Influenza virus characterization

Summary report, Europe, September 2022

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Summary

This is the ninth and final report for the 2021-2022 influenza season. The July 2022 characterisation report[1], gave a breakdown of influenza detections across the World Health Organisation (WHO) European Region reported to TESSy up to week 30/2022. As of week 39/2022, 149 372 detections had been reported, resulting from extended late season influenza activity. Of these 149 372 detections, 98% were type A viruses, with A(H3N2) dominating (91%) over A(H1N1)pdm09 (9%), and 2% type B of which only 156 were ascribed to a lineage, with all but two being B/Victoria. This represents a large increase (148 096, 117-fold) in detections compared to the 2020-2021 season, on the back of a great increase (1 957 744, 151%) in the number of samples tested. However, while there have been clear indications of an influenza epidemic in 2021-2022 with the epidemic threshold of 10% positivity within sentinel specimens having been crossed for 17 weeks (unlike in 2020-2021), numbers of detections are reduced compared to earlier seasons (e.g., 9.4% reduced compared to 2019-2020, when the number of samples tested was over 3-fold lower). The increased testing but reduced number of influenza detections is undoubtedly related to the emergence of SARS-CoV-2 and measures introduced to combat it.

Five shipments from countries within the WHO European Region were received at the London WHO Collaborating Centre, the Francis Crick Worldwide Influenza Centre (WIC) since the July report. This report focuses on viruses with collection dates within 2022 for which HA gene sequences were submitted to, and released in, the EpiFlu™ database of the Global Initiative on Sharing All Influenza Data (GISAID) after July 2022, together with sequences generated and antigenic data determined at the WIC.

Globally relatively few A(H1N1)pdm09 viruses have been detected in the course of the 2021-2022 season. 6B.1A.5a.1 and 6B.1A.5a.2 genetic subgroups have been detected which are clearly antigenically different. 6B.1A.5a.1 viruses have been the most numerous in Europe but 6B.1A.5a.2 viruses have circulated globally and greater numbers of this subgroup have recently been detected in Europe. At the February 2022 WHO influenza vaccine composition meeting (VCM) the recommendation was to retain A/Victoria/2570/2019-like viruses (6B.1A.5a.2) as the vaccine component for the northern hemisphere 2022-2023 influenza season. At the September 2022 VCM the recommendation was to change the southern hemisphere A(H1N1)pdm09 vaccine virus for the 2023 season to an A/Sydney/5/2021-like virus as all recently circulating 6B.1A.5a.2 viruses carry HAI K54Q, A186T, Q189E, E224A, R259K and K308R amino acid substitutions compared to A/Victoria/2570/2019; while these viruses are well recognised by post-infection ferret antisera raised against A/Victoria/2570/2019, they are recognised less well by human post-vaccination sera.

In Europe and across the world A(H3N2) viruses have been dominant with the vast majority of recently detected viruses falling in the ‘Bangladesh-like’ (3C.2a1b.2a.2) subgroup, except in China where significant numbers of 3C.2a1b.2a.1 viruses have been detected. While clusters of viruses showing antigenic drift have emerged among the ‘Bangladesh-like’ viruses, the great majority of these viruses retained good recognition by post-infection ferret antisera raised against egg-propagated A/Darwin/9/2021 (3C.2a1b.2a.2) which has been recommended for egg-based vaccines to be used in the 2022 and 2023 southern hemisphere, and 2022-23 northern hemisphere seasons. Antisera raised against a range of cell culture- and egg-propagated 3C.2a1b.2a.2 viruses generally gave good recognition of 3C.2a1b.2a.2 test viruses

In Europe and across the world few B/Victoria-lineage viruses have been detected during the 2021-2022 influenza season. All fall within subclade V1A.3 represented by B/Washington/02/2019, the vaccine virus recommended for inclusion in influenza vaccines for the 2021-2022 northern hemisphere season. A large majority of HA sequences from recently detected viruses, in geographically dispersed countries, have fallen in the V1A.3a group defined by a series of HA1 amino acid substitutions including N150K, with most falling in the V1A.3a.2 subgroup with defining HA1 A127T, P144L and K203R amino acid substitutions. B/Austria/1359417/2021-like (V1A.3a.2) viruses have been recommended for use in the southern hemisphere 2022 and 2023, and the northern hemisphere 2022-2023 influenza seasons. A B/Washington/02/2019-like (V1A.3) virus cluster that emerged and spread in the Netherlands, which showed poor recognition by the panel of post-infection ferret antisera used at the WIC, has now been detected in Spain.

No cases of infection with circulating B/Yamagata-lineage viruses have been confirmed since March of 2020. All HA gene sequences from the 77 viruses detected in 2020, inclusive of 16 from the WHO European Region, belonged to genetic clade Y3 and had three HA1 amino acid substitutions (L172Q,

[1]Influenza virus characterization: summary report, Europe, July 2022. World Health Organization Regional Office for Europe and European Centre for Disease Prevention and Control; Copenhagen and Stockholm;
2022 (https://apps.who.int/iris/handle/10665/363632, accessed 19 October 2022).

D229N and M251V) compared to B/Phuket/3073/2013-like viruses which are still recommended for use in quadrivalent influenza vaccines. **There is need to share all B/Yamagata-lineage viruses detected recently for detailed characterisation to determine if there are any in circulation that are not related to Live Attenuated Influenza Vaccines.**

Table 1 shows a summary of influenza virus detections in the WHO European Region reported to The European Surveillance System (TESSy) database during the 2021-2022 season (weeks 40/2021-39/2022), compared to the same period in the 2020-2021 season. There has been a great increase in the number of samples from patients fulfilling Influenza-Like Illness (ILI) and/or Acute Respiratory Infection (ARI) criteria being tested (1 957 744, 151%), even when compared with a more 'normal' season, 2019-2020 (2 268 305, 231%: results not shown), which led into the COVID-19 pandemic. With this increased testing there has been a rise in the number of influenza-positive samples (148 096, 117-fold), though there was a reduction compared to the same period in 2019-2020 (15 545, 9.4%: results not shown). These data probably relate to a number of factors: (i) significant numbers of samples taken from patients fulfilling ILI and/or ARI criteria being infected with other agents, possibly SARS-CoV-2, the virus responsible for the COVID-19 pandemic; (ii) residual effects of measures introduced to help curtail the spread of SARS-CoV-2, and; (iii) with large swathes of the human population now carrying a significant level of immunity to SARS-CoV-2 following either infection and/or vaccination, influenza has been able to re-establish itself after nearly two years of low-level circulation.

With these caveats, and being mindful of the low number of detections during of the 2020-2021 season, the ratio of type A to type B detections has increased compared to the 2020-2021 season (1.5:1 to 51:1), with a greater dominance of A(H3N2) over A(H1N1)pdm09 viruses. While the number of influenza B virus detections has increased from 514 to 2 881 (561%), only small numbers were ascribed to a lineage in both time periods (Table 1) though, based on sequences available in GISAID, B/Yamagata lineage viruses with collection dates after March 2020 have not been characterised genetically. Currently, it appears that measures introduced relating to the COVID-19 pandemic are still having an effect but there has been clear indication of an influenza season in the Region during 2021-2022 with the rate of influenza positivity in sentinel samples having been at or above 10%, the epidemic threshold set for the Region, for 17 weeks during a bi-phasic season (weeks 49/2021 to 1/2022 and weeks 8-19/2022) with A(H3N2) viruses dominating (Figure 1).

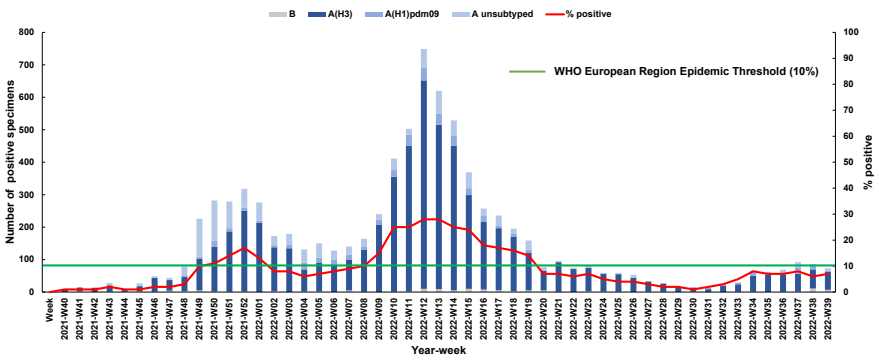
Table 1. Influenza virus detections in the WHO European Region from the start of reporting for the 2021-2022 season (weeks 40/2021-39/2022)[a]

Virus type/subtype/lineage	Cumulative number of detections for weeks 40/2021-39/2022			Totals*		Cumulative number of detections for weeks 40/2020-39/2021			Totals*	
	Sentinel sources	Non-sentinel sources	Totals	%	Ratios	Sentinel sources	Non-sentinel sources	Totals	%	Ratios
Influenza A	**8172**	**138319**	**146491**	**98.1**	**51:1**	**52**	**710**	**762**	**59.7**	**1.5:1**
A(H1N1)pdm09	477	3010	3487	8.8		11	33	44	15.0	
A(H3N2)	6478	29882	36360	91.2	10.4:1	13	236	249	85.0	5.7:1
A not subtyped	1217	105427	106644			28	441	469		
Influenza B	**137**	**2744**	**2881**	**1.9**		**14**	**500**	**514**	**40.3**	
Victoria lineage	24	130	154	98.7	77:1	2	13	15	93.8	15:1
Yamagata lineage	0	2	2	1.3		0	1	1	6.2	
Lineage not ascribed	113	2612	2725			12	486	498		
Total detections (total tested)	**8 309 (85 293)**	**141 063 (>3 165 913)**	**149 372 (>3 251 206)**			**66 (52 783)**	**1 210 (>1 240 679)**	**1 276 (>1 293 462)**		

[a] Numbers taken from Flu News Europe to week 39/2022, week 39/2021 and week 39/2020 reports for the three influenza seasons

* Percentages are shown for total detections (types A & B [in bold type], and for viruses ascribed to influenza A subtype and influenza B lineage). Ratios are given for type A:B [in bold type], A(H3N2):A(H1N1)pdm09 and Victoria:Yamagata lineages.

Figure 1. Influenza positivity in sentinel-source specimens by week (2021-2022) – WHO Europe[a]



[a] Figure adapted from FluNewsEurope week 36-39/2022 (https://flunewseurope.org/Archives)

Genetic and antigenic characterisation data generated at the WIC for viruses with collection dates after 31 August 2020 until 31 January 2021, up to a report deadline of 15 February 2021, contributed to the WIC

virus characterisation report that was presented at the WHO influenza vaccine composition meeting (VCM) in February 2021 when recommendations were made for the northern hemisphere 2021-2022 season [1]. Data generated on viruses with collection dates after 31 January 2021 until 31 August 2021 informed the September 2021 VCM when recommendations were made for the 2022 southern hemisphere season [2]. Data presented for viruses with collection dates after 31 August 2021 until 31 January 2022 contributed to the VCM (21-24 February) where it was recommended to change the A(H3N2) and B/Victoria-lineage components of influenza vaccines to match those used in 2022 southern hemisphere vaccination campaigns [3]. At the recent VCM (19-22 September), which focussed on data from viruses collected after 31 January 2022 until 31 August 2022, it was recommended to change the A(H1N1)pdm09 vaccine component for the 2023 southern hemisphere season [4].

Due to the relatively low number of influenza-positive specimens detected until recently, and thereby available for sharing with WIC, this and recent influenza characterisation reports (https://www.ecdc.europa.eu/en/seasonal-influenza/surveillance-and-disease-data/influenza-virus-characterisation) have been based mainly on phylogenetic analyses of complete HA gene sequences submitted to GISAID's EpiFlu™ database, inclusive of sequences generated at the WIC. Here A(H1N1)pdm09, A(H3N2) and B/Victoria-lineage HA gene phylogenies for viruses with collection dates after 31 December 2021, for representative WIC- and non-WIC-generated sequences available in GISAID, generated for the July report are presented (Figures 2a, 3a and 4a). Additional phylogenies (Figures 2b, 3b and 4b) are presented for HA sequences derived from viruses with collection and HA sequence submission dates from the days indicated in Table 2, with a sequence download date of 28 September 2022. The numbers of HA sequences, downloaded from GISAID, numbers remaining after de-duplication and the numbers used in the new representative phylogenies generated for this September report are shown.

Table 2. Summary of the numbers of HA gene sequences available and used in generating the new phylogenies presented in this report

Virus subtype/lineage	Global HA sequences available for viruses collected in the 2021-2022 season as of 2022-09-28				
	Virus collection date (from)	Sequence submission date (from)	Number Downloaded	Number de-duplicated and aligned	Number used in phylogenies*
A(H1N1)pdm09	2022-06-01	2022-08-01	223	203	203
A(H3N2)	2022-08-01	2022-08-01	226	226	226
B/Victoria	2022-03-01	2022-08-01	217	213	213
B/Yamagata	2022-01-01	2022-08-01	0	0	0

*** Inclusive of sequences generated recently at the WIC, but not including sequences from reference and vaccine viruses**

Eighty-nine shipments of specimens (virus isolates and/or clinical specimens) were received at the WIC from WHO Global Influenza Surveillance and Response System (GISRS) recognised National Influenza Centres (NICs) in a total of 39 WHO European Region Member States (Table 3). Of the 2 342 samples received 2 209 (94%) were type A viruses and 133 (6%) were type B viruses. Five of the shipments were received in August through September 2022 and contained samples from the second phase of the epidemic (Figure 1), a number of which are still in the virus characterization process (Table 3). NICs were requested to send clinical specimens with real-time RTPCR Ct values of ≤30 and/or virus isolates, all those available for A(H1N1)pdm09 and influenza type B (as relatively few have been detected), and a representative selection of A(H3N2) samples.

A total of 139 viruses from the WHO European Region, 24 A(H1N1)pdm09, 97 A(H3N2) and 18 B/Victoria-lineage, have been characterised antigenically since the July report (Tables 4, 5 and 6 respectively).

Table 3. Summary of seasonal influenza clinical samples and virus isolates* with collection dates after 2021-08-31 contained in packages received from WHO European Region Member States

MONTH / Country/area	TOTAL RECEIVED Seasonal viruses	A Number received	A Number propagated[1]	H1N1pdm09 Number received	H1N1pdm09 Number propagated[1]	H3N2 Number received	H3N2 Number propagated[2]		B Number received	B Number propagated[1]	B Victoria lineage Number received	B Victoria lineage Number propagated[1]	B Yamagata lineage Number received	B Yamagata lineage Number propagated[1]
2021														
September														
Belgium	1					1	1							
Croatia	3					3	2	0						
Denmark	5					5	5							
France	11			1	0	10	9	0						
Israel	2					2	2							
Italy	1					1	1	0						
Netherlands	13					12	12				1	1		
Spain	1					1	0	0						
Sweden	2			1	1	1	1							
the United Kingdom (England)	2					2	2							
October														
Denmark	2			1	1	1	1	0						
Estonia	1					1	0	0						
France	12			9	8	3	3							
Germany	2					2	2							
Ireland	1					1	1							
Italy	5			3	3	2	2							
Kyrgyzstan	28					28	0	0						
Netherlands	36					36	17	0						
Norway	7					7	7							
Portugal	3					2	0	0	1	0				
Russian Federation	3					3	3							
Spain	4					4	3	0						
Sweden	2					2	2							
Tajikistan	7	6	0			1	1							
the United Kingdom (England)	8					8	8							
the United Kingdom (Scotland)	5										1		4	
November														
Armenia	2					2	0	0						
Belgium	2					2	2							
Croatia	1			1	1									
Estonia	1					1	0	0						
France	29			19	in process	10	8	0						
Germany	5					4	4				1	1		
Ireland	3					2	0	0			1	1		
Ireland	1					1								
Israel	10					10	6	0						
Italy	5					5	5							
Kazakhstan	13					13	0	0						
Kyrgyzstan	22					22	0	0						
Netherlands	24					24	20	0						
Norway	8					8	5	0						
Romania	1										1	1		
Russian Federation	36					36	35	0						
Slovenia	2					2	1	0						
Spain	36			1	1	33	10	0	1	0	1	0		
Sweden	5					5	5							
Switzerland	4					2	2				2	2		
Tajikistan	8	7	0	1	0									
the United Kingdom (Scotland)	2					2								
the United Kingdom (N. Ireland)	3					2			1					
Kosovo[§]	2					2	1	0						
December														
Albania	39	1	0	3	3	35	10	0						
Armenia	21					21	10	0						
Belgium	15	1	0	7	6	7	2	0						
Bosnia and Herzegovina	3					3	0	0						
Croatia	7			1	1	6	5	0						
Estonia	7					7	1	0						
France	8			4	in process	4	in process							
Georgia	11			1	0	9	4	0			1	0		
Germany	10					10	10							
Hungary	2					2	2							
Ireland	4			1	0	3	3	0						
Ireland	1					1								
Israel	30					30	5	0						
Kazakhstan	17					17	2	0						
Latvia	5					5	5							
Montenegro	6					6	1	0						
Netherlands	29			5	5	24	23	1						
Norway	1					1	1							
Portugal	18	1	0			14	3	0	1	0	2	1		
Romania	5					5	5							
Russian Federation	5					5	5							
Serbia	7			5	0	2	1	0						
Slovenia	1					1	1							
Spain	57			4	2	52	10	0			1	0		
Switzerland	10	1	0			9	6	0						
Ukraine	14					14	in process							
Kosovo[§]	56	3	0	5	0	48	7	0						
2022														
January														
Armenia	2					2	1	0						
Belgium	19			10	9	9	2	0						
Bosnia and Herzegovina	5					5	0	0						
Bulgaria	8					8	8							
Estonia	4					4	4							
France	3			3	3									
Georgia	4					4	2	0						
Germany	11					11	11							
Hungary	2					2	2							
Ireland	2					2	0	0						
Ireland	2			1		1								
Israel	9					9	0	0						
Italy	1					1	1							
Latvia	1					1	1							
Montenegro	8	2	0			6	1	0						
Netherlands	6			3	3	3	3							
Norway	10			1	0	9	4	0						
Portugal	7					7	0	0						
Romania	4			1	1	3	3							
Russian Federation	3					3	3							
Serbia	21					21	11	0						
Slovenia	2					2	1	0						
Spain	16			13	3	3	3							
Switzerland	7			1	1	6	4	0						
Ukraine	21					21	9	0						
Kosovo[§]	2	1	0			1	0	0						

* Note: Where clinical sample and a virus isolate from the same patient were received, this is counted as one in the Total Received and following columns.

[§] All references to Kosovo in this document should be understood to be in the context of the United Nations Security Council resolution 1244 (1999).

1. Propagated to sufficient titre to perform HI assay (the totalled number does not include any from batches that are in process)
2. Propagated to sufficient titre to perform HI assay in the presence of 20nM oseltamivir (the totalled number does not include any from batches that are in process)

Numbers in red indicate viruses recovered but with insufficient HA titre to permit HI assay (H3N2 only)

Samples provided in lysis buffer, so only genetic characterisation possible

Some samples are RNA, so only genetic characterisation possible

Some samples not cultured because Ct value high (>30), failed sequence, identical sequence, mixed sequence or SARS-COV-2 positive

Some samples not cultured because when received they were too old for consideration at the September 2022 VCM

As of 2022-10-02

MONTH / Country/area	TOTAL RECEIVED Seasonal viruses	A		H1N1pdm09		H3N2			B		B Victoria lineage		B Yamagata lineage	
		Number received	Number propagated[1]	Number received	Number propagated[1]	Number received	Number propagated[2]		Number received	Number propagated[1]	Number received	Number propagated[1]	Number received	Number propagated[1]
FEBRUARY														
Austria	3			1	1	2	2							
Belgium	15			5	5	10	1	0						
Bosnia and Herzegovina	1	1	0											
Bulgaria	4					4	4							
Croatia	2					2	0	0						
Denmark	1					1	1							
Estonia	4					3	2	0			1	1		
France	8			4	2	4	4							
Germany	12			1	1	11	11							
Hungary	3					3	3							
Italy	6			1	1	5	5							
Moldova	1					1	1							
Netherlands	4			3	3						1	1		
Norway	2					2	2							
Poland	1					1	1							
Portugal	32			1	0	31	23	0						
Slovakia	1					1	0	0						
Slovenia	12					12	12							
Spain	12			2	1	10	10							
Sweden	2										2	2		
Switzerland	4			4	3									
Ukraine	1					1	1							
MARCH														
Austria	27			4	4	23	21	0						
Belgium	91			16	14	75	18	0						
Bosnia and Herzegovina	2					2	0	0						
Bulgaria	16					16	16							
Croatia	12					12	1	0						
Denmark	12			1	1	11	11							
France	18			8	7	10	in process							
Germany	8			1	1	7	7							
Hungary	4					4	4							
Iceland	4					4	0	0						
Ireland	39					39	4	0						
Italy	12			2	2	10	10							
Kyrgyzstan	6										6	6		
Lithuania	1					1	0	0						
Moldova	7			2	2	5	5							
Montenegro	19					19	4	0						
Netherlands	12			4	4	4	4				4	4		
Norway	20			2	1	16	13	0			2	2		
Poland	27	2	0			25	15	0						
Portugal	10					10	8	0						
Romania	1			1	0									
Russian Federation	3										3	3		
Serbia	13			4	1	9	7	0						
Slovakia	2					2	0	0						
Slovenia	40					40	39	0						
Spain	31			5	3	26	26							
Sweden	7					4	4				3	3		
Switzerland	20			6	6	14	13	0						
Ukraine	3					2	1	0			1	0		
the United Kingdom (N. Ireland)	3					3								
APRIL														
Austria	23			1	1	22	13	0						
Belgium	19			4	4	15	14	0						
Bosnia and Herzegovina	5					5	3	0						
Bulgaria	3					3	2	0						
Croatia	37					37	6	1						
Denmark	8			6	6	2	2							
Estonia	26					26	24	0						
France	12			3	2	8	in process				1	1		
Germany	8			2	2	6	6							
Hungary	2					2	2							
Iceland	27			2	0	25	1	0						
Ireland	11			1	1	10	3	0						
Italy	14					13	12	0			1	1		
Kyrgyzstan	6										6	6		
Latvia	15			2	2	12	12				1	0		
Lithuania	46					46	7	0						
Moldova	7			1	2	6	6							
Montenegro	6					6	1	0						
Netherlands	27			1	1	6	5	0			20	16		
Norway	38			10	10	25	21	0			3	1		
Poland	64	5	0			45	19	0	3	0	11	5		
Portugal	10					10	10							
Romania	28			4	4	24	24							
Russian Federation	8										8	8		
Serbia	11			5	2	4	4				2	2		
Slovakia	7					7	0	0						
Slovenia	11					11	11							
Spain	60			5	4	54	9	0			1	1		
Sweden	9			1	1	7	7				1	1		
Switzerland	14			2	0	12	6	0						
Ukraine	3					2	2				1	1		
the United Kingdom (N. Ireland)	24					24								
MAY														
Austria	2					2	2							
Belgium	2					1	1				1	1		
Bosnia and Herzegovina	1					1	0	0						
Croatia	3					3	3							
Denmark	3			2	2						1	1		
France	6			1	1	4	4				1	1		
Germany	11			1	1	8	8				2	2		
Iceland	18					18	1	0						
Italy	1					1	1							
Lithuania	2					2	2							
Netherlands	2										2	0		
Norway	3										3	3		
Poland	9					7	6	0	1	0	1	1		
Portugal	7			3	3	4	4							
Romania	9			1	1	5	4	0			3	2		
Russian Federation	4										4	4		
Serbia	5								1	0	4	3		
Spain	50	2	0			48	29	0						
Sweden	1					1	1							
Ukraine	1										1	1		
JUNE														
Croatia	1			1	1									
Denmark	1										1	1		
France	2					2	2							
Norway	5			3	3	2	2							
Romania	2					2	2							
Russian Federation	1										1	1		
Spain	5			1	0	4	2	0						
the United Kingdom (N. Ireland)	6			1		4			1					
JULY														
Croatia	2			1	1	1	0	0						
France	11			1	1	10	10							
Norway	12			1	0	10	8	0			1	0		
AUGUST														
Norway	3			1	1						2	0		
TOTAL	2342	33	0	252	172	1924	1023	2	10	0	119	93	4	0
39 Countries/areas		1.4%		10.8%		82.2%			0.4%		5.1%		0.2%	
		94.3%							5.7%					

* Note: Where clinical sample and a virus isolate from the same patient were received, this is counted as one in the Total Received and following columns.

[$] All references to Kosovo in this document should be understood to be in the context of the United Nations Security Council resolution 1244 (1999).

1. Propagated to sufficient titre to perform HI assay (the totalled number does not include any from batches that are in process)
2. Propagated to sufficient titre to perform HI assay in the presence of 20nM oseltamivir (the totalled number does not include any from batches that are in process)

Numbers in red indicate viruses recovered but with insufficient HA titre to permit HI assay (H3N2 only)

Samples provided in lysis buffer, so only genetic characterisation possible

Some samples are RNA, so only genetic characterisation possible

Some samples not cultured because Ct value high (>30), failed sequence, identical sequence, mixed sequence or SARS-COV-2 positive

Some samples not cultured because when received they were too old for consideration at the September 2022 VCM

As of 2022-10-02

Influenza A(H1N1)pdm09 virus analyses

All recently circulating viruses have fallen into clade **6B.1A**, defined by the amino acid substitutions **S74R**, **S84N**, **S162N** (introducing a potential N-linked glycosylation site), **S164T** (which alters the glycosylation motif at residues 162 to 164), **I216T** and **I295V** in **HA1**. Within clade **6B.1A**, clusters of viruses (genetic groups) encoding a range of **HA** amino acid substitutions have emerged, with most recently circulating viruses carrying the substitution **S183P** in **HA1**, although this is not retained in all genetic groups. Figures 2a and 2b are annotated with **HA1 S183P** substitution groups assigned for the February 2019 WHO VCM, updated for the September 2020 WHO VCM, and with a new nomenclature introduced at the time of the September 2021 WHO VCM (**6B.1A.1 to 6B.1A.7**). The recommended vaccine viruses for the northern hemisphere 2021-2022 and 2022-2023, and southern hemisphere 2022 (egg-based A/Victoria/5270/2019-like and cell-based A/Wisconsin/588/2019-like) influenza seasons are shown in red [1, 3, 2] as is the case for the recent recommendation for the southern hemisphere2023 season, egg- and cell-based A/Sydney/5/2021-like [4]. The seven subclades are defined by the following HA amino acid substitutions:

1. Subclade **6B.1A.1** viruses, represented by the 2019-2020 vaccine virus **A/Brisbane/02/2018**, carry an HA gene mutation encoding **HA1 S183P** amino acid substitution.
2. Subclade **6B.1A.2** viruses, represented by **A/Denmark/2728/2019**, carry HA gene mutations encoding **HA1 S183P** and **L233I** with **HA2 V193A** amino acid substitutions – a group within this subclade has emerged with additional **HA1** amino acid substitutions of **N129D, K130N, P137S, N156K** and **K211R** (e.g. **A/Hong Kong/110/2019**).
3. Subclade **6B.1A.3** viruses, represented by **A/Norway/3737/2018**, carry HA gene mutations encoding **HA1 T120A** and **S183P** amino acid substitutions.
4. Subclade **6B.1A.4** represented by **A/Hungary/20/2018** carries HA gene mutations encoding **HA1 N129D, A144E** and **S183P** amino acid substitutions.
5. Subclade **6B.1A.5** viruses carry HA gene mutations encoding **HA1 S183P** and **N260D** amino acid substitutions and split into two groups designated **6B.1A.5a** represented by **A/Norway/3433/2018** with additional **HA1** amino acid substitutions of **N129D** and **T185A**, and **6B.1A.5b** represented by **A/Switzerland/3330/2017** with additional amino acid substitutions of **HA1 E235D** and **HA2 V193A**. Two subgroups within the **6B.1A.5a** group have been defined based on **HA1** amino acid substitutions of **D187V/A** and **Q189E** (**6B.1A.5a.1**) or **K130N**, **N156K**, **L161I** and **V250A** (**6B.1A.5a.2**).
6. Subclade **6B.1A.6** viruses, represented by **A/Ireland/84630/2018**, carry HA gene mutations encoding **HA1 T120A** and **S183P** amino acid substitutions, like subclade **6B.1A.3** viruses, but fall within a separate phylogenetic branch which is closer to subclade **6B.1A.5** viruses.
7. Subclade **6B.1A.7** viruses, represented by **A/Slovenia/1489/2019**, carry HA gene mutations encoding **HA1 K302T** and **HA2 I77M**, **N169S** and **E179D** amino acid substitutions sometimes with additional **HA1** substitutions of **E68D, S121N** and **L161I** (e.g. **A/Moscow/193/2019**). Note: a group within this subclade has emerged with **P183S** (reversion)**, T185I, I240V** and **I286L** substitutions in **HA1** (e.g. **A/Estonia/120012/2019**).

The phylogeny prepared for the July report focused on HA sequences derived from viruses with collection dates after 30 April 2022 for which sequences were submitted to GISAID after June 2022. Of the 19 sequences derived from viruses detected in the WHO European Region, 17 fell in subgroup **6B.1A.5a.1** and two in subgroup **6B.1A.5a.2** (Figure 2a). Sequences derived from small numbers of **6B.1A.5a.1** viruses recently detected in Australia, South Africa and the USA were also reported. Subgroup **6B.1A.5a.2** viruses continued to dominate in countries outside of the WHO European Region, notably those in the southern hemisphere.

The phylogeny prepared for this September report focused on HA sequences derived from viruses with collection dates after 31 May 2022 for which sequences were submitted to GISAID after July 2022 (Table 2). As indicated in both phylogenies, recently detected viruses in subgroup **6B.1A.5a.2** all have **HA1 K54Q**, **A186T**, **Q189E**, **E224A**, **R259K** and **K308R** substitutions compared to the vaccine virus, A/Victoria/2570/2019 (Figures 2a and 2b) and virus clusters have emerged defined by amino acid substitutions: (i) **HA1 T216A** often with **D94N** , the cluster showing wide geographic distribution; (ii) **HA1 A48P**, and; (iii) **HA1 K142R**, **D260E** and **HA2 I91V**, **N124H**, often with **HA1 P137S**, **T277A** and **HA2 E29D**. Viruses in cluster (iii) with the additional substitutions have recently been detected in countries of the WHIO European Region (Croatia, Germany, Netherlands, Norway, Spain, Sweden and the United Kingdom; Figure 2b).

The panel of post-infection ferret antisera used in HI assays, five raised against subgroup **6B.1A.5a.1** viruses and three against **6B.1A.5a.2** viruses, gives clear discrimination of test viruses in the two subgroups (Tables 4-1 and 4-2). Of the 21 **6B.1A.5a.1** test viruses, 19 (90%), 21 (100%), 19 (90%), 21 (100%) and 20 (95%) were recognised well (within fourfold of the homologous titres) by antisera raised against A/Ireland/87733/2019, cell culture- and egg-propagated A/Guangdong-Maonan/SWL1536/2019 (vaccine

viruses for the 2020-2021 northern hemisphere season), A/Ghana/1894/2021 and A/Lyon/820/2021, respectively.

The three **6B.1A.5a.2** test viruses from Norway were all recognised well (within twofold of the homologous titres) by antisera raised against three different **6B.1A.5a.2** reference viruses. This included the vaccine virus (IVR-215: A/Victoria/2570/2019) for the 2021-2022 northern hemisphere season and indicates that a variety of genetically clustered viruses, defined by specific HA1 amino acid substitutions, cannot be discriminated antigenically by the post-infection ferret antisera used in HI assays.

At the WHO VCM held in Geneva 21-24 February 2022, A/Victoria/2570/2019-like viruses were recommended for use in the northern hemisphere 2022-2023 influenza season [3]. This decision was largely based on antisera induced by **6B.1A.5a.1** subgroup viruses in ferrets and humans yielding poor recognition of **6B.1A.5a.2** subgroup viruses and the likelihood that many humans were unlikely to have been exposed to **6B.1A.5a.2** subgroup viruses given their low-level circulation during the COVID-19 pandemic. While the different clusters of **6B.1A.5a.2** subgroup viruses were not differentiated by post-infection ferret antisera, human serology data presented at the WHO VCM held in Dublin 19-22 September 2022 indicated poor recognition of many **6B.1A.5a.2** subgroup viruses. For this reason, egg- and cell culture-propagated A/Sydney/5/2021-like viruses, carrying the **HA1 K54Q**, **A186T**, **Q189E**, **E224A**, **R259K** and **K308R** substitutions compared to A/Victoria/2570/2019, were recommended for vaccine formulations to be used in the 2023 southern hemisphere season [4].

Figure 2a. Phylogenetic comparison of influenza A(H1N1)pdm09 HA genes (GISAID/WIC, July 2022)

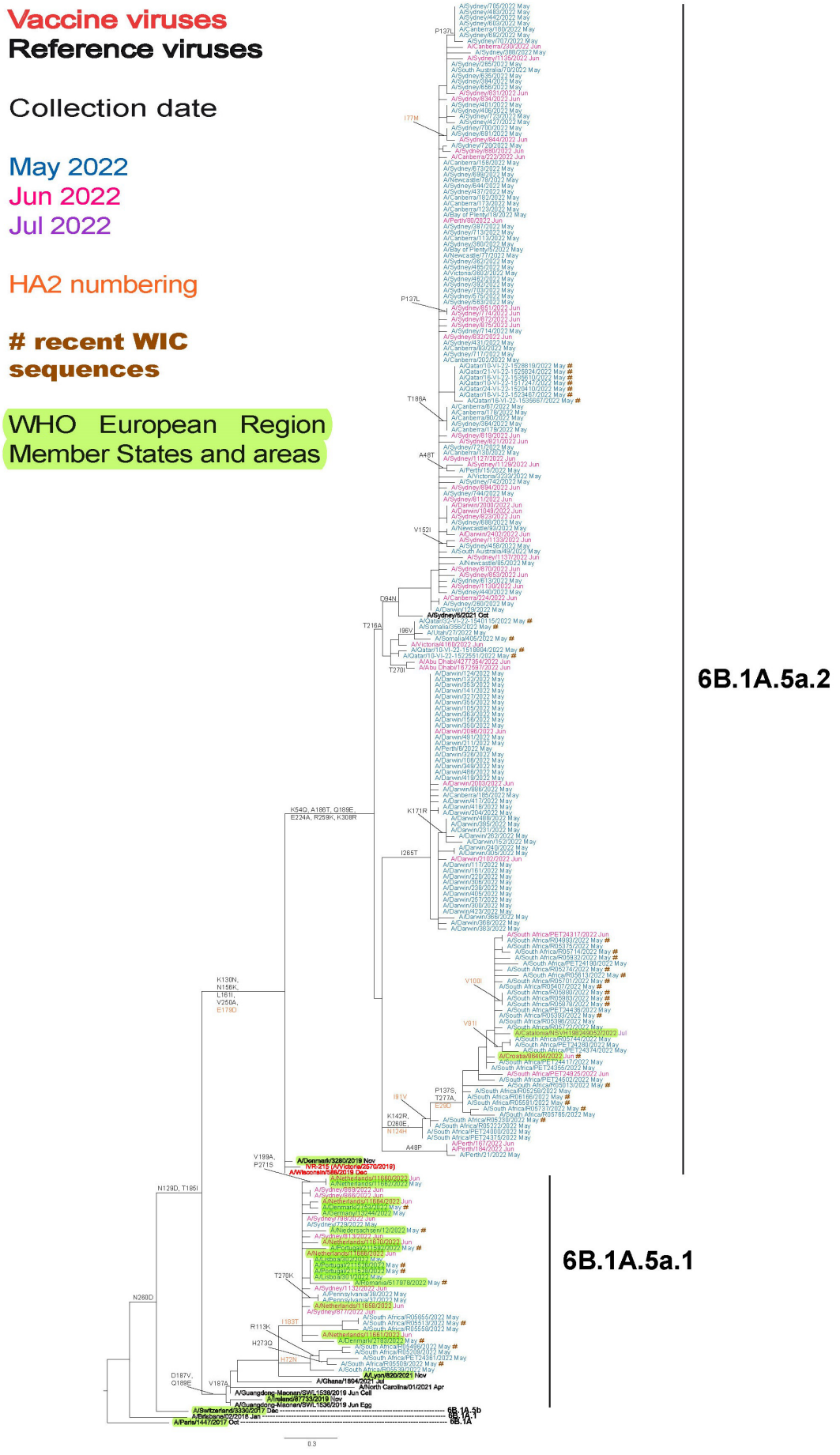


Figure 2b. Phylogenetic comparison of influenza A(H1N1)pdm09 HA genes (GISAID/WIC, Sept 2022)

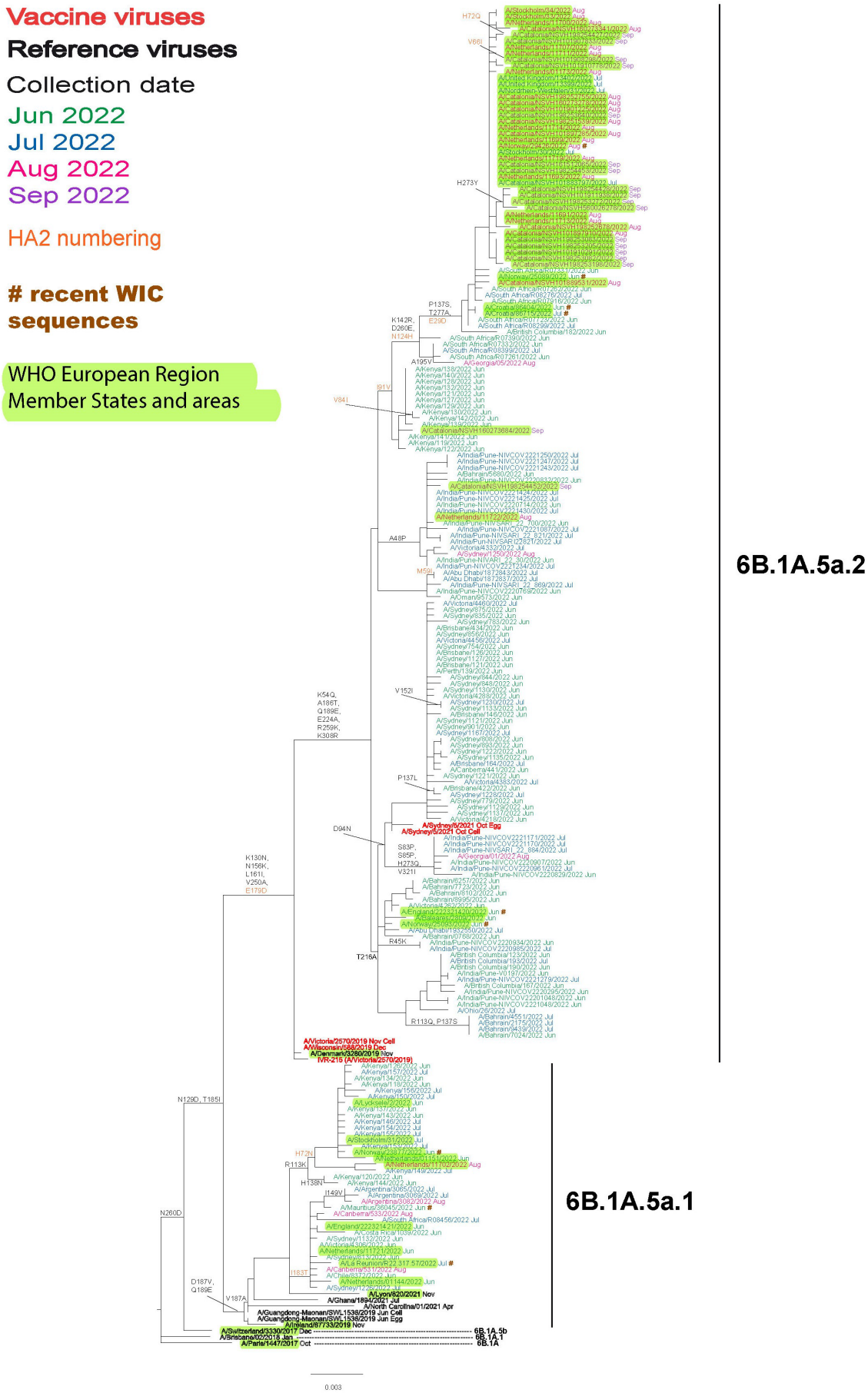


Table 4-1. Antigenic analysis of influenza A(H1N1)pdm09 viruses by HI

Viruses	Other information		Collection date	Passage history	Haemagglutination inhibition titre: Post-infection fereret antisera							
		Passage history			A/Ire 87733/19 Egg	A/G-M SWL1536/19 MDCK	A/G-M SWL1536/19 Egg	A/Ghana 1894/21 Egg	A/Lyon 820/21 Egg	A/Denmark 3280/19 MDCK	IVR-215 A/Vic/2570/19 Egg	A/Sydney 5/21 Egg
		Ferret number			St Jude's F18/20*1	F09/20*1	F12/20*1	F02/22*1	F06/22*1	F28/20*1	F37/21*1	F04/22*1
		Genetic group			6B.1A.5a.1	6B.1A.5a.1	6B.1A.5a.1	6B.1A.5a.1	6B.1A.5a.1	6B.1A.5a.2	6B.1A.5a.2	6B.1A.5a.2
REFERENCE VIRUSES												
A/Ireland/87733/2019		6B.1A.5a.1	2019-11-03	E4	640	1280	1280	640	320	40	80	40
A/Guangdong-Maonan/SWL1536/2019		6B.1A.5a.1	2019-06-17	C2/MDCK1	640	1280	1280	1280	320	80	80	40
A/Guangdong-Maonan/SWL1536/2019		6B.1A.5a.1	2019-06-17	E3/E2	320	1280	1280	640	160	40	80	40
A/Ghana/1894/2021		6B.1A.5a.1	2021-07-21	E2/E1	640	2560	2560	1280	320	80	160	80
A/Lyon/820/2021		6B.1A.5a.1	2021-11-16	E1/E2	80	320	320	160	640	40	40	40
A/Denmark/3280/2019		6B.1A.5a.2	2019-11-10	MDCK4/MDCK5	40	40	80	<	80	1280	1280	1280
IVR-215 (A/Victoria/2570/2019)		6B.1A.5a.2	2018-11-22	E4/D7/E2	40	80	80	80	80	640	1280	1280
A/Sydney/5/2021		6B.1A.5a.2		E3/E1	40	80	40	40	40	1280	1280	1280
TEST VIRUSES												
A/Tours/37554/2021		6B.1A.5a.1	2021-11-02	MDCK1	640	1280	1280	640	320	40	80	40
A/Dijon/48658/2021		6B.1A.5a.1	2021-12-08	MDCK2	640	1280	1280	640	160	40	80	80
A/Alsace/48917/2021		6B.1A.5a.1	2021-12-15	MDCK1	640	1280	1280	1280	320	40	80	80
A/Ile de France/52132/2021		6B.1A.5a.1	2021-12-27	MDCK1	640	1280	1280	640	160	40	80	80
A/Ile de France/54452/2021		6B.1A.5a.1	2022-01-03	MDCK1	640	1280	1280	640	320	40	80	40
A/Lyon/215/2022		6B.1A.5a.1	2022-01-24	MDCKx/MDCK1	80	320	160	320	80	160	320	160
A/Clermont-Ferrand/184/2022		6B.1A.5a.1	2022-01-25	MDCKx/MDCK1	320	1280	1280	640	160	40	40	40
A/Paris/10105/2022		6B.1A.5a.1	2022-02-03	MDCK1	320	640	1280	640	160	40	80	40
A/Le Mans/15006/2022		6B.1A.5a.1	2022-02-24	MDCK1	640	1280	1280	1280	320	80	80	80
A/Grenoble/465/2022		6B.1A.5a.1	2022-03-02	MDCKx/MDCK1	640	1280	1280	1280	320	40	80	80
A/Belgium/S0497/2022		6B.1A.5a.1	2022-03-07	MDCK1/MDCK2	640	1280	2560	1280	320	80	80	40
A/Romans/478/2022		6B.1A.5a.1	2022-03-14	MDCKx/MDCK1	640	1280	1280	640	160	40	80	40
A/Lyon/614/2022		6B.1A.5a.1	2022-03-21	MDCKx/MDCK1	640	1280	1280	640	160	40	80	80
A/Lyon/572/2022		6B.1A.5a.1	2022-03-21	MDCKx/MDCK1	320	1280	1280	640	160	40	80	40
A/Lyon/CHU-R.22.172.23/2022	N156S, N162* (-cho)	6B.1A.5a.1	2022-03-27	MDCK2/MDCK1	80	640	160	320	160	40	80	80
A/Toulon/759/2022		6B.1A.5a.1	2022-03-27	MDCKx/MDCK1	640	1280	1280	640	160	40	80	80
A/Dunkerque/26698/2022		6B.1A.5a.1	2022-03-31	MDCK2	640	1280	2560	1280	320	80	80	40
A/Lyon/CHU-R22.224.12/2022		6B.1A.5a.1	2022-04-25	MDCKx/MDCK1	320	1280	1280	640	160	40	80	80
A/Lyon/CHU-R22.242.34/2022		6B.1A.5a.1	2022-05-09	MDCKx/MDCK1	640	1280	1280	640	320	40	80	80
							Vaccine NH 2020-21				Vaccine SH 2021 NH 2021-22 SH 2022 NH 2022-23	Vaccine SH 2023

*Superscripts refer to antiserum properties (< relates to the lowest dilution of antiserum used)

1 < = <40; 2 < = <80; ND = Not Done

Table 4-2. Antigenic analysis of influenza A(H1N1)pdm09 viruses by HI

Viruses	Other information	Collection date	Passage history	Haemagglutination inhibition titre										
				Post-infection ferret antisera										
								NEW						NEW
	Passage history			A/Ire 87733/19 Egg St Jude's	A/G-M SWL1536/19 MDCK	A/G-M SWL1536/19 Egg	A/Ghana 1894/21 Egg	A/Ghana 1894/21 Egg	A/Lyon 820/21 Egg	A/Denmark 3280/19 MDCK	IVR-215 A/Vic/2570/19 Egg	A/Sydney 5/21 Egg	A/Sydney 5/21 Egg
	Ferret number			F18/20[*1]	F09/20[*1]	F12/20[*1]	F02/22[*1]	F35/22[*1]	F06/22[*1]	F28/20[*1]	F37/21[*1]	F04/22[*1]	F34/22[*1]
	Genetic group			6B.1A.5a.1	6B.1A.5a.1	6B.1A.5a.1	6B.1A.5a.1	6B.1A.5a.1	6B.1A.5a.1	6B.1A.5a.2	6B.1A.5a.2	6B.1A.5a.2	6B.1A.5a.2	6B.1A.5a.2
REFERENCE VIRUSES														
A/Ireland/87733/2019	6B.1A.5a.1	2019-11-03	E4	1280	2560	2560	1280	1280	320	40	80	80	80	40
A/Guangdong-Maonan/SWL1536/2019	6B.1A.5a.1	2019-06-17	C2/MDCK1	1280	2560	2560	1280	1280	320	80	80	80	80	40
A/Guangdong-Maonan/SWL1536/2019	6B.1A.5a.1	2019-06-17	E3/E2	640	1280	1280	640	640	320	40	80	40	40	40
A/Ghana/1894/2021	6B.1A.5a.1	2021-07-21	E2/E1	640	1280	2560	1280	1280	320	80	160	80	80	80
A/Lyon/820/2021	6B.1A.5a.1	2021-11-16	E1/E2	160	320	320	160	160	320	40	40	40	40	<
A/Denmark/3280/2019	6B.1A.5a.2	2019-11-10	MDCK4/MDCK5	40	80	80	<	40	40	1280	1280	1280	1280	640
IVR-215 (A/Victoria/2570/2019)	6B.1A.5a.2	2018-11-22	E4/D7/E2	40	160	80	40	40	80	640	1280	640	640	320
A/Sydney/5/2021	6B.1A.5a.2		E3/E1	80	80	80	40	40	40	1280	1280	1280	1280	1280
TEST VIRUSES														
A/Lorraine/28657/2022	6B.1A.5a.1	2022-04-11	MDCK3	320	640	640	640	320	160	40	40	40	40	<
A/Norway/23877/2022	6B.1A.5a.1	2022-06-04	MDCK1	640	1280	1280	1280	40	160	40	<	40	40	640
A/Norway/25089/2022	6B.1A.5a.2	2022-06-15	MDCK1	<	<	<	<	<	<	640	1280	640	640	640
A/Norway/25093/2022	6B.1A.5a.2	2022-06-15	MDCK1	<	40	<	<	<	<	640	1280	640	640	640
A/Norway/29426/2022	6B.1A.5a.2	2022-08-02	MDCK1	<	80	40	<	<	<	2560	2560	2560	2560	2560
						Vaccine NH 2020-21					Vaccine SH 2021 NH 2021-22 SH 2022 NH 2022-23	Vaccine SH 2023		

*Superscripts refer to antiserum properties (< relates to the lowest dilution of antiserum used)
1 < = <40; 2 < = <80; ND = Not Done

Influenza A(H3N2) virus analyses

A(H3N2) viruses with HA sequences in clade **3C.2a** have been dominant since the 2014-15 influenza season with group **3C.2a1b** viruses predominating over the course of the 2019-2020 season in most WHO-defined regions of the world but for the European Region where there was equivalence of clade **3C.3a** viruses. The HA gene sequences of viruses in both clades **3C.2a** and **3C.3a** continue to diverge. Notably, clade **3C.3a.1** viruses had evolved to carry **HA1** amino acid substitutions of **L3I, S91N**, **N144K** (loss of a N-linked glycosylation motif at residues 144-146), **F193S** and **K326R**, and **D160N** in **HA2**, compared with cell culture-propagated A/Stockholm/6/2014. Greater variation has been observed among clade **3C.2a** viruses, resulting in the designation of new subclades/groups/subgroups. Amino acid substitutions that define these subclades/groups/subgroups are:

- Subclade **3C.2a1**: Those in clade **3C.2a** plus **N171K** in **HA1** and **I77V** and **G155E** in **HA2**, most also carry **N121K** in **HA1**, e.g. **A/Singapore/INFIMH-16-0019/2016** (a former vaccine virus).
- Group **3C.2a1a**: Those in subclade **3C.2a1** plus **T135K** in **HA1**, resulting in the loss of a potential glycosylation site, and **G150E** in **HA2**, e.g. **A/Greece/4/2017.**
- Group **3C.2a1b**: Those in subclade **3C.2a1** plus **E62G, R142G** and **H311Q** in **HA1**, often with additional amino acid substitutions – notably **HA1 T135K** (resulting in the loss of a potential glycosylation site) commonly with **T128A** (resulting in the loss of a potential glycosylation site), the **3C.2a1b.1** subgroup (e.g. **A/La Rioja/2202/2018**) or **HA1 T131K** and **HA2 V200I**, the **3C.2a1b.2** subgroup (e.g. **A/South Australia/34/2019**). Distinct clusters of viruses within both these subgroups have emerged defined by specific **HA1** and/or **HA2** amino acid substitutions: **3C.2a1b.1a** with additional amino acid substitutions of **HA1 A138S**, **F193S** and **S198P**, many also with **G186D** and **D190N** (e.g. **A/Denmark/3284/2019**); **3C.2a1b.1b** with additional amino acid substitutions of **HA1 S137F, A138S** and **F193S** (e.g. **A/Hong Kong/2671/2019**); **3C.2a1b.2a** with additional amino acid substitutions of **HA1 K83E** and **Y94N** with **HA2 I193M** (e.g. **A/Slovenia/1637/2020**); **3C.2a1b.2b** with **HA2 V18M** substitution, often with additional **HA1** substitutions (e.g. **A/Bretagne/1323/2020**).
- Clade **3C.3a**: represented by a former vaccine virus, **A/Switzerland/9715293/2013**, with recently circulating clade **3C.3a.1** viruses carrying additional substitutions of **S91N, N144K** (resulting in the loss of a potential glycosylation site)**, and F193S** in **HA1** and **D160N** in **HA2**, e.g. **A/England/538/2018** and **A/Kansas/14/2017**, the A(H3N2) vaccine virus for the 2019-2020 northern hemisphere influenza season.

The significant geographic spread of viruses in the antigenically distinct **3C.2a1b.1b** cluster, influenced the selection of an A/Hong Kong/2671/2019-like or an A/Hong Kong/45/2019-like virus as the A(H3N2) component of vaccines for the 2020-2021 northern hemisphere and 2021 southern hemisphere influenza seasons.

The first phylogeny was based on a representative set of HA sequences derived from viruses with collection dates after 30 April 2022 made available in GISAID and generated at the WIC from 01 July 2022 (Figure 3a). Small numbers of 'Cambodia-like' **3C.2a1b.2a.1** (from China) and **3C.2a1b.1a** (from Denmark, Germany and Sweden) viruses were reported on. The vast majority of recently collected viruses were 'Bangladesh-like' (**3C.2a1b.2a.2** with **HA1** substitutions of **Y159N**, **T160I** (loss of a glycosylation site), **L164Q**, **G186D**, **D190N** and **Y195F**). The latter viruses were split into four major subgroups defined by specific **HA1** amino acid substitutions: (i) **E50K**; (ii) **D53N** and **P289S**; (iii) **D53N**, **N96S** (gain a glycosylation site) and **I192F**; (iv) **D53G** often with **I25V**, **R201K** and **S219Y** or **D104G** and **K276R**. Subgroups (ii), (iii) and (iv) also share **HA1 H156S** amino acid substitution. Sequences derived from samples collected in the WHO European Region were dispersed throughout the trees with the 'Bangladesh-like' (**3C.2a1b.2a.2**) viruses falling into multiple virus clusters defined by specific amino acid substitutions (Figure 3a).

The second phylogeny is based on HA sequences derived from viruses with collection dates after 31 July 2022 made available in GISAID and generated at the WIC from 01 August 2022 and shows a very similar profile to the first phylogeny (Table 2 and Figure 3b). With the caveat that a large number of sequences from viruses with collection dates in August and September 2022, detected in Spain, are now available in GISAID, subgroups (i; HA1 substitution **E50K**) and (iv; HA1 substitutions of **D53G**, **D104G** and **K276R**) dominate in both phylogenies and there is expansion subgroup (iv) with additional **HA1 I140K** and **R299K** substitutions.

The locations of HA sequences for egg- and cell culture-propagated cultivars of A/Cambodia/e0826360/2020 (**3C.2a1b.2a.1**) recommended for use in northern hemisphere 2021-2022 vaccines [1], are indicated in red on the phylogenies, as are egg- and cell-culture based 'Bangladesh-like' vaccines to be used in the 2022 and 2023 southern hemisphere and 2022-2023 northern hemisphere seasons, A/Darwin/9/2021 and A/Darwin/6/2021 (**3C.2a1b.2a.2**) respectively [2, 4, 3] (Figures 3a and 3b).

As described in many previous reports[2], influenza A(H3N2) viruses had been difficult to characterise antigenically by HI assay due to variable agglutination of red blood cells (RBCs) from guinea pigs, turkeys, and humans, often with the loss of ability to agglutinate any of these RBCs. As was highlighted first in the November 2014 report[3], this was a significant problem for most viruses that fell in genetic clade **3C.2a**, although there was some alleviation of this during 2019-2020 with continuation into the 2020-2021 influenza season. This issue is now much alleviated for 'Bangladesh-like' **3C.2a1b.2a.2** viruses which agglutinate guinea pig RBCs well, allowing HI assays to be performed with single A(H3N2) viruses from Croatia and the Netherlands failing to yield a sufficient HA titre with guinea pig RBCs to allow HI analysis (Table 3).

While the number of detections of seasonal influenza viruses was low from April 2020 to July 2021, compared to previous years, the WHO Collaborating Centres for Influenza have shown viruses in these emerged virus clusters to be antigenically distinguishable from one another and other A(H3N2) virus subgroups.

Results for 97 A(H3N2) viruses fully characterised antigenically since the July report are shown in Tables 5-1 to 5-5. Of the test viruses, three fell in the **3C.2a1b.1a** cluster, one in the **3C.2a1b.1b** cluster, 92 were 'Bangladesh-like' **3C.2a1b.2a.2** viruses and the one virus for which gene sequencing is pending gave an HI profile indicative of a **3C.2a1b.2a.2** virus. The two **3C.2a1b.1a** viruses detected in France were recognised well, within fourfold of the respective homologous titres, by antisera raised against five reference viruses inclusive of that raised against the northern hemisphere 2022-2023 vaccine virus, A/Darwin9/2021 (Table 5-3). The **3C.2a1b.1b** virus was recognised well by antisera raised against cell culture-propagated A/Denmark/3264/2019 (**3C.2a1b.1a**), A/Hong Kong/2671/2019 (**3C.2a1b.1b**) and A/Cambodia/925256/2020 (**3C.2a1b.2a.1**) (Table 5-4).

Viruses with **3C.2a1b.2a.2** HAs are arranged by genetic cluster **H156** (i; HA1 substitution **E50K**), **H156S** (iii; HA1 substitutions **D53N**, **H156S**), **D53G** (iv; HA1 substitutions **D53G**, **H156S**) and **D104G** (iv; HA1 substitutions **D53G**, **D104G**, **H156S**, **K276R**) (Tables 5-1 to 5-5). These 'Bangladesh-like' **3C.2a1b.2a.2** test viruses were recognised well only by post-infection ferret antisera raised against viruses with **3C.2a1b.2a.2** HAs, and only the **H156S** substitution resulted in slight loss of reactivity. Overall, antisera raised against cell culture-propagated A/Bangladesh/4005/2020, A/Stockholm/5/2021 and A/England/214191723/2021 all recognised greater than 97% of the test viruses at titres within fourfold of the respective homologous titres. Although only small numbers of test viruses were analysed for antisera raised against cell culture-propagated A/Slovenia/8720/2022 and A/Thuringen10/2022, and egg-propagated A/Slovenia/8720/2022, at least 95% were recognised at titres within fourfold of the respective homologous titres. The antiserum raised against egg-propagated A/Darwin/9/2021, the northern hemisphere 2022-2023 vaccine virus, recognised 84 (90%) of the test viruses at titres within fourfold of the homologous titres.

Results of HI assays with panels of post-infection ferret antisera raised against A(H3N2) vaccine and reference viruses for viruses detected in EU/EEA countries can be seen in previous influenza characterisation reports on ECDC's website. Overall, these data show strong clade/subclade-specific recognition of test viruses by post-infection ferret antisera raised against cell culture-propagated reference viruses, with limited cross-clade/subclade recognition and further reductions in recognition of cell culture-propagated recently circulating viruses by antisera raised against A(H3N2) egg-propagated vaccine viruses.

[2] For example, the September 2013 report: European Centre for Disease Prevention and Control. Influenza virus characterisation, summary Europe, September 2013. Stockholm: ECDC; 2013. Available from: https://ecdc.europa.eu/sites/portal/files/media/en/publications/Publications/influenza-virus-characterisation-sep-2013.pdf

[3] European Centre for Disease Prevention and Control. Influenza virus characterisation, summary Europe, November 2014. Stockholm: ECDC; 2014. Available from: https://www.ecdc.europa.eu/sites/default/files/media/en/publications/Publications/ERLI-Net%20report%20November%202014.pdf

Figure 3a. Phylogenetic comparison of influenza A(H3N2) HA genes (GISAID/WIC, July 2022)

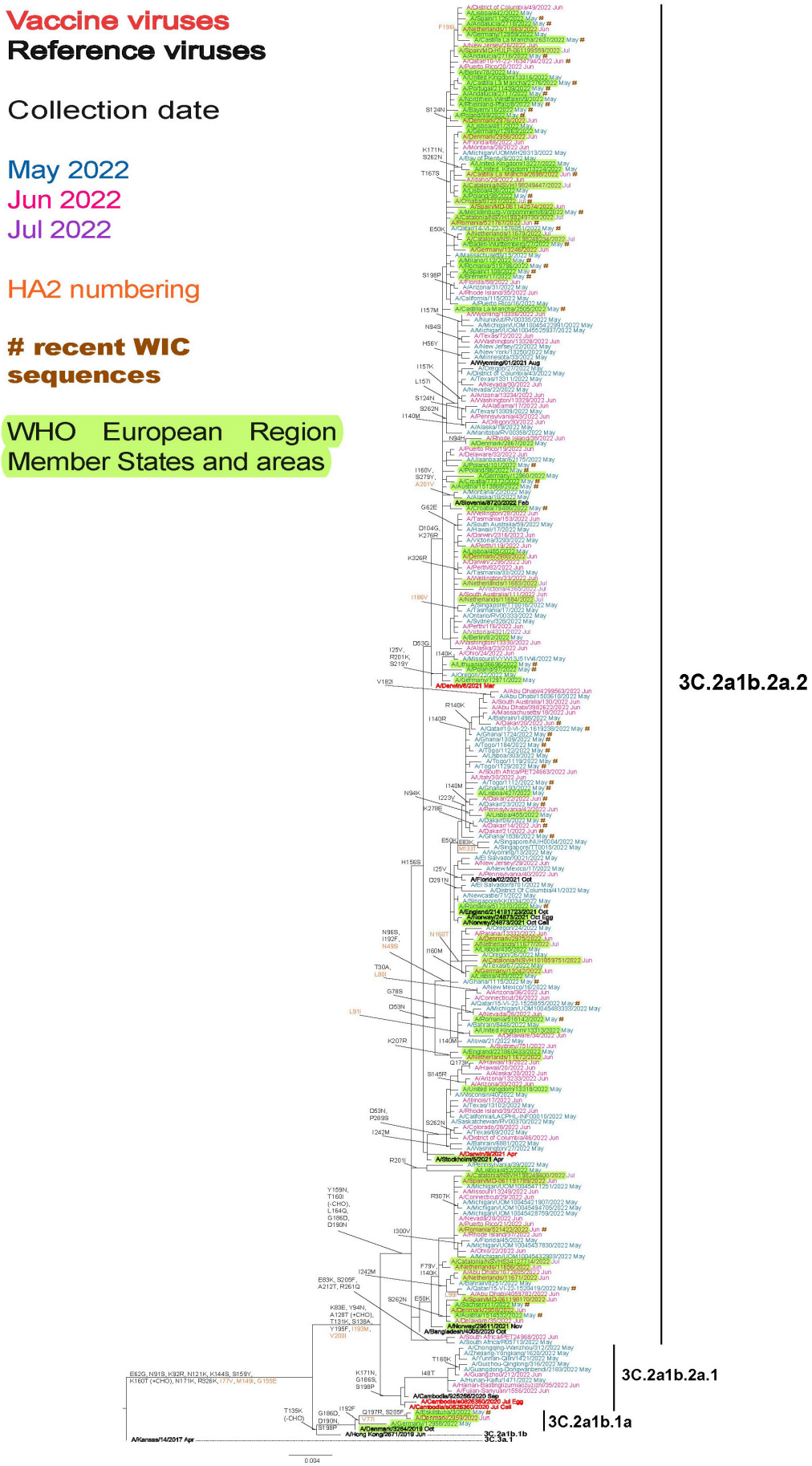


Figure 3b. Phylogenetic comparison of influenza A(H3N2) HA genes (GISAID/WIC, Sept 2022)

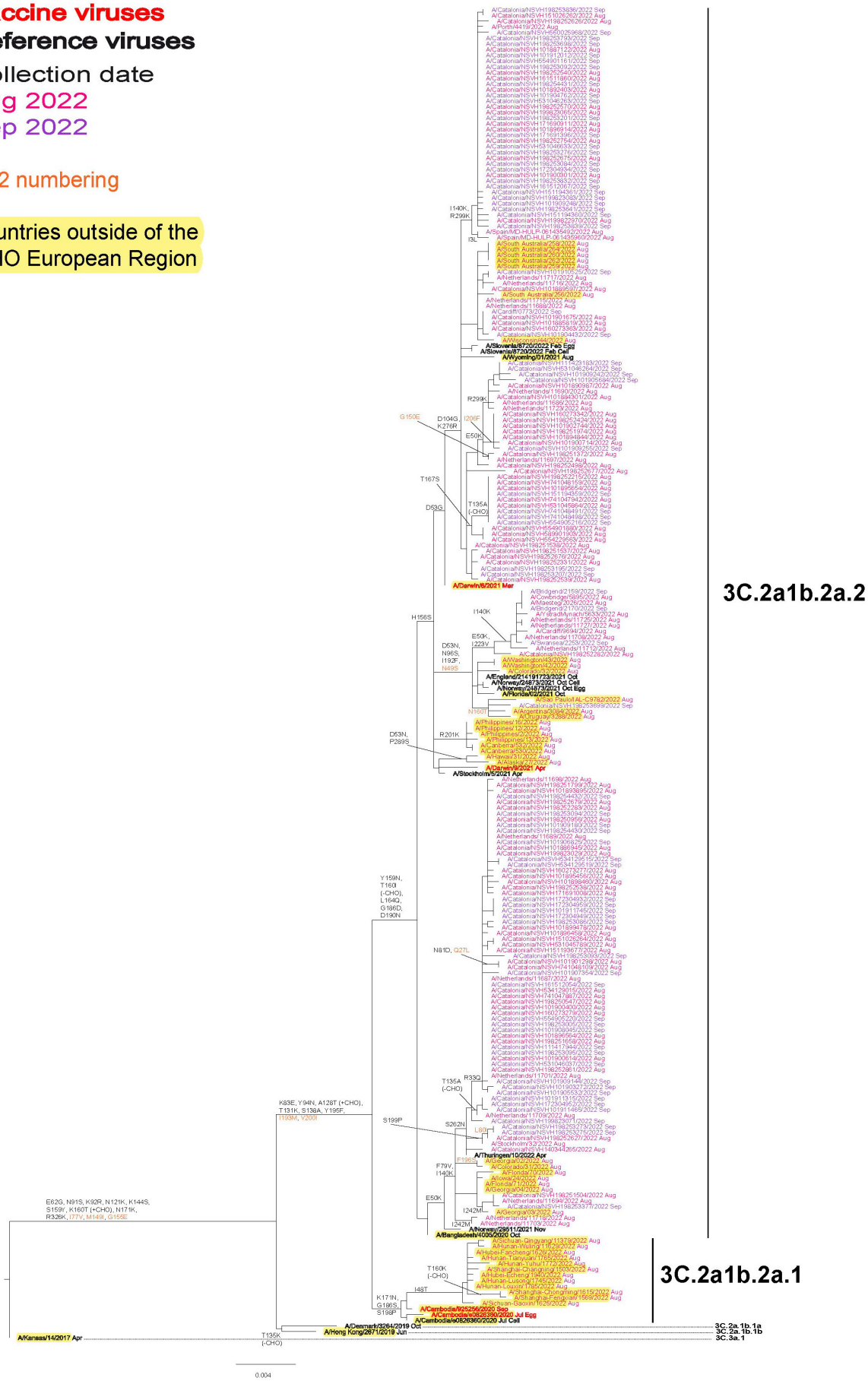


Table 5-1. Antigenic analysis of influenza A(H3N2) viruses by HI

Viruses	Other information	Collection date	Passage history	Haemagglutination inhibition titre									
				Post-infection ferret antisera									
	Passage history			A/Denmark/3264/19 SIAT F19/20[1]	A/HK/2671/19 Cell St Judes F21/20[1]	A/Camb/925256/20 SIAT F03/21[1]	A/Camb/e0826360/20 Egg F10/21[1]	A/Bang/4005/20 SIAT F07/21[1]	A/Stock/5/21 SIAT F35/21[1]	A/Eng/21419172 3/21 SIAT F07/22[1]	A/Darwin 9/21 Egg F39/21[1]	A/Kansas 14/17 SIAT F17/19[1]
	Ferret number											
	Genetic group			3C.2a1b.1a	3C.2a1b.1b	3C.2a1b.2a.1	3C.2a1b.2a.1	3C.2a1b.2a.2	3C.2a1b.2a.2	3C.2a1b.2a.2	3C.2a1b.2a.2	3C.3a.1
REFERENCE VIRUSES												
A/Denmark/3264/2019		3C.2a1b.1a	2019-10-25	SIAT3/SIAT4	320	160	640	320	320	160	40	320	160
A/Hong Kong/2671/2019		3C.2a1b.1b	2019-06-17	MDCK1/SIAT4	320	320	640	160	320	80	40	160	160
A/Cambodia/925256/2020		3C.2a1b.2a.1	2020-09-25	SIAT5	160	160	320	320	320	160	40	320	160
A/Cambodia/e0826360/2020		3C.2a1b.2a.1	2020-07-16	E5/E2	160	<	80	1280	320	160	160	160	80
A/Bangladesh/4005/2020	H156	3C.2a1b.2a.2	2020-10-04	SIAT3	160	40	160	320	640	640	640	640	160
A/Stockholm/5/2021	H156S	3C.2a1b.2a.2	2021-04-16	SIAT0/SIAT3	80	<	80	160	320	640	320	640	80
A/England/214191723/2021	H156S	3C.2a1b.2a.2	2021-10-12	MDCK1/SIAT2	40	<	80	160	160	320	640	640	40
A/Darwin/9/2021	H156S	3C.2a1b.2a.2	2021-04-17	E3/E4	160	<	80	640	640	1280	640	2560	160
A/Kansas/14/2017		3C.3a.1	2017-12-14	SIAT3/SIAT2	40	<	80	80	80	80	80	80	320
TEST VIRUSES													
A/Portugal/210273/2022	D104G	3C.2a1b.2a.2	2022-02-21	SIAT1/SIAT2	40	<	40	40	160	320	320	320	<
A/Portugal/210274/2022	D104G	3C.2a1b.2a.2	2022-02-21	SIAT2/SIAT2	80	<	40	80	320	640	320	640	<
A/Portugal/210372/2022	D104G	3C.2a1b.2a.2	2022-03-08	SIAT2/SIAT2	80	<	40	80	160	640	320	640	<
A/Portugal/210588/2022	D104G	3C.2a1b.2a.2	2022-03-09	SIAT2/SIAT2	40	<	40	80	160	640	320	640	<
A/Portugal/210592/2022	D104G	3C.2a1b.2a.2	2022-03-15	SIAT1/SIAT2	80	<	40	80	160	640	320	640	<
A/Portugal/210603/2022	D104G	3C.2a1b.2a.2	2022-03-15	SIAT2/SIAT2	80	<	40	80	160	640	320	320	<
A/Portugal/210611/2022	D104G	3C.2a1b.2a.2	2022-03-15	SIAT2/SIAT2	80	<	40	80	160	640	320	320	<
A/Ireland/16347/2022	D104G	3C.2a1b.2a.2	2022-03-21	SIAT2	80	<	40	80	160	640	320	640	<
A/Ireland/24347/2022	D104G	3C.2a1b.2a.2	2022-04-27	SIAT2	80	<	40	80	320	640	320	640	<
A/Castilla La Mancha/2234/2022	D104G	3C.2a1b.2a.2	2022-05-03	SIAT1	80	<	40	80	160	640	320	640	<
A/Castilla La Mancha/2224/2022	D104G	3C.2a1b.2a.2	2022-05-08	SIAT1	80	<	40	80	160	320	320	320	<
A/Castilla La Mancha/2333/2022	D104G	3C.2a1b.2a.2	2022-05-16	SIAT1	40	<	40	40	160	320	320	320	<
A/Castilla La Mancha/2358/2022	D104G	3C.2a1b.2a.2	2022-05-17	SIAT1	40	<	40	40	160	320	320	320	<
A/Castilla La Mancha/2356/2022	D104G	3C.2a1b.2a.2	2022-05-19	SIAT1	80	<	40	40	160	320	320	320	<
A/Portugal/210269/2022	H156S	3C.2a1b.2a.2	2022-02-21	SIAT1/SIAT2	80	<	80	160	320	640	1280	640	<
A/Portugal/210307/2022	H156S	3C.2a1b.2a.2	2022-02-25	SIAT2/SIAT2	80	<	40	80	320	320	640	640	<
A/Portugal/210312/2022	H156S	3C.2a1b.2a.2	2022-02-26	SIAT2/SIAT2	80	<	80	80	320	640	1280	640	<
A/Portugal/210366/2022	H156S	3C.2a1b.2a.2	2022-03-04	SIAT2/SIAT2	40	<	40	80	160	320	640	320	<
							Vaccine NH 2021-22					Vaccine SH 2022 NH 2022-23 SH 2023	

*Superscripts refer to antiserum properties (< relates to the lowest dilution of antiserum used)
1 < = <40, ND = Not Done

Table 5-2. Antigenic analysis of influenza A(H3N2) viruses by HI

Viruses	Other information	Collection date	Passage history	Haemagglutination inhibition titre									
				Post-infection ferret antisera									
				A/Denmark	A/HK	A/Camb	A/Camb	A/Bang	A/Stock	A/Eng	A/Darwin	A/Kansas
				3264/19	2671/19	925256/20	e0826360/20	4005/20	5/21	21419723/21	9/21	14/17
	Passage history			SIAT	Cell	SIAT	Egg	SIAT	SIAT	SIAT	Egg	SIAT
	Ferret number			F19/20^{-1}	St Judes F21/20^{-1}	F03/21^{-1}	F10/21^{-1}	F07/21^{-1}	F35/21^{-1}	F07/22^{-1}	F39/21^{-1}	F17/19^{-1}
	Genetic group			3C.2a1b.1a	3C.2a1b.1b	3C.2a1b.2a.1	3C.2a1b.2a.1	3C.2a1b.2a.2	3C.2a1b.2a.2	3C.2a1b.2a.2	3C.2a1b.2a.2	3C.3a.1
REFERENCE VIRUSES												
A/Denmark/3264/2019	3C.2a1b.1a	2019-10-25	SIAT3/SIAT4	640	160	640	320	320	160	40	320	160
A/Hong Kong/2671/2019	3C.2a1b.1b	2019-06-17	MDCK1/SIAT4	320	640	640	160	320	80	40	160	160
A/Cambodia/925256/2020	3C.2a1b.2a.1	2020-09-25	SIAT5	160	160	640	320	320	160	40	320	160
A/Cambodia/e0826360/2020	3C.2a1b.2a.1	2020-07-16	E5/E2	160	<	80	1280	320	160	160	160	80
A/Bangladesh/4005/2020	H156 3C.2a1b.2a.2	2020-10-04	SIAT3	160	40	160	320	640	640	640	640	160
A/Stockholm/5/2021	H156S 3C.2a1b.2a.2	2021-04-16	SIAT0/SIAT3	80	<	80	160	320	320	320	640	80
A/England/214191723/2021	H156S 3C.2a1b.2a.2	2021-10-12	MDCK1/SIAT2	40	<	80	160	160	320	640	640	40
A/Darwin/9/2021	H156S 3C.2a1b.2a.2	2021-04-17	E3/E4	160	<	80	640	640	1280	640	1280	160
A/Kansas/14/2017	3C.3a.1	2017-12-14	SIAT3/SIAT2	40	<	80	80	80	80	80	80	160
TEST VIRUSES												
A/Dunkerque/61979/2021	D104G 3C.2a1b.2a.2	2021-12-24	SIAT1	40	<	40	40	160	320	320	320	40
A/Portugal/210259/2022	D104G 3C.2a1b.2a.2	2022-02-17	SIAT1/SIAT2	80	<	80	80	160	640	320	640	40
A/Nord Pas de Calais/11659/2022	D104G 3C.2a1b.2a.2	2022-02-17	SIAT1	80	<	80	80	160	320	320	320	40
A/Portugal/210266/2022	D104G 3C.2a1b.2a.2	2022-02-18	SIAT1/SIAT2	40	<	40	40	160	320	320	320	40
A/Dunkerque/16908/2022	D104G 3C.2a1b.2a.2	2022-03-01	SIAT1	80	<	40	160	160	320	320	320	40
A/Portugal/210597/2022	D104G 3C.2a1b.2a.2	2022-03-09	SIAT1/SIAT2	80	<	40	40	160	640	320	640	40
A/Montenegro/155721202/2022	D104G 3C.2a1b.2a.2	2022-03-09	SIAT1	80	<	80	80	160	320	320	640	40
A/Montenegro/161482202/2022	D104G 3C.2a1b.2a.2	2022-03-17	SIAT1	40	<	40	40	160	320	320	320	40
A/Montenegro/165163202/2022	D104G 3C.2a1b.2a.2	2022-03-23	SIAT1	40	<	40	160	160	320	320	320	40
A/Montenegro/165169202/2022	D104G 3C.2a1b.2a.2	2022-03-23	SIAT1	80	<	160	160	320	640	640	640	80
A/Pays de Loire/223333/2022	D104G 3C.2a1b.2a.2	2022-03-24	SIAT1	80	<	40	80	160	640	320	640	40
A/Montenegro/171447202/2022	D104G 3C.2a1b.2a.2	2022-04-01	SIAT1	80	<	40	80	160	320	320	640	40
A/Garches/28367/2022	D104G 3C.2a1b.2a.2	2022-04-06	SIAT1	80	<	40	80	160	320	320	320	40
A/Alsace/28544/2022	D104G 3C.2a1b.2a.2	2022-04-08	SIAT1	80	<	80	80	160	640	320	640	40
A/Picardie/29331/2022	D104G 3C.2a1b.2a.2	2022-04-13	SIAT1	40	<	40	40	80	320	320	320	40
A/Sarajevo/192G/2022	D104G 3C.2a1b.2a.2	2022-04-19	SIAT2/SIAT2	80	<	40	80	160	320	320	640	40
A/Saint-Denis/48407/2021	H156S 3C.2a1b.2a.2	2021-12-06	SIAT1	<	<	80	80	80	160	320	320	<
A/Portugal/210192/2022	H156S 3C.2a1b.2a.2	2022-02-08	SIAT2/SIAT2	80	<	40	80	160	320	640	320	40
A/Portugal/210210/2022	H156S 3C.2a1b.2a.2	2022-02-09	SIAT2/SIAT2	80	<	80	160	160	320	640	320	40
A/Portugal/210214/2022	H156S 3C.2a1b.2a.2	2022-02-10	SIAT1/SIAT2	80	<	80	160	320	320	640	640	40
A/Portugal/210212/2022	H156S 3C.2a1b.2a.2	2022-02-11	SIAT2/SIAT2	80	<	80	160	320	640	1280	640	40
A/Portugal/210220/2022	H156S 3C.2a1b.2a.2	2022-02-11	SIAT1/SIAT2	80	<	80	160	320	640	1280	640	40
A/Portugal/210218/2022	H156S 3C.2a1b.2a.2	2022-02-14	SIAT1/SIAT2	80	<	80	80	320	320	640	640	40
A/Portugal/210219/2022	H156S 3C.2a1b.2a.2	2022-02-14	SIAT2/SIAT2	80	<	40	40	160	320	640	320	40
A/Portugal/210224/2022	H156S 3C.2a1b.2a.2	2022-02-14	SIAT2/SIAT2	80	<	40	80	320	320	640	640	40
A/Portugal/210255/2022	H156S 3C.2a1b.2a.2	2022-02-16	SIAT1/SIAT2	80	<	80	160	320	640	1280	640	40
A/Portugal/210256/2022	H156S 3C.2a1b.2a.2	2022-02-16	SIAT2/SIAT2	80	<	80	80	320	640	640	640	40
A/Portugal/210257/2022	H156S 3C.2a1b.2a.2	2022-02-16	SIAT2/SIAT2	80	<	80	160	320	640	1280	640	80
A/Portugal/210258/2022	H156S 3C.2a1b.2a.2	2022-02-16	SIAT2/SIAT2	80	<	80	80	320	640	1280	640	40
A/Portugal/210270/2022	H156S 3C.2a1b.2a.2	2022-02-21	SIAT1/SIAT2	80	<	80	160	320	640	1280	640	40
A/Portugal/210271/2022	H156S 3C.2a1b.2a.2	2022-02-22	SIAT1/SIAT2	80	<	80	80	160	320	640	640	40
A/Le Mans/16907/2022	H156S 3C.2a1b.2a.2	2022-03-02	SIAT1	40	<	40	80	160	320	640	320	40
A/Moulins/R22.321.98/2022	H156 3C.2a1b.2a.2	2022-07-20	MDCKx/SIAT1	160	<	80	320	640	320	320	320	80
A/Moulins/R22.321.96/2022	H156 3C.2a1b.2a.2	2022-07-20	MDCKx/SIAT1	160	<	80	160	320	320	320	320	80
A/Lyon/CHUR22.320.85/2022	H156 3C.2a1b.2a.2	2022-07-24	MDCKx/SIAT1	80	<	40	80	320	320	320	160	80
							Vaccine NH 2021-22				Vaccine SH 2022 NH 2022-23 SH 2023	

*Superscripts refer to antiserum properties (< relates to the lowest dilution of antiserum used)
1 <= <40, ND = Not Done

Table 5-3. Antigenic analysis of influenza A(H3N2) viruses by HI

Viruses	Other information	Collection date	Passage history	Haemagglutination inhibition titre															
				Post-infection ferret antisera															
										NEW				NEW					
	Passage history			A/Denmark	A/HK	A/Camb	A/Camb	A/Bang	A/Bang	A/Stock	A/Eng	A/Eng	A/Slov	A/Darwin	A/Slo	A/Kansas
				3264/19	2671/19	925256/20	e0826360/20	4005/20	4005/20	5/21	21419172 3/21	21419172 3/21	8720/2022	9/21	8720/22	14/17
				SIAT	Cell	SIAT	Egg	SIAT	SIAT	SIAT	SIAT	SIAT	SIAT	Egg	Egg	SIAT
	Ferret number			F19/20[-1]	St Judes F21/20[-1]	F03/21[-1]	F10/21[-1]	F07/21[-1]	F31/22[-1]	F35/21[-1]	F07/22[-1]	F32/22[-1]	F24/22[-1]	F39/21[-1]	F25/22[-1]	F17/19[-1]
	Genetic group			3C.2a1b.1a	3C.2a1b.1b	3C.2a1b.2a.1	3C.2a1b.1a.1	3C.2a1b.2a.2	3C.2a1b.2a.2	3C.2a1b.2a.2	3C.2a1b.2a.2	3C.2a1b.2a.2	3C.2a1b.2a.2	3C.2a1b.2a.2	3C.2a1b.2a.2	3C.3a.1
REFERENCE VIRUSES																
A/Denmark/3264/2019	3C.2a1b.1a	2019-10-25	SIAT3/SIAT4	320	160	640	320	320	320	160	40	<	ND	320	40	160
A/Hong Kong/2671/2019	3C.2a1b.1b	2019-06-17	MDCK1/SIAT4	320	320	640	160	320	320	80	40	40	<	160	40	160
A/Cambodia/9252256/2020	3C.2a1b.2a.1	2020-09-25	SIAT5	160	160	1280	320	320	640	160	40	<	ND	320	40	160
A/Cambodia/e0826360/2020	3C.2a1b.2a.1	2020-07-16	E5/E2	160	<	80	2560	320	640	160	160	160	320	160	80	80
A/Bangladesh/4005/2020 H156	3C.2a1b.2a.2	2020-10-04	SIAT3	160	40	160	320	640	640	640	640	160	1280	640	320	160
A/Stockholm/5/2021 H156S	3C.2a1b.2a.2	2021-04-16	SIAT0/SIAT3	80	<	80	160	320	160	640	320	160	1280	640	320	80
A/England/2141917 23/2021 H156S	3C.2a1b.2a.2	2021-10-12	MDCK1/SIAT2	40	<	80	160	160	160	320	640	320	1280	640	320	40
A/Slovenia/8720/2022 D104G	3C.2a1b.2a.2	2022-02-10	SIAT1/MDCK1/SIAT2	160	<	160	80	320	ND	1280	1280	ND	320	640	ND	40
A/Darwin/9/2021 H156S	3C.2a1b.2a.2	2021-04-17	E3/E2	160	<	80	640	640	320	1280	640	320	640	640	1280	160
A/Slovenia/8720/2022 D104G	3C.2a1b.2a.2	2022-02-10	E3(Am1A/2)	160	<	80	320	320	ND	640	640	ND	320	640	640	80
A/Kansas/14/2017	3C.3a.1	2017-12-14	SIAT3/SIAT2	40	<	80	80	80	80	80	80	<	80	80	<	640
TEST VIRUSES																
A/Croatia/66213/2022 D104G	3C.2a1b.2a.2	2022-03-23	SIAT1	80	<	40	80	160	ND	320	320	ND	160	320	320	80
A/Croatia/70723/2022 D104G	3C.2a1b.2a.2	2022-04-06	SIAT1	80	<	40	80	160	ND	640	640	ND	640	640	1280	<
A/Croatia/70708/2022 D104G	3C.2a1b.2a.2	2022-04-06	SIAT1	40	<	40	40	160	ND	640	320	ND	320	640	640	<
A/Croatia/70697/2022 D104G	3C.2a1b.2a.2	2022-04-06	SIAT2	80	<	40	40	160	ND	640	320	ND	320	320	640	<
A/Croatia/70654/2022 D104G	3C.2a1b.2a.2	2022-04-06	SIAT2	<	<	<	<	80	ND	80	160	ND	40	160	160	<
A/Croatia/70648/2022 D104G	3C.2a1b.2a.2	2022-04-06	SIAT2	40	<	40	<	160	ND	160	160	ND	320	160	640	<
A/Croatia/70645/2022 D104G	3C.2a1b.2a.2	2022-04-06	SIAT2	80	<	40	80	160	ND	160	320	ND	160	320	320	<
A/Sarajevo/186G/2022 D104G	3C.2a1b.2a.2	2022-04-09	SIAT1	80	<	40	80	160	ND	640	320	ND	320	640	640	<
A/Sarajevo/189G/2022 D104G	3C.2a1b.2a.2	2022-04-18	SIAT1	40	<	40	40	160	ND	320	320	ND	320	320	320	<
A/Croatia/77372/2022 D104G	3C.2a1b.2a.2	2022-05-07	SIAT1	80	<	40	40	160	ND	640	320	ND	320	320	640	<
A/Croatia/79486/2022 D104G	3C.2a1b.2a.2	2022-05-17	SIAT1	80	80	80	80	160	ND	320	320	ND	320	320	640	<
A/Portugal/210209/2022 H156S	3C.2a1b.2a.2	2022-02-09	SIAT1/SIAT3	40	<	40	40	160	ND	320	640	ND	80	320	320	40
A/Portugal/210207/2022 H156S	3C.2a1b.2a.2	2022-02-10	SIAT2/SIAT3	40	<	40	80	160	ND	320	1280	ND	320	320	640	40
A/Ile de France/08440/2022	3C.2a1b.1a	2022-02-01	SIAT3	80	80	320	160	80	ND	160	40	ND	<	160	40	80
A/Pays de Loire/13561/2022	3C.2a1b.1a	2022-02-24	SIAT2	80	80	320	160	80	ND	160	<	ND	<	160	<	80
							Vaccine NH 2021-22							Vaccine SH 2022 NH 2022-23 SH 2023		

* Superscripts refer to antiserum properties (< relates to the lowest dilution of antiserum used)
1 < = <40, ND = Not Done

Table 5-4. Antigenic analysis of influenza A(H3N2) viruses by HI

Viruses	Other information	Collection date	Passage history	Haemagglutination inhibition titre											
				Post-infection ferret antisera											
	Passage history			A/Denmark	A/HK	A/Camb	A/Camb	A/Bang	A/Stock	A/Eng	A/Slov	A/Darwin	A/Slo	A/Kansas
	Ferret number			3264/19	2671/19	925256/20	e0826360/20	4005/20	5/21	2141917123/21	8720/2022	9/21	8720/22	14/17
				SIAT	Cell	SIAT	Egg	SIAT	SIAT	SIAT	SIAT	Egg	Egg	SIAT
	Genetic group			F19/20[-1]	St Judes F21/20[-1]	F03/21[-1]	F10/21[-1]	F07/21[-1]	F35/21[-1]	F07/22[-1]	F24/22[-1]	F39/21[-1]	F25/22[-1]	F17/19[-1]
				3C.2a1b.1a	3C.2a1b.1b	3C.2a1b.2a.1	3C.2a1b.2a.1	3C.2a1b.2a.2	3C.2a1b.2a.2	3C.2a1b.2a.2	3C.2a1b.2a.2	3C.2a1b.2a.2	3C.2a1b.2a.2	3C.3a.1
REFERENCE VIRUSES														
A/Denmark/3264/2019	3C.2a1b.1a	2019-10-25	SIAT3/SIAT4	320	320	640	320	320	160	40	ND	320	40	160
A/Hong Kong/2671/2019	3C.2a1b.1b	2019-06-17	MDCK1/SIAT4	320	320	640	160	320	160	80	<	160	40	160
A/Cambodia/925256/2020	3C.2a1b.2a.1	2020-09-25	SIAT5	160	160	1280	320	320	160	80	ND	640	40	160
A/Cambodia/e0826360/2020	3C.2a1b.2a.1	2020-07-16	E5/E2	160	<	160	1280	320	160	320	320	320	160	80
A/Bangladesh/4005/2020	H156 3C.2a1b.2a.2	2020-10-04	SIAT3	160	40	320	320	640	640	640	1280	640	320	160
A/Stockholm/5/2021	H156S 3C.2a1b.2a.2	2021-04-16	SIAT0/SIAT3	80	<	80	160	320	640	320	1280	640	320	40
A/England/214191723/2021	H156S 3C.2a1b.2a.2	2021-10-12	MDCK1/SIAT3	40	<	80	160	160	320	640	1280	640	320	<
A/Slovenia/8720/2022	D104G 3C.2a1b.2a.2	2022-02-10	SIAT1/MDCK1/SIAT2	80	<	80	80	160	640	640	640	640	1280	<
A/Darwin/9/2021	H156S 3C.2a1b.2a.2	2021-04-17	E3/E2	160	<	80	640	320	640	640	640	1280	1280	80
A/Slovenia/8720/2022	D104G 3C.2a1b.2a.2	2022-02-10	E3(Am1Al2)	160	<	80	320	320	640	640	320	640	1280	40
A/Kansas/14/2017	3C.3a.1	2017-12-14	SIAT3/SIAT2	40	40	80	80	80	160	80	80	320	<	640
TEST VIRUSES														
A/Belgium/S0448/2022	D104G 3C.2a1b.2a.2	2022-02-21	SIAT1/SIAT1	40	<	40	80	160	320	320	ND	320	640	<
A/Brest/932/2022	D104G 3C.2a1b.2a.2	2022-03-28	MDCKx/SIAT1	40	<	40	80	160	320	320	ND	320	640	<
A/Toulon/760/2022	D104G 3C.2a1b.2a.2	2022-03-28	MDCKx/SIAT1	80	<	80	160	320	320	320	ND	320	1280	<
A/Lyon/808/2022	D104G 3C.2a1b.2a.2	2022-04-15	MDCKx/SIAT1	80	<	40	80	160	320	320	ND	320	640	<
A/Lyon/854/2022	D104G 3C.2a1b.2a.2	2022-05-04	MDCKx/SIAT1	40	<	40	80	160	320	320	ND	320	640	<
A/Lyon/CHU-R22.242.82/2022	D104G 3C.2a1b.2a.2	2022-05-09	MDCKx/SIAT1	40	<	40	80	160	320	320	ND	320	640	<
A/Norway/25483/2022	D104G 3C.2a1b.2a.2	2022-06-13	SIAT1	80	<	40	80	160	320	320	ND	640	1280	<
A/Lyon/CHU-R22.285.92/2022	D104G 3C.2a1b.2a.2	2022-06-26	MDCKx/SIAT1	80	<	40	80	320	320	320	640	640	640	<
A/Norway/26959/2022	D104G 3C.2a1b.2a.2	2022-06-29	SIAT1	80	<	40	80	320	640	640	ND	640	1280	<
A/Norway/27942/2022	D104G 3C.2a1b.2a.2	2022-07-09	SIAT1	80	<	40	80	320	640	320	ND	640	640	<
A/Norway/27459/2022	D104G 3C.2a1b.2a.2	2022-07-11	SIAT1	40	<	<	40	160	320	320	320	320	640	<
A/Norway/28542/2022	D104G 3C.2a1b.2a.2	2022-07-12	SIAT1	40	<	40	80	160	320	320	320	320	640	<
A/Norway/27849/2022	D104G 3C.2a1b.2a.2	2022-07-13	SIAT1	40	<	<	40	160	160	160	320	320	640	<
A/Belgium/S0891/2022	D53G 3C.2a1b.2a.2	2022-03-20	SIAT1/SIAT1	160	<	160	320	640	1280	640	640	1280	1280	80
A/Belgium/G0116/2022	H156S 3C.2a1b.2a.2	2022-03-14	SIAT1/SIAT1	40	<	80	80	160	640	640	ND	640	320	40
A/Lyon/CHU-R22.264.84/2022	H156S 3C.2a1b.2a.2	2022-06-02	MDCKx/SIAT1	80	<	80	160	320	320	640	160	640	320	40
A/Bourgoine/758/2022	H156 3C.2a1b.2a.2	2022-04-09	MDCKx/SIAT1	160	<	160	320	640	320	320	ND	320	160	80
A/Lyon/271/2022	3C.2a1b.1b	2022-02-07	MDCKx/SIAT1	320	320	640	<	80	80	<	ND	80	<	40
							Vaccine NH 2021-22					Vaccine SH 2022 NH 2022-23 SH 2023		

*Superscripts refer to antiserum properties (< relates to the lowest dilution of antiserum used)
1 < = <40, ND = Not Done

Table 5-5. Antigenic analysis of influenza A(H3N2) viruses by HI

Viruses	Other information	Collection date	Passage history	Haemagglutination inhibition titre										
				Post-infection ferret antisera							NEW			
				A/Denmark	A/HK	A/Camb	A/Camb	A/Bang	A/Stock	A/Eng	A/Thuringen	A/Darwin	A/Kansas
				3264/19	2671/19	925256/20	e0826360/20	4005/20	5/21	214191723/21	10/22	9/21	14/17
				SIAT	Cell	SIAT	Egg	SIAT	SIAT	SIAT	SIAT	Egg	SIAT
				F19/20^{-1}	St Judes F21/20^{-1}	F03/21^{-1}	F10/21^{-1}	F07/21^{-1}	F35/21^{-1}	F07/22^{-1}	F36/22^{-1}	F39/21^{-1}	F17/19^{-1}
	Passage history			3C.2a1b.1a	3C.2a1b.1b	3C.2a1b.2a.1	3C.2a1b.2a.1	3C.2a1b.2a.2	3C.2a1b.2a.2	3C.2a1b.2a.2	3C.2a1b.2a.2	3C.2a1b.2a.2	3C.3a.1
	Ferret number												
	Genetic group												
REFERENCE VIRUSES													
A/Denmark/3264/2019		3C.2a1b.1a	2019-10-25	SIAT3/SIAT5	320	320	640	320	320	160	40	ND	320	160
A/Hong Kong/2671/2019		3C.2a1b.1b	2019-06-17	MDCK1/SIAT5	320	320	640	160	320	160	40	<	320	160
A/Cambodia/925256/2020		3C.2a1b.2a.1	2020-09-25	SIAT5	160	160	1280	320	320	160	80	ND	640	160
A/Cambodia/e0826360/2020		3C.2a1b.2a.1	2020-07-16	E5/E2	80	<	80	1280	160	160	320	80	320	80
A/Bangladesh/4005/2020	H156	3C.2a1b.2a.2	2020-10-04	SIAT3	160	40	160	160	640	640	640	320	640	160
A/Stockholm/5/2021	H156S	3C.2a1b.2a.2	2021-04-16	SIAT0/SIAT3	80	<	80	160	320	640	320	160	640	40
A/England/214191723/2021	H156S	3C.2a1b.2a.2	2021-10-12	MDCK1/SIAT3	80	<	80	80	320	640	640	160	640	<
A/Thuringen/10/2022	H156, I140K	3C.2a1b.2a.2	2022-04-01	P1/SIAT2	80	<	160	160	320	640	640	320	320	<
A/Darwin/9/2021	H156S	3C.2a1b.2a.2	2021-04-17	E3/E2	160	<	80	640	320	640	640	320	1280	80
A/Kansas/14/2017		3C.3a.1	2017-12-14	SIAT3/SIAT2	40	40	160	160	80	160	80	40	320	640
TEST VIRUSES														
A/Poland/52/2022	D104G	3C.2a1b.2a.2	2022-03-30	SIAT2	80	<	40	80	320	640	320	80	640	<
A/Poland/58/2022	D104G	3C.2a1b.2a.2	2022-04-07	SIAT1	80	<	40	80	160	640	320	80	640	<
A/Poland/65/2022	D104G	3C.2a1b.2a.2	2022-04-14	SIAT1	80	<	80	80	320	640	640	160	640	<
A/Norway/28394/2022	D104G	3C.2a1b.2a.2	2022-07-20	SIAT2	80	<	40	80	320	640	640	80	640	<
A/Norway/28359/2022	D104G	3C.2a1b.2a.2	2022-07-24	SIAT3	80	<	80	80	320	640	640	160	640	40
A/Norway/29040/2022	D104G	3C.2a1b.2a.2	2022-07-27	SIAT2	80	<	160	160	320	640	640	160	1280	40
A/Belgium/G0096/2022	H156S	3C.2a1b.2a.2	2022-03-07	SIAT1/SIAT1	40	<	80	80	160	320	640	160	320	<
A/Belgium/S0822/2022	H156S	3C.2a1b.2a.2	2022-03-18	SIAT1/SIAT1	40	<	80	160	160	320	640	160	320	40
A/Belgium/S0826/2022	H156S	3C.2a1b.2a.2	2022-03-19	SIAT1/SIAT1	80	<	80	160	320	320	640	160	640	40
A/Belgium/G0153/2022	H156S	3C.2a1b.2a.2	2022-03-23	SIAT1/SIAT1	40	<	80	160	320	320	640	160	640	40
A/Norway/27853/2022		pending	2022-07-18	SIAT2	80	<	160	320	320	640	640	160	640	40
							Vaccine NH 2021-22						Vaccine SH 2022 NH 2022-23 SH 2023	

*Superscripts refer to antiserum properties (< relates to the lowest dilution of antiserum used)
1 < = <40, ND = Not Done

Influenza B virus analyses

Influenza B/Victoria-lineage

All recently circulating B/Victoria-lineage viruses have fallen in genetic clade **V1A**, represented by **B/Brisbane/60/2008**, a former vaccine virus, but with additional **HA1** amino acid substitutions of **I117V** and **N129D** (e.g., **B/Ireland/3154/2016**). Viruses retaining full-length HAs remained antigenically similar to B/Brisbane/60/2008. However, three genetic groups (described below with amino acid substitutions/deletions relative to B/Brisbane/60/2008 indicated) containing deletions of HA gene codons emerged. Viruses in these groups were/are antigenically distinct from B/Brisbane/60/2008 and each other (as noted in the September 2018 characterisation report[4] and earlier ones), such that four antigenically distinguishable groups had been circulating:

- A group with double deletion of **HA1** residues **162** and **163** (subclade **V1A.1**) with amino acid substitutions of **D129G** and **I180V**, and **HA2 R151K** that spread worldwide and is represented by a previous vaccine virus, **B/Colorado/06/2017**. No detections of viruses in this group have been reported recently.
- A group with triple deletion of **HA1** residues **162** to **164** (subclade **V1A.2**) first detected in Asia, with amino acid substitutions of **I180T** and **K209N** that showed limited geographic spread, represented by **B/Hong Kong/269/2017**. No detections of viruses in this group have been reported recently.
- A group with triple deletion of **HA1** residues **162** to **164** (subclade **V1A.3**) first detected in Africa, with amino acid substitution **K136E** often with **G133R** that showed geographic spread and became dominant, represented by **B/Washington/02/2019** the vaccine virus first recommended for use in the 2020 southern hemisphere season and thereafter up to the 2021-2022 northern hemisphere season.

The phylogeny generated for the July report, was based on sequences from viruses with collection dates after 31 March 2022 that were submitted to GISAID after March 2022 (Figure 4a). All viruses were **V1A.3** subclade represented by **B/Washington/02/2019**. Overall, the great majority of viruses fell in the **V1A.3a** group characterised by **HA1 N150K**, **G184E**, **N197D** (resulting in loss of a glycosylation site) and **R279K**, with this group splitting into two subgroups designated **V1A.3a.1** (characterised by **HA1 V220M** and **P241Q** substitutions, detected in China) and **V1A.3a.2** (characterised by **HA1 A127T**, **P144L** and **K203R**, often with additional substitutions, which has spread worldwide and is represented by the **B/Austria/1359417/2021** vaccine virus). Sequences submitted by the Netherlands split between the **V1A.3a.2** subgroup and subclade **V1A.3**, with the latter viruses being similar to those from Kenya having **HA1 K75E**, **E128K**, **T155A** and **G230N** substitutions, but with an additional **HA1 G184R** substitution sometimes with **D129N** (Figure 4a).

The phylogeny generated for this September report contains HA sequences from viruses with collection dates after 28 February 2022 that were submitted to GISAID after July 2022 (Figure 4b). Of the sequences released for **V1A.3a** viruses, only two from China fall in the **V1A.3a.1** subgroup, all others were from **V1A.3a.2** subgroup viruses that show wide geographic spread with emergence of virus clusters defined by specific **HA1** amino acid substitutions in some countries, e.g., **H122Q** in China, **K56N** in Timore-Leste and **Q200P** in Brazil. Sequences for viruses in subclade V1A.3 (B/Washington/02/2019-like) available since the July report were detected in Germany (n =1), China (n = 1), Netherlands (n = 8) and Spain (n = 1). Of note the virus from Spain, with a collection date in August 2022, clustered with those from the Netherlands and carried the **HA1 G184R** amino acid substitution; this is the first report of such a virus outside of the Netherlands.

The WHO Collaborating Centres for Influenza Research and Response have shown the **V.1A.3a** group viruses with additional HA1 substitutions to be antigenically distinct from one another. While relatively few B/Victoria-lineage viruses have been available for detailed antigenic characterisation, those characterised earlier in the 2021-2022 season were subgroup **V1A.3a.2** viruses which were recognised poorly by post-infection ferret antiserum raised against **B/Washington/02/2019**, the 2021-2022 northern hemisphere vaccine virus [1]. However, the **V1A.3a.2** viruses were recognised well (with HI titres of at least 160 with the antiserum raised against the egg-propagated variant with **HA1 G141R** substitution) by antisera raised against **B/Austria/1359417/2021**, the recommended vaccine virus for southern hemisphere 2022 and 2023, and northern hemisphere 2022-2023 influenza seasons [2, 4, 3]. This was observed for the 12 subgroup **V1A.3a.2** viruses characterised antigenically since the July report (Tables 6-1 to 6-3). All test viruses were recognised well, within twofold of the homologous titres, by post-infection ferret antisera raised against cell culture-propagated and egg-propagated **B/Austria/1359417/2021** viruses carrying **HA1 G141**. In contrast the **B/Austria/1359417/2021** vaccine virus, which has an 'egg-adaptation' **HA1 G141R** amino acid substitution, induced a high homologous titre (5120) antiserum and all test viruses showed a drop in recognition of at least eightfold compared to the homologous titre, but all test viruses reacted with a titre of at least 160, well above the threshold of 40 that has been determined as the cut-off for a protective effect. All

[4] European Centre for Disease Prevention and Control. Influenza virus characterisation, summary Europe, September 2018. Stockholm: ECDC; 2018. Available from: https://ecdc.europa.eu/sites/portal/files/documents/ECDC-Flu-Characterisation-Report-Sep-2018.pdf

three cell culture-propagated subclade **V1A.3** viruses from the Netherlands, all of which contained a **HA1 G184R** amino acid substitution, were poorly recognised by the hyperimmune sheep serum raised against B/Brisbane/60/2008 and all the post-infection ferret antisera except for that raised against cell culture-propagated B/Netherlands/11267/2022 (Table 6-1). Conversely, the three egg-propagated **V1A.3** viruses from the Netherlands were well recognised by the sheep hyperimmune serum, less efficiently by the post-infection ferret antiserum raised against cell culture-propagated B/Netherlands/11267/2022 and somewhat better by ferret antisera raised against B/Colorado/06/2017 (**V1A.1**) and B/Washington/02/2019 (**V1A.3**) (Table 6-3). The latter is related to loss of a **HA1** glycosylation sequon at positions **194-196** (**V1A.3** numbering) or **197-199** (**V1A** numbering) on adaptation to replication in hens' eggs.

Influenza B/Yamagata-lineage

It is assumed that no B/Yamagata-lineage viruses have been detected after March 2020 as no sequences for such viruses with collection dates after this had been released is GISAID as of 28 September 2022. Figure 5 is repeated from the September 2021 report. All sequences fell in genetic clade **Y3**, the B/Wisconsin/1/2010–B/Phuket/3073/2013 clade, within a subgroup defined by **HA1 L172Q** and **M251V** amino acid substitutions compared to B/Phuket/3073/2013 which was recommended for inclusion in quadrivalent vaccines for the 2021-2022 and 2022-2023 northern and, 2022 and 2023 southern hemisphere seasons [1, 3, 2, 4]. Some sub-clustering of sequences, defined by specific amino acid substitutions (e.g., **HA1 N164K, K211R, D229N** or **D232N** [introducing a potential N-linked glycosylation site] sometimes with **R48K**), had occurred. As noted in previous characterisation reports, none of these amino acid substitutions have any obvious antigenic effects based on HI assays using post-infection ferret antisera raised against egg-propagated B/Phuket/3073/2013. Of the four samples shared with WIC by the United Kingdom (Scotland: Table 3) only one yielded good sequence which showed it to be associated with Live Attenuated Influenza Vaccine (LAIV).

A concerted effort by all NICs of GISRS is required to identify B/Yamagata-lineage viruses for detailed characterisation to determine if there are any in circulation that are not LAIV-related.

Figure 4a. Phylogenetic comparison of B/Victoria-lineage HA genes (GISAID/WIC, July 2022)

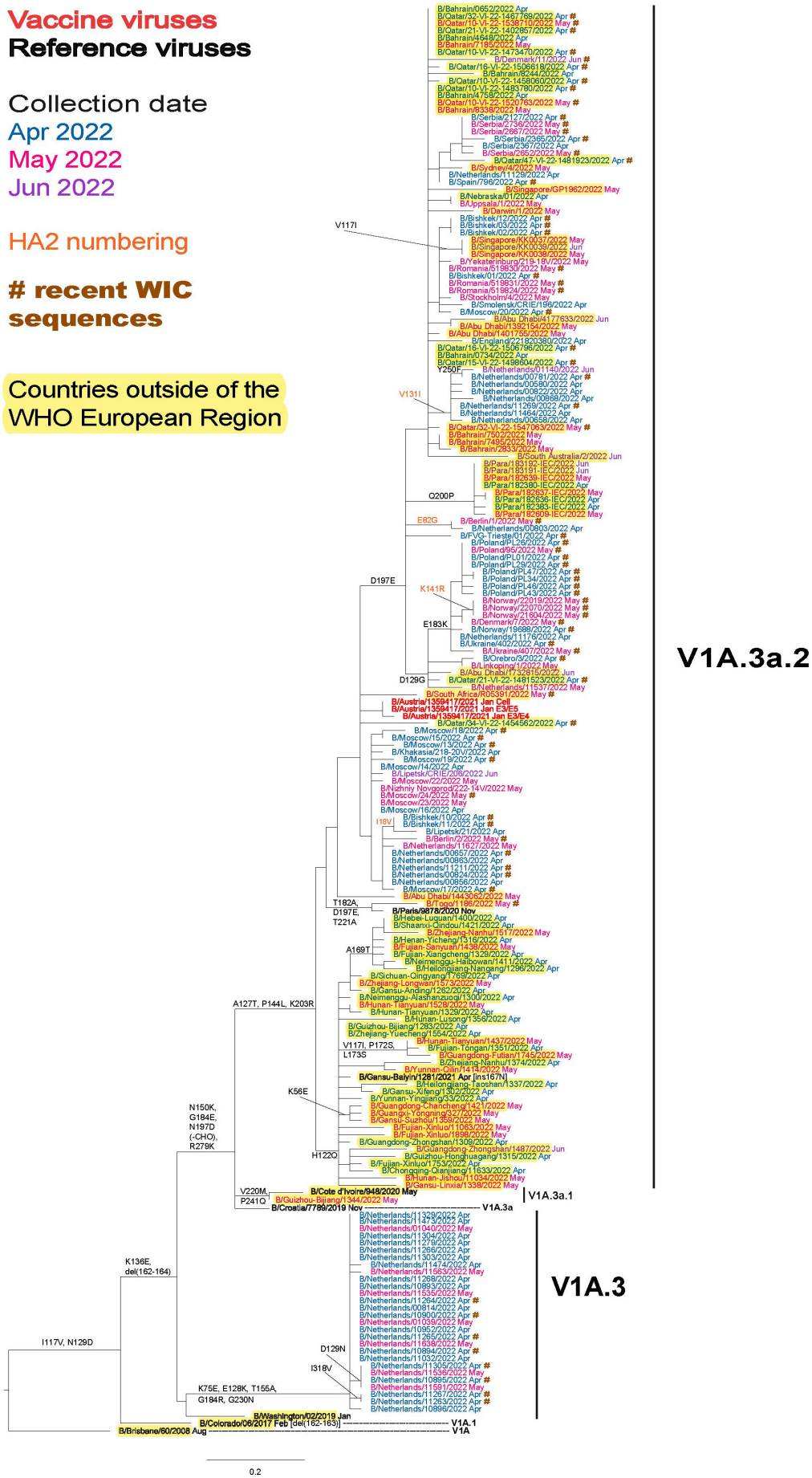


Figure 4b. Phylogenetic comparison of B/Victoria-lineage HA genes (GISAID/WIC, Sept 2022)

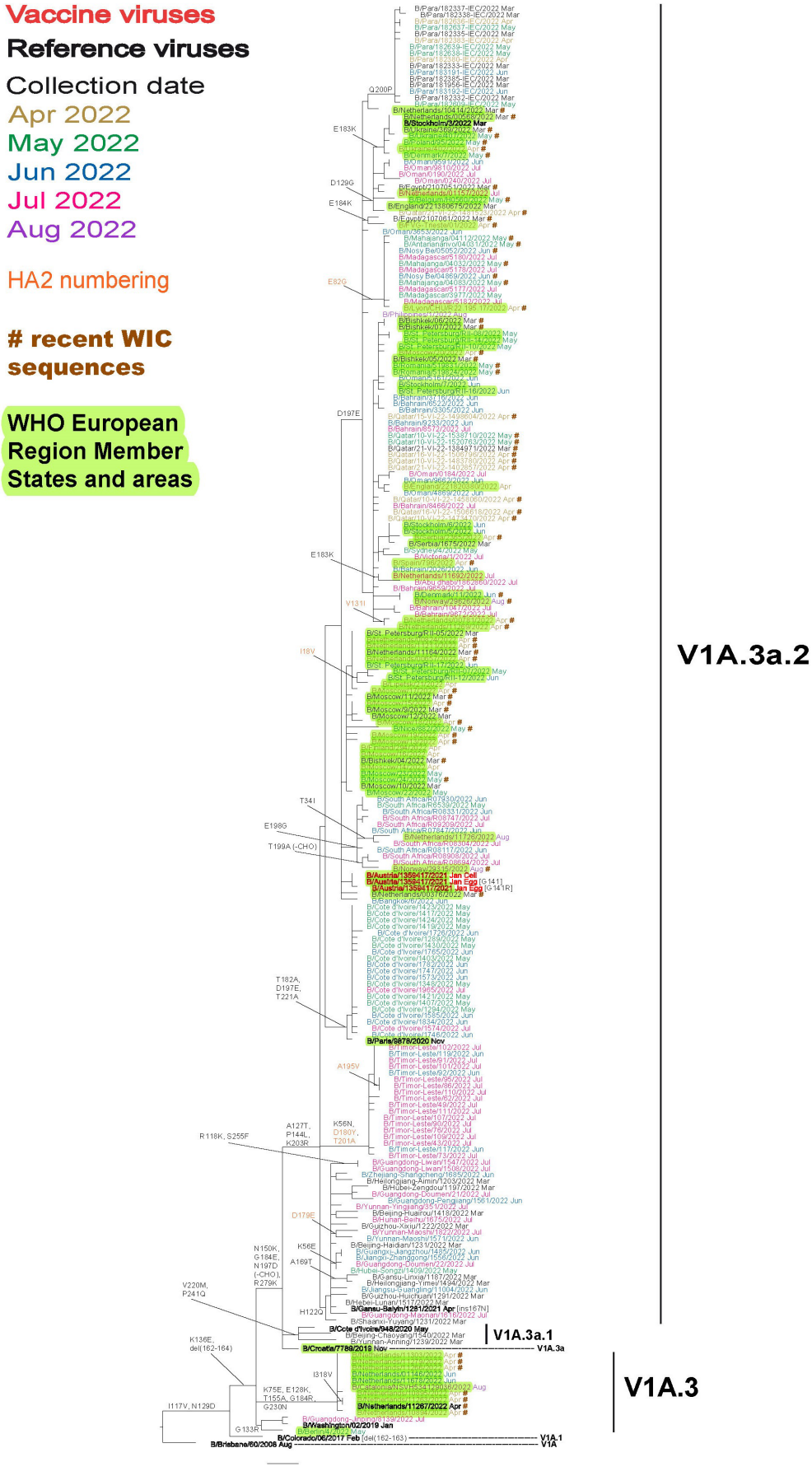


Table 6-1. Antigenic analysis of influenza B/Victoria-lineage viruses by HI

Viruses	Other information	Collection date	Passage history	Haemagglutination inhibition titre											
				Post-infection ferret antiserum											NEW
							NEW								
	Passage history			B/Bris 60/08 Egg	B/Colorado 06/17 Egg	B/Wash'ton 02/19 Egg	B/Neth 11267/22 MDCK	B/CIV 948/20 MDCK	B/Paris 9878/20 MDCK	B/G-Baiyin 1281/21 MDCK	B/Austria 1359417/21 MDCK	B/Austria 1359417/21 Egg G141	B/Austria 1359417/21 Egg G141R	B/Austria 1359417/21 Egg G141R
	Ferret number			Sh 539, 540, 543, 544, 570, 571, 574[1,3]	F11/18[*2]	F20/20[*2]	F29/22[*1]	F08/21[*5]	F12/21[*1]	F08/22[*1]	NIB F01/21[*1]	F15/21[*1]	F44/21[*1]	F30/22[*1]
	Genetic group			V1A	V1A.1	V1A.3	V1A.3	V1A.3a.1	V1A.3a.2	V1A.3a.2	V1A.3a.2	V1A.3a.2	V1A.3a.2	V1A.3a.2
REFERENCE VIRUSES														
B/Brisbane/60/2008	V1A	2008-08-04	E4/E4	2560	160	40	<	<	<	<	<	<	<	<
B/Colorado/06/2017	V1A.1	2017-02-05	E5/E2	1280	640	80	<	<	<	<	<	<	<	<
B/Washington/02/2019	V1A.3	2019-01-19	E3/E3	640	160	160	<	<	<	<	<	<	<	<
B/Netherlands/11267/2022	V1A.3	2022-04-14	MDCK-MIX/MDCK1	40	10	<	320	<	<	<	<	<	<	<
B/Cote d'Ivoire/948/2020	V1A.3a.1	2020-05-28	MDCK4	320	40	40	40	640	40	40	160	80	80	40
B/Paris/9878/2020	V1A.3a.2	2020-11-20	MDCK2	640	80	10	<	160	640	160	1280	1280	320	160
B/Gansu-Baiyin/1281/2021	V1A.3a.2	2021-04-13	C1/C1/MDCK2	640	40	<	40	160	640	320	1280	1280	320	320
B/Austria/1359417/2021	V1A.3a.2	2021-01-09	SIAT1/MDCK4	640	80	10	<	160	640	320	1280	1280	320	320
B/Austria/1359417/2021 Isolate 2	G141 V1A.3a.2	2021-01-09	E3/E5	640	40	10	40	320	640	320	2560	1280	640	640
B/Austria/1359417/2021 Isolate 2	G141R V1A.3a.2	2021-01-09	E3/E5	320	40	<	40	320	320	320	1280	1280	2560	>5120
TEST VIRUSES														
B/Netherlands/11266/2022	G184R V1A.3	2022-04-13	MDCK1	40	10	<	160	<	<	<	<	<	<	<
B/Netherlands/11303/2022	G184R V1A.3	2022-04-19	MDCK1	80	10	<	320	<	<	<	<	<	<	<
B/Netherlands/11279/2022	G184R V1A.3	2022-04-26	MDCK1	80	10	10	160	<	<	<	<	<	<	<
B/Lyon/CHU/R22.195.17/2022	V1A.3a.2	2022-04-09	MDCKx/MDCK1	1280	80	20	40	160	640	320	1280	1280	640	320
B/Ukraine/402/2022	V1A.3a.2	2022-04-18	MDCK1	1280	80	10	40	160	640	320	1280	1280	640	320
B/Belgium/H0560/2022	V1A.3a.2	2022-05-04	MDCK1/MDCK1	640	40	<	40	160	320	160	1280	1280	320	160
B/Nice/882/2022	V1A.3a.2	2022-05-05	MDCKx/MDCK1	640	80	10	40	160	320	320	1280	1280	320	320
B/Ukraine/407/2022	V1A.3a.2	2022-05-30	MDCK1	1280	160	10	40	160	640	320	1280	1280	640	320

Vaccine
SH 2020
NH 2020-21
SH 2021
NH 2021-22
NH 2022-23
SH 2023

*Superscripts refer to antiserum properties (< relates to the lowest dilution of antiserum used):
[1] < = <40; [2] < = <10; [3] hyperimmune sheep serum; [4] < = <20; [5] < = <80; ND = Not Done

Table 6-2. Antigenic analysis of influenza B/Victoria-lineage viruses by HI

Viruses	Other information	Collection date	Passage history	Haemagglutination inhibition titre										
				Post-infection ferret antiserum										
				B/Bris 60/08	B/Colorado 06/17	B/Wash'ton 02/19	B/Neth 11267/22	B/CIV 948/20	B/Paris 9878/20	B/G-Baiyin 1281/21	B/Austria 1359417/21	B/Austria 1359417/21	B/Austria 1359417/21
	Passage history			Egg	Egg	Egg	MDCK	MDCK	MDCK	MDCK	MDCK	Egg G141	Egg G141R
	Ferret number			Sh 539, 540, 543, 544, 570, 571, 574[*1,3]	F11/18[*2]	F20/20[*2]	F29/22[*1]	F08/21[*5]	F12/21[*1]	F08/22[*1]	NIB F01/21[*1]	F15/21[*1]	F44/21[*1]
	Genetic group			V1A	V1A.1	V1A.3	V1A.3	V1A.3a.1	V1A.3a.2	V1A.3a.2	V1A.3a.2	V1A.3a.2	V1A.3a.2
REFERENCE VIRUSES													
B/Brisbane/60/2008	V1A	2008-08-04	E4/E4	1280	160	40	<	<	<	<	<	<	<
B/Colorado/06/2017	V1A.1	2017-02-05	E5/E2	1280	640	80	<	<	<	<	<	<	<
B/Washington/02/2019	V1A.3	2019-01-19	E3/E3	640	160	160	<	<	<	<	<	<	<
B/Netherlands/11267/2022	V1A.3	2022-04-14	MDCK-MIX/MDCK1	40	10	<	320	<	<	<	<	<	<
B/Cote d'Ivoire/948/2020	V1A.3a.1	2020-05-28	MDCK4	320	40	40	40	640	40	40	160	80	80
B/Paris/9878/2020	V1A.3a.2	2020-11-20	MDCK2	640	80	10	<	160	640	160	1280	1280	320
B/Gansu-Baiyin/1281/2021	V1A.3a.2	2021-04-13	C1/C1/MDCK2	640	40	<	40	160	640	640	1280	1280	320
B/Austria/1359417/2021	V1A.3a.2	2021-01-09	SIAT1/MDCK4	640	80	10	<	160	640	320	2560	1280	320
B/Austria/1359417/2021 Isolate 2	G141 V1A.3a.2	2021-01-09	E3/E5	640	40	10	40	320	640	320	2560	2560	640
B/Austria/1359417/2021 Isolate 2	G141R V1A.3a.2	2021-01-09	E3/E5	320	40	<	40	320	320	320	1280	1280	2560
TEST VIRUSES													
B/Moscow/RII-01/2022	V1A.3a.2	2022-04-28	MDCK3/MDCK1	1280	80	10	80	320	640	640	2560	2560	640
B/S. Petersburg/RII-09/2022	V1A.3a.2	2022-05-13	MDCK1/MDCK1	1280	80	20	80	320	640	640	2560	2560	640
B/S. Petersburg/RII-11/2022	V1A.3a.2	2022-05-25	MDCK1/MDCK1	1280	80	10	40	320	640	320	2560	2560	320
B/S. Petersburg/RII-15/2022	V1A.3a.2	2022-05-26	MDCK1/MDCK1	1280	160	20	80	320	640	640	1280	2560	640
B/S. Petersburg/RII-13/2022	V1A.3a.2	2022-06-06	MDCK1/MDCK1	1280	80	20	80	160	640	320	1280	1280	320

Vaccine
SH 2020
NH 2020-21
SH 2021
NH 2021-22

Vaccine
SH 2022
NH 2022-23
SH 2023

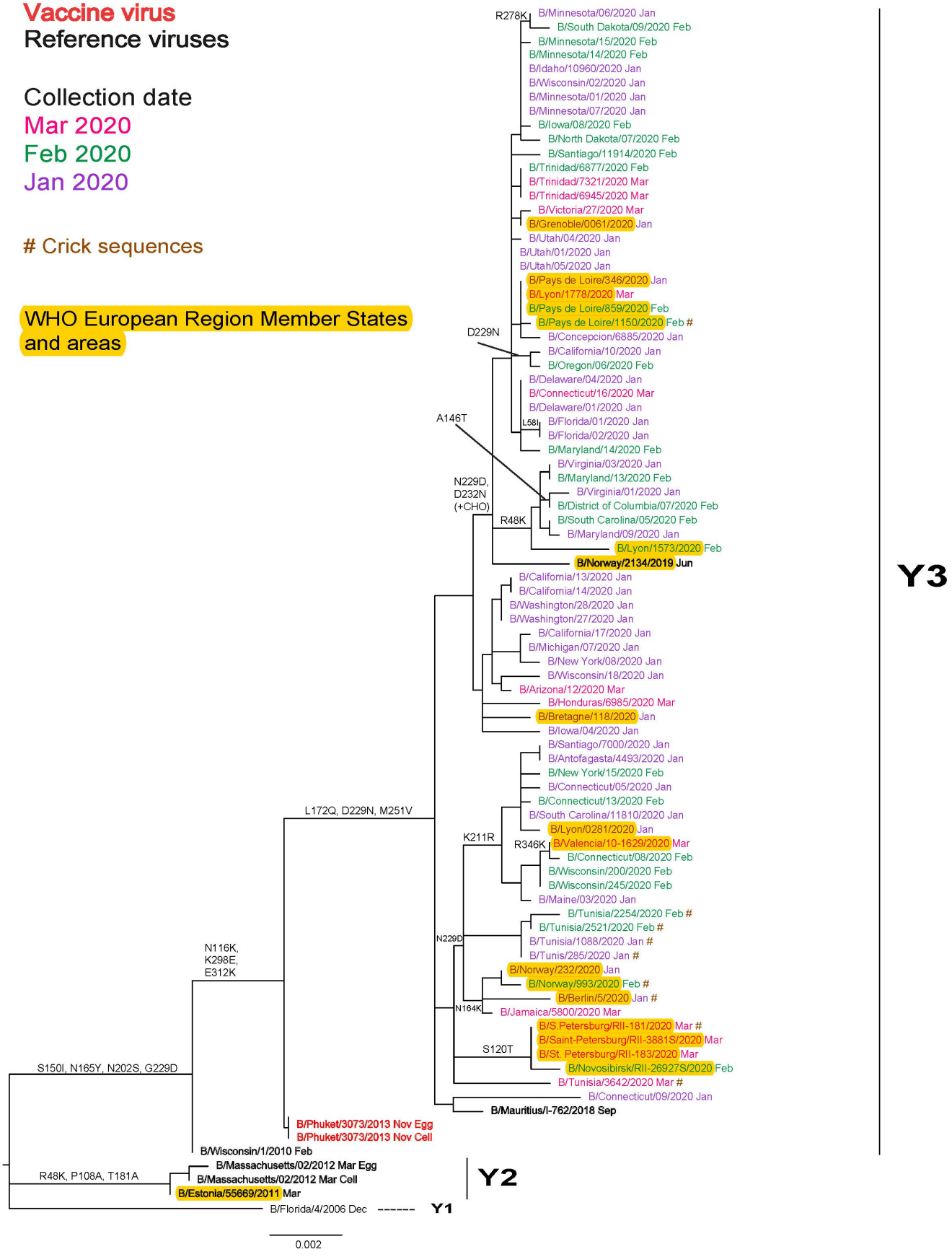
*Superscripts refer to antiserum properties (< relates to the lowest dilution of antiserum used):
[1] < = <40; [2] < = <10; [3] hyperimmune sheep serum; [4] < = <20; [5] < = <80; ND = Not Done

Table 6-3. Antigenic analysis of influenza B/Victoria-lineage viruses by HI

Viruses	Other information	Collection date	Passage history	Haemagglutination inhibition titre: Post-infection ferret antiserum											
				NEW											
	Passage history			B/Bris/60/08 Egg	B/Colorado/06/17 Egg	B/Wash'ton/02/19 Egg	B/Neth/11267/22 MDCK	B/CIV/948/20 MDCK	B/Paris/9878/20 MDCK	B/G-Baiyin/1281/21 MDCK	B/Austria/1359417/21 MDCK	B/Austria/1359417/21 Egg G141	B/Austria/1359417/21 Egg G141R
				Sh 539, 540, 543, 544, 570, 571, 574[1,3]	F44/18[*2]	F20/20[*2]	F29/22[*1]	F08/21[*5]	F12/21[*1]	F08/22[*1]	NIB F01/21[*1]	F15/21[*1]	F44/21[*1]
	Ferret number			V1A	V1A.1	V1A.3	V1A.3	V1A.3a.1	V1A.3a.2	V1A.3a.2	V1A.3a.2	V1A.3a.2	V1A.3a.2
	Genetic group												
REFERENCE VIRUSES													
B/Brisbane/60/2008	V1A	2008-08-04	E4/E4	1280	160	40	<	<	<	<	<	<	<
B/Colorado/06/2017	V1A.1	2017-02-05	E5/E2	1280	640	40	<	<	<	<	<	<	<
B/Washington/02/2019	V1A.3	2019-01-19	E3/E3	1280	160	80	40	<	<	<	<	<	<
B/Netherlands/11267/2022	V1A.3	2022-04-14	MDCK-MIX/MDCK1	40	10	<	320	<	<	<	<	<	<
B/Cote d'Ivoire/948/2020	V1A.3a.1	2020-05-28	MDCK4	320	40	40	40	640	80	40	160	160	80
B/Paris/9878/2020	V1A.3a.2	2020-11-20	MDCK2	640	80	10	40	160	640	320	1280	1280	320
B/Gansu-Baiyin/1281/2021	V1A.3a.2	2021-04-13	C1/C1/MDCK2	640	40	<	<	160	320	320	1280	1280	320
B/Austria/1359417/2021	V1A.3a.2	2021-01-09	SIAT1/MDCK4	640	40	<	40	160	320	320	1280	1280	320
B/Austria/1359417/2021 Isolate 2	G141 V1A.3a.2	2021-01-09	E3/E5	640	20	<	40	160	320	320	2560	1280	320
B/Austria/1359417/2021 Isolate 2	G141R V1A.3a.2	2021-01-09	E3/E5	320	20	<	40	320	320	320	1280	1280	2560
TEST VIRUSES													
B/Netherlands/10894/2022	G184R, T196(199)A (-cho) V1A.3	2022-04-02	E3(Am1AL2)	640	40	20	40	<	<	<	<	<	<
B/Netherlands/11264/2022	G184R, N194(197)S (-cho) V1A.3	2022-04-13	E4(Am1AL3)	640	160	80	80	<	<	<	<	<	<
B/Netherlands/11264/2022	G184R, N194(197)S (-cho) V1A.3	2022-04-13	E4(Am2AL2)	1280	160	40	80	<	<	<	<	<	<
B/S. Petersburg/RII-04/2022	V1A.3a.2	2022-03-10	MDCK3/MDCK1	640	40	<	40	160	320	320	1280	1280	320
B/S. Petersburg/RII-06/2022	V1A.3a.2	2022-04-27	MDCK3/MDCK1	640	40	<	40	160	320	320	1280	1280	320
						Vaccine SH 2020 NH 2020-21 SH 2021 NH 2021-22						Vaccine SH 2022 NH 2022-23 SH 2023	

*Superscripts refer to antiserum properties (< relates to the lowest dilution of antiserum used):
[1] < = <40; [2] < = <10; [3] hyperimmune sheep serum; [4] < = <20; [5] < = <80; ND = Not Done

Figure 5. Phylogenetic comparison of B/Yamagata-lineage HA genes (GISAID, September 2021)



Summaries of data submitted to TESSy

Genetic characterisation

5 355 viruses detected over the course of the 2021-2022 season (weeks 40/2021-39/2022) were genetically characterised:

- Of 429 A(H1N1)pdm09 viruses, 373 belonged to clade 6B.1A.5a.1 (represented by A/Guangdong-Maonan/SWL1536/2019) and 56 belonged to clade 6B.1A.5a.2 (represented by A/Victoria/2570/2019).
- Of 4 818 A(H3N2) viruses, 4 766 belonged to the 'Bangladesh-like' clade (3C.2a1b.2a.2) represented by A/Bangladesh/4005/2020, three to the 'Cambodia-like' clade (3C.2a1b.2a.1) and 21 were attributed to clade 3C.2a1b.1a (represented by A/Denmark/3264/2019). Twenty-eight were not attributed to a listed subgroup.
- Of 108 influenza B viruses, 101 were ascribed to the B/Victoria-lineage: 65 were B/Austria/1359417/2021-like (V1A.3a.2), 33 were B/Washington/02/2019-like (V1A.3) and three were not attributed to a listed subgroup. Of the seven B/Yamagata-lineage viruses, four were B/Phuket/3073/2013-like (Y3) and three were not ascribed to a clade. *Note: of the B/Yamagata-lineage specimens shared with WIC, all were from children and those that yielded gene sequence were derived from Live Attenuated Influenza Vaccine (LAIV)*.

Antiviral susceptibility

Up to week 20/2022, 2 547 viruses were assessed for susceptibility to neuraminidase inhibitors (NAIs): 1 715 A(H3), 258 A(H1)pdm09 and 54 B virus were assessed genotypically, and 476 A(H3), 31 A(H1)pdm09 and 13 B viruses were assessed phenotypically. Susceptibility to the PA inhibitor baloxavir marboxil was assessed genotypically for 1 792 viruses: 1 528 A(H3), 227 A(H1)pdm09 and 37 B viruses. For weeks 21-30/2022, 18 viruses were assessed for susceptibility to NAIs and baloxavir marboxil. For weeks 35-39/2022 a further14 viruses were assessed for susceptibility to NAIs and baloxavir marboxil. Phenotypically no viruses with reduced susceptibility were identified. Genotypically, two A(H3) viruses showed PA amino acid substitutions potentially associated with reduced susceptibility to baloxavir marboxil and one A(H1)pdm09 virus with potential highly reduced inhibition by oseltamivir was identified.

At the WIC, 1 194 influenza viruses detected within the WHO European Region during the 2021-2022 season have been assessed phenotypically against oseltamivir and zanamivir: 186 A(H1)pdm09, 915 A(H3) and 93 B/Victoria-lineage. All viruses showed normal inhibition (NI) by both NAIs and PA gene sequences from three A(H3) viruses had markers (amino acid substitutions) associated with reduced susceptibility to baloxavir marboxil, E23G (n = 1) and L28P (n = 2) respectively.

Animal influenza and zoonotic events

Influenza A(H7N9) virus

On 1 April 2013, the WHO Global Alert and Response System [5] reported that the China Health and Family Planning Commission had notified WHO of three cases of human infection with influenza A(H7N9). Increased numbers of cases were reported over the course of the following seasons, and cases were reported in 2017, including the fifth (2016-17) and largest wave to date, which included the emergence of highly pathogenic avian influenza (HPAI) strains that have caused some zoonoses, although few human cases were reported during the 2017-18 season [6]. Current risk assessments for influenza at the human-animal interface can be found on WHO's website https://www.who.int/teams/global-influenza-programme/avian-influenza/monthly-risk-assessment-summary (accessed 06 October 2022). The assessment published on 27 June 2022 indicated that there had been no publicly available reports from animal health authorities in China or other countries on influenza A(H7N9) virus detections in animals in recent months [7]. On 01 June 2022 the Food and Agricultural Organization of the United Nations announced that it was discontinuing monthly H7N9 updates as there had been no notifications of avian infections since October 2020. The most recent human case was detected in mid-March 2019 [8]. The latest overview of avian influenza by ECDC in collaboration with the European Food Safety Authority and the EU Reference Laboratory for Avian Influenza was approved on 28 September 2022 and can be found on ECDC's website [9].

Influenza A(H5) virus

The most recent monthly risk assessment of influenza at the human-animal interface was published by WHO on 30 August 2022. Since the previous risk assessment on 27 June 2022, one human case of infection with an A(H5N6) avian influenza virus was reported by China [7]. The case was in a 6-year-old female with no underlying medical conditions who had disease onset on 30 July 2022, was hospitalised with severe pneumonia and passed away on 24 April. The second case was in a 58-year-old male who had disease onset on 02 June 2022, was hospitalised with severe pneumonia and was still in a severe condition at the time of reporting. The patient was exposed to poultry at a live poultry market and no family members had developed disease symptoms at the time of reporting. The most recent confirmed case of human infection with an A(H5N1) virus was reported by England and a full report into the investigation of this case has been published [10].

The latest collaborative report from ECDC and the European Food Safety Authority (EFSA), reported 788 highly pathogenic avian influenza (HPAI) A(H5) detections between 11 June and 09 September 2022, 56 in poultry, 710 in wild birds and 22 in captive birds [9]. Detections occurred in 16 European countries and high mortality was observed in colony-breeding seabird species along the northwest coast of Europe involving HPAI A(H5N1). Overall, the HPAI epidemic season in 2021-2022 is the largest so far observed in Europe with 2 467 outbreaks in poultry and 47.7 million birds culled, 187 outbreaks in captive birds, and 3 573 detections in wild birds. Genetic analyses indicated that the circulating viruses belonged to clade 2.3.4.4b. Such viruses have been circulating in Europe since October 2020 and now exist as seven genotypes, three of which were identified over the summer period. The risk of human infection was assessed as low for the general population in EU/EEA countries, and low to medium for occupationally exposed persons. According to reports compiled by the Food and Agricultural Organization of the United Nations (FAO) as of 28 September 2022, various highly pathogenic avian influenza (HPAI) subtypes continued to be detected in wild and/or domestic birds in Africa, Americas, Asia and Europe, and since 24 August 2022 a total of 1 729 HPAI outbreaks (19 H5Nx, 1 706 H5N1, two H5N2, one H5N8 and one HPAI not confirmed as H5) and no low pathogenic avian influenza (LPAI) outbreaks had been reported [11].

HPAI A(H5) viruses have also been detected in wild mammal species in Europe and North America, with some viruses showing genetic markers of adaptation to replication in mammals.

Influenza A(H9N2) virus

Since the previous WHO risk assessment on 27 June 2022, China reported one case of H9N2 infection in a six-month old male with onset of symptoms on 01 August. He had mild disease, was hospitalized, and made a full recovery [7]. Poultry exposure was reported, environmental samples from the poultry market were A(H9)-positive and no family members had developed symptoms at the time of reporting. Public Health England has published an updated risk assessment for avian influenza A(H9N2) [12]. Avian influenza A(H9N2) viruses are enzootic in poultry in Asia and increasingly reported in poultry in Africa.

Other influenza zoonotic events

Since the previous WHO update on 27 June 2022 the United States of America (USA) reported zoonoses involving swine influenza variant viruses [7]. Two cases of A(H1N2)v infection were reported in patients under 18 years of age, one in Oregon and the other in Ohio. Both patients recovered, one reported potential swine exposure at an agricultural fair, and in neither case was transmission to close human contacts suspected.

Three cases of A(H3N2)v infection resulting from attendance of an agricultural fair in West Virginia were reported. None of the patients were hospitalized and all made a full recovery. While human-to-human transmission at the fair cannot be ruled out, no sustained human-to-human transmission was identified.

Gene sequencing showed the zoonotic viruses to be closely related to viruses known to be circulating in pigs in the USA.

WHO Collaborating Centre reports

A description of results generated by the London WHO Collaborating Centre at the WIC and used at the September 2022 WHO VCM (19-22 September 2022 for seasonal influenza viruses), and previous ones, can be found at https://www.crick.ac.uk/partnerships/worldwide-influenza-centre/annual-and-interim-reports (accessed 07 October 2022).

Note on the figures

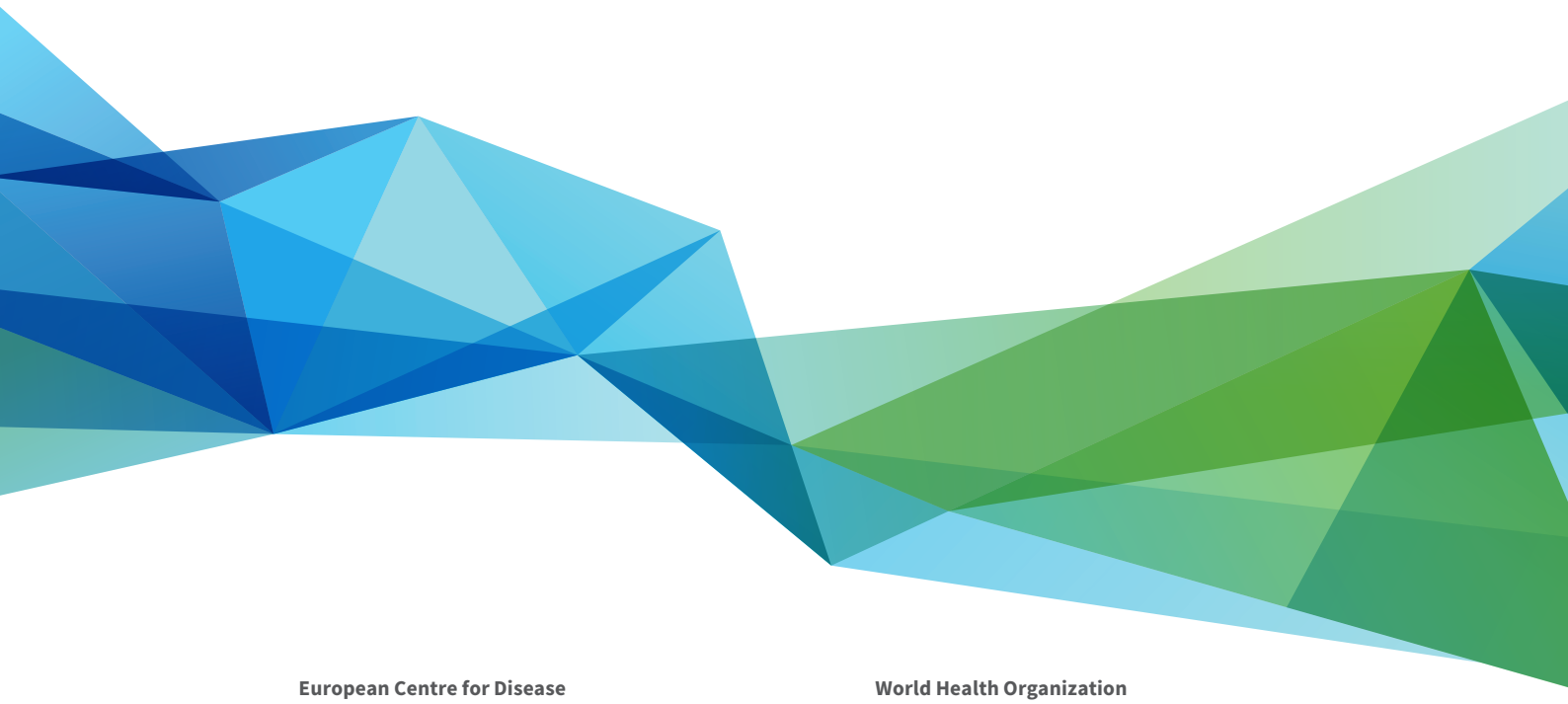
The phylogenetic trees were constructed using RAxML, drawn using FigTree, and annotated using Adobe Illustrator. The bars indicate the proportion of nucleotide changes between sequences. Reference strains are viruses to which post-infection ferret antisera have been raised. The colours indicate the month(s) of sample

collection. Sequences for many viruses from non-WHO Europe countries were recovered from the GISAID EpiFlu™ database. We gratefully acknowledge the authors, originating and submitting laboratories of the sequences from the GISAID EpiFlu™ database, which were downloaded for use in the preparation of this report (all submitters of data may be contacted directly via the GISAID website), along with all laboratories who submitted sequences directly to WHO CC London.

References[5]

1. Recommended composition of influenza virus vaccines for use in the 2021-2022 northern hemisphere influenza season. Weekly Epidemiological Record 19 March 2021, vol. 96, (11):77-88. Geneva: World Health Organization; 2021 (https://reliefweb.int/sites/reliefweb.int/files/resources/WER9611-eng-fre.pdf).
2. Recommended composition of influenza virus vaccines for use in the 2022 southern hemisphere influenza season. Weekly Epidemiological Record 22 October 2021, vol. 96(42):509-520. Geneva: World Health Organization; 2021 (https://reliefweb.int/sites/reliefweb.int/files/resources/WER9642-eng-fre.pdf).
3. Recommended composition of influenza virus vaccines for use in the 2022-2023 northern hemisphere influenza season. Weekly Epidemiological Record 25 March 2022, vol. 97(12):109-132. Geneva: World Health Organization; 2022 (https://reliefweb.int/sites/reliefweb.int/files/resources/WER9712-eng-fre.pdf).
4. Recommended composition of influenza virus vaccines for use in the 2023 southern hemisphere influenza season [website]. Geneva: World Health Organization; 2022 [Accessed 05 October 2022] (https://www.who.int/publications/m/item/recommended-composition-of-influenza-virus-vaccines-for-use-in-the-2023-southern-hemisphere-influenza-season).
5. Human infection with influenza A(H7N9) virus in China. 2013 – China, 1 April 2013 [website]. In: World Health Organization, disease outbreak news. Geneva: World Health Organization; 2013 (https://www.who.int/emergencies/disease-outbreak-news/item/2013_04_01-en).
6. Human infection with avian influenza A(H7N9) virus – China, 2017 – China, 26 October 2017 [website]. In: World Health Organization, disease outbreak news. Geneva: World Health Organization; 2017. (https://www.who.int/emergencies/disease-outbreak-news/item/26-october-2017-ah7n9-china-en).
7. World Health Organization. Influenza at the human-animal interface. Summary and assessment, from 28 June to 30 August 2022. Geneva: World Health Organization; 2022 (https://cdn.who.int/media/docs/default-source/influenza/human-animal-interface-risk-assessments/influenza_summary_ira_ha_interface_aug_2022.pdf).
8. World Health Organization. Influenza at the human–animal interface. Summary and assessment, 13 February to 9 April 2019. Geneva: World Health Organization; 2019 (https://cdn.who.int/media/docs/default-source/influenza/human-animal-interface-risk-assessments/influenza_summary_ira_ha_interface_09_04_2019.pdf).
9. European Centre for Disease Prevention and Control, European Food Safety Authority, European Union Reference Laboratory for Avian Influenza. Avian influenza overview June – September 2022. Parma and Stockholm: EFSA, ECDC; 2022 (https://www.ecdc.europa.eu/sites/default/files/documents/avian-influenza-overview-September-2022_0.pdf).
10. Oliver Isabel et al. A case of avian influenza A(H5N1) in England, January 2022. Euro Surveill. 2022;27(5):pii=2200061 (https://doi.org/10.2807/1560-7917.ES.2022.27.5.2200061).
11. Global AIV with zoonotic potential situation update, 28 September 2022. Rome: Food and Agricultural Organization of the United Nations; 2022)https://www.fao.org/animal-health/situation-updates/global-aiv-with-zoonotic-potential), accessed 06 October 2022).
12. Public Health England. Guidance, risk assessment of avian influenza A(H9N2) update, 9 August 2021. UK.gov: PHE; 2021 (https://www.gov.uk/government/publications/risk-assessment-of-avian-influenza-ah9n2/risk-assessment-of-avian-influenza-ah9n2).

[5] All references except reference 11 accessed 14 September 2022.



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