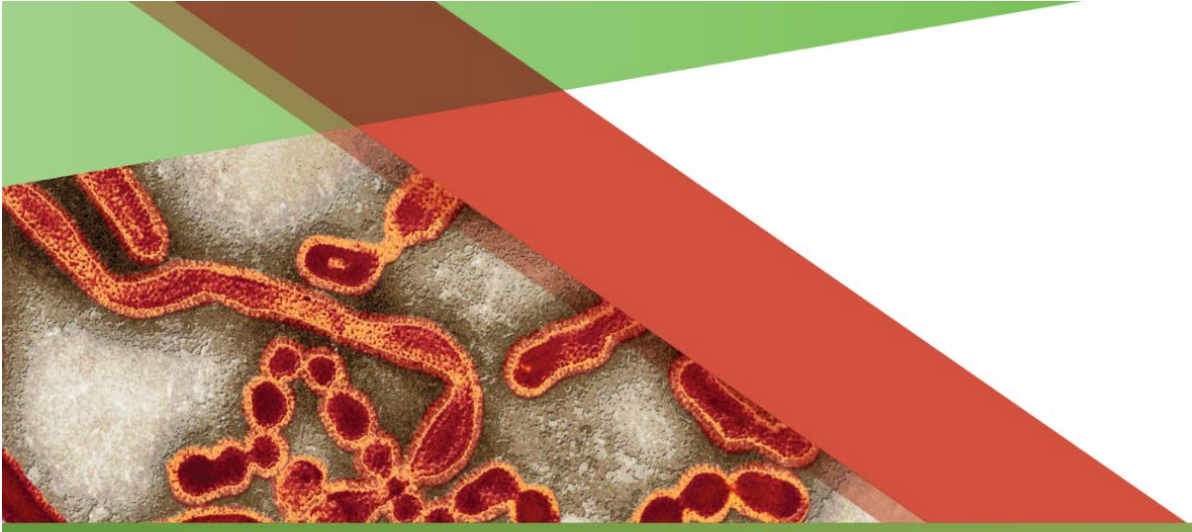

SURVEILLANCE REPORT

Influenza virus characterisation

Summary Europe, September 2021

Summary

This is the 10th and final report for the 2020-2021 influenza season. As of week 39/2021, only 1 276 influenza detections across the WHO European Region were reported to TESSy; 60% type A viruses, with A(H3N2) (85%) dominating over A(H1N1)pdm09 (15%), and 40% type B viruses, with only 16 having been ascribed to a lineage, 15 B/Victoria and one B/Yamagata. This represents a 99.2% drop in detections compared to the 2020-2021 season, probably due to the COVID-19 pandemic and measures introduced to combat it.

Since the July 2021 characterisation report[1], two shipments from EU/EEA countries (the Netherlands and Norway) containing three virus isolates were received at the London WHO Collaborating Centre, the Francis Crick Worldwide Influenza Centre (WIC). This report therefore focuses on genetic characterisation of HA genes of representative seasonal influenza viruses submitted and/or released in GISAID up to 31 August 2021, together with sequences recently determined at the WIC. The new genetic clade nomenclature system proposed during the course of the September 2021 VCM is indicated in red in this summary and the most recent HA gene phylogenies. The data continued to show extremely low levels of influenza detections globally. However, there were a number of detections reported to TESSy since week 36/2021 which could indicate an early start to the 2021-2022 influenza season in the WHO European Region.

While the majority of A(H1N1)pdm09 detections have been in the 6B.1A5A+187V/A (6B.1A.5a.1) subgroup, represented by the vaccine virus for the northern hemisphere 2020-2021 season, A/Guangdong-Maonan/SWL1536/201960, recent detections of 6B.1A5A+156K (6B.1A.5a.2) viruses have been reported in India. A/Victoria/2570-like and A/Wisconsin/588/2019-like (6B.1A.5a.2) viruses have been recommended respectively for egg- and cell-based vaccines in the 2021-2022 northern and 2022 southern hemisphere influenza seasons.

The great majority of recently detected A(H3N2) viruses have fallen in subgroup 3C.2a1b+T131K-A (3C.2a1b.2a), being split between Cambodia-like (3C.2a1b.2a.1) and Bangladesh-like (3C.2a1b.2a.2) viruses. A/Cambodia/e0826360/2020-like (3C.2a1b.2a.1) viruses were recommended for use in the 2021-2022 northern hemisphere season, while A/Darwin/9/2021-like and A/Darwin/6/2021-like (3C.2a1b.2a.2) viruses were recommended

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

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for egg- and cell-based vaccines in the 2022 southern hemisphere season. Recently detected viruses in the Netherlands and Norway were Bangladesh-like (3C.2a1b.2a.2) genetically and antigenically.

The vast majority of B/Victoria-lineage HA sequences derived from viruses collected after 31 January 2021were subclade 1A(△3)B (V.1A.3), represented by B /Washington/02/2019, the vaccine virus recommended for inclusion in influenza vaccines for the 2021-2022 northern hemisphere season. The vast majority of these viruses have fallen in the HA1 N150K, G184E, N197D and R279K amino acid substitutions group (V.1A.3a) being split between the HA1 V117I and V220M (V.1A.3.1) and HA1 A127T, P144L and K203R (V.1A.3.2) subgroups, with the latter subgroup showing the greatest geographic spread. B/Austria/1359417/2021-like (V.1A.3.2) viruses have been recommended for use in the southern hemisphere 2022 influenza season. Antigenically, viruses in subgroups of the V.1A.3a group differ and show some loss of reactivity with post-infection ferret antisera raised against B/Washington/02/2019. The V.1A.3.2 virus from France detected in July and characterised here clearly shows good reactivity with post-infection ferret antisera raised against B/Austria/1359417/2021 and poor reactivity with antisera raised against B/Washington/02/2019.

No B/Yamagata-lineage HA sequences from clinical specimens collected in 2021, and none with collection dates after March 2020, were available. All of the 77 sequences from viruses detected in 2020, inclusive of 12 from EU/EEA countries, belong to genetic clade 3 (Y3)and carry three HA1 amino acid substitutions (L172Q, D229N and M251V) compared to B/Phuket/3073/2013-like viruses which have been recommended for use in quadrivalent influenza vaccines for the 2020-2021 and 2021-2022 northern hemisphere seasons and 2021 and 2022 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 during the 2020-2021 season (weeks 40/2020-39/2021), compared to the 2019-2020 season. While there was an increase in the numbers of samples from patients fulfilling Influenza-Like Illness (ILI) and/or Acute Respiratory Infection (ARI) criteria being tested (~310 561, 31.6%), notably during the inter-seasonal period (weeks 21-39/2021), there was a vast reduction in the number of samples testing positive for an influenza virus (163 641, 99.2%). This was 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 during of the 2020-2021 season, the ratio of type A to type B detections was reduced compared to the 2019-2020 season (2.7:1 to 1.5:1), with a reversal in the proportions of influenza A subtypes while B/Victoria lineage viruses again predominated over B/Yamagata lineage viruses, although only 16/498 (3.2%) of type B viruses detected in the 2020-2021 season were ascribed to a lineage.

Compared to Table 1 presented in the July 2021 report (to week 28/2021) an additional 333 influenza detections were reported (280 type A, with 189 being subtyped as H3N2 and two as H1N1pdm09, and 53 type B two of which were ascribed to the B/Victoria-lineage). This equates to 26.1% of the total 2020-2021 season influenza detections in just 11 weeks while the level of detections overall, as a percentage of the samples tested, increased slightly from 0.092% (weeks 40/2020-28/2021) to 0.126% (weeks 29-39/2021). This may herald an earlier start than usual to the 2021-2022 influenza season in the European Region, with likelihood of A(H3N2) viruses dominating.

Table 1. Influenza virus detections in the WHO European Region from the start of reporting for the 2020-21 season (weeks 40/2020-39/2021)[a]

Virus type/subtype/lineage	Cumulative number of detections for weeks 40/2020-39/2021			Totals*		Cumulative number of detections for weeks 40/2019-39/2020			Totals*	
	Sentinel sources	Non-sentinel sources	Totals	%	Ratios	Sentinel sources	Non-sentinel sources	Totals	%	Ratios
Influenza A	**52**	**710**	**762**	**59.7**	**1.5:1**	**11303**	**108968**	**120271**	**72.9**	**2.7:1**
A(H1N1)pdm09	11	33	44	15.0		6126	20305	26431	56.0	
A(H3N2)	13	236	249	85.0	5.7:1	4175	16597	20772	44.0	0.8:1
A not subtyped	28	441	469			1002	72066	73068		
Influenza B	**14**	**500**	**514**	**40.3**		**6326**	**38320**	**44646**	**27.1**	
Victoria lineage	2	13	15	93.8	15:1	2450	2030	4480	98.1	50.3:1
Yamagata lineage	0	1	1	6.2		23	66	89	1.9	
Lineage not ascribed	12	486	498			3853	36224	40077		
Total detections (total tested)	**66 (52 783)**	**1 210 (>1 240 679)**	**1 276 (>1 293 462)**			**17 629 (53 287)**	**147 288 (>929 614)**	**164 917 (>982 901)**		

[a] Numbers taken from Flu News Europe to week 39/2021 and week 39/2020 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, eleven shipments of specimens (virus isolates and/or clinical specimens) were received at the Crick Worldwide Influenza Centre (WIC), two of which were received in August 2021 from the Netherlands and Norway containing one and two samples, respectively (Table 2). Overall, the 11 packages contained 40 virus-related samples with collection dates after 31 August 2020 and were made up of 25 type A viruses and 15 type B viruses.

Genetic and antigenic characterisation data generated at the WIC for viruses with collection dates after 31 August 2020 until 31 January 2021, up to a report deadline of 15 February 2021, contributed to the WIC virus characterisation report that was presented at the WHO influenza vaccine composition meeting (VCM) in February 2021 when recommendations were made for the northern hemisphere 2021-2022 season. Data generated on viruses with collection dates after 31 January 2021 informed the recent VCM where recommendations were made for the 2022 southern hemisphere season. Recommendations for the 2020-2021 northern hemisphere, the 2021 southern hemisphere and upcoming 2021-2022 northern hemisphere and 2022 southern hemisphere seasons, have been published [1, 2, 3, 4].

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. Only four viruses from EU/EEA countries were characterised genetically and antigenically since the July 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							
May														
June														
France	2			2	2									
July														
France	4			2	2	1	1				1	1		
August														
Netherlands	1					1	1							
Norway	2					2	2							
6 Countries	40	0	0	7	6	18	12	0	1	0	14	9	0	0
		0.00%		17.5%		45.0%			2.5%		35.0%		0.0%	
		62.5%							37.5%					

*** 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)
Samples from Abidjan
Includes RNA extracts for which genetic characterisation only can be performed.

As of 2021-10-01

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, 2022 and northern hemisphere 2021-2022 (egg-based A/Victoria/5270/2019-like and cell-based A/Wisconsin/588/2019-like) influenza seasons are shown in red [1, 2, 3, 4]. The seven subclades are defined by the following HA amino acid substitutions:

1. Subclade **6B.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 similar profiles. The first is repeated from the July 2021 report and was generated based on the HA sequences deposited/released in GISAID during July. There were 60 with collection dates in 2021, all from Togo collected in January through March (Figure 1a). These 60 sequences were derived from subgroup **6B.1A5A+187V/A** viruses and the majority (35) had additional **HA1 I166T** and **A186T** substitutions. The second phylogeny is based on representative HA sequences from viruses collected after 31 January 2021, as available in GISAID at the end of August and/or generated at the WIC, and shows the new nomenclature system proposed during the course of the September 2021 VCM (Figure 1b). The great majority were **6B.1A5A+187V/A** (**6B.1A.5a.1**) viruses from countries in West Africa with single detections in Qatar and India, while recently emerged **6B.1A5A+156K** (**6B.1A.5a.2**) viruses were detected in India that carried additional **HA1** amino acid substitutions of **K54Q**, **K130N**, **A186T**, **Q189E** and **E224A**, often with **R259K** and **K308R**. Detailed antigenic characterisation of these viruses from India is ongoing. A single **6B.1A7** (**6B.1A.7**) virus was detected in Norway in February 2021.

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 18 October 2021].

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

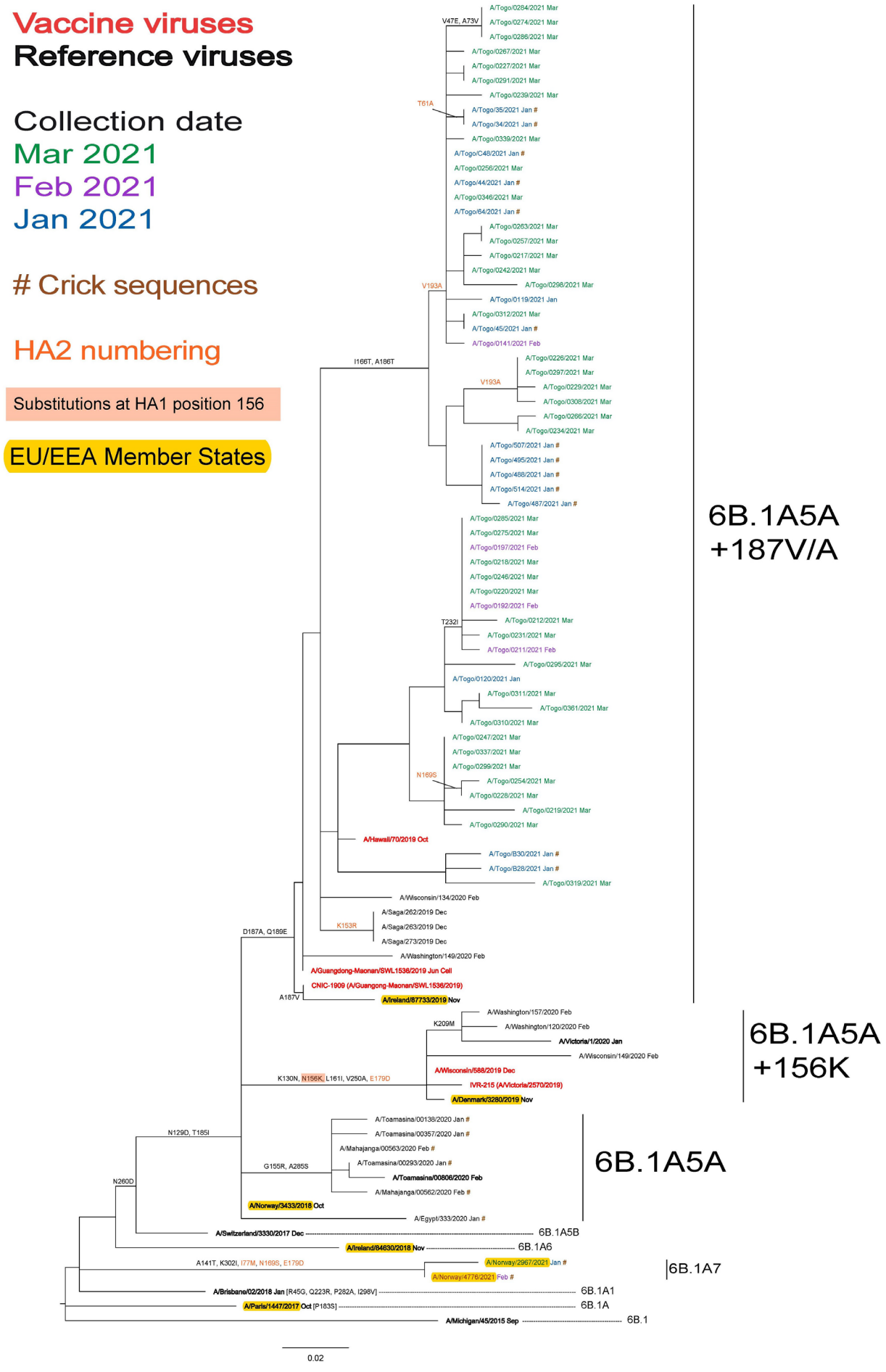
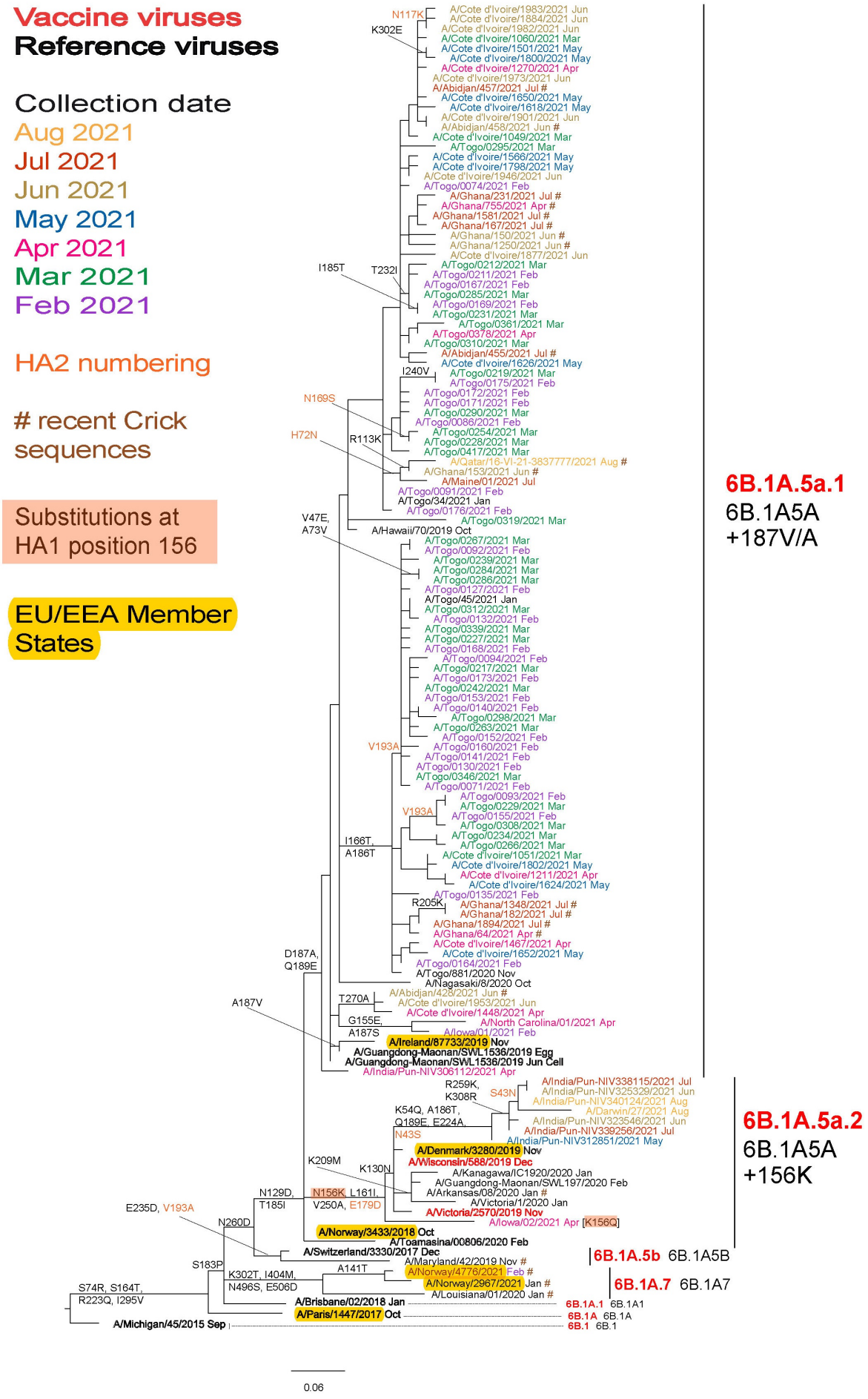


Figure 1b. Phylogenetic comparison of influenza A(H1N1)pdm09 HA genes (GISAID, September 2021)



Influenza A(H3N2) virus analyses

The first A(H3N2) HA phylogeny is repeated from the July 2021 report and was based on sequences from viruses collected in the course of 2021 that became available in GISAID during July (Figure 2a). The second phylogeny is based on representative HA sequences from viruses collected after 31 January 2021, as available in GISAID at the end of August and/or generated at the WIC, and shows the new nomenclature system proposed during the course of the September 2021 VCM (Figure 2b).

Viruses in clade 3C.2a have been dominant since the 2014-15 influenza season with group 3C.2a1b viruses predominating over the course of the 2019-2020 season in most WHO-defined regions of the world but for the European Region where there was equivalence of clade 3C.3a viruses. The HA gene sequences of viruses in both clades 3C.2a and 3C.3a continue to diverge. Notably, clade 3C.3a 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 or an A/Hong Kong/45/2019-like virus as the A(H3N2) component of vaccines for the 2020-2021 northern hemisphere and 2021 southern hemisphere influenza seasons [1, 2].

The HA phylogeny generated for the July report was based on the 57 HA sequences from viruses with collection dates in 2021 that became available in July (Figure 2a). All were **3C.2a1b+T131K-A** viruses with 13 being 'Cambodia-like' carrying additional **HA1** substitutions of **G186S**, **F193S**, **Y195F** and **S198P** (one from Australia, two from Japan and 10 from Timor-Leste) and 44 were 'Bangladesh-like' carrying additional **HA1** substitutions of **Y159N**, **T160I** (loss of a glycosylation site), **L164Q**, **G186D**, **D190N**, **F193S** and **Y195F** (four from Australia, four from India, 21 from Kenya, one from Nepal, one from Norway, three from Singapore, six from Sweden and four from the United Arab Emirates).

The second phylogeny shows that small numbers of **3C.3a** (**3C.3a.1**), **3C.2a1b+T135K-B** (**3C.2a1b.1b**) and **3C.2a1b+T135K-B** (**3C.2a1b.1a**) viruses, the latter mainly from West Africa, were detected (Figure 2b). The vast majority of detections nave been **3C.2a1b+T131K-A** (**3C.2a1b.2a**) viruses falling in the Cambodia-like (**3C.2a1b.2a.1**) and Bangladesh-like (**3C.2a1b.2a.2**), with the great majority of the most recent detections including viruses from EU/EEA countries, being **3C.2a1b.2a.2** viruses. Bangladesh-like viruses, A/Darwin/9/2021 and A/Darwin/6/2021 for egg- and cell-based vaccines respectively, were recently recommended for use in the southern hemisphere 2022 influenza season [4].

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. Antigenic characterisation of three A(H3N2) viruses is presented here, all having HI-reactivity profiles most similar to 'Bangladesh-like' reference viruses (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 egg- and cell culture-propagated cultivars of A/Cambodia/e0826360/2020 (**3C.2a1b+T131K-A**) recommended for use in northern hemisphere 2021-2022 vaccines [3] (Figures 2a and 2b).The recent virus recommendations for egg- and cell-culture based vaccines to be used in the 2022 southern hemisphere season, A/Darwin/9/2021 and A/Darwin/6/2021 respectively [4], are indicated in Figure 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, July 2021)

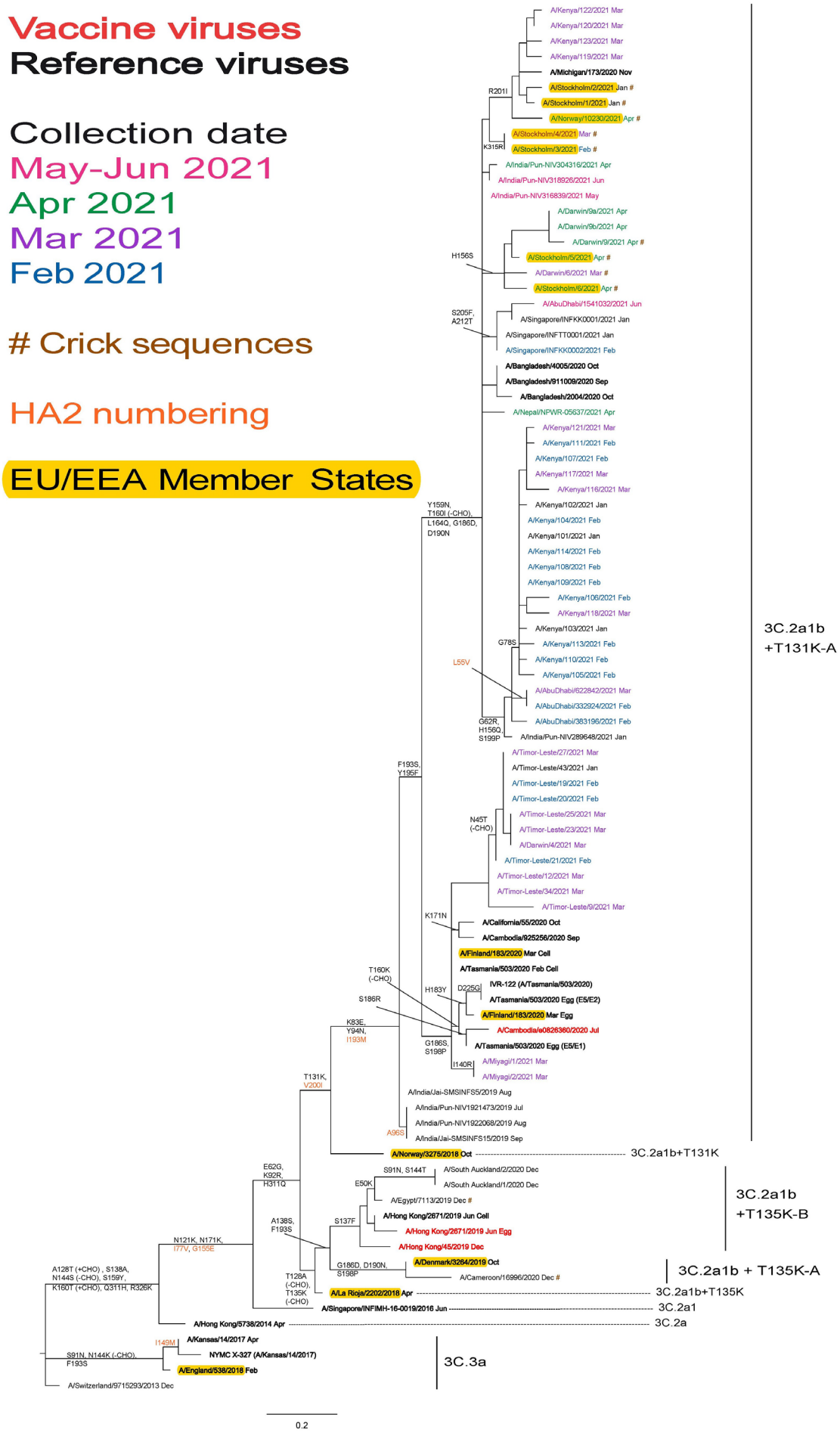


Figure 2b. Phylogenetic comparison of influenza A(H3N2) HA genes (GISAID, September 2021)

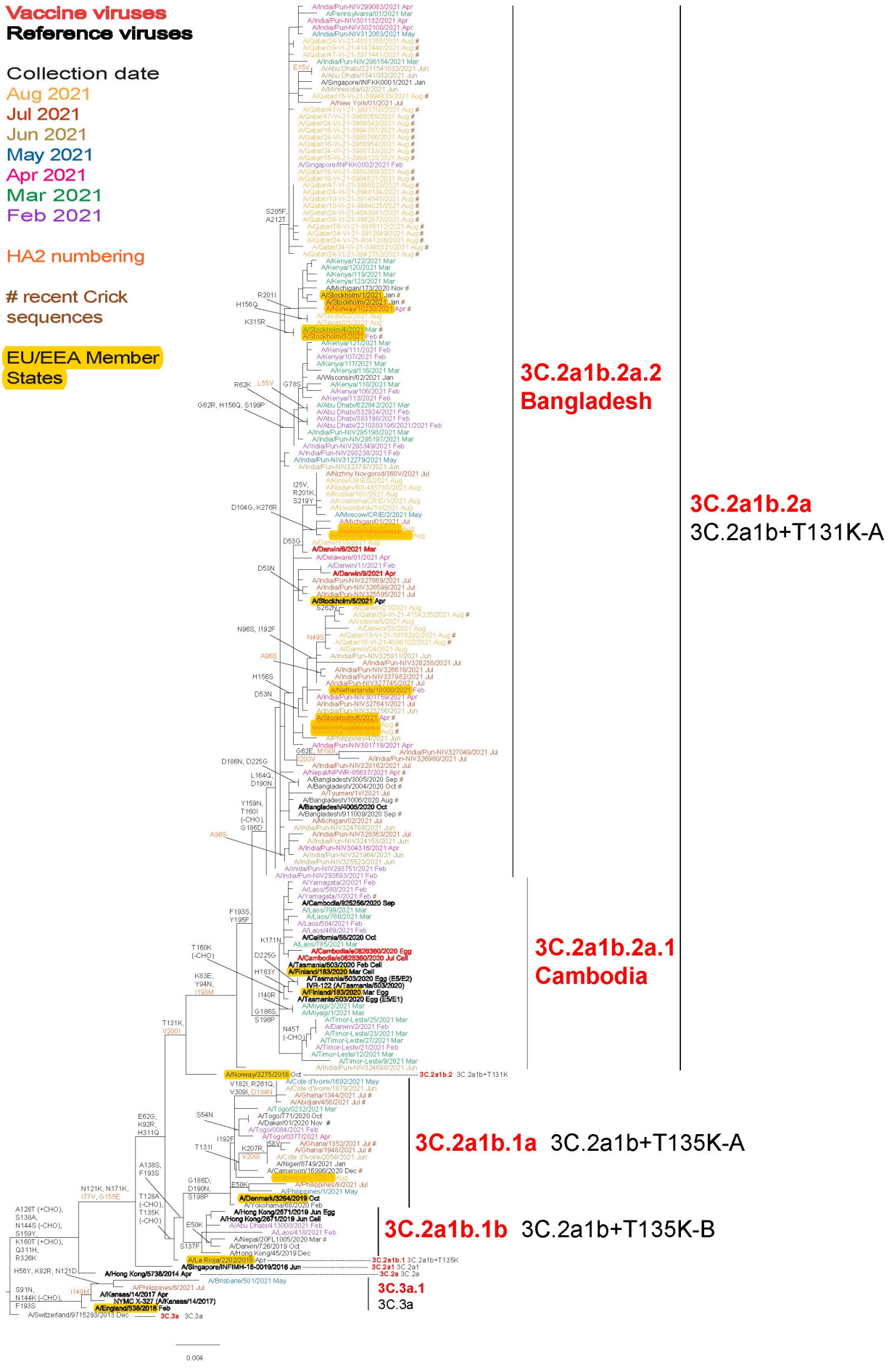


Table 3. Antigenic analysis of A(H3N2) viruses by HI

Viruses	Other information	Collection date	Passage history	Haemagglutination inhibition titre													
				Post-infection ferret antisera													
	Passage history			A/HK 5738/14 MDCK St Judes F60/17[-1]	A/Singapore 0019/16 Egg 10^{-4} F13/19[-1]	A/Denmark 3264/19 SIAT F19/20[-1]	A/HK 2671/19 Egg F44/19[-1]	A/HK 2671/19 Cell St Judes F21/20[-1]	A/Camb e0826360/20 Egg F10/21[-1]	A/Camb 925256/20 SIAT F03/21[-1]	A/Bang 4005/20 SIAT F07/21[-1]	A/Stock 5/21 SIAT F35/21[-1]	A/Eng 538/18 SIAT F31/18[-1]	NYMC X-327 A/Kansas/14/17 Egg F16/19[-1]	A/Kansas 14/17 SIAT F17/19[-1]
	Genetic group			3C.2a	3C.2a1	3C.2a1b+T135K-A	3C.2a1b+T135K-B	3C.2a1b+T138K-B	3C.2a1b+T131K-A	3C.2a1b+T131K-A	3C.2a1b+T131K-A	3C.2a1b+T131K-A	3C.3a	3C.3a	3C.3a
REFERENCE VIRUSES															
A/Hong Kong/5738/2014	3C.2a	2014-04-30	MDCK1/MDCK2/SIAT2	160	320	40	<	40	40	160	80	80	320	160	160
A/Singapore/INFIMH-16-0019/2016	3C.2a1	2016-04-14	E5/E3	80	320	80	40	<	<	160	<	<	40	<	<
A/Denmark/3264/2019	3C.2a1b+T135K-A	2019-10-25	SIAT5	80	160	320	40	160	160	640	320	320	320	80	160
A/Hong Kong/2671/2019	3C.2a1b+T135K-B	2019-06-17	E8/E2	<	80	160	640	80	160	160	80	160	160	320	80
A/Hong Kong/2671/2019	3C.2a1b+T135K-B	2019-06-17	MDCK1/SIAT4	80	160	320	160	160	80	640	160	160	160	80	80
A/Cambodia/e0826360/2020	3C.2a1b+T131K-A	2020-07-16	E5/E2	40	80	160	80	<	1280	160	320	320	160	80	80
A/Cambodia/925256/2020	3C.2a1b+T131K-A	2020-09-25	SIAT4	40	160	160	<	80	80	1280	160	160	160	40	80
A/Bangladesh/4005/2020	3C.2a1b+T131K-A	2020-10-04	SIAT2	40	40	160	80	<	80	160	640	640	160	80	160
A/Stockholm/5/2021	3C.2a1b+T131K-A	2021-04-16	S0/S2	<	40	80	80	<	80	80	320	640	160	80	<
A/England/538/2018	3C.3a	2018-02-26	MDCK1/SIAT4	<	40	40	<	<	40	40	40	80	320	80	320
NYMC X-327 (A/Kansas/14/17)	3C.3a	2017-12-14	Ex/E1	<	<	40	320	<	40	<	<	40	320	1280	320
A/Kansas/14/2017	3C.3a	2017-12-14	SIAT3/SIAT1	<	40	80	<	<	40	80	40	80	640	160	320
					Vaccine NH 2018-19 SH 2018		Vaccine NH 2020-21 SH 2021		Vaccine NH 2021					Vaccine NH 2019-20	
TEST VIRUSES															
A/Norway/16606/2021	3C.2a1b+T131K-A	2021-08-02	hCK1/SIAT1	<	<	40	<	<	<	40	80	320	40	<	<
A/Norway/16980/2021	3C.2a1b+T131K-A	2021-08-07	SIAT1	<	<	80	40	<	40	40	160	320	80	40	<
A/Netherlands/00007/2021	3C.2a1b+T131K-A	2021-08-13	SIAT1	<	<	40	40	<	40	40	160	320	80	40	<

*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 had 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. 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 became dominant, 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 July report contained HA sequences of recently detected viruses all of which belonged to **subclade 1A(△3)B** represented by **B/Washington/02/2019** (Figure 3a). The great majority of these viruses belonged to the **N150K group,** defined by **HA1 N150K**, **G184E**, **N197D** (loss of a glycosylation site) and **R279K** amino acid substitutions, which split into two subgroups. The first had **HA1 V117I** and **V220M** substitutions and was seen mainly in China. The second had **HA1 A127T**, **P144L** and **K203R** substitutions, sometimes with additional **HA1 T182A**, **D197E** and **T221A** substitutions, while viruses from China often had **HA1 H122Q** substitution with **HA1** amino acid insertion (**ins167N**) and a set of 19 sequences derived from viruses detected in Singapore in June carried an additional **A202V** substitution in **HA1**. Viruses in the **HA1 A127T**, **P144L** and **K203R** subgroup showed wider geographic spread. Among a set of 13 sequences derived from viruses detected in Kenya during February to May, five fell in the **B/Washington/02/2019** vaccine group and carried **HA1 G133R** substitution and a further five fell in a group defined by **HA1** substitutions **K75E**, **E128K**, **T155A**, **G230N** and **I267V**, while three of four viruses detected in May fell in the **N150K subgroup** with additional **HA1 A127T**, **P144L** and **K203R** substitutions.

The updated phylogeny is based on representative HA sequences from viruses collected after 31 January 2021, as available in GISAID at the end of August and/or generated at the WIC, and shows the new nomenclature system proposed during the course of the September 2021 VCM (Figure 3b). All viruses fall in the **1A** (**V.1A**) clade with a single virus from China being **A/Brisbane/60/2008**-like. The remaining viruses all fall in **subclade 1A(△3)B** (**V.1A.3**) represented by **B/Washington/02/2019** with the vast majority being split between the **HA1 V117I** and **V220M** (**V.1A.3.1**) and **HA1 A127T**, **P144L** and **K203R** (**V.1A.3.2**) subgroups. **B/Austria/1359417/2021**-like (**V.1A.3.2**) viruses were recently recommended for southern hemisphere 2022 vaccines [4].

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. The single **N150K group** virus from France, with **HA1 A127T**, **P144L** and **K203R** substitutions, showed good reactivity with post-infection ferret antisera raised against **B/Austria/1359417/2021**, but poor reactivity with antisera raised against the current vaccine virus, **B/Washington/02/2019** (Table 4).

Influenza B/Yamagata-lineage

It is assumed that no B/Yamagata-lineage viruses have been detected after March 2020 as no sequences for such viruses with collection dates after this had been released is GISAID as of 30 September 2021. Figure 4 is repeated from the July report, but with recently designated nomenclature indicted in bold/red type, and was generated based on the 77 HA sequences from viruses with collection after 31 December 2019 to 31 March 2020 available in GISAID. All sequences fell in genetic **clade 3** (**Y3**), the B/Wisconsin/1/2010–B/Phuket/3073/2013 clade, within a subgroup defined by **HA1 L172Q** and **M251V** amino acid substitutions compared to B/Phuket/3073/2013 which is recommended for inclusion in quadrivalent vaccines for the 2020-2021 and 2021-2022 northern hemisphere, 2021 and 2022 southern hemisphere seasons [1, 2, 3, 4]. Some sub-clustering of sequences, defined by specific amino acid substitutions (e.g. **HA1 N164K, K211R, D229N** or **D232N** [introducing a potential N-linked glycosylation site] sometimes with **R48K**), has occurred. As noted in previous characterisation reports, none of these amino acid substitutions have any obvious antigenic effects based on HI assays using post-infection ferret antisera raised against egg-propagated B/Phuket/3073/2013.

[4] European Centre for Disease Prevention and Control. Influenza virus characterisation, summary Europe, September 2018. Stockholm: ECDC; 2018. Available 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, July 2021)

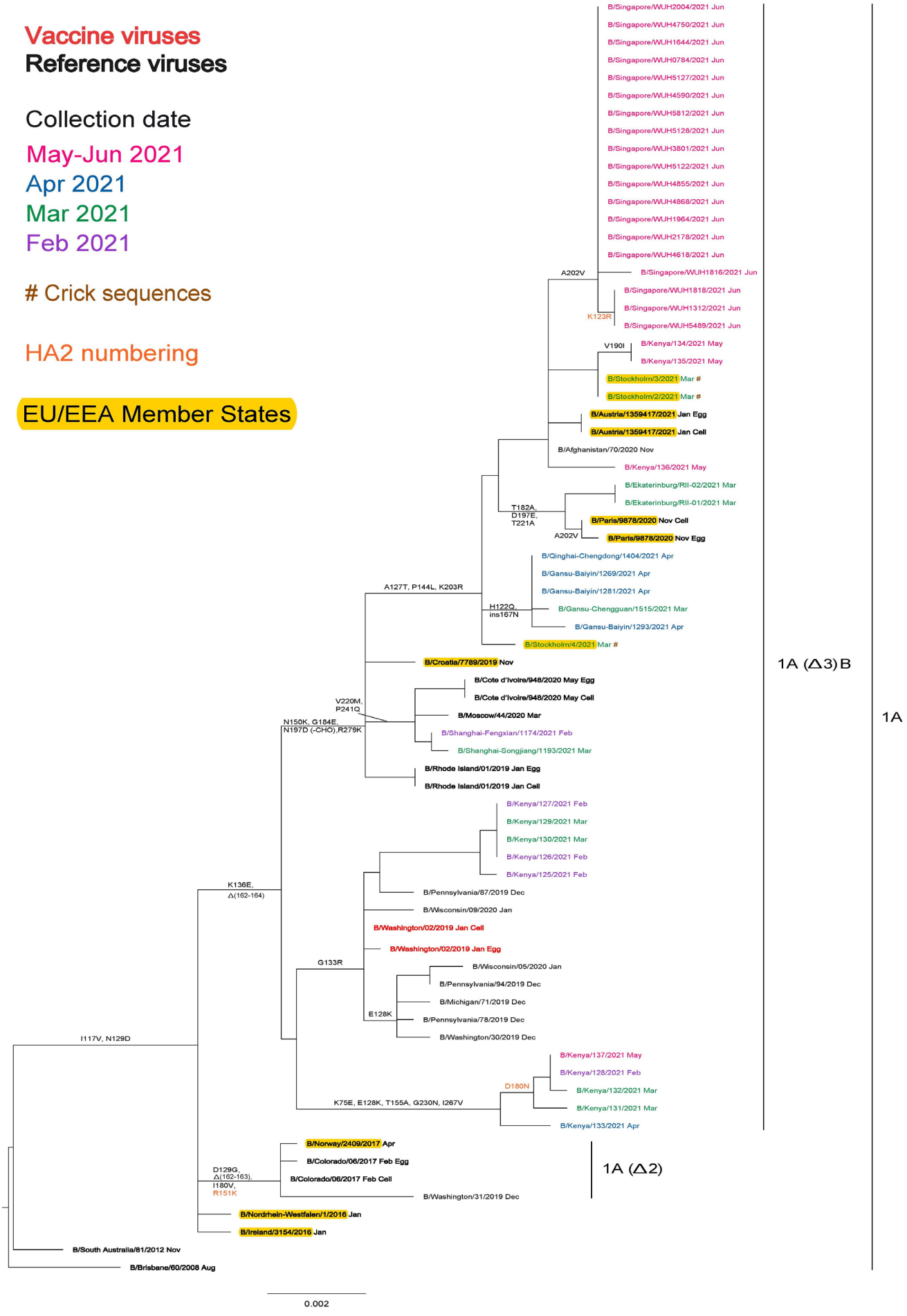


Figure 3b. Phylogenetic comparison of influenza B/Victoria-lineage HA genes (GISAID, September 2021)

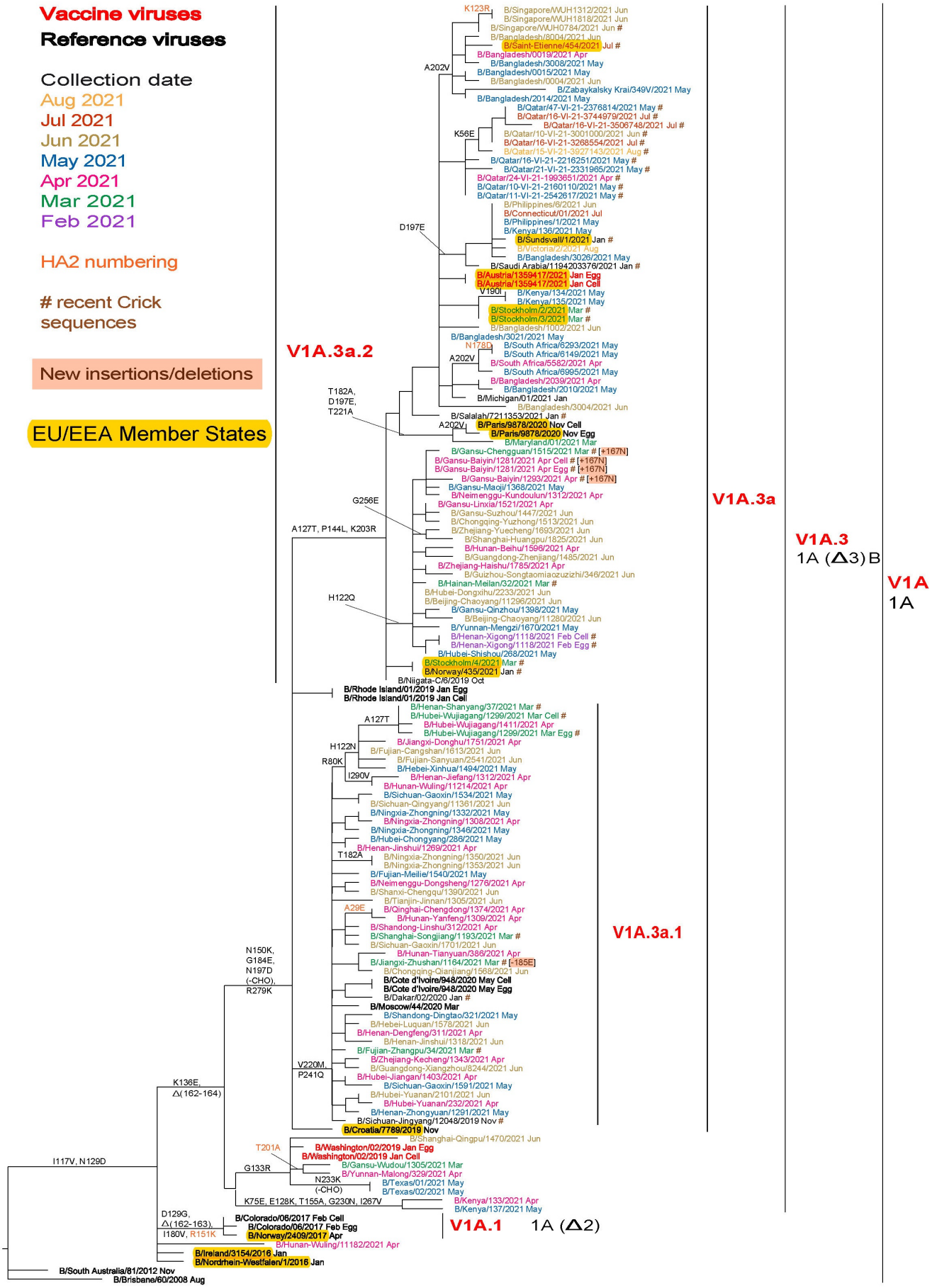


Table 4. Antigenic analysis of influenza B/Victoria-lineage viruses by HI

Viruses	Other information	Collection date	Passage history	Haemagglutination inhibition titre											
				Post-infection ferret antisera											
	Passage history			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 Isl 2
	Ferret number			F44/17 [*4]	F44/17 [*4]	F40/17 [*2]	F11/18 [*4]	F37/19 [*2]	F20/20 [*4]	NIB F01/21 [*1]	F15/21 [*1]	F12/21 [*1]	F23/21 [*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		2008-08-04	E4/E4	2560	640	<	80	<	40	<	<	<	<
B/Norway/2409/2017		2017-04-27	MDCK1/MDCK3	80	10	40	160	<	<	<	<	<	<
B/Colorado/06/2017		2017-02-05	E5/E2	1280	160	20	320	<	80	<	<	<	<
B/Washington/02/2019		2019-01-19	C2/MDCK3	1280	80	<	160	20	80	<	<	<	<
B/Washington/02/2019		2019-01-19	E3/E2	1280	160	<	320	20	160	<	<	<	<
B/Austria/1359417/2021	N150K grp + A127T, P144L, K203R	2021-01-09	SIAT1/MDCK4	640	80	<	40	<	<	1280	1280	640	320
B/Austria/1359417/2021 Isolate 2	N150K grp + A127T, P144L, K203R	2021-01-09	E3/E2	1280	80	10	80	20	10	2560	1280	640	320
B/Paris/9878/2020	N150K grp + A127T, P144L, T182A, D197E, A202V, K203R, T221A	2020-11-20	MDCK2	1280	80	<	160	<	10	1280	1280	640	320
B/Paris/9878/2020 Isolate 2 (G141V)	N150K grp + A127T, P144L, T182A, D197E, A202V, K203R, T221A	2020-11-20	E3/E2	1280	80	<	160	10	10	1280	640	320	1280
TEST VIRUSES													
B/Saint-Etienne/454/2021	N150K grp + K52N, A127T, P144L, A202V, K203R	2021-07-06	MDCK2/MDCK1	640	80	<	40	<	<	2560	1280	640	320

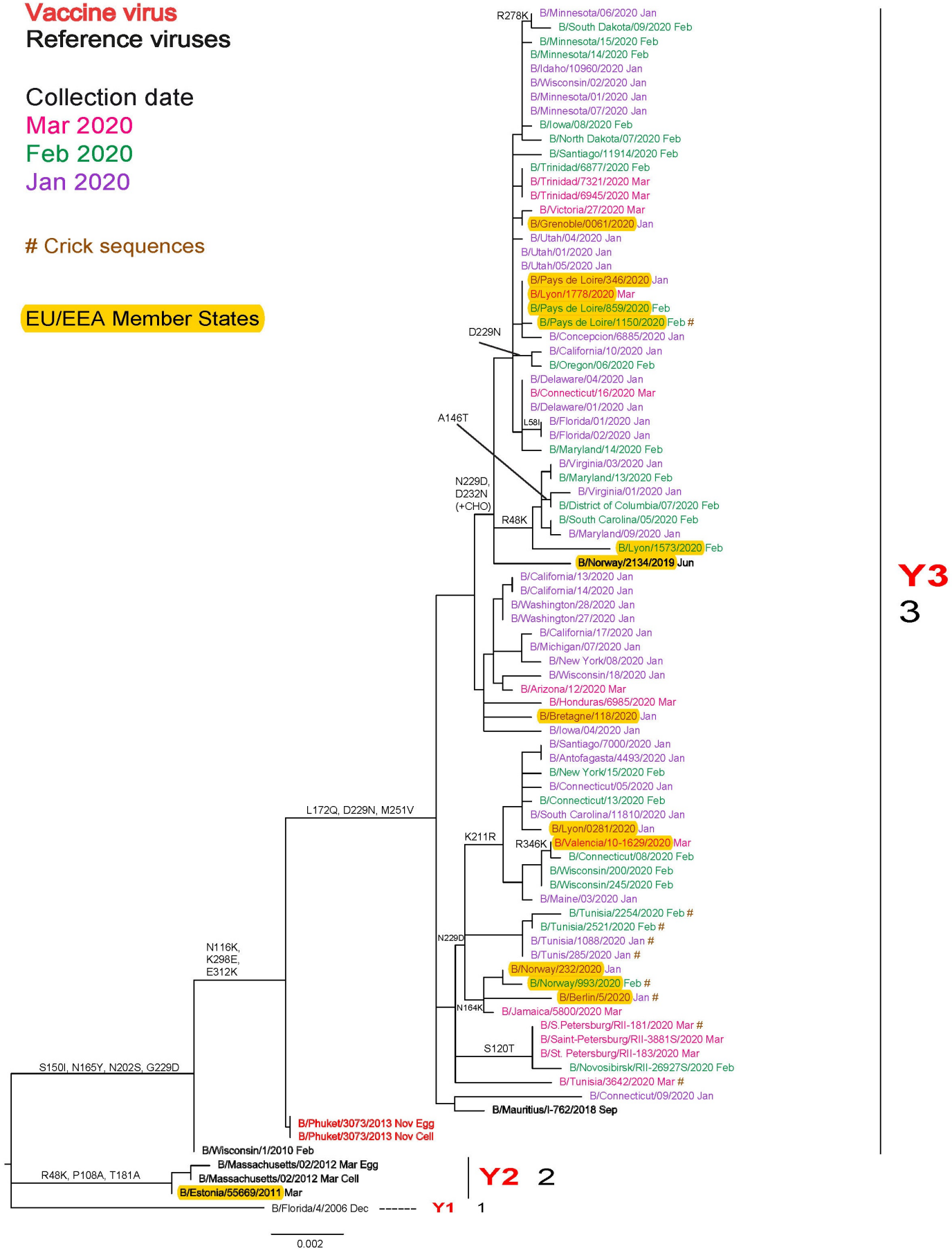
Vaccine SH 2019 NH 2019-20

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

Vaccine SH 2022

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

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



Summaries of data submitted to TESSy

Genetic characterisation

Twenty-seven viruses detected over the course of the 2020-2021 season (weeks 40/2020-39/2021) were genetically characterised:

- Two A(H1N1)pdm09 viruses, one attributed to the 6B.1A5A subclade represented by A/Norway/3433/2018 and one attributed to the 6B.1A5A+187V/A group represented by A/Guangdong-Maonan/SWL1536/2019.
- Nineteen A(H3N2) viruses with seven attributed to subgroup 3C.2a1b+T131K-A represented by A/Slovenia/1637/2020, two 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. The remaining nine were attributed to a subgroup not listed (relating to a recently emerged subgroup).
- Six B/Victoria-lineage viruses, five of which were ascribed to subclade 1A(Δ3)B represented by B/Washington/02/2019, while the sixth was ascribed to a subgroup not listed (relating to a recently emerged subgroup).

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, 24 influenza viruses detected within EU/EEA countries during the 2020-2021 season have been assessed phenotypically against oseltamivir and zanamivir: six A(H1N1)pdm09, 10 A(H3N2) and eight 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 [5] reported that the China Health and Family Planning Commission had notified WHO of three cases of human infection with influenza A(H7N9). Increased numbers of cases were reported over the course of the following seasons, and cases were reported in 2017, including the fifth (2016-17) and largest wave to date, which included the emergence of highly pathogenic avian influenza (HPAI) strains that have caused some zoonoses, although few human cases were reported during the 2017-18 season [6]. WHO posted an analysis of information on A(H7N9) viruses on 10 February 2017 [7], and ECDC published a rapid risk assessment on the implications of A(H7N9) for public health on 3 July 2017 [8]. Current risk assessments can be found on WHO's website https://www.who.int/teams/global-influenza-programme/avian-influenza/monthly-risk-assessment-summary (accessed 18 October 2021). The assessment published on 8 August 2021 indicated that there had been no publicly available reports from animal health authorities in China or other countries on influenza A(H7N9) virus detections in animals in recent months [9]. The H7N9 situation update published by the Food and Agricultural Organization of the United Nations on 3 February 2021 indicated there had been 14 detections in chickens in Shandong province, China during October 2020, but the report published on 8 September 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 29 September 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 8 August 2021. Since the previous risk assessment on 22 June 2021, one human case of infection with an avian influenza A(H5N1) virus and six human cases of infection with avian influenza A(H5N6) viruses were reported officially [9]. The source of exposure to A(H5N1) in India of a male child with underlying immunodeficiency was unknown, but he was also infected with an influenza B/Victoria-lineage virus, and the outcome was fatal. This latest human case of known A(H5N1) infection is the first since that reported on 31 October 2020 by Lao People's Democratic Republic [13].The six cases of A(H5N6) infection were all related to sporadic infections in China and at the time of reporting, one case was fatal, four were critical and one showed mild symptoms; the cases involved adults in the age range 51-66 and all reported exposure to poultry [9].

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 162 highly pathogenic avian influenza (HPAI) A(H5) detections between 25 May and 15 September 2021, 51 in poultry, 91 in wild birds and 20 in domestic birds [12]. Detections occurred in 17 EU/EEA countries and the UK. Of the poultry detections, 20 were reported by Kosovo, 17 by Poland, and six by Albania, and the wild bird detections were reported in resident populations mainly in northern Europe. Nineteen different virus genotypes were detected in Europe and Central Asia since July 2020, confirming a high propensity for A(H5) viruses to undergo reassortment events, with most recent detections being subtype A(H5N8). According to reports compiled by the Food and Agricultural Organization of the United Nations (FAO) as of 29 September 2021, various influenza A(H5Nx) subtypes continued to be detected in wild and/or domestic birds in Africa, Asia and Europe, and since 25 August 2021 a total of 109 HPAI and three LPAI outbreaks had been reported together with three A(H5N6) zoonotic cases in China [15].

Influenza A(H9N2) virus

Since the previous WHO update on 22 June 2021 no laboratory-confirmed human cases of influenza A(H9N2) virus infection were reported as of 8 August 2021 [9]. However, the latest FAO report indicated two cases of A(H9N2) infection in children having been reported by China since 25 August 2021 [15]. Public Health England recently published and updated risk assessment of avian influenza A(H9N2) [16]. 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 earlier human infections with H9N2 viruses, following-on from the previous report up to 14 May 2021 [12].

Other influenza zoonotic events

Since the previous WHO update on 22 June 2021, no zoonotic events with swine-related variant influenza A viruses (H1N1v, H1N2v or H3N2v) had been reported to WHO as of 8 August 2021[9].

WHO Collaborating Centre reports

A description of results generated by the London WHO Collaborating Centre at the WIC and used at the September 2021 WHO vaccine composition meeting (held online: 13-23 September 2021 for seasonal influenza viruses), and previous ones, can be found at https://www.crick.ac.uk/partnerships/worldwide-influenza-centre/annual-and-interim-reports (accessed 18 October 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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