

## **Recommended composition of influenza virus vaccines for use in the 2021-2022 northern hemisphere influenza season**

**February 2021**

WHO convenes technical consultations<sup>1</sup> in February and September each year to recommend viruses for inclusion in influenza vaccines<sup>2</sup> for the northern and southern hemisphere influenza seasons, respectively. This recommendation relates to the influenza vaccines for use in the northern hemisphere 2021-2022 influenza season. A recommendation will be made in September 2021 relating to vaccines that will be used for the southern hemisphere 2022 influenza season. For countries in tropical and subtropical regions, WHO recommendations for influenza vaccine composition (northern hemisphere or southern hemisphere) are available on the WHO Global Influenza Programme website<sup>3</sup>.

### **Seasonal influenza activity**

Public health and laboratory responses to the COVID-19 pandemic, caused by the coronavirus SARS-CoV-2, initially led to reduced influenza surveillance and/or reporting activities in many countries, which have been improving. Additionally, COVID-19 mitigation strategies including restrictions on travel, use of respiratory protection, and social-distancing measures in most countries have contributed to decreased influenza activity. Overall, record-low levels of influenza detections were reported and fewer viruses were available for characterization during the September 2020 to January 2021 time-period than in previous years.

**Between September 2020 and January 2021**, influenza A(H1N1)pdm09, A(H3N2) and influenza B viruses circulated in very low numbers and the relative proportions of the viruses circulating varied among reporting countries. Globally, since September 2020, influenza activity was mostly reported from countries in the tropics and subtropics and some countries in the temperate zone of the northern hemisphere. Overall, the percent positivity for influenza viruses in all specimens tested during this period was less than 0.2%. In contrast, the average percent positivity during the same reporting period of the three previous seasons (2017-2020) was 17%.

**In the temperate zone of the northern hemisphere**, influenza activity remained far lower than usual for this time of year, with very low-level detections of influenza A and B viruses in reporting countries. In Europe, there were only sporadic detections of influenza A or B viruses. By comparison with previous years, there was a 20% reduction in the number of specimens tested, but a 99% reduction in influenza positive samples. In North America, the percentage of tests that were positive for influenza virus was very low, despite testing at usual or increased levels. The majority of detections were influenza B, and where subtyping was performed, both A(H1N1)pdm09 and A(H3N2) viruses were reported. In Asia, influenza activity was also lower than usual for this time of year. Influenza A and B viruses were detected in most reporting countries with a predominance of influenza B viruses in Afghanistan, China, the Islamic Republic of Iran, and Saudi Arabia. In the Democratic People's Republic of Korea only influenza A viruses were reported, with A(H1N1)pdm09 predominating. Japan reported a slight increase in influenza activity in week 5 of 2021, with a small outbreak of A(H3N2).

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<sup>1</sup> <http://www.who.int/influenza/vaccines/virus/en/>

<sup>2</sup> Description of the process of influenza vaccine virus selection and development available at: [http://www.who.int/gb/pip/pdf\\_files/Fluvaccvirusselection.pdf](http://www.who.int/gb/pip/pdf_files/Fluvaccvirusselection.pdf)

<sup>3</sup> Influenza in the tropics and sub-tropics: <http://www.who.int/influenza/vaccines/tropics/en/>

**Influenza activity in tropical and subtropical countries** was generally very low, with co-circulation of influenza A(H1N1)pdm09, A(H3N2) and influenza B viruses. In tropical countries of Africa, influenza activity was reported mainly from countries in East and West Africa. In East Africa, small numbers of influenza A(H3N2) and influenza B viruses were reported, with a predominance of influenza B in Kenya. In West Africa, the countries of Burkina Faso, Côte d'Ivoire, Mali and Mauritania reported a predominance of influenza A(H3N2), followed by influenza B, and a few detections of A(H1N1)pdm09 viruses. Influenza A(H3N2) and influenza B viruses were reported in equal proportions in Ghana and Senegal, while influenza B viruses predominated in Guinea and Sierra Leone. A(H1N1)pdm09 viruses were predominant in Niger and Togo. In tropical countries of Asia, most influenza detections were reported from Bangladesh, Cambodia, India, Lao People's Democratic Republic, Thailand and Viet Nam; influenza A(H3N2) was predominant with a few detections of influenza B and A(H1N1)pdm09 viruses. In the tropical countries of the Caribbean and Central America, influenza activity was also very low; most detections were reported by Haiti, where the majority were influenza B viruses.

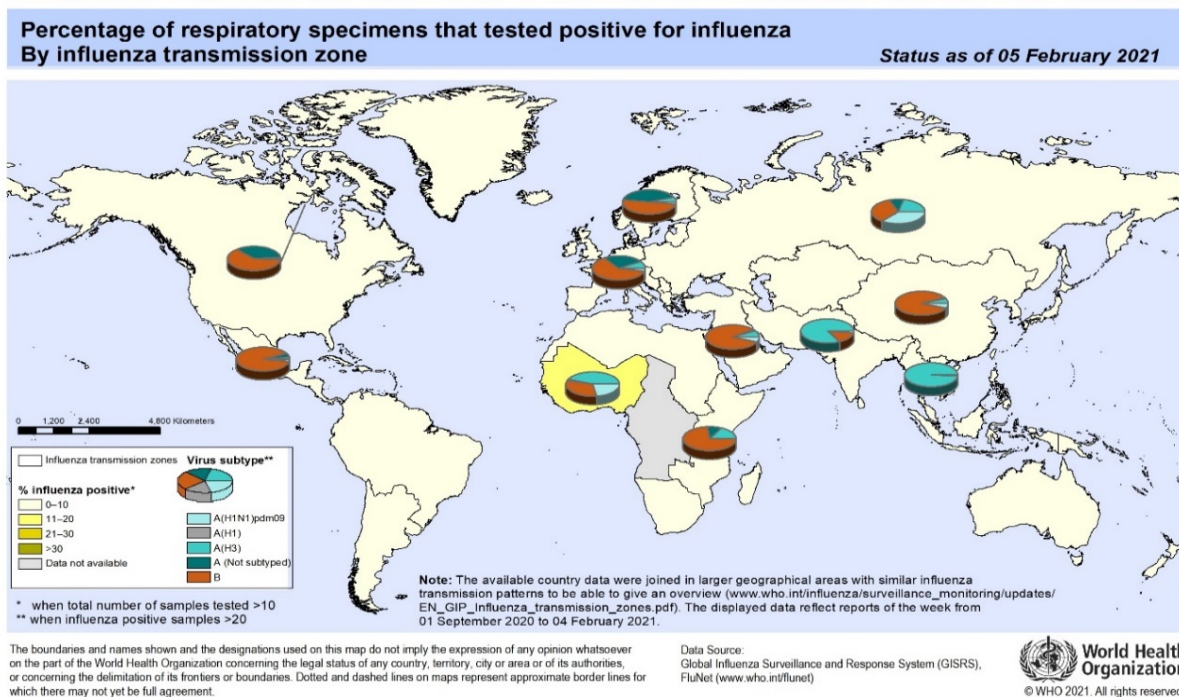
**In the temperate zones of the southern hemisphere**, influenza activity was much lower than usual inter-seasonal levels with sporadic detections in some countries. Over 59,000 specimens were tested for influenza viruses during this period, and only 11 specimens, originating from Argentina and Chile, were positive for influenza A or B viruses. Among reporting countries in Oceania and Southern Africa, influenza viruses were not detected despite testing.

## **Influenza A**

Globally, from September 2020 through January 2021, overall influenza A virus detections were in the minority during this period compared to influenza B virus detections. However, from September to November 2020, influenza A virus detections predominated in some countries. In most countries, areas and territories reporting influenza A viruses, both A(H1N1)pdm09 and A(H3N2) subtypes were detected. Influenza A(H3N2) viruses were detected in higher proportions than influenza A(H1N1)pdm09 in some countries in Africa (Burkina Faso, Côte d'Ivoire, Ghana, Mali, Mauritania and Senegal) and Asia (Bangladesh, Cambodia, India, Lao People's Democratic Republic, Thailand and Viet Nam). Influenza A(H1N1)pdm09 viruses predominated in other countries in Africa (Egypt, Niger and Togo), Asia (the Democratic People's Republic of Korea) and Europe (Ukraine).

## **Influenza B**

Globally, more influenza B viruses were detected than influenza A viruses during this period and influenza B viruses have predominated since November 2020. Of the influenza B viruses where lineage was determined, nearly all were the B/Victoria/2/87 lineage and the majority were reported from Afghanistan, China, Côte d'Ivoire, Ghana, Guinea, Haiti and Senegal. B/Yamagata/16/88 lineage viruses were reported in very low numbers by a few countries (Afghanistan, Sweden and the United States of America).



Detailed information of the extent of seasonal influenza activity by country and type/subtype of viruses worldwide is available on the WHO website: <http://www.who.int/influenza/resources/charts/en/>.

## Antigenic and genetic characteristics of recent seasonal influenza viruses, human serology and antiviral susceptibility

### Influenza A(H1N1)pdm09 viruses

A(H1N1)pdm09 viruses that have circulated since February 2020 have haemagglutinin (HA) genes that belong to phylogenetic clade 6B.1A5, with the vast majority clustering within subclade 6B.1A5A characterized by HA1 amino acid substitutions N129D, T185I and N260D, taking the HA sequence of A/Idaho/07/2018 as the reference (a parental clade 6B.1A virus closely related to the former vaccine virus A/Brisbane/02/2018). Subclade 6B.1A5A (5A) has further diverged into two major subclades: 5A-187A (also called, 5A+187A), characterized by D187A and Q189E (located in HA antigenic site Sb), and 5A-156K (also called 5A+156K) defined by N156K (located in antigenic site Sa), K130N, L161I, V250A and E506D (E179D in HA2). Viruses belonging to both groups have co-circulated during 2020. While the global frequency of 5A-156K viruses had rapidly increased during the first half of 2020 until reaching similar proportions as 5A-187A, the majority of viruses characterized since September 2020 belong to group 5A-187A.

The antigenic characteristics of A(H1N1)pdm09 viruses were assessed with post-infection ferret antisera in haemagglutination inhibition (HI) assays. However, antigenic analysis of viruses with collection dates after August 2020 has been very limited due to the small number of viruses available. Results showed that viruses in the 5A-187A group were well recognized by antisera raised against the 2020–2021 northern hemisphere vaccine viruses (egg-propagated A/Guangdong-Maonan/SWL1536/2019 and cell culture-propagated A/Hawaii/70/2019). However, viruses in the 5A-156K group were poorly recognized by these antisera. Antisera raised against the 2021 southern hemisphere vaccine viruses (egg-propagated A/Victoria/2570/2019 and cell culture-propagated

A/Wisconsin/588/2019) recognized viruses within the 5A-156K group well, but showed poor recognition of all the viruses that lack the N156K substitution in the HA (e.g. 5A, 5A-187A and 5B).

Human serology studies used nineteen serum panels, from children (6 months to 17 years), adults (18-64 years) and older adults ( $\geq 65$  years) who had received egg-based trivalent or quadrivalent inactivated vaccines (standard or high dose) or cell culture-based quadrivalent inactivated vaccine or recombinant HA quadrivalent vaccine. Egg-based vaccine formulations contained antigens from A/Guangdong-Maonan/SWL1536/2019 (H1N1)pdm09-like, A/Hong Kong/2671/2019 (H3N2)-like, B/Washington/02/2019-like and B/Phuket/3073/2013-like viruses (the latter not included in trivalent vaccines) according to the recommendation for the northern hemisphere 2020-2021 season. Cell culture-based and recombinant HA vaccines contained A/Hawaii/70/2019 (H1N1)pdm09-like and A/Hong Kong/45/2019 (H3N2)-like virus antigens as well as the required influenza B components.

When compared to titres against egg-propagated A/Guangdong-Maonan/SWL1536/2019 (H1N1)pdm09-like or cell culture-propagated A/Hawaii/70/2019 (H1N1)pdm09-like 5A-187A vaccine reference viruses, post-vaccination HI geometric mean titres (GMTs) against cell culture-propagated viruses in the 5A-156K HA subclade were significantly reduced in almost all serum panels. Post-vaccination HI GMTs were also reduced to a cell culture-propagated virus in the 5B HA subclade in some serum panels, but not reduced to cell culture-propagated 6B.1A3 or 6B.1A7 HA subclade viruses.

Twenty influenza A(H1N1)pdm09 viruses collected after August 2020 were tested for neuraminidase inhibitor (NAI) susceptibility using phenotypic and/or genotypic methods. None showed reduced inhibition by any of the inhibitors tested. Of 20 A(H1N1)pdm09 viruses analysed for susceptibility to the endonuclease inhibitor baloxavir, none had amino acid substitutions in the PA protein known to be associated with reduced susceptibility to this inhibitor.

### **Influenza A(H3N2) viruses**

HA phylogenetic analysis indicated that A(H3N2) viruses collected from September 2020 to January 2021 had HA genes belonging to 3C.2a1b subclades 1a (also called T135K-A), which share HA1 substitutions T135K, A138S, G186D, D190N, F193S and S198P; 1b (also called T135K-B) that share HA1 substitutions T135K, S137F, A138S and F193S; and 2a (also called T131K-A) that share HA1 substitutions K83E, Y94N and T131K. Viruses with HA genes belonging to 3C.2a1b subclade 2b (also called T131K-B) which share HA1 substitutions T131K, Q197R and S219F, or clade 3C.3a were not detected in this period. Viruses from subclade 3C.2a1b.1a with an additional substitution I192F predominated in the West African countries Côte d'Ivoire, Ghana, Senegal and Togo while viruses from subclade 3C.2a1b.2a with additional substitutions F193S and Y195F in HA1 predominated in South and South-East Asia. Two groups formed among the latter subclade: viruses from Cambodia, Côte d'Ivoire, France, Lao People's Democratic Republic, Spain and the United States of America shared additional HA1 substitutions K171N, G186S and S198P, while those from Bangladesh, India, Oman, Sweden, United Arab Emirates and the United States of America shared additional HA1 substitutions Y159N, T160I (resulting in the loss of a glycosylation site), L164Q, G186D and D190N. Both groups of 3C.2a1b.2a viruses shared D463N and N465S amino acid substitutions in the neuraminidase, which creates a potential N-linked glycosylation motif.

Antigenic characterization of A(H3N2) viruses was performed by haemagglutination inhibition (HI) assays and virus neutralization (VN) assays. Ferret antisera raised against cell culture-propagated A/Hong Kong/45/2019-like viruses (3C.2a1b.1b), representing the cell/recombinant-based vaccine viruses for the 2020-2021 northern hemisphere and 2021 southern hemisphere influenza seasons,

recognized viruses belonging to subclade 3C.2a1b.1a well. However, the majority of viruses detected after August 2020 fell in HA subclade 3C.2a1b.2a and shared additional HA1 F193S and Y195F substitutions. Of the two virus groups that emerged within this subclade those with further HA1 substitutions K171N, G186S and S198P were recognized less well and those with HA1 substitutions Y159N, T160I, L164Q, G186D and D190N were recognized poorly. Ferret antisera raised against egg-propagated A/Hong Kong/2671/2019-like viruses (3C.2a1b.1b), representing the egg-based vaccine viruses for the 2020-2021 northern hemisphere and 2021 southern hemisphere influenza seasons, recognized all viruses poorly.

Viruses belonging to subclade 3C.2a1b.1a and those of subclade 3C.2a1b.2a with additional HA1 substitutions K171N, G186S and S198P were recognized well by ferret antisera raised against cell culture-propagated A/Cambodia/e0826360/2020 and A/Tasmania/503/2020 (3C.2a1b.2a) in HI assays. In VN assays, ferret antisera raised against cell culture-propagated A/Cambodia/e0826360/2020 and A/Tasmania/503/2020 recognized viruses of subclade 3C.2a1b.2a with HA1 substitutions K171N, G186S and S198P well, but those with substitutions Y159N, T160I, L164Q, G186D and D190N were recognized less well (Table 1). Compared to ferret antisera raised against cell culture-propagated viruses, neither group of 3C.2a1b.2a viruses was recognized as well by antisera raised against egg-propagated A/Cambodia/e0826360/2020-like viruses in HI and VN assays.

**Table 1: Antigenic Analysis of A(H3N2) viruses – focus reduction assay**

			Reference Ferret Antisera							
			CELL	EGG	CELL	EGG	CELL	EGG	CELL	
			A/Dar	A/HK	A/Cam	A/Cam	A/Tas	A/Tas	A/Ban	
Reference Antigens	Passage	Clade	3C.2a1b.1b	3C.2a1b.1b	3C.2a1b.2a	3C.2a1b.2a	3C.2a1b.2a	3C.2a1b.2a	3C.2a1b.2a	Collection Date
A/Darwin/726/2019	SIAT2	3C.2a1b.1b	5120	320	1280	160	1280	160	320	
A/Hong Kong/2671/2019	E8	3C.2a1b.1b	5120	2560	320	640	320	640	160	
A/Cambodia/e0826360/2020	SIAT2	3C.2a1b.2a	640	160	2560	320	2560	320	320	
A/Cambodia/e0826360/2020	E5	3C.2a1b.2a	80	160	320	2560	320	2560	320	
A/Tasmania/503/2020	SIAT2	3C.2a1b.2a	640	160	2560	320	2560	640	320	
A/Tasmania/503/2020	E5	3C.2a1b.2a	160	320	640	2560	640	5120	320	
A/Bangladesh/10006/2020	SIAT4	3C.2a1b.2a	320	160	1280	640	640	2560	1280	
Test Antigens										
A/Malaysia/RP2217/2020	MDCK2, SIAT1	3C.2a1b.1a	640	80	320	160	320	160	80	2020-03-04
A/Malaysia/RP2204/2020	MDCK2, SIAT2	3C.2a1b.1b	1280	320	160	160	80	80	80	2020-03-06
A/Cambodia/e0908364/2020	SIAT1	3C.2a1b.2a	1280	320	5120	640	5120	1280	320	2020-07-01
A/Cambodia/e0826360/2020	SIAT1	3C.2a1b.2a	640	80	1280	160	1280	160	160	2020-07-16
A/Cambodia/e0925256/2020	SIAT1	3C.2a1b.2a	320	80	1280	80	1280	80	80	2020-09-25
A/Cambodia/e1009251/2020	SIAT2	3C.2a1b.2a	640	80	1280	160	1280	160	160	2020-10-08
A/Cambodia/e1009251/2020	SIAT2	3C.2a1b.2a	320	80	1280	160	1280	160	160	2020-10-08
A/Cambodia/e0925253/2020	SIAT3	3C.2a1b.2a	320	80	1280	160	2560	80	160	2020-09-23
A/Timor-Leste/2/2020	SIAT2	3C.2a1b.2a	640	160	2560	320	2560	320	320	2020-08-27
A/Timor-Leste/17/2020	SIAT4	3C.2a1b.2a	320	160	1280	160	2560	320	160	2020-07-05

Human serology studies were conducted using serum panels described above, from children, adults and older adults who had received 2020-2021 northern hemisphere influenza vaccines, in HI and VN assays. When compared to titres against cell culture-propagated A/Hong Kong/45/2019-like reference viruses, post-vaccination GMTs of most serum panels were significantly reduced against cell culture-propagated subclade – 3C.2a1b.1b and 3C.2a1b.2a viruses but not against those of either 3C.2a1b.1a or 3C.2a1b.2b subclades or the 3C.3a HA clade. When compared to titres against egg-propagated A/Hong Kong/2671/2019-like reference viruses, almost all serum panels showed significant reductions in GMTs against cell culture-propagated viruses from all HA subclades.

Of 140 A(H3N2) viruses collected after August 2020 and examined by genetic or phenotypic analysis, none showed evidence of reduced inhibition by neuraminidase inhibitors. Of 147 A(H3N2) viruses collected in this period and examined by genetic or phenotypic analysis, none showed evidence of reduced susceptibility to baloxavir.

## Influenza B viruses

Influenza B viruses accounted for 55% of the viruses typed with the vast majority being of the B/Victoria/2/87 lineage in all regions, while B/Yamagata/16/88 lineage viruses were very rarely detected and no viruses collected after August 2020 were available for characterization.

HA gene sequences of B/Victoria lineage viruses characterized belonged to genetic clade 1A, with all belonging to subclade 1A.3 (also called 1A( $\Delta$ 3)B) which has a triple amino acid deletion in HA1 (positions 162-164) and the substitution K136E. Distinct virus groups have emerged within the 1A.3 HA subclade viruses. Many possessed HA1 amino acid substitution G133R, and some of these had an additional E128K substitution. However, of the low number (<200) of B/Victoria lineage viruses with collection dates after August 2020 the majority belonged to a group referred to as 1A.3-150K (also called 1A( $\Delta$ 3)B+150K), which share HA1 substitutions of N150K, G184E, N197D (resulting in loss of a glycosylation site) and R279K, but lack G133R. This 1A.3-150K HA group further diversified into two subgroups that had HA1 substitutions of either V220M and P241Q, which were identified primarily in China, or A127T, P144L and K203R, which were found in viruses from Asia, Europe, the Middle East, North America, and West Africa.

Antigenic analysis showed that the great majority of B/Victoria lineage viruses with a triple amino acid deletion in HA1 (positions 162-164) and K136E substitution (HA subclade 1A.3) that predominated early in 2020 were inhibited well by ferret antisera raised against both cell culture- and egg-propagated triple deletion viruses, such as B/Washington/02/2019. However, the majority of viruses with collection dates after August 2020 contained subgroup 1A.3-150K HA and showed reduced inhibition by ferret antisera raised against cell culture- and egg-propagated viruses, such as B/Washington/02/2019 (current prototype vaccine virus). The vast majority of characterized viruses in this period were from China where subgroup 1A.3-150K viruses with additional HA1 V220M and P241Q substitutions dominated. Representative 1A.3-150K viruses with additional HA1 A127T, P144L and K203R substitutions also showed reduced inhibition by antisera to cell culture- and egg-propagated viruses, such as B/Washington/02/2019. While ferret antisera raised against cell culture-propagated reference viruses that contain 1A.3-150K subgroup HA proteins neutralised closely related viruses well, these antisera poorly inhibited other 1A.3 HA subclade viruses that circulated at high levels prior to the COVID-19 pandemic. Antisera to both egg- and cell culture-propagated double deletion viruses (B/Colorado/06/2017-like) inhibited HA subclade 1A.3 viruses poorly.

Very few B/Yamagata lineage viruses were available for characterization and none had collection dates after August 2020. Those that were characterized all had HA gene sequences belonging to genetic clade 3 and in HI assays the viruses were inhibited by post-infection ferret antisera raised against either cell culture- or egg-propagated B/Phuket/3073/2013.

Human serology studies were conducted using serum panels described above. Post-vaccination HI GMTs against most recent viruses of the B/Victoria lineage representing the dominant 1A.3 HA subclade, including viruses in the 1A.3-150K HA group, were not significantly reduced when compared to titres against cell culture-propagated B/Washington/02/2019-like vaccine viruses. When compared to the egg-propagated B/Washington/02/2019 vaccine virus, HI GMTs of a few serum panels against some cell culture-propagated viruses were somewhat reduced, notably against cell culture-propagated 1A.3-150K HA subgroup viruses with the additional HA1 substitutions of V220M and P241Q, or A127T, P144L and K203R.

Post-vaccination HI GMTs against representative B/Yamagata lineage viruses were not significantly reduced when compared to the cell culture-propagated B/Phuket/3073/2013 reference virus.

Of the 144 influenza B viruses screened for NAI susceptibility, all showed normal inhibition by oseltamivir and one virus showed reduced inhibition by zanamivir. Sixteen of these viruses were also tested against laninamivir and peramivir, all showed normal inhibition by both NAIs. A total of 41 viruses were screened for susceptibility to baloxavir by genetic and/or phenotypic analysis, and none showed evidence of reduced susceptibility.

### **Recommended composition of influenza virus vaccines for use in the 2021-2022 northern hemisphere influenza season**

The HAs of currently circulating A(H1N1)pdm09 viruses belong to phylogenetic clade 6B.1A5, with subclade 5A viruses predominating. While viruses belonging to 5A-187A and 5A-156K groups co-circulated during 2020, of the few viruses collected after August 2020 the majority belong to the 5A-187A group. Antigenic analyses using post-infection ferret antisera showed that antisera raised against viruses with 5A-187A HA (e.g. A/Hawaii/70/2019) inhibited most viruses well but not those in the 5A-156K group. Group 5A-156K viruses were inhibited well by ferret antisera raised against reference viruses belonging to the same group, such as cell culture-propagated A/Wisconsin/588/2019 and egg-propagated A/Victoria/2570/2019. Analyses with post-vaccination human sera showed significant reductions in GMTs against cell-culture propagated viruses in the 5A-156K HA subclade in almost all serum panels.

A(H3N2) viruses collected in the period September 2020 to January 2021 belonged to subclade 3C.2a1b that split into three groups defined by specific sets of additional HA1 substitutions (1a, 1b and 2a, also called T135K-A, T135K-B and T131K-A, respectively). The great majority of these recently circulating viruses were poorly recognized by ferret antisera raised against egg-propagated A/Hong Kong/2671/2019, the A(H3N2) vaccine component for the 2020-2021 northern hemisphere influenza season. However, the majority of viruses in subclade 3C.2a1b were inhibited well by ferret antisera raised against 3C.2a1b.2a cell culture-propagated A/Cambodia/e0826360/2020-like viruses, though less well by ferret antisera raised against egg-propagated A/Cambodia/e0826360/2020-like viruses. Human serology assays showed GMTs were significantly reduced against circulating subclade 3C.2a1b. - 1b and 3C.2a1b.2a viruses when compared to GMTs of cell culture-propagated A/Hong Kong/45/2019-like reference viruses.

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