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 pandemic preparedness.

Selection and development of CVVs are the first steps towards timely vaccine production and do not imply a recommendation for initiating manufacture. National authorities may consider the use of one or more of these CVVs for pilot lot vaccine production, clinical trials and other pandemic preparedness purposes based on their assessment of public health risk and need.

Zoonotic influenza viruses continue to be identified and evolve both genetically and antigenically, leading to the need for additional CVVs for pandemic preparedness purposes. Changes in the genetic and antigenic characteristics of these viruses relative to existing CVVs and their potential risks to public health justify the need to select and develop new CVVs.

This document summarizes the genetic and antigenic characteristics of recent zoonotic influenza viruses and related viruses circulating in animals[1] that are relevant to CVV updates. Institutions interested in receiving these CVVs should contact WHO at gisrs-whohq@who.int or the institutions listed in announcements published on the WHO website[2].

Influenza A(H5)

Since their emergence in 1997, highly pathogenic avian influenza (HPAI) A(H5) viruses of the A/goose/Guangdong/1/96 haemagglutinin (HA) lineage have become enzootic in some countries, have infected wild birds and continue to cause outbreaks in poultry and sporadic human infections. These viruses have diversified genetically and antigenically, leading to the need for multiple CVVs. Through reassortment, viruses with replacement of the N1 gene segment by N2, N3, N5, N6, N8 or N9 gene segments have also emerged. This summary provides updates on the characterization of A/goose/Guangdong/1/96-lineage A(H5) viruses and the current status of the development of influenza A(H5) CVVs.

Influenza A(H5) activity from 18 February 2019 to 24 September 2019

One A(H5N6) human infection in China and one A(H5N1) human infection in Nepal were detected in this period. Since 2003, there have been 24 A(H5N6) and 861 A(H5N1) human infections confirmed. A/goose/Guangdong/1/96-lineage A(H5) viruses were detected in poultry and wild birds in several countries (Table 1).

[1] For information relevant to other notifiable influenza virus infections in animals refer to http://www.oie.int/wahis_2/public/wahid.php/Wahidhome/Home

[2] http://www.who.int/influenza/vaccines/virus/candidates_reagents/home/en/

Table 1. Recent A(H5) activity

Country, area or territory	Host	Genetic clade*
Bangladesh	Poultry	2.3.2.1a (H5N1)
Bhutan	Poultry	2.3.2.1a (H5N1)
Bulgaria	Poultry	2.3.4.4b (H5N8)
Cambodia	Poultry	2.3.4.4h (H5N6)
China	Human (1)†	2.3.4.4h (H5N6)
	Poultry	2.3.2.1d (H5N1); 2.3.4.4h (H5N6)
Taiwan, China	Poultry	2.3.4.4c (H5N2)
	Wild birds	2.3.4.4c (H5N2)
Egypt	Poultry	2.3.4.4b (H5N8)
India	Poultry	2.3.2.1a (H5N1)
Iran (Islamic Republic of)	Poultry	2.3.4.4b (H5N8)
Iraq	Poultry	2.3.4.4b (H5N8)
Israel	Poultry	2.3.4.4b (H5N8)
Lao People's Democratic Republic	Poultry	2.3.2.1c (H5N1)
Namibia	Wild birds	2.3.4.4b (H5N8)
Nepal	Human (1) †	2.3.2.1a (H5N1)
	Poultry	2.3.2.1a (H5N1)
	Wild birds	2.3.2.1a (H5N1)
Nigeria	Poultry	2.3.4.4b (H5N8)
Russian Federation	Poultry	2.3.4.4b (H5N8)
Viet Nam	Poultry	2.3.2.1c (H5N1); 2.3.4.4g; 2.3.4.4h (H5N6)

* Utilizing proposed update to the unified nomenclature for highly pathogenic avian influenza A(H5) viruses

† Denotes number of human cases reported to WHO within the reporting period (18 February 2019 to 24 September 2019)

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]. An update of this nomenclature has been made during 2019 defining additional clades within existing clades 2.3.2.1c and 2.3.4.4. and will be published on the WHO website by the end of year.

A(H5) viruses circulating and characterized from 18 February 2019 to 24 September 2019 belong to the following clades:

Clade 2.3.2.1a viruses were detected in a human in Nepal and in birds in Bangladesh, Bhutan, India and Nepal. The majority of viruses tested were inhibited well by post-infection ferret antisera raised against A/duck/Bangladesh/17D1012/2018, for which a CVV is in development, or genetically related viruses.

Clade 2.3.2.1c viruses were detected in Lao People's Democratic Republic and Viet Nam. These viruses had HA genes similar to viruses detected in South-East Asia in previous periods. Despite the viruses from Lao People's Democratic Republic having up to 11 amino acid substitutions in HA proteins compared to the CVV A/duck/Vietnam/NCVD-1584/2012, they reacted well with post-infection ferret antiserum raised to the CVV. Antigenic data for the viruses from Viet Nam are pending.

Clade 2.3.2.1d viruses were detected in birds and environmental samples in China. The HA genes of these viruses were genetically similar to that of A/chicken/Guiyang/1153/2016, from which a CVV has been produced

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

and is undergoing safety testing. Assessment of the antigenic relatedness of the recent clade 2.3.2.1d viruses to the A/chicken/Guiyang/1153/2016 CVV is pending.

Clade 2.3.4.4b viruses were detected in birds in Bulgaria, Egypt, Iran (Islamic Republic of), Iraq, Israel, Namibia, Nigeria and the Russian Federation. Although there was diversity within the available HA gene sequences, the HA protein sequences of most viruses were similar to that of A/Fujian-Sanyuan/21099/2017, from which a CVV is in development. There is considerable antigenic diversity among viruses within this group when compared with antisera raised to A/Fujian-Sanyuan/21099/2017-like viruses. The antigenic similarity of recent clade 2.3.4.4b viruses to A/Fujian-Sanyuan/21099/2017 is being determined.

Clade 2.3.4.4c viruses were detected in birds in Taiwan, China. Compared to the most closely related CVV, A/gyrfalcon/Washington/41088-6/2014, there were 8-10 amino acid differences in the HA protein. No antigenic data are available for these viruses.

Clade 2.3.4.4g viruses were detected in Viet Nam following outbreaks in poultry. These viruses were genetically similar to viruses detected in Viet Nam in recent years. No CVV has been proposed from clade 2.3.4.4g. The HA1 proteins of the recent viruses from Viet Nam had up to 10 amino acid substitutions relative to that of A/chicken/Viet Nam/15A59/2015 (clade 2.3.4.4f), from which a CVV is being developed. Antigenic information on the clade 2.3.4.4g viruses is being generated.

Clade 2.3.4.4h viruses were detected in a human in China and birds in China and Viet Nam. The HA genes of these viruses were closely related to that of A/Guangdong/18SF020/2018, from which a CVV is being developed. Viruses isolated from birds in China were tested in hemagglutination inhibition assays and had antigenic profiles similar to A/Guangdong/18SF020/2018.

Influenza A(H5) candidate vaccine viruses

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

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

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

* Institutions developing and/or distributing the candidate vaccine viruses:

CDC – Centers for Disease Control and Prevention, United States of America
NIV – National Institute of Virology, India
CCDC – Chinese Center for Disease Control and Prevention
FDA – Food and Drug Administration, United States of America
HKU – University of Hong Kong, Hong Kong Special Administrative Region, China
NIBSC – National Institute for Biological Standards and Control, a centre of the Medicines and Healthcare products Regulatory Agency (MHRA), United Kingdom
NIID – National Institute of Infectious Diseases, Japan
SJCRH – St Jude Children's Research Hospital, United States of America

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

‡ These CVVs are being rederived.

Influenza A(H7)

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

Influenza A(H7) activity from 18 February 2019 to 24 September 2019
One human case of HPAI A(H7N9) infection was detected in China in this period. HPAI A(H7N9) viruses were also detected in environmental samples collected in the poultry market epidemiologically linked to the human case. Since their emergence, there have been 1568 confirmed human infections with A/Anhui/1/2013 HA lineage A(H7N9) viruses.

Antigenic and genetic characteristics of influenza A(H7) viruses
The HA proteins of the A(H7N9) viruses isolated from the infected human and associated poultry market had 16 amino acid substitutions relative to previously characterized viruses and available CVVs (Figure 1). Correspondingly, these viruses were not inhibited well by antisera raised against available CVVs or previously described wild type viruses (Table 3).

Table 3. Haemagglutination inhibition assays of A(H7N9) influenza viruses

Reference Antigen	RG32A	HK/125	RG56B	GD/17SF003	RG56N
A/Shanghai/2/2013 IDCDC-RG32A	**640**	320	160	1280	1280
A/Hong Kong/125/2017	320	**320**	160	2560	1280
IDCDC-RG56B	320	640	**320**	2560	1280
A/Guangdong/17SF003/2016	80	40	40	**640**	320
IDCDC-RG56N	80	80	40	1280	**640**
Test Antigen					
A/Gansu/23277/2019	10	<10	<10	80	20

Influenza A(H7) candidate vaccine viruses
Based on the current antigenic, genetic and epidemiologic data, development of a new A/Gansu/23277/2019-like CVV is proposed. Availability of A(H7N9) CVVs is listed in Table 4.

Table 4. Status of influenza A(H7N9) candidate vaccine virus development

Candidate vaccine virus (like virus)	Type	Institution*	Available
IDCDC-RG33A (A/Anhui/1/2013)	Reverse genetics	CDC	Yes
NIBRG-268 (A/Anhui/1/2013)	Reverse genetics	NIBSC	Yes
NIIDRG-10.1 (A/Anhui/1/2013)	Reverse genetics	NIID	Yes
SJ005 (A/Anhui/1/2013)	Reverse genetics	SJCRH	Yes
NIBRG-267 (A/Shanghai/2/2013)	Reverse genetics	NIBSC	Yes
CBER-RG4A (A/Shanghai/2/2013)	Reverse genetics	FDA	Yes
IDCDC-RG32A (A/Shanghai/2/2013)	Reverse genetics	CDC	Yes
IDCDC-RG32A.3 (A/Shanghai/2/2013)	Reverse genetics	CDC	Yes
IDCDC-RG56B (A/Hong Kong/125/2017)	Reverse genetics	CDC	Yes
IDCDC-RG56N (A/Guangdong/17SF003/2016)	Reverse genetics	CDC	Yes
NIBRG-375 (A/Guangdong/17SF003/2016)	Reverse genetics	NIBSC	Yes
CBER-RG7C (A/Guangdong/17SF003/2016)	Reverse genetics	FDA	Yes
CBER-RG7D (A/Guangdong/17SF003/2016)	Reverse genetics	FDA	Yes
Candidate vaccine virus in preparation	**Type**	**Institution**	**Availability**
A/Guangdong/17SF003/2016-like†	Reverse genetics	CCDC	Pending
A/Hunan/02650/2016-like†	Reverse genetics	CCDC	Pending
A/Gansu/23277/2019-like	Reverse Genetics	CDC	Pending

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

† These CVVs are being rederived.

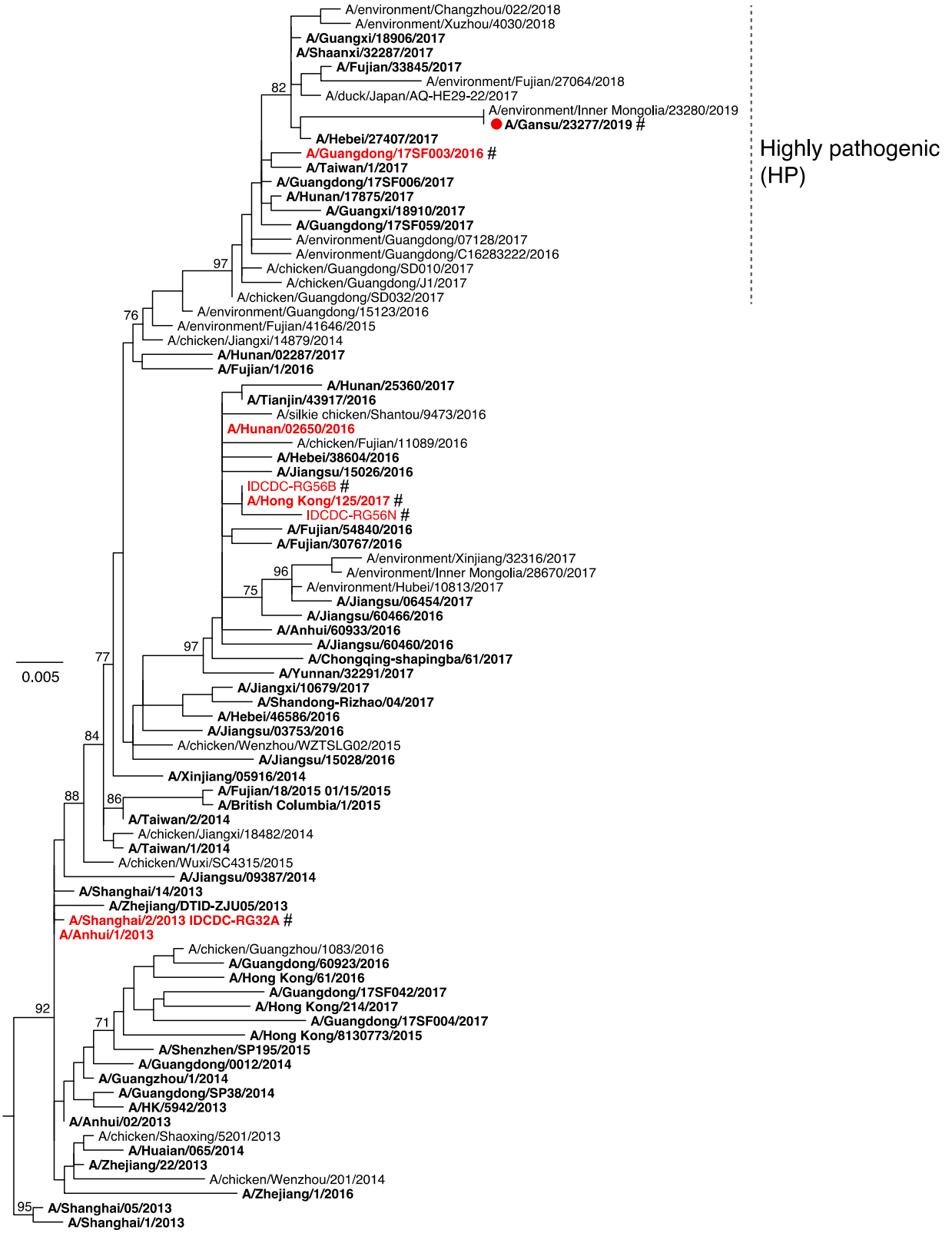

Figure 1. Phylogenetic relationships of A(H7N9) HA genes. CVVs that are available or in preparation are in red. The proposed CVV is indicated by a red dot(●). Human viruses are in bold font. The viruses tested in haemagglutination inhibition assay are indicated by hashes (#). The scale bar represents the number of substitutions per site. Bootstrap supports of topology are shown above selected nodes.

Influenza A(H9N2)

Influenza A(H9N2) viruses are enzootic in poultry in parts of Africa, Asia and the Middle East. The majority of viruses sequenced from these regions belongs to the A/quail/Hong Kong/G1/97 (G1) or A/chicken/Beijing/1/94 (Y280/G9) lineages. Since the late 1990s, when the first human infection was identified, the detection of A(H9N2) viruses from humans and swine has been reported infrequently. In most human cases, the associated illness has been mild and there has been no evidence of human-to-human transmission.

Influenza A(H9N2) activity from 18 February 2019 to 24 September 2019

Single human cases of A(H9N2) virus infections were reported by China and Oman in this period. The virus from China belonged to the Y280/G9 lineage and that from Oman to the G1 lineage. The Y280/G9 lineage A(H9N2) viruses continue to predominate in environmental and/or poultry samples in Cambodia, China and Viet Nam. As in previous reporting periods, G1 lineage viruses were detected in poultry in a number of countries within Africa and Asia.

Antigenic and genetic characteristics of influenza A(H9N2) viruses

All recent A(H9N2) infections of humans and poultry in China, and all poultry infections in Cambodia, Lao People's Democratic Republic and Viet Nam, were caused by viruses of the Y280/G9 lineage. Representatives of these recent viruses, including the virus isolated from the human infection in China, reacted well to post-infection ferret antiserum raised against A/Anhui-Lujiang/39/2018, from which a CVV is in development. A subset of viruses detected in China, Lao People's Democratic Republic and Viet Nam that were not well inhibited by this post-infection ferret antiserum but reacted well with post-infection ferret antiserum raised against the A/chicken/Hong Kong/G9/97 CVV.

The virus isolated from the human case in Oman had an HA gene similar to viruses detected in surrounding countries in recent years and reacted well with post-infection ferret antiserum raised against A/Bangladesh/0994/2011, from which a CVV has been developed. Increasing genetic and antigenic diversity was detected in recent G1 lineage viruses circulating in birds in different geographic regions, notably Africa and the Middle East, with some loss of reactivity with post-infection ferret antisera raised against existing CVVs. Additional data from these regions will allow a more accurate determination of the significance of this diversity.

Influenza A(H9N2) candidate vaccine viruses

Based on the available antigenic, genetic and epidemiologic data, development of new CVVs is not proposed. Availability of A(H9N2) CVVs is listed in Table 5.

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

Candidate vaccine viruses (like virus)	Type	Clade	Institution*	Available
A/Hong Kong/1073/99	Wild type	G1	NIBSC	Yes
NIBRG-91 (A/chicken/Hong Kong/G9/97)	Reverse genetics	Y280/G9	NIBSC	Yes
IBCDC-2 (A/chicken/Hong Kong/G9/97)	Conventional	Y280/G9	CDC	Yes
IDCDC-RG26 (A/Hong Kong/33982/2009)	Reverse genetics	G1	CDC	Yes
IDCDC-RG31 (A/Bangladesh/994/2011)	Reverse genetics	G1	CDC	Yes
SJ008 (A/Hong Kong/308/2014)	Reverse genetics	Y280/G9	SJCRH	Yes
Candidate vaccine viruses in preparation	**Type**	**Clade**	**Institution**	**Availability**
A/Anhui-Lujiang/39/2018-like	Reverse genetics	Y280/G9	CCDC	Pending
	Conventional	Y280/G9	NIBSC	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
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(H1)v[4]

Influenza A(H1) viruses are enzootic in swine populations in most regions of the world. Depending on geographic location, the genetic and antigenic characteristics of these viruses differ. Human infections with swine influenza A(H1) viruses (designated as A(H1)v viruses[4]) have been previously documented in Asia, Europe and the Americas[5].

Influenza A(H1)v activity from 18 February 2019 to 24 September 2019
One human case of an A(H1N1)v virus infection was identified in the USA in this period. Since 2005, 48 human infections with A(H1)v viruses have been reported in the USA.

Antigenic and genetic characteristics of the influenza A(H1N1)v virus
The A(H1N1)v virus had HA and NA genes similar to recent A(H1N1)pdm09 viruses circulating in swine and humans. The remaining gene segments were closely related to those of swine viruses circulating in the USA. Ferret antisera raised against recommended human seasonal A(H1N1)pdm09 vaccine viruses (e.g., A/Michigan/45/2015, A/Brisbane/02/2018 and A/Idaho/7/2018) reacted well with the A(H1N1)v virus and closely related swine influenza viruses. Similarly, sera from vaccinated children and adults inhibited this virus at titers comparable to those seen with 2018-2019 seasonal A(H1N1)pdm09 vaccine viruses.

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

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

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

* Institution distributing the candidate vaccine viruses:
CDC – Centers for Disease Control and Prevention, United States of America
CCDC – Chinese Center for Disease Control and Prevention
NIBSC - National Institute for Biological Standards and Control, a centre of the Medicines and Healthcare products Regulatory Agency (MHRA), United Kingdom

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[4] http://www.who.int/influenza/gisrs_laboratory/terminology_variant/en/
[5] https://www.eurosurveillance.org/images/dynamic/EE/V19N18/art20793.pdf