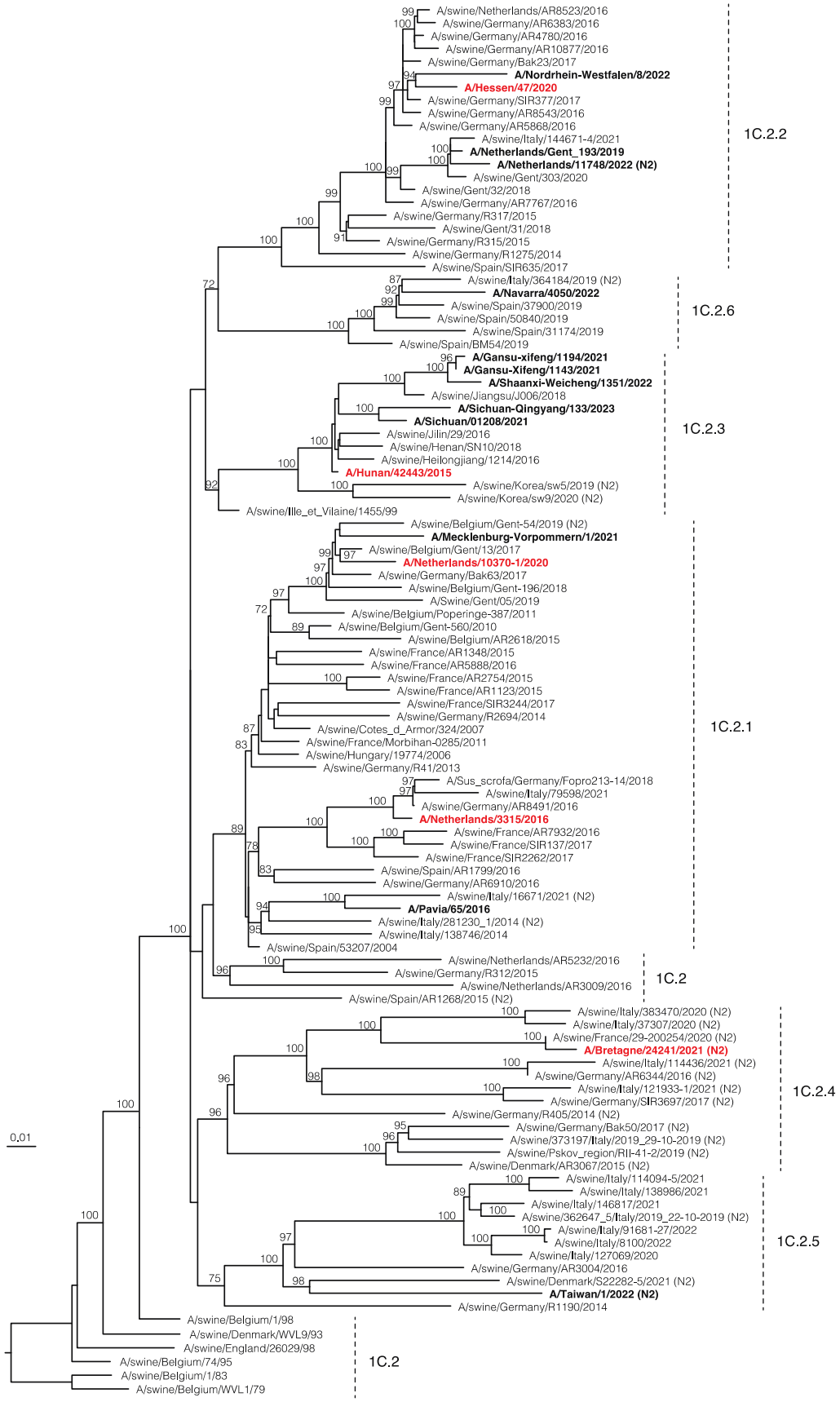

Figure 2. Phylogenetic relationships of influenza A(H1)v HA genes of 1C clades. CVVs that are available or in preparation are in red. Human viruses are in bold font. The tree was built from the nucleotide sequences coding for the mature HA1 protein. The scale bar represents the number of substitutions per site. Bootstrap supports of topology are shown above selected nodes.

Influenza A(H3N2)v

Influenza A(H3N2) viruses with diverse genetic and antigenic characteristics are enzootic in swine populations in most regions of the world. Human infections with influenza A(H3N2)v viruses originating from swine have been documented in Asia, Australia, Europe and North America.

Influenza A(H3N2)v activity from 20 September 2022 to 20 February 2023
Two cases of A(H3N2)v virus infection were reported from the USA. Both cases reported exposure to swine and recovered following mild illness.

Genetic and antigenic characteristics of influenza A(H3N2)v viruses
Virus gene sequences from the two cases identified in the USA showed a close genetic relationship to contemporaneous 3.2010.1[6] lineage A(H3N2) swine influenza viruses detected in the USA and the A/Ohio/13/2017 CVV. Virus was recovered from one case and it reacted well with post-infection ferret antisera raised against the A/Ohio/13/2017 CVV.

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 6.

Table 6. Status of influenza A(H3N2)v candidate vaccine virus development

Candidate vaccine viruses (like viruses)	Lineage	Type	Institution*	Available
NYMC X-203 (A/Minnesota/11/2010)	3.1990.4.A	Conventional	CDC	Yes
NYMC X-213 (A/Indiana/10/2011)	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	MHRA	Pending

*Institution distributing the candidate vaccine viruses:
CDC – Centers for Disease Control and Prevention, United States of America
MHRA – Medicines and Healthcare products Regulatory Agency (previously known as NIBSC), United Kingdom

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[6] Anderson TK, Chang J, Arendsee ZW, Venkatesh D, Souza CK, Kimble JB, et al. Swine Influenza A Viruses and the Tangled Relationship with Humans. Cold Spring Harb Perspect Med 2021;11(3). Available at: Swine Influenza A Viruses and the Tangled Relationship with Humans - PubMed (nih.gov)