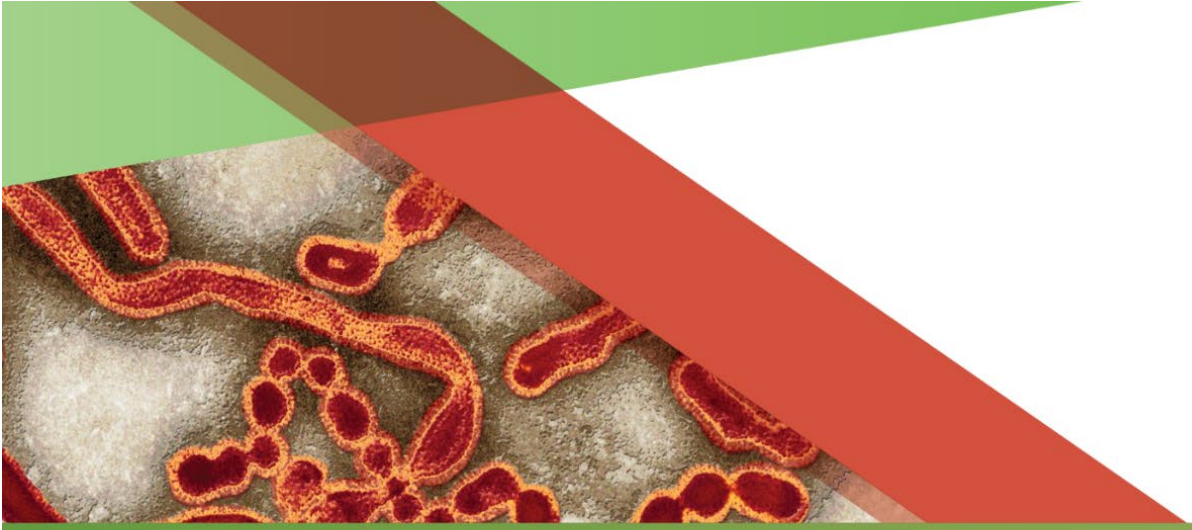

SURVEILLANCE REPORT

Influenza virus characterisation

Summary Europe, December 2020

Summary

This is the third report for the 2020–2021 influenza season. As of week 53/2020, only 415 influenza detections across the WHO European Region had been reported; 50% type A viruses, with A(H3N2) prevailing over A(H1N1)pdm09, and 50% type B viruses with only four having been ascribed to a lineage, three B/Victoria and one B/Yamagata. This represents a 98% drop in detections compared to the same period in 2019, probably due to the COVID-19 pandemic and measures introduced to combat it.

Since the November 2020 characterisation report[1], no shipments of influenza-positive specimens from European Union/European Economic Area (EU/EEA) countries have been received at the London WHO Collaborating Centre, the Francis Crick Worldwide Influenza Centre (WIC). Therefore, this report focuses on genetic characterisation of influenza viruses, the majority of which have collection dates prior to the start (week 40) of weekly influenza surveillance reporting for the 2020-2021 influenza season, based on HA sequences deposited in GISAID during December.

All 39 A(H1N1)pdm09 HA sequences deposited in GISAID in December were from viruses detected before April 2020 and fell in the 6B.1A5A group. 6B.1A5A viruses have continued to evolve and two subgroups have emerged designated 6B.1A5A+187V/A, representatives of which are recommended for use in the northern hemisphere 2020-2021 season, and 6B.1A5A+156K, an antigenically distinct group representatives of which are recommended for use in the southern hemisphere 2021 season. Following a rise in the number of 6B.1A5A+156K viruses detected, the two subgroups appear to be circulating in approximately equal proportions currently, based on low numbers of viruses with collection dates after March 2020 having been detected and characterised genetically.

Recently circulating A(H3N2) viruses have continued to fall in clades 3C.2a and 3C.3a, with the vast majority of clade 3C.2a viruses being in the 3C.2a1b group, which splits into four subgroups designated 3C.2a1b+T131K-A, 3C.2a1b+T131K-B, 3C.2a1b+T135K-A and 3C.2a1b+T135K-B. Antisera raised in ferrets show high levels of clade/group specificity, although there is some subgroup cross-reactivity. Viruses representative of subgroup 3C.2a1b+T135K-B have been recommended for use in influenza vaccines for the 2020-2021 northern hemisphere and 2021 southern hemisphere influenza seasons. The most recently detected viruses, with collection dates in September through November, have been reported from Bangladesh, Cambodia and India; all have subgroup 3C.2a1b+T131K-A

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

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HA genes that encode amino acid substitutions at positions in HA1 that are likely to affect antigenic properties of the viruses.

Of four antigenically distinct groups of viruses in the B/Victoria-lineage, all sequences deposited in GISAID in December were derived from subclade 1A(△3)B viruses with a three amino acid deletion in HA1. The four viruses with collection dates in October and November, all detected in France, contain a series of HA1 amino acid substitutions that are likely to affect antigenic properties of the viruses. Viruses representative of subclade 1A(△3)B have been recommended for use in influenza vaccines for the 2020-2021 northern hemisphere and 2021 southern hemisphere influenza seasons.

Six additional sequences for B/Yamagata-lineage viruses were deposited and/or released in GISAID during December (since the November report), but all had collection dates in January through March as has been the case throughout 2020. All HA sequences belong to genetic clade 3 and contain at least two HA amino acid substitutions (HA1 L172Q and M251V) compared to B/Phuket/3073/2013-like viruses which have been recommended for use in quadrivalent influenza vaccines for the northern hemisphere 2020-2021 and southern hemisphere 2021 seasons. The antigenic effects of these amino acid substitutions have been minimal as assessed in earlier reports.

Table 1 shows a summary of influenza virus detections in the WHO European Region reported to The European Surveillance System (TESSy) database for the 2020–2021 season (weeks 40-53/2020), compared with the same period (weeks 40-52/2019) for the 2019-2020 season. While there has been a significant reduction in numbers of samples from patients fulfilling Influenza-Like Illness (ILI) and/or Acute Respiratory Infection (ARI) criteria being tested (~29 791, 13%), there has been a vast reduction in the number of samples testing positive for an influenza virus (26 110, 98.4%). This is probably due to a number of factors: (i) the number of centres within the Region reporting over these periods having dropped from 50 to 45; (ii) 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; (iii) 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; (iv) viral interference, with SARS-CoV-2 infection impeding infection by influenza viruses. With these caveats, and being mindful of the low number of detections over the first 14 weeks of the 2020-2021 season, the ratio of type A to type B detections is reduced compared to the 2019–2020 season (5.5:1 to 1:1), with similar proportions of influenza A subtypes while B/Victoria lineage viruses appear, again, to be predominating over B/Yamagata lineage viruses although only 5/209 (2.4%) of type B viruses detected in the 2020-2021 season have been ascribed to a lineage as of week 53/2020.

Table 1. Influenza virus detections in the WHO European Region from the start of reporting for the 2020–21 season (weeks 40-53/2020)[a]

Virus type/subtype/lineage	Cumulative number of detections for weeks 40-53/2020			Totals*		Cumulative number of detections for weeks 40-52/2019			Totals*	
	Sentinel sources	Non-sentinel sources	Totals	%	Ratios	Sentinel sources	Non-sentinel sources	Totals	%	Ratios
Influenza A	**2**	**204**	**206**	**49.6**	**1:1**	**1650**	**20796**	**22446**	**84.6**	**5.5:1**
A(H1N1)pdm09	2	10	12	28.6		641	1547	2188	26.3	
A(H3N2)	0	30	30	71.4	2.5:1	932	5188	6120	73.7	2.8:1
A not subtyped	0	164	164			77	14061	14138		
Influenza B	**6**	**203**	**209**	**50.4**		**729**	**3350**	**4079**	**15.4**	
Victoria lineage	1	3	4	80.0	4:1	194	218	412	90.7	9.8:1
Yamagata lineage	0	1	1	20.0		6	36	42	9.3	
Lineage not ascribed	5	199	204			529	3096	3625		
Total detections (total tested)	**8 (12999)**	**407 (>185251)**	**415 (>198250)**			**2379 (14369)**	**24146 (>213672)**	**26525 (>228041)**		

[a] Numbers taken from Flu News Europe week 53/2020 and week 52/2019 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.

No shipments of specimens (virus isolates and/or clinical specimens) relating to the 2020-2021 influenza season have been received at the Crick Worldwide Influenza Centre (WIC) due to the low numbers of influenza virus detections within the European Region and elsewhere. Consequently, recent influenza characterisation reports, and this one, have been primarily based on phylogenetic analyses of complete HA gene sequences submitted to the EpiFlu™ database of the Global Initiative on Sharing All Influenza Data (GISAID), inclusive of sequences generated at the WIC, with those from EU/EEA countries highlighted. Antigenic and antiviral susceptibility data for viruses received from EU/EEA countries, generated by the WIC, will be presented when it becomes available.

Genetic and antigenic characterisation data generated at the WIC for viruses with collection dates after 31 August 2019 and until 31 January 2020 contributed to the WIC virus characterisation report (the deadline for the report was 21 February 2020) that was presented at WHO's influenza vaccine composition meeting (VCM) in February 2020. At this meeting, recommendations were made for the northern hemisphere 2020–2021 season [1]. Subsequently, data generated for viruses with collection dates after 31 January 2020 and until 31 August 2020 was used to inform the most recent WHO VCM (held online from 16–24 September 2020) when recommendations were made for the southern hemisphere 2021 season [2].

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 (egg-based A/Victoria/5270/2019-like and cell-based A/Wisconsin/588/2019-like) influenza seasons are shown in red [1, 2]. 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 phylogenies have very similar profiles and are largely made up of sequences from viruses detected in the later part of the 2019-2020 northern hemisphere and early part of the 2020 southern hemisphere influenza seasons. The first A(H1N1)pdm09 HA phylogeny is repeated from the November 2020 report and was generated based on sequences deposited in GISAID for recently circulating viruses, with collection dates from 1 February 2020, submitted to GISAID during November 2020 (Figure 1a). All but 14 sequences were determined for viruses collected in February and March: one was collected in April, one in May, four in June, two in August, three in September and three in October. The second phylogeny is based on sequences from all A(H1N1)pdm09 viruses that were deposited and/or released in GISAID during December 2020. All sequences were derived from viruses with collection dates before the end of March 2020, the great majority being from viruses detected in France, Lebanon and Tunisia (Figure 1b). The vast majority of recently circulating viruses have fallen in group **6B.1A5A**, with approximately equal proportions falling in the parent group and the **6B.1A5A+187V/A** and **6B.1A5A+156K** subgroups. Relatively few viruses in subgroup **6B.1A5B** (with **HA1 K130N**, **K160M**, **T216K**, **E235D**, **H296N** and **HA2 V193A** substitutions) have also been detected and even fewer in subclade **6B.1A7**. Of the 14 viruses with collection dates in April through October, one belongs to group **6B.1A5B**, two to group **6B.1A5A**, six to subgroup **6B.1A5A+187V/A** and five to subgroup **6B.1A5A+156K** (Figure 1a).

The great majority of 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**, remained antigenically similar to A/Brisbane/02/2018, the northern hemisphere 2019–2020 vaccine virus, and 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).

As was the case at the time of the November report, no A(H1N1)pdm09 viruses were characterised antigenically at the WIC during December.

Figure 1a. Phylogenetic comparison of influenza A(H1N1)pdm09 HA genes (GISAID, November 2020)

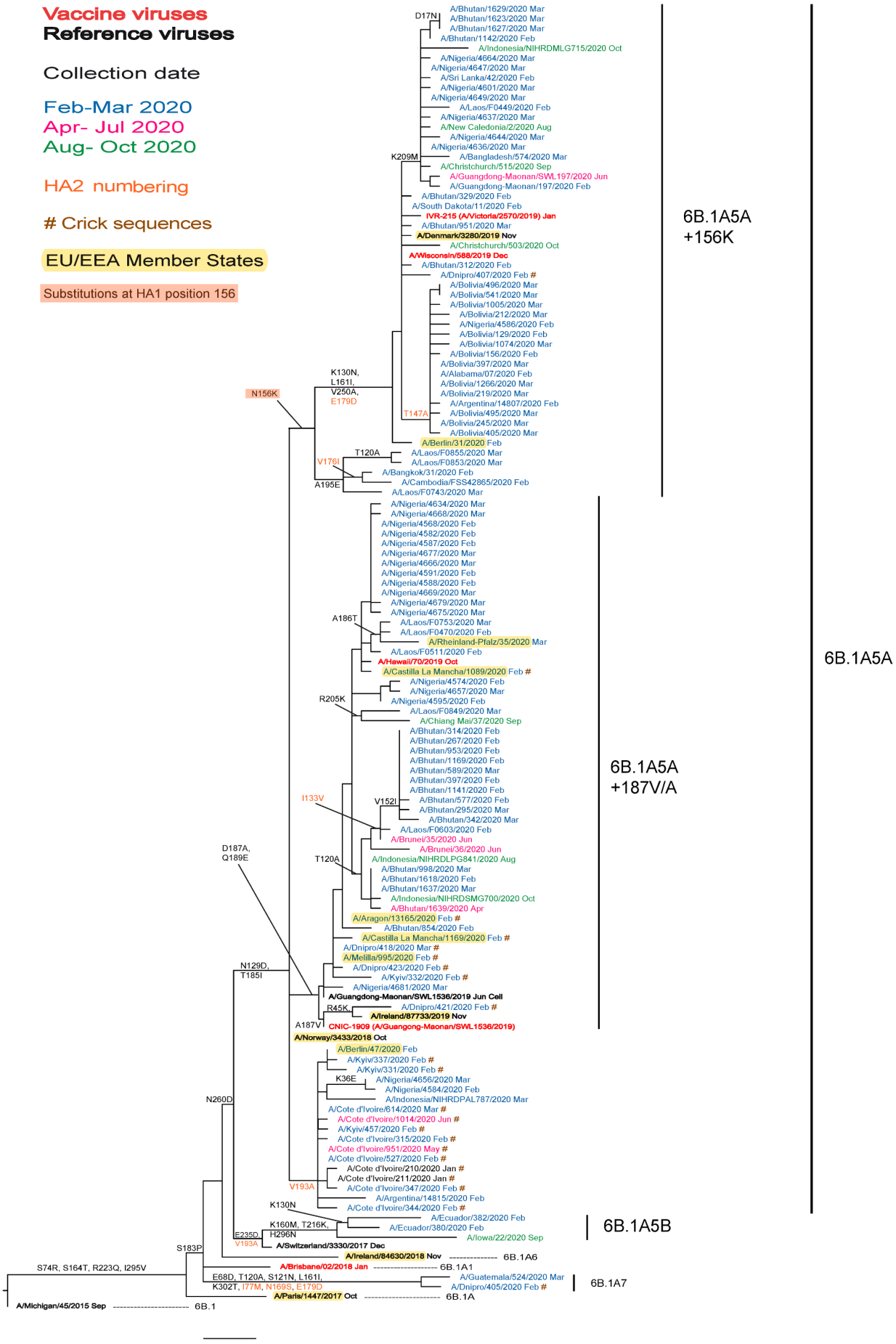
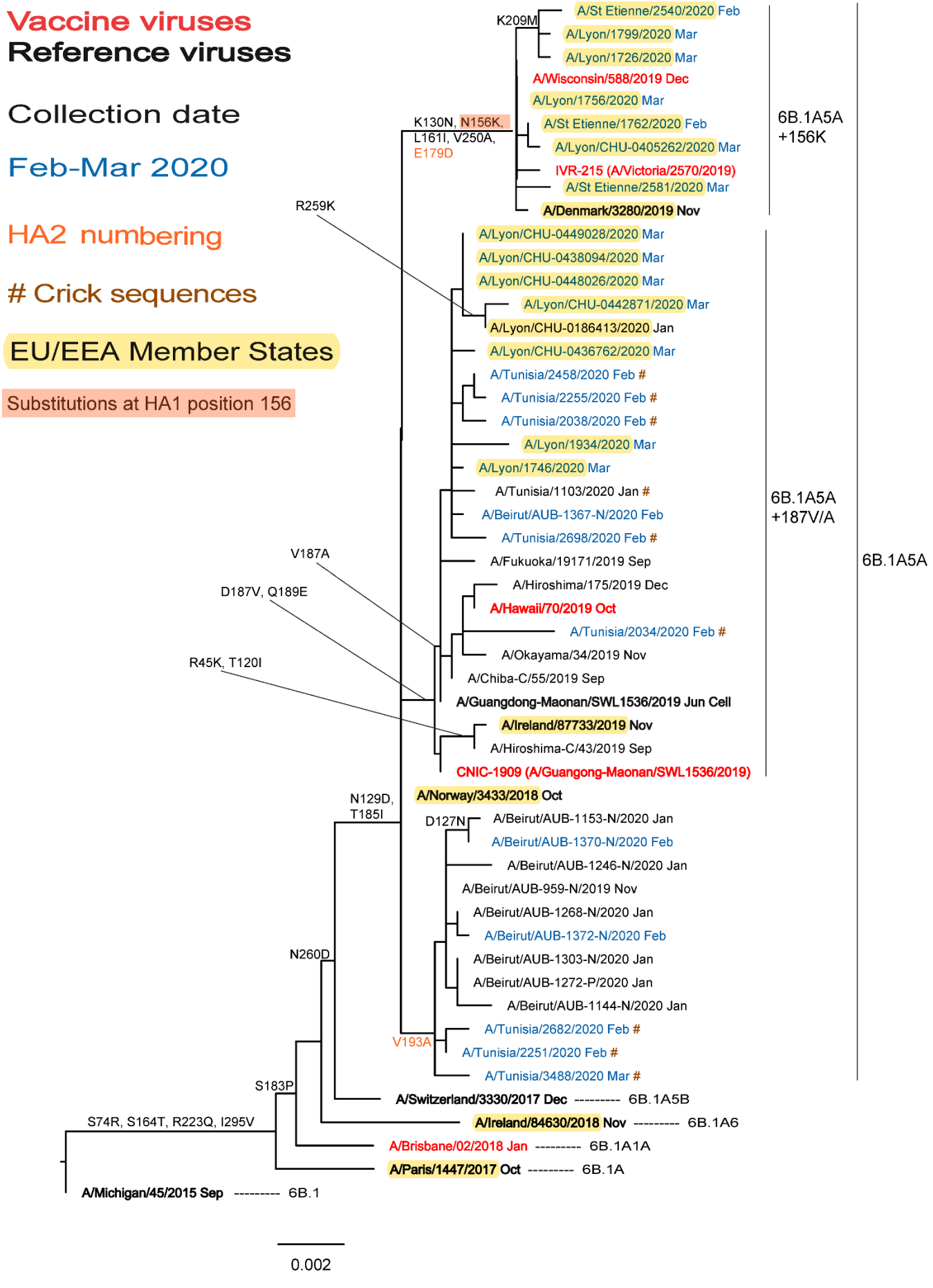


Figure 1b. Phylogenetic comparison of influenza A(H1N1)pdm09 HA genes (GISAID, December 2020)



Influenza A(H3N2) virus analyses

The first A(H3N2) HA phylogeny is repeated from the November 2020 report and was generated based on sequences, derived from viruses with collection dates in 2020, that had been deposited in GISAID during November 2020; a total of 65 sequences (Figure 2a). The second is based on sequences deposited in GISAID during December 2020 derived from viruses with collection dates from October 2019; a total of 127 sequences (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 virus as the A(H3N2) component of vaccines for the 2020–2021 northern hemisphere and 2021 southern hemisphere influenza seasons [1, 2].

The HA phylogeny generated for the November report, based on sequences recently deposited in GISAID, showed a preponderance of group **3C.2a1b** viruses over clade **3C.3a**, but with the great majority of viruses having collection dates in February and March (Figure 2a). Sequences were derived from viruses detected mainly in Europe and countries of the Tropics and southern hemisphere; only two viruses had collection dates after March (one each in July and August, detected in Timor-Leste), both of which fell within the subgroup **3C.2a1b+T131K-A** cluster. Figure 2b shows a phylogeny based on sequences deposited in GISAID during December 2020, it having a similar profile to that of Figure 2a. However, all sequences derived from viruses with collection dates from July onwards fall in the subgroup **3C.2a1b+T131K-A** cluster: 34 from Cambodia carrying additional **HA1** substitutions of **K171N**, **G186S**, **F193S**, **Y195F** and **S198P**, and 27 from Bangladesh (n = 18) and India (n = 7) with additional **HA1** substitutions of **Y159N**, **T160I** (loss of a glycosylation site), **L164Q**, **G186D**, **D190N**, **F193S** and **Y195F**. Given the locations of these HA1 amino acid substitutions there is need to assess the antigenic properties of such viruses and monitor their geographic spread.

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, recently 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 (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],

[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

this has been a significant problem for most viruses that fall in genetic clade **3C.2a**, although there has been some alleviation of this over the course of the 2019-2020 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 (https://www.ecdc.europa.eu/en/seasonal-influenza/surveillance-and-disease-data/influenza-virus-characterisation). 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.

As was the case at the time of the November report, no A(H3N2) viruses were characterised antigenically at the WIC during December.

Figure 2a. Phylogenetic comparison of influenza A(H3N2) HA genes (GISAID, November 2020)

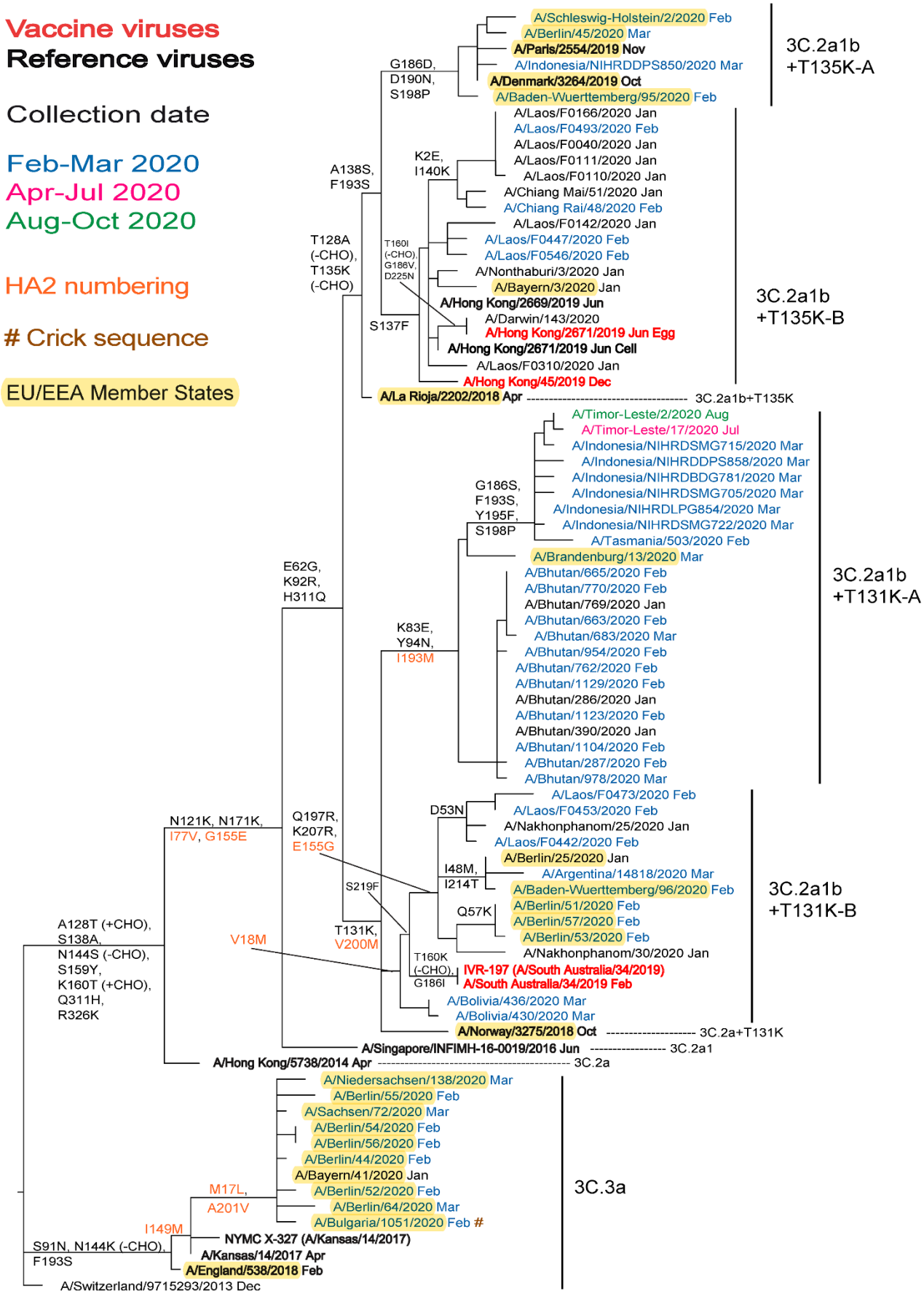
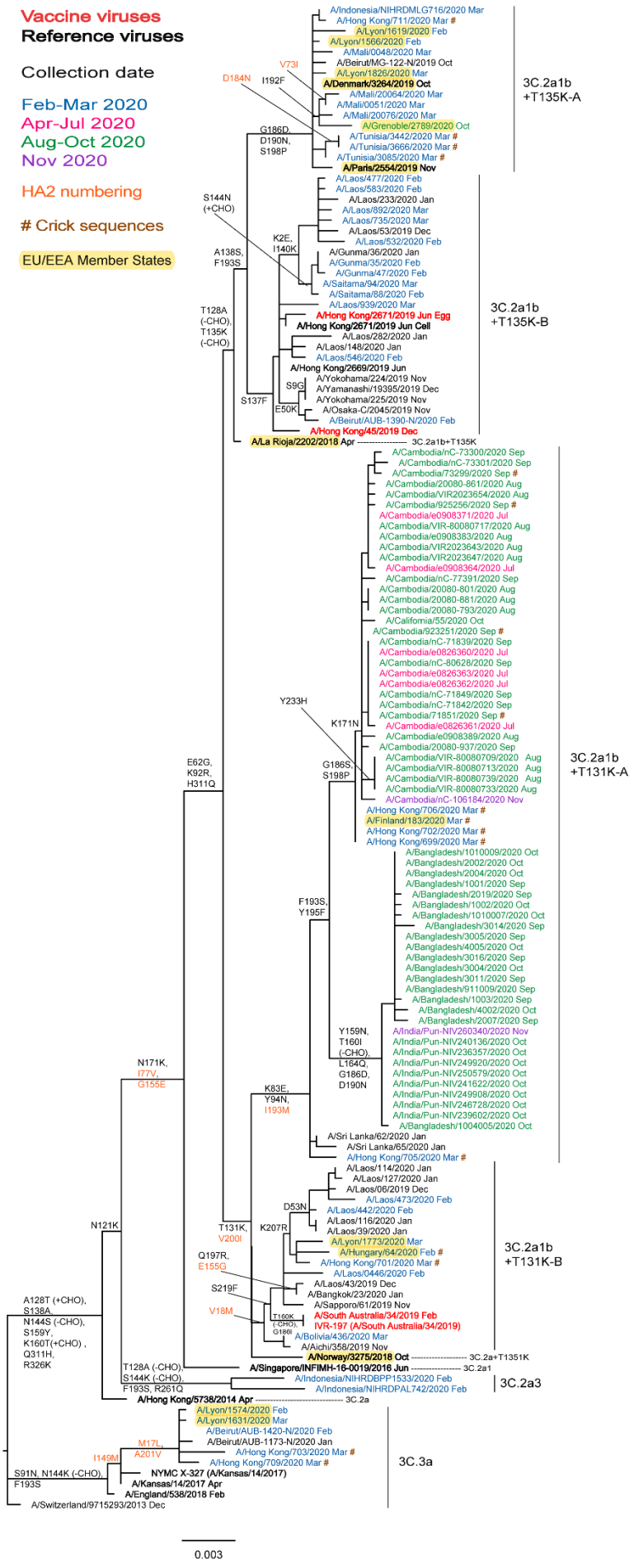


Figure 2b. Phylogenetic comparison of influenza A(H3N2) HA genes (GISAID, December 2020)



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, N129D** and **V146I** (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.

The HA phylogeny generated for the November report showed continued dominance of **subclade 1A(△3)B** viruses having **HA1 K136E,** often with **G133R** substitution, with several virus clusters having emerged defined by specific amino acid substitutions, e.g. **HA1 E128K** or **D129N** with **N233S** (loss of a glycosylation site) or **N150K** with **G184E** or **N233K** (loss of a glycosylation site), with relatively few **subclade 1A(△2)** viruses having been detected (Figure 3a). Sequences, all in **subclade 1A(△3)B**, were derived from just four viruses with collection dates after March (two in April and one each in May and June).

All 71 sequences deposited in GISAID during December fell in **subclade 1A(△3)B** and were derived mainly from viruses detected in France, Japan and Lebanon, with collection dates from October 2019 to March 2020 (Figure 3b). Viruses with collection dates up to March 2020 mainly fell in virus clusters defined by **HA1** substitutions **N126K** or **E128K** or **D129N** with **N233S** (loss of a glycosylation site) or **N233K** (loss of a glycosylation site). However, four viruses from France, two each with collection dates in October and November 2020, fell in the **N150K** with **G184E** cluster with additional **HA1** substitutions of **A127T**, **P144L**, **N197D** (loss of a glycosylation site), **K203R** and **R279K**, with three of the viruses having further **HA1** substitutions of **T128A**, **D197E** and **T221A**. The Figure 3b phylogeny profile is very similar to that of Figure 3a.

Following the spread of **1A(Δ2)** viruses a representative, B/Colorado/06/2017, was recommended for use in trivalent influenza vaccines for the 2019–2020 northern hemisphere season, but recent predominance of **1A(Δ3)B** viruses led to the recommendation of a representative (B/Washington/02/2019) for use in trivalent influenza vaccines for the northern hemisphere 2020–2021 [1] and 2021 southern hemisphere [2] seasons.

Since the November 2020 report, no B/Victoria-lineage viruses were analysed by HI assay.

Influenza B/Yamagata-lineage

As was the case at the time of the November report, no B/Yamagata-lineage viruses from WHO European Region countries were characterised at the WIC during December. The HA phylogeny, for viruses with collection dates from 1 January 2020, has been updated with six new B/Yamagata-lineage sequences submitted to GISAID in December; all were derived from viruses detected in France and Tunisia with collection dates in January to March 2020 (Figure 4). As for other recently detected B/Yamagata-lineage viruses, the HA genes fall 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. Some sub-clustering of sequences from recently collected viruses, 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 which is recommended for inclusion in quadrivalent vaccines for the 2020–2021 northern hemisphere and 2021 southern hemisphere seasons [1, 2].

[4] European entre 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, November 2020)

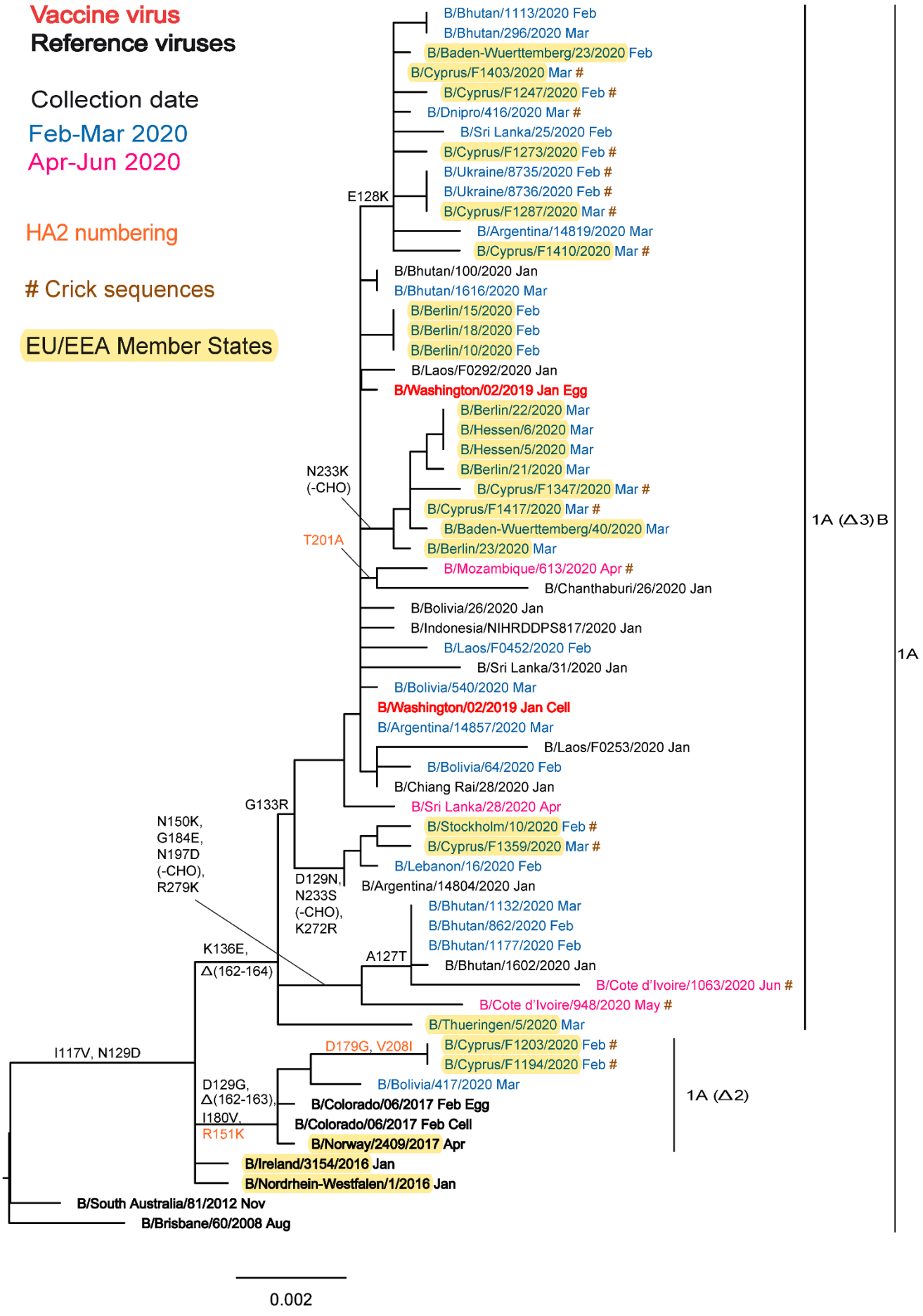


Figure 3b. Phylogenetic comparison of influenza B/Victoria-lineage HA genes (GISAID, December 2020)

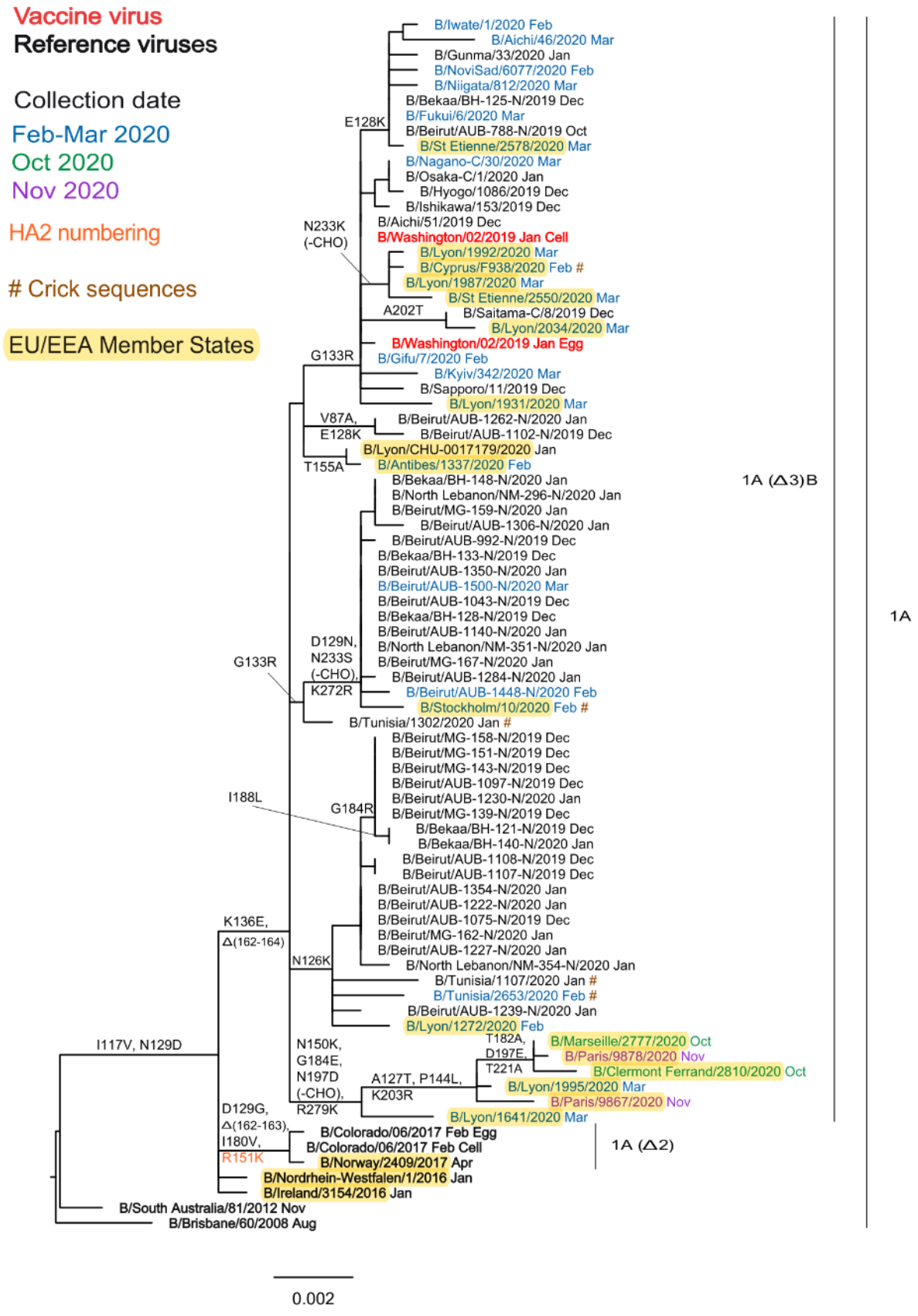
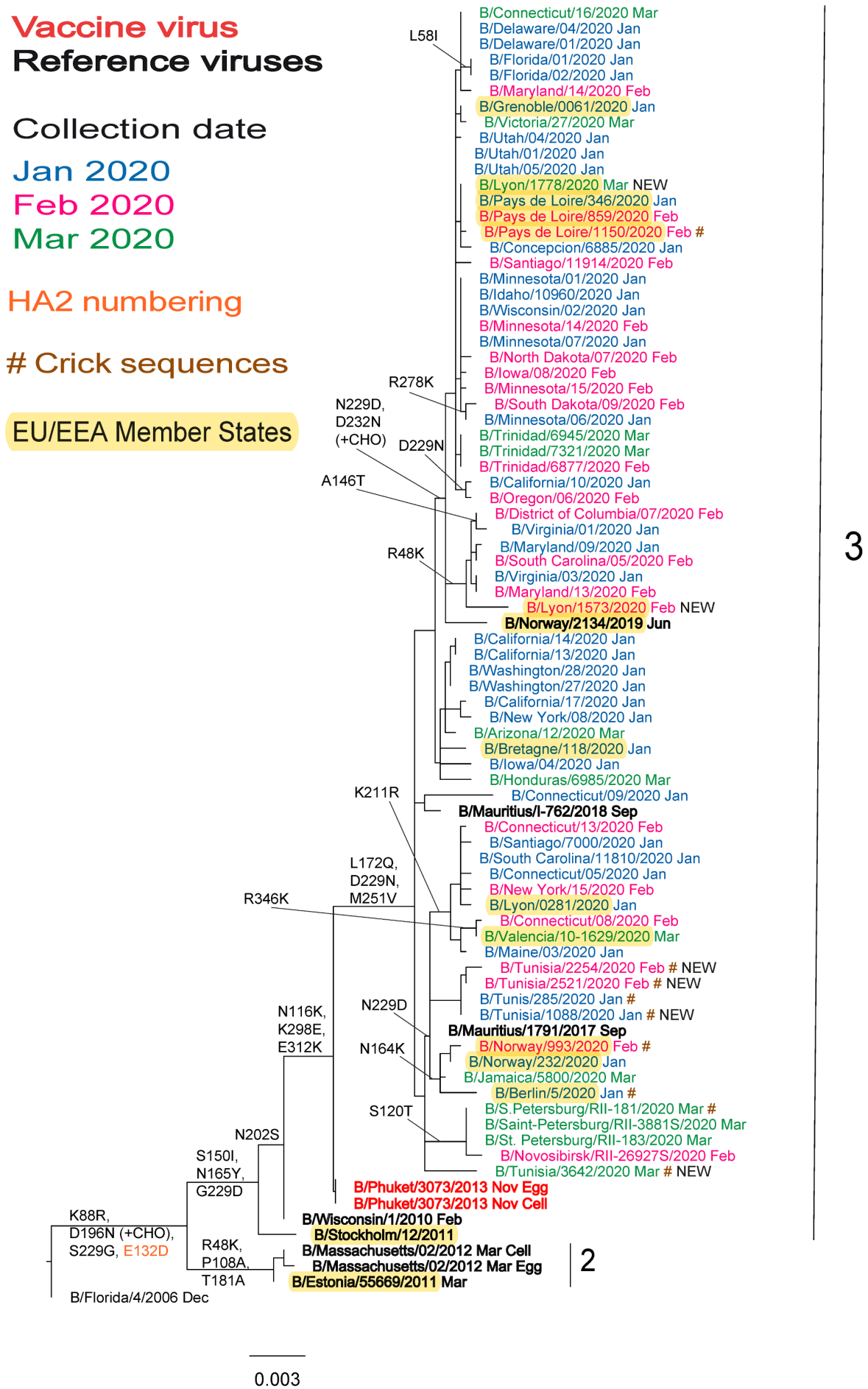


Figure 4. Phylogenetic comparison of influenza B/Yamagata-lineage HA genes (GISAID, December 2020)



Summaries of data submitted to TESSy

Genetic characterisation

No viruses detected over the course of the 2020-2021 season (weeks 40-53/2020) have been genetically characterised. 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

No influenza viruses detected within the WHO European Region during the 2020-2021 season have been tested for susceptibility to neuraminidase inhibitors (NAIs: 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, no viruses detected within EU/EEA countries during the 2020-2021 season have been assessed phenotypically against NAIs oseltamivir and zanamivir. Over the course of the 2019-2020 influenza season of 1 030 viruses assessed for susceptibility to NAIs, only five (0.49%) showed either RI or HRI by at least one NAI.

Influenza A(H7N9) virus

On 1 April 2013, the World Health Organization (WHO) Global Alert and Response [3] reported that the China Health and Family Planning Commission 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 [4]. 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 [5]. WHO posted an analysis of information on A(H7N9) viruses on 10 February 2017 [6], and ECDC published a rapid risk assessment on the implications of A(H7N9) for public health on 3 July 2017 [7]. Current risk assessments are included in WHO's monthly summary and assessment of influenza at human-animal interface (accessed 4 January 2021). The assessment published on 9 December 2020 indicates 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 [8]. The most recent human case was detected in mid-March 2019 [9]. 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 10 December 2020 and can be found on ECDC's website [10].

Influenza A(H5) virus

The most recent monthly risk assessment of influenza at the human–animal interface was published by WHO on 9 December 2020. Since the last risk assessment on 23 October 2020 laboratory-confirmed two H5Nx cases have been reported: one H5N1 by Lao People's Democratic Republic in a 1-year-old female who recovered and one H5N6 in a 81-year-old female who died, both of whom had exposure to poultry [8]. According to reports received by the World Organisation for Animal Health (OIE), various influenza A(H5Nx) subtypes continue to be detected in wild and/or domestic birds in Africa, Europe and Asia. This is the first human case of A(H5N1) infection reported to WHO since the case in Nepal in March 2019 [11]. On 30 September 2020, ECDC published an alert related to outbreaks of avian influenza viruses in Europe [12]. The latest collaborative report from ECDC and the European Food Safety Authority, reports 561 highly pathogenic avian influenza (HPAI) A(H5) detections between 15 August and 17 December 2020 with the majority (n=510) being in wild birds and 43 outbreaks of HPAI in poultry [10]. Detections occurred in 15 EU/EEA countries and the UK, with Germany, Denmark and the Netherlands accounting for 370, 65 and 57 detections respectively. Three HPAI virus subtypes, A(H5N8) (n=518), A(H5N5) (n=17) and A(H5N1) (n=6), and four different genotypes were identified, suggesting the occurrence of multiple virus introductions into Europe.

Influenza A(H9N2) virus

Since the previous update on 23 October 2020, one new laboratory-confirmed human case of influenza A(H9N2) virus infection in China has been reported [8]. The case was in a three-year-old female in Guangdong province who had exposure to poultry and developed mild symptoms on 12 October 2020 and was admitted to hospital. Avian influenza A(H9N2) viruses are enzootic in poultry in Asia and increasingly reported in poultry in Africa.

Other influenza zoonotic events

Since the previous update on 23 October 2020, two zoonotic events with swine influenza viruses were reported to WHO [8]. An historic case of A(H1N1)v infection was reported from the Netherlands in a 43-year-old male farmer who developed ILI-symptoms on 25 September 2019 and was infected with a Eurasian avian-like influenza A(H1N1)v swine influenza virus. The second case, reported from Canada on 31 October 2020, involved infection of a child who made a complete recovery with a swine A(H1N2)v virus; there was indirect contact with pigs via the child's father.

WHO Collaborating Centre reports

A description of results generated by the London WHO Collaborating Centre at the WIC and used at the most recent WHO vaccine composition meeting (held online 16-24 September 2020 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 4 January 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.

References

1. World Health Organization. Recommended composition of influenza virus vaccines for use in the 2020-2021 northern hemisphere influenza season. Wkly Epidemiol Rec. 2020 Mar 20;95(12):105-116. Available from: http://extranet.who.int/iris/restricted/bitstream/handle/10665/331503/WER9512-eng-fre.pdf
2. World Health Organization. Recommended composition of influenza virus vaccines for use in the 2021 southern hemisphere influenza season. Wkly Epidemiol Rec. 2020 Oct 16;95(42):497-508. Available from: https://apps.who.int/iris/bitstream/handle/10665/336144/WER9542-eng-fre.pdf
3. World Health Organization. Emergencies preparedness, response – Human infection with influenza A(H7N9) virus in China. 1 April 2013 [Internet]. Geneva: WHO; 2013 [accessed 4 January 2021]. Available from: http://www.who.int/csr/don/2013_04_01/en/index.html
4. World Health Organization. Influenza – Avian influenza A(H7N9) virus [Internet]. Geneva: WHO; 2017 [accessed 4 January 2021]. Available from: http://www.who.int/influenza/human_animal_interface/influenza_h7n9/en/
5. World Health Organization. Emergencies preparedness, response –Human infection with avian influenza A(H7N9) virus – China [Internet]. Geneva: WHO; 2017 [accessed 4 January 2021]. Available from: http://www.who.int/csr/don/26-october-2017-ah7n9-china/en/
6. World Health Organization. Analysis of recent scientific information on avian influenza A(H7N9) virus. 10 February 2017 [Internet]. Geneva: WHO, 2017 [accessed 4 January 2021]. Available from: http://www.who.int/influenza/human_animal_interface/avian_influenza/riskassessment_AH7N9_201702/en
7. European Centre for Disease Prevention and Control. Influenza A(H7N9) virus in China - implications for public health - 7th update, 3 July 2017. Stockholm: ECDC; 2017. Available from: https://www.ecdc.europa.eu/sites/default/files/documents/2017-07-03-RRA-Disease-China_H7N9_0.pdf
8. World Health Organization. Influenza at the human-animal interface. Summary and assessment, 24 October to 9 December 2020. Geneva: WHO; 2020. Available from: https://www.who.int/influenza/human_animal_interface/Influenza_Summary_IRA_HA_interface_09_12_2020.pdf
9. World Health Organization. Influenza at the human–animal interface. Summary and assessment, 13 February to 9 April 2019. Geneva: WHO; 2019. Available from: https://www.who.int/influenza/human_animal_interface/Influenza_Summary_IRA_HA_interface_09_04_2019.pdf
10. European Centre for Disease Prevention and Control, European Food Safety Authority, European Union Reference Laboratory for Avian Influenza. Avian influenza overview August-December 2020. Parma and Stockholm: EFSA, ECDC; 2020. Available from: https://www.ecdc.europa.eu/sites/default/files/documents/avian-influenza-overview-august-december-2020_1.pdf.pdf
11. World Health Organization. Cumulative number of confirmed human cases for avian influenza A(H5N1) reported to WHO, 2003–2020. Geneva: WHO; 2020. Available from: https://www.who.int/influenza/human_animal_interface/2020_DEC_tableH5N1.pdf
12. European Centre for Disease Prevention and Control. Avian influenza: EU on alert for new outbreaks. 30 September 2020 [internet]. Stockholm: ECDC; 2020 [accessed 4 January 2021]. Available from: https://www.ecdc.europa.eu/en/news-events/avian-influenza-eu-alert-new-outbreaks