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 antigenically and genetically, 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 21 February to 25 September 2023

Eleven human infections or detections with A/goose/Guangdong/1/96-lineage viruses have been reported in this period. Since 2003, 3 A(H5), 7 A(H5N8), 88 A(H5N6) and 878 A(H5N1) human infections have been reported. Since February 2023, A/goose/Guangdong/1/96-lineage A(H5) viruses have been detected in both domestic and wild birds in many countries, with spillover to 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] Global Influenza Programme (who.int)

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

Table 1. H5 activity reported to international agencies since February 2023

Country, area or territory	Host	Genetic clade
Argentina	Poultry	2.3.4.4b (H5N1)
	Mammals (seal, sea lion)	unknown* (H5)
	Wild Birds	2.3.4.4b (H5N1)
Austria	Wild Birds	2.3.4.4b (H5N1)
Bangladesh	Poultry	2.3.2.1a (H5N1); 2.3.4.4b (H5N1)
	Wild Birds	2.3.4.4b (H5N1)
Belgium	Poultry	2.3.4.4b (H5N1)
	Mammals (fox, polecat)	2.3.4.4b (H5N1)
	Wild Birds	2.3.4.4b (H5N1)
Bhutan	Poultry	unknown
	Wild Birds	unknown
Bolivia (Plurinational State of)	Poultry	unknown (H5N1)
	Wild Birds	unknown (H5N1)
Brazil	Poultry	2.3.4.4b (H5N1)
	Wild Birds	2.3.4.4b (H5N1)
Bulgaria	Poultry	2.3.4.4b (H5N1)
Cambodia	Human (2)†	2.3.2.1c (H5N1)
	Poultry	2.3.2.1c (H5N1), 2.3.4.4b (H5N1)
	Wild Birds	unknown (H5N1)
Canada	Poultry	2.3.4.4b (H5N1)
	Mammals (dog, fox, racoon, skunk)	2.3.4.4b (H5N1/5)
	Wild Birds	2.3.4.4b (H5N1/5)
Chile	Human (1)	2.3.4.4b (H5N1)
	Poultry	2.3.4.4b (H5N1)
	Mammals (sea lion, otter, dolphin)	2.3.4.4b (H5N1)
	Wild Birds	2.3.4.4b (H5N1)
China	Human (4)	unknown (H5N6); 2.3.4.4b (H5N6)
	Poultry	2.3.4.4b (H5N1/6); 2.3.4.4h (H5N6)
	Mammals (dog)	2.3.4.4b (H5N6)
	Wild Birds	2.3.4.4b (H5N1)
Taiwan, China	Poultry	unknown (H5N1/5)
	Wild Birds	unknown (H5N1)
Colombia	Poultry	2.3.4.4b (H5N1)
	Wild Birds	2.3.4.4b (H5N1)
Costa Rica	Wild Birds	2.3.4.4b (H5N1)
Croatia	Wild Birds	2.3.4.4b (H5N1)
Cuba	Wild Birds	2.3.4.4b (H5N1)
Czechia	Poultry	2.3.4.4b (H5N1)
	Wild Birds	2.3.4.4b (H5N1)
Denmark	Poultry	2.3.4.4b (H5N1)
	Mammals (seal)	2.3.4.4b (H5N1)
	Wild Birds	2.3.4.4b (H5N1)
Ecuador	Poultry	unknown (H5)
	Wild Birds	unknown (H5N1)
Egypt	Poultry	2.3.4.4b (H5N1/8)
Estonia	Poultry	2.3.4.4b (H5N1)
	Wild Birds	2.3.4.4b (H5N1)
Finland	Poultry	2.3.4.4b (H5N1)
	Mammals (fox, mink, racoon dog)	2.3.4.4b (H5N1)
	Wild Birds	2.3.4.4b (H5N1)
France	Poultry	2.3.4.4b (H5N1)
	Mammals (fox)	2.3.4.4b (H5N1)
	Wild Birds	2.3.4.4b (H5N1)

Gambia	Wild Birds	2.3.4.4b (H5N1)
Germany	Poultry	2.3.4.4b (H5N1)
	Mammals (fox, seal)	2.3.4.4b (H5N1)
	Wild Birds	2.3.4.4b (H5N1)
Guatemala	Wild Birds	unknown (H5N1)
Guinea	Wild Birds	2.3.4.4b (H5N1)
Honduras	Wild Birds	unknown (H5N1)
Hungary	Poultry	2.3.4.4b (H5N1)
	Wild Birds	2.3.4.4b (H5N1)
Iceland	Wild Birds	unknown (H5N1)
India	Poultry	2.3.2.1a (H5N1)
Indonesia	Poultry	2.3.2.1e (H5N1); 2.3.4.4b (H5N1)
Ireland	Wild Birds	2.3.4.4b (H5N1)
Isle of Man	Wild Birds	unknown (H5N1)
Israel	Wild Birds	2.3.4.4b (H5N1)
Italy	Poultry	2.3.4.4b (H5N1)
	Mammals (cat, dog, fox)	2.3.4.4b (H5N1)
	Wild Birds	2.3.4.4b (H5N1)
Japan	Poultry	2.3.4.4b (H5N1)
	Mammals (fox)	2.3.4.4b (H5N1)
	Wild Birds	2.3.4.4b (H5N8)
Jersey	Wild Birds	unknown (H5N1)
Lao People's Democratic Republic	Poultry	2.3.2.1c (H5N1); 2.3.4.4b (H5N1)
Latvia	Mammals (fox)	unknown (H5N1)
	Wild Birds	unknown (H5N1)
Lithuania	Wild Birds	unknown (H5N1)
Luxembourg	Wild Birds	2.3.4.4b (H5N1)
Mexico	Poultry	2.3.4.4b (H5N1)
	Wild Birds	2.3.4.4b (H5N1)
Nepal	Poultry	unknown (H5N1)
	Wild Birds	unknown (H5N1)
Netherlands (Kingdom of the)	Poultry	2.3.4.4b (H5N1)
	Wild Birds	2.3.4.4b (H5N1)
Niger	Poultry	2.3.4.4b (H5N1)
Nigeria	Poultry	2.3.4.4b (H5N1)
Norway	Poultry	2.3.4.4b (H5N1)
	Mammals (fox)	2.3.4.4b (H5N1)
	Wild Birds	2.3.4.4b (H5N1/5)
Panama	Poultry	2.3.4.4b (H5N1)
	Wild Birds	unknown (H5)
Paraguay	Poultry	unknown (H5N1)
	Wild Birds	unknown (H5N1)
Peru	Poultry	2.3.4.4b (H5N1)
	Mammals (lion, sea lion, dolphin)	2.3.4.4b (H5N1)
	Wild Birds	2.3.4.4b (H5N1)
Philippines	Poultry	unknown (H5N1)
Poland	Poultry	2.3.4.4b (H5N1)
	Mammals (cat, caracal)	2.3.4.4b (H5N1)
	Wild Birds	2.3.4.4b (H5N1)
Republic of Korea	Poultry	2.3.4.4b (H5N1)
	Mammals (cat)	2.3.4.4b (H5N1)
Réunion	Poultry	unknown (H5N1)
Romania	Wild Birds	2.3.4.4b (H5N1)
Russian Federation	Poultry	2.3.4.4b (H5N1)
	Mammals (seal)	2.3.4.4b (H5N1)
	Wild Birds	2.3.4.4b (H5N1)

Senegal	Poultry	2.3.4.4b (H5N1)
	Wild Birds	2,3,4,4b (H5N1)
Serbia	Wild Birds	unknown (H5N1)
Slovenia	Poultry	2.3.4.4b (H5N1)
	Wild Birds	2.3.4.4b (H5N1)
South Africa	Poultry	2.3.4.4b (H5N1)
	Wild Birds	2.3.4.4b (H5N1)
Spain	Wild Birds	2.3.4.4b (H5N1)
Svalbard and Jan Mayen	Wild Birds	unknown (H5N1)
Sweden	Poultry	2.3.4.4b (H5N1)
	Wild Birds	2.3.4.4b (H5N1/5)
Switzerland	Poultry	2.3.4.4b (H5N1)
	Wild Birds	2.3.4.4b (H5N1)
Togo	Poultry	2.3.4.4b (H5N1)
Türkiye	Poultry	2.3.4.4b (H5N1)
United Kingdom of Great Britain and Northern Ireland	Human (4)	2.3.4.4b (H5N1)
	Poultry	2.3.4.4b (H5N1)
	Mammals (dolphin, porpoise, fox)	2.3.4.4b (H5N1)
	Wild Birds	2.3.4.4b (H5N1)
United States of America	Poultry	2.3.4.4b (H5N1)
	Mammals (bear, bobcat, cat, cougar, fisher, marten, seal, lion, otter, racoon, fox, skunk, opossum)	2.3.4.4b (H5N1)
	Wild Birds	2.3.4.4b (H5N1/N5/N6)
Uruguay	Poultry	unknown (H5)
	Mammals (coati, sea lion, seal)	unknown (H5)
	Wild Birds	unknown (H5)
Viet Nam	Poultry	2.3.2.1c (H5N1); 2.3.4.4b (H5N1)

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

Genetic and antigenic characteristics of influenza A(H5) viruses

Four A(H5N6) human infections were identified in China, two A(H5N1) infections in Cambodia, one A(H5N1) infection in Chile and four A(H5N1) detections in the United Kingdom of Great Britain and Northern Ireland. The majority of cases reported exposure to poultry. One each of the A(H5N1) and A(H5N6) cases were fatal, one A(H5N1) and three A(H5N6) cases were severe. One of the cases from Cambodia and the four individuals from the United Kingdom of Great Britain and Northern Ireland were asymptomatic. The viruses from humans in Chile, China, and the United Kingdom of Great Britain and Northern Ireland from which sequence information was available (n=8) belonged to clade 2.3.4.4b. The HAs of all but one sequenced virus had 1 to 2 amino acid substitutions compared with A/Astrakhan/3212/2020 or A/American wigeon/South Carolina/22-000345-001/2022, from which clade 2.3.4.4b CVVs have been developed. One virus from China had accumulated 11 HA amino acid substitutions compared with A/Astrakhan/3212/2020; antigenic data for the virus were not available. The two cases from Cambodia were caused by clade 2.3.2.1c viruses that had 11 amino acid substitutions compared with the HA of the clade 2.3.2.1c A/duck/Vietnam/NCVD-1584/2012 CVV. Post-infection ferret antisera raised against this CVV reacted well with the Cambodian viruses.

A(H5) viruses from birds and non-human mammals belonged to the following clades:

Clade 2.3.2.1a viruses were detected in poultry in Bangladesh and India. There were up to 11 amino acid substitutions in the HA of recent viruses compared to the A/duck/Bangladesh/17D1012/2018 CVV. Some of the recent viruses did not react well with 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. Viruses with HA 154N reacted well with post-infection ferret antisera raised against the A/duck/Bangladesh/17D1012/2018 CVV, those with HA 154D reacted better with post-infection ferret antisera raised against the A/duck/Bangladesh/19097/2013 CVV.

Clade 2.3.2.1c viruses were detected in birds in Cambodia, Lao People's Democratic Republic and Viet Nam. The HAs of these viruses were similar to those detected in recent periods and had up to 11 amino acid substitutions relative to the 2.3.2.1c A/duck/Vietnam/NCVD-1584/2012 CVV. The viruses from Cambodia were genetically similar to those associated with the two 2.3.2.1c human infections. A subset of viruses from Viet Nam were characterised antigenically. All but one of these viruses reacted well with a post-infection ferret antiserum raised against the A/duck/Vietnam/NCVD-1584/2012 CVV. The other virus reacted well with a post-infection ferret antiserum raised against the clade 2.3.2.1f A/chicken/Ghana/20/2015 CVV.

Clade 2.3.2.1e viruses were detected in Indonesia. No antigenic data were available for these viruses. The HAs of the viruses were genetically similar to viruses previously detected in Indonesia and The Democratic Republic of Timor-Leste. There are no CVVs representative of this HA clade. 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 South America. Infections in wild and captive mammals have continued to be reported with spread between mammals suspected in some cases. Although the 2.3.4.4b viruses have continued to diversify through reassortment, their HAs remain genetically (Figure 1) and antigenically similar to the A/Astrakhan/3212/2020 (H5N8), A/chicken/Ghana/AVL-76321VIR7050-39/2021-like (H5N1) or A/American wigeon/South Carolina/22-000345-001/2021 (H5N1) CVVs. There was considerable antigenic overlap between 2.3.4.4b CVVs and circulating viruses, with post-infection ferret antisera raised against the A/Astrakhan/3212/2020 CVV reacting well to most viruses tested. Furthermore, the diversity of viruses from the Americas was better covered by post-infection ferret antisera raised against the A/American wigeon/South Carolina/22-000345-001/2021 CVV and the diversity in Asia was better covered by post-infection ferret antisera raised against the A/Astrakhan/3212/2020 CVV. Viruses from Europe, and those from Africa, the Americas and Asia that contained HA156T/S reacted better with post-infection ferret antisera raised against A/chicken/Ghana/AVL-76321VIR7050-39/2021-like viruses.

A number of 2.3.4.4b viruses from wild birds in the United States of America had an NA T438I substitution leading to reduced inhibition by zanamivir and peramivir but not oseltamivir.

Clade 2.3.4.4h viruses were detected in Fujian Province in China. The HA of these viruses had accumulated up to 13 amino acid substitutions compared with the clade 2.3.4.4h A/Guangdong/18SF020/2018 CVV. Post-infection ferret antiserum raised against the A/Guangdong/18SF020/2018 CVV reacted poorly with the Fujian viruses. Viruses from this clade have been infrequently detected in recent periods and the extent of their circulation appears limited.

Figure 1. Phylogenetic relationships of A(H5) clade 2.3.4.4 HA genes. The available CVVs are in red. Human viruses are in bold font. Viruses collected in 2023 are underlined. 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 genetic, antigenic, 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	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
IDCDC-RG63A (A/duck/Bangladesh/17D1012/2018)	2.3.2.1a	CDC	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-RG78A (A/Am. wigeon/South Carolina/22-000345-001/2021)	2.3.4.4b	CDC	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-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
A/Ezo red fox/Hokkaido/1/2022 (A/Astrakhan/3212/2020-like)	2.3.4.4b	NIID	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-76321VIR7050-39/2021-like	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(H3N8)

Diverse A(H3) viruses circulate in wild birds in many regions of the world. A(H3N8) infections have been detected in dogs, donkeys, horses, pigs, poultry, seals and wild birds. A(H3N8) viruses with genes encoding internal proteins derived from A(H9N2) viruses have been detected in poultry in China since 2021. Prior to this reporting period two human infections have been reported in China in 2022.

Influenza A(H3N8) activity from 21 February to 25 September 2023

There has been one report of a fatal human infection with an A(H3N8) virus in China in an immunocompromised 56-year-old female with a history of poultry exposure.

Genetic and antigenic characteristics of influenza A(H3N8) viruses

Genetic analyses of the HA of the A(H3N8) virus from the human case confirmed it was genetically related to the A(H3N8) viruses causing disease in humans in 2022, accumulating eight amino acid changes compared to the A/Henan/4-10CNIC/2022 CVV. Genetically similar viruses detected in samples taken from live bird markets in 2022 also possessed up to eight amino acid changes compared to the A/Henan/4-10CNIC/2022 CVV.

Transmission studies in ferrets with A/Henan/4-10CNIC/2022 demonstrated both direct contact and airborne transmission[4]. This, together with detection of molecular changes associated with mammalian adaptation in the HA and PB2 genes of the most recent human virus warrants enhanced monitoring for avian origin A(H3N8) viruses.

Influenza A(H3N8) candidate vaccine viruses

Based on the available genetic, antigenic, and epidemiologic data, no new CVVs are proposed. The available and pending A(H3N8) CVVs are listed in Table 3.

Table 3. Status of influenza A(H3N8) candidate vaccine virus development

Candidate vaccine viruses (like virus)	Lineage	Type	Institution*	Available
A/Henan/4-10CNIC/2022	Eurasian	Reverse Genetics	CDC/CCDC	pending

*Institutions distributing the candidate vaccine virus:
CDC – Centers for Disease Control and Prevention, United States of America
CCDC – Chinese Center for Disease Control and Prevention

Influenza A(H7)

Influenza A(H7) viruses are maintained in waterfowl and occasionally spillover to poultry populations with the associated disease ranging from mild to severe. A total of 1,568 laboratory-confirmed human infections with avian influenza A(H7N9) virus of the A/Anhui/1/2013-lineage, including 616 fatal cases (CFR: 39%), have been reported to WHO since early 2013. The last case of human infection with avian influenza A(H7N9) reported to WHO in the Western Pacific Region was in 2019.

Influenza A(H7) activity from 21 February to 25 September 2023

No A(H7N9) human infections were reported in this period. A/Anhui/1/2013-lineage A(H7N9) viruses were reported in chickens and environmental samples from China.

In May 2023, a genetically distinct HPAI A(H7N6) virus emerged in poultry in South Africa and continues to circulate. No associated A(H7N6) human infections were reported.

Genetic and antigenic characteristics of influenza A(H7) viruses

The HAs of A/Anhui/1/2013-lineage A(H7N9) viruses were similar to those detected in 2022 and possessed up to 18 amino acid substitutions relative to the A/Gansu/23277/2019 CVV. No antigenic data are available.

Sequence information was available for one A(H7N6) virus from South Africa. Phylogenetic analyses showed that this virus belongs to the Eurasian lineage of A(H7) viruses and groups with sequences of low pathogenicity avian influenza A(H7N1) viruses circulating in ostriches in South Africa in 2020. Compared to the genetically

[4] Airborne transmission of human-isolated avian H3N8 influenza virus between ferrets: Cell

closest CVVs, derived from the A(H7N3) A/mallard/Netherlands/12/2000 virus, the A(H7N6) virus has 13 amino acid substitutions in HA1. Antigenic data are not yet available.

Influenza A(H7N9) candidate vaccine viruses

Based on the current epidemiologic and virologic data, no new A(H7) CVVs are proposed. Available A(H7) CVVs are shown in Table 4.

Table 4. 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	MHRA	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	MHRA	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	MHRA	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)	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	MHRA	Yes
IBCDC-1 (A/mallard/Netherlands/12/2000)	Eurasian (H7N7)	Conventional	CDC	Yes
NIBRG-60 (A/mallard/Netherlands/12/2000)	Eurasian (H7N3)	Reverse genetics	MHRA	Yes
NIBRG-63 (A/mallard/Netherlands/12/2000)	Eurasian (H7N1)	Reverse genetics	MHRA	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 developing and/or 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
MHRA – Medicines and Healthcare products Regulatory Agency (previously known as NIBSC), United Kingdom
NIID – National Institute of Infectious Diseases, Japan

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 21 February to 25 September 2023

Five A(H9N2) human infections have been identified in China in this period. One of these infections had an illness onset date prior to 21 February 2023. All the infected individuals reported exposure to poultry, had mild disease and subsequently recovered.

Genetic and antigenic characteristics of influenza A(H9N2) viruses

Sequence information was available for four of the five viruses detected in humans. All four of these viruses belong to the Y280/G9 lineage (Figure 2) with one of them accumulating 30 HA amino acid substitutions relative to the genetically closest CVV. Antigenic data are forthcoming. A(H9N2) viruses from birds characterized from February to September 2023 belonged to the following lineages:

Y280/G9 lineage A(H9N2) viruses continued to circulate in poultry in Cambodia, China, Indonesia, Lao People's Democratic Republic and Viet Nam. Viruses from this lineage continue to diversify genetically. Although post-infection ferret antisera raised against the A/Anhui-Lujiang/39/2018 CVV reacted well with many of the tested viruses, reduced reactivity was observed with some (Table 5). While some of the poorly reacting viruses exhibited better reactivity with post-infection ferret antisera raised against the A/chicken/Hong Kong/G9/97 CVV, their HAs had many amino acid changes.

G1 lineage A(H9N2) viruses were detected in birds in Africa and Asia and remained genetically and antigenically similar to viruses detected in previous periods. Some of the tested viruses reacted well to post-infection ferret antisera raised against available CVVs, while others, particularly some from Egypt, showed reduced reactivity. Further reagent generation is planned to determine if additional CVVs are warranted.

Table 5. Haemagglutination inhibition assay* of avian influenza A(H9N2) viruses

Reference Antigen	Lineage	HK/G9	HK/308	AH-LJ/39	HK/G1
A/chicken/Hong Kong/G9/97	Y280/G9	**640**	20	20	<20
A/Hong Kong/308/2014	Y280/G9	40	**5120**	320	40
A/Anhui-Lujiang/39/2018	Y280/G9	40	320	**2560**	<20
A/Quail/Hong Kong/G1/97	G1	<20	<20	<20	**640**
Test Antigen					
A/Hunan-Louxin/11086/2022	Y280/G9	40	160	320	<20
A/Anhui-Tianjiaan/11086/2022	Y280/G9	40	80	320	<20
A/Gansu/00805/2022	Y280/G9	80	160	320	<20
A/Environment/Fujian/25726/2022	Y280/G9	40	160	320	<20
A/Environment/Yunnan/20309/2022	Y280/G9	40	80	320	<20
A/Environment/Guangxi/18648/202	Y280/G9	80	160	1280	<20
A/Environment/Hunan/19974/2022	Y280/G9	40	80	1280	<20
A/Jiangxi/16794/2022	Y280/G9	<20	160	160	<20
A/Anhui-Yingjiang/12475/2021	Y280/G9	20	320	1280	<20

*Haemagglutination inhibition assay was conducted using turkey red blood cells

Influenza A(H9N2) candidate vaccine viruses

Based on the available genetic, antigenic, and epidemiologic data, a new CVV that is antigenically like A/Anhui-Tianjiaan/11086/2022 is 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)	Lineage	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
IDCDC-RG66A (A/Oman/2747/2019)	G1	Reverse genetics	CDC	Yes
Candidate vaccine viruses in preparation	**Clade**	**Type**	**Institution**	**Availability**
A/Anhui-Lujiang/39/2018-like	Y280/G9	Conventional	MHRA	Pending
A/Anhui-Tianjiaan/11086/2022-like	Y280/G9	Reverse genetics	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
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

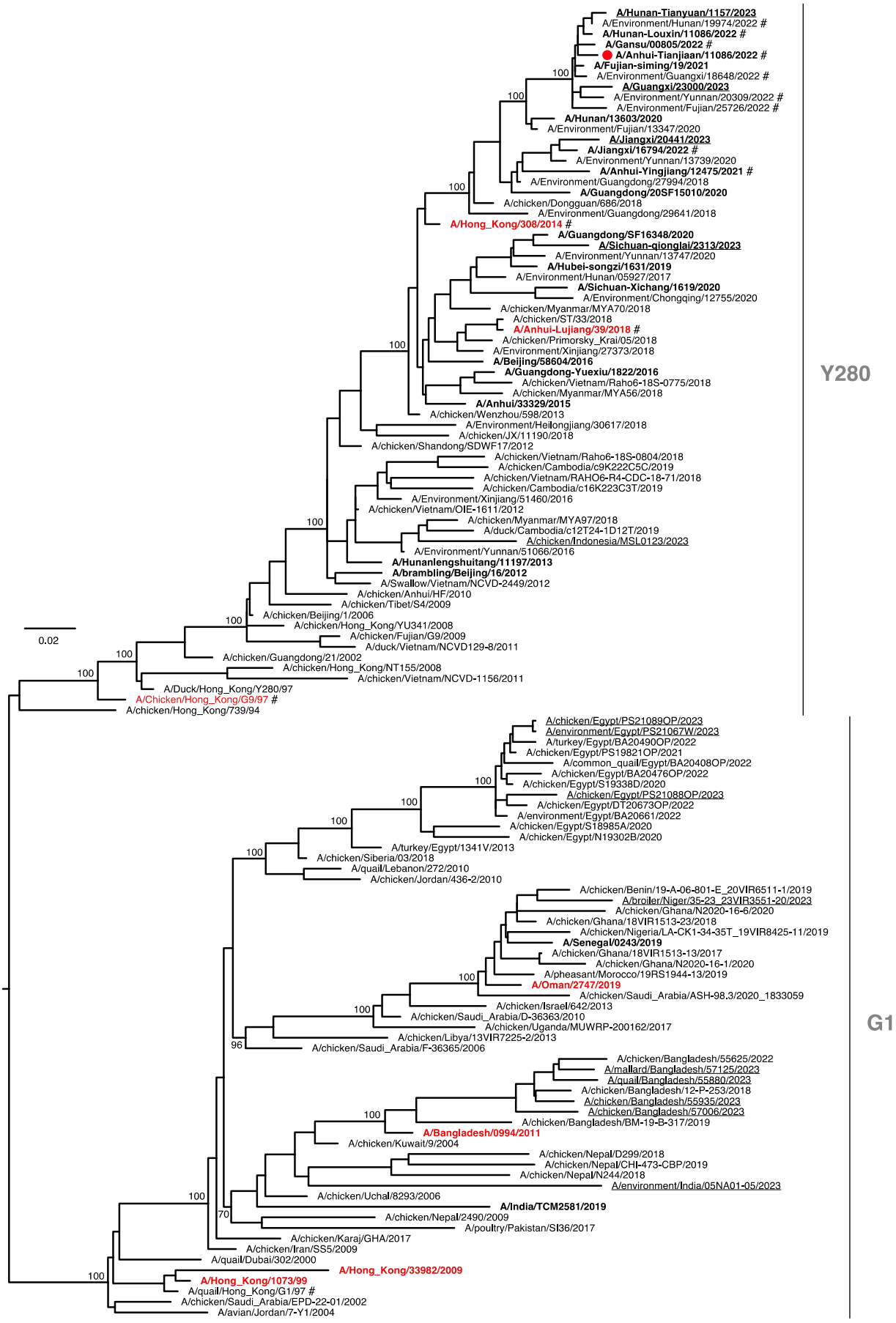

Figure 2. Phylogenetic relationships of A(H9) Y280-like and G1-like HA genes. CVVs that are available or in preparation are in red. Human viruses are in bold font. The proposed CVV is indicated by a red dot(●). The viruses tested in haemagglutination inhibition assay are indicated by hashes (#). Viruses collected in 2023 are underlined. The scale bar represents the number of substitutions per site. Bootstrap supports of topology are shown above selected nodes.

Influenza A(H1)v[5]

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. Viruses isolated from human infections with swine influenza A(H1) viruses are designated as A(H1)variant ((H1)v) viruses and continue to be detected in the Americas, Asia and Europe.

Influenza A(H1)v activity from 21 February to 25 September 2023

Two A(H1N1)v virus infections were identified, one each in Brazil (clade 1A.3.3.2[6]) and the Netherlands (clade 1C.2.2). Three cases of A(H1N2)v were reported, one in Taiwan, China (clade 1A.1.4) and two in the United States of America (clade 1B.2.1). A summary of recent A(H1) activity in swine and humans is shown in Table 7. The case in Brazil was fatal, the remaining four cases were mild. Swine exposure prior to illness was reported for the cases in Brazil, Taiwan, China and the United States of America but was not apparent for the case in the Netherlands.

Table 7. Recent swine and variant A(H1) activity shared with international agencies and collected from sequence repositories.

Country, area or territory	Host#	Clade
Belgium	Swine	1A.3.3.2; 1B.1.2.1;1C.2.1; 1C.2.2
Brazil	Human (1)*	1A.3.3.2
Cambodia	Swine	1A.1.2; 1A.3.3.2; 1C.2.3
Canada	Swine	1A.1.1; 1A.1.1.3; 1A.2;1A.3.3.2; 1A.3.3.3-c3
Chile	Swine	1A.3.3.2; 1B.2.5
China	Swine	1C.2.3
Taiwan, China	Human (1)	1A.1.4
Denmark	Swine	1A.3.3.2; 1C.2.5
France	Swine	1C.2.4
Germany	Swine	1C.2.2; 1C.2.4
Italy	Swine	1A.3.3.2; 1B.1.2.2; 1C.2.1; 1C.2.2; 1C.2.4; 1C.2.5
Japan	Swine	1A.3.3.2; 1A.5.1
Mexico	Swine	1A.3.3.2; 1A.4
Netherlands (Kingdom of the)	Human (1)	1C.2.2
Republic of Korea	Swine	1C.2.3
United Kingdom of Great Britain and Northern Ireland	Swine	1B.1.1; 1C.2.2
United States of America	Human (2)	1B.2.1
	Swine	1A.1.1.3; 1A.3.3.2; 1A.3.3.3-c1; 1A.3.3.2-c3; 1B.2.1; 1B.2.2.1; 1B.2.2.2

#Swine H1 clades by country collected in the past 24 months and sequences deposited July 2021 – June 2023
*Number of cases and/or detections

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

Sequence was available for the variant viruses from Brazil, the Netherlands, Taiwan, China and the United States of America and showed varying levels of similarity to existing CVVs. The viruses from Brazil and Taiwan, China were most similar to variant viruses detected previously in these countries; information on the relevant viruses circulating in swine in these countries was not available. The variant viruses from the United States of America had accumulated 19 HA amino acid substitutions compared to the A/Michigan/383/2018 CVV. Nevertheless, these variant viruses and related viruses circulating in swine reacted well with post-infection ferret antiserum raised against A/Michigan/383/2018, albeit with reduced titers. The variant virus from the Netherlands had accumulated 14 HA amino acid changes compared to the A/Hessen/47/2020 CVV. There are no CVVs representative of clade 1A.1.4 to which the variant virus from Taiwan, China belongs. No viruses were available for antigenic characterization from the cases in Brazil, the Netherlands and Taiwan, China.

Influenza A(H1)v candidate vaccine viruses

[5] 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

[6] A Phylogeny-Based Global Nomenclature System and Automated Annotation Tool for H1 Hemagglutinin Genes from Swine Influenza A Viruses | mSphere (asm.org)

Based on the current genetic, antigenic, and epidemiologic data, no new A(H1)v CVVs are 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)	Clade	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	Reverse genetics	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	Reverse genetics	MHRA	Pending
NIB-124 (A/Hessen/47/2020) (H1N1)v	1C.2.2	Conventional	MHRA	Pending
A/Bretagne/24241/2021 (H1N2)v	1C.2.4	Reverse genetics	SJCRH	Pending
NIB-131 (A/Bretagne/24241/2021 (H1N2)v)		Conventional	MHRA	Pending
A/Wisconsin/03/2021 (H1N1)v	1A.3.3.3	Reverse genetics	CDC	Pending
A/California/71/2021 (H1N2)v	1A.1.1	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
MHRA – Medicines and Healthcare products Regulatory Agency (previously known as NIBSC), United Kingdom
SJCRH – St. Jude Children's Research Hospital, United States of America

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. Viruses isolated from human infections with swine influenza A(H3) viruses are designated as A(H3)variant ((H3)v) viruses and have been detected in Asia, Australia, Europe and North America.

Influenza A(H3N2)v activity from 21 February to 25 September 2023

One case of A(H3)v virus infection was reported from the United States of America. The case reported exposure to swine and recovered following mild illness. A summary of recent detections in swine and humans is shown in Table 9.

Table 9. Recent swine influenza A(H3) and A(H3)v activity shared with international agencies and collected from sequence repositories.

Country, area or territory	Host[#]	Clade
Canada	Swine	1990.4; 1990.4.b2; 1990.4.c; 1990.4.g;1990.4.i; 2010.1; 2020-era human seasonal
Cambodia	Swine	2000.4
Italy	Swine	1970.1; 2010-era human seasonal
Japan	Swine	2000.5
Mexico	Swine	1990.4
United States of America	Human (1)*	unknown
	Swine	1990.4.a; 1990.4.b1; 1990.4.b2; 1990.4.i; 2010.1; 2010.2; 2020-era human seasonal

[#]Swine H3 clades by country collected in the past 24 months and sequences deposited July 2021 – June 2023
*Number of cases and/or detections

Genetic and antigenic characteristics of influenza A(H3N2)v viruses

Virus gene sequences from the human case identified in the United States of America could not be determined but the case reported swine exposure at an agricultural fair. Swine influenza viruses detected in North America

belonged to the 2010.1[7] and 1990.4 lineages and showed close genetic relationships to previous swine influenza A(H3N2) viruses detected in Canada and the United States of America, including in agricultural fairs that were epidemiologically linked to the human case (Figure 3). Recent A(H3) 2010.1 virus HAs were genetically similar to the A/Ohio/13/2017 CVV and the viruses that were tested reacted well with post-infection ferret antisera raised against the A/Ohio/13/2017 CVV. Post-infection ferret antisera raised against the A/Minnesota/11/2010 CVV reacted poorly with recent swine influenza viruses from the 1990.4.a clade (Table 10). While sera pooled from adults who received the seasonal influenza vaccine demonstrated cross-reactivity with these viruses, pooled sera from immunized children reacted poorly with these viruses. Other 1990.4 lineage viruses detected in the United States of America, including those from the 1990.4.b and 1990.4.i clades, also reacted poorly with post-infection ferret antisera raised against the A/Minnesota/11/2010 CVV.

Table 10. Haemagglutination inhibition assay* of swine influenza A(H3N2) viruses

Reference Antigens	Lineage or Clade	Dar/9	Dar/6	RG60	X-203	Adult#	Child^
A/Darwin/9/2021 (egg)	Seasonal	**1280**	640	<20	<20	1280	1280
A/Darwin/6/2021 (cell)	Seasonal	1280	**1280**	40	<20	1280	2560
IDCDC-RG60A (A/Ohio/13/2017-like)	2010.1	40	20	**2560**	<20	640	320
X-203 (A/Minnesota/11/2010-like)	1990.4.a	80	40	<20	**2560**	160	<20
Test antigens							
A/swine/Iowa/22Tosu3985/2022	2010.1	80	40	1280	<20	640	320
A/swine/Ohio/23Tosu0496/2023	2010.1	80	80	1280	<20	1280	640
A/swine/Iowa/23TOSU0845/2023	1990.4.a	<20	<20	80	320	320	20
A/swine/Iowa/23TOSU0850/2023	1990.4.a	<20	<20	40	320	320	20
A/swine/Iowa/23TOSU1494/2023	1990.4.a	<20	<20	80	320	320	20

*Haemagglutination inhibition assay was conducted using guinea pig red blood cells
#19-49 years (adult) pool; post-immunization with 2022-2023 seasonal vaccine
^0-3 years (paediatric) pool; post-immunization with 2022-2023 seasonal vaccine

Influenza A(H3N2)v candidate vaccine viruses

Based on the available genetic, antigenic, and epidemiologic data, a new CVV that is antigenically like A/swine/Iowa/23TOSU0850/2023 is proposed. The available A(H3N2)v CVVs are listed in Table 11.

Table 11. Status of influenza A(H3N2)v candidate vaccine virus development

Candidate vaccine viruses (like viruses)	Clade	Type	Institution*	Available
NYMC X-203 (A/Minnesota/11/2010)	1990.4.A	Conventional	CDC	Yes
NYMC X-213 (A/Indiana/10/2011)	1990.4.A	Conventional	CDC	Yes
IDCDC-RG55C (A/Ohio/28/2016)	2010.1	Reverse genetics	CDC	Yes
Candidate vaccine viruses in preparation		**Type**	**Institution**	**Availability**
A/Ohio/13/2017-like	2010.1	Reverse genetics	CDC	Pending
A/Ohio/28/2016-like	2010.1	Conventional	MHRA	Pending
A/swine/Iowa/23TOSU0850/2023	1990.4a	Reverse genetics	CDC	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

[7] Swine Influenza A Viruses and the Tangled Relationship with Humans - PubMed (nih.gov)

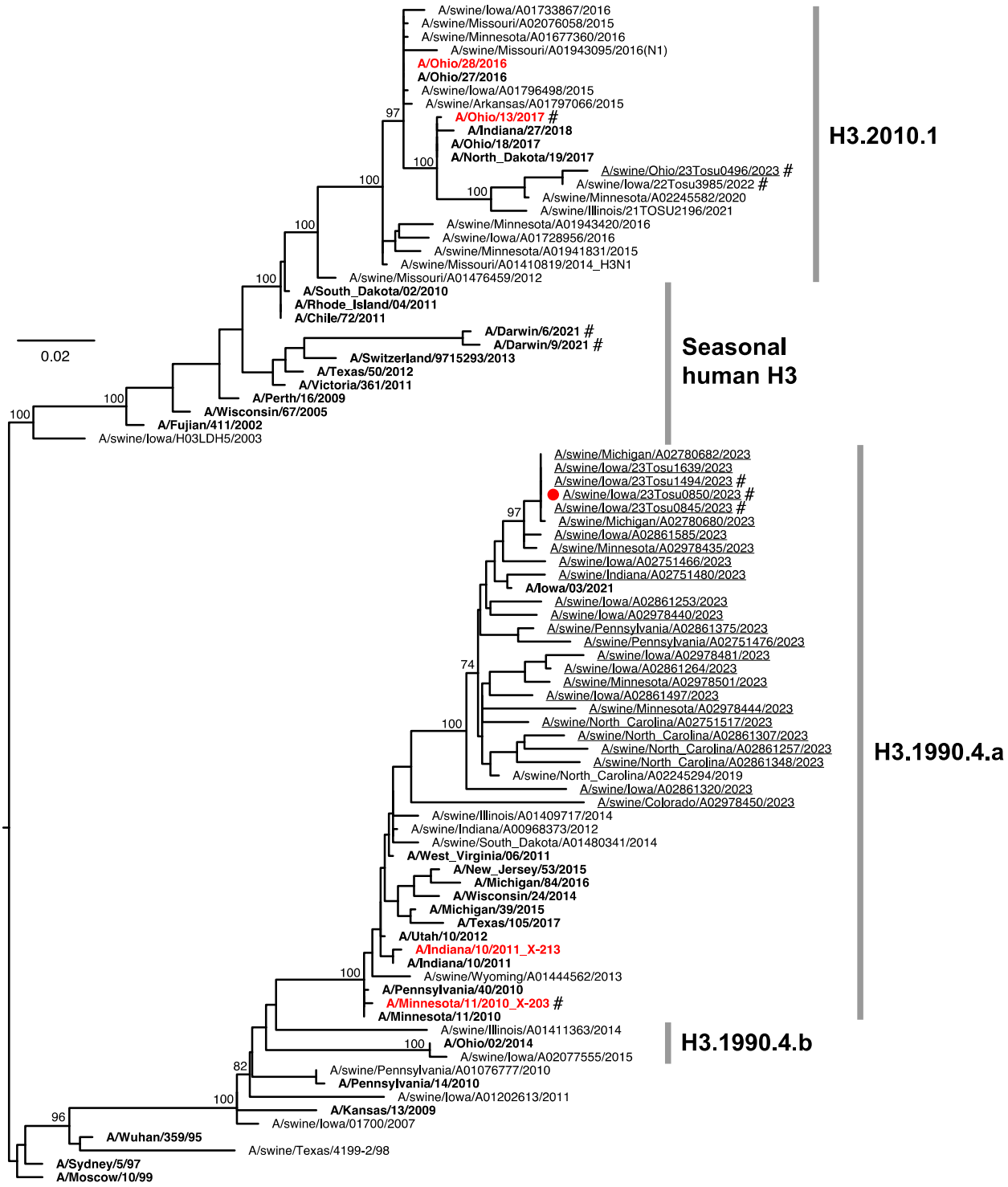

Figure 3. Phylogenetic relationships of A(H3) HA genes. CVVs that are available or in preparation are in red. The proposed CVV is indicated by a red dot(●). Human viruses are in bold font. The viruses tested in haemagglutination inhibition assay are indicated by hashes (#). Viruses collected in 2023 are underlined. The scale bar represents the number of substitutions per site. Bootstrap supports of topology are shown above selected nodes.

Acknowledgements

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