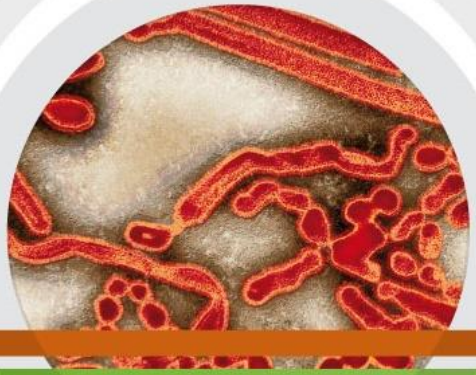

SURVEILLANCE REPORT

Influenza virus characterisation

Summary Europe, September 2018

Summary

This is the eighth, and final, report of the 2017–18 influenza season. As of week 39/2018, over 240 000 influenza detections across the WHO European Region have been reported. Forty-four percent of the detected viruses were type A, with A(H1N1)pdm09 and A(H3N2) viruses being detected in equal numbers. Type B viruses accounted for 56%; B/Yamagata viruses prevailed over B/Victoria viruses at a ratio of over 50:1.

Twenty-nine EU/EEA countries have shared influenza-positive specimens with the London WHO CC, Crick Worldwide Influenza Centre (WIC), since week 40/2017, with 1 586 specimens having collection dates after August 2017.

All 15 A(H1N1)pdm09 test viruses characterised antigenically since the July 2018 report showed good reactivity with antiserum raised against the 2017–18 vaccine virus, A/Michigan/45/2015. The 332 test viruses with collection dates from week 40/2017 genetically characterised at the WIC, as others from the European Region recently deposited in the GISAID EpiFlu database, have all fallen in subclade 6B.1, defined by HA1 amino acid substitutions S84N, S162N and I216T, the great majority with additional substitutions of S74R, S164T and I295V.

Of 376 A(H3N2) viruses successfully recovered to date, from specimens collected during the 2017–2018 season, only 99 (26%) had sufficient HA titre to allow antigenic characterisation by HI assay in the presence of oseltamivir. The single virus tested since the last report fell in genetic clade 3C.3a and was generally recognised well by antisera raised against cell culture-propagated A(H3N2) viruses, but those raised against subclade 3C.2a2 viruses recognised the tested virus poorly. Of the 407 viruses with collection dates from week 40/2017 genetically characterised at the WIC, 397 were clade 3C.2a (with 224 3C.2a2, 147 3C.2a1, 22 3C.2a3 and four 3C.2a4 subclade viruses) and 10 were clade 3C.3a. Of the 147 subclade 3C.2a1 viruses, 141 fell in subgroup 3C.2a1b and three belonged to subgroup 3C.2a1a.

Of the 12 B/Victoria-lineage viruses tested by HI, four (clade 1A) reacted well with antisera raised against cell culture-propagated surrogates of B/Brisbane/60/2008 and eight reacted well with post-infection ferret antisera raised against tissue culture-propagated cultivars of B/Norway/2409/2017 and B/Colorado/06/2017, viruses with a deletion of two amino acids (Δ162-163) in HA1. Of the 78 viruses characterised genetically at the WIC with a collection date after week 40/2017, 20 fell within clade 1A and 58 fell within the subgroup (1A(Δ2)) carrying the HA1 double amino acid deletion.

Of 44 B/Yamagata viruses characterised antigenically, all reacted well (within twofold of the homologous titre) with post-infection ferret antiserum raised against egg-propagated B/Phuket/3073/2013, the recommended vaccine virus for use in quadrivalent vaccines for the northern hemisphere 2017–18 and 2018–19 and southern hemisphere 2019 seasons and for trivalent vaccines in the southern hemisphere 2018 season. The 481 viruses with collection dates from week 40/2017 genetically characterised at the WIC – as others recently circulating in the European Region and reported to the GISAID EpiFlu database – fall within genetic clade 3.

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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 2017–18 season (weeks 40/2017–39/2018), with detections having exceeded the number for the 2016–17 season by nearly 65%, while numbers of clinical specimens tested increased by only 32%. Over 240 000 detections have been reported, with type B (56%) predominating over type A (44%) viruses. Of the type A viruses subtyped (n = 45 689) and the type B viruses ascribed to lineage (n = 16 002), A(H1N1)pdm09 and A(H3N2) viruses have been detected in nearly equal proportions, with a ratio of 1.02:1, and B/Yamagata prevailed over B/Victoria, at a ratio of 52.2:1; these ratios are comparable to those summarised in the July 2018 report[1]. Compared with the 2016–17 season, significant numbers of influenza type B viruses were detected early in the 2017–18 season and predominated over type A up to week 11/2018. The dominance of B/Yamagata over B/Victoria has increased from 2.7:1 in the 2016–17 season to 52.5:1 for the 2017–18 season. Overall, the ratio of type A to type B detections has decreased significantly compared with the 2016–17 season (0.8:1 from 6.5:1), and of the A subtyped viruses, a significant increase in the proportion of A(H1N1)pdm09 has been seen (50.6% in 2017–18 compared with 1.1% in 2016–17).

Since week 40/2017, 72 shipments of specimens have been received at the Crick Worldwide Influenza Centre (WIC) from 29 EU/EEA countries. These packages contained 1 586 specimens, a mix of clinical samples and virus isolates, with specimen collection dates after August 2017 (Table 2). The majority (858: 54%) were type A viruses, and A(H3N2) outnumbered A(H1N1)pdm09 at a ratio of 1.2:1. Of the 728 type B specimens received (46% of the specimens), 93 were B/Victoria-lineage and 558 were B/Yamagata-lineage. The antigenic and genetic properties of influenza viruses, characterised since the July 2018 report[1], are presented and discussed in this surveillance report.

Table 1. Influenza virus detections in the WHO European Region from the start of reporting for the 2017–18 season (weeks 40/2017–39/2018)[a]

	Cumulative number of detections			Totals*		Totals for 2016-17 season*		
Virus type/subtype/lineage	Sentinel sources	Non-sentinel sources	Totals	%	Ratios	Number	%	Ratios
Influenza A	**9 164**	**96 839**	**106 003**	**44.1**	**0.8:1**	**126 614**	**86.6**	**6.5:1**
A(H1N1)pdm09	4 990	18 131	23 121	50.6		591	1.1	
A(H3N2)	2 705	19 863	22 568	49.4	1:1	53 101	98.9	89.8:1
A not subtyped	1 469	58 845	60 314			**72 922**		
Influenza B	**15 648**	**118 970**	**134 618**	**55.9**		**19 570**	**13.4**	
Victoria lineage	209	92	301	1.9		749	27.1	
Yamagata lineage	7 304	8 397	15 701	98.1	52.2:1	2 016	72.9	2.7:1
Lineage not ascribed	8 135	110 481	118 616			16 805		
Total detections (total tested)	**24 812 (62 977)**	**215 809 (840 205)**	**240 621 (903 182)**			**146 184 (686 477)**		

[a] **Numbers taken from Flu News Europe weeks 20/2018 and 21-39/2018**

*** Percentages are shown for total detections (types A & B [in bold type], and for viruses ascribed to influenza A subtype and influenza B lineage).**

[1] European Centre for Disease Prevention and Control. Influenza virus characterisation, summary Europe, July 2018. Stockholm: ECDC; 2018. Available from: https://ecdc.europa.eu/sites/portal/files/documents/influenza-virus-characterisation-July-2018.pdf

Table 2 (part 1). Summary of clinical samples and virus isolates, contained in packages received from EU/EEA Member States since week 40/2017

MONTH	Total	A		H1N1pdm09		H3N2			B		B Victoria lineage		B Yamagata lineage	
Country	Number received	Number received	Number propagated[1]	Number received	Number propagated[1]	Number received	Number propagated[2]		Number received	Number propagated[1]	Number received	Number propagated[1]	Number received	Number propagated[1]
2017														
SEPTEMBER														
Finland	2					2	0	2						
France	4			2	2						1	1	1	1
Germany	1												1	1
Netherlands	1					1	0	1						
Norway	2			1	1								1	1
Spain	1			1	1									
Sweden	1					1	0	1						
United Kingdom	2					1	0	1			1	1		
OCTOBER														
Belgium	1			1	1									
Croatia	2					2	0	2						
Denmark	2					2	1	1						
Finland	1					1	0	1						
France	12			4	4	7	7	0					1	1
Ireland	4			2	2	1	0	1					1	1
Netherlands	3					1	0	1					2	0
Norway	21			3	2	15	0	15					3	2
Slovakia	1					1	0	1						
Slovenia	1					1	1	0						
Spain	7			1	1	5	0	5					1	1
Sweden	3					3	2	1						
United Kingdom	7			2	2	3	0	3			1	1	1	1
NOVEMBER														
Austria	3	1	0			2	0	2						
Belgium	1												1	1
Croatia	4												4	4
Denmark	2					1	0	1					1	1
Estonia	1					1	0							
Finland	7					3	0	3			1	0	3	3
France	23			7	7	10	1	9			1	1	5	5
Germany	6			2	2	2	0	2					2	2
Greece	2												2	1
Hungary	1												1	1
Ireland	5			1	1	2	0	2					2	2
Italy	1												1	1
Latvia	4			1	1	3	3	0						
Netherlands	3			1	1	2	0	1						
Norway	24			3	3	10	1	9			2	1	9	7
Portugal	5					1	0	1			2	2	2	2
Slovakia	1			1	1									
Slovenia	1												1	1
Spain	30			1	1	9	1	7	1	0	6	5	13	10
Sweden	11			1	1	7	3	4					3	2
United Kingdom	5					3	0	3			1	1	1	1
DECEMBER														
Austria	37			18	17	7	0	7					12	12
Belgium	19			7	6	1	0	1					11	6
Bulgaria	3			2	1								1	1
Croatia	6			3	3	3	1	2						
Cyprus	3	2	0			1	0	1						
Czech Republic	1												1	1
Denmark	17					9	2	7					8	8
Estonia	5	2	0			2	0						1	1
Finland	1					1	0	1						
France	36			12	12	11	2	9			1	1	12	12
Germany	17			5	5	5	0	5					7	7
Greece	3			2	2	1	0	1						
Hungary	6			1	1								5	5
Iceland	15			1	1	8	3	5					6	6
Ireland	13			1	1	5	0	5					7	5
Italy	25			12	12	2	0	2					11	11
Latvia	2			2	2									
Lithuania	9			3	1						1	1	5	3
Malta	1			1	0									
Netherlands	16			1	0	1	0	1					14	5
Norway	35			5	1	15	0	9			2	1	13	7
Poland	9	1	0	2	2				3	0	3	3		
Portugal	33			2	2	4	0	4			8	8	19	19
Romania	9			4	4	2	0						3	2
Slovakia	5												5	5
Slovenia	12			4	4	3	1	2			3	2	2	2
Spain	52			18	15	8	0	6	3	0	7	7	16	10
Sweden	5			1	1	4	2	1						
United Kingdom	14			1	0	2	0		3	0			8	6

Table 2 (part 2). Summary of clinical samples and virus isolates, contained in packages received from EU/EEA Member States since week 40/2017

MONTH / Country	Total Number received	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														
JANUARY														
Belgium	37			17	10	9	8	0			3	3	8	3
Bulgaria	23			9	6	3	2	0					11	7
Cyprus	12	2	0	3	3				2	0			5	5
Czech Republic	1			1	1									
Denmark	5			1	1								4	2
Estonia	16	2	0	3	2	4	0	4	1	0			6	5
Finland	12			3	3	3	0	3			5	4	1	1
France	4			2	2	1	0	1					1	1
Germany	25			6	6	6	0	6			5	5	8	8
Greece	26			9	3	3	0	2					14	7
Hungary	10			6	6								4	4
Iceland	6					2	2	0					4	4
Ireland	18			1	0	6	2	3	3	0	1	1	7	7
Italy	17			4	3	4	0	4			2	2	7	7
Lithuania	16					3	0		2	0	2	1	9	1
Malta	39			3	2	13	1		11	0			12	4
Netherlands	22			5	5	9	2	6			1	1	7	3
Norway	19			5	3	6	2	2			4	2	4	0
Poland	2	1	0								1	1		
Portugal	15			1	1						3	3	11	11
Romania	9			3	0				4	0			2	2
Slovakia	1			1	1									
Slovenia	19			7	7	2	0	2	3	0			7	6
Spain	5			3	3	2	0	2						
Sweden	4			1	1	2	2	0					1	1
United Kingdom	37			3	0	22	0		8	0			4	0
FEBRUARY														
Belgium	26			7	7	4	0	4					15	15
Bulgaria	21			13	12								8	7
Cyprus	18	1	0	1	1	1	0	1	4	0			11	11
Denmark	0													
Estonia	1												1	1
Finland	3					2	0	2					1	1
France	13			6	6	1	1	0			1	1	5	5
Germany	12			3	3	3	0	3			4	4	2	2
Greece	12			3	2	3	1	0					6	5
Hungary	8			1	1						3	3	4	4
Iceland	3			1	1								2	2
Ireland	9			3	3	2	0	2			1	1	3	2
Italy	18			8	8	2	1	1					8	8
Netherlands	6			4	4	2	0	2						
Norway	3					1	0	0			2	2		
Poland	34	6	0	3	3								25	25
Portugal	12			6	5						1	1	5	5
Spain	8			3	0	4	0	4	1	0				
Sweden	6			2	2	3	1						1	1
United Kingdom	6					6	4	2						
MARCH														
Belgium	7			1	1								6	6
Bulgaria	5			3	3						2	2		
Denmark	4												4	4
Estonia	17	2	0	5	5	9	0	9					1	1
Finland	5					3	0	3					2	2
France	31			9	9	8	6	2			1	1	13	13
Germany	7			2	2	1	0	1			2	2	2	2
Greece	7			3	1								4	2
Hungary	4			1	1						2	2	1	1
Iceland	6			1	1	2	1	1					3	3
Ireland	5			1	1	3	0	3					1	1
Italy	8			5	5	1	0	1					2	2
Lithuania	13			7	7	2	1	1	1	0	2	2	1	0
Norway	15			5	4	4	3	1			1	1	5	3
Poland	10	2	0	3	3								5	5
Portugal	16			5	5	8	1	7			1	1	2	1
Spain	45	1	0	2	1	28	12	16					14	13
Sweden	2												2	2
United Kingdom	9			2	2	2	1	0	1	0			4	4
APRIL														
Denmark	6			2	2	3	0	3					1	1
Estonia	10	1	0	2	2	5	0	5					2	2
Finland	2					2	0	2						
France	12					7	4	3					5	5
Germany	3			1	1	1	1	0					1	1
Hungary	1					1	0	0						
Iceland	8			4	4	2	0	2					2	2
Ireland	5					3	0	3	1	0			1	1
Lithuania	4			1	0	2	0	2					1	0
Norway	21			6	6	9	4	4			2	1	4	2
Spain	4					3	2	1					1	1
Sweden	1												1	1
United Kingdom	30			1	0	7	0		22	0				
MAY														
Iceland	8			1	1	4	3	1					3	3
Ireland	4			1	1	1	0	1	2	0				
Lithuania	1			1	1									
United Kingdom	3			1	0	1	0	0	1	0				
29 Countries	1586	24	0	380	323	454	99	277	77	0	93	83	558	454
					24.0%		28.6%					5.9%		35.2%
					54.1%					45.9%				

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

* As of 2018-09-08

Influenza A(H1N1)pdm09 virus analyses

Results of haemagglutination inhibition (HI) analyses of viruses performed since the July 2018 report are shown in Table 3. Fourteen of 15 A(H1N1)pdm09 test viruses antigenically characterised were similar to the vaccine virus for the present northern hemisphere 2017–18 influenza season, A/Michigan/45/2015 [1], being recognised at titres within twofold of the titre of the antiserum for the homologous virus; A/Denmark/26/2018 was recognised at a titre within fourfold. Generally, the test viruses showed good reactivity with eight other antisera in the panel, all being recognised at titres within fourfold of the respective homologous titres. The antisera raised against egg-propagated A/California/7/2009 (the former vaccine virus) and cell culture-propagated A/Lviv/N6/2009 (which has HA1 amino acid substitutions of G155E and D222G) recognised the test viruses less well with five and seven viruses, respectively, being recognised at titres that were at least eightfold reduced compared to the respective homologous titres.

All 15 test viruses were genetically characterised and, as is the case for EU/EEA A(H1N1)pdm09 viruses characterised throughout the 2016–17 and 2017–18 seasons for which sequences have been submitted to the GISAID EpiFlu database, all carried haemagglutinins (HAs) belonging to genetic subclade 6B.1. The majority of HA genes of recently circulating viruses from EU/EAA countries cluster in a genetic subgroup defined by HA1 amino acid substitutions of S74R, S164T and I295V within which a number of subclusters have emerged (Figure 1). These subclusters are defined by HA1 amino acid substitutions, e.g. S183P, E235D and N260D, or S183P with P137S, or V250A, or P271S, or T120A sometimes with S183P.

Table 3. 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 NIB F42/16[*1] 6B.1	A/Cal 7/09 Egg F07/16[*1]	A/Bayern 69/09 MDCK F09/15[*1]	A/Lviv N6/09 MDCK F14/13[*1]	A/Astrak 1/11 MDCK F22/13[*1] 5	A/HK 5659/12 MDCK F30/12[*1] 6A	A/Slov 2903/2015 Egg F02/16[*1] 6B.1	A/Paris 1447/17 MDCK F03/18[*2] 6B.1	A/Swit 2656/17 Egg F20/18[*1] 6B.1	A/Swit 3330/17 Egg F23/18[*1] 6B.1	A/N Jers 13/18 MDCK CDC F74/18[*1] 6B.1
REFERENCE VIRUSES															
A/Michigan/45/2015		6B.1	2015-09-07	E3/E3	1280	1280	640	320	1280	1280	1280	1280	2560	640	1280
A/California/7/2009	clone 38-32		2009-04-09	E3/E5	1280	2560	1280	1280	1280	1280	1280	1280	2560	1280	1280
A/Bayern/69/2009	G155E		2009-07-01	MDCK5/MDCK1	40	80	640	320	80	80	80	160	160	80	40
A/Lviv/N6/2009	G155E, D222G		2009-10-27	MDCK4/SIAT1/MDCK2	160	160	1280	1280	160	320	320	640	640	320	320
A/Astrakhan/1/2011		5	2011-02-28	MDCK1/MDCK7	1280	2560	1280	640	1280	1280	2560	2560	2560	1280	2560
A/Hong Kong/5659/2012		6A	2012-05-21	MDCK4/MDCK2	320	640	320	160	640	640	640	640	640	320	640
A/Slovenia/2903/2015	clone 37	6B.1	2015-10-26	E4/E2	1280	1280	320	320	640	1280	1280	1280	1280	640	1280
A/Paris/1447/2017		6B.1	2017-10-20	MDCK1/MDCK3	1280	1280	320	160	640	640	1280	1280	1280	640	1280
A/Switzerland/2656/2017		6B.1	2017-12-21	E5/E1	1280	2560	1280	640	1280	1280	2560	1280	2560	1280	2560
A/Switzerland/3330/2017	clone 35	6B.1	2017-12-20	E6/E1	640	1280	320	160	640	640	1280	640	1280	1280	1280
A/New Jersey/13/2018		6B.1	2018-02-18	MDCK1/MDCK1	640	640	320	320	640	640	1280	1280	1280	640	1280
TEST VIRUSES															
A/Denmark/26/2018		6B.1	2018-01-08	MDCK2/MDCK1	320	160	160	80	320	160	640	320	640	320	640
A/Hungary/34/2018		6B.1	2018-01-22	MDCK1/MDCK1	640	1280	640	320	640	640	1280	1280	1280	640	1280
A/Hungary/55/2018		6B.1	2018-01-26	MDCK1/MDCK1	640	160	320	320	320	640	1280	640	1280	640	1280
A/Hungary/53/2018		6B.1	2018-01-29	MDCK1/MDCK1	640	1280	320	320	640	640	1280	1280	1280	1280	1280
A/Hungary/99/2018		6B.1	2018-02-01	MDCK2/MDCK1	640	640	320	160	640	320	640	640	1280	640	640
A/Ireland/10413/2018		6B.1	2018-02-06	MDCK2/MDCK1	640	320	320	160	320	640	640	2560	1280	640	ND
A/Ireland/15622/2018		6B.1	2018-02-21	MDCK2/MDCK1	640	320	320	160	320	640	640	1280	1280	640	ND
A/Ireland/17498/2018		6B.1	2018-02-26	MDCK2/MDCK1	640	640	320	320	640	640	1280	2560	2560	640	ND
A/Ireland/19112/2018		6B.1	2018-03-05	MDCK2/MDCK1	1280	640	640	320	640	640	1280	2560	2560	1280	ND
A/Lithuania/7487/2018		6B.1	2018-03-05	MDCK1	1280	640	320	160	640	640	1280	2560	2560	1280	ND
A/Hungary/279/2018		6B.1	2018-03-14	MDCKx/MDCK1	640	1280	320	160	640	640	1280	1280	1280	640	1280
A/Denmark/792/2018		6B.1	2018-04-07	MDCK4/MDCK1	640	1280	320	320	640	640	1280	1280	1280	640	1280
A/Denmark/793/2018		6B.1	2018-04-09	MDCK4/MDCK1	640	640	320	320	320	640	1280	640	1280	1280	1280
A/Ireland/36789/2018		6B.1	2018-05-11	MDCK1	640	320	320	160	320	320	1280	2560	1280	640	ND
A/Lithuania/14564/2018		6B.1	2018-05-15	MDCK1	1280	1280	640	640	1280	1280	2560	5120	2560	1280	ND

* Superscripts refer to antiserum properties (< relates to the lowest dilution of antiserum used)

Vaccine

1 < = <40; 2 < = <80; ND = Not Done

Sequences in phylogenetic tree

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

Influenza A(H3N2) virus analyses

As described in many previous reports[2], influenza A(H3N2) viruses have continued to be difficult to characterise antigenically by HI assay due to variable agglutination of red blood cells (RBCs) from guinea pigs, turkeys and humans, often with the loss of ability to agglutinate any of these RBCs. As was highlighted first in the November 2014 report[3], this is a particular problem for most viruses that fall in genetic clade 3C.2a.

All 454 A(H3N2) virus specimens with collection dates after week 40/2017, 31 of which were lysed specimens, have been characterised (Table 2). However, of those successfully isolated (n = 376), as shown by positive neuraminidase activity, only 99 (26%) had sufficient HA activity in the presence of 20nM oseltamivir to allow antigenic analysis by HI assay. Since the July 2018 report, only one virus recovered, based on positive neuraminidase activity, retained sufficient HA activity to allow antigenic analysis by HI and the HA fell in clade 3C.3a (see below for definitions) (Table 4). A/Ireland/05415/2018 was recognised well by antisera raised against cell culture-propagated 3C.3a and 3C.2a viruses, but poorly (at least eightfold reduced compared to homologous titres) by antisera raised against both cell culture- and egg-propagated 3C.2a2 viruses, and the egg-propagated 3C.2a1 vaccine virus A/Singapore/INFIMH-16-0019/2016.

Three antisera for which no homologous titres are given, due to the inability of these cell culture-propagated reference viruses to agglutinate RBCs, were used in the HI test. All three antisera, raised against A/La Rioja/2202/2018 (3C.2a1b), A/Norway/4436/2016 (3C.2a1) and A/Greece/4/2017 (3C.2a1a), recognised the test virus at titres of 160 which were comparable to the titres seen with the panel of reference viruses.

Phylogenetic analysis of the HA genes of representative A(H3N2) viruses from Europe with recent collection dates, after 31 August 2017 available in the GISAID EpiFlu database, is shown in 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 predominating since the 2014–15 influenza season and continuing to predominate in recent months (Figure 2) but the HA gene sequences 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, compared to A/Stockholm/6/2014 (Figure 2), and new genetic groups have 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/4801/2014
- 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
- 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 **H311K** in **HA1**, e.g. A/Alsace/1746/2018, 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/Norway/4465/2016
- 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 (this subclade is not represented in Figure 2 as sequences of viruses with recent collection dates, falling into this subclade, have not been deposited in the GISAID EpiFlu database)
- 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/Switzerland/9715293/2013.

The great majority of recently circulating viruses have HA genes that fall into genetic groups within clade 3C.2a, with a low number of viruses falling in clade 3C.3a. In EU/EEA countries, recently circulating viruses have fallen in approximately equal proportions into subclades 3C.2a2 and 3C.2a1, with the majority of viruses in the latter subclade having HA genes that fell into genetic subgroup 3C.2a1b (Figure 2). The location of A/Singapore/INFIMH-16-0019/2016 (3C.2a1), the A(H3N2) virus recommended for inclusion in vaccines for the southern hemisphere 2018 [2] and the northern hemisphere 2018–2019 influenza seasons [3], is indicated in Figure 2, as is A/Switzerland/8060/2017 (3C.2a2), the A(H3N2) virus recommended for inclusion in vaccines for the southern hemisphere 2019 [4].

[2] For example, the September 2013 report: European Centre for Disease Prevention and Control. Influenza virus characterisation, summary Europe, September 2013. Stockholm: ECDC; 2014. 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: http://www.ecdc.europa.eu/en/publications/Publications/ERLI-Net report November 2014.pdf

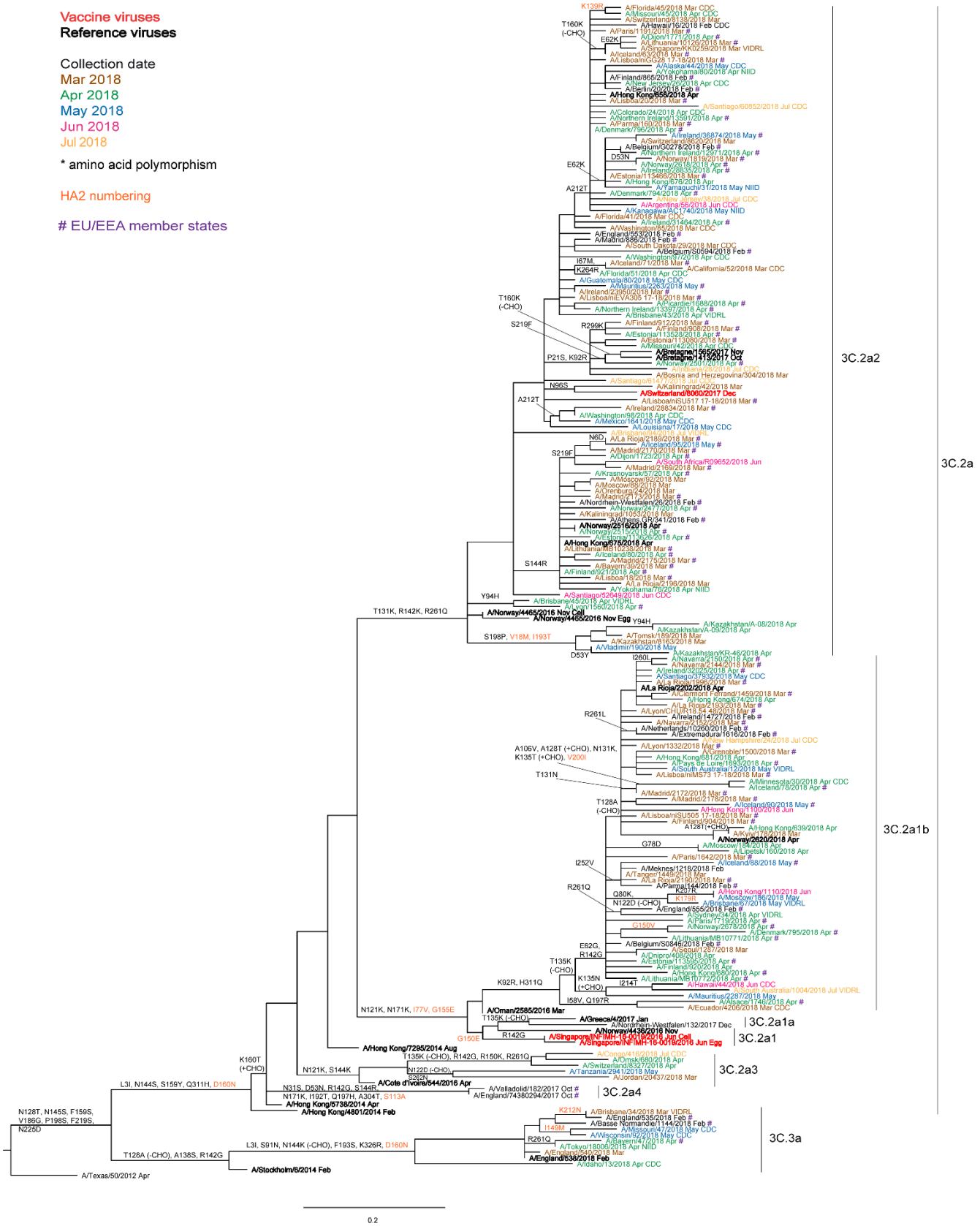
Table 4. Antigenic analysis of A(H3N2) viruses by HI

Viruses	Other information	Collection date	Passage history	Haemagglutination inhibition titre									
				Post-infection ferret antisera									
				A/Stock 6/14 SIAT F14/14*1 3C.3a	A/HK 5738/14 MDCK F30/14*1 3C.2a	A/Bretagne 1413/17 SIAT F01/18 3C.2a2	A/Nor 4436/16 SIAT F03/17*1 3C.2a1	A/Greece 4/17 SIAT F27/17*1 3C.2a1a	A/Sing 0019/16 Egg 10^{-4} F41/17*1 3C.2a1	A/HK 656/18 SIAT F25/18*1 3C.2a2	A/La Rioja 2202/18 SIAT F26/18*1 3C.2a1b	A/Switz 8060/17 Egg F27/18*1 3C.2a2
REFERENCE VIRUSES													
A/Stockholm/6/2014		3C.3a	2017-11-20	SIAT1/SIAT3	320	160	80	320	160	160	160	80	160
A/Hong Kong/5738/2014		3C.2a	2017-11-16	MDCK1/MDCK2/SIAT1	160	160	160	320	160	320	320	160	160
A/Bretagne/1413/2017		3C.2a2	2018-06-28	MDCK1/SIAT4	160	160	1280	320	320	320	640	160	1280
A/Singapore/INFIMH-16-0019/2016		3C.2a1	2017-10-05	E5/E2	40	40	80	160	160	640	80	160	160
A/Hong Kong/656/2018	clone 57	3C.2a2	2018-07-30	MDCK1/SIAT3	320	320	1280	320	320	320	2560	160	1280
A/Switzerland/8060/2017		3C.2a2	2018-08-13	E7 (AM2AL5)	40	160	2560	160	320	640	2560	160	2560
TEST VIRUSES													
A/Ireland/05415/2018		3C.3a	2018-01-30	SIAT1/SIAT1	160	80	80	160	160	80	160	160	160

Vaccine SH 2018 NH 2018-19

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

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



Influenza B virus analyses

A total of 728 influenza type B-positive specimens with collection dates after August 2017 have been received, with 651 being ascribed to a lineage: 93 B/Victoria-lineage and 558 B/Yamagata-lineage (Table 2).

Influenza B – Victoria lineage

Twelve tissue culture-propagated test viruses have been antigenically characterised by HI assay since the July 2018 report (Tables 5). All viruses were poorly recognised by the three antisera raised against egg-propagated clade 1A viruses, B/Malta/636714/2011, B/South Australia/81/2012 and the vaccine virus B/Brisbane/60/2008. Two patterns of reactivity were seen with the other antisera. Those raised against cell culture-propagated B/Norway/2409/2017 and B/Colorado/06/2017, viruses carrying a deletion of two amino acids in HA1 Δ(K162, N163), recognised six and seven test viruses, respectively, at titres within twofold of those with the homologous viruses and the same eight within fourfold. Antisera raised against cell culture-propagated viruses with no deletion, B/Ireland/3154/2016, B/Nordrhein-Westfalen/1/2016 (both clade 1A viruses) and B/Hong Kong/514/2009 (clade 1B) each recognised the four test viruses which lacked the two amino acid deletion in HA at titres within twofold of the homologous titres. The test viruses with the deletion were recognised less well by antiserum raised against the egg-propagated cultivar of B/Colorado/06/2017, the virus recommended for use in northern hemisphere 2018–19 and southern hemisphere 2019 vaccines: it recognised none of the eight Δ(K162, N163) test viruses at titres within twofold and only six within fourfold of the titre with the homologous virus. The egg-propagated cultivar of B/Colorado/06/2017 has lost the glycosylation site at HA1 position 195-197, leading to unmasking of an immunogenic antigenic epitope that is obscured by carbohydrate in the cell culture-propagated test viruses. The effect of the loss of the glycosylation site in egg-propagated B/Colorado/06/2017 can also be seen in its reactivity with the sheep hyperimmune antisera pool raised against egg-propagated B/Brisbane/60/2008 compared to that seen with the two cell culture-propagated Δ(K162, N163) reference viruses. The results clearly confirm that viruses with the two amino acid deletion in HA1 are antigenically distinct from those without the deletion, and previously we have reported that they are also antigenically distinct from those with a deletion of three amino acids in HA1 [5].

Recently circulating viruses of the B/Victoria lineage continue to have HA genes that fall in the B/Brisbane/60/2008 clade (clade 1A; Figure 3) and in a subcluster defined by **HA1** amino acid substitutions **I117V**, **N129D** and **V146I** within clade 1A. Two new groups within this cluster have deletions in the HA gene. Low numbers of viruses with HA genes encoding a deletion of three amino acids K162, N163 and D164 (1A(Δ3)) have been detected primarily in the Far East and Africa, many of which share the substitutions **I180T** and **K209N** in **HA1**, though other viruses with similar deletions have been detected elsewhere, notably a group with the substitution **K136E** in **HA1** which is antigenically distinct from others in the 1A(Δ3) group. The major group of viruses, seen in the Americas, Europe, Asia and Oceania, have HA genes encoding an HA with deletion of residues 162 and 163 of HA1, as discussed above (1A(Δ2) in Figure 3); these viruses have additional substitutions of **D129G** and **I180V** in **HA1**, and **R151K** in **HA2**. Eight of the recently characterised test viruses carry the **HA1** double deletion (1A(Δ2) in Table 5 and Figure 3), and of the 78 B/Victoria lineage viruses with collection dates after week 40/2017, characterised genetically at the WIC, 20 were B/Brisbane/60/2008-like viruses (clade 1A), and 58 fell within the HA1 double amino acid deletion subgroup (1A(Δ2)).

Influenza B – Yamagata lineage

HI results for 44 B/Yamagata-lineage test viruses analysed since the July 2018 report are shown in Tables 6-1 and 6-2. The 477 viruses analysed genetically to date, with collection dates since week 40/2017, all belong to genetic clade 3, the B/Wisconsin/1/2010–Phuket/3073/2013 clade.

The antiserum raised against egg-propagated B/Phuket/3073/2013, recommended for inclusion in quadrivalent vaccines for the 2017–18 [1] and 2018–19 [3] northern hemisphere and the 2019 [4] southern hemisphere seasons and trivalent vaccines for the southern hemisphere 2018 season [2], recognised all test viruses at titres within twofold of the titre of the antiserum with the homologous virus. An antiserum raised against the cell culture-propagated cultivar of B/Phuket/3073/2013 recognised 35 (80%) test viruses at titres within twofold of the homologous titre of the antiserum and a further seven (16%) within fourfold. Antisera raised against two other egg-propagated clade 3 viruses, B/Wisconsin/1/2010 (a former vaccine virus) and B/Stockholm/12/2011, recognised all (100%) and 29 (66%) test viruses, respectively, at titres within twofold of the homologous titres; the remaining 15 test viruses were recognised by the antiserum raised against B/Stockholm/12/2011 at titres within fourfold. An antiserum raised against a recently circulating clade 3 cell culture-propagated virus, B/Mauritius/1791/2017, recognised all test viruses at titres within twofold of the homologous titre.

Generally, antisera raised against clade 2 viruses, cell culture-propagated B/Estonia/55669/2011 and B/Massachusetts/02/2012 and egg-propagated B/Massachusetts/02/2012, recognised the test viruses less well: only 22 (50%), 42 (95%) and 40 (91%) test viruses, respectively, were recognised at titres within fourfold of the titres of the antisera with their homologous viruses.

The 41 genetically characterised test viruses all carried HA genes in genetic clade 3 (Tables 6-1 and 6-2). Figure 4 shows a phylogenetic analysis of the HA genes of representative B/Yamagata-lineage viruses, including recently circulating ones. Worldwide, all HA genes from viruses collected in 2017–18 have fallen in clade 3, the B/Wisconsin/1/2010–B/Phuket/3073/2013 clade. The vast majority of viruses, including those with collection dates after 31 August 2017 from Europe as deposited in the GISAID EpiFlu database, fall in a subgroup defined by **HA1 L172Q** and **M251V** amino acid substitutions. Some subclustering of sequences, defined by specific amino acid substitutions (e.g. HA1 G183E or D229N or D232N [introducing a potential N-linked glycosylation site]), is occurring but with no obvious antigenic effects (Tables 6-1 and 6-2).

Table 5. Antigenic analysis of influenza B/Victoria-lineage viruses by HI

Viruses	Other information	Collection date	Passage history	Haemagglutination inhibition titre: Post-infection ferret antisera											
	Passage history			B/Bris	B/Bris	B/Malta	B/Sth Aus	B/HK	B/Ireland	B/Nord-West	B/Nor	B/Colorado	B/Colorado		
				60/08	60/08	636714/11	81/12	514/09	3154/16	1/16	2409/17	06/17	06/17		
				Egg	Egg	Egg	Egg	MDCK	MDCK	MDCK	MDCK	MDCK	Egg		
			Sh	539, 540, 543, 544, 570, 571, 574[*1,3]	NIB F52/16[-2]	F29/13[-2]	F25/16[-4]	F47/16[-2]	F15/16[-2]	F16/16[-2]	F40/17[-2]	F09/18[-2]	F10/18[-2]		
	Ferret number														
	Genetic group			1A	1A	1A	1A	1B	1A	1A	1A(Δ2)	1A(Δ2)	1A(Δ2)		
REFERENCE VIRUSES															
B/Brisbane/60/2008	1A	2008-08-04	E4/E4	2560	640	320	640	320	40	40	<	40	80		
B/Malta/636714/2011	1A	2011-03-07	E4/E1	2560	320	640	640	320	40	40	<	20	80		
B/South Australia/81/2012	1A	2012-11-28	E4/E2	2560	640	320	640	320	40	40	<	40	80		
B/Hong Kong/514/2009	1B	2009-10-11	MDCK1/MDCK2	5120	40	160	80	160	80	80	<	10	<		
B/Ireland/3154/2016	1A	2016-01-14	MDCK1/MDCK4	2560	20	40	40	80	160	160	<	10	<		
B/Nordrhein-Westfalen/1/2016	1A	2016-01-04	C2/MDCK2	2560	20	40	40	40	80	80	<	<	<		
B/Norway/2409/2017	1A(Δ2)	2017-04-27	MDCK1/MDCK2	80	<	<	20	<	20	10	80	160	40		
B/Colorado/06/2017	1A(Δ2)	2017-02-05	MDCK1/MDCK2	80	<	<	20	<	10	10	40	160	40		
B/Colorado/06/2017	1A(Δ2)	2017-02-05	E5/E1	1280	80	80	80	20	<	<	40	160	160		
TEST VIRUSES															
B/Lisboa/niSU041 17-18/2017	1A	2017-11-28	SIAT1/MDCK2	2560	40	40	40	80	80	160	<	<	<		
B/Lisboa/niEVA101 17-18/2018	1A	2018-01-05	SIAT1/MDCK2	2560	40	40	40	80	80	160	<	<	<		
B/Ireland/03390/2018	1A(Δ2)	2018-01-25	MDCK3/MDCK1	40	<	<	10	<	10	10	40	80	20		
B/Lisboa/niGG15 17-18/2018	1A	2018-01-27	SIAT1/MDCK1	2560	20	40	40	80	80	80	<	10	<		
B/Ireland/12771/2018	1A(Δ2)	2018-02-13	MDCK2/MDCK1	40	<	<	10	<	10	<	40	80	40		
B/Hungary/183/2018	1A(Δ2)	2018-02-19	MDCKx/MDCK1	80	<	<	<	<	<	10	40	80	40		
B/Hungary/167/2018	1A	2018-02-20	MDCK2/MDCK1	2560	20	40	40	80	80	80	<	<	<		
B/Hungary/210/2018	1A(Δ2)	2018-02-26	MDCK1/MDCK1	40	<	<	<	<	<	10	20	80	40		
B/Hungary/253/2018	1A(Δ2)	2018-03-02	MDCK1/MDCK1	80	<	<	<	<	<	10	40	80	40		
B/Lithuania/7431/2018	1A(Δ2)	2018-03-05	MDCK1	80	<	<	<	<	<	10	40	80	40		
B/Hungary/288/2018	1A(Δ2)	2018-03-12	MDCKx/MDCK1	40	<	<	<	<	<	<	20	40	20		
B/Lithuania/8294/2018	1A(Δ2)	2018-03-14	MDCK1	80	<	<	<	<	<	10	40	80	40		
					Vaccine[#]									Vaccine[$]	

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

[#] B/Victoria-lineage virus recommended for use in trivalent vaccines NH 2017-18 and quadravalent vaccines SH 2018

[$] B/Victoria-lineage virus recommended for use in trivalent vaccines NH 2018-19

Sequences in phylogenetic trees

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

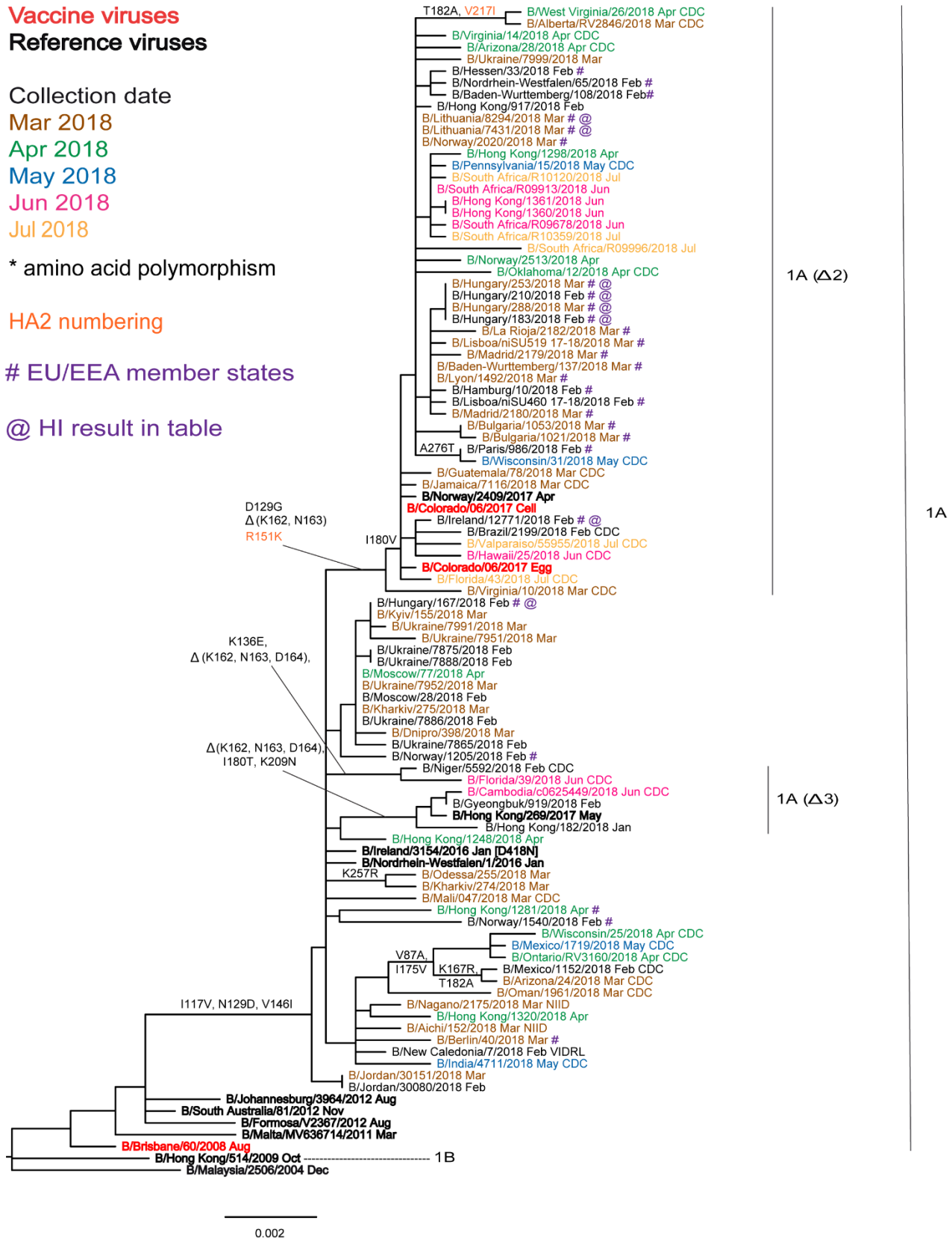


Table 6-1. Antigenic analysis of influenza B/Yamagata-lineage viruses by HI

Viruses	Other information	Passage history / Ferret number / Genetic Group	Collection date	Passage history	Haemagglutination inhibition titre								
					Post-infection ferret antisera								
					B/Phuket 3073/13 Egg SH614[*1,3]	B/Estonia 55669/11 MDCK F27/13[*2]	B/Mass 02/12 MDCK F10/16[*2]	B/Mass 02/12 Egg F16/14[*2]	B/Wis 1/10 Egg F36/15[*2]	B/Stock 12/11 Egg F06/15[*2]	B/Phuket 3073/13 MDCK F27/15[*2]	B/Phuket 3073/13 Egg F25/17*[2]	B/Maur 1791/17 MDCK F04/18[*2]
		Genetic Group			3	2	2	2	3	3	3	3	3
REFERENCE VIRUSES													
B/Estonia/55669/2011		2	2011-03-14	MDCK2/MDCK3	640	640	40	160	80	20	40	20	20
B/Massachusetts/02/2012		2	2012-03-13	MDCK1/C2/MDCK3	640	320	40	640	160	80	40	160	20
B/Massachusetts/02/2012		2	2012-03-13	E3/E3	640	80	20	1280	160	160	40	160	<
B/Wisconsin/1/2010		3	2010-02-20	E3/E2	1280	40	10	320	160	80	40	80	40
B/Stockholm/12/2011		3	2011-03-28	E4/E1	1280	40	<	160	80	160	40	80	40
B/Phuket/3073/2013		3	2013-11-21	MDCK2/MDCK2	2560	160	80	160	320	80	160	160	320
B/Phuket/3073/2013		3	2013-11-21	E4/E3	1280	20	<	160	80	80	20	80	20
B/Mauritius/1791/2017		3	2017-09-20	MDCK1/MDCK4	1280	40	20	80	80	20	40	40	80
TEST VIRUSES													
B/Lisboa/niSU182-17-18/2018		3	2018-01-04	SIAT1/MDCK1	2560	80	80	160	160	80	160	160	160
B/Estonia/111660/2018		3	2018-01-19	SIAT1/MDCK1	2560	80	80	160	160	40	80	160	160
B/Estonia/112242/2018		3	2018-02-09	SIAT1/MDCK1	2560	80	80	160	160	40	80	160	160
B/Belgium/S0589/2018		3	2018-02-11	MDCKx/MDCK1	2560	160	80	160	160	80	160	320	160
B/Belgium/S1368/2018		3	2018-02-12	MDCKx/MDCK1	2560	160	160	320	160	80	160	160	160
B/Belgium/S0806/2018		3	2018-02-13	MDCKx/MDCK1	5120	160	160	160	160	80	160	160	160
B/Belgium/S0820/2018		3	2018-02-14	MDCKx/MDCK1	2560	80	40	160	160	40	80	160	160
B/Belgium/S0777/2018		3	2018-02-15	MDCKx/MDCK1	2560	80	80	160	160	40	80	160	160
B/Belgium/S0916/2018		3	2018-02-17	MDCKx/MDCK1	5120	80	80	160	160	80	80	160	160
B/Belgium/S0943/2018		3	2018-02-18	MDCKx/MDCK1	2560	80	80	160	160	40	80	160	160
B/Belgium/S0942/2018		3	2018-02-18	MDCKx/MDCK1	2560	80	80	160	160	40	80	160	160
B/Belgium/S0917/2018		3	2018-02-18	MDCKx/MDCK1	2560	80	80	160	160	40	80	160	160
B/Belgium/S0944/2018		3	2018-02-18	MDCKx/MDCK1	2560	80	80	160	160	80	80	160	160
B/Sassari/14/2018			2018-02-21	MDCK2/MDCK1	2560	160	160	160	320	80	160	320	320
B/Belgium/S0984/2018		3	2018-02-22	MDCKx/MDCK1	2560	80	80	160	160	40	80	160	160
B/Belgium/S1304/2018		3	2018-02-23	MDCKx/MDCK1	5120	160	160	320	160	80	160	320	320
B/Belgium/S1242/2018		3	2018-02-23	MDCKx/MDCK1	2560	80	40	160	160	40	80	160	160
B/Friuli Venezia Giulia/79/2018			2018-02-26	MDCK2/MDCK1	5120	80	80	320	320	80	160	320	320
B/Belgium/S1480/2018		3	2018-02-26	MDCKx/MDCK1	2560	160	80	160	160	80	80	160	160
B/Belgium/S1230/2018		3	2018-02-26	MDCKx/MDCK1	2560	160	160	320	320	80	160	320	320
B/Belgium/G0419/2018		3	2018-03-01	MDCKx/MDCK1	2560	80	80	160	160	40	80	160	160
B/Belgium/S1223/2018		3	2018-03-02	MDCKx/MDCK1	2560	160	160	160	320	80	160	320	320
B/Belgium/G0416/2018		3	2018-03-05	MDCKx/MDCK1	2560	80	160	160	160	80	160	320	160
B/Belgium/S1283/2018		3	2018-03-05	MDCKx/MDCK1	2560	160	160	160	320	80	160	160	160
B/Belgium/G0425/2018		3	2018-03-06	MDCKx/MDCK1	2560	80	80	160	160	40	80	160	160
B/Estonia/113498/2018		3	2018-03-28	SIAT1/MDCK1	5120	160	80	320	160	80	160	320	320
B/Estonia/113531/2018		3	2018-04-02	SIAT1/MDCK1	2560	80	80	160	160	40	80	160	160
B/Estonia/113587/2018		3	2018-04-03	SIAT1/MDCK1	2560	80	80	160	160	40	80	160	160
												Vaccine[#]	

* Superscripts refer to antiserum properties (< relates to the lowest dilution of antiserum used):

1 < = <40; 2 < = <10; 3 hyperimmune sheep serum

[#] B/Yamagata-lineage virus recommended for use in trivalent vaccines SH 2018 and quadravalent vaccines NH 2017-18 & 2018-19

Sequences in phylogenetic trees

Table 6-2. Antigenic analysis of influenza B/Yamagata-lineage viruses by HI

Viruses	Other information	Collection date	Passage history	Haemagglutination inhibition titre										
				Post-infection ferret antisera										
	Passage history			B/Phuket 3073/13 Egg	B/Estonia 55669/11 MDCK	B/Mass 02/12 MDCK	B/Mass 02/12 Egg	B/Wis 1/10 Egg	B/Stock 12/11 Egg	B/Phuket 3073/13 MDCK	B/Phuket 3073/13 Egg	B/Maur 1791/17 MDCK		
	Ferret number			SH614[-1,3]	F27/13[+2]	F10/16[+2]	F16/14[+2]	F36/15[+2]	F05/17[+2]	F27/15[+2]	F25/17[+2]	F04/18[+2]		
	Genetic Group			3	2	2	2	3	3	3	3	3		
REFERENCE VIRUSES														
B/Estonia/55669/2011	2	2011-03-14	MDCK2/MDCK3	640	320	80	160	80	20	40	80	20		
B/Massachusetts/02/2012	2	2012-03-13	MDCK1/C2/MDCK3	1280	320	160	640	160	40	80	320	40		
B/Massachusetts/02/2012	2	2012-03-13	E3/E3	1280	80	40	640	160	80	20	160	10		
B/Wisconsin/1/2010	3	2010-02-20	E3/E2	1280	40	20	320	160	40	40	320	80		
B/Stockholm/12/2011	3	2011-03-28	E4/E1	1280	40	10	160	80	80	40	160	40		
B/Phuket/3073/2013	3	2013-11-21	MDCK2/MDCK2	5120	160	160	320	320	160	320	320	320		
B/Phuket/3073/2013	3	2013-11-21	E4/E3	1280	20	10	320	80	40	40	160	40		
B/Mauritius/1791/2017	3	2017-09-20	MDCK1/MDCK4	1280	80	40	160	80	40	80	80	160		
TEST VIRUSES														
B/Ireland/02866/2018		2018-01-18	MDCK2/MDCK1	2560	40	40	160	80	40	80	160	80		
B/Ireland/05096/2018	3	2018-01-30	MDCK3/MDCK1	2560	80	40	160	160	80	160	160	160		
B/Hungary/145/2018	3	2018-02-07	MDCK1/MDCK1	2560	80	40	160	160	40	80	160	160		
B/Ireland/14708/2018	3	2018-02-14	MDCK4/MDCK1	2560	160	160	160	160	80	160	160	160		
B/Hungary/148/2018	3	2018-02-14	MDCK1/MDCK1	2560	160	160	320	320	80	160	320	320		
B/Hungary/166/2018	3	2018-02-16	MDCK1/MDCK1	1280	40	20	80	80	20	40	80	80		
B/Hungary/185/2018	3	2018-02-19	MDCKx/MDCK1	2560	80	40	160	160	40	80	160	160		
B/Ireland/19082/2018	3	2018-02-26	MDCK1/MDCK1	2560	40	40	80	80	40	80	160	80		
B/Ireland/19107/2018	3	2018-03-05	MDCK1	2560	80	40	160	160	80	80	160	160		
B/Hungary/227/2018	3	2018-03-06	MDCK1/MDCK1	5120	80	160	320	320	40	160	320	320		
B/Denmark/2897/2018	3	2018-03-28	SIAT3/MDCK1	2560	160	80	160	160	80	160	160	320		
B/Denmark/2898/2018	3	2018-03-28	SIAT2/MDCK1	2560	160	80	160	160	80	160	160	320		
B/Denmark/2901/2018	3	2018-03-30	SIAT2/MDCK1	2560	80	40	160	160	40	80	160	160		
B/Denmark/2900/2018	3	2018-03-30	SIAT2/MDCK1	1280	80	40	80	80	20	40	80	160		
B/Denmark/2899/2018	3	2018-04-02	SIAT3/MDCK1	2560	80	80	160	160	40	160	160	320		
B/Ireland/33271/2018	3	2018-04-29	MDCK2	1280	40	10	80	80	40	80	80	80		
													Vaccine[#]	

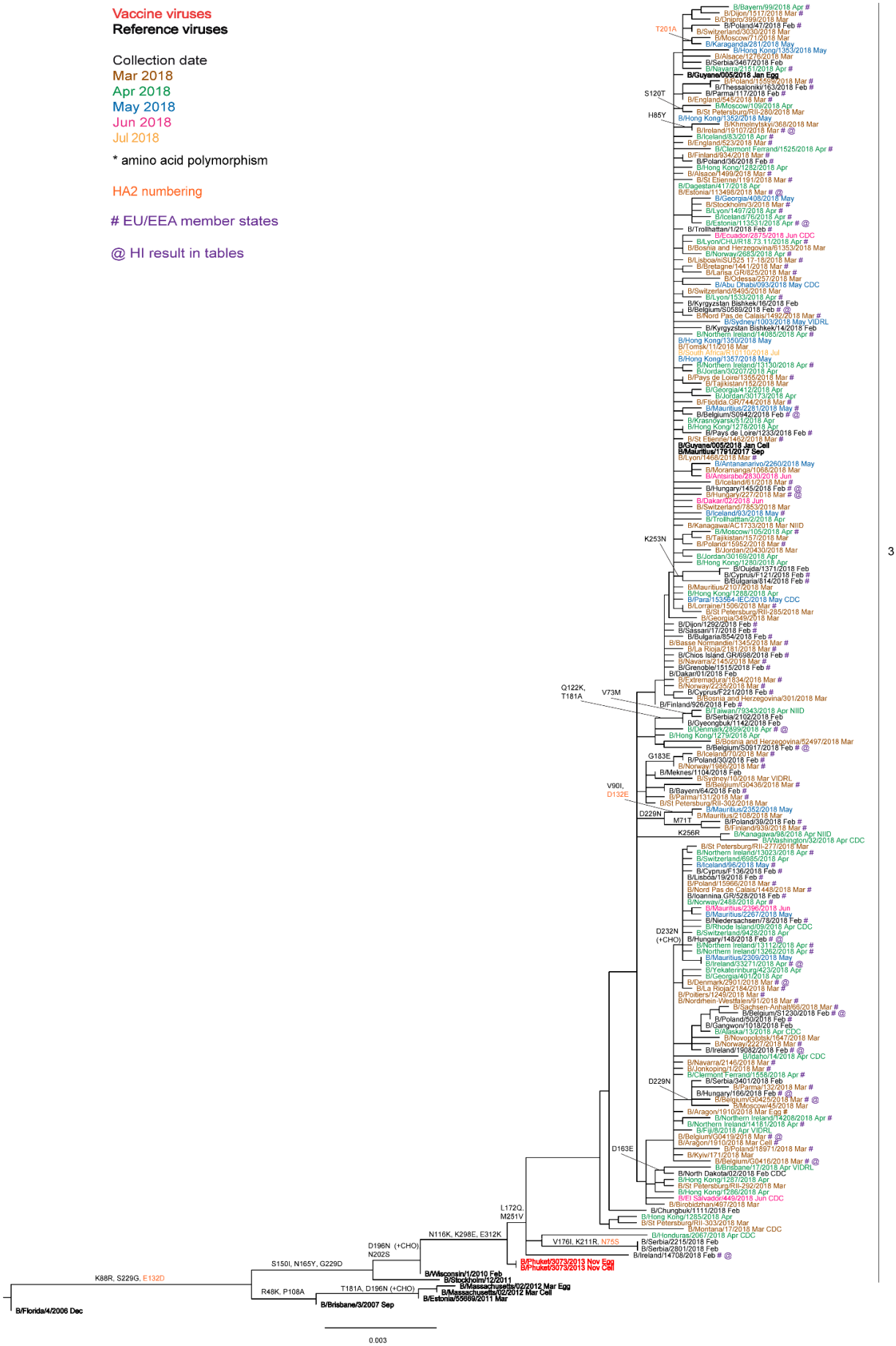
*Superscripts refer to antiserum properties (< relates to the lowest dilution of antiserum used):

1 < = <40; 2 < = <10; 3 hyperimmune sheep serum

[#] B/Yamagata-lineage virus recommended for use in trivalent vaccines SH 2018 and quadravalent vaccines NH 2017-18 & 2018-19

Sequences in phylogenetic trees

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



Summary of genetic data submitted to TESSy

For the 2017–18 season, weeks 40/2017–39/2018, 3 910 viruses were characterised genetically and ascribed to a genetic clade:

- 840 A(H1N1)pdm09 were subclade 6B.1, represented by A/Michigan/45/2015, and 2 clade 6B, represented by A/South Africa/3626/2013
- 651 were A(H3N2) clade 3C.2a, represented by A/Hong Kong/4801/2014, 452 were subclade 3C.2a1 represented by A/Singapore/INFIMH-16-0019/2016, 11 were clade 3C.3a represented by A/Switzerland/9715293/2013 and 9 were clade 3C.3, represented by A/Samara/73/2013
- 154 were B/Victoria-lineage clade 1A represented by B/Brisbane/60/2008, with 74 (48%) falling in the 1A Δ162-163 subclade
- 1 790 were B/Yamagata-lineage clade 3, represented by B/Phuket/3073/2013 and 1 was B/Yamagata-lineage clade 2 represented by B/Massachusetts/02/2012
- A further 3 A(H1N1)pdm09, 35 A(H3N2), 1 B/Victoria-lineage and 20 B/Yamagata-lineage viruses were not ascribed to genetic clades listed in reporting categories for the 2017–18 season.

Antiviral susceptibility

Phenotypic testing for susceptibility to oseltamivir and zanamivir was conducted on 1 187 viruses, with collection dates from week 40/2017, at the WIC: 324 A(H1N1)pdm09, 343 A(H3N2), 82 B/Victoria-lineage, and 438 B/Yamagata-lineage viruses. Of these, three A(H1N1)pdm09 viruses showed reduced susceptibility to oseltamivir (A/Bretagne/002/2018: I223R and A/Catalonia/2242523NS/2018: H275Y>H showed reduced inhibition (RI), while A/Lyon/CHU-R18.41.16/2018: H275Y showed highly reduced inhibition (HRI)); three A(H3N2) viruses showed RI by oseltamivir (A/Poitiers/2028/2017: S334R, A/Estonia/113228/2018: sequence pending, and A/Milano/60/2018: sequence pending) with the latter virus also showing RI by zanamivir; and one B/Victoria virus (B/Galicia/2465/2017: T325N) showed RI by oseltamivir, with the neuraminidases of the viruses carrying the amino acid substitutions indicated. Interestingly, the B/Victoria virus was received as both cell culture- and egg propagated-cultivars and only the egg propagated-cultivar contained the NA T325N substitution and showed RI by oseltamivir.

As of week 39/2018 of the 2017–18 influenza season, countries reported to TESSy on the antiviral susceptibility of 3 703 viruses with collection dates since week 40/2017: 1 174 A(H1N1)pdm09 viruses, 990 A(H3N2) viruses, and 1 539 influenza type B viruses from sentinel and non-sentinel sources:

- Nineteen A(H1N1)pdm09 viruses carried neuraminidase (NA) amino acid substitution H275Y and showed HRI by oseltamivir, and a further two viruses showed RI by oseltamivir only.
- Two A(H3N2) viruses carried NA amino acid substitution R292K and showed RI by both oseltamivir and zanamivir.
- Two type B viruses carried NA amino acid substitution D197N and showed RI by oseltamivir and zanamivir, while another two viruses showed RI by oseltamivir only.

Influenza A(H7N9) virus

On 1 April 2013, the World Health Organization (WHO) Global Alert and Response [6] reported that the China Health and Family Planning Commission notified the WHO of three cases of human infection with influenza A(H7N9). A description of the characteristics of A(H7N9) viruses can be found on the WHO website [7]. 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, though few human cases were reported during the 2017–18 season [8]. WHO posted an analysis of information on A(H7N9) viruses on 10 February 2017 [11]; a summary and assessment of influenza viruses at the human–animal interface on 20 July 2018 indicates that A(H7N9) avian influenza viruses continue to be detected by agricultural authorities in China [12], with the latest human case having occurred early in February 2018 [13]. 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 27 September 2018 and can be found on the ECDC website [19].

Influenza A(H5) virus

The most recent monthly risk assessment of influenza at the human–animal interface was published by WHO on 20 July 2018, indicating that various A(H5Nx) subtypes continue to be detected in birds in Africa, Europe and Asia: notably A(H5N6) viruses, though these viruses differ from A(H5N6) viruses that previously infected humans in China [12]. By 20 July 2018, no cases of human infection by A(H5N1) viruses had been reported to WHO for 2018 [15]. On 18 November 2016, ECDC published a rapid risk assessment related to outbreaks of highly pathogenic avian influenza H5N8 viruses in Europe [18]. 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 27 September 2018 and can be found on the ECDC website [19].

WHO CC reports

A description of results generated by the London WHO CC at the WIC and used at WHO vaccine composition meetings held at 1) The Peter Doherty Institute, University of Melbourne, 25–27 September 2017, and 2) WHO Geneva, 19–21 February 2018, can be found at:

https://www.crick.ac.uk/media/393884/crick_sh2017_vcm_report_to_post.pdf [accessed 09 Oct 2018]

and

https://crick.ac.uk/media/409431/crick_feb2018_report_for_the_web.pdf [accessed 09 Oct 2018]

The report for the vaccine composition meeting held from 24 to 26 September 2018 for the 2019 southern hemisphere season will be added shortly to the relevant section of the WIC website (https://www.crick.ac.uk/partnerships/worldwide-influenza-centre/annual-and-interim-reports).

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 of sample collection. Isolates from WHO NICs in EU/EEA countries are marked (#). Sequences for some 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 GISAID's 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 the London WHO Collaborating Centre.

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