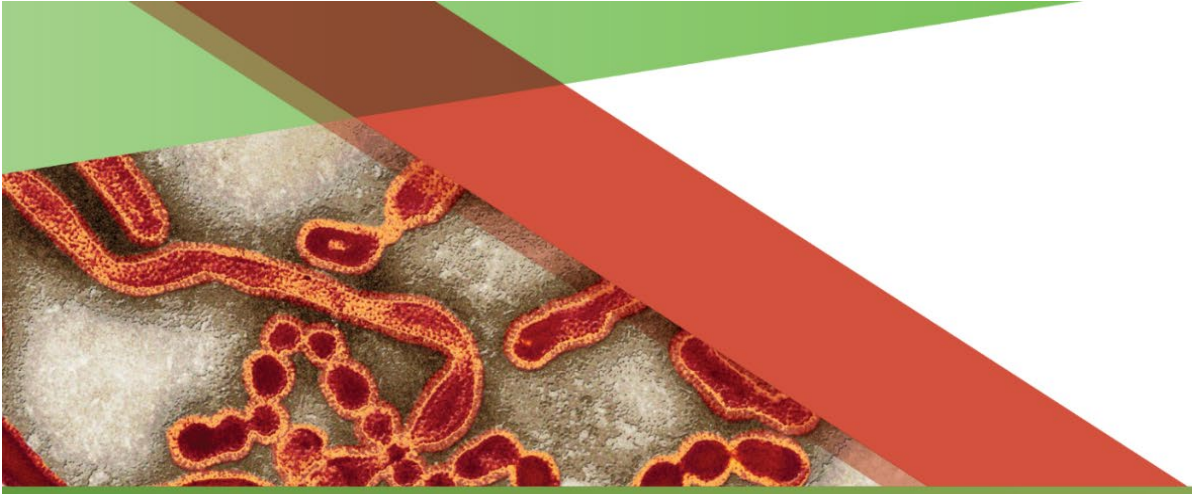

SURVEILLANCE REPORT

Influenza virus characterisation

Summary Europe, May 2021

Summary

This is the seventh report for the 2020–2021 influenza season. As of week 20/2021, only 909 influenza detections across the WHO European Region had been reported to TESSy; 52% type A viruses, with A(H3N2) and A(H1N1)pdm09 being approximately equally represented, and 48% type B viruses, with only 16 having been ascribed to a lineage, 13 B/Victoria and three B/Yamagata. This represents a 99.4% drop in detections compared to the same period in 2020, probably due to the COVID-19 pandemic and measures introduced to combat it.

Since the April 2021 characterisation report[1], only one shipment from an EU/EEA country (Norway) containing three clinical specimens has been received at the London WHO Collaborating Centre, the Francis Crick Worldwide Influenza Centre (WIC): consequently, little virus characterisation data has been generated. This report therefore focuses on genetic characterisation of the HA genes of seasonal influenza viruses deposited and/or released in GISAID during May 2021, with collection date periods adjusted for each virus subtype/lineage to allow production of readable phylogenies with sequences from viruses with the most recent collection dates included. The data continue to show extremely low levels of influenza detections. Few or no detections of A(H1N1)pdm09 and B/Yamagata-lineage viruses have been reported globally, while low numbers of A(H3N2) and B/Victoria-lineage viruses have been detected.

Just four A(H1N1)pdm09 HA sequences from viruses detected in the 2020–2021 season were made available in GISAID during May, three from infections with subgroup 6B.1A5A+187V/A viruses, represented by A/Guangdong-Maonan/SWL1536/2019 (the vaccine virus for the northern hemisphere 2020–2021 season), and one from a zoonotic H1N1v case (swine clade 1A.3.3.3). Two viruses from Norway with recent collection dates were recognised well in HI assays by post-infection ferret antiserum raised against the 2020–2021 vaccine virus, but poorly by antiserum raised against the 2021–2022 vaccine virus, A/Victoria/2570/2019.

Of the 26 HA sequences from recently collected A(H3N2) viruses, one each fell into the subgroups 3C.2a1b+T135K-A and 3C.2a1b+T135K-B, and 24 fell into the subgroup 3C.2a1b+T131K-A. The 3C.2a1b+T131K-A subgroup viruses were split into two antigenically distinguishable clusters, originally defined by viruses from Cambodia (n=10: with HA1 amino acid substitutions of G186S, F193S, Y195F and S198P, many also having K171N) and Bangladesh (n=14: with HA1 amino acid substitutions of Y159N, T160I (loss of a glycosylation site), L164Q, G186D, D190N, F193S and Y195F); with Bangladesh-like viruses showing the greatest geographical spread. The single virus from Norway characterised by HI in May showed a profile of reactivity, with a panel of post-infection ferret antisera, characteristic of

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

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that seen with a Bangladesh-like virus. An A/Cambodia/e0826360/2020-like virus (subgroup 3C.2a1b+T131K-A) has been recommended for use in the 2021–2022 northern hemisphere influenza season.

All 10 newly available B/Victoria-lineage HA sequences from viruses with collection dates during the 2020–2021 season fell within the N150K group of subclade 1A(△3)B, with HA1 amino acid substitutions of N150K, G184E, N197D (loss of a glycosylation site) and R279K. When the N150K group was split into two subgroups, one of them, defined by HA1 substitutions A127T, P144L, E164K and K203R (often with additional substitutions), showed significant geographical spread, while a subgroup defined by HA1 substitutions V117I and V220M has been identified in the Russian Federation. Antigenically, viruses in subgroups of the N150K group differ and show some loss of reactivity with post-infection ferret antisera raised against the B /Washington/02/2019 vaccine virus, recommended for inclusion in influenza vaccines for the 2020–2021 and 2021–2022 northern hemisphere seasons and 2021 southern hemisphere season.

Seven B/Yamagata-lineage HA sequences from clinical specimens collected in the United States during the 2019–2020 season were deposited in and/or released to GISAID during May. Similar to previously released sequences from viruses with collection dates in 2020, they belong to genetic clade 3 and carry three HA1 amino acid substitutions (L172Q, D229N and M251V), compared to the B/Phuket/3073/2013-like viruses which have been recommended for use in quadrivalent influenza vaccines for the 2020-2021 and 2021-2022 northern hemisphere seasons and 2021 southern hemisphere season. 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 for the 2020–2021 season (weeks 40/2020–20/2021), compared with the same period for the 2019–2020 season. While there has been a small reduction in the number of samples tested from patients fulfilling Influenza-Like Illness (ILI) and/or Acute Respiratory Infection (ARI) criteria (~21 113, 2.3%), there has been a vast reduction in the number of samples testing positive for an influenza virus (163 959, 99.4%). This is probably due to a number of factors: (i) the number of centres within the Region reporting during these periods has dropped from 52 to 45; (ii) significant numbers of samples taken from patients fulfilling ILI and/or ARI criteria are infected with other agents, possibly SARS-CoV-2, the virus responsible for the COVID-19 pandemic; (iii) restrictions on travel and social/work-place gatherings, imposed to help curtail the spread of SARS-CoV-2, have also restricted the spread of influenza viruses, and (iv) 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 the first 34 weeks of the 2020–2021 season, the ratio of type A to type B detections is reduced compared to the 2019–2020 season (2.7:1 to 1:1). There has also been a reversal in the proportions of influenza A subtypes, with B/Victoria lineage viruses appearing, once again, to be predominant over B/Yamagata lineage viruses, although only 16/425 (3.8%) of type B viruses detected in the 2020–2021 season had been ascribed to a lineage as of week 20/2021.

Table 1. Influenza virus detections in the WHO European Region from the start of reporting for the 2020–21 season (weeks 40/2020-20/2021)[a]

Virus type/subtype/lineage	Cumulative number of detections for weeks 40/2020-20/2021			Totals*		Cumulative number of detections for weeks 40/2019-20/2020			Totals*	
	Sentinel sources	Non-sentinel sources	Totals	%	Ratios	Sentinel sources	Non-sentinel sources	Totals	%	Ratios
Influenza A	**30**	**438**	**468**	**51.5**	**1.1:1**	**11302**	**108940**	**120242**	**72.9**	**2.7:1**
A(H1N1)pdm09	13	28	41	40.6		6126	20302	26428	56	
A(H3N2)	9	51	60	59.4	1.5:1	4174	16591	20765	44	0.8:1
A not subtyped	8	359	367			1002	72047	73049		
Influenza B	**16**	**425**	**441**	**48.5**		**6324**	**38302**	**44626**	**27.1**	
Victoria lineage	2	11	13	81.3	4.3:1	2449	2030	4479	98.1	50.3:1
Yamagata lineage	0	3	3	18.7		23	66	89	1.9	
Lineage not ascribed	14	411	425			3852	36206	40058		
Total detections (total tested	**46 (43 474)**	**863 (>845 810)**	**909 (>889 284)**			**17 626 (51 764)**	**147 242 (>858 633)**	**164 868 (>910 397)**		

[a] Numbers taken from Flu News Europe week 20/2021 and week 20/2020 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 40/2020, seven shipments of specimens (virus isolates and/or clinical specimens) have been received at the Crick Worldwide Influenza Centre (WIC), one of which was received in May 2021 from Norway containing three clinical specimens (Table 2). The packages contained 23 virus-related samples, with collection dates after 31 August 2020 and were made up of 12 type A viruses and 11 type B viruses.

Genetic and antigenic characterisation data generated at the WIC for viruses with collection dates after 31 August 2020 and 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. Recommendations for the 2020–2021 northern hemisphere, the upcoming 2021 southern hemisphere and 2021–2022 northern hemisphere seasons, have been published [1, 2, 3].

Due to the low number of influenza-positive specimens detected and therefore available for sharing with WIC, recent influenza characterisation reports, including this one, have been based mainly 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. A single A(H3N2) virus and two A(H1N1)pdm09 viruses from Norway have been characterised genetically and phenotypically since the April 2021 report.

Table 2. Summary of seasonal influenza clinical samples and virus isolates*, with collection dates from 1 September 2020, contained in packages received from EU/EEA Member States since week 40/2020

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]
2020 SEPTEMBER														
Slovakia	6			1	0	5	0							
OCTOBER														
France	3					1	1				2	1		
Slovakia	2					1	0		1	0				
NOVEMBER														
France	2										2	1		
DECEMBER														
France	2										2	1		
2021 JANUARY														
Austria	1										1	1		
Norway	2			1	1						1	1		
Sweden	3					1	1				2	0		
FEBRUARY														
Norway	1			1	1									
March														
April														
Norway	1					1	1							
	23	0	0	3	2	9	3	0	1	0	10	5	0	0
5 Countries		0.00%		13.0%		39.1%			4.3%		43.5%		0.0%	
		52.2%							47.8%					

* Note – where clinical sample and a virus sample isolate from the same patient were received, this is counted as one in the column 'Total received' and the 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 20 nM 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).
As of 7 June 2021.

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 the 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 (6B.1A/183P-1 to -7, abbreviated to 6B.1A1 to 6B.1A7) with updates introduced for the September 2020 WHO VCM. 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 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]. The seven subclades are defined by the HA amino acid substitutions set out below.

1. Subclade **6B.1A1** 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.1A2** 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.1A3** viruses, represented by **A/Norway/3737/2018**, carry HA gene mutations encoding **HA1 T120A** and **S183P** amino acid substitutions.
4. Subclade **6B.1A4** represented by **A/Hungary/20/2018** carries HA gene mutations encoding **HA1 N129D, A144E** and **S183P** amino acid substitutions.
5. Subclade **6B.1A5** viruses carry HA gene mutations encoding **HA1 S183P** and **N260D** amino acid substitutions and are split into two groups designated **6B.1A5A** represented by **A/Norway/3433/2018** with additional **HA1** amino acid substitutions of **N129D** and **T185A**, and **6B.1A5B** represented by **A/Switzerland/3330/2017** with additional amino acid substitutions of **HA1 E235D** and **HA2 V193A**. Two subgroups within the **6B.1A5A** group have been defined based on **HA1** amino acid substitutions of **D187V/A** and **Q189E** (**6B.1A5A+187V/A**) or **K130N**, **N156K**, **L161I** and **V250A** (**6B.1A5A+156K**).
6. Subclade **6B.1A6** viruses, represented by **A/Ireland/84630/2018**, carry HA gene mutations encoding **HA1 T120A** and **S183P** amino acid substitutions, like subclade **6B.1A3** viruses, but fall within a separate phylogenetic branch which is closer to subclade **6B.1A5** viruses.
7. Subclade **6B.1A7** 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 somewhat different profiles. The first is repeated from the April 2021 report and was generated based on sequences from all (n = 51) A(H1N1)pdm09 viruses with collection dates after 31 August 2020 that were deposited and/or released in GISAID as of 30 April 2021 (Figure 1a). Of these, one was from Ghana, **6B.1A5A** group, 44 were **6B.1A5A+187V/A** subgroup (41 from West Africa [with many having additional HA1 substitutions of I166T and A186T], two from Japan and one from the US) and two were **6B.1A5A+156K** subgroup (one each from China and Ghana); two from the US were **6B.1A5B** group (with **HA1 P137S**, K142R, **K160M**, **T216K**, **E235D**, **H296N** and **HA2 V193A** substitutions); and two were from zoonotic cases (swine subclade 1A.3.3.2) one of which, A/Denmark/1/2021, was detected in a human sample collected in January 2021 (Figure 1a). The virus recovered from the zoonotic case in Denmark was not recognised in HI assays performed with post-infection ferret antisera raised against any of the human seasonal A(H1N1)pdm09 vaccine viruses (results not shown). The second phylogeny is based on complete HA sequences that were deposited/released in GISAID (n=417) during May 2021. The great majority of these had collection dates within the 2019−2020 influenza season and were derived from clinical specimens collected in the US, so a collection date cut-off of 1 March 2020 was selected to give a reasonable number (n=114) for inclusion in the phylogeny (Figure 1b). The phylogeny clearly shows a dominance of **6B.1A5A+156K** subgroup viruses in the US at the end of the 2019−2020 season, but of the four viruses with collection dates in January 2021, the three from Togo fall in the **6B.1A5A+187V/A** subgroup while A/Manitoba/02/2021 is a zoonotic H1N1v virus derived from the swine 1A.3.3.2 subclade.

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.1A5A+156K**, were antigenically similar to A/Guangdong-Maonan/SWL1536/2019 (H1N1)pdm09-like viruses (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 7 June 2021].

Since the April 2021 report, two A(H1N1)pdm09 viruses detected in Norway were characterised antigenically at the WIC (Table 3). Both viruses were recognised well by post-infection ferret antisera raised against the 2020−2021 vaccine virus, A/Guangdong-Maonan/SWL1536/2019, and poorly by antiserum raised against the 2021−2022 vaccine virus, A/Victoria/5270/2019. As regards A/Norway/2697/2021, this has an HA falling in subclade 6B.1A7, while sequence is pending for A/Norway/4776/2021.

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

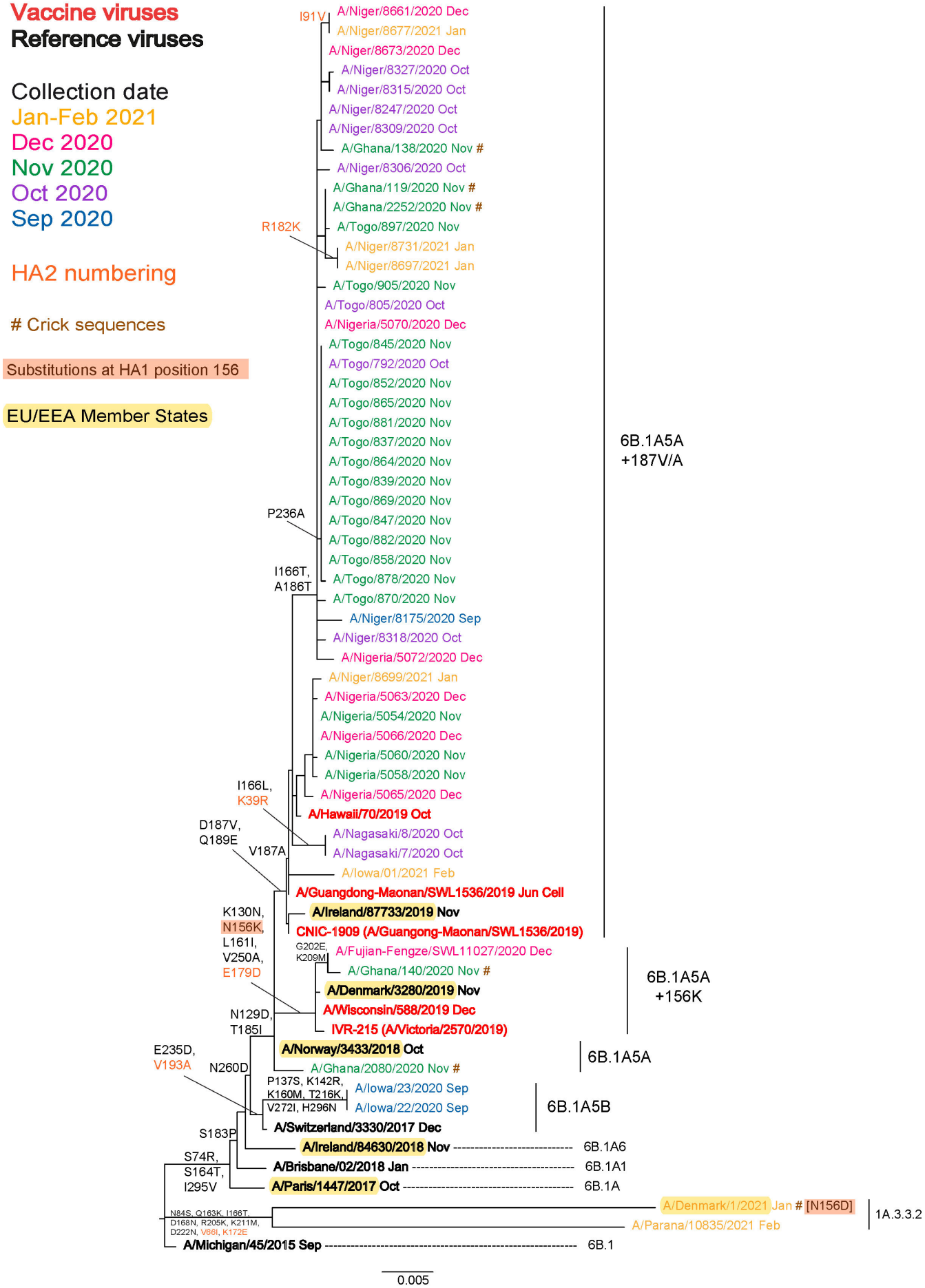


Figure 1b. Phylogenetic comparison of influenza A(H1N1)pdm09 HA genes (GISAID, May 2021)

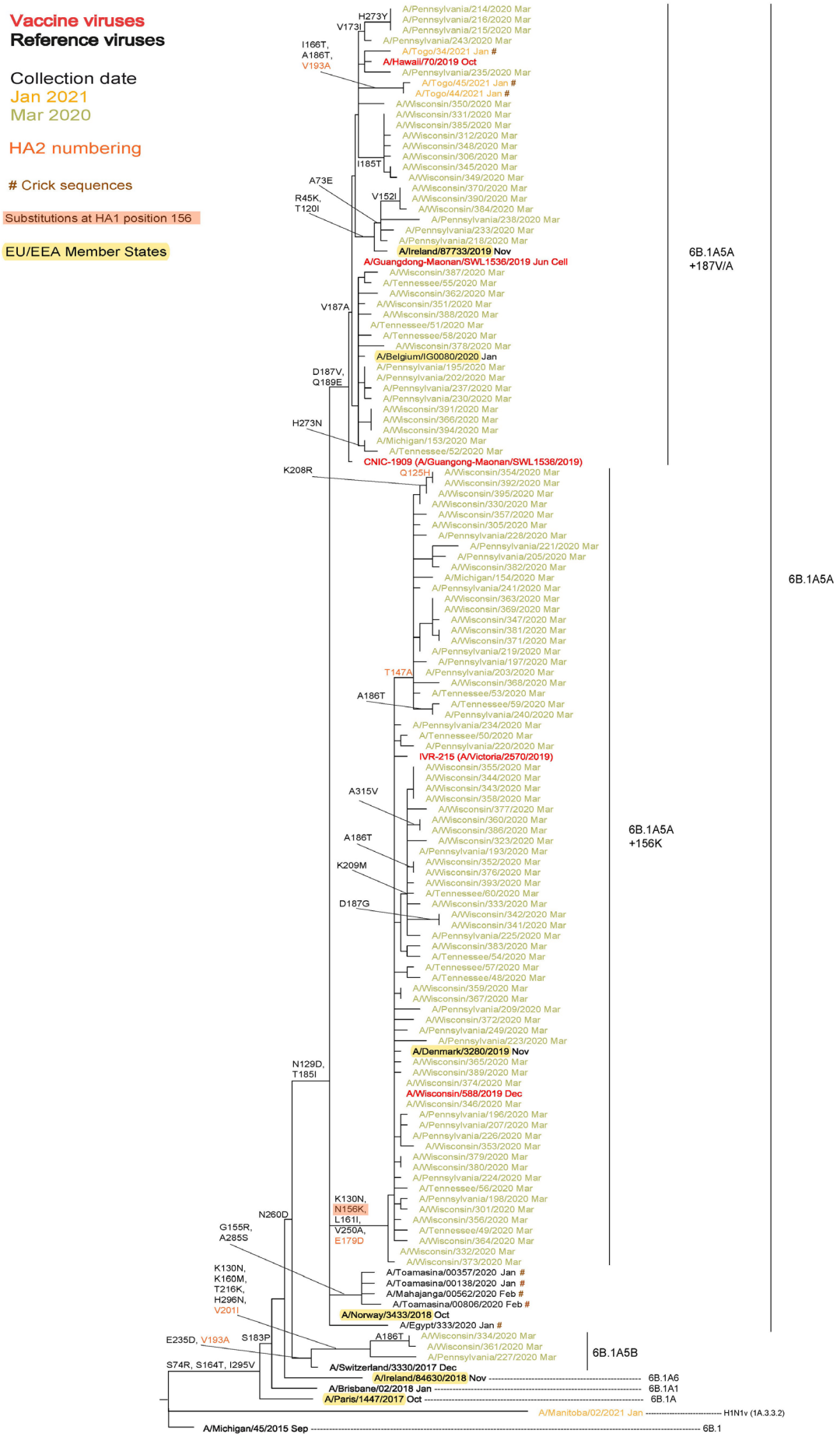


Table 3. Antigenic analysis of A(H1N1)pdm09 viruses by HI

Viruses	Other information	Collection date	Passage history	Haemagglutination inhibition titre							
				Post-infection fereret antisera							
	Passage history			A/Paris 1447/17 MDCK	A/Bris 02/18 Egg	A/Ire 87733/19 Egg St Jude's	A/G-M SWL1536/19 Egg	A/G-M SWL1536/19 MDCK	A/Denmark 3280/19 MDCK	A/Vict 2570/19 Egg	A/Swit 3330/17 Egg
	Ferret number			F03/18*2	F09/19*1	F18/20*1	F12/20*1	F09/20*1	F08/20*1	F26/20*1	F23/18*1
	Genetic group			6B.1A	6B.1A1	6B.1A5A	6B.1A5A	6B.1A5A	6B.1A5A	6B.1A5A	6B.1A5
REFERENCE VIRUSES											
A/Paris/1447/2017	6B.1A	2017-10-20	MDCK1/MDCK3	2560	640	640	1280	640	<	<	640
A/Brisbane/02/2018	6B.1A1	2018-01-04	E3/E2	2560	640	1280	2560	1280	40	80	1280
A/Ireland/87733/2019	D187A, Q189E 6B.1A5A+187V/A	2019-11-03	E4	1280	640	640	2560	1280	40	80	640
A/Guangdong-Maonan/SWL1536/2019	D187A, Q189E 6B.1A5A+187V/A	2019-06-17	E3/E2	1280	320	640	1280	1280	<	40	320
A/Guangdong-Maonan/SWL1536/2019	D187A, Q189E 6B.1A5A+187V/A	2019-06-17	C2/MDCK1	2560	640	1280	2560	2560	40	80	640
A/Denmark/3280/2019	N156K 6B.1A5A+156K	2019-11-10	MDCK4/MDCK5	160	<	80	<	160	>5120	>5120	160
A/Victoria/2570/2019	N156K 6B.1A5A+156K	2018-11-22	E4/E2	80	<	80	80	80	1280	1280	40
A/Switzerland/3330/2017	clone 35 6B.1A5	2017-12-20	E6/E2	1280	640	320	1280	640	<	40	640
TEST VIRUSES											
A/Norway/2967/2021	6B.1A7	2021-01-30	MDCK2	>5120	2560	1280	2560	2560	80	40	1280
A/Norway/4776/2021	Seq pending	2021-02-24	MDCK1	2560	1280	640	2560	1280	<	40	1280
					Vaccine NH 2019-20 SH 2020		Vaccine NH 2020-21			Vaccine SH 2021 NH 2021-22	

* Superscripts refer to antiserum properties (< relates to the lowest dilution of antiserum used)
1 < = <40; 2 < = <80

Influenza A(H3N2) virus analyses

The first A(H3N2) HA phylogeny is repeated from the April 2021 report and was based on sequences from viruses with collection dates after 31 October 2020, available in GISAID as of 30 April 2021, together with sequences from viruses recently characterised at the WIC (Figure 2a). The second is based on sequences deposited/released in GISAID during May 2021 (Figure 2b).

Viruses in clade 3C.2a have been dominant since the 2014–15 influenza season with group 3C.2a1b viruses predominant during the course of the 2019–2020 season in most WHO-defined regions of the world apart from 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. In particular, clade 3C.3a 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. The amino acid substitutions that define these subclades/groups/subgroups are:

8. 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).
9. 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.**
10. Group **3C.2a1b**: those in subclade **3C.2a1** plus **E62G, R142G** and **H311Q** in **HA1**, often with additional amino acid substitutions – notably **HA1 T131K** and **HA2 V200I**, the **3C.2a1b+T131K** subgroup (e.g. **A/Norway/3275/2018**) or **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+T135K** subgroup (e.g. **A/La Rioja/2202/2018**). Distinct clusters of viruses within both these subgroups have emerged, defined by specific **HA1** and/or **HA2** amino acid substitutions: **3C.2a1b+T131K-A** with additional amino acid substitutions of **HA1 K83E** and **Y94N** with **HA2 I193M** (e.g. **A/Christchurch/502/2020**); **3C.2a1b+T131K-B** with **HA2 V18M** substitution, often with additional **HA1** substitutions (e.g. A/South Australia/34/2019); **3C.2a1b+T135K-A** with additional amino acid substitutions of **HA1 A138S**, **F193S** and **S198P**, many also with **G186D** and **D190N** (e.g. **A/Denmark/3284/2019**); and **3C.2a1b+T135K-B** with additional amino acid substitutions of **HA1 S137F, A138S** and **F193S** (e.g. **A/Hong Kong/2671/2019**).
11. Clade **3C.3a**: represented by a former vaccine virus, **A/Switzerland/9715293/2013**, with recently circulating clade **3C.3a** 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 geographical spread of viruses in the antigenically distinct **3C.2a1b+T135K-B** cluster influenced the selection of an A/Hong Kong/2671/2019-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 April report, based on sequences from viruses with collection dates after 31 October 2020 deposited and/or released in GISAID during April 2021, showed a huge preponderance of viruses in group **3C.2a1b** over those in clade **3C.3a** (Figure 2a). Those in the subgroup **3C.2a1b+T135K-A** cluster (n=37) were detected in countries of West Africa, while those in the subgroup **3C.2a1b+T131K-A** cluster (n=39) were split between 'Cambodia-like' viruses (n = 14) carrying additional **HA1** substitutions of **G186S**, **F193S**, **Y195F** and **S198P,** with 13 also having **K171N** (detected in Australia, Cambodia, Japan and Thailand) and 'Bangladesh-like' viruses (n = 25) carrying additional **HA1** substitutions of **Y159N**, **T160I** (loss of a glycosylation site), **L164Q**, **G186D**, **D190N**, **F193S** and **Y195F** (detected in Australia, Bahrain, Bangladesh, India, Sweden, United Arab Emirates and US). The updated phylogeny is based on HA sequences deposited and/or released in GISAID during May 2021 (n=40; Figure 2b). Of the 26 viruses with collection dates during the 2021–2022 season, two single viruses fell into the **3C.2a1b+T131K-A** (A/Cameroon/16996/2020) and **3C.2a1b+T131K-B** (A/Laos/418/2021) clusters, while 10 fell into the 'Cambodia-like' **3C.2a1b+T131K-A** cluster (from Australia and Lao People's Democratic Republic) and 14 into the 'Bangladesh-like' **3C.2a1b+T131K-A** cluster (from Australia, Bangladesh, Nepal, Netherlands, Russian Federation and Sweden).

While the number of detections of seasonal influenza viruses remains low compared to previous seasons, the WHO Collaborating Centres for Influenza have shown viruses in these recently emerged virus clusters to be antigenically distinguishable from one another and other A(H3N2) virus subgroups. A single A(H3N2) virus from Norway was antigenically characterised at the WIC during May and, while gene sequencing is pending, it gave an HI-reactivity profile most similar to a **3C.2a1b+T131K-A** cluster 'Bangladesh-like' virus with the panel of post-infection ferret antisera used (Table 3).

The locations of HA sequences for A/Hong Kong/2671/2019 (**3C.2a1b+T135K-B**) and its cell culture-equivalent A/Hong Kong/45/2019, recommended for egg- and cell culture-generated vaccines to be used in the 2020–2021 northern hemisphere [1] and 2021 southern hemisphere [2] seasons, are indicated on the phylogenies, as are the egg- and cell culture-propagated cultivars of A/Cambodia/e0826360/2020 (**3C.2a1b+T131K-A**), recently recommended for use in northern hemisphere 2021–2022 vaccines [3] (Figures 2a and 2b).

As described in many previous reports[2], influenza A(H3N2) viruses have continued to be 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 has been 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.

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

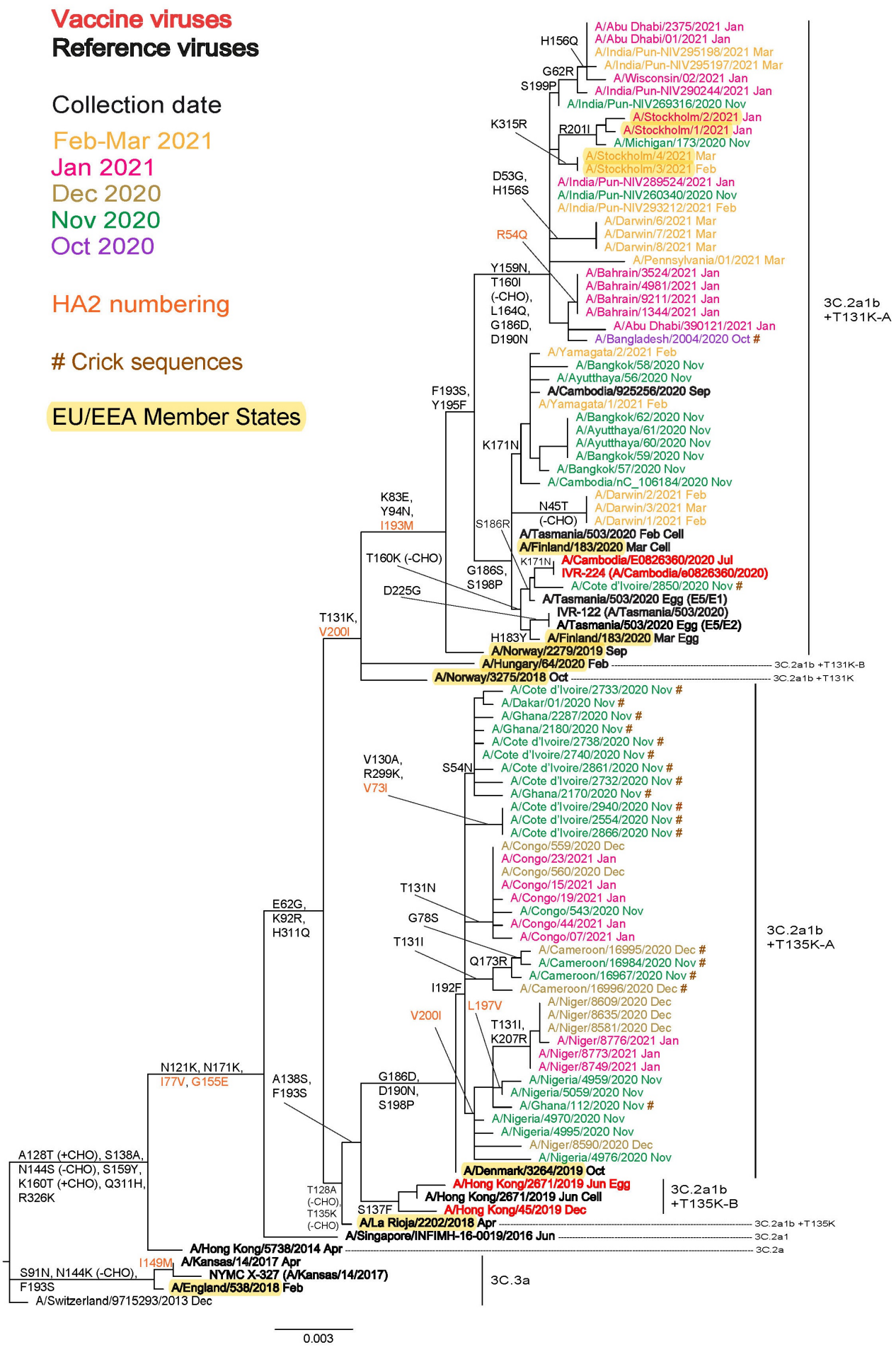


Figure 2b. Phylogenetic comparison of influenza A(H3N2) HA genes (GISAID, May 2021)

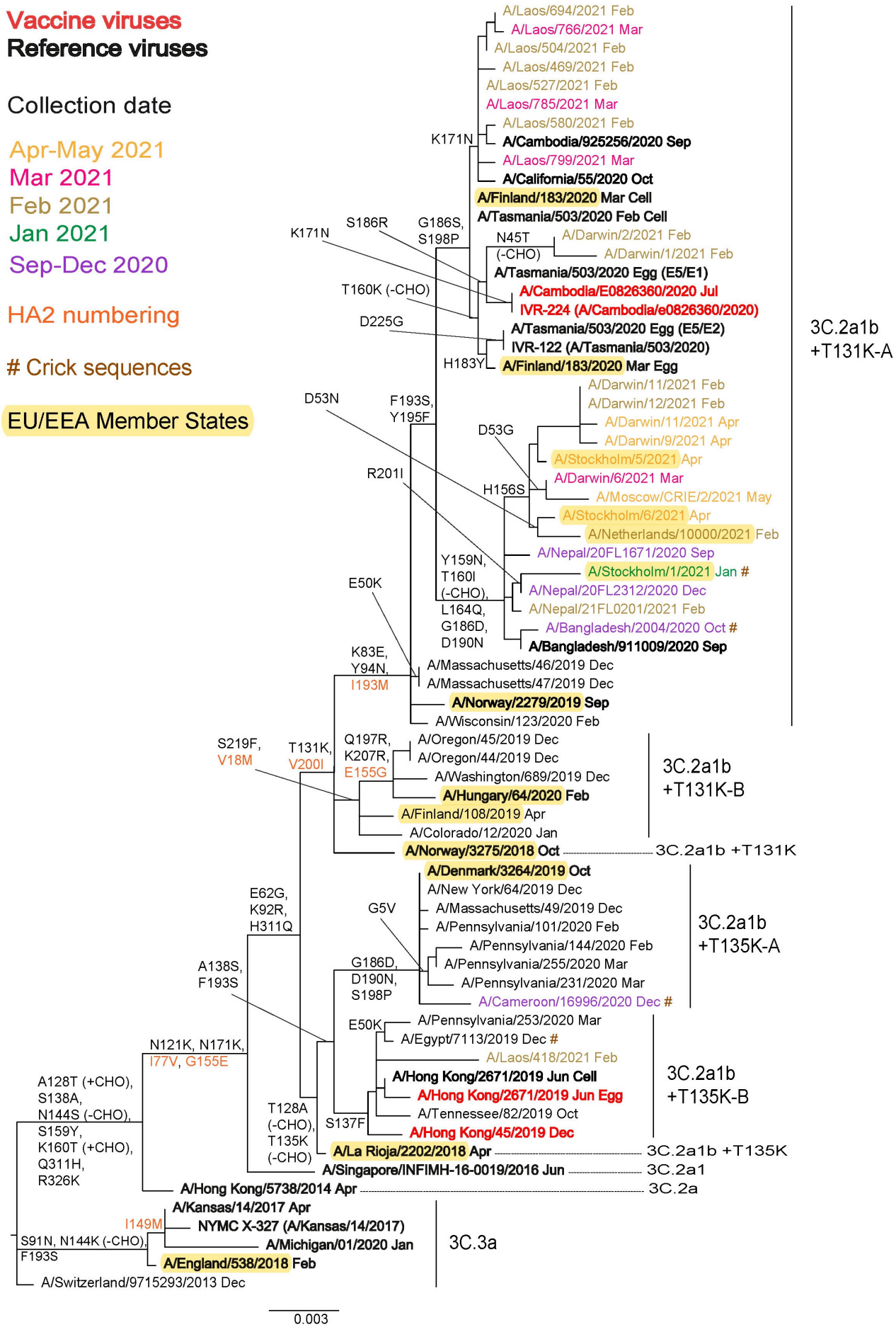


Table 4. Antigenic analysis of A(H3N2) viruses by HI

				Haemagglutination inhibition titre											
				Post-infection ferret antisera											
Viruses	Other information	Collection date	Passage history	A/HK 5738/14 MDCK St Judes F60/17[+1] 3C.2a	A/Singapore 0019/16 Egg 10^{-4} F13/19[+1] 3C.2a1	A/Denmark 3264/19 SIAT F19/20[-1] 3C.2a1b+T135K-A	A/HK 2671/19 Egg F44/19[+1] 3C.2a1b+T135K-B	A/HK 2671/19 Cell St Judes F21/20[-1] 3C.2a1b+T135K-B	A/Camb e0826360/20 Egg F10/21[+1] 3C.2a1b+T131K-A	A/Bang 4005/20 SIAT F07/21[-1] 3C.2a1b+T131K-A	A/Eng 538/18 SIAT F31/18[-1] 3C.3a	NYMC X-327 A/Kansas/14/17 Egg F16/19[-1] 3C.3a	A/Kansas 14/17 SIAT F17/19[-1] 3C.3a
REFERENCE VIRUSES													
A/Hong Kong/5738/2014	3C.2a	2014-04-30	MDCK1/MDCK2/SIAT2	320	320	40	40	40	80	80	320	320	160
A/Singapore/INFIMH-16-0019/2016	3C.2a1	2016-04-14	E5/E3	160	320	80	80	<	40	<	40	40	<
A/Denmark/3264/2019	3C.2a1b+T135K-A	2019-10-25	SIAT5	160	320	320	80	160	160	160	160	160	160
A/Hong Kong/2671/2019	3C.2a1b+T135K-B	2019-06-17	E8/E3	40	160	80	1280	160	160	80	160	640	80
A/Hong Kong/2671/2019	3C.2a1b+T135K-B	2019-06-17	MDCK1/SIAT4	160	320	160	160	320	160	160	160	80	160
A/Cambodia/e0826360/2020	3C.2a1b+T131K-A	2020-07-16	E5/E2	40	80	160	160	<	1280	160	160	80	40
A/Bangladesh/4005/2020	3C.2a1b+T131K-A	2020-10-04	SIAT2	80	80	160	80	40	160	640	320	160	320
A/England/538/2018	3C.3a	2018-02-26	MDCK1/SIAT3	40	80	<	40	<	40	40	640	160	320
NYMC X-327 (A/Kansas/14/17)	3C.3a	2017-12-14	E×/E1	40	<	<	320	<	80	<	320	1280	320
A/Kansas/14/2017	3C.3a	2017-12-14	SIAT3/SIAT2	40	80	40	40	<	80	40	640	320	320
TEST VIRUSES													
A/Norway/10230/2021	Seq pending	2021-04-14	SIAT1	40	80	320	160	40	320	640	320	160	160
					Vaccine NH 2018-19 SH 2018		Vaccine NH 2020-21 SH 2021		Vaccine NH 2021-22			Vaccine NH 2019-20	

* 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 into genetic **clade 1A**, 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 have remained similar antigenically 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 and the 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, as below.

12. A group with double deletion of **HA1** residues **162** and **163** (**subclade △162-163** or **1A(△2)**) 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**.
13. A group with triple deletion of **HA1** residues **162** to **164** (**subclade △162-164A** or **1A(△3)A**) first detected in Asia, with amino acid substitutions of **I180T** and **K209N** that showed limited geographical spread (with no detections having been made recently), represented by **B/Hong Kong/269/2017**.
14. A group with triple deletion of **HA1** residues **162** to **164** (**subclade △162-164B** or **1A(△3)B**) first detected in Africa, with amino acid substitution **K136E** often with **G133R** that showed geographical spread and dominance in recent months, represented by **B/Washington/02/2019**, the vaccine virus recommended after WHO VCMs in February and September 2020, and February 2021 [1,2,3].

The phylogeny generated for the April report focused on HA sequences available in GISAID up to 30 April 2021, for viruses with collection dates after 31 December 2020, together with viruses that had been characterised recently at the WIC (Figure 3a). Only **subclade 1A(△3)B** detections had been reported during 2021, with the vast majority falling in a group defined by **HA1 N150K**, **G184E**, **N197D** (loss of a glycosylation site) and **R279K** (**N150K group**) amino acid substitutions. This **N150K group** split into two subgroups: one showing predominance in China, with additional **HA1** substitutions of **V220M** and **P241Q**, while the second had additional **A127T**, **P144L** and **K203R** substitutions with viruses having been detected in Austria, Bahrain, China, France, Niger, Oman, Saudi Arabia, Spain, Sweden and the US. The latter subgroup could be split further into a cluster of viruses with additional **T182A**, **D197E** and **T221A** substitutions and another cluster of viruses from China with **H122Q** substitution. A single virus, B/Florida/01/2021, fell into a group defined by **HA1 G133R** amino acid substitution.

The second phylogeny is based on complete HA sequences that were deposited/released in GISAID (n=579) during May 2021. The great majority of these had collection dates within the 2019–2020 influenza season and were derived from clinical specimens collected in the US, so a collection date cut-off of 16 February 2020 was selected to give a reasonable number (n=108) for inclusion in the phylogeny (Figure 3b). All the 2019–2020 season viruses from the US clustered with the **B/Washington/02/2019** vaccine virus while the few from the 2020–2021 season fell into the **N150K group,** with all but two falling into a subgroup having additional **A127T**, **P144L**, **E164K** and **K203R** substitutions. The remaining two viruses from the Russian Federation formed a subgroup with **V117I** and **V220M** substitutions.

The WHO Collaborating Centres for Influenza have shown the **HA1 N150K** with **G184E** 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 is indication of geographical spread of viruses in these recently emerged virus subgroups, notably those with **HA1 A127T**, **P144L** and **K203R** substitutions.

Influenza B/Yamagata-lineage

No B/Yamagata-lineage viruses from WHO European Region countries were characterised at the WIC during May 2021 and seven HA sequences, from viruses collected in the US during the 2019–2020 season, were deposited and/or released in GISAID during this month (Figure 4). No HA sequences from viruses with collection dates after March 2020 have been deposited in GISAID and all sequences fell into genetic **clade 3**, 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 northern hemisphere, 2021 southern hemisphere and 2021–2022 northern hemisphere seasons [1, 2, 3]. 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 from: 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, April 2021)

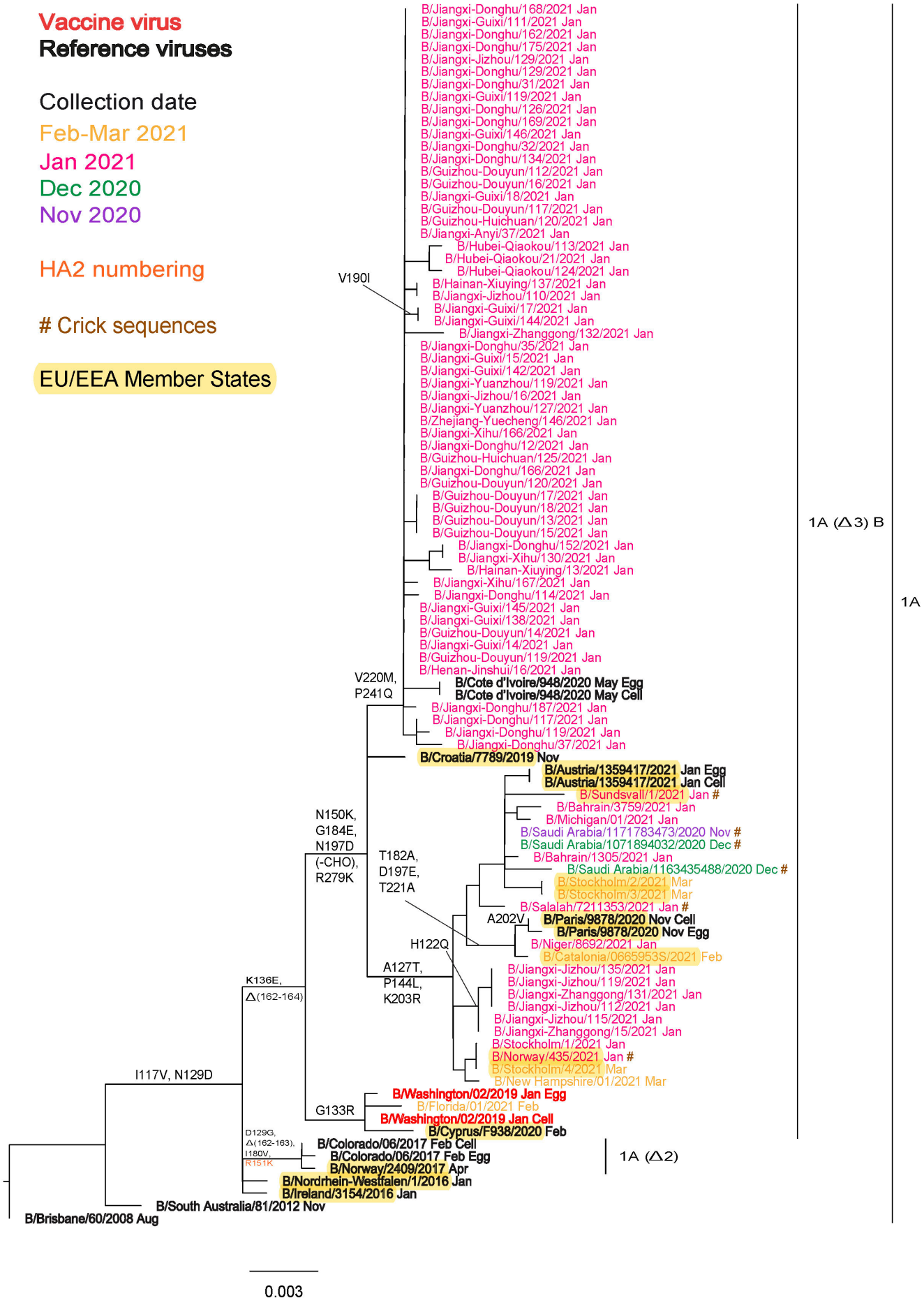


Figure 3b. Phylogenetic comparison of influenza B/Victoria-lineage HA genes (GISAID, May 2021)

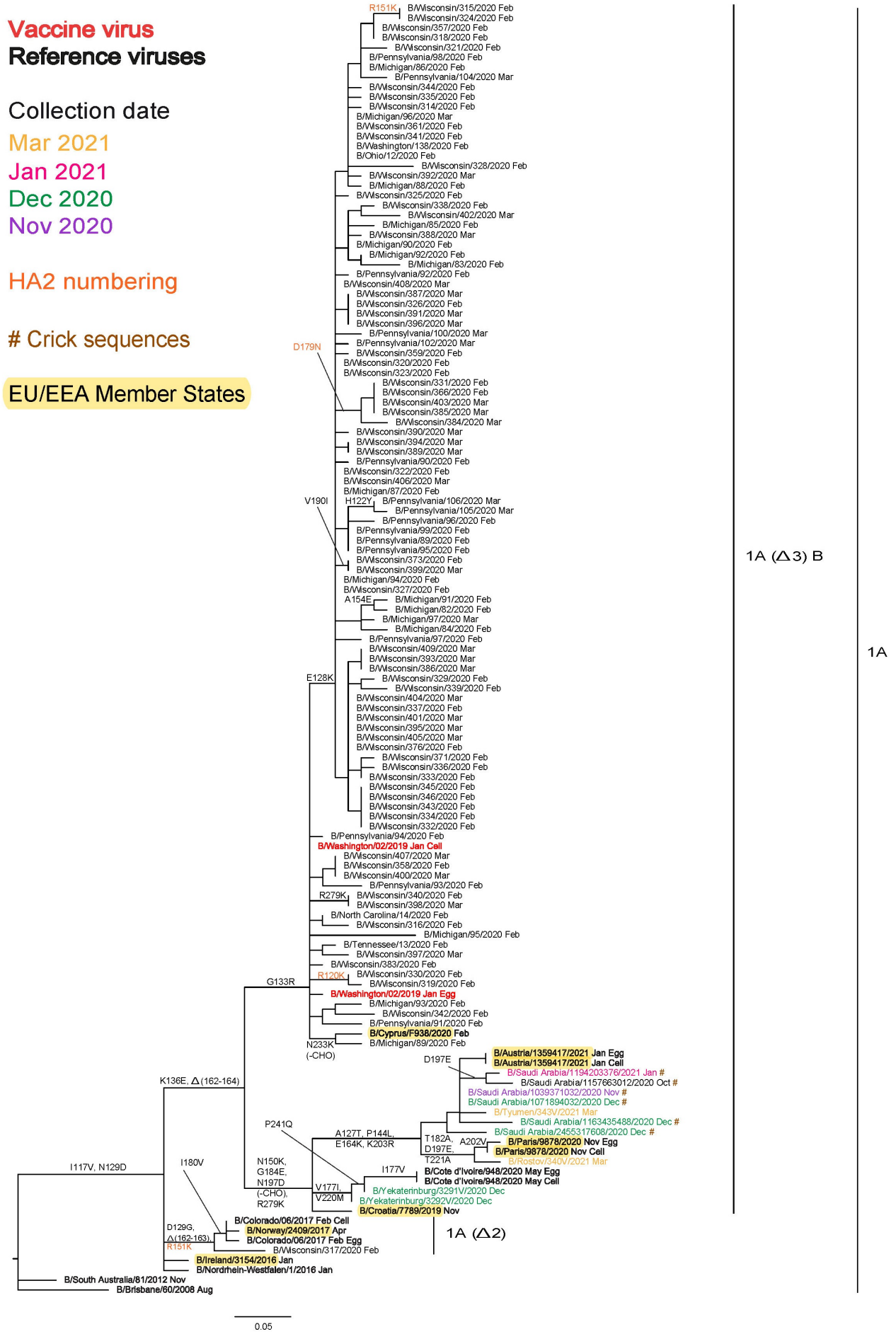
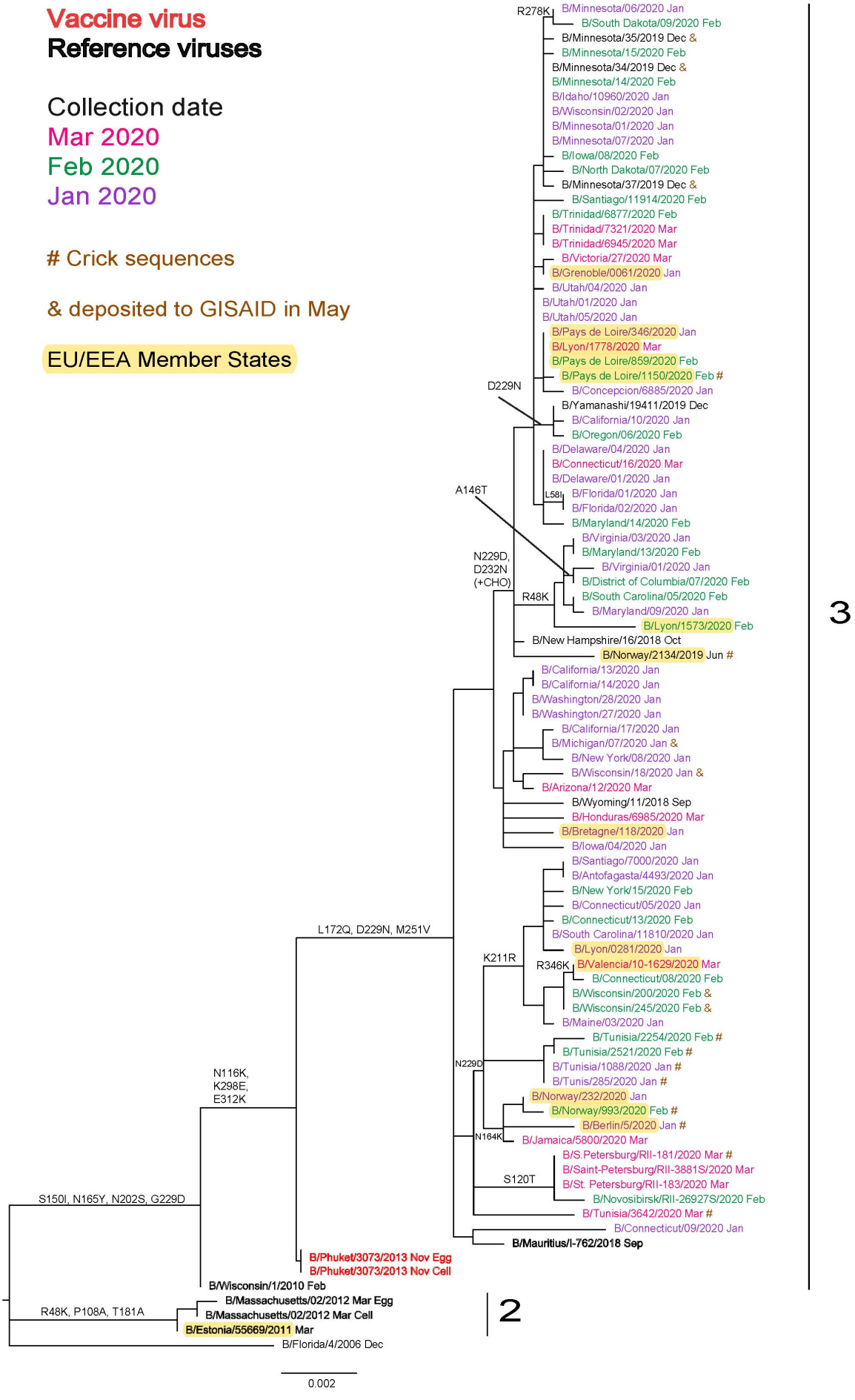


Figure 4. Phylogenetic comparison of influenza B/Yamagata-lineage HA genes (GISAID, May 2021)



Summaries of data submitted to TESSy

Genetic characterisation

Fourteen viruses detected over the course of the 2020–2021 season (weeks 40/2020-20/2021) have been genetically characterised, as detailed below.

15. One A(H1N1)pdm09 virus attributed to the 6B.1A5A+187V/A group represented by A/Guangdong-Maonan/SWL1536/2019.
16. Eight A(H3N2) viruses with six attributed to subgroup 3C.2a1b+T131K-A represented by A/Slovenia/1637/2020, one attributed to subgroup 3C.2a1b+T135K-A represented by A/Denmark/3264/2019 and one attributed to subgroup 3C.2a1b+T131K-B represented by A/Bretagne/1323/2020.
17. Five B/Victoria-lineage viruses, all of which were ascribed to subclade 1A(Δ3)B represented by B/Washington/02/2019.

For the 2019–20 season, 2 752 viruses were characterised genetically and ascribed to a genetic clade up to week 20/2020 (no additional characterisations were reported during weeks 21–39/2020).

18. In total, 982 were A(H1N1)pdm09 viruses, with 945 being subclade 6B.1A5 (904 subgroup 6B.1A5A represented by A/Norway/3433/2018 and 41 subgroup 6B.1A5B represented by A/Switzerland/3330/2018), 19 being subgroup 6B.1A7 represented by A/Slovenia/1489/2019, 11 being subgroup 6B.1A1 represented by A/Brisbane/02/2018 and seven attributed to a known group not listed in the 2019–20 reporting categories.
19. There were 1 048 A(H3N2) viruses, with 342 being subgroup 3C.2a1b+T131K represented by A/South Australia/34/2019, 560 being clade 3C.3a represented by A/Kansas/14/2017, 81 being subgroup 3C.2a1b+T135K-B represented by A/Hong Kong/2675/2019, 64 being subgroup 3C.2a1b+T135K-A represented by A/Denmark/3264/2019 and one attributed to a known group not listed in the 2019–20 reporting categories.
20. A total of 26 were B/Yamagata-lineage clade 3, represented by the vaccine virus B/Phuket/3073/2013, with a further two attributed to a known group not listed in the 2019–20 reporting categories.
21. There were 694 B/Victoria-lineage viruses, with 630 being subclade 1A(Δ3)B represented by B/Washington/02/2019, 19 being subclade 1A(Δ2) represented by the vaccine virus B/Colorado/06/2017, five being subclade 1A(Δ3)A represented by B/Hong Kong/269/2017 and 40 attributed to a known group not listed in the 2019–20 reporting categories.

Antiviral susceptibility

Very few influenza viruses, just four as of week 15/2021 (two each A(H3N2) and B/Victoria-lineage viruses), have been tested for susceptibility to neuraminidase inhibitors (NAIs) and sequence analysis indicated normal inhibition (NI) by both oseltamivir and zanamivir.

Over the course of the 2019–2020 influenza season of 2 292 viruses assessed for susceptibility to NAIs, only nine (0.39%) showed either reduced or highly reduced inhibition (RI/HRI) by at least one NAI.

At the WIC, six influenza viruses detected within EU/EEA countries during the 2020-2021 season have been assessed phenotypically against oseltamivir and zanamivir: two A(H3N2) and four B/Victoria-lineage. All showed NI by both NAIs.

Influenza A(H7N9) virus

On 1 April 2013, the World Health Organization (WHO) Global Alert and Response System [4] reported that the China Health and Family Planning Commission had notified WHO of three cases of human infection with influenza A(H7N9). A description of the characteristics of H7N9 viruses can be found on WHO's website [5]. 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 [six – report currently unavailable due to WHO updating its website]. On 10 February 2017, WHO posted an analysis of information on A(H7N9) viruses [7] and on 3 July 2017 ECDC published a rapid risk assessment on the implications of A(H7N9) for public health [8]. Current risk assessments are included in WHO's monthly summary[5]. The assessment published on 15 April 2021 indicated that there have 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 5 May 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 published on 31 May 2021 and can be found on ECDC's website [12].

[5] WHO monthly summary available at: https://www.who.int/teams/global-influenza-programme/avian-influenza/monthly-risk-assessment-summary (accessed 9 June 2021).

Influenza A(H5) virus

The most recent monthly risk assessment of influenza at the human-animal interface was published by WHO on 15 April 2021. Since the previous risk assessment on 29 January 2021, 12 laboratory-confirmed zoonotic cases have been reported: two involving H5N6 viruses (one each in China and Lao People's Democratic Republic), seven involving H5N8 viruses (the Russian Federation) and three involving H5 viruses (Nigeria at the time of H5N1 outbreaks in poultry) [9]. All cases reported exposure to poultry, and only the case identified in China resulted in death. The latest human case of known A(H5N1) infection was reported on 31 October 2020 by Lao People's Democratic Republic and was the first reported to WHO since the case in Nepal in March 2019 [13].

On 30 September 2020, ECDC published an alert related to outbreaks of avian influenza viruses in Europe [14]. The latest collaborative report from ECDC and the European Food Safety Authority (EFSA), reports 1 672 highly pathogenic avian influenza (HPAI) A(H5) detections between 24 February and 14 May 2021, 580 in poultry, 1 051 in wild birds and 41 in domestic birds [12]. Detections occurred in 24 EU/EEA countries and the UK. Of the poultry detections, 297 were reported by Poland and 168 by Germany, and of the wild bird detections 603 were reported by Germany, 167 by Denmark and 56 by Poland. A second peak of HPAI-associated wild bird mortality in north-west Europe was recorded between February and April 2021. While a variety of HPAI virus subtypes and different genotypes were detected, suggesting the occurrence of multiple virus introductions into Europe, the great majority of recent detections were subtype A(H5N8). According to reports compiled by the Food and Agricultural Organization of the United Nations (FAO) as of 26 May, various influenza A(H5Nx) subtypes have continued to be detected in wild and/or domestic birds in Africa, Europe and Asia. Since 28 April 2021, a total of 488 outbreaks had been reported, but no official reports of any zoonotic events [15].

Influenza A(H9N2) virus

Since the previous WHO update on 29 January 2021 ten laboratory-confirmed human cases of influenza A(H9N2) virus infection have been reported, nine in China and one in Cambodia [9]. Nine cases were in children and one in an adult aged 54 with underlying conditions, with six cases reporting exposure to poultry while four of the child cases reported either unknown exposure (n=3) or no exposure (n= 1). Recovery was reported for nine of the cases with no outcome reported for the case involving a six-year old. Avian influenza A(H9N2) viruses are enzootic in poultry in Asia and increasingly reported in poultry in Africa. The latest ECDC/EFSA report includes mention of these 10 human infections with H9N2 viruses, following on from the previous report up to 23 February 2021 [12]. The latest FAO situation update on Global AIV with zoonotic potential reported no cases of human infection with A(H9N2) since the previous update on 28 April 2021 [15].

Other influenza zoonotic events

Since the previous WHO update on 29 January 2021, two zoonotic events with swine-related influenza viruses, A(H1N1)v, have been reported to WHO, one by Denmark and one by US [9]. Both patients recovered and, while the 73-year old Danish patient had no exposure to animals before disease onset, the >18-year old US patient had worked with swine.

A single zoonosis with a swine A(H3N2)v virus was reported from Australia [9]. A 10-year old male was infected in January 2021, without identified exposure to swine, and the virus was nearly identical to a virus detected in a sample from a person in Australia in 2018. Phylogenetically, both Australian viruses grouped with other A(H3N2)v swine influenza viruses detected in Australia and US over the last decade.

WHO Collaborating Centre reports

A description of results generated by the London WHO Collaborating Centre at the WIC and used at the February 2021 WHO vaccine composition meeting (held online 17–25 February 2021 for seasonal influenza viruses), and previous results can be found at https://www.crick.ac.uk/partnerships/worldwide-influenza-centre/annual-and-interim-reports (accessed 7 June 2021).

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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