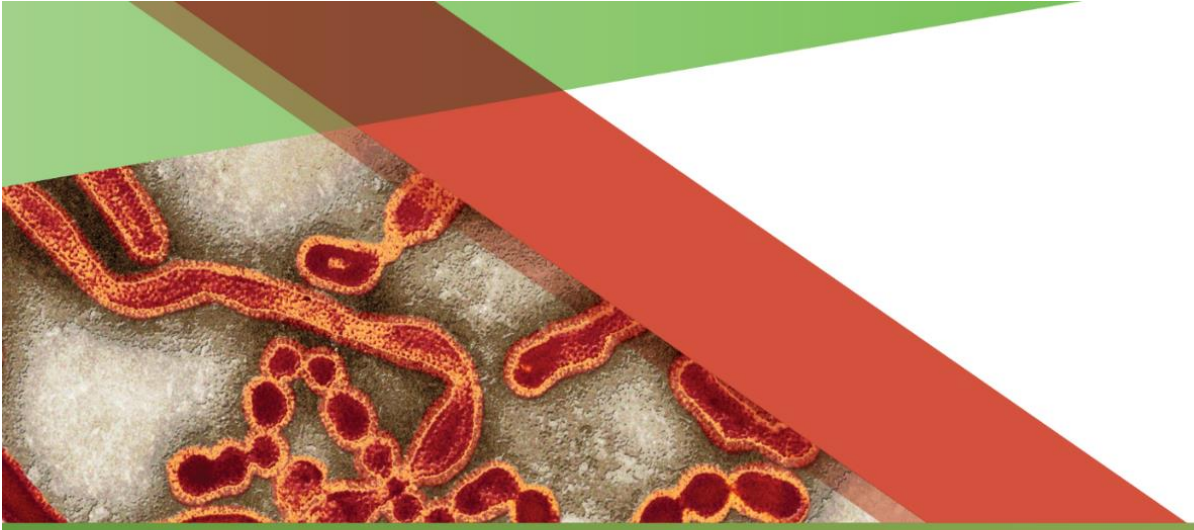

SURVEILLANCE REPORT

Influenza virus characterisation

Summary Europe, December 2021

Summary

This is the third report for the 2021-2022 influenza season. As of week 52/2021, 23 246 influenza detections across the WHO European Region were reported to TESSy, a rise of over 20 000 since week 47/2021, with most being reported from week 49/2021 onwards. Of these 23 246 detections, 96% were type A viruses, with A(H3N2) (96%) dominating over A(H1N1)pdm09 (4%), and 4% type B with only 13 having been ascribed to a lineage, one of which was B/Yamagata. This represents a large increase (22 831, 5 601%) in detections compared to the 2020-2021 season, on the back of a large increase (670 166, 438%) in the number of samples tested, and is closer to the more usual number of detections seen at this time in earlier seasons. The increased testing is probably related to the emergence of SARS-CoV-2 and measures introduced to combat it.

Since the November 2021 characterisation report[1], 12 shipments from EU/EEA countries were received at the London WHO Collaborating Centre, the Francis Crick Worldwide Influenza Centre (WIC), and the great majority of samples therein have yet to be fully characterised. This report therefore focuses on genetic characterisation of HA genes of representative seasonal influenza viruses submitted and/or released in GISAID during December 2021, with a focus on those viruses with collection dates after 31 August 2021, together with sequences recently determined at the WIC. The genetic clade nomenclature system adopted during the September 2021 vaccine composition meeting (VCM) is used throughout the document. The data show increased levels of influenza detections globally with a maintained predominance of A(H3N2) viruses.

Very low numbers of A(H1N1)pdm09 detections have been reported. Of 11 viruses with collection dates after 31 August 2021, three fell in the 6B.1A.5a.1 subgroup, represented by the vaccine virus for the northern hemisphere 2020-2021 season, A/Guangdong-Maonan/SWL1536/201960, and eight fell in the 6B.1A.5a.2 subgroup, represented by A/Victoria/2570-like and A/Wisconsin/588/2019-like viruses, which have been recommended respectively for egg- and cell-based vaccines in the 2021-2022 northern and 2022 southern hemisphere influenza seasons, but with additional HA amino acid substitutions seen previously in viruses from India. A single 6B.1A.5a.2 virus with these additional substitutions, A/Denmark/18/2021, showed a fourfold reduction in HI titre compared to the homologous titre with post-infection ferret antiserum raised against IVR-215 (A/Victoria/2570/2019) vaccine virus.

[1] European Centre for Disease Prevention and Control. Influenza virus characterisation, summary Europe, November 2021. Stockholm: ECDC; 2020. Available at: https://www.ecdc.europa.eu/sites/default/files/documents/Influenza-characterisation-report-Nov-2021.pdf

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The vast majority of recently detected A(H3N2) viruses have fallen in subgroup 3C.2a1b.2a and been 'Bangladesh-like' (3C.2a1b.2a.2), with many EU/EEA countries reporting detections. A/Cambodia/e0826360/2020-like (3C.2a1b.2a.1) viruses were recommended for use in the 2021-2022 northern hemisphere season, while A/Darwin/9/2021-like and A/Darwin/6/2021-like (3C.2a1b.2a.2) viruses were recommended for egg- and cell-based vaccines in the 2022 southern hemisphere season. Six 3C.2a1b.2a.2 viruses isolated in Denmark all showed good recognition by post-infection ferret antisera raised against representative 3C.2a1b.2a.2 viruses, but only one, with rare HA1 I140K and R201I amino acid substitutions showed good reactivity with antisera raised against 3C.2a1b.2a.1 viruses.

While all B/Victoria-lineage HA gene sequences derived from viruses collected after 31 January 2021 have lost encoding of a three amino acid triplet (HA1 residues 162-164) and fall in subclade V.1A.3 represented by B/Washington/02/2019, the vaccine virus recommended for inclusion in influenza vaccines for the 2021-2022 northern hemisphere season, such viruses have been detected only in Kenya and the United States (US) recently. The great majority of 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 (V.1A.3a.2) viruses have been recommended for use in the southern hemisphere 2022 influenza season. Antigenically, viruses in subgroups of the V.1A.3a group differ and show some loss of reactivity with post-infection ferret antisera raised against B/Washington/02/2019. A single V.1A.3a.2 virus, B/Netherlands/10007/2021, showed good recognition by post-infection ferret antisera raised against B/Austria/1359417/2021, but poor recognition by an antiserum raised against B/Washington/02/2019.

No B/Yamagata-lineage HA sequences from clinical specimens collected in 2021, and none with collection dates after March 2020, were available. All sequences from the 77 viruses detected in 2020, inclusive of 12 from EU/EEA countries, belong to genetic clade Y3 and carry three HA1 amino acid substitutions (L172Q, D229N and M251V) compared to B/Phuket/3073/2013-like viruses which have been recommended for use in quadrivalent influenza vaccines for the 2021-2022 northern hemisphere and 2022 southern hemisphere seasons. The antigenic effects of these amino acid substitutions have been minimal as assessed in earlier reports.

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 40-52/2021), compared to the 2019-2020 season. There has been a vast increase in the number of samples from patients fulfilling Influenza-Like Illness (ILI) and/or Acute Respiratory Infection (ARI) criteria being tested (670 166, 438%), even when compared with a more 'normal' season, 2019-2020 (640 375, 381%: 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 (22 831, 5 601%), though there was a reduction compared to the same period in 2019-2020 (3 279, 12.4%: 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) restrictions on travel and social/work place gatherings, imposed to help curtail the spread of SARS-CoV-2, also impeding the spread of influenza viruses; and (iii) viral interference, with SARS-CoV-2 infection impeding infection by influenza viruses.

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 (1:1 to 22:1), with a greater dominance of A(H3N2) over A(H1N1)pdm09 viruses. While the number of influenza B virus detections has increased from 209 to 1 022 (489%), only small numbers were ascribed to a lineage in both time periods (Table 1), although, 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 that A(H3N2) viruses will dominate in 2021-2022.

Table 1. Influenza virus detections in the WHO European Region from the start of reporting for the 2021-22 season (weeks 40-52/2021)[a]

Virus type/subtype/lineage	Cumulative number of detections for weeks 40-52/2021			Totals*		Cumulative number of detections for weeks 40-53/2020			Totals*	
	Sentinel sources	Non-sentinel sources	Totals	%	Ratios	Sentinel sources	Non-sentinel sources	Totals	%	Ratios
Influenza A	**1116**	**21108**	**22224**	**95.6**	**22:1**	**2**	**204**	**206**	**49.6**	**1:1**
A(H1N1)pdm09	46	274	320	3.6		2	10	12	28.6	
A(H3N2)	679	7991	8670	96.4	27:1	0	30	30	71.4	2.5:1
A not subtyped	391	12843	13234			0	164	164		
Influenza B	**19**	**1003**	**1022**	**4.4**		**6**	**203**	**209**	**50.4**	
Victoria lineage	5	7	12	92.3	12:1	1	3	4	80.0	4:1
Yamagata lineage	0	1	1	7.7		0	1	1	20.0	
Lineage not ascribed	14	995	1009			5	199	204		
Total detections (total tested)	**1 135 (26 648)**	**22 111 (> 841 768)**	**23 246 (> 868 416)**			**8 (12 999)**	**407 (> 185 251)**	**415 (> 198 250)**		

[a] Numbers taken from Flu News Europe to week 52/2021 and week 53/2020 reports

* 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.

Since week 40/2021, 14 shipments of specimens (virus isolates and/or clinical specimens) were received at the Crick Worldwide Influenza Centre (WIC) from a total of 10 EU/EEA countries (Table 2). Of the 196 samples received, 189 (96%) are type A viruses and seven (4%) are B/Victoria-lineage. Twelve of these shipments were received in December 2021, hence characterisation of most samples is 'in process'.

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. Data generated on viruses with collection dates after 31 January 2021 until 31 August 2021 informed the recent VCM where recommendations were made for the 2022 southern hemisphere season. Recommendations for the 2020-2021 northern hemisphere, the 2021 southern hemisphere, current 2021-2022 northern hemisphere, and upcoming 2022 southern hemisphere seasons have been published [1-4].

Due to the low number of influenza-positive specimens detected until recently, and thereby available for sharing with WIC, this and recent influenza characterisation reports have mainly been based on phylogenetic analyses of complete HA gene sequences submitted to the EpiFlu™ database of the Global Initiative on Sharing All Influenza Data (GISAID), inclusive of sequences generated at the WIC, with those from EU/EEA countries highlighted. Only eight viruses, one A(H1N1)pdm09, six A(H3N2) and one B/Victoria-lineage, have been characterised antigenically since the November 2021 report (Tables 3 to 5 respectively).

Table 2. Summary of seasonal influenza clinical samples and virus isolates* contained in packages received from EU/EEA Member States since week 40/2021

MONTH / Country	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]
2021														
August														
Croatia	2					2	2							
Netherlands	1					1	1							
Norway	2					2	in process							
Portugal	1								1	in process				
Sweden	2					2	in process							
September														
Croatia	3					3	2	0						
Denmark	5					5	5							
France	11			1	in process	10	in process							
Netherlands	13					12	in process				1	1		
Spain	1					1	in process							
Sweden	2			1	in process	1	in process							
United Kingdom	2					2	in process							
October														
Denmark	3			1	1	2	1							
France	12			9	in process	3	in process							
Ireland	1			1	in process									
Netherlands	29					29	in process							
Norway	7					7	in process							
Portugal	3					2	in process		1	in process				
Spain	3					3	in process							
Sweden	2					2	in process							
United Kingdom	8					8	in process							
November														
Ireland	3					2	in process				1	in process		
France	28			18	in process	10	in process							
Norway	8					8	in process							
Spain	25			1	in process	22	in process		1	in process	1	in process		
Sweden	5					5	in process							
United Kingdom	3					2	in process		1	in process				
December														
Ireland	1					1	in process							
France	1					1	in process							
Spain	9					9	in process							
10 Countries	196	0	0	32	1	157	11	0	4	0	3	1	0	0
		0.00%		16.3%		80.1%			2.0%		1.5%		0.0%	
		96.4%							3.6%					

*** 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.**

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)
Specimens provided in lysis buffer so only genetic characterisation possible
Characterisation of Specimens with collection dates from 1 September 2021 (below red line) will be considered for the northern hemisphere VCM in February 2022

As of 2022-01-13

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 1a and 1b 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 2020–2021 (egg-based A/Guangdong-Maonan/SWL1536-like and cell-based A/Hawaii/70/2019-like) and southern hemisphere 2021, 2022 and northern hemisphere 2021-2022 (egg-based A/Victoria/5270/2019-like and cell-based A/Wisconsin/588/2019-like) influenza seasons are shown in red [1, 2, 3, 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 splits 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 two A(H1N1)pdm09 HA phylogenies show similar profiles. The first is repeated from the November 2021 report and included 39 sequences submitted/released in November, only 23 of which had collection dates after 31 August (Figure 1a). Three of the latter viruses, one each from England, Spain and the US, fell in subgroup **6B.1A.5a.1**, with the remainder falling in subgroup **6B.1A.5a.2**, 19 from Bangladesh and one from the US. The 20 **6B.1A.5a.2** viruses were like those first detected in India, carrying additional **HA1** amino acid substitutions of **K54Q**, **K130N**, **A186T**, **Q189E**, **E224A**, **R259K** and **K308R**.

The second phylogeny is based on sequences submitted/released in GISAID in December (n = 13) for viruses with collection dates from 1 January 2021 together with four sequences generated recently by WIC (Figure 1b). Of these 17, two were from H1N1v viruses detected in the US while the others were equally split between viruses in the **6B.1A.5a.1** and **6B.1A.5a.2** subgroups. However, the most recently detected viruses (October and November) in Australia and Oman all fell in a **6B.1A.5a.2** cluster of viruses with additional **HA1** substitutions of **K54Q, A196T, Q189E, E224A, R259K** and **K308R** compared to the vaccine virus A/Victoria/2570/2019. A/Denmark/18/2021 falls in this recently emerged virus cluster and is recognised poorly by post-infection ferret antiserum raised against A/Guangdong-Maonan/SWL1536/2019 and shows a fourfold reduction compared to the homologous titre with antiserum raised against IVR-215 (A/Victoria/2570/2019) vaccine virus (Table 3).

The great majority of A(H1N1)pdm09 viruses characterised antigenically by the WIC in the course of the 2019-2020 influenza season, with the exception of those in subgroup **6B.1A.5a.2**, were antigenically similar to A/Guangdong-Maonan/SWL1536/2019 (H1N1)pdm09-like viruses (**6B.1A.5a.1** with **HA1 D187A** and **Q189E** amino acid substitutions), recommended for use in the northern hemisphere 2020-2021 influenza season [1], as assessed by haemagglutination inhibition (HI) assays with a panel of post-infection ferret antisera raised against vaccine and reference viruses. Results of HI assays for viruses detected in EU/EEA countries can be seen in previous influenza characterisation reports: https://www.ecdc.europa.eu/en/seasonal-influenza/surveillance-and-disease-data/influenza-virus-characterisation [accessed 6 January 2022].

Figure 1a. Phylogenetic comparison of influenza A(H1N1)pdm09 HA genes (GISAID, November 2021)

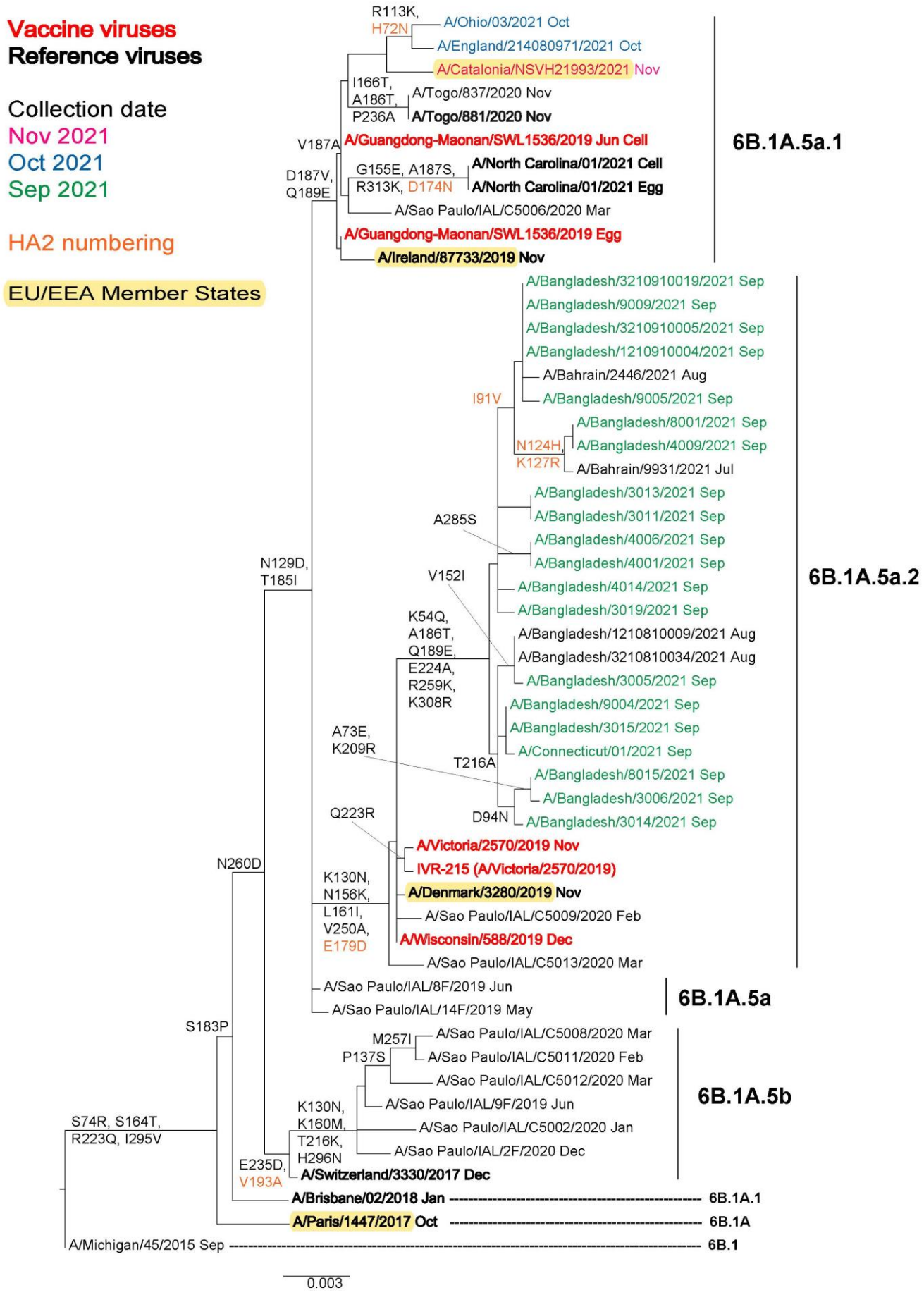


Figure 1b. Phylogenetic comparison of influenza A(H1N1)pdm09 HA genes (GISAID, December 2021)

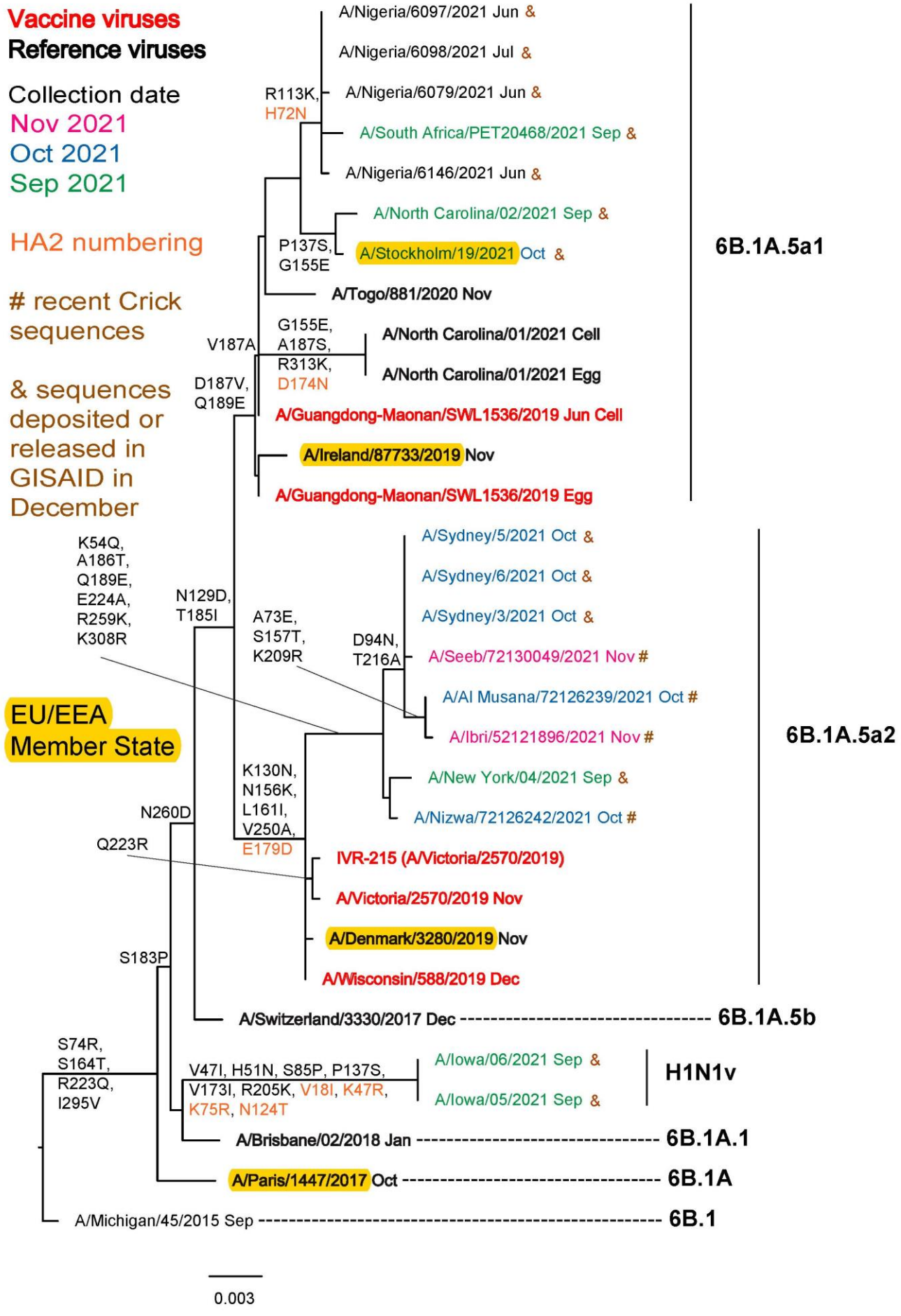


Table 3. Antigenic analysis of influenza A(H1N1)pdm09 viruses by HI

Viruses	Other information	Collection date	Passage history	Haemagglutination inhibition titre							
				Post-infection fereret antisera							
				A/Paris/1447/2017 MDCK F03/18*2	A/Bris/02/18 Egg F09/19*1	A/Swit/3330/17 Egg F23/18*1	A/Ire/87733/19 Egg St Jude's F18/20*1	A/G-M/SWL1536/19 Egg F12/20*1	A/G-M/SWL1536/19 MDCK F09/20*1	A/Denmark/3280/19 MDCK F08/20*1	IVR-215/A/Vic/2570/19 Egg F37/21*1
Passage history											
Ferret number											
Genetic group				6B.1A	6B.1A.1	6B.1A.5b	6B.1A.5a.1	6B.1A.5a.1	6B.1A.5a.1	6B.1A.5a.2	6B.1A.5a.2
REFERENCE VIRUSES											
A/Paris/1447/2017	6B.1A	2017-10-20	MDCK1/MDCK3	2560	1280	1280	1280	2560	2560	40	80
A/Brisbane/02/2018	6B.1A.1	2018-01-04	E3/E2	2560	1280	640	640	2560	1280	40	160
A/Switzerland/3330/2017	clone 35 6B.1A.5b	2017-12-20	E6/E2	1280	320	640	320	1280	1280	<	80
A/Ireland/87733/2019	6B.1A.5a.1	2019-11-03	E4	1280	640	640	640	1280	1280	<	80
A/Guangdong-Maonan/SWL1536/2019	6B.1A.5a.1	2019-06-17	E3/E2	640	320	320	640	1280	1280	40	80
A/Guangdong-Maonan/SWL1536/2019	6B.1A.5a.1	2019-06-17	C2/MDCK1	1280	640	640	1280	2560	2560	40	80
A/Denmark/3280/2019	6B.1A.5a.2	2019-11-10	MDCK4/MDCK5	160	40	80	80	80	160	1280	2560
IVR-215 (A/Victoria/2570/2019)	6B.1A.5a.2	2018-11-22	E4/D7/E1	<	80	40	80	160	160	1280	2560
TEST VIRUSES											
A/Denmark/18/2021	6B.1A.5a.2	2021-10-21	MDCK2/MDCK1	<	<	40	40	40	40	320	640
					Vaccine NH 2019-20 SH 2020			Vaccine NH 2020-21			Vaccine SH 2021 NH 2021-22 SH 2022

*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

The first A(H3N2) HA phylogeny is repeated from the November 2021 report and was based on H3 HA sequences deposited/released in GISAID in November (n = 511) but with only those with collection dates from 21 October included (n = 147) together with sequences generated recently at the WIC (Figure 2a). The second phylogeny is based on H3 HA sequences deposited/released in GISAID in December with virus collection dates after 31 August (n = 528) and a representative selection of these, together with sequences generated recently at the WIC, are included in the tree (Figure 2b).

Viruses 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 have 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 [1, 2].

The HA phylogeny generated for the November report incorporated 147 sequences submitted/released in GISAID in November with collection dates from 21 October 2021, together with sequences recently determined at the WIC (Figure 2a). All viruses with collection dates after 31 August 2021 (n = 176) 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 three subgroups defined by specific **HA1** amino acid substitutions: (i) **S205F** and **A212T** (n = 5) with viruses from the Netherlands, Spain and the Russian Federation; (ii) **D53G** (n = 58), often with additional amino acid substitutions, in viruses from Lebanon, Spain, the Russian Federation and the US; and (iii) **D53N**, **N96S** and **I192F** (n = 113) with viruses from Croatia, Italy, the Netherlands (n = 86), Spain (n = 23) and the US. Subgroups (ii) and (iii) also share **HA1 H156S** amino acid substitution.

The second phylogeny shows a very similar profile, with the vast majority of sequences being derived from 'Bangladesh-like' (**3C.2a1b.2a.2**) and none from 'Cambodia-like' (**3C.2a1b.2a.1**) viruses (Figure 2b). The **3C.2a1b.2a.2** viruses have continued to evolve with virus clusters emerging defined by additional HA1 amino acid substitutions, but basically falling within the three subgroups identified above: (i) **S205F** and **A212T**; (ii) **D53G**, often with additional amino acid substitutions; and (iii) **D53N**, **N96S** and **I192F**. All but one sequence derived from viruses detected recently in EU/EEA countries fall within the 'Bangladesh-like' group with examples from all of the three subgroups identified. Sequences from a cluster of **3C.2a1b.1b** viruses detected in Kenya in September and three **3C.2a1b.1a** viruses with collection dates spanning September to November, including one from Sweden in October, have also been submitted to GISAID.

'Bangladesh-like' **3C.2a1b.2a.2** viruses, A/Darwin/9/2021 and A/Darwin/6/2021 for egg- and cell-based vaccines respectively, were recently recommended for use in the southern hemisphere 2022 influenza season [4].

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 [3], are indicated on the phylogenies, as are egg- and cell-culture based vaccines to be used in the 2022 southern hemisphere season, A/Darwin/9/2021 and A/Darwin/6/2021 (**3C.2a1b.2a.2**) respectively [4] (Figures 2a and 2b).

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 fall 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.

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.

Antigenic characterisation of six A(H3N2) viruses from Denmark, all of which are **3C.2a1b.2a.2** viruses is presented here (Table 3). All test viruses were inhibited well, by antisera raised against **3C.2a1b.2a.2** viruses, notably so for antisera raised against cell culture-propagated A/Stockholm/5/2021 and slightly less well by antisera raised against cell culture-propagated A/Bangladesh/4005/2020 and egg-propagated A/Darwin/9/2021. Antisera raised against single 3C.2a1b.1a and 3C.3a1 viruses, and two 3C.2a1b.2a.1 recognised only one test virus well, A/Denmark/21/2021, which has **HA1 I140K** and **R201I** substitutions, while the other five test viruses fall in the subgroup with **D53N**, **N96S** and **I192F** substitutions (with **H156S**).

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 at: 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 at: https://www.ecdc.europa.eu/sites/default/files/media/en/publications/Publications/ERLI-Net%20report%20November%202014.pdf

Figure 2a. Phylogenetic comparison of influenza A(H3N2) HA genes (GISAID, November 2021)

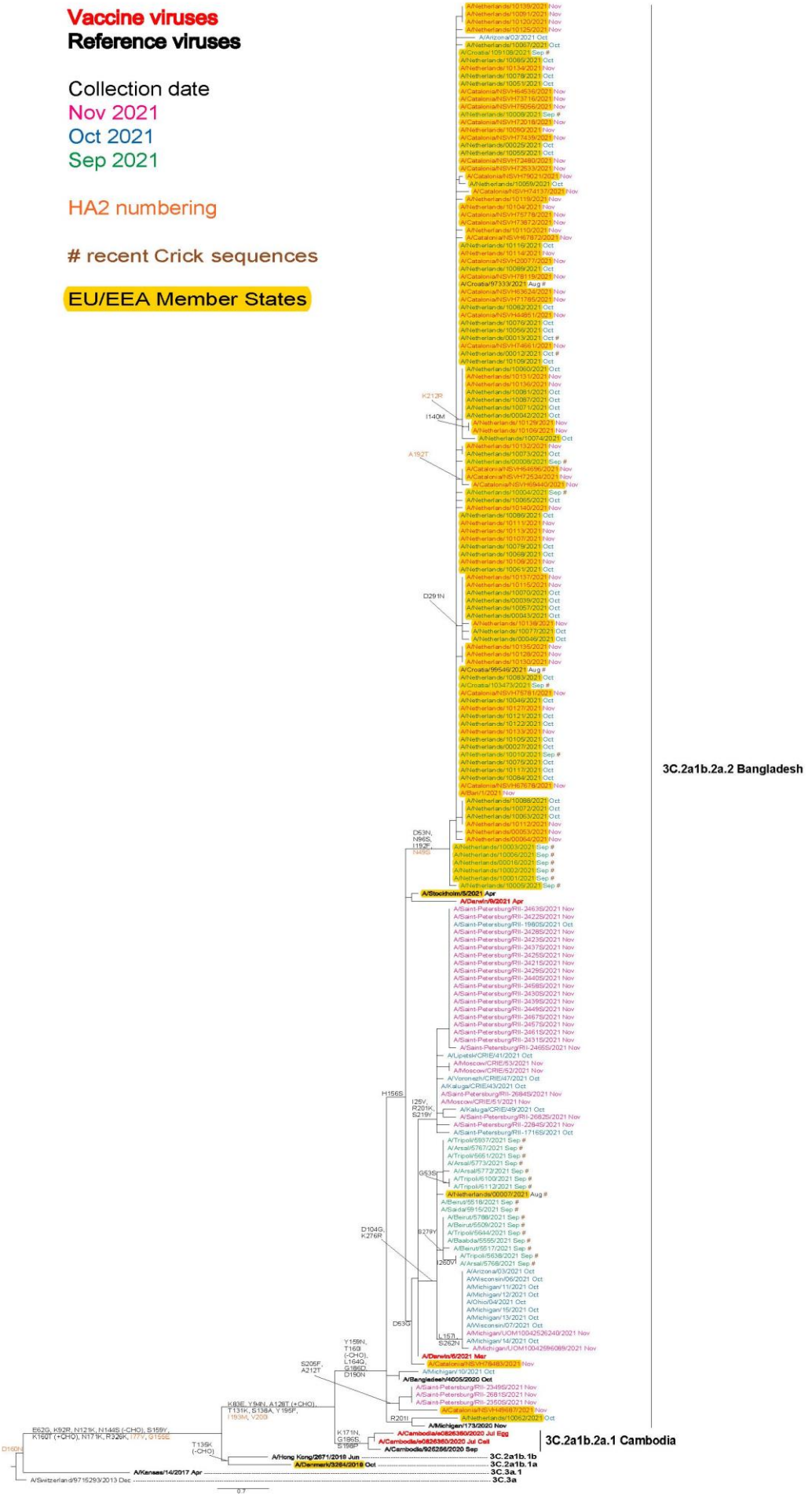


Figure 2b. Phylogenetic comparison of influenza A(H3N2) HA genes (GISAID, December 2021)

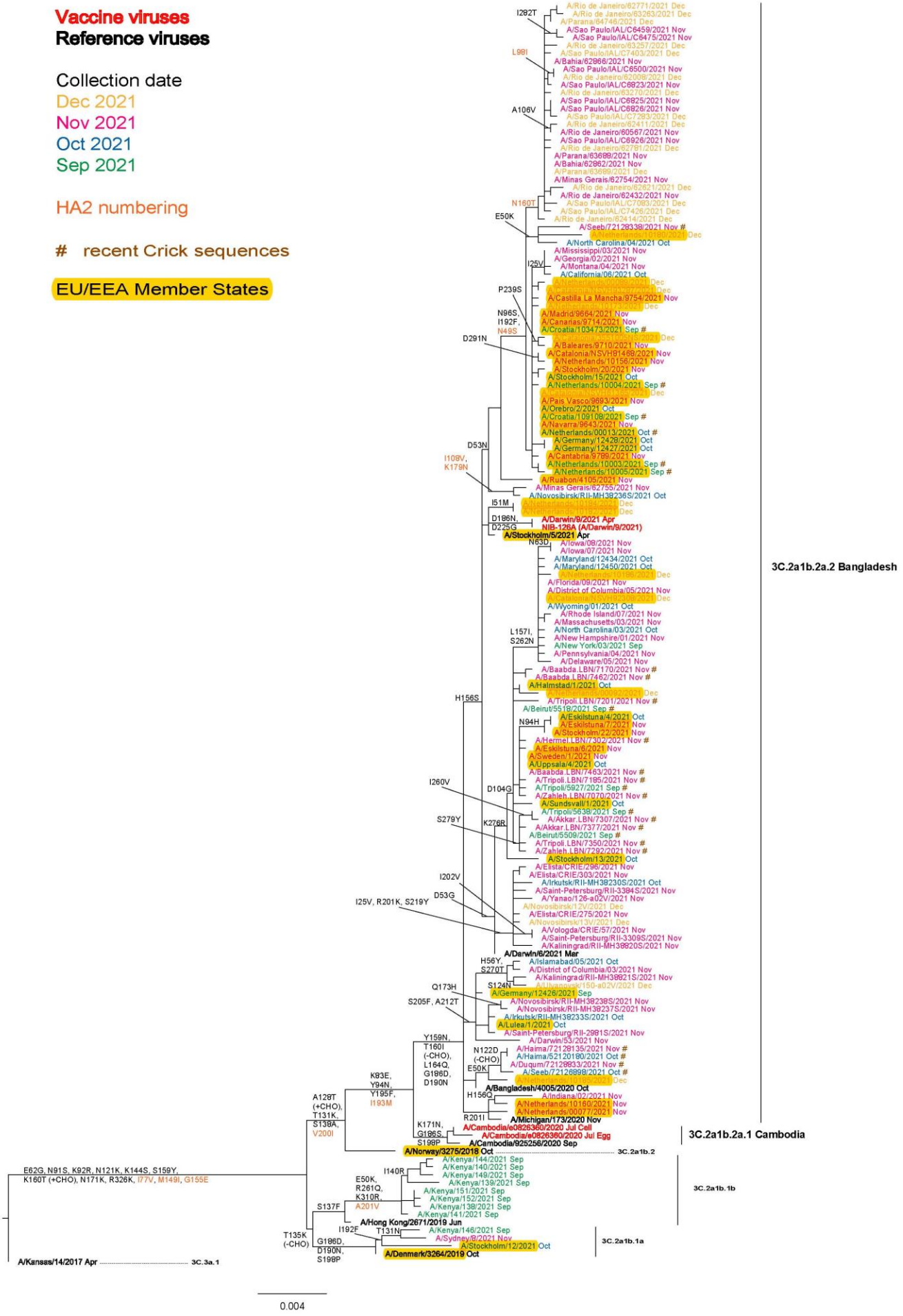


Table 4. Antigenic analysis of influenza A(H3N2) viruses by HI

Viruses	Other information		Collection date	Passage history	Haemagglutination inhibition titre							
					Post-infection ferret antisera							
					A/Denmark 3264/19	A/HK 2671/19	A/Camb e0826360/20	A/Camb 925256/20	A/Bang 4005/20	A/Darwin 9/21	A/Stock 5/21	A/Kansas 14/17
		Passage history			SIAT	Cell	Egg	SIAT	SIAT	Egg	SIAT	SIAT
		Ferret number			F19/20*1	St Judes F21/20*1	F10/21*1	F03/21*1	F07/21*1	F38/21*1	F35/21*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.3a1
REFERENCE VIRUSES												
A/Denmark/3264/2019		3C.2a1b.1a	2019-10-25	SIAT5	320	320	160	640	160	160	80	80
A/Hong Kong/2671/2019		3C.2a1b.1b	2019-06-17	MDCK1/SIAT4	320	320	160	640	160	160	80	80
A/Cambodia/e0826360/2020		3C.2a1b.2a.1	2020-07-16	E5/E2	160	<	1280	160	160	320	160	80
A/Cambodia/925256/2020		3C.2a1b.2a.1	2020-09-25	SIAT4	160	160	160	640	320	320	160	80
A/Bangladesh/4005/2020		3C.2a1b.2a.2	2020-10-04	SIAT3	160	<	160	160	640	640	640	160
A/Darwin/9/2021		3C.2a1b.2a.2	2021-04-17	E3/E4	160	<	320	80	320	2560	640	40
A/Stockholm/5/2021		3C.2a1b.2a.2	2021-04-16	S0/S3	80	<	80	80	160	1280	640	40
A/Kansas/14/2017		3C.3a1	2017-12-14	SIAT3/SIAT2	40	<	40	80	80	80	80	640
TEST VIRUSES												
A/Denmark/04/2021		3C.2a1b.2a.2	2021-09-15	SIAT3/SIAT1	40	<	80	40	160	640	640	40
A/Denmark/08/2021		3C.2a1b.2a.2	2021-09-17	SIAT3/SIAT1	40	<	40	40	160	320	160	<
A/Denmark/07/2021		3C.2a1b.2a.2	2021-09-17	SIAT2/SIAT1	40	<	40	40	160	320	160	<
A/Denmark/13/2021		3C.2a1b.2a.2	2021-09-21	SIAT3/SIAT1	40	<	40	40	160	320	320	<
A/Denmark/12/2021		3C.2a1b.2a.2	2021-09-25	SIAT3/SIAT1	40	<	40	40	160	320	320	<
A/Denmark/21/2021	I140K, R201I	3C.2a1b.2a.2	2021-10-29	SIAT3/SIAT1	160	<	320	160	640	640	640	160
							Vaccine NH 2021-22			Vaccine SH 2022		

*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 had 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 have emerged. Viruses in these groups 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**.
- 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 (with no detections having been made recently), represented by **B/Hong Kong/269/2017**.
- 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 recommended after WHO VCMs in February and September 2020, and February 2021 [1-3].

The phylogeny generated for the November report included 52 sequences submitted/released in GISAID in November with virus collection dates from 1 July 2021 (Figure 3a). Of these just 20 had collection dates after 31 August 2021, seven viruses from the US fell in subclade **V1A.3** being **B/Washington/02/2019**-like, and 13 (three from England, one from the Netherlands and nine from India) fell in subgroup **V1A.3a.2** being **B/Austria/1359417/2021**-like with **HA1 A127T**, **P144L** and **K203R** substitutions).

The second phylogeny incorporated 56 sequences submitted/released in GISAID in December with virus collection dates from 1 January 2021 (Figure 3b). The profiles of the two phylogenies are very similar with viruses of the **V1A.3** subclade still circulating in the US (characterised by **HA1 T73I** and **N233K** [resulting in loss of a glycosylation site] substitutions) and identification of another cluster of viruses in Kenya (characterised by **HA1 K75E, E128K, T155A** and **G230N** substitutions). Similarly, viruses of the **V1A.3a.2** subgroup continue to circulate with viruses in clusters defined by **HA1** substitutions, either **D197E** or **A202V**, predominating. The single **V1A.3a.2** virus, B/Netherlands/10007/2021, characterised antigenically was recognised well by post-infection ferret antiserum raised against egg-propagated B/Austria/1359417/2021 (Table 5).

The WHO Collaborating Centres for Influenza have shown the **V.1A.3a** group viruses with additional HA1 substitutions to be antigenically distinct from one another and, despite the low number of B/Victoria-lineage viruses detected, there has been geographic spread of viruses in these recently emerged virus subgroups, notably those in the **V.1A.3a.2** subgroup. **B/Austria/1359417/2021**-like (**V.1A.3a.2**) viruses were recently recommended for southern hemisphere 2022 vaccines [4].

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 in GISAID as of 31 December 2021. Figure 4 is repeated from the September report with recently designated nomenclature indicated in bold/red type and was generated based on the 77 HA sequences from viruses with collection dates after 31 December 2019 to 31 March 2020 available in GISAID. All sequences fell in genetic clade **3** (**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 is recommended for inclusion in quadrivalent vaccines for the 2020-2021 and 2021-2022 northern hemisphere, 2021 and 2022 southern hemisphere seasons [1, 2, 3, 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**), has 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.

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

Figure 3a. Phylogenetic comparison of influenza B/Victoria-lineage HA genes (GISAID, November 2021)

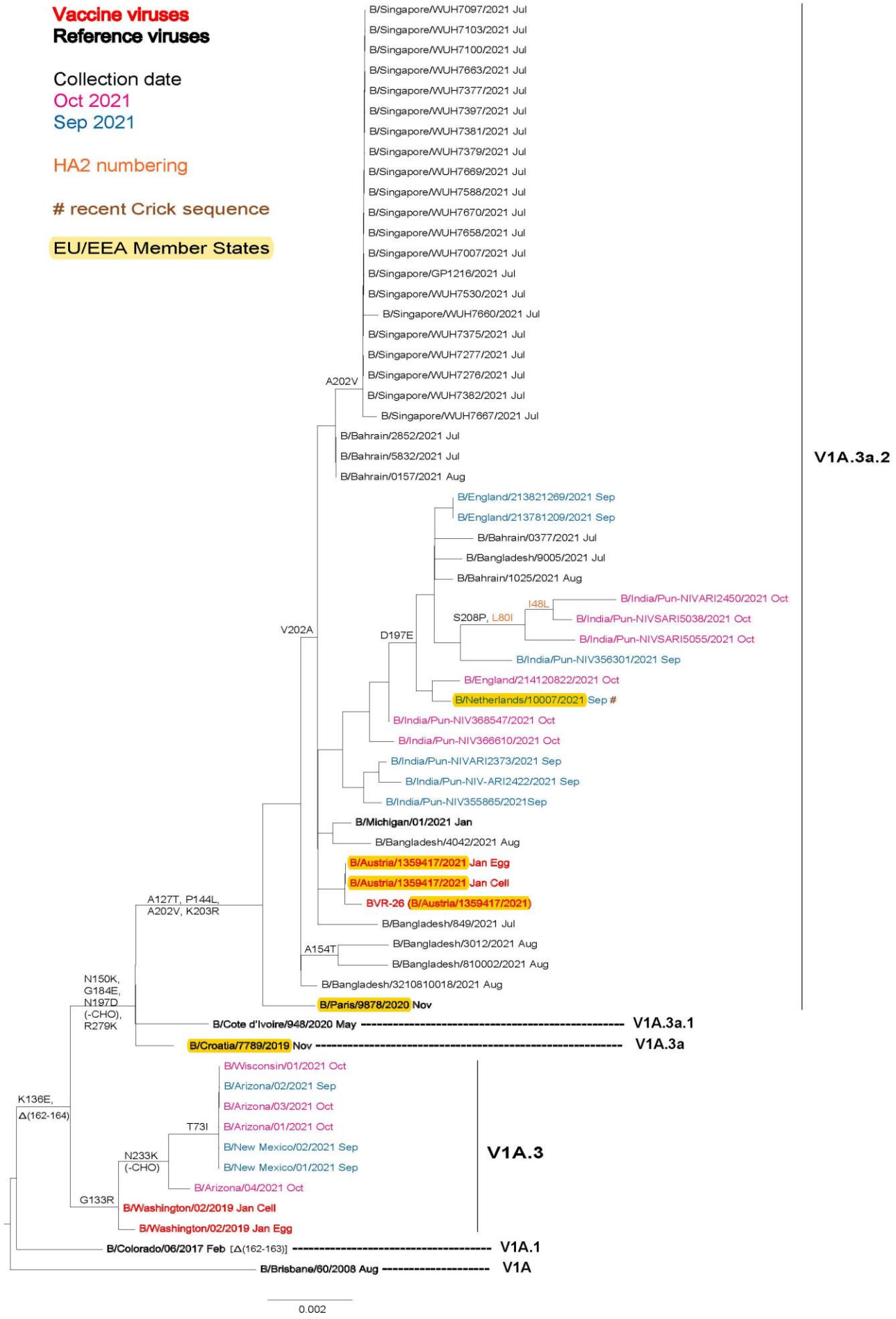


Figure 3b. Phylogenetic comparison of influenza B/Victoria-lineage HA genes (GISAID, December 2021)

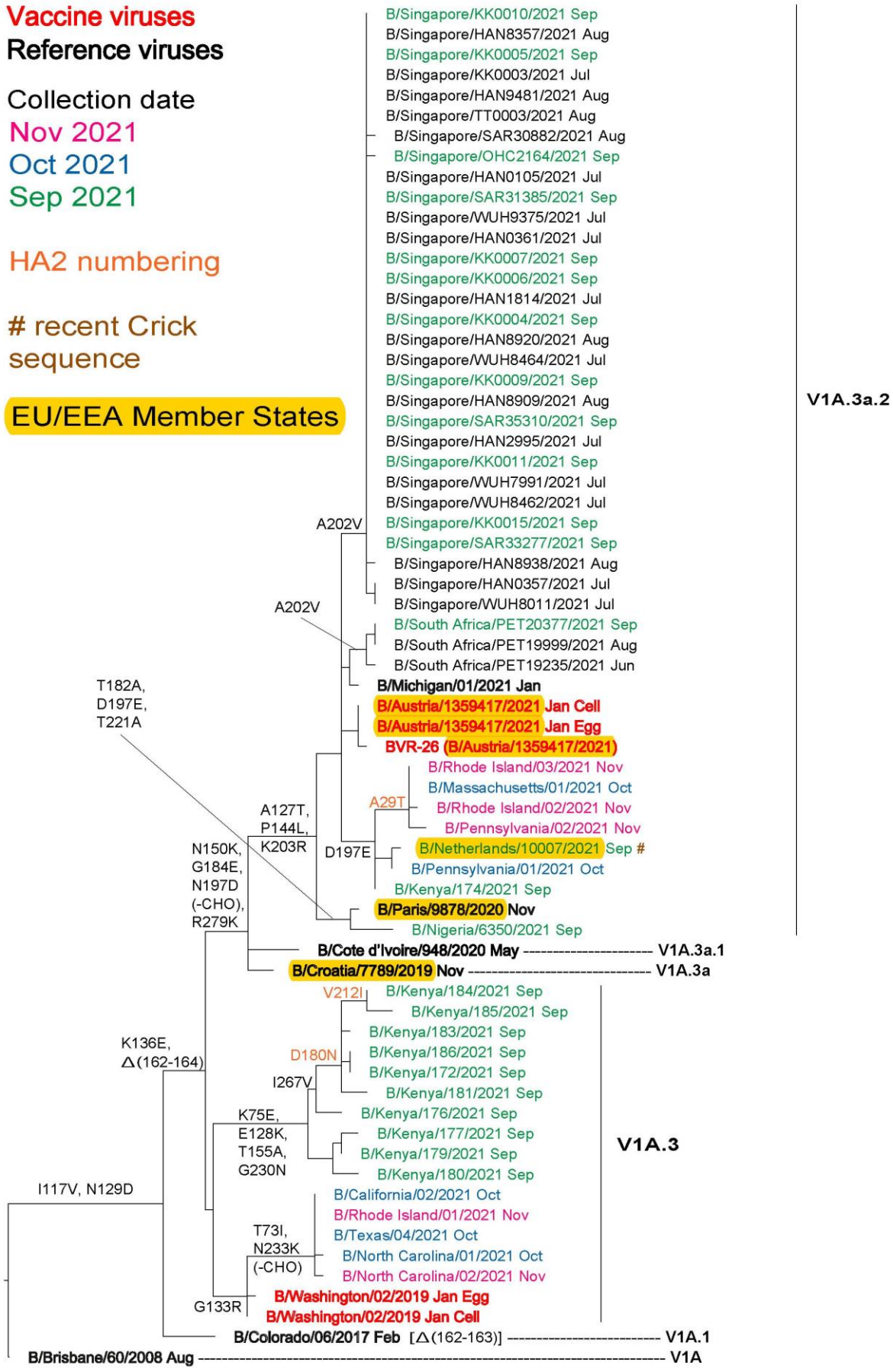
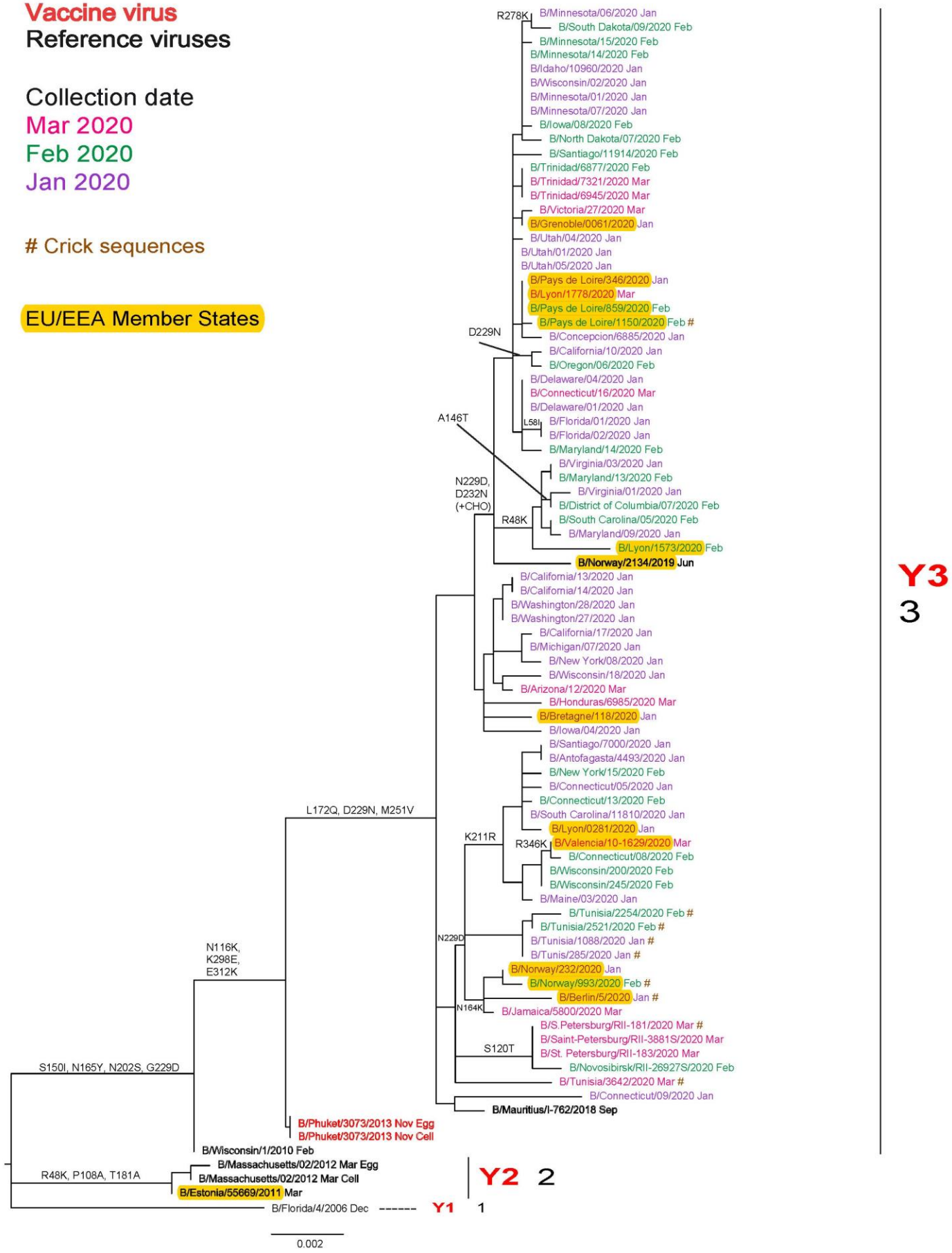


Table 5. Antigenic analysis of influenza B/Victoria-lineage viruses by HI

Viruses	Other information	Collection date	Passage history	Haemagglutination inhibition titre							
				Post-infection ferret antisera							
				B/Bris	B/Colorado	B/Wash'ton	A/Croatia	B/CIV	B/Austria	B/Austria	B/Paris
				60/08	06/17	02/19	7889/19	948/20	1359417/21	1359417/21	9878/20
	Passage history			Egg	Egg	Egg	MDCK	MDCK	MDCK	Egg	MDCK
	Ferret number			Sh 539, 540, 543, 544, 570, 571, 574[*1,3]	F11/18[*4]	F20/20[*2]	F19/21[*1]	F08/21[*1]	NIB F01/21[*1]	F15/21[*1]	F12/21[*1]
	Genetic group			V1A	V1A.1	V1A.3	V1A.3a	V1A.3a.1	V1A.3a.2	V1A.3a.2	V1A.3a.2
REFERENCE VIRUSES											
B/Brisbane/60/2008	V1A	2008-08-04	E4/E4	2560	40	40	160	<	<	<	<
B/Colorado/06/2017	V1A.1	2017-02-05	E5/E2	1280	320	80	160	<	<	<	<
B/Washington/02/2019	V1A.3	2019-01-19	E3/E2	1280	80	320	160	40	<	<	<
B/Croatia/7789/2019	V1A.3a	2019-11-11	MDCKx/MDCK2	1280	160	ND	640	320	160	80	<
B/Cote d'Ivoire/948/2020	V1A.3a.1	2020-05-28	MDCK2	320	<	ND	640	640	160	80	<
B/Austria/1359417/2021	V1A.3a.2	2021-01-09	SIAT1/MDCK4	640	<	<	320	160	2560	1280	320
B/Austria/1359417/2021 Isolate 2	V1A.3a.2	2021-01-09	E3	320	20	10	320	160	2560	1280	320
B/Austria/1359417/2021 Isolate 2 G141X	V1A.3a.2	2021-01-09	E3/E2	ND	ND	ND	ND	ND	ND	2560	ND
B/Austria/1359417/2021 Isolate 2 G141R	V1A.3a.2	2021-01-09	E3/E4	ND	ND	ND	ND	ND	ND	1280	ND
B/Paris/9878/2020	V1A.3a.2	2020-11-20	MDCK2	640	80	10	320	160	1280	640	320
TEST VIRUSES											
B/Netherlands/10007/2021	V1A.3a.2	2021-09-09	MDCK-MIX2	640	40	10	160	80	640	1280	320
					Vaccine SH 2019 NH 2019-20	Vaccine SH 2020 NH 2020-21 SH 2021 NH 2021-22				Vaccine SH 2022	

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

Figure 4. Phylogenetic comparison of influenza B/Yamagata-lineage HA genes (GISAID, September 2021)



Summaries of data submitted to TESSy

Genetic characterisation

325 viruses detected over the course of the 2021-2022 season (weeks 40-52/2021) were genetically characterised:

- Two A(H1N1)pdm09 viruses, one of which was not ascribed to a genetic group, while the other belonged to clade 6B.1A.5a.1 (represented by A/Guangdong-Maonan/SWL1536/2019).
- Of 320 A(H3N2) viruses, 319 belonged to the 'Bangladesh-like' clade (3C.2a1b.2a.2) represented by A/Bangladesh/4005/2020 and one was attributed to clade 3C.2a1b.1a.
- Three B/Victoria-lineage viruses, two belonging to clade V1A.3 (represented by B/Washington/02/2019) and one to clade V1A.3a.2 (represented by B/Austria/1359417/2021).

Antiviral susceptibility

Up to week 52/2021, 225 viruses (224 A(H3) and one A(H1)pdm09) and 125 viruses (124 A(H3) and one A(H1)pdm09) were assessed for susceptibility to neuraminidase inhibitors (NAIs) and the PA inhibitor baloxavir marboxil, respectively. No amino acid substitutions previously associated with reduced susceptibility to any of the antivirals were identified.

At the WIC, 22 influenza viruses detected within EU/EEA countries during the 2021-2022 season have been assessed phenotypically against oseltamivir and zanamivir: one A(H1)pdm09, 20 A(H3) and one B/Victoria-lineage. All viruses showed normal inhibition (NI) by both NAIs.

Influenza A(H7N9) virus

On 1 April 2013, the World Health Organization (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]. WHO posted an analysis of information on A(H7N9) viruses on 10 February 2017 [7], and ECDC published a rapid risk assessment on the implications of A(H7N9) for public health on 3 July 2017 [8]. Current risk assessments can be found on WHO's website https://www.who.int/teams/global-influenza-programme/avian-influenza/monthly-risk-assessment-summary (accessed 12 January 2022). The assessment published on 23 December 2021 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 [9]. The H7N9 situation update published by the Food and Agricultural Organization of the United Nations on 3 February 2021 indicated there had been 14 detections in chickens in Shandong province, China during October 2020, but the report published on 1 December 2021 indicated that there have been no additional detections since then [10]. The most recent human case was detected in mid-March 2019 [11]. 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 22 December 2021 and can be found on ECDC's website [12].

Influenza A(H5) virus

The most recent monthly risk assessment of influenza at the human-animal interface was published by WHO on 23 December 2021. Since the previous risk assessment on 1 October 2021, nine human cases of infection with avian influenza A(H5N6) viruses were reported by China with disease onset dates in September through December [9]. All cases reported exposure to poultry and, at the time of report publication, one case was fatal (a 54-year-old female with underlying conditions), seven were severe/critical and one was mild. The last confirmed case of human infection with an A(H5N1) virus was reported by India [13]. However, a potential case is under investigation in England [14].

On 30 September 2020, ECDC published an alert related to outbreaks of avian influenza viruses in Europe [15]. The latest collaborative report from ECDC and the European Food Safety Authority (EFSA), reported 867 highly pathogenic avian influenza (HPAI) A(H5) detections between 16 September and 8 December 2021, 316 in poultry, 523 in wild birds and 28 in domestic birds [12]. Detections occurred in 27 EU/EEA countries and the UK. Of the poultry detections 167 were reported by Italy and 35 each by Hungary and Poland. Majorities of wild bird detections were reported by Germany (280), Netherlands (65) and the UK (53). Genetic analyses indicated that the circulating viruses belonged to clade 2.3.4.4b, with such viruses having been circulating in Europe since October 2020. According to reports compiled by the Food and Agricultural Organization of the United Nations (FAO) as of 23 December 2021, various influenza A(H5Nx) subtypes continued to be detected in wild and/or domestic birds in Africa, Asia and Europe, and since 24 November 2021 a total of 651 HPAI (44 H5Nx, 594 H5N1, four H5N5 and nine H5N8) and 16 LPAI outbreaks had been reported, with eight A(H5N6) human infection in China (latest symptom onset date of 22 December 2021) [16].

Influenza A(H9N2) virus

Since the previous WHO update on 1 October 2021 four laboratory-confirmed human cases of influenza A(H9N2) virus infection, three in children and one in a 39-year-old male who died, were reported by China with onset dates in

September through December [9]. All cases reported poultry exposure and disease symptoms were mild in the three child cases. The most recent FAO report mentions two of these cases in China with the latest disease onset date being 6 December 2021 [16]. Public Health England recently published and updated risk assessment of avian influenza A(H9N2) [17]. 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 1 October 2021, six A(H1)v zoonotic events with swine-related variant influenza A viruses were reported by Canada (n = 1) and the US (n = 5) with disease onset dates in September and October 2021 [9]. All patients reported a history of swine exposure, three were infected with A(H1N1)v viruses, two with A(H1N2)v and one with an A(H1Nx)v virus. Five patients made a full recovery, but the one with A(H1Nx)v infection had underlying conditions and died.

One case of A(H3N2)v infection was reported from Ohio, US. The infected child showed illness onset on 10 October 2021 was not hospitalised and made a full recovery. No contact with swine was identified.

In all swine influenza zoonotic incidents, no human-to-human transmission was identified.

WHO Collaborating Centre reports

A description of results generated by the London WHO Collaborating Centre at the WIC and used at the September 2021 WHO vaccine composition meeting (held online: 13-23 September 2021 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 6 January 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. Isolates from WHO NICs in EU/EEA countries are highlighted in yellow. Sequences for most viruses from non-EU/EEA 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.

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