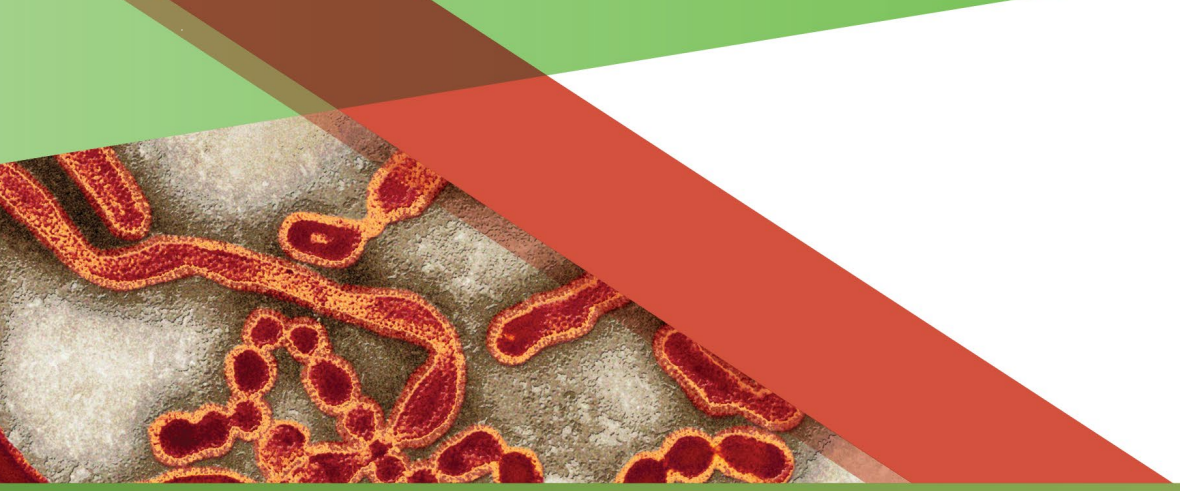

SURVEILLANCE REPORT

Influenza virus characterisation

Summary Europe, May 2019

Summary

This is the seventh report for the 2018–19 influenza season. As of week 20 in 2019, 204 512 influenza detections across the WHO European Region have been reported. Ninety-nine per cent were type A viruses, with A(H1N1)pdm09 prevailing over A(H3N2), and 1% type B viruses, with 83 (60%) of 139 ascribed to a B/Yamagata-lineage.

Since the April 2019 characterisation report[1], an additional four shipments of influenza-positive specimens from EU/EEA countries were received at the London WHO CC, the Francis Crick Worldwide Influenza Centre (WIC). A total of 1 184 virus specimens with collection dates after 31 August 2018 have been received.

Nine A(H1N1)pdm09 test viruses from Slovenia characterised antigenically since the April 2019 characterisation report all showed good reactivity with antiserum raised against the 2018–19 vaccine virus, A/Michigan/45/2015 (clade 6B.1). Four hundred test viruses with collection dates from week 40 of 2018 genetically characterised at the WIC, including an H1N2 reassortant, all fell in a 6B.1 subclade designated 6B.1A, defined by HA1 amino acid substitutions of S74R, S164T and I295V. Of these recently circulating viruses, 365 also had HA1 S183P substitution, often with additional substitutions in HA1 and/or HA2.

Since the last report, only one successfully recovered A(H3N2) virus had sufficient haemagglutinin (HA) titre to allow antigenic characterisation by haemagglutination inhibition (HI) assay in the presence of oseltamivir. The virus was poorly recognised by antisera raised against the currently used vaccine virus, egg-propagated A/Singapore/INFIMH-16-0019/2016, in HI assays. Of the 337 viruses with collection dates from week 40 of 2018 genetically characterised at the WIC, 273 were clade 3C.2a (with 32 3C.2a2, 13 3C.2a3, six 3C.2a4 and 222 3C.2a1b) and 64 were clade 3C.3a.

No B/Victoria-lineage viruses have been characterised in this reporting period. All recent viruses carry HA genes that fall in clade 1A, but encode HA1 amino acid substitutions of I117V, N129D and V146I compared

[1] European Centre for Disease Prevention and Control. Influenza virus characterisation – Summary Europe, April 2019. Stockholm: ECDC; 2019. Available from: http://ecdc.europa.eu/publications-data/influenza-virus-characterisation-summary-europe-april-2019

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Stockholm, June 2019

to a previous vaccine virus, B/Brisbane/60/2008. Groups of viruses defined by deletions of two [Δ162–163, 1A(Δ2)] or three [Δ162–164, 1A(Δ3)] amino acids in HA1 have emerged, with the triple deletion group having subgroups of Asian and African origin. HI analyses with panels of post-infection ferret antisera have shown these virus groups to be antigenically distinguishable. Of the five viruses characterised from EU/EEA countries this season, one has been Δ162–163 and four Δ162–164 (three African and one Asian subgroup).

No B/Yamagata-lineage viruses have been characterised in the reporting period. Eleven from the 2018–19 season have been characterised. All have HA genes that fall in clade 3 and encode HA1 amino acid substitutions of L172Q and M251V compared to the vaccine virus B/Phuket/3073/2013, but remain antigenically similar to the vaccine virus that is recommended for use in quadrivalent vaccines for current and subsequent northern hemisphere influenza seasons.

Table 1 shows a summary of influenza virus detections in the WHO European Region reported to ECDC's TESSy database since the start of the 2018–19 season from weeks 40 of 2018 to 20 of 2019). Since week 1 of 2019, the cumulative number of detections has increased from 18 049 to 202 409, with type A (99%) predominating over type B (1%) viruses, which is a common pattern, unlike the 2017–18 season when type B predominated over type A at the start of the season and throughout most of it. Of the type A viruses subtyped (n=76 591) and the type B viruses ascribed to a lineage (n=139), A(H1N1)pdm09 (n=44 046) has continued to prevail over A(H3N2) (n=32 545) viruses and 83 of 139 type B viruses have been B/Yamagata-lineage. These relative proportions have increased in favour of A(H3N2) and decreased slightly for B/Yamagata-lineage viruses compared to the summary in the April 2019 characterisation report. Overall, the ratio of type A to type B detections has dramatically increased compared with the 2017–18 season (0.8:1 to 92:1) and as the 2018–19 influenza season has progressed, the early prevalence of A(H1N1)pdm09 over A(H3N2) viruses has decreased such that levels observed in the two seasons have become comparable (57.5% in 2018–19 compared with 50.6% in 2017–18).

Table 1. Influenza virus detections in WHO European Region from start of reporting for 2018–19 season (weeks 40 of 2018 to 20 of 2019)[a]

	Cumulative number of detections			Totals*		Totals for 2017-18 season*		
Virus type/subtype/lineage	Sentinel sources	Non-sentinel sources	Totals	%	Ratios	Number	%	Ratios
Influenza A	**21073**	**181336**	**202409**	**99**	**92:1**	**106003**	**44.1**	**0.8:1**
A(H1N1)pdm09	8761	35285	44046	57.5		23121	50.6	
A(H3N2)	7256	25289	32545	42.5	0.7:1	22568	49.4	1:1
A not subtyped	5056	120762	125818			60314		
Influenza B	**296**	**1907**	**2203**	**1**		**134618**	**55.9**	
Victoria lineage	13	43	56	40.3		301	1.9	
Yamagata lineage	50	33	83	59.7	1.5:1	15701	98.1	52.2:1
Lineage not ascribed	233	1831	2064			118616		
Total detections (total tested)	**21369 (53544)**	**183243 (792987)**	**204512 (846531)**			**240621 (903182)**		

*** 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 Yamagata:Victoria lineages.**

Since week 40 of 2018, 52 shipments of specimens (virus isolates and/or clinical specimens) from 34 centres across 29 EU/EEA countries have been received at WIC containing 1 184 individual virus-related samples with collection dates after 31 August 2018 (Table 2). The proportions of received samples are similar to those reported to TESSy (Table 1) in terms of virus type and virus subtype or lineage. The genetic and antigenic characterisation data generated at the WIC for many of these viruses was presented at the WHO influenza vaccine composition meeting for the northern hemisphere 2019–20 season. Recommendations emerging from the meeting held on 18–21 February 2019 and the subsequent update on 21 March 2019 have been published [1].

Table 2. Summary of clinical samples and virus isolates contained in packages received from EU/EEA Member States since week 40 of 2018

MONTH / Country	TOTAL RECEIVED Seasonal viruses	A Number received	A Number propagated[1]	H1N1pdm09 Number received	H1N1pdm09 Number propagated[1]	H3N2 Number received	H3N2 Number propagated[2]		B Number received	B Number propagated[1]	B Victoria lineage Number received	B Victoria lineage Number propagated[1]	B Yamagata lineage Number received	B Yamagata lineage Number propagated[1]
2018														
SEPTEMBER														
France	7					6	3	3					1	1
Spain	1			1	1									
Sweden	1			1	1									
OCTOBER														
Czech Republic	2			2	2									
Denmark	2					2	0	2						
Estonia	3	1	0	1	0	1	0	1						
Finland	2			1	1	1	0	1						
France	11			3	3	7	5	2					1	1
Germany	1					1	0	1						
Iceland	2					1	0	1					1	1
Ireland	3			2	1	1	0	1						
Latvia	1			1	1									
Netherlands	1					1	0	1						
Norway	29			12	8	14	0	8					3	1
Portugal	2			2	2									
Slovenia	1			1	1									
United Kingdom	3			1	1	2	0	2						
NOVEMBER														
Austria	4			1	1	3	1	2						
Belgium	5			3	2	2	0	2						
Bulgaria	1			1	0									
Croatia	1			1	1									
Czech Republic	1			1	1									
Denmark	12			8	8	3	0	3			1	1		
Estonia	3			3	1									
Finland	4			2	2	2	0	2						
France	17			10	10	7	4	2						
Germany	8			4	4	4	0	4						
Iceland	15			4	3	11	7	3						
Ireland	17			12	10	4	0	3					1	1
Italy	10			2	2	8	5	3						
Latvia	2					2	1	1						
Lithuania	5					5	0	4						
Netherlands	3			2	2	1	0	1						
Norway	26			14	13	12	1	10						
Portugal	1												1	0
Spain	8			2	1	6	0	2						
Sweden	1			1	1									
United Kingdom	14			6	6	6	2	1			1	0	1	1
DECEMBER														
Austria	4			2	in process	2	in process							
Belgium	6			2	1	4	0	2						
Bulgaria	9			5	4	4	0	4						
Croatia	8			6	6	2	0	1						
Cyprus	3			3	1									
Denmark	7			5	5	2	0	2						
Estonia	18	1	0	16	11	1	0							
France	33			17	17	14	10	4			1	1	1	1
Germany	11			5	5	6	0	6						
Greece	11			8	5	3	0	1						
Hungary	6			4	4	2	1	1						
Iceland	3			3	3									
Ireland	3			3	3									
Italy	1			1	1									
Latvia	6			5	5	1	1	0						
Lithuania	14	1	0	5	3	8	0	3						
Netherlands	5			4	4	1	0	1						
Norway	15			6	4	7	1	4			2	1		
Poland	1			1	0									
Portugal	18			8	8	9	0	9					1	1
Romania	12			2	2	10	1	9						
Slovenia	3			1	1						2	2		
Spain	28			15	8	13	2	3						
Sweden	11			7	7	4	3	1						
United Kingdom	8			5	5	3	1							
2019														
JANUARY														
Austria	17			6	in process	10	in process						1	in process
Belgium	47			8	3	39	2	18						
Bulgaria	13			12	in process	1	0	1						
Croatia	2												2	1
Cyprus	22			21	in process	1	in process							
France	26			11	11	15	13	2						
Germany	34			15	15	19	5	14						
Greece	30			19	8	8	0	4	3	0				
Hungary	2					2	2							
Italy	4			3	3	1	0	1						
Latvia	6			6	6									
Lithuania	1			1	1									
Luxembourg	25			10	8	14	3	6					1	1
Malta	42			23	4	19	1	0						
Netherlands	12			8	8	4	2	2						
Norway	19			10	9	7	0	6					2	1
Poland	17			13	in process	4	in process							
Portugal	5			1	1	4	3	1						
Romania	13			11	6	2	1	1						
Slovenia	14			9	9	4	0	4			1	in process		
Spain	73			32	27	41	19	12						
United Kingdom	38	3	0	31	2	4	1	0						
FEBRUARY														
Austria	5			4	in process	1	in process							
Bulgaria	42			22	in process	20	in process							
Cyprus	15			14	in process	1	in process							
Germany	26			9	9	17	9	8						
Greece	17			11	10	5	1	4					1	1
Latvia	7			1	1	6	5	1						
Malta	8			5	2	3	0	1						
Poland	28	3	in process	22	in process	3	in process							
Slovenia	7			3	3	3	1	2			1	in process		
MARCH														
Austria	2												2	in process
Bulgaria	1					1	in process							
Cyprus	1					1	in process							
Germany	23			7	7	16	12	4						
Greece	15			8	3	6	1	4					1	1
Latvia	2			1	1	1	1	0						
Poland	7			7	in process									
Slovenia	8			4	4	3	in process		1	in process				
United Kingdom	16			11	0	5	0							
APRIL														
Cyprus	1					1	in process							
Slovenia	2			2	in process									
United Kingdom	15					15	0							
	1184	9	0	625	364	516	131	213	4	0	9	5	21	13
29 Countries					52.8%		43.6%					0.8%		1.8%
					97.1%							2.9%		

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

Numbers highlighted in blue show the number of viruses subjected to HI assay for 'completed' sample sets. Under a 'sequence first' virus characterisation scheme: (i) sequencing only was possible for some clinical specimens that had been collected in lysis buffer; (ii) where sequencing failed, despite samples having good Ct values, virus propagation was attempted for only a few samples; and (iii) where multiple viruses shared the same HA sequence only a selection were propagated to allow assay by HI

one virus was H1N2

As of 2019-06-04

Influenza A(H1N1)pdm09 virus analyses

Tables 3-1 and 3-2 show the results of HI assays of A(H1N1)pdm09 viruses performed with a panel of post-infection ferret antisera. Table 3-1 is repeated from the April 2019 characterisation report, but with genetic group data now included, while Table 3-2 was generated during May 2019. Test viruses in each table are sorted by genetic group where known at the time of preparing this report, then by date of collection. A summary of the HI results for all test viruses in both tables is shown in Table 3-3.

The vast majority of A(H1N1)pdm09 test viruses, 53 of 54 (98%), were antigenically indistinguishable from the egg-propagated vaccine virus for the northern hemisphere 2018–19 influenza season, A/Michigan/45/2015 [2], as assessed with post-infection ferret antisera, being recognised at titres within twofold of the titre of the antiserum with the homologous virus (Table 3-3).

Antisera raised against five reference viruses (A/Bayern/69/2009, A/Slovenia/2903/2015, A/Paris/1447/2017, A/Norway/3433/2018 and A/Ireland/84630/2018) recognised all 54 test viruses at titres within twofold of those of the antisera with their homologous viruses. Similarly, good reactivity was seen with antisera raised against A/Switzerland/2656/2017, A/Switzerland/3330/2017 and A/Brisbane/02/2018, the vaccine virus recommended for the 2019–20 northern hemisphere influenza season [1]. Over 90% of test viruses were recognised at titres within twofold of the respective homologous titres and 100% within fourfold (Table 3-3).

The antiserum raised against cell culture-propagated A/Lviv/N6/2009 is an unusual virus/antiserum combination, with A/Lviv/N6/2009 encoding HA1 amino acid substitutions of G155G/E, with E predominating, and D222G. This antiserum recognised only 11% of test viruses at titres within twofold of the homologous titre and 72% within fourfold (Table 3-3).

All test viruses for which HA gene sequencing have been completed fell into clade 6B.1, which is defined by the amino acid substitutions S84N, S162N (introducing a potential N-linked glycosylation site) and I216T in HA1, with all recently circulating viruses clustering in a genetic subclade designated as 6B.1A and defined by the HA1 amino acid substitutions S74R, S164T (which alters the glycosylation motif at residues 162–164) and I295V. A number of genetic subgroups defined by specific amino acid substitutions have emerged, but the great majority of viruses in various subgroups have remained antigenically similar to A/Michigan/45/2015 as shown in the April 2019 and earlier characterisation reports and assessed with post-infection ferret antisera.

Figure 1 shows a phylogenetic tree for the HA genes of a selection of A(H1N1)pdm09 viruses from the WHO European Region, all with collection dates since the start of the 2018–19 influenza season, that were sequenced at the Francis Crick Institute during April and May 2019. Within subclade 6B.1A, clusters of viruses (genetic groups) encoding a range of HA1 amino acid substitutions have emerged, e.g. T120A, or N260D in combination with N129D many with T185I, or N260D with E235D and V193A in HA2, or N129D with A141E, or K302T and N169S and E179D in HA2, or L161I and I77M in HA2. The HA of most recently circulating viruses carry the substitution S183P in HA1, although this is not retained in all genetic groups, and the phylogenetic tree is annotated with HA1 S183P substitution groups assigned for the February 2019 WHO Vaccine Consultation Meeting [1]: 6B.1A/183P-1–7, abbreviated to 6B.1A1–6B.1A7 in Figure 1. The location of vaccine viruses A/Michigan/45/2015 [2] and the recently recommended A/Brisbane/02/2018 for the northern hemisphere 2019-20 influenza season [1] are indicated on the phylogeny (Figure 1).

Table 3-4 summarises the data in Table 3-1 by genetic groups 183P-2, 5, 6 and 7. Generally, test viruses showed good reactivity, ≥90% reacting within twofold of respective homologous titres, with all antisera but for that raised against A/Lviv/N6/2009. However, group 6B.1A5 test viruses (defined by HA1 S183P and N260D amino acid substitutions, with the great majority also having N129D and T185I substitutions) showed lower proportions reacting within twofold of homologous titres with antisera raised against A/Switzerland/2656/2017 (88%) and A/Brisbane/02/2018 (79%), although all group 183P-5 test viruses reacted within fourfold of the respective homologous titres. While such HI studies conducted with post-infection ferret antisera indicated low levels of antigenic drift in A(H1N1)pdm09 viruses, panels of post-vaccination human antisera recognised viruses containing the HA1 substitution S183P less well and based on these results, A/Brisbane/02/2018 was recommended as the A(H1N1)pdm09 vaccine component for the northern hemisphere 2019–20 influenza season [1].

Table 3-1. Antigenic analysis of A(H1N1)pdm09 viruses by HI

Viruses	Other information	Passage history / Ferret number / Genetic group	Collection date	Passage history	Haemagglutination inhibition titre: Post-infection ferret antisera									
					A/Mich 45/15 Egg F31/16*1 6B.1	A/Bayern 69/09 MDCK F09/15*1	A/Lviv N6/09 MDCK F13/18*1	A/Slov 2903/2015 Egg NIB F48/16*1 6B.1	A/Paris 1447/17 MDCK F03/18*2 6B.1A	A/Swit 2656/17 Egg F20/18*1 6B.1A	A/Swit 3330/17 Egg F23/18*1 6B.1A5	A/Norway 3433/18 MDCK F04/19*1 6B.1A5	A/Ire 84630/18 MDCK F08/19*1 6B.1A6	A/Bris 02/18 Egg F09/19*1 6B.1A1
REFERENCE VIRUSES														
A/Michigan/45/2015		6B.1	2015-09-07	E3/E3	640	320	160	1280	1280	1280	640	1280	640	640
A/Bayern/69/2009	G155E		2009-07-01	MDCK5/MDCK1	40	160	160	40	160	80	40	160	40	80
A/Lviv/N6/2009	G155E, D222G		2009-10-27	MDCK4/SIAT1/MDCK3	160	640	640	160	640	320	160	640	160	320
A/Slovenia/2903/2015	clone 37	6B.1	2015-10-26	E4/E2	640	160	160	640	1280	640	320	1280	640	640
A/Paris/1447/2017		6B.1A	2017-10-20	MDCK1/MDCK3	640	160	80	640	1280	640	320	1280	640	640
A/Switzerland/2656/2017		6B.1A	2017-12-21	E5/E2	1280	640	320	1280	1280	1280	640	1280	1280	640
A/Switzerland/3330/2017	clone 35	6B.1A5	2017-12-20	E6/E2	320	160	80	640	1280	640	640	640	640	320
A/Norway/3433/2018		6B.1A5	2018-10-30	MDCK3	160	80	40	320	640	320	160	640	320	160
A/Ireland/84630/2018		6B.1A6	2018-11-28	MDCK1/MDCK2	320	80	40	320	640	320	320	640	640	320
A/Brisbane/02/2018		6B.1A1	2018-01-04	E3/E1	1280	320	320	1280	2560	1280	640	2560	1280	1280
TEST VIRUSES														
A/Navarra/2907/2018		6B.1A5	2018-11-15	MDCK1	640	160	80	640	1280	640	320	1280	640	320
A/Baleares/3014/2018		6B.1A5	2018-12-07	MDCK1	320	160	80	320	640	320	160	1280	320	320
A/Galicia/296/2019		6B.1A5	2019-01-04	MDCK1	640	160	80	640	640	640	320	1280	640	640
A/Extremadura/280/2019		6B.1A5	2019-01-04	SIAT1/MDCK1	640	320	160	640	1280	640	320	1280	640	640
A/Andalucia/268/2019		6B.1A5	2019-01-05	SIAT1/MDCK1	640	160	80	640	1280	640	320	1280	640	320
A/Andalucia/271/2019		6B.1A5	2019-01-07	SIAT1/MDCK1	640	160	160	640	1280	640	320	1280	640	640
A/Galicia/174/2019		6B.1A5	2019-01-07	MDCK1	640	320	160	640	1280	640	320	1280	1280	640
A/Galicia/173/2019		6B.1A5	2019-01-07	MDCK1	640	320	160	640	1280	640	640	2560	640	640
A/Andalucia/276/2019		6B.1A5	2019-01-10	SIAT1/MDCK1	640	160	160	640	1280	640	320	1280	640	640
A/Malta/53463/2019		6B.1A5	2019-01-23	MDCK1	320	160	80	320	640	320	320	1280	1280	640
A/Greece/261/2019		6B.1A5	2019-01-30	MDCK1	1280	320	320	1280	2560	1280	640	2560	1280	1280
A/Malta/54659/2019		6B.1A5	2019-02-02	MDCK1	640	160	80	640	1280	640	320	1280	640	320
A/Malta/516155/2019		6B.1A5	2019-02-03	MDCK1	1280	160	160	1280	2560	640	640	2560	1280	640
A/Greece/1046/19/2019		6B.1A5	2019-02-20	MDCK1	320	80	40	320	640	320	320	1280	640	320
A/Greece/1078/19/2019		6B.1A5	2019-02-21	MDCK1	640	320	160	640	1280	640	640	1280	1280	640
A/Greece/1092/19/2019		6B.1A5	2019-02-22	MDCK3	1280	640	320	1280	1280	1280	640	2560	1280	640
A/Greece/1125/19/2019		6B.1A5	2019-02-25	MDCK1	1280	640	320	1280	2560	1280	640	2560	2560	640
A/Greece/1383/19/2019		6B.1A5	2019-03-07	MDCK1	1280	640	320	1280	2560	1280	640	5120	1280	640
A/Niedersachsen/116/2019		6B.1A5	2019-03-07	C1/MDCK1	640	320	160	640	1280	1280	320	1280	640	640
A/Greece/1387/19/2019		6B.1A5	2019-03-12	MDCK1	640	160	80	1280	1280	640	320	1280	640	640
A/Sachsen-Anhalt/43/2019		6B.1A5	2019-03-12	C1/MDCK1	640	160	160	640	640	640	320	1280	640	640
A/Bremen/19/2019		6B.1A5	2019-03-18	C1/MDCK1	640	160	80	640	1280	640	320	1280	640	640
A/Niedersachsen/150/2019		6B.1A5	2019-03-19	C1/MDCK1	640	160	160	640	640	640	320	1280	640	640
A/Bayern/104/2019		6B.1A5	2019-03-26	C1/MDCK1	640	160	160	640	1280	640	320	2560	640	640
A/Pais Vasco/3139/2018		6B.1A7	2018-12-11	SIAT1/MDCK2	1280	320	160	1280	2560	1280	640	2560	1280	1280
A/Pais Vasco/3135/2018		6B.1A7	2018-12-13	MDCK1	1280	320	160	1280	2560	1280	640	2560	1280	1280
A/Pais Vasco/3130/2018		6B.1A7	2018-12-17	SIAT1/MDCK2	640	160	80	640	1280	640	320	1280	640	640
A/Extremadura/282/2019		6B.1A7	2019-01-03	SIAT1/MDCK1	640	320	160	640	1280	640	320	1280	1280	640
A/Extremadura/278/2019		6B.1A7	2019-01-03	SIAT1/MDCK1	640	320	160	640	1280	640	320	1280	640	640
A/Madrid/209/2019		6B.1A7	2019-01-13	MDCK1	1280	320	160	640	1280	640	640	1280	1280	640
A/Thuringen/61/2019		6B.1A7	2019-03-05	C1/MDCK1	640	160	160	640	1280	1280	320	1280	640	1280
A/Aragon/190085/2018		6B.1A6	2018-12-30	SIAT1/MDCK2	1280	160	160	1280	2560	1280	1280	>5120	2560	1280
A/Greece/311/2019		6B.1A6	2019-02-04	MDCK1	640	160	80	640	1280	640	320	1280	1280	640
A/Greece/1170/19/2019		6B.1A6	2019-02-25	MDCK1	640	160	80	640	1280	640	320	1280	640	640
A/Greece/1428/19/2019		6B.1A6	2019-03-10	MDCK1	1280	320	160	1280	1280	1280	640	2560	1280	640
A/Greece/237/2019		6B.1A2	2019-01-30	MDCK2	640	160	160	640	2560	1280	640	2560	1280	640
A/Greece/324/2019		6B.1A2	2019-02-03	MDCK1	1280	320	160	1280	2560	1280	1280	2560	1280	1280
A/Greece/351/2019		6B.1A2	2019-02-05	MDCK1	640	160	160	640	1280	640	320	1280	640	640
A/Greece/1063/19/2019		6B.1A2	2019-02-21	MDCK1	2560	320	160	1280	2560	2560	1280	2560	1280	2560
A/Nordrhein-Westfalen/90/2019		6B.1A2	2019-03-14	C1/MDCK1	640	160	80	640	1280	640	320	1280	640	640
A/Andalucia/190267/2018		6B.1A	2018-12-14	SIAT1/MDCK1	1280	320	160	1280	2560	1280	640	2560	1280	640
A/Malta/53336/2019		6B.1A	2019-01-21	MDCK1	320	160	80	320	640	320	320	640	320	640
A/Malta/53480/2019		6B.1A	2019-01-23	MDCK1	640	160	80	640	640	640	640	1280	1280	640
A/Malta/53465/2019		6B.1A	2019-01-23	MDCK1	1280	320	160	1280	2560	1280	640	2560	1280	1280
A/Greece/341/2019		6B.1A	2019-02-04	MDCK2	1280	320	160	1280	2560	1280	640	2560	2560	1280
					Vaccine NH 2018-19									Vaccine NH 2019-20
					SH 2019									

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

Table 3-2. Antigenic analysis of A(H1N1)pdm09 viruses by HI

Viruses	Other information	Passage history	Collection date	Passage history	Haemagglutination inhibition titre – Post-infection ferret antisera: A/Mich 45/15 Egg	A/Bayern 69/09 MDCK	A/Lviv N6/09 MDCK	A/Slov 2903/2015 Egg	A/Paris 1447/17 MDCK	A/Swit 2656/17 Egg	A/Swit 3330/17 Egg	A/Norway 3433/18 MDCK	A/Ire 84630/18 MDCK	A/Bris 02/18 Egg
		Ferret number			F31/16*1	F09/15*1	F13/18*1	NIB F48/16*1	F03/18*2	F20/18*1	F23/18*1	F04/19*1	F08/19*1	F09/19*1
		Genetic group			6B.1			6B.1	6B.1A	6B.1A	6B.1A5	6B.1A5	6B.1A6	6B.1A1
REFERENCE VIRUSES														
A/Michigan/45/2015		6B.1	2015-09-07	E3/E3	2560	320	320	1280	1280	1280	640	1280	1280	640
A/Bayern/69/2009	G155E		2009-07-01	MDCK5/MDCK1	40	320	160	<	160	80	80	160	40	80
A/Lviv/N6/2009	G155E, D222G		2009-10-27	MDCK4/SIAT1/MDCK3	160	640	640	160	640	320	320	1280	160	320
A/Slovenia/2903/2015	clone 37	6B.1	2015-10-26	E4/E2	1280	320	160	640	1280	1280	640	1280	640	640
A/Paris/1447/2017		6B.1A	2017-10-20	MDCK1/MDCK3	640	160	40	640	640	640	320	1280	640	320
A/Switzerland/2656/2017		6B.1A	2017-12-21	E5/E2	2560	640	320	1280	2560	2560	1280	2560	2560	1280
A/Switzerland/3330/2017	clone 35	6B.1A5	2017-12-20	E6/E2	640	160	80	640	640	640	640	1280	640	320
A/Norway/3433/2018		6B.1A5	2018-10-30	MDCK3	320	80	40	160	320	320	320	1280	320	320
A/Ireland/84630/2018		6B.1A6	2018-11-28	MDCK1/MDCK3	2560	320	160	1280	2560	2560	1280	2560	1280	1280
A/Brisbane/02/2018		6B.1A1	2018-01-04	E3/E1	2560	320	320	1280	2560	1280	1280	2560	1280	1280
TEST VIRUSES														
A/Slovenia/382/2019			2019-01-18	MDCKx/MDCK1	1280	320	160	1280	640	1280	640	2560	1280	1280
A/Slovenia/888/2019			2019-02-05	MDCKx/MDCK1	1280	320	160	640	640	1280	640	1280	1280	640
A/Slovenia/999/2019			2019-02-09	SIATx/SIAT1	1280	320	160	1280	1280	1280	640	2560	1280	1280
A/Slovenia/1170/2019			2019-02-18	MDCKx/MDCK1	640	320	160	640	640	640	640	2560	640	640
A/Slovenia/1377/2019			2019-03-02	MDCKx/MDCK1	1280	320	160	1280	1280	2560	1280	2560	2560	1280
A/Slovenia/1424/2019			2019-03-05	MDCKx/MDCK1	1280	320	160	1280	640	1280	640	2560	1280	1280
A/Slovenia/1489/2019			2019-03-10	MDCKx/MDCK1	2560	640	320	2560	2560	2560	2560	2560	2560	2560
A/Slovenia/1512/2019			2019-03-12	MDCKx/MDCK1	1280	320	160	1280	1280	1280	640	2560	1280	1280
A/Slovenia/1772/2019			2019-04-10	MDCKx/MDCK1	2560	320	320	1280	1280	1280	1280	2560	1280	1280
					Vaccine NH 2018-19 SH 2019									Vaccine NH 2019-20

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

Table 3-3. Antigenic analysis of A(H1N1)pdm09 viruses by HI – Summary all test viruses

Viruses	Other information	Passage history	Haemagglutination inhibition titre: Post-infection ferret antisera									
			A/Mich 45/15	A/Bayern 69/09	A/Lviv N6/09	A/Slov 2903/2015	A/Paris 1447/17	A/Swit 2656/17	A/Swit 3330/17	A/Norway 3433/18	A/Ire 84630/18	A/Bris 02/18
		Passage history	Egg	MDCK	MDCK	Egg	MDCK	Egg	Egg	MDCK	MDCK	Egg
		Ferret number	F31/16[*1]	F09/15[*1]	F13/18[*1]	NIB F48/16[*1]	F03/18[*2]	F20/18[*1]	F23/18[*1]	F04/19[*1]	F08/19[*1]	F09/19[*1]
		Genetic group	6B.1			6B.1	6B.1A	6B.1A	6B.1A5	6B.1A5	6B.1A6	6B.1A1
REFERENCE VIRUSES												
A/Michigan/45/2015		6B.1	2560	320	320	1280	1280	1280	640	1280	1280	640
A/Bayern/69/2009	G155E		40	320	160	<	160	80	80	160	40	80
A/Lviv/N6/2009	G155E, D222G		160	640	640	160	640	320	320	1280	160	320
A/Slovenia/2903/2015	clone 37	6B.1	1280	320	160	640	1280	1280	640	1280	640	640
A/Paris/1447/2017		6B.1A	640	160	40	640	640	640	320	1280	640	320
A/Switzerland/2656/2017		6B.1A	2560	640	320	1280	2560	2560	1280	2560	2560	1280
A/Switzerland/3330/2017	clone 35	6B.1A5	640	160	80	640	640	640	640	1280	640	320
A/Norway/3433/2018		6B.1A5	320	80	40	160	320	320	320	1280	320	320
A/Ireland/84630/2018		6B.1A6	2560	320	160	1280	2560	2560	1280	2560	1280	1280
A/Brisbane/02/2018		6B.1A1	2560	320	320	1280	2560	1280	1280	2560	1280	1280
TEST VIRUSES												
Number of viruses tested*			54	54	54	54	54	54	54	54	54	54
No with titre reduction ≤2-fold			53	54	6	54	54	49	53	54	54	49
%			*98.1*	*100*	*11.1*	*100*	*100*	*90.7*	*98.1*	*100*	*100*	*90.7*
No with titre reduction =4-fold			1		33			5	1			5
%			*1.9*		*61.1*			*9.3*	*1.9*			*9.3*
No with titre reduction ≥8-fold					15							
%					*27.8*							
			Vaccine NH 2018-19 SH 2019									Vaccine NH 2019-20

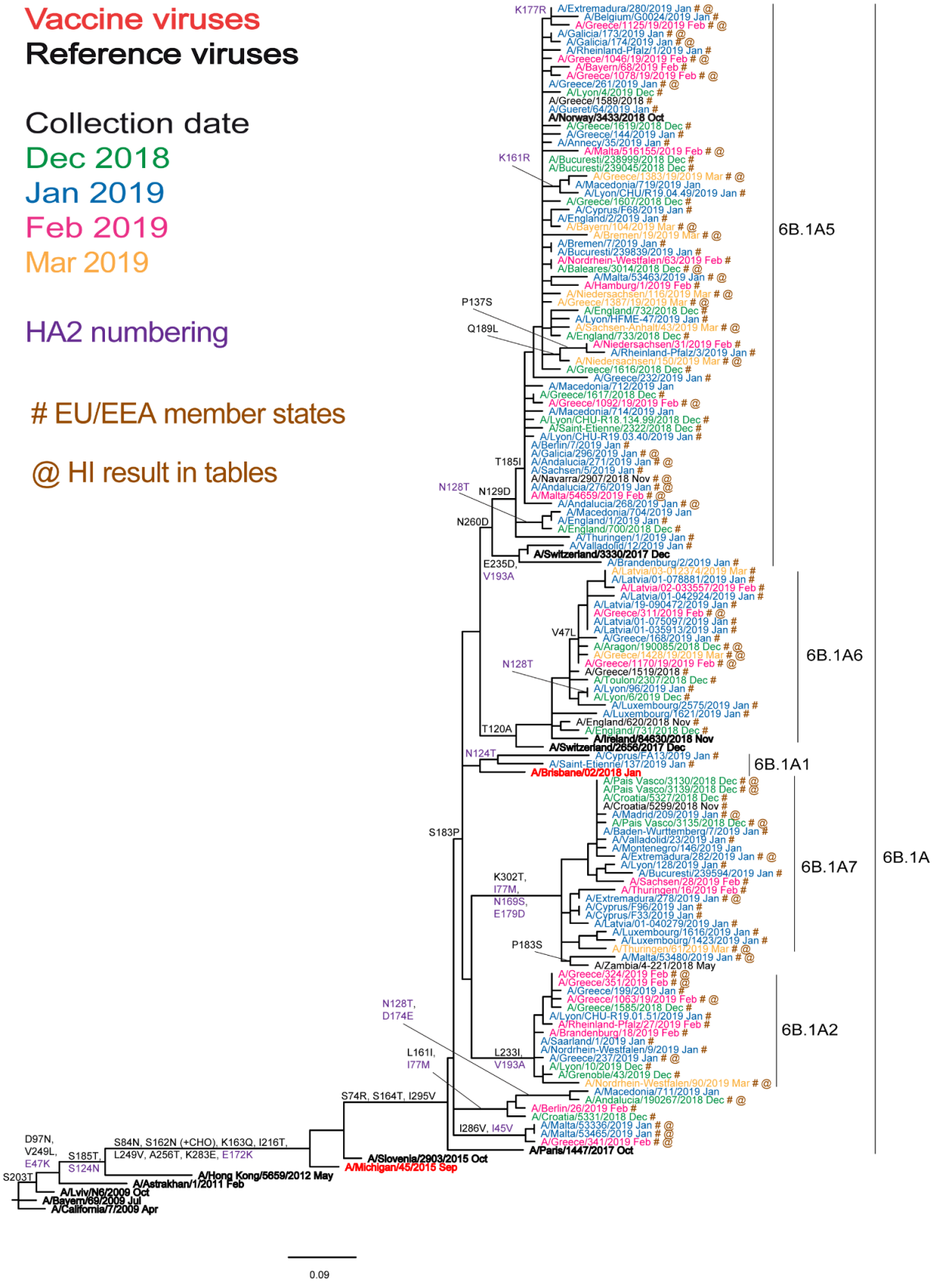
* Of those with available HA sequence, all were clade 6B.1A

Reference virus results are taken from an individual table as an example. Summaries for each antiserum are based on fold-reductions observed on the days that HI assays were performed.

Table 3-4. Antigenic analysis of A(H1N1)pdm09 viruses by HI – Summary by test virus genetic group

Viruses		Haemagglutination inhibition titre Post-infection ferret antisera									
	Passage history	A/Mich 45/15 Egg	A/Bayern 69/09 MDCK	A/Lviv N6/09 MDCK	A/Slov 2903/2015 Egg	A/Paris 1447/17 MDCK	A/Swit 2656/17 Egg	A/Swit 3330/17 Egg	A/Norway 3433/18 MDCK	A/Ire 84630/18 MDCK	A/Bris 02/18 Egg
	Ferret number	F31/16[*1]	F09/15[*1]	F13/18[*1]	NIB F48/16[*1]	F03/18[*2]	F20/18[*1]	F23/18[*1]	F04/19[*1]	F08/19[*1]	F09/19[*1]
	Genetic group	6B.1			6B.1	6B.1A	6B.1A	6B.1A5	6B.1A5	6B.1A6	6B.1A1
TEST VIRUSES											
Total number tested		45	45	45	45	45	45	45	45	45	45
Number tested	6B.1A	5	5	5	5	5	5	5	5	5	5
No with titre reduction ≤2-fold		5	5		5	5	4	5	5	5	5
No with titre reduction =4-fold				3			1				
No with titre reduction ≥8-fold				2							
Number tested	6B.1A2	5	5	5	5	5	5	5	5	5	5
No with titre reduction ≤2-fold		5	5		5	5	5	5	5	5	5
No with titre reduction =4-fold				4							
No with titre reduction ≥8-fold				1							
Number tested	6B.1A5	24	24	24	24	24	24	24	24	24	24
No with titre reduction ≤2-fold		24	24	4	24	24	21	23	24	24	19
%				*16.7*			*87.5*	*95.8*			*79.2*
No with titre reduction =4-fold				11			3	1			5
%				*45.8*			*12.5*	*4.2*			*20.8*
No with titre reduction ≥8-fold				9							
%				*37.5*							
Number tested	6B.1A6	4	4	4	4	4	4	4	4	4	4
No with titre reduction ≤2-fold		4	4		4	4	4	4	4	4	4
No with titre reduction =4-fold				2							
No with titre reduction ≥8-fold				2							
Number tested	6B.1A7	7	7	7	7	7	7	7	7	7	7
No with titre reduction ≤2-fold		7	7		7	7	7	7	7	7	7
No with titre reduction =4-fold				6							
No with titre reduction ≥8-fold				1							
		Vaccine NH 2018-19 SH 2019									Vaccine NH 2019-20

Figure 1. Phylogenetic comparison of influenza A(H1N1)pdm09 HA genes



Influenza A(H3N2) virus analyses

As described in 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 first highlighted in the November 2014 report[3], this is a particular problem for most viruses that fall in genetic clade 3C.2a.

Since the April 2019 characterisation report of the viruses recovered, based on positive neuraminidase activity, only one retained sufficient HA activity to allow antigenic analysis by HI (Table 4-2). Table 4-1 is repeated from the April 2019 characterisation report, but with genetic group data now included. A/Slovenia/1213/2019 was poorly recognised by the antiserum raised against the currently used vaccine virus, egg-propagated A/Singapore/INFIMH-16-0019/2016 (subclade 3C.2a1). This was also the case with antisera raised against other egg-propagated vaccine viruses: A/Switzerland/8060/2017 (subclade 3C.2a2) and A/Kansas/14/2017 (clade 3C.3a).

Similarly, antisera raised against cell culture-propagated reference viruses for which homologous titres were available, A/Hong Kong/5738/2014 (clade 3C.2a), A/Bretagne/1413/2017 (subclade 3C.2a2), A/England/538/2018 and A/Kansas/14/2017 (both clade 3C.3a), recognised the test virus poorly. Of the two antisera raised against cell culture-propagated subgroup 3C.2a1b viruses, A/La Rioja/2202/2018 and A/Norway/3275/2018, for which no homologous titres are given due to the inability of the cell culture-propagated reference viruses to agglutinate RBCs, only that raised against A/La Rioja/2208/2018 recognised the test viruses at a titre of ≥160.

The HI data shown in Table 4-1 for test viruses of known genetic clade/subclade shows:

- poor recognition of test viruses by post-infection ferret antisera raised against egg-propagated vaccine/reference viruses
- poor cross-reactivity of antisera raised against a subclade 3C.2a2 virus
- clade specificity of the antiserum raised against the cell culture-propagated clade 3C.3a A/England/538/2018 virus; and
- the antisera raised against cell culture-propagated viruses that raised against A/Hong Kong/5738/2014 (clade 3C.2a) gives the broadest cross-clade/subclade reactivity.

HA gene sequences of the test viruses characterised antigenically in the April 2019 report are now available and the genetic clades are shown in Table 4-1, with most included in the HA phylogenetic analysis (Figure 2). Viruses in clades 3C.2a and 3C.3a have been in circulation since the 2013–14 northern hemisphere influenza season, with clade 3C.2a viruses having dominated since the 2014–15 influenza season, notably subclade 3C.2a2 viruses, though subgroup 3C.2a1b viruses have predominated in over the course of the 2018–19 season (Figure 2). The HA gene sequences of viruses in both clades continue to diverge. Notably, clade 3C.3a viruses have evolved to carry HA1 amino acid substitutions of L3I, S91N, N144K (loss of an N-linked glycosylation motif at residues 144–146), F193S and K326R compared to A/Stockholm/6/2014 and levels of detection since January 2019 have increased in a number of WHO European Region countries (Figure 2) and North America. New genetic groups have also emerged among the clade 3C.2a viruses, designated as subclades/subgroups. Amino acid substitutions that define these subclades/subgroups are:

- clade 3C.2a – L3I, N144S (resulting in the loss of a potential glycosylation site), F159Y, K160T (in the majority of viruses, resulting in the gain of a potential glycosylation site) and Q311H in HA1, and D160N in HA2, e.g. A/Hong Kong/7295/2014 a cell culture-propagated surrogate for A/Hong Kong/4801/2014 (a former vaccine virus)
- 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 (2018-19 northern hemisphere vaccine virus)
- subgroup 3C.2a1a – those in subclade 3C.2a1 plus T135K in HA1, resulting in the loss of a potential glycosylation site, and also G150E in HA2, e.g. A/Greece/4/2017
- subgroup 3C.2a1b – those in subclade 3C.2a1 plus K92R and H311Q in HA1, e.g. A/La Rioja/2202/2018, with many viruses in this subgroup carrying additional HA1 amino acid substitutions
- subclade 3C.2a2 – those in clade 3C.2a plus T131K, R142K and R261Q in HA1, e.g. A/Switzerland/8060/2017 (2019 southern hemisphere vaccine virus)
- subclade 3C.2a3 – those in clade 3C.2a plus N121K and S144K in HA1, e.g. A/Cote d'Ivoire/544/2016
- subclade 3C.2a4 – those in clade 3C.2a plus N31S, D53N, R142G, S144R, N171K, I192T, Q197H and A304T in HA1 and S113A in HA2, e.g. A/Valladolid/182/2017; and

[2] European Centre for Disease Prevention and Control. Influenza virus characterisation – Summary Europe, September 2013. Stockholm: ECDC; 2014. Available from: http://ecdc.europa.eu/publications-data/influenza-virus-characterisation-september-2013

[3] European Centre for Disease Prevention and Control. Influenza virus characterisation – Summary Europe, November 2014. Stockholm: ECDC; 2014. Available from: http://ecdc.europa.eu/publications-data/influenza-virus-characterisation-november-2014

- clade 3C.3a – T128A (resulting in the loss of a potential glycosylation site), R142G and N145S in HA1, which defined clade 3C.3 plus A138S, F159S and N225D in HA1, many with K326R, e.g. A/England/538/2018.

Globally, the majority of viruses with collection dates from 1 September 2018 have HA genes that continue to fall into genetic groups within clade 3C.2a, with those in subgroup 3C.2a1b more numerous than those in subclade 3C.2a2 from September 2018–March 2019 (Figure 2). Notably, a significant number of subgroup 3C.2a1b viruses have fallen in two recently emerged clusters:. one defined by amino acid substitutions T131K in HA1 with V200I in HA2 and the other by T128A and T135K substitutions in HA1 (both resulting in loss of potential glycosylation sequons). Furthermore, as indicated above, the number of clade 3C.3a virus detections has increased over the course of the 2018–19 season in a number of countries/regions.

The locations of A/Singapore/INFIMH-16-0019/2016 (3C.2a1), the A(H3N2) virus recommended for inclusion in vaccines for the northern hemisphere 2018–19 influenza season [2], A/Switzerland/8060/2017 (3C.2a2), the A(H3N2) virus recommended for inclusion in vaccines for the southern hemisphere 2019 influenza season [3], and A/Kansas/14/2017, the A(H3N2) virus recommended for inclusion in vaccines for the northern hemisphere 2019–20 influenza season [1], are indicated in Figure 2.

Table 4-1. Antigenic analysis of A(H3N2) viruses by HI

Viruses	Other information		Collection date	Passage history	Haemagglutination inhibition titre									
					Post-infection ferret antisera									
							NEW					NEW		
					A/HK 5738/14	A/Bretagne 1413/17	A/Singapore 0019/16	A/Singapore 0019/16	A/La Rioja 2202/18	A/Switz 8060/17	A/Eng 538/18	A/Eng 538/18	A/Norway 3275/18	A/Kansas 14/17
		Passage history			MDCK	SIAT	Egg 10^{-4}	Egg 10^{-4}	SIAT	Egg	SIAT	SIAT	SIAT	Egg
		Ferret number			St Judes F60/17[*1]	F01/18[*1]	F46/17[*1]	F13/19[*1]	F26/18[*1]	F27/18[*1]	F31/18[*1]	F14/19[*1]	F03/19[*1]	F11/19[*1]
		Genetic group			3C.2a	3C.2a2	3C.2a1	3C.2a1	3C.2a1b	3C.2a2	3C.3a	3C.3a	3C.2a1b	3C.3a
REFERENCE VIRUSES														
A/Hong Kong/5738/2014		3C.2a	2014-04-30	MDCK1/MDCK2/SIAT1	160	80	160	160	160	160	160	80	160	160
A/Bretagne/1413/2017		3C.2a2	2017-10-09	MDCK1/SIAT4	160	640	320	320	80	640	160	160	160	80
A/Singapore/INFIMH-16-0019/2016		3C.2a1	2016-04-14	E5/E2	80	40	320	320	160	160	40	40	40	<
A/Switzerland/8060/2017	clone 57	3C.2a2	2017-12-12	E7/E1	160	640	320	320	80	1280	80	40	40	<
A/England/538/2018		3C.3a	2018-02-26	MDCK1/SIAT3	<	<	40	40	<	<	320	640	<	160
A/Kansas/14/2017		3C.3a	2017-12-14	E7/E2	<	<	40	40	<	<	320	160	<	640
A/Kansas/14/2017		3C.3a	2017-12-14	SIAT3/SIAT2	40	<	40	80	<	40	320	640	<	160
TEST VIRUSES														
A/Hessen/42/2019		3C.3a	2019-02-27	C1/SIAT1	40	40	40	40	<	40	320	640	<	80
A/Rheinland-Pfalz/34/2019		3C.2a1b	2019-03-01	C1/SIAT1	80	40	40	40	160	40	<	<	160	40
A/Berlin/48/2019		3C.3a	2019-03-04	C1/SIAT1	80	40	40	40	<	40	320	640	<	80
A/Baden-Wurttemberg/132/2019		3C.2a1b	2019-03-06	C1/SIAT1	80	40	40	80	160	80	<	<	160	40
A/Saarland/15/2019		3C.3a	2019-03-11	C2/SIAT1	<	<	<	40	<	<	320	320	<	80
A/Bremen/17/2019		3C.3a	2019-03-11	C1/SIAT1	40	<	40	80	<	40	320	320	<	80
A/Nordrhein-Westfalen/82/2019		3C.3a	2019-03-11	C1/SIAT1	40	40	40	40	<	40	320	640	<	80
A/Nordrhein-Westfalen/97/2019		3C.3a	2019-03-14	C1/SIAT1	40	40	40	40	<	40	320	320	<	80
A/Nordrhein-Westfalen/89/2019		3C.3a	2019-03-15	C1/SIAT1	80	40	80	80	<	80	320	640	<	160
A/Hessen/56/2019		3C.2a1b	2019-03-20	C1/SIAT1	160	40	40	40	160	40	<	<	160	40
A/Niedersachsen/151/2019		3C.3a	2019-03-25	C1/SIAT1	40	<	40	40	<	40	320	320	<	80
A/Bremen/20/2019		3C.3a	2019-03-25	C1/SIAT1	40	<	40	40	<	40	320	320	<	80
A/Nordrhein-Westfalen/101/2019		3C.3a	2019-03-25	C1/SIAT1	40	40	40	40	<	40	320	320	<	80
							Vaccine SH 2018 NH 2018-19			Vaccine SH 2019				Vaccine NH 2019-20

[*] Superscripts refer to antiserum properties (< relates to the lowest dilution of antiserum used) [1] < = <40; ND = Not Done

Sequences in phylogenetic trees

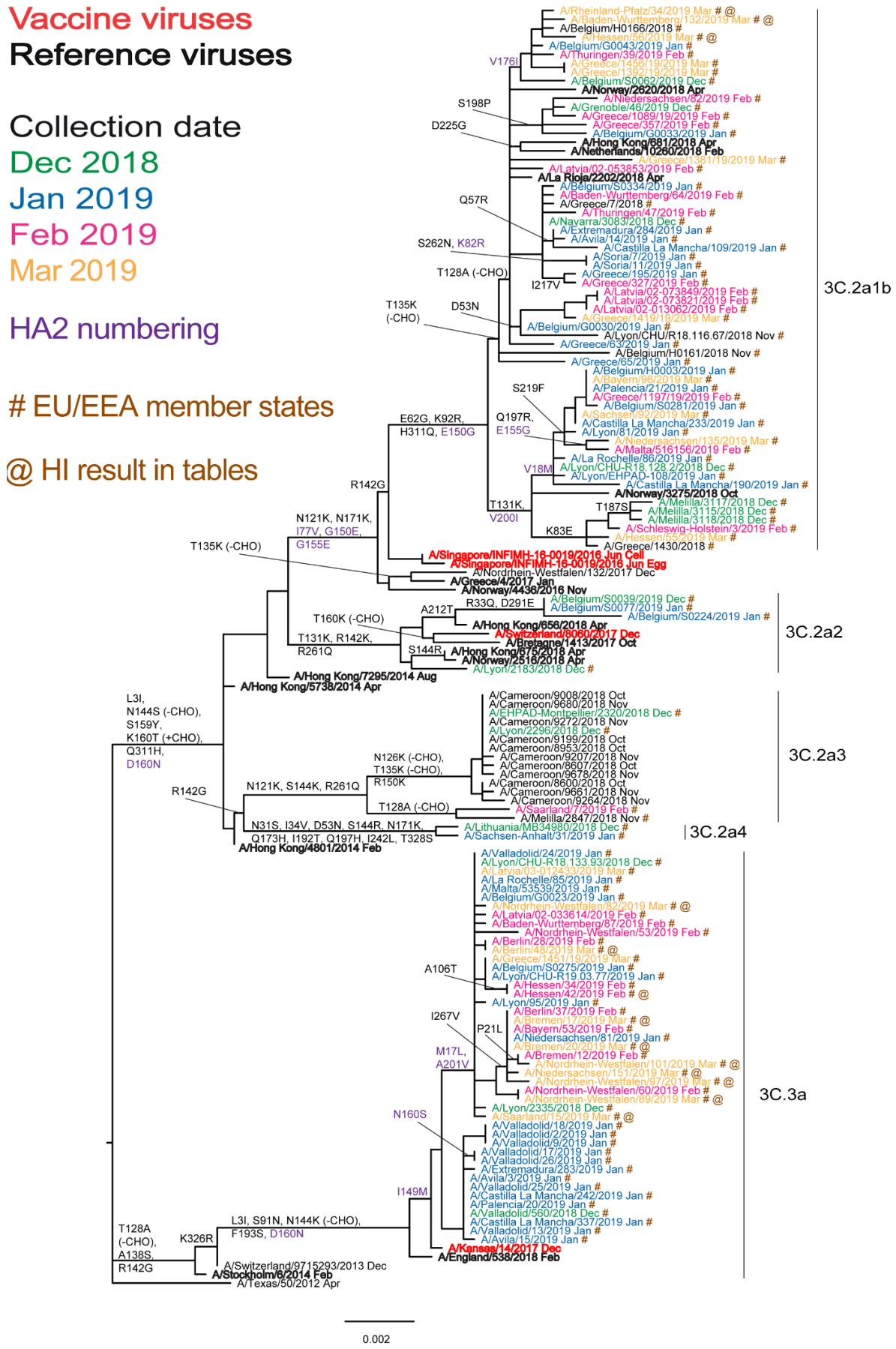
Table 4-2. Antigenic analysis of A(H3N2) viruses by HI

Viruses	Other information		Collection date	Passage history	A/HK 5738/14	A/Bretagne 1413/17	A/Singapore 0019/16	A/La Rioja 2202/18	A/Switz 8060/17	A/Eng 538/18	A/Norway 3275/18	A/Kansas 14/17	A/Kansas 14/17
		Passage history			MDCK	SIAT	Egg 10^{-4}	SIAT	Egg	SIAT	SIAT	Egg	SIAT
		Ferret number			St Judes F60/17[*1]	F01/18[*1]	F46/17[*1]	F26/18[*1]	F27/18[*1]	F31/18[*1]	F03/19[*1]	F11/19[*1]	F17/19[*1]
		Genetic group			3C.2a	3C.2a2	3C.2a1	3C.2a1b	3C.2a2	3C.3a	3C.2a1b	3C.3a	3C.3a
REFERENCE VIRUSES													
A/Hong Kong/5738/2014		3C.2a	2014-04-30	MDCK1/MDCK2/SIAT1	320	160	320	160	320	320	320	160	160
A/Bretagne/1413/2017		3C.2a2	2017-10-09	MDCK1/SIAT4	320	1280	320	80	1280	160	160	80	160
A/Singapore/INFIMH-16-0019/2016		3C.2a1	2016-04-14	E5/E2	160	40	640	160	160	80	40	<	40
A/Switzerland/8060/2017	clone 57	3C.2a2	2017-12-12	E7/E1	160	1280	640	80	1280	80	80	40	40
A/England/538/2018		3C.3a	2018-02-26	MDCK1/SIAT3	<	<	40	<	<	640	<	160	320
A/Kansas/14/2017		3C.3a	2017-12-14	E7/E2	<	<	80	<	<	320	<	640	320
A/Kansas/14/2017		3C.3a	2017-12-14	SIAT3/SIAT2	40	40	80	<	80	640	40	160	640
TEST VIRUSES													
A/Slovenia/1213/2019			2019-02-19	MDCKx/MDCK1	40	<	<	160	40	<	80	40	<
							Vaccine SH 2018 NH 2018-19		Vaccine SH 2019			Vaccine NH 2019-20	

[*] Superscripts refer to antiserum properties (< relates to the lowest dilution of antiserum used) [1] < = <40

Sequences in phylogenetic trees

Figure 2. Phylogenetic comparison of influenza A(H3N2) HA genes



Influenza B virus analyses

Influenza B viruses represented only 2.9% of the samples received with collection dates after 31 August 2018 and were received from national influenza centres (NICs) in 12 countries: Austria, Croatia, Denmark, France, Greece, Iceland, Ireland, Luxembourg, Norway, Portugal, Slovenia and the United Kingdom (Table 1). Of the small number received, 21 were B/Yamagata-lineage and nine were B/Victoria-lineage.

Influenza B/Victoria-lineage

No B/Victoria-lineage viruses from EU/EEA countries have been tested by HI since the March 2019 characterisation report[4].

A relatively small number (903, of which 776 were full-length as of 4 June 2019) of HA sequences for viruses collected from 1 September 2018 have been deposited in the EpiFlu database of the Global Initiative on Sharing All Influenza Data (GISAID) and the majority of these are from China and the US, with only 41 (24 full-length) from countries in Europe. All recent viruses with collection dates from 1 February–4 June 2019 that have data deposited in GISAID continue to have HA genes that fall in the B/Brisbane/60/2008 clade (clade 1A; Figure 3), with all falling in a subclade defined by HA1 amino acid substitutions I117V, N129D and V146I within clade 1A. Two groups within this subclade have deletions in the HA gene. A geographically dispersed group seen in the Americas, Asia, Europe and Oceania have HA genes encoding an HA1 with deletion of residues K162 and N163 [1A(Δ2); Figure 3]. The viruses have additional substitutions of D129G and I180V in HA1 and R151K in HA2. The second group of B/Victoria-lineage viruses detected recently had HA genes encoding a deletion of three HA1 amino acids, K162, N163 and D164 [1A(Δ3); Figure 3]. This group splits into an Asian subgroup with viruses carrying additional substitutions of I180T and K209N in HA1 and a West African subgroup with viruses carrying the HA1 substitution K136E, often with additional HA1 substitutions of G74E and E198G (within the 197–199 glycosylation site) or G133R. The great majority of recently collected viruses fall equally among these two deletion groups, with the great majority of 1A(Δ3) viruses falling in the West African subgroup.

It was noted in the September 2018 characterisation report[5] and earlier ones that the clade 1A viruses without deletions, the 1A(Δ2) group and the 1A(Δ3) subgroups are antigenically distinct from one another. Following the emergence and spread of viruses in the 1A(Δ2) group, a representative, B/Colorado/06/2017, was recommended for use in trivalent influenza vaccines for the 2018–19 and 2019–20 northern hemisphere [1,2] and 2019 southern hemisphere seasons [3].

The majority of all recently circulating B/Victoria-lineage viruses was collected in Asia and the US. The viruses detected in EU/EEA countries all fall in the 1A(Δ3) West African subgroup (Figure 3).

Influenza B/Yamagata-lineage

No B/Yamagata-lineage viruses from EU/EEA countries have been tested by HI since the April 2019 characterisation report.

A smaller number (675, of which 618 were full-length as of 4 June 2019) of B/Yamagata-lineage HA sequences for viruses collected from 1 September 2018 have been deposited in the EpiFlu database of GISAID and the majority of these are from China and the US, with only 48 (31 full-length) from countries in Europe. Figure 4 shows a phylogenetic analysis of the HA genes of recently circulating B/Yamagata-lineage viruses with collection dates from 1 February–4 June 2019 that have data deposited in GISAID, with just three from EU/EEA countries. HA sequences of all viruses collected in the 2017–2018 season and since carry HA genes in genetic clade 3, the B/Wisconsin/1/2010–B/Phuket/3073/2013 clade, with those from viruses collected after 31 August 2018 falling in a subgroup defined by HA1 L172Q and M251V amino acid substitutions compared to B/Phuket/3073/2013. Some subclustering of sequences defined by specific amino acid substitutions (e.g. HA1 S120T or D229N or D232N introducing a potential N-linked glycosylation site) is occurring. It has been noted in previous characterisation reports for 2018 that none of the 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 was recommended for inclusion in quadrivalent vaccines for the 2018–2019 and 2019–2020 northern hemisphere [1,2] and 2019 southern hemisphere seasons [3].

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[4] European Centre for Disease Prevention and Control. Influenza virus characterisation – Summary Europe, March 2019. Stockholm: ECDC; 2019. Available from: http://ecdc.europa.eu/publications-data/influenza-virus-characterisation-march-2019

[5] European Centre for Disease Prevention and Control. Influenza virus characterisation – Summary Europe, September 2018. Stockholm: ECDC; 2018. Available from: http://ecdc.europa.eu/publications-data/influenza-virus-characterisation-summary-europe-september-2018

Figure 3. Phylogenetic comparison of influenza B/Victoria-lineage HA genes

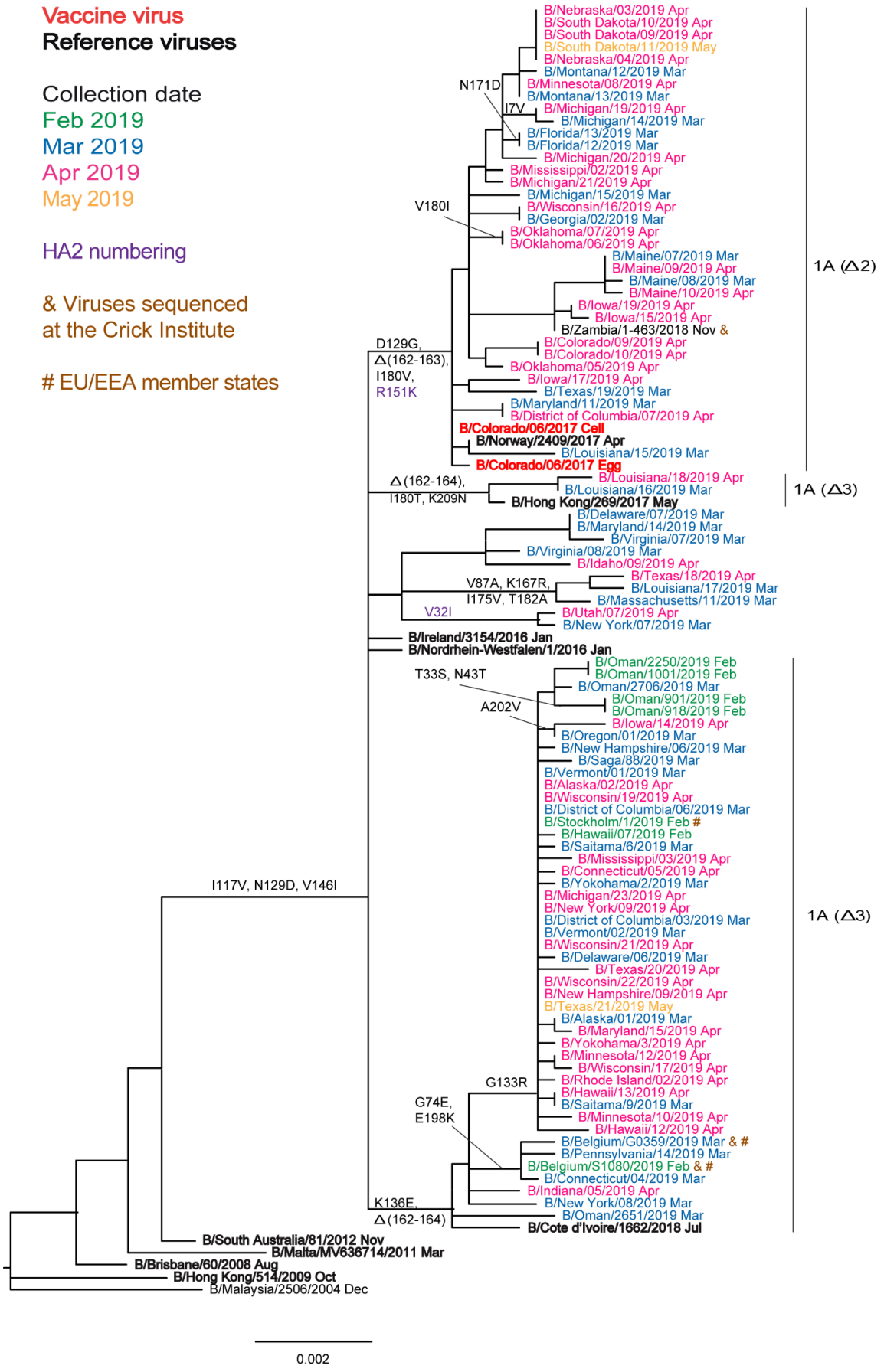
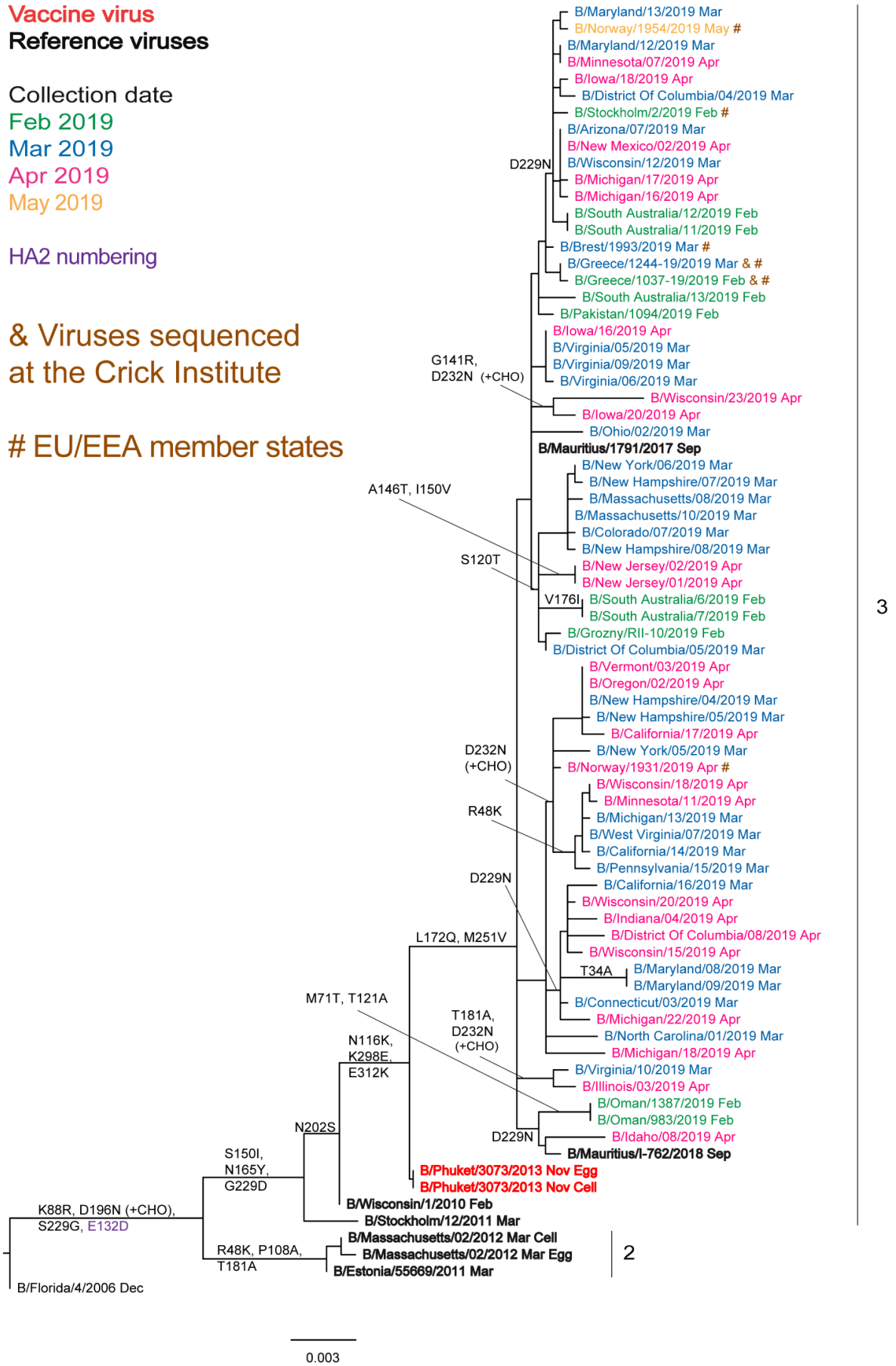


Figure 4. Phylogenetic comparison of influenza B/Yamagata-lineage HA genes



Summaries of data submitted to TESSy

Genetic characterisation

For the 2018–19 season, as of week 20 in 2019, 4 102 viruses have been characterised genetically and ascribed to a genetic clade:

- 1 882 A(H1N1)pdm09 were subclade 6B.1 represented by vaccine virus A/Michigan/45/2015, with a further 3 attributed to a subgroup not listed
- 2 163 were A(H3N2) viruses, with 1 435 being subgroup 3C.2a1b represented by A/Alsace/1746/2018, 70 subclade 3C.2a2 represented by A/Switzerland/8060/2017, 33 subclade 3C.2a3 represented by A/Cote d'Ivoire/544/2016, 548 clade 3C.3a represented by A/England/538/2018, 57 subclade 3C.2a1 represented by A/Singapore/16-0019/2016, 5 clade 3C.2a represented by A/Hong Kong/4801/2014, 9 subgroup 3C.2a1a represented by A/Greece/4/2017 and 6 attributed to a subgroup not listed in current TESSy reporting categories
- 29 were B/Yamagata-lineage clade 3 represented by vaccine virus B/Phuket/3073/2013; and
- 25 were B/Victoria-lineage viruses, with 5 being clade 1A represented by B/Brisbane/60/2008, 5 subclade 1A.Δ2 with a two amino acid deletion in HA represented by the vaccine virus B/Colorado/06/2017 and 15 subclade 1A.Δ3 with a three amino acid deletion in HA represented by B/Hong Kong/269/2017.

Antiviral susceptibility

For viruses collected in the course of the 2018–19 season, as of week 20 in 2019, 1 668 A(H1N1)pdm09, 1 121 A(H3N2) and 35 type B have been tested for susceptibility to neuraminidase inhibitors. Eight A(H1N1)pdm09 viruses carried NA H275Y amino acid substitution indicative of highly reduced inhibition (confirmed phenotypically for 3) and an additional 3 showed evidence of reduced inhibition (RI) by oseltamivir in phenotypic assays. One type B virus showed evidence of RI by oseltamivir and zanamivir.

At the WIC for this season, 688 viruses from EU/EEA countries have been assessed phenotypically against oseltamivir and zanamivir: 354 A(H1N1)pdm09, 314 A(H3N2), 7 B/Victoria-lineage and 13 B/Yamagata-lineage. All but two viruses showed normal inhibition by the two neuraminidase inhibitors. B/Norway/3241/2018 (Victoria-lineage) showed RI by the inhibitors and the NA gene encoded D197N amino acid substitution. A/Latvia/03-0738053/2019 (H3N2) showed RI by zanamivir and sequence is pending.

Influenza A(H7N9) virus

On 1 April 2013, the World Health Organization (WHO) Global Alert and Response [4] 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 the WHO website [5]. Increased numbers of cases have been 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 strains that have caused some zoonoses, though 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], A summary and assessment of influenza viruses at the human-animal interface on 10 May 2019 reports that no new cases of human infection had been detected since the 9 April 2019 report and indicates that there have been no publicly available reports from animal health authorities in China of 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 28 March 2019 and can be found on the ECDC website [10].

Influenza A(H5) virus

The most recent monthly risk assessment of influenza at the human-animal interface was published by WHO on 10 May 2019, indicating that various A(H5Nx) subtypes continue to be detected in birds in Africa, Asia and Europe. One new human case of A(H5N1) infection was detected in Nepal in March, where there have been reports of A(H5N1) infection in domestic birds since February 2019 [8]. This is the first human case of A(H5N1) infection reported to WHO since 2017 [11]. On 18 November 2016, ECDC published a rapid risk assessment related to outbreaks of highly pathogenic avian influenza H5N8 viruses in Europe [12]. As described above, the EU Reference

Laboratory for Avian Influenza, in collaboration with ECDC and the European Food Standards Agency published on 28 March 2019 the latest overview of avian influenza, which can be found on the ECDC website [10].

WHO CC reports

A description of results generated by the London WHO CC at the WIC and used at the most recent WHO vaccine composition meeting held in Beijing, China from 18–20 February 2019 and previous ones can be found at: http://www.crick.ac.uk/partnerships/worldwide-influenza-centre/annual-and-interim-reports

Note on figures

The phylogenetic trees were constructed using RAxML (http://sco.h-its.org/exelixis/software.html), drawn using FigTree (http://tree.bio.ed.ac.uk/software/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 of sample collection. Isolates from WHO NICs in EU/EEA countries are marked '#'. Sequences for most viruses from non-EU/EEA countries were recovered from the EpiFlu database of GISAID. ECDC gratefully acknowledges the authors and originating and submitting laboratories of the sequences from the EpiFlu database of GISAID that were downloaded for use in the preparation of this report (all submitters of data may be contacted directly via the GISAID website at http://www.gisaid.org), along with all laboratories who submitted sequences directly to WHO CC London.

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