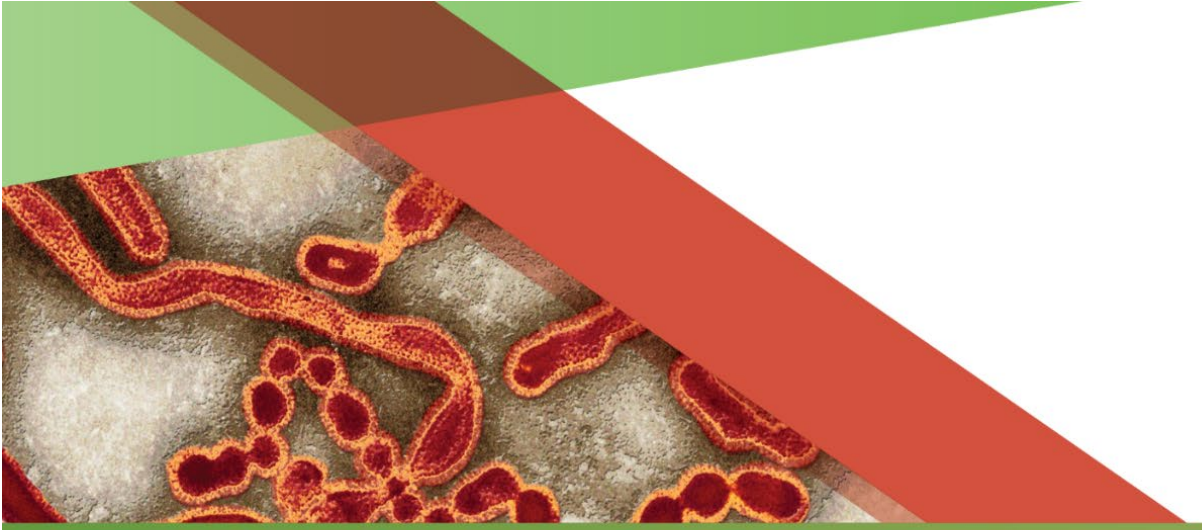

SURVEILLANCE REPORT

Influenza virus characterisation

Summary Europe, June 2021

Summary

This is the eighth report for the 2020-2021 influenza season. As at week 24/2021, only 934 influenza detections across the World Health Organization (WHO) European Region had been reported to The European Surveillance System (TESSy); 51% were type A viruses, with A(H3N2) and A(H1N1)pdm09 being approximately equally represented and 49% were 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 May 2021 characterisation report[1], one shipment from an EU/EEA country (Sweden) containing eight virus isolates was 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 with collection dates after 31 December 2020, which are available in GISAID together with sequences recently determined at the WIC. The data continue to show extremely low levels of influenza detections globally.

Just 79 A(H1N1)pdm09 HA sequences from viruses detected in the 2021 season were available in GISAID, 76 of which were subgroup 6B.1A5A+187V/A, represented by A/Guangdong-Maonan/SWL1536/2019 (the vaccine virus for the northern hemisphere 2020-2021 season), and 72 of these were detected in West Africa. Sporadic detections occurred elsewhere: Belgium (n = 1), India (n=1), Norway (n = 2; both subclade 6B.1A7) and the United States (US; n = 3; one subclade 6B.1A5A+156K).

Of the 74 HA sequences from recently collected A(H3N2) viruses, one fell in subgroup 3C.2a1b+T135K-B, 13 in subgroup 3C.2a1b+T135K-A (all from Africa), and 60 in subgroup 3C.2a1b+T131K-A. The 3C.2a1b+T131K-A subgroup viruses split into two antigenically distinguishable clusters originally defined by viruses from Cambodia (n = 13; with HA1 amino acid substitutions of G186S, F193S, Y195F and S198P, and many also having K171N) and Bangladesh (n = 47; 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 geographic spread. The five viruses from Sweden characterised in June were Bangladesh-like genetically and showed a HI profile of reactivity, with a panel of post-

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

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Suggested citation: European Centre for Disease Prevention and Control. Influenza virus characterisation, summary Europe, June 2021. Stockholm: ECDC; 2021.

infection ferret antisera that was characteristic of 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 91 B/Victoria-lineage HA sequences were subclade 1A(△3)B, with just four from the US falling in a group defined by HA1 G133R substitution; all others were from N150K group viruses with HA1 amino acid substitutions of N150K, G184E, N197D (loss of a glycosylation site) and R279K. N150K group sequences split into two subgroups, one of which, defined by HA1 substitutions V117I and V220M, was confined to 58 sequences from viruses detected in China in January while the second (n = 29 sequences), defined by HA1 substitutions A127T, P144L, E164K and K203R (with eight having additional substitutions of T182A, D197E and T221A), shows significant geographic spread. The eight viruses detected in EU/EEA countries all fell in the latter subgroup, with just one having the additional amino acid substitutions. 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). This is clearly the case for the three N150K group viruses from Sweden, characterised by HI in June.

No B/Yamagata-lineage HA sequences from clinical specimens collected in 2021, and none with collection dates after March 2020, were available. All of the 77 sequences from viruses detected in 2020, inclusive of 12 from EU/EEA countries, belong to genetic clade 3 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 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 World Health Organization (WHO) European Region reported to The European Surveillance System (TESSy) database for the 2020-2021 season (weeks 40/2020-24/2021), compared with the same period for the 2019-2020 season. While there has been a small increase in the numbers of samples from patients fulfilling influenza-like illness (ILI) and/or acute respiratory infection (ARI) criteria being tested (~20 335, 2.2%), there has been a vast reduction in the number of samples testing positive for an influenza virus (163 949, 99.4%). This is probably due 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 over the first 38 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), with a reversal in the proportions of influenza A subtypes, while B/Victoria lineage viruses appear, again, to be predominating over B/Yamagata lineage viruses. However, only 16/456 (3.5%) of type B viruses detected in the 2020-2021 season have been ascribed to a lineage as at week 24/2021.

Table 1. Influenza virus detections in the WHO European Region from the start of reporting for the 2020-21 season (weeks 40/2020-24/2021)[a]

Virus type/subtype/lineage	Cumulative number of detections for weeks 40/2020-24/2021			Totals*		Cumulative number of detections for weeks 40/2019-25/2020			Totals*	
	Sentinel sources	Non-sentinel sources	Totals	%	Ratios	Sentinel sources	Non-sentinel sources	Totals	%	Ratios
Influenza A	**30**	**448**	**478**	**51.2**	**1.1:1**	**11302**	**108948**	**120250**	**72.9**	**2.7:1**
A(H1N1)pdm09	14	28	42	41.6		6126	20302	26428	56.0	
A(H3N2)	8	51	59	58.4	1.4:1	4174	16593	20767	44.0	0.8:1
A not subtyped	8	369	377			1002	72053	73055		
Influenza B	**17**	**439**	**456**	**48.8**		**6325**	**38308**	**44633**	**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	15	425	440			3853	36212	40065		
Total detections (total tested)	**47 (43 238)**	**887 (>903 556)**	**934 (>946 794)**			**17 627 (51 946)**	**147 256 (>874 513)**	**164 883 (>926 459)**		

[a] Numbers taken from Flu News Europe to week 24/2021 and week 25/2020 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, eight shipments of specimens (virus isolates and/or clinical specimens) were received at the Crick Worldwide Influenza Centre (WIC). One shipment was received from Sweden in June 2021 and contained eight virus isolates (Table 2). In total, the packages contained 31 virus-related samples with collection dates after 31 August 2020 and were made up of 17 type A viruses and 14 type B viruses.

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

Due to the low number of influenza-positive specimens detected and thereby available for sharing with WIC, recent influenza characterisation reports, and 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. Five A(H3N2) viruses and three B/Victoria-lineage viruses from Sweden were characterised genetically and antigenically since the May 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	4					2	2				2	0		
FEBRUARY														
Norway	1			1	1									
Sweden	1					1	1							
March														
Sweden	4					1	1				3	3		
April														
Norway	1					1	1							
Sweden	2					2	2							
5 Countries	31	0	0	3	2	14	8	0	1	0	13	8	0	0
		0.00%		9.7%		45.2%			3.2%		41.9%		0.0%	
		54.8%							45.2%					

* 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)

Includes RNA extracts for which genetic characterisation only can be performed.

As of 2021-06-30

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 (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 following HA amino acid substitutions:

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 splits 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 May 2021 report and was generated 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 United States (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 1a). 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 second phylogeny is based on sequences from viruses collected in the course of 2021, as available in GISAID at the end of June and/or generated at the WIC: just 79 in total, with none having collection dates after April (Figure 2b). Of these 79, two viruses detected in Norway were subclade **6B.1A7**, a single virus from the US was subgroup **6B.1A5A+156K** but with **HA1 K156Q** amino acid substitution, and 76 were subgroup **6B.1A5A+187V/A** viruses. The great majority (n = 68) of these viruses were detected in Togo and 45 had additional **HA1 I166T** and **A186T** substitutions. The remaining eight subgroup **6B.1A5A+187V/A** viruses were detected in Belgium (n = 1), India (n = 1), Niger (n =4) and the US (n = 2).

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 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 5 July 2021).

Since the May 2021 report, no A(H1N1)pdm09 viruses detected in EU/EEA countries were characterised antigenically at the WIC, but the two viruses from Norway reported on in May fell into subclade **6B.1A7**.

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

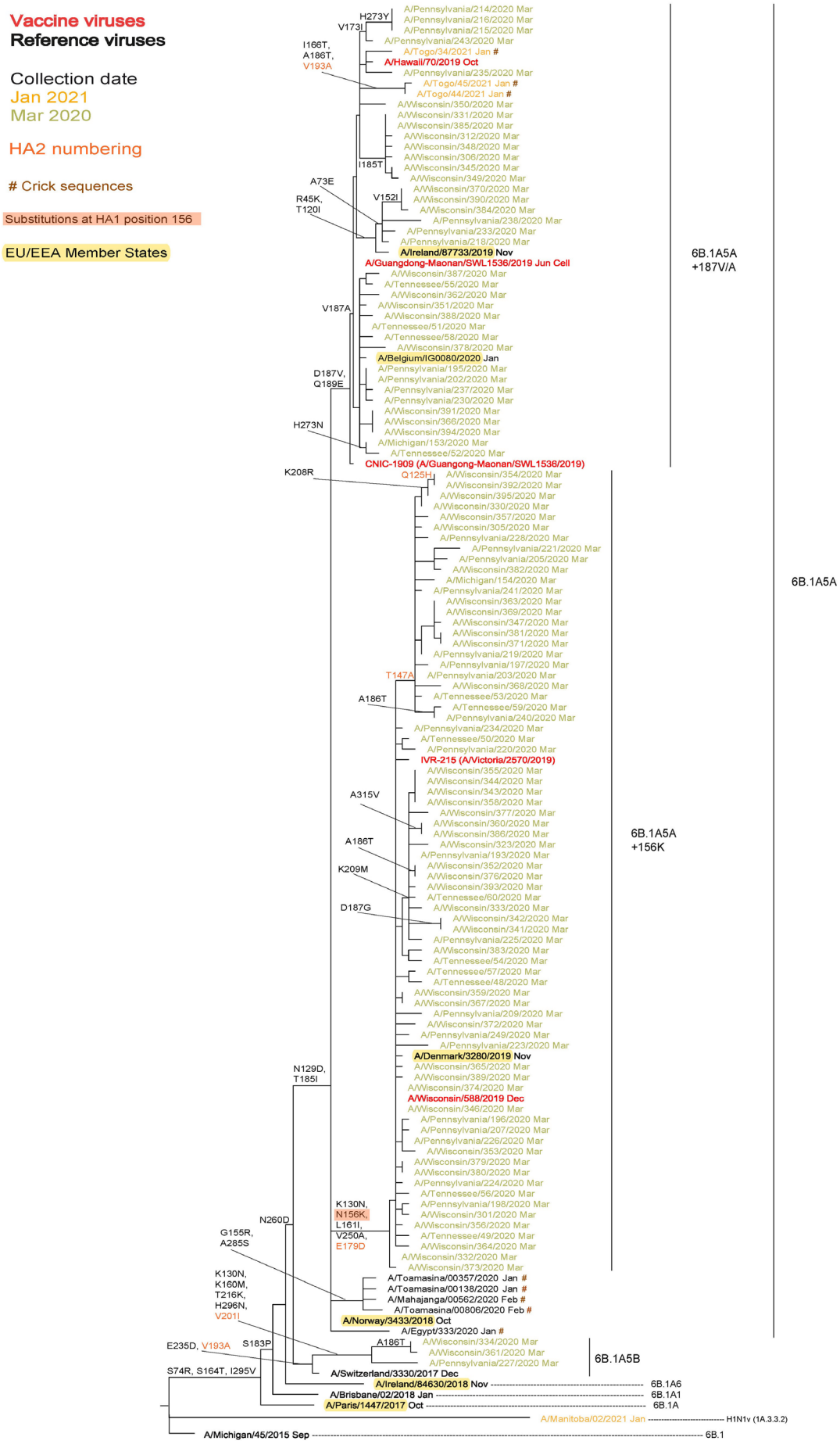
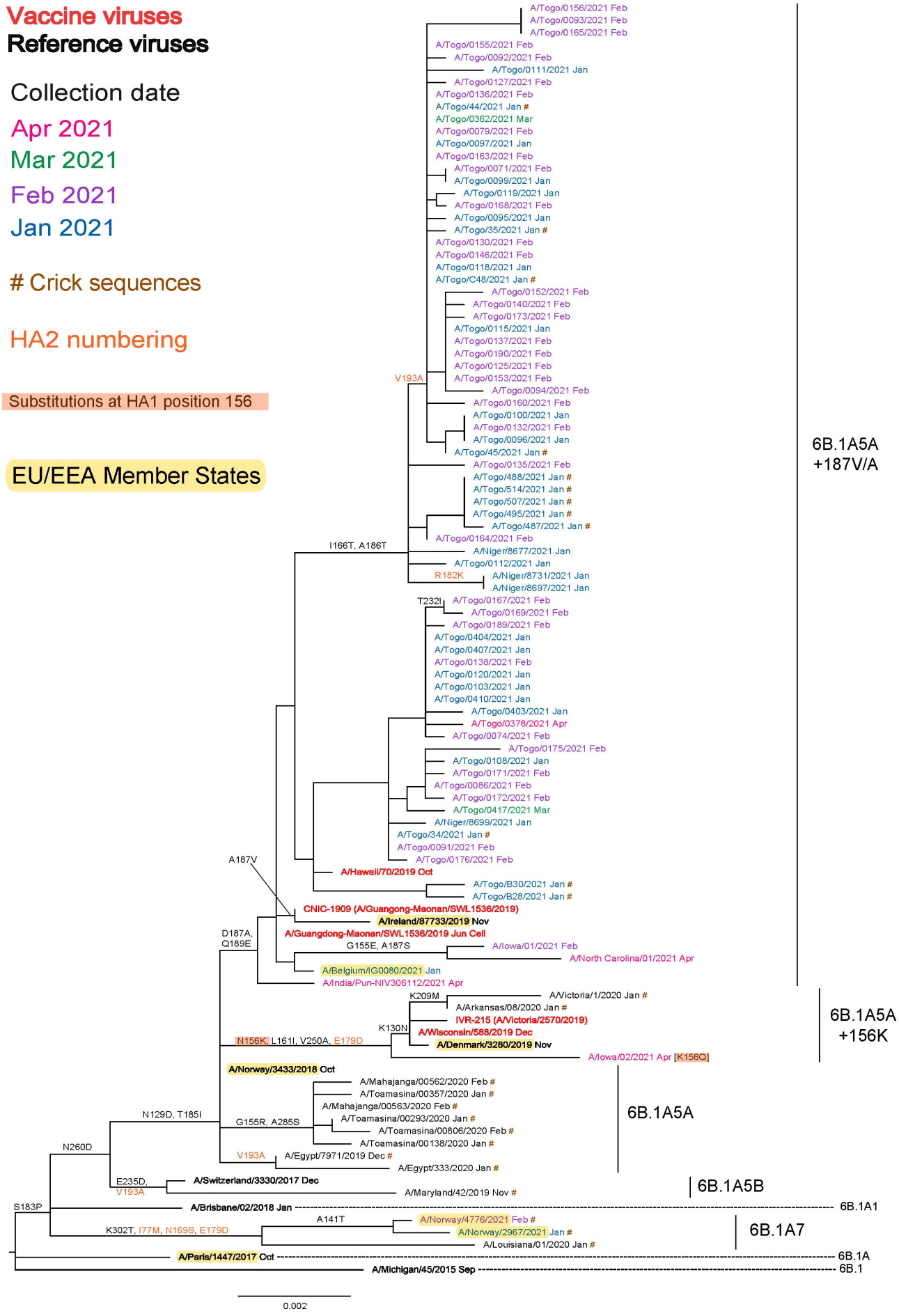


Figure 1b. Phylogenetic comparison of influenza A(H1N1)pdm09 HA genes (GISAID, June 2021)



Influenza A(H3N2) virus analyses

The first A(H3N2) HA phylogeny is repeated from the May 2021 report and was based on sequences deposited/released in GISAID during May 2021 (Figure 2a). The second is based on sequences from viruses collected in the course of 2021, as available in GISAID at the end of June and/or generated at the WIC (just 74 in total).

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, except 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 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 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**).
- 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 geographic 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 May report was based on sequences deposited and/or released in GISAID during May 2021 (n = 40; Figure 2a). Of the 26 viruses with collection dates during the 2020-2021 season, single viruses fell in the **3C.2a1b+T135K-A** (A/Cameroon/16996/2020) and **3C.2a1b+T135K-B** (A/Laos/418/2021) clusters, while 10 fell in the Cambodia-like **3C.2a1b+T131K-A** cluster, carrying additional **HA1** substitutions of **G186S**, **F193S**, **Y195F** and **S198P** with eight also having **K171N** (from Australia and Lao People's Democratic Republic) and 14 in the Bangladesh-like **3C.2a1b+T131K-A** cluster carrying additional **HA1** substitutions of **Y159N**, **T160I** (loss of a glycosylation site), **L164Q**, **G186D**, **D190N**, **F193S** and **Y195F** (from Australia, Bangladesh, Nepal, the Netherlands, the Russian Federation and Sweden). The updated phylogeny based on HA sequences from viruses within collection dates in 2021 again contains the single **3C.2a1b+T135K-B** virus (A/Laos/418/2021), 13 **3C.2a1b+T135K-A** viruses (all from Africa: Congo (n =5), Niger (n =3) and Togo (n = 5)), 13 Cambodia-like **3C.2a1b+T131K-A** viruses from Australia (n = 3), Japan (n = 2) and Laos (n = 8), and 47 Bangladesh-like **3C.2a1b+T131K-A** viruses showing wider geographic spread, with eight being detected in EU/EEA countries (the Netherlands (n = 1), Norway (n = 1) and Sweden (n = 6)). All eight viruses from EU/EEA countries carried additional **HA1 L164Q** and **D190N** substitutions.

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. Five A(H3N2) viruses from Sweden were antigenically characterised at the WIC in June and all 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), which is supported by the phylogenetic analysis (Figure 2b).

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 recently recommended 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, May 2021)

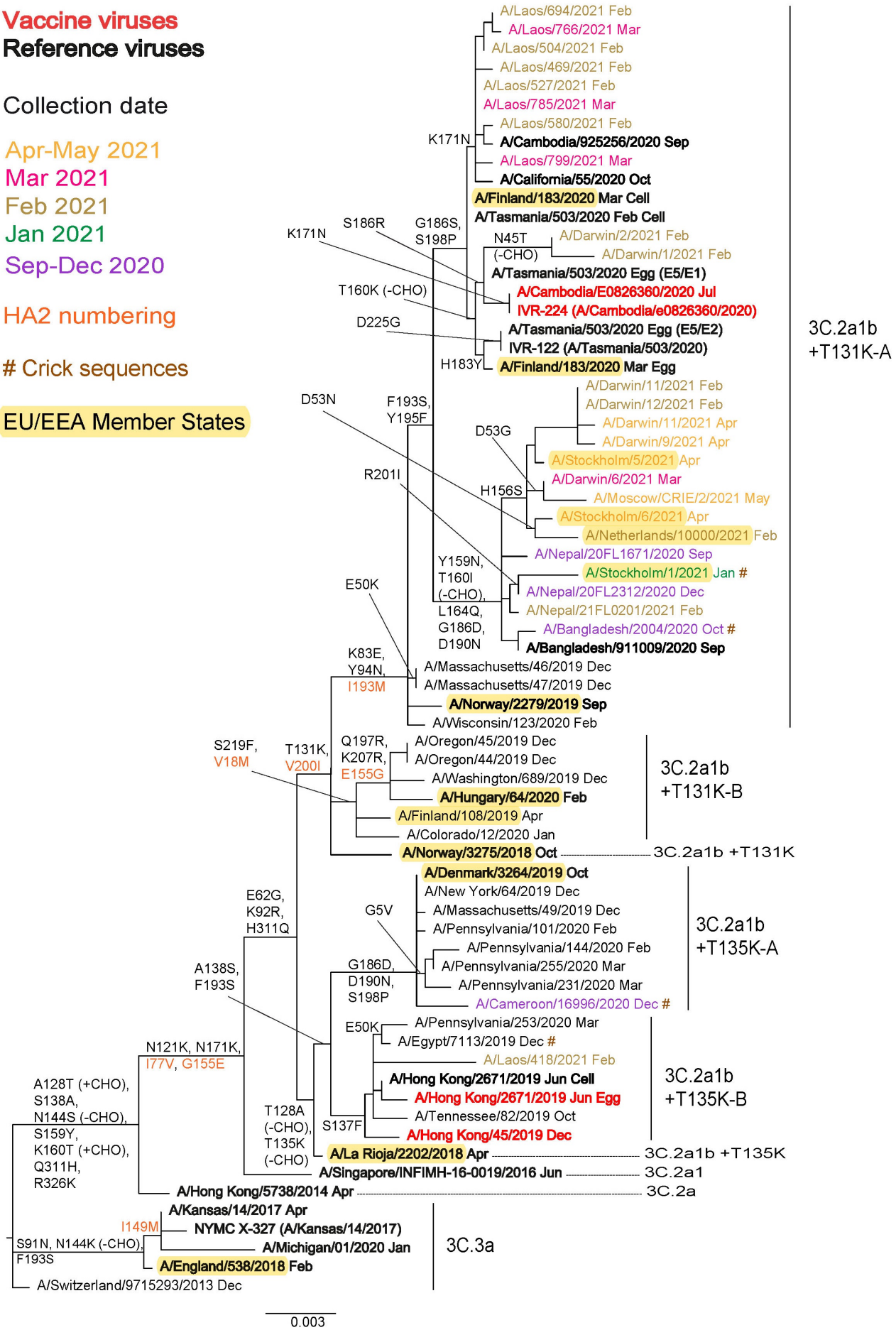


Figure 2b. Phylogenetic comparison of influenza A(H3N2) HA genes (GISAID, June 2021)

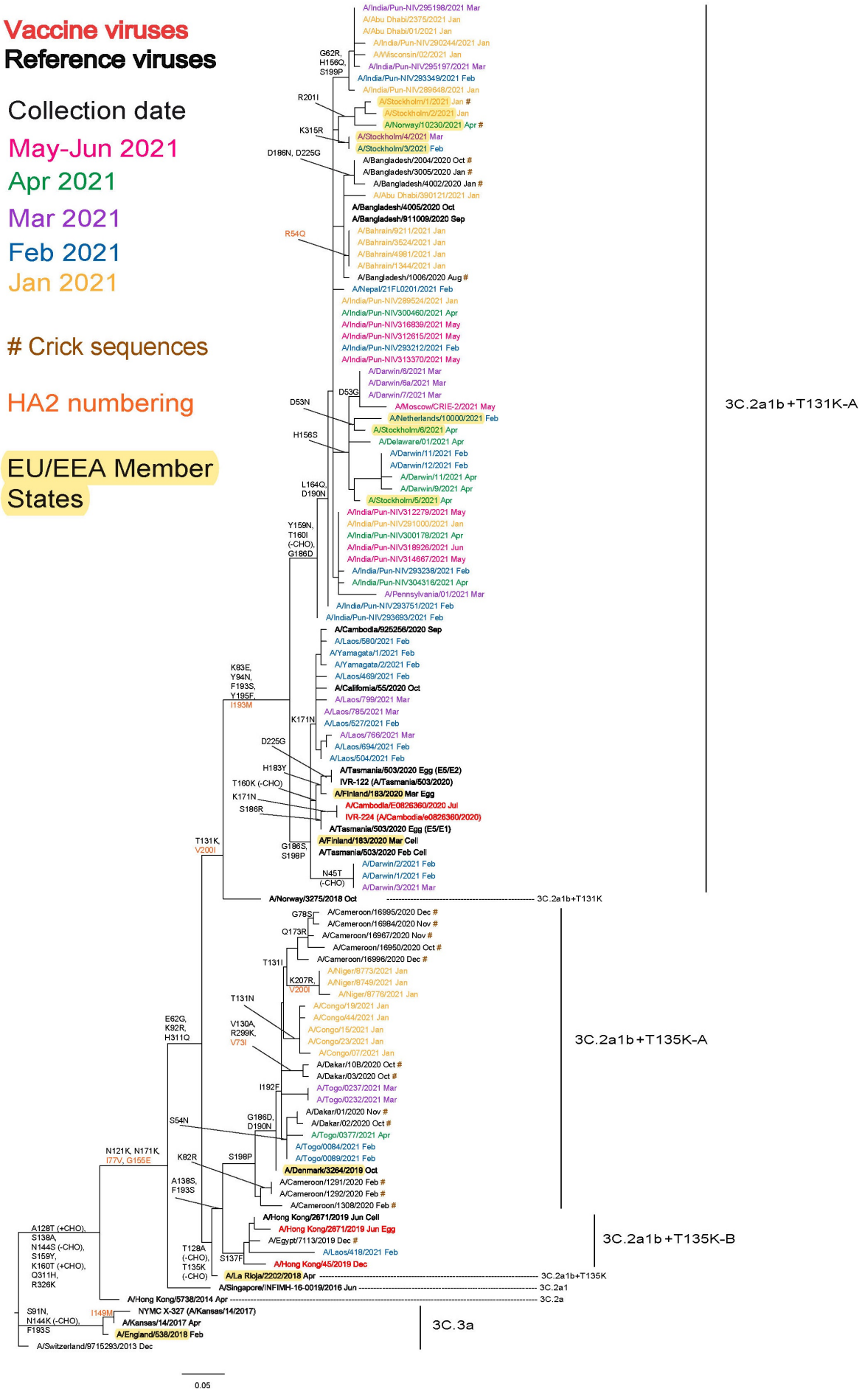


Table 3. Antigenic analysis of A(H3N2) viruses by HI

Viruses	Other information	Collection date	Passage history	Haemagglutination inhibition titre								
				Post-infection ferret antisera								
	Passage history			A/HK 5738/14 MDCK St Judes	A/Singapore 0019/16 Egg 10^{-4}	A/Denmark 3264/19 SIAT	A/HK 2671/19 Egg	A/HK 2671/19 Cell St Judes	A/Camb e082636O/20 Egg	A/Bang 4005/20 SIAT	A/Eng 538/18 SIAT	NYMC X-327 A/Kansas/14/17 Egg
	Ferret number			F60/17[*1]	F13/19[*1]	F19/20[*1]	F44/19[*1]	F21/20[*1]	F10/21[*1]	F07/21[*1]	F31/18[*1]	F16/19[*1]
	Genetic group			3C.2a	3C.2a1	3C.2a1b+T135K-A	3C.2a1b+T135K-B	3C.2a1b+T135K-B	3C.2a1b+T131K-A	3C.2a1b+T131K-A	3C.3a	3C.3a
REFERENCE VIRUSES												
A/Hong Kong/5738/2014	3C.2a	2014-04-30	MDCK1/MDCK2/SIAT2	160	320	<	<	40	40	80	160	160
A/Singapore/INFIMH-16-0019/2016	3C.2a1	2016-04-14	E5/E3	80	320	40	40	<	<	<	80	<
A/Denmark/3264/2019	3C.2a1b+T135K-A	2019-10-25	SIAT5	80	160	80	40	160	80	160	160	40
A/Hong Kong/2671/2019	3C.2a1b+T135K-B	2019-06-17	E8/E2	<	80	80	640	160	160	80	320	320
A/Hong Kong/2671/2019	3C.2a1b+T135K-B	2019-06-17	MDCK1/SIAT4	80	160	160	160	160	80	160	160	40
A/Cambodia/e0826360/2020	3C.2a1b+T131K-A	2020-07-16	E5/E2	<	80	80	80	<	1280	160	160	80
A/Bangladesh/4005/2020	3C.2a1b+T131K-A	2020-10-04	SIAT2	<	40	80	80	<	160	320	320	80
A/England/538/2018	3C.3a	2018-02-26	MDCK1/SIAT3	<	40	<	<	<	<	40	640	160
NYMC X-327 (A/Kansas/14/17)	3C.3a	2017-12-14	E×/E1	<	<	<	160	<	40	40	320	1280
A/Kansas/14/2017	3C.3a	2017-12-14	SIAT3/SIAT2	40	40	<	<	<	<	40	640	160
TEST VIRUSES												
A/Stockholm/2/2021	3C.2a1b+T131K-A	2021-01-23	SIAT0/SIAT1	<	40	80	80	<	160	320	320	80
A/Stockholm/3/2021	3C.2a1b+T131K-A	2021-02-19	SIAT0/SIAT1	40	40	80	80	<	80	640	320	80
A/Stockholm/4/2021	3C.2a1b+T131K-A	2021-03-11	SIAT0/SIAT1	<	40	80	80	<	160	320	160	80
A/Stockholm/5/2021	3C.2a1b+T131K-A	2021-04-16	SIAT0/SIAT1	<	<	40	40	<	40	160	80	40
A/Stockholm/6/2021	3C.2a1b+T131K-A	2021-04-23	SIAT0/SIAT1	<	<	<	<	<	80	320	160	80
					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 in 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:

- 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**.
- 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 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 △162-164B** or **1A(△3)B**) first detected in Africa, with amino acid substitution **K136E** often with **G133R** that showed geographic 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 May report focused 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 3a). All the 2019-2020 season viruses from the US clustered with the **B/Washington/02/2019** (**subclade 1A(△3)B**) vaccine virus, while the few from the 2020-2021 season fell in the **N150K group,** defined by **HA1 N150K**, **G184E**, **N197D** (loss of a glycosylation site) and **R279K** (**N150K group**) amino acid substitutions, with all but two falling in 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 second phylogeny is based on sequences from viruses collected in the course of 2021, as available in GISAID at the end of June and/or generated at the WIC: just 91 in total, all belonging to **subclade 1A(△3)B** (Figure 3b). Of these, four detected in the US (with three detected in Texas in May) belong to the current **B/Washington/02/2019** vaccine group and carry **HA1 G133R** substitution, 58 (all from China, with collection dates in January) belong to the **N150K group** and have additional **HA1 V117I** and **V220M** substitutions, and 29 (detected in Africa, Asia, Europe, the Middle East and North America, with 8 reported by EU/EEA countries; Austria (n = 1), Norway (n = 1), Spain (n = 1) and Sweden (n = 5)) belong to the **N150K group** and have additional **HA1 A127T**, **P144L** and **K203R** substitutions with eight of these 29 also carrying **HA1 T182A**, **D197E** and **T221A** substitutions.

The WHO Collaborating Centres for Influenza have shown the **N150K 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 geographic spread of viruses in these recently emerged virus subgroups, notably those with **HA1 A127T**, **P144L** and **K203R** substitutions. Since the May report, three **N150K group** viruses with **HA1 A127T**, **P144L** and **K203R** substitutions from Sweden have been characterised antigenically with a panel of post-infection ferret antisera (Table 4). All three showed poor reactivity with antisera raised against the current vaccine virus but good reactivity with antisera raised against either B/Austria/1359417/2021 or B/Paris/9878/2020.

Influenza B/Yamagata-lineage

It is assumed that no B/Yamagata-lineage viruses were detected after March 2020, as no sequences for such viruses with collection dates after this have been released in GISAID as at 30 June 2021. Figure 4 was generated based on the 77 HA sequences from viruses with collection from 31 December 2019 to 31 March 2020, available in GISAID. All sequences fell in 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, May 2021)

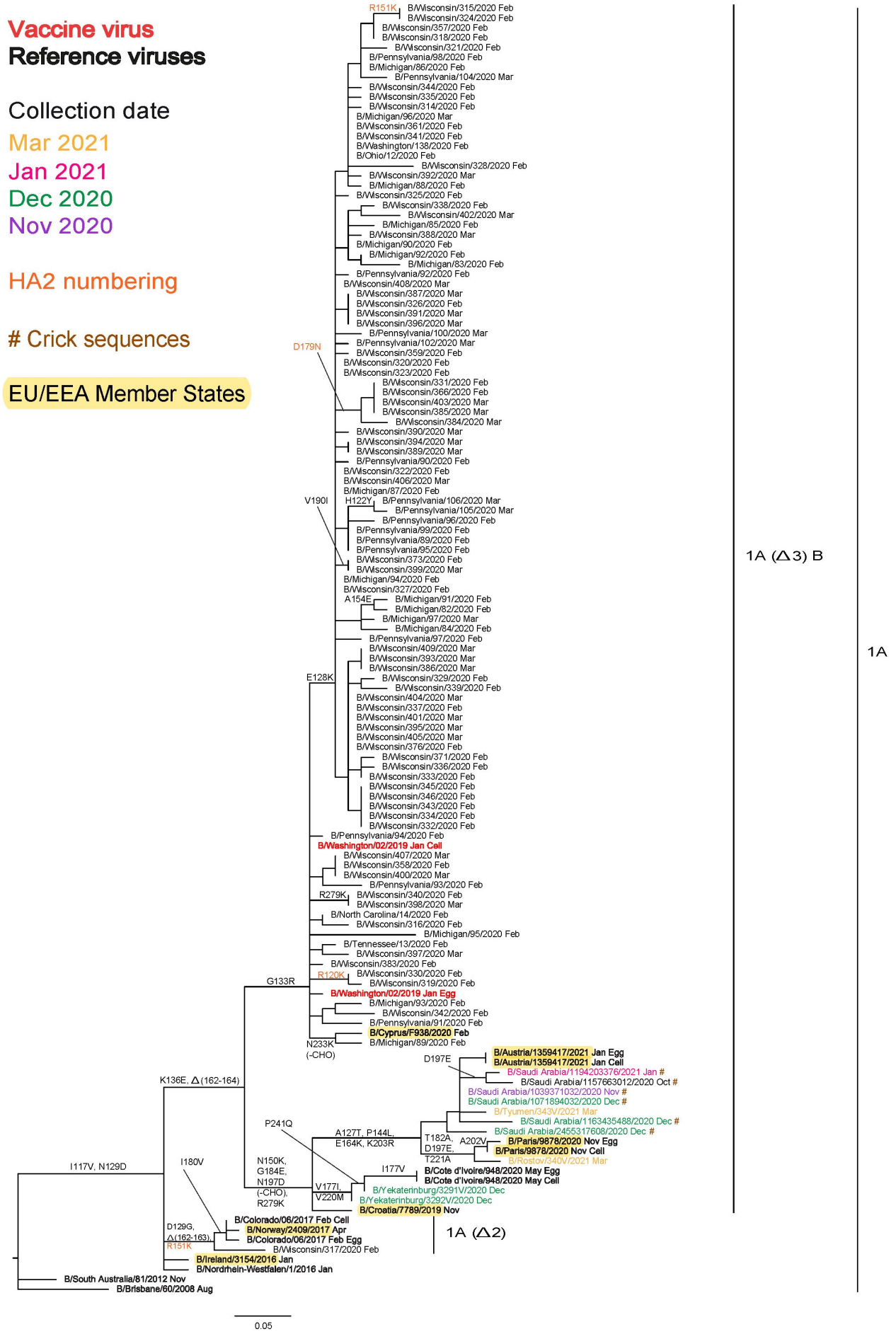


Figure 3b. Phylogenetic comparison of influenza B/Victoria-lineage HA genes (GISAID, June 2021)

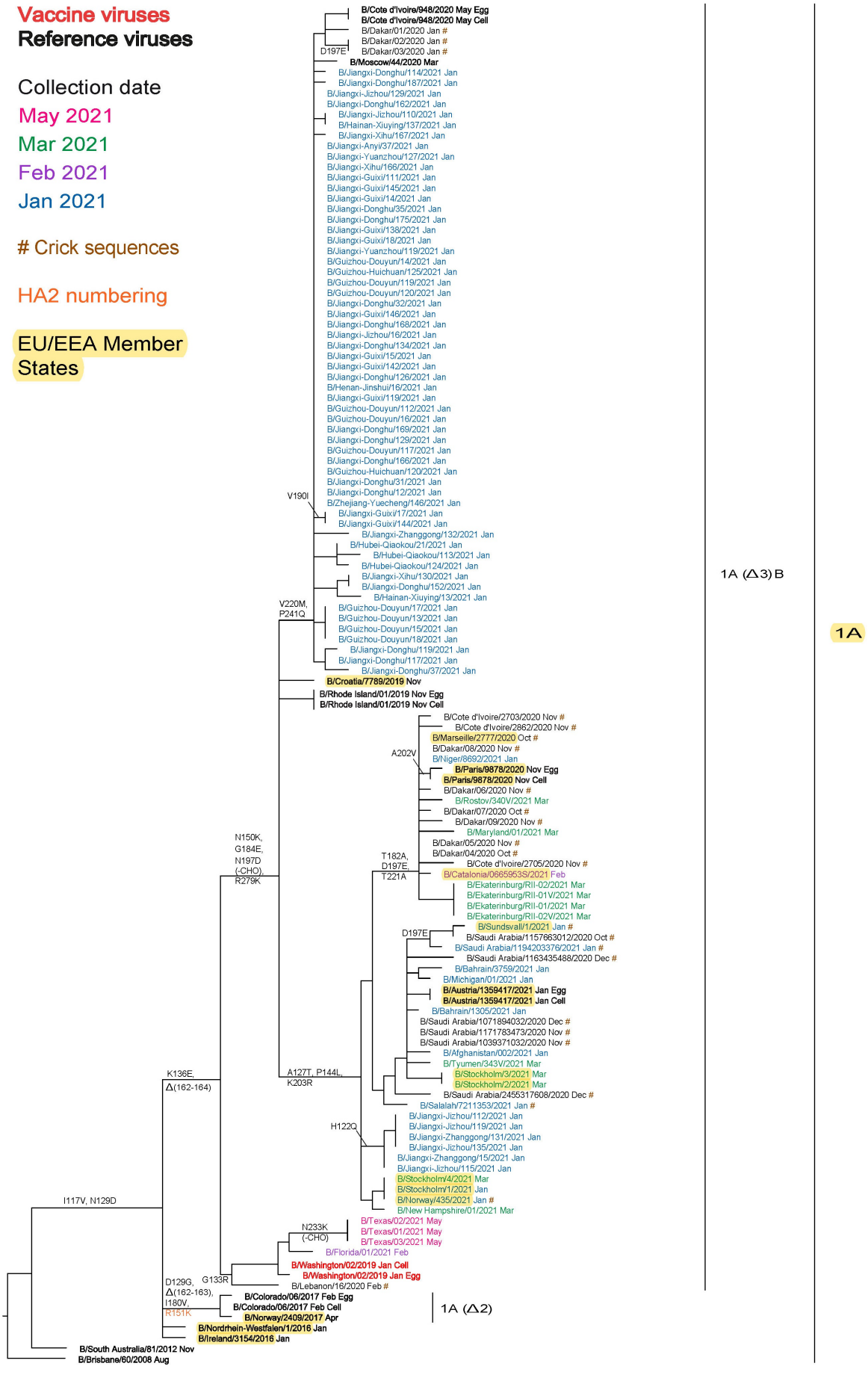


Table 4. Antigenic analysis of influenza B/Victoria-lineage viruses by HI

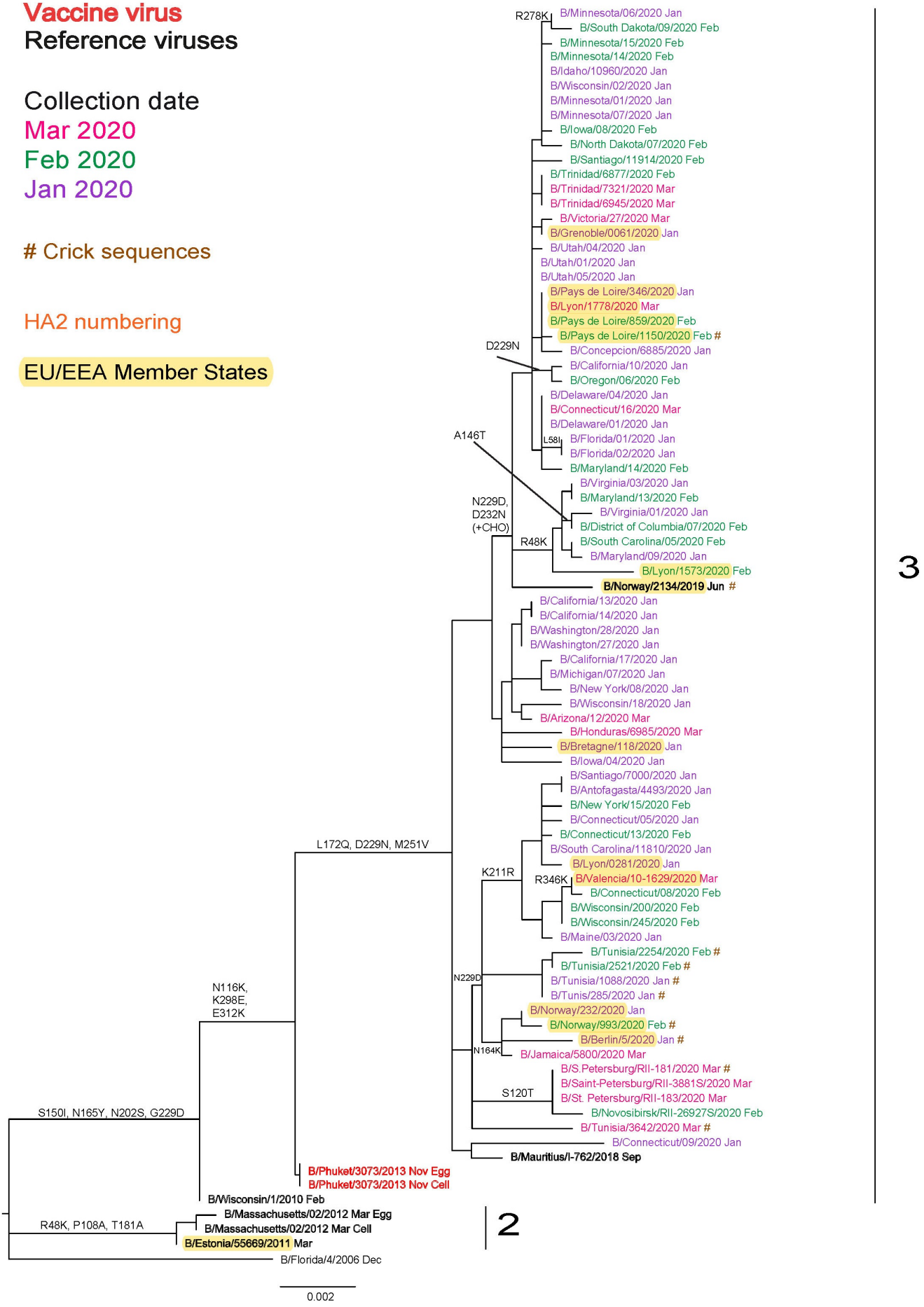
Viruses	Other information	Collection date	Passage history	Haemagglutination inhibition titre										
				Post-infection ferret antisera										
				B/Bris 60/08 Egg Sh 539, 540, 543, 544, 570, 571, 574 [1,3]	B/Bris 60/08 Egg	B/Norway/ 2409/17 MDCK	B/Colorado 06/17 Egg	B/Wash'ton 02/19 MDCK	B/Wash'ton 02/19 Egg	B/Austria 1359417/21 MDCK	B/Austria 1359417/21 Egg	B/Paris 9878/20 MDCK	B/Paris 9878/20 Egg Isolate 1#
		Passage history												
		Ferret number		F44/17 [4]		F40/17 [2]	F11/18 [4]	F37/19 [2]	F20/20 [2]	NIB F01/21 [1]	F15/21 [1]	F12/21 [1]	F14/21 [1]
		Genetic group		1A	1A	1A(Δ2)	1A(Δ2)	1A(Δ3)B	1A(Δ3)B	1A(Δ3)B	1A(Δ3)B	1A(Δ3)B	1A(Δ3)B
REFERENCE VIRUSES													
B/Brisbane/60/2008		1A	2008-08-04	E4/E4	2560	640	<	80	<	40	<	<	<	80
B/Norway/2409/2017		1A(Δ2)	2017-04-27	MDCK1/MDCK3	80	10	40	160	<	<	<	<	<	<
B/Colorado/06/2017		1A(Δ2)	2017-02-05	E5/E2	1280	160	20	320	<	80	<	<	<	<
B/Washington/02/2019		1A(Δ3) B	2019-01-19	C2/MDCK3	1280	80	<	160	20	80	<	<	<	<
B/Washington/02/2019		1A(Δ3) B	2019-01-19	E3/E2	1280	160	<	320	20	160	<	<	<	<
B/Austria/1359417/2021	N150K grp + A127T, P144L, K203R	1A(Δ3) B	2021-01-09	SIAT1/MDCK3	640	80	<	40	<	<	2560	1280	640	1280
B/Austria/1359417/2021 Isolate 2	N150K grp + A127T, P144L, K203R	1A(Δ3) B	2021-01-09	E3/E2	1280	80	10	80	20	10	2560	2560	640	2560
B/Paris/9878/2020	N150K grp + A127T, P144L, T182A, D197E, A202V, K203R, T221A	1A(Δ3) B	2020-11-20	MDCK2	1280	80	<	160	<	10	1280	1280	640	1280
B/Paris/9878/2020 Isolate 2	N150K grp + A127T, P144L, T182A, D197E, A202V, K203R, T221A	1A(Δ3) B	2020-11-20	E3/E2	1280	80	<	160	10	10	1280	640	320	1280
TEST VIRUSES														
B/Stockholm/2/2021	N150K grp + A127T, P144L, K203R	1A(Δ3) B	2021-03-01	SIAT0/MDCK1	640	80	<	40	<	<	2560	1280	640	1280
B/Stockholm/3/2021	N150K grp + A127T, P144L, K203R	1A(Δ3) B	2021-03-05	SIAT0/MDCK1	640	40	<	40	<	<	2560	1280	320	640
B/Stockholm/4/2021	N150K grp + A127T, P144L, K203R	1A(Δ3) B	2021-03-15	SIAT0/MDCK1	640	40	<	40	<	<	1280	640	320	640

Vaccine
SH 2019
NH 2019-20

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

* Superscripts refer to antiserum properties (< relates to the lowest dilution of antiserum used):
[1] < = <40; [2] < = <10; [3] hyperimmune sheep serum; [4] < = <20
G141G/R

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



Summaries of data submitted to TESSy

Genetic characterisation

Fourteen viruses detected over the course of the 2020-2021 season (weeks 40/2020-24/2021) have been genetically characterised:

- One A(H1N1)pdm09 virus attributed to the 6B.1A5A+187V/A group represented by A/Guangdong-Maonan/SWL1536/2019
- 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
- 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):

- 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.
- 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.
- 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.
- 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 has 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, 15 influenza viruses detected within EU/EEA countries during the 2020-2021 season have been assessed phenotypically against oseltamivir and zanamivir: two A(H1N1)pdm09, six A(H3N2) and seven B/Victoria-lineage. All showed NI by both NAIs.

Influenza A(H7N9) virus

On 1 April 2013, the 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 [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 are available on WHO's website: https://www.who.int/teams/global-influenza-programme/avian-influenza/monthly-risk-assessment-summary (accessed 5 July 2021). The assessment, published on 22 June 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 (FAO) on 3 February 2021, indicated that there had been 14 detections in chickens in Shandong province, China in October 2020, but the report published on 7 July 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 (EFSA) and the EU Reference Laboratory for Avian Influenza was published on 31 May 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 22 June 2021. Since the previous risk assessment on 21 May 2021, a single fatal H5N6 zoonotic case in a 49-year-old female was reported from China, together with a non-fatal H10N3 zoonotic case in a 41-year-old male [9]. Neither case had been exposed to live poultry prior to illness onset. 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 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 United Kingdom. Poultry detections were reported by Poland (297) and Germany (168), and wild bird detections were reported by Germany (603), Denmark (167) and Poland (56). A second peak of HPAI-associated wild bird mortality in north-west Europe was recorded from February to 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 FAO, as at 23 June, various influenza A(H5Nx) subtypes continued to be detected in wild and/or domestic birds in Africa, Europe and Asia. Since 26 May, a total of 137 (136 HPAI and one LPAI) outbreaks had been reported [15].

Influenza A(H9N2) virus

Since the previous WHO update on 21 May 2021, two laboratory-confirmed human cases of influenza A(H9N2) virus infection were reported by China [9]. The cases were detected in a 2-year-old male and a 78-year-old female, with both patients making a full recovery. Both cases had a history of live poultry market exposure prior to illness onset, and there was no indication of onward transmission among family members. The latest FAO Global AIV with Zoonotic Potential situation update also reported the two cases of human infection with A(H9N2) in China [15]. Avian influenza A(H9N2) viruses are enzootic in poultry in Asia and are increasingly reported in poultry in Africa. The latest ECDC/EFSA report includes a mention of earlier human infections with H9N2 viruses, following the previous report that covered up to 23 February 2021 [12].

Other influenza zoonotic events

Since the previous WHO update on 21 May 2021, a single zoonotic event with swine-related influenza A(H1N1)v was reported to WHO by the US [9]. The case involved an adult with exposure to swine who was not hospitalised and made a full recovery. There was no evidence for human-to-human transmission.

Two zoonoses with swine A(H1N2)v viruses were reported, one each from Taiwan and the US [9]. The Taiwan case involved a 5-year-old female exposed to swine on her family's farm, and samples taken from family members and livestock all tested negative for A(H1N2)v. The US case involved an older child (<18 years of age), again with swine contact on the family farm, who was not hospitalised and recovered.

Canada reported a zoonotic case of A(H3N2)v infection in an older child (<18 years of age) who made a full recovery. Neither the case nor family members reported direct contact with swine, but they reside in a rural area where many swine farms are present.

All four cases were confirmed by genome sequencing and the viruses identified were like those circulating in swine in their respective geographic locations.

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 meetings, can be found at: https://www.crick.ac.uk/partnerships/worldwide-influenza-centre/annual-and-interim-reports (accessed 2 July 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, as well as the 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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* These references are currently unavailable online, as the WHO website is being updated and 'the archiving of previous summaries and risk assessments is in progress'.