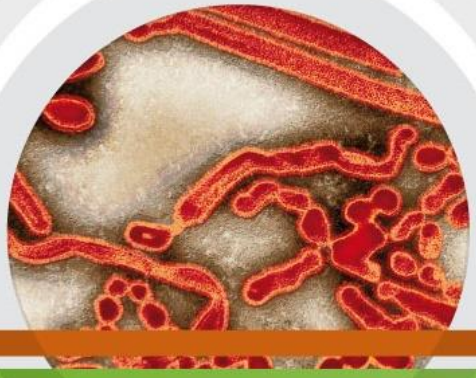

SURVEILLANCE REPORT

Influenza virus characterisation

Summary Europe, July 2018

Summary

This is the seventh report of the 2017–18 influenza season. As of week 30/2018, over 239 000 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 1 530 specimens having collection dates after August 2017.

All 78 A(H1N1)pdm09 test viruses characterised antigenically showed good reactivity with antiserum raised against the 2017–18 vaccine virus, A/Michigan/45/2015. The 274 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 352 A(H3N2) viruses successfully recovered to date, only 93 (26%) had sufficient HA titre to allow antigenic characterisation by HI assay in the presence of oseltamivir. The 12 viruses tested since the last report all showed poor recognition, HI titres reduced by at least eightfold compared with the homologous titre, by antiserum raised against the currently used vaccine virus, egg-propagated A/Hong Kong/4801/2014. Of the 360 viruses with collection dates from week 40/2017 genetically characterised at the WIC, 351 were clade 3C.2a (with 195 3C.2a2, 130 3C.2a1, 22 3C.2a3 and four 3C.2a4 subclade viruses) and nine were clade 3C.3a. Of the 130 subclade 3C.2a1 viruses, 124 fell in subgroup 3C.2a1b, and three belonged to subgroup 3C.2a1a.

Of the 24 B/Victoria-lineage viruses tested by HI, six (clade 1A) reacted well with antisera raised against cell-culture-propagated surrogates of B/Brisbane/60/2008, and 18 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 60 viruses characterised genetically at the WIC with a collection date after week 40/2017, 15 fell within clade 1A and 45 fell within the subgroup (1A(Δ2)) carrying the HA1 double amino acid deletion.

Of 68 B/Yamagata viruses characterised antigenically, all but one reacted well (within fourfold 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 seasons and for trivalent vaccines in the southern hemisphere 2018 season. The 405 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.

This report was prepared by Rod Daniels, Burcu Ermetal, Aine Rattigan and John McCauley (Crick Worldwide Influenza Centre) for the European Centre for Disease Prevention and Control under an ECDC framework contract.

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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 40/2017–30/2018), with detections having exceeded the number for the entire 2016–17 season by over 64%, while numbers of clinical specimens tested increased by only 24%. Over 239 000 detections have been reported, with type B (56%) predominating over type A (44%) viruses. Of the type A viruses subtyped (n = 44 385) and the type B viruses ascribed to lineage (n = 16 000), A(H3N2) and A(H1N1)pdm09 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 52.5:1; these ratios match those observed as of week 25/2018 (as summarised in the June 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 (49.4% in 2017–18 compared with 1.1% in 2016–17).

Since week 40/2017, 68 shipments of specimens have been received at the Crick Worldwide Influenza Centre (WIC) from 29 EU/EEA countries. These packages contained 1 530 specimens, a mix of clinical samples and virus isolates, with specimen collection dates after August 2017 (Table 2). The majority (54%) were type A viruses, and A(H3N2) outnumbered A(H1N1)pdm09 at a ratio of 1.2:1. Of the 701 type-B specimens received (46% of the specimens), 88 were B/Victoria-lineage and 535 were B/Yamagata-lineage. The antigenic and genetic properties of influenza viruses, characterised since the June 2018 report[1], are presented and discussed in this surveillance report. A significant number of the specimens are still undergoing characterisation (in process: Table 2).

Table 1. Influenza virus detections in the WHO European Region from the start of reporting for the 2017–18 season (weeks 40/2017–30/2018)[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	**9 165**	**95 371**	**104 536**	**43.7**	**0.8:1**	**126 614**	**86.6**	**6.5:1**
A(H1N1)pdm09	4 989	16 954	21 943	49.4		591	1.1	
A(H3N2)	2 706	19 736	22 442	50.6	1:1	53 101	98.9	89.8:1
A not subtyped	1 470	58 681	60 151			**72 922**		
Influenza B	**15 646**	**118 823**	**134 469**	**56.3**		**19 570**	**13.4**	
Victoria lineage	209	90	299	1.9		749	27.1	
Yamagata lineage	7 305	8 396	15 701	98.1	52.5:1	2 016	72.9	2.7:1
Lineage not ascribed	8 132	110 337	118 469			16 805		
Total detections (total tested)	**24 811 (61 407)**	**214 194 (790 234)**	**239 005 (851 641)**			**146 184 (686 477)**		

[a] Numbers taken from Flu News Europe weeks 21-25/2018 and 26-30/2018

*** 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, June 2018. Stockholm: ECDC; 2018. Available from: https://ecdc.europa.eu/sites/portal/files/documents/ECDC-Flu-Characterisation-Report-Jun-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 / Country	Total	A		H1N1pdm09		H3N2			B		B Victoria lineage		B Yamagata lineage	
	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	in process	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	in process	7	in process						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	in process	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	in process	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	4												4	2
Estonia	16	2	0	3	2	4	0	4	2	in process			5	4
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	7			3	3								4	4
Iceland	6					2	2	0					4	4
Ireland	13			1	1	4	1	2	3	0			5	5
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						4	in process	10	10
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	in process
Bulgaria	21			13	12								8	7
Cyprus	18	1	0	1	1	1	0	1	4	0			11	11
Estonia	1												1	in process
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
Iceland	3			1	1								2	2
Italy	18			8	8	2	1	1					8	in process
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						1	in process	5	in process
Bulgaria	5			3	3						2	2		
Estonia	17	2	0	5	5	9	0	9	1	in process				
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
Iceland	6			1	1	2	1	1					3	3
Italy	8			5	5	1	0	1					2	2
Lithuania	13			7	in process	2	in process		1	0	2	in process	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	in process	2	1	28	12	16					14	13
Sweden	2												2	2
United Kingdom	9			2	2	2	1	0	1	0			4	4
APRIL														
Estonia	10	1	0	2	2	5	0	5	2	in process				
Finland	2					2	0	2						
France	12					7	4	3					5	5
Germany	3			1	1	1	1	0					1	1
Iceland	8			4	4	2	0	2					2	2
Lithuania	4			1	0	2	0	2					1	0
Norway	21			6	6	9	4	4			2	1	4	2
Spain	3					2	1	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
Lithuania	1	1	in process											
United Kingdom	3			1	0	1	0	0	1	0				
29 Countries	1530	25	0	366	301	438	93	259	78	0	88	61	535	403
				23.9%		28.6%					5.8%		35.0%	
		54.2%							45.8%					

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 2018-08-02

Influenza A(H1N1)pdm09 virus analyses

Results of haemagglutination inhibition (HI) analyses of viruses performed since the June 2018 report are shown in Tables 3-1 to 3-3. All 78 of the 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. Generally, the test viruses showed good reactivity with the other 10 antisera in the panel with 73 to 78 viruses being recognised by individual antisera at titres within fourfold of the respective homologous titres, and 67 to 78 within twofold.

All 78 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 3-1. 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	A/Cal 7/09	A/Bayern 69/09	A/Lviv N6/09	A/Astrak 1/11	A/St. P 27/11	A/HK 5659/12	A/Sth Afr 3626/13	A/Slov 2903/2015	A/Israel Q-504/15	A/Paris 1447/17
		Passage history			Egg	Egg	MDCK	MDCK	MDCK	Egg	MDCK	Egg	Egg	MDCK	MDCK
		Ferret number			NIB F42/16*1	F06/16*1	F09/15*1	F14/13*1	F22/13*1	F26/14*1	F30/12*1	F13/16*1	F02/16*1	F08/16*1	F03/18*2
		Genetic group			6B.1				5	6	6A	6B	6B.1	6B.2	6B.1
REFERENCE VIRUSES															
A/Michigan/45/2015		6B.1	2015-09-07	3E3/E3	1280	1280	640	640	1280	640	1280	1280	2560	1280	2560
A/California/7/2009	clone38-32		2009-04-09	E3/E3	640	1280	640	640	1280	320	1280	1280	1280	1280	2560
A/Bayern/69/2009	G155E		2009-07-01	MDCK5/MDCK1	40	40	320	320	80	40	40	80	80	40	160
A/Lviv/N6/2009	G155E, D222G		2009-10-27	MDCK4/SIAT1/MDCK2	80	160	1280	640	80	80	160	160	160	80	640
A/Astrakhan/1/2011		5	2011-02-28	MDCK1/MDCK7	640	640	640	640	640	320	640	1280	1280	640	1280
A/St. Petersburg/27/2011		6	2011-02-14	E1/E3	1280	1280	1280	640	1280	640	1280	2560	2560	2560	2560
A/Hong Kong/5659/2012		6A	2012-05-21	MDCK4/MDCK2	640	320	320	160	640	160	640	1280	640	640	1280
A/South Africa/3626/2013		6B	2013-06-06	E1/E3	1280	1280	1280	1280	1280	640	1280	2560	1280	1280	2560
A/Slovenia/2903/2015	clone 37	6B.1	2015-10-26	E4/E2	640	640	320	320	640	320	640	640	1280	1280	1280
A/Israel/Q-504/2015		6B.2	2015-12-15	C1/MDCK2	1280	640	640	320	1280	320	1280	1280	1280	2560	2560
A/Paris/1447/2017		6B.1	2017-10-20	MDCK1/MDCK3	640	640	320	160	640	160	640	640	1280	640	2560
TEST VIRUSES															
A/Halmstad/4/2017		6B.1	2017-11-27	MDCK0/MDCK1	1280	1280	640	320	1280	640	1280	2560	2560	1280	2560
A/Stockholm/58/2017		6B.1	2017-12-28	MDCK0/MDCK1	640	640	320	320	640	320	640	1280	1280	1280	2560
A/Sweden/9/2018		6B.1	2018-01-29	MDCK1/MDCK1	640	640	320	320	640	160	640	1280	1280	1280	2560
A/Centre/960/2018		6B.1	2018-02-05	MDCK1/MDCK1	640	320	160	160	320	160	320	640	640	320	1280
A/Halmstad/1/2018		6B.1	2018-02-10	MDCK0/MDCK1	1280	640	320	320	640	320	640	1280	1280	1280	2560
A/Jonkoping/2/2018		6B.1	2018-02-13	MDCK0/MDCK1	1280	1280	640	640	1280	640	1280	1280	2560	2560	2560
A/Iceland/36/2018		6B.1	2018-02-13	MDCK1/MDCK1	640	40	320	320	320	80	160	320	640	640	1280
A/Haute Normandie/1046/2018		6B.1	2018-02-14	MDCK2/MDCK1	640	640	640	640	1280	640	1280	1280	1280	1280	2560
A/Dijon/1035/2018		6B.1	2018-02-15	MDCK1/MDCK1	640	640	640	320	640	320	640	1280	1280	1280	2560
A/Paris/1321/2018		6B.1	2018-02-19	MDCK2/MDCK1	640	320	320	160	320	160	320	640	640	640	1280
A/Basse Normandie/1216/2018		6B.1	2018-02-23	MDCK1/MDCK1	1280	640	320	320	640	320	640	1280	1280	1280	2560
A/Dijon/1290/2018		6B.1	2018-03-02	MDCK1/MDCK1	640	640	320	320	640	320	640	640	1280	1280	2560
A/Haute Normandie/1274/2018		6B.1	2018-03-02	MDCK1/MDCK1	1280	1280	640	640	1280	640	1280	1280	2560	2560	2560
A/Aragon/1908/2018		6B.1	2018-03-02	SIAT1/MDCK1	2560	1280	640	320	1280	640	1280	2560	2560	2560	5120
A/Alsace/1264/2018		6B.1	2018-03-05	MDCK1/MDCK1	1280	640	640	320	640	320	1280	1280	1280	1280	2560
A/Iceland/51/2018		6B.1	2018-03-06	MDCK1/MDCK1	640	80	320	320	320	160	320	640	640	640	2560
A/Poland/709/2018		6B.1	2018-03-08	MDCK2	1280	1280	640	320	640	640	1280	1280	1280	1280	2560
A/Paris/1479/2018		6B.1	2018-03-17	MDCK2/MDCK1	640	320	160	160	640	160	640	640	640	640	1280
A/Nord Pas de Calais/1473/2018		6B.1	2018-03-19	MDCK1/MDCK1	1280	640	640	320	640	320	1280	1280	1280	1280	2560
A/Iceland/73/2018		6B.1	2018-04-03	MDCK1/MDCK1	1280	640	320	320	640	320	640	1280	1280	1280	2560
A/Iceland/75/2018		6B.1	2018-04-09	MDCK1/MDCK1	640	40	320	160	320	80	160	320	640	640	1280
A/Iceland/77/2018		6B.1	2018-04-12	MDCK1/MDCK1	1280	640	640	320	640	320	640	640	1280	1280	2560
A/Iceland/84/2018		6B.1	2018-04-30	MDCK1/MDCK1	640	640	320	160	640	160	640	640	1280	640	2560
A/Iceland/85/2018		6B.1	2018-05-02	MDCK1/MDCK1	640	80	320	320	320	160	320	640	640	640	1280

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

1 < = <40; 2 < = <80

Vaccine

Sequences in phylogenetic trees

Table 3-2. 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]	A/Cal 7/09 Egg F06/16[*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]	A/St. P 27/11 Egg F26/14[*1]	A/HK 5659/12 MDCK F30/12[*1]	A/Sth Afr 3626/13 Egg F13/16[*1]	A/Slov 2903/2015 Egg F02/16[*1]	A/Israel Q-504/15 MDCK F08/16[*1]	A/Paris 1447/17 MDCK F03/18[*2]	NEW A/Slo 2794/17 Egg F19/18[*1]	NEW A/Swit 2656/17 Egg F20/18[*1]	NEW A/Swit 3330/17 Egg F23/18[*1]	NEW A/HK 4989/17 Egg F24/18[*1]
		Genetic group			6B.1				5	6	6A	6B	6B.1	6B.2	6B.1	6B.1	6B.1	6B.1	6B.1
REFERENCE VIRUSES																			
A/Michigan/45/2015		6B.1	2015-09-07	3E3/E3	640	640	320	320	640	320	1280	640	1280	1280	1280	1280	1280	640	640
A/California/7/2009	clone 38-32		2009-04-09	E3/E3	320	640	320	320	640	160	640	640	640	640	1280	1280	1280	640	320
A/Bayern/69/2009	G155E		2009-07-01	MDCK5/MDCK1	40	40	320	160	40	40	40	80	40	40	160	80	160	80	80
A/Lviv/N6/2009	G155E, D222G		2009-10-27	MDCK4/SIAT1/MDCK2	40	80	640	640	80	40	80	160	160	80	320	160	320	160	320
A/Astrakhan/1/2011		5	2011-02-28	MDCK1/MDCK7	640	640	640	320	1280	320	640	1280	1280	640	1280	1280	1280	640	640
A/St. Petersburg/27/2011		6	2011-02-14	E1/E3	640	640	640	320	640	320	640	1280	1280	1280	1280	1280	1280	640	640
A/Hong Kong/5659/2012		6A	2012-05-21	MDCK4/MDCK2	320	320	160	80	320	160	320	640	640	320	640	1280	640	320	320
A/South Africa/3626/2013		6B	2013-06-06	E1/E3	320	320	320	320	320	160	320	640	320	320	640	640	640	320	320
A/Slovenia/2903/2015	clone 37	6B.1	2015-10-26	E4/E2	320	320	160	160	320	160	640	640	640	640	1280	1280	1280	640	320
A/Israel/Q-504/2015		6B.2	2015-12-15	C1/MDCK2	1280	1280	640	320	640	320	1280	1280	1280	2560	2560	2560	2560	1280	640
A/Paris/1447/2017		6B.1	2017-10-20	MDCK1/MDCK3	640	640	320	160	640	160	640	1280	1280	1280	2560	2560	2560	640	640
A/Slovenia/2794/2017		6B.1	2017-12-29	E5(AL5)	640	640	320	320	640	320	1280	1280	1280	1280	2560	2560	2560	1280	640
A/Switzerland/2656/2017		6B.1	2017-12-21	E5(AL5)	1280	1280	1280	1280	2560	640	2560	2560	2560	2560	5120	5120	5120	2560	1280
A/Switzerland/3330/2017		6B.1	2017-12-20	E6(AL6)	640	640	320	320	640	160	640	640	1280	1280	1280	1280	1280	1280	640
A/Hong Kong/4989/2017		6B.1	2017-12-17	E5(AL5)	640	640	640	320	640	320	640	1280	1280	640	1280	1280	1280	640	640
TEST VIRUSES																			
A/Finland/822/2018		6B.1	2018-01-08	MDCK1/MDCK1	640	640	320	160	640	160	640	640	1280	1280	2560	2560	2560	1280	640
A/Lisboa/6/2018		6B.1	2018-01-11	SIAT1/MDCK1	1280	1280	640	320	1280	320	640	1280	2560	1280	2560	2560	2560	1280	640
A/Finland/855/2018		6B.1	2018-01-15	MDCK1/MDCK1	640	320	320	160	640	160	320	640	640	1280	2560	1280	2560	640	640
A/Belgium/S0132/2018		6B.1	2018-01-18	SIATx/MDCK1	320	640	320	160	640	160	640	640	1280	1280	1280	2560	1280	640	640
A/Belgium/S0131/2018		6B.1	2018-01-18	SIATx/MDCK1	640	640	320	320	640	320	640	640	1280	1280	1280	2560	1280	640	640
A/Belgium/G0107/2018		6B.1	2018-01-22	SIATx/MDCK1	640	640	320	320	640	320	640	1280	1280	1280	2560	2560	2560	1280	640
A/Finland/870/2018		6B.1	2018-01-27	MDCK1/MDCK1	640	640	320	160	640	320	640	640	1280	1280	2560	2560	2560	1280	640
A/Belgium/G0171/2018		6B.1	2018-01-29	SIATx/MDCK1	640	640	320	320	640	320	640	1280	1280	1280	2560	2560	2560	640	640
A/Belgium/S0359/2018		6B.1	2018-01-29	SIATx/MDCK1	320	320	160	160	640	160	640	640	1280	1280	1280	2560	1280	640	320
A/Friuli Venezia Giulia/22/2018		6B.1	2018-02-02	MDCK2/MDCK1	640	640	320	320	640	320	640	640	1280	1280	2560	2560	2560	640	640
A/Lisboa/16/2018		6B.1	2018-02-03	MDCK1/MDCK1	640	640	320	320	640	320	640	640	1280	1280	2560	2560	2560	640	640
A/Belgium/G0218/2018		6B.1	2018-02-05	SIATx/MDCK1	320	320	160	160	640	160	640	640	1280	640	1280	1280	1280	640	320
A/Belgium/S0556/2018		6B.1	2018-02-06	SIATx/MDCK1	640	640	320	160	640	160	640	1280	1280	1280	2560	1280	1280	640	320
A/Lisboa/niEVA244-17-18/2018		6B.1	2018-02-08	MDCK1/MDCK1	640	640	320	160	640	160	640	640	1280	1280	2560	1280	1280	640	640
A/Belgium/G0238/2018		6B.1	2018-02-08	SIATx/MDCK1	640	640	320	320	640	320	640	1280	1280	1280	2560	2560	2560	1280	640
A/Belgium/G0251/2018		6B.1	2018-02-09	SIATx/MDCK1	640	640	320	320	640	320	640	1280	1280	1280	2560	2560	2560	1280	640
A/Sassari/08/2018		6B.1	2018-02-12	MDCK2/MDCK1	640	640	320	160	640	160	640	640	1280	640	1280	1280	1280	640	640
A/Milano/125/2018		6B.1	2018-02-12	MDCK3/MDCK1	640	320	320	320	640	160	640	640	1280	1280	1280	1280	1280	640	640
A/Perugia/30/2018		6B.1	2018-02-12	MDCK3/MDCK1	640	160	320	320	640	160	320	640	640	640	1280	1280	1280	640	640
A/Belgium/S0789/2018		6B.1	2018-02-12	MDCKx/MDCK1	1280	640	640	320	640	320	1280	1280	1280	1280	2560	2560	2560	1280	640
A/Lisboa/niGG22-17-18/2018		6B.1	2018-02-14	MDCK1/MDCK1	1280	640	640	320	1280	320	640	1280	2560	1280	2560	2560	2560	1280	640
A/Belgium/S1450/2018		6B.1	2018-02-16	SIATx/MDCK1	640	320	320	160	640	160	640	640	1280	1280	2560	2560	1280	640	640
A/Belgium/S0874/2018		6B.1	2018-02-17	MDCKx/MDCK1	1280	1280	640	320	1280	320	1280	1280	2560	1280	2560	2560	2560	1280	1280
A/Parma/134/2018		6B.1	2018-02-19	MDCK2/MDCK1	640	640	320	320	640	320	640	640	1280	1280	2560	2560	2560	1280	640
A/Milano/135/2018		6B.1	2018-02-20	MDCK3/MDCK1	640	160	320	320	320	160	320	320	640	640	1280	1280	1280	640	320
A/Parma/150/2018		6B.1	2018-02-23	MDCK2/MDCK1	1280	160	640	320	640	160	640	640	1280	1280	2560	1280	2560	640	640
A/Friuli Venezia Giulia/33/2018		6B.1	2018-02-26	MDCK2/MDCK1	640	320	320	160	640	160	640	640	1280	640	2560	1280	1280	640	640
A/Lisboa/niEVA301-17-18/2018		6B.1	2018-02-27	MDCK1/MDCK1	1280	1280	640	320	1280	320	1280	1280	2560	1280	2560	5120	2560	1280	1280
A/Lisboa/niEVA279-17-18/2018		6B.1	2018-02-28	SIAT1/MDCK1	640	640	320	160	640	160	640	640	1280	1280	1280	2560	1280	640	320
A/Lisboa/niSU508-17-18/2018		6B.1	2018-03-01	MDCK1/MDCK1	640	640	320	320	640	160	640	1280	1280	1280	2560	2560	2560	640	320
A/Lisboa/niSU523-17-18/2018		6B.1	2018-03-06	MDCK1/MDCK1	640	640	320	160	640	320	640	640	1280	1280	2560	2560	1280	640	640
A/Lisboa/niEVA304-17-18/2018		6B.1	2018-03-06	SIAT2/MDCK1	1280	640	320	320	640	160	640	1280	1280	1280	2560	2560	2560	1280	640
A/Milano/161/2018		6B.1	2018-03-07	MDCK3/MDCK1	640	640	320	320	640	320	640	1280	1280	1280	2560	2560	2560	640	640
A/Perugia/36/2018		6B.1	2018-03-08	MDCK3/MDCK1	640	80	320	160	320	160	320	320	640	640	1280	1280	1280	640	320
A/Belgium/S1531/2018		6B.1	2018-03-08	SIATx/MDCK1	1280	640	640	320	1280	320	1280	1280	2560	1280	2560	2560	2560	1280	640
A/Lisboa/niSU532-17-18/2018		6B.1	2018-03-10	SIAT1/MDCK1	640	640	320	160	640	160	640	640	640	640	1280	1280	1280	640	320
A/Sassari/11/2018		6B.1	2018-03-13	MDCK2/MDCK1	640	320	320	320	640	160	320	640	1280	640	1280	1280	1280	640	640
A/Friuli Venezia Giulia/46/2018		6B.1	2018-03-17	MDCK2/MDCK1	1280	1280	640	640	1280	320	1280	1280	2560	1280	5120	2560	2560	1280	1280
A/Lisboa/niGG30-17-18/2018		6B.1	2018-03-19	MDCK1/MDCK1	640	640	320	160	640	320	640	1280	1280	640	2560	2560	2560	640	640
A/Parma/170/2018		6B.1	2018-03-26	MDCK2/MDCK1	640	640	320	160	640	160	640	640	1280	1280	1280	1280	2560	640	640
A/Estonia/113499/2018		6B.1	2018-03-28	SIAT1/MDCK1	320	320	160	80	320	80	320	320	640	640	1280	1280	1280	320	320
A/Estonia/113532/2018		6B.1	2018-04-02	SIAT1/MDCK1	640	640	320	320	640	320	640	1280	1280	1280	2560	2560	2560	1280	640
A/Estonia/113580/2018		6B.1	2018-04-03	SIAT1/MDCK1	640	640	320	320	640	320	640	1280	1280	1280	1280	2560	1280	640	640

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

1 < = <40; 2 < = <80

Sequences in phylogenetic trees

Vaccine

Table 3-3. 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	A/Cal 7/09 Egg F06/16*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	A/St. P 27/11 Egg F26/14*1	A/HK 5659/12 MDCK F30/12*1	A/Sth Afr 3626/13 Egg F13/16*1	A/Slov 2903/2015 Egg F02/16*1	A/Israel Q-504/15 MDCK F08/16*1	A/Paris 1447/17 MDCK F03/18*2
		Genetic group			6B.1				5	6	6A	6B	6B.1	6B.2	6B.1
REFERENCE VIRUSES															
A/Michigan/45/2015		6B.1	2015-09-07	3E3/E3	640	1280	640	320	640	320	1280	1280	1280	1280	2560
A/California/7/2009	clone 38-32		2009-04-09	E3/E3	640	640	320	320	640	320	640	640	1280	640	1280
A/Bayern/69/2009	G155E		2009-07-01	MDCK5/MDCK1	40	40	320	320	40	40	40	160	80	40	160
A/Lviv/N6/2009	G155E, D222G		2009-10-27	MDCK4/SIAT1/MDCK2	80	160	640	640	80	80	160	160	160	80	640
A/Astrakhan/1/2011		5	2011-02-28	MDCK1/MDCK7	640	1280	1280	640	1280	640	1280	1280	1280	1280	2560
A/St. Petersburg/27/2011		6	2011-02-14	E1/E3	640	640	640	640	640	320	640	1280	1280	640	2560
A/Hong Kong/5659/2012		6A	2012-05-21	MDCK4/MDCK2	320	320	320	160	640	160	640	640	640	640	1280
A/South Africa/3626/2013		6B	2013-06-06	E1/E3	320	320	320	320	320	160	320	640	320	320	640
A/Slovenia/2903/2015	clone 37	6B.1	2015-10-26	E4/E2	640	640	320	320	640	320	640	640	1280	640	2560
A/Israel/Q-504/2015		6B.2	2015-12-15	C1/MDCK2	640	640	320	320	640	320	1280	1280	1280	1280	2560
A/Paris/1447/2017		6B.1	2017-10-20	MDCK1/MDCK3	640	640	320	160	640	320	640	1280	1280	640	2560
TEST VIRUSES															
A/Estonia/112776/2018		6B.1	2018-03-02	SIAT1/MDCK1	640	640	640	320	640	160	640	1280	1280	1280	2560
A/Estonia/113109/2018		6B.1	2018-03-12	SIAT1/MDCK1	640	640	320	160	640	160	640	640	1280	640	2560
A/Lithuania/MB8114/2018		6B.1	2018-03-12	MDCK1/MDCK1	1280	640	640	320	1280	320	640	2560	2560	1280	2560
A/Lithuania/MB8277/2018		6B.1	2018-03-12	MDCK1/MDCK1	1280	1280	640	320	1280	320	1280	2560	2560	2560	5120
A/Lithuania/MB8293/2018		6B.1	2018-03-12	MDCK2/MDCK1	1280	640	320	160	640	160	640	1280	1280	640	2560
A/Lithuania/MB8636/2018		6B.1	2018-03-12	MDCK2/MDCK1	1280	1280	640	320	1280	640	1280	2560	2560	2560	5120
A/Estonia/113112/2018		6B.1	2018-03-14	SIAT1/MDCK1	1280	1280	640	320	1280	320	1280	1280	2560	1280	5120
A/Lithuania/MB8512/2018		6B.1	2018-03-14	MDCK2/MDCK1	2560	1280	640	640	1280	640	1280	2560	2560	2560	5120
A/Lithuania/MB8638/2018		6B.1	2018-03-14	MDCK1/MDCK1	1280	640	320	320	640	320	640	1280	1280	1280	2560
A/Estonia/113103/2018		6B.1	2018-03-15	SIAT1/MDCK1	640	640	320	160	640	160	640	640	1280	640	1280
A/Lithuania/MB12533/2018		6B.1	2018-04-23	MDCK2/MDCK1	1280	640	320	160	640	320	640	1280	1280	1280	2560

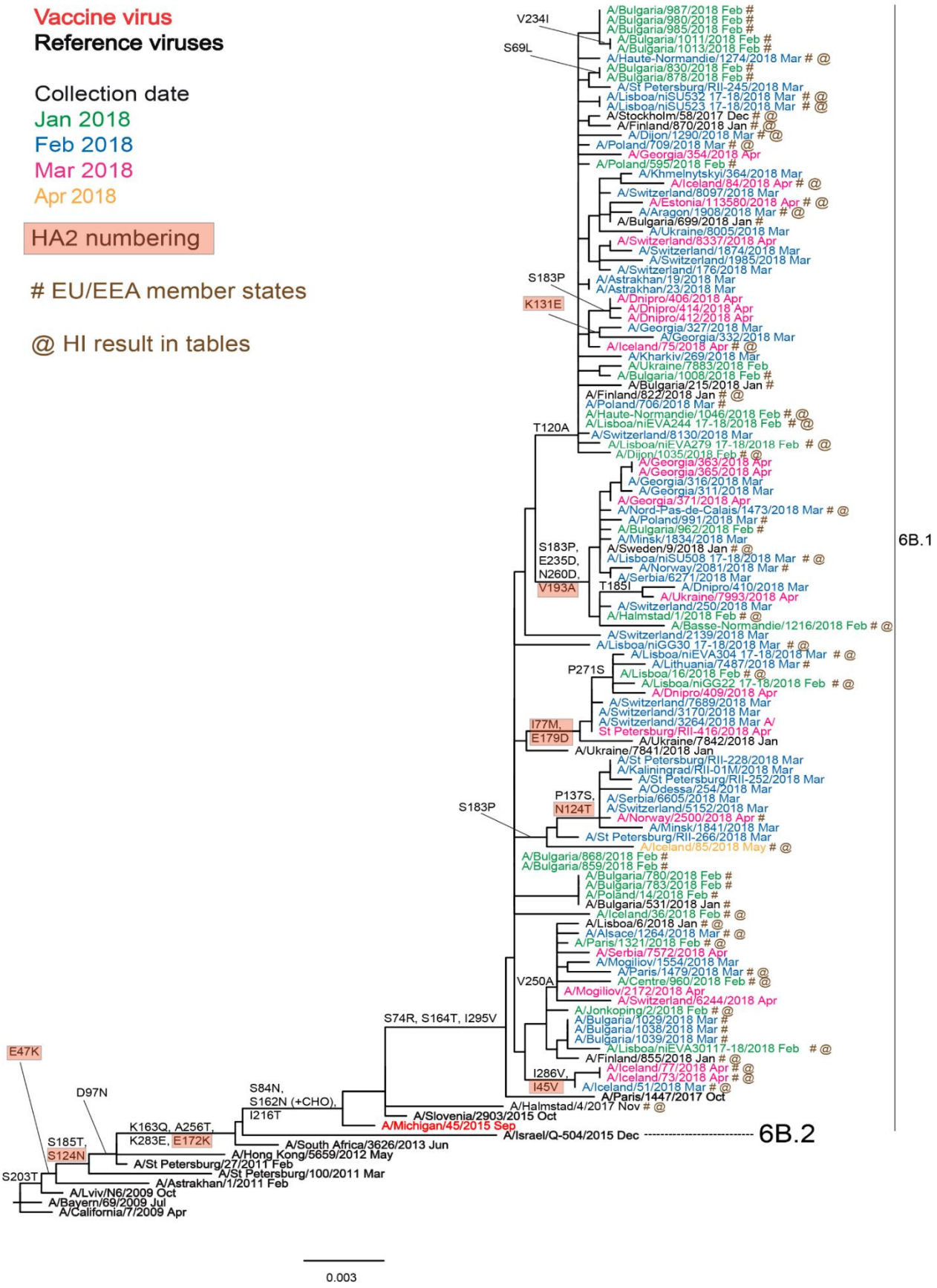
* Superscripts refer to antiserum properties (< relates to the lowest dilution of antiserum used)

1 < = <40; 2 < = <80

Vaccine

Sequences in phylogenetic trees

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.

A number of the 438 A(H3N2) virus specimens with collection dates after week 40/2017, 31 of which were lysed specimens, are in process for antigenic and genetic characterisation (Table 2). However, of those successfully isolated to date (n = 352), as shown by positive neuraminidase activity, only 93 (26%) had sufficient HA activity in the presence of 20nM oseltamivir to allow antigenic analysis by HI assay. Since the June 2018 report, only 12 viruses recovered, based on positive neuraminidase activity, retained sufficient HA activity to allow antigenic analysis by HI and the HAs fell in subclades (see below for definitions) 3C.2a1b (n = 5) and 3C.2a2 (n = 7) (Tables 4-1). None of the tested viruses were recognised well by the antiserum raised against the currently used vaccine virus, egg-propagated A/Hong Kong/4801/2014. However, the antiserum raised against cell-culture-propagated A/Hong Kong/5738/2014, a virus closely related genetically to A/Hong Kong/4801/2014, recognised all test viruses at titres within fourfold of the homologous titre of the antiserum, nine (75%) within twofold. An antiserum raised against egg-propagated A/Singapore/INFIMH-16-0019/2016, recommended for use in vaccines for the southern hemisphere 2018 and northern hemisphere 2018–19, recognised all 12 test viruses poorly at titres reduced at least eightfold compared to the titre of the antiserum for the homologous virus.

An antiserum raised against A/Bretagne/1413/2017, a 3C.2a2 subclade virus, recognised four of seven subclade 3C.2a2 test viruses at titres within fourfold (one within twofold) of the homologous titre of the antiserum. The 3C.2a1b subclade viruses were recognised poorly. The three poorly recognised 3C.2a2 subclade viruses, A/Madrid/2175/2018, A/Madrid/2173/2018 and A/Lisboa/18/2018, all carried additional HA1 amino acid substitutions of S21P, R92K, S144R, K160T (resulting in the N-linked glycosylation motif at residues 158-160 being retained) and F219S, compared to A/Bretagne/1413/2017.

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 tests. All three, A/Oman/2585/2016, A/Norway/4436/2016 and A/Greece/4/2017, had HA genes that fell into genetic subclade 3C.2a1, with A/Greece/4/2017 falling into a genetic subgroup 3C.2a1a (see below). The antisera raised against A/Oman/2585/2016, A/Norway/4436/2016 and A/Greece/4/2017 recognised, respectively, 11, 10 and 12 of the 12 test viruses at titres of at least 160, similar to the titres of the antisera for the majority of the panel of reference viruses.

Antiserum raised against the cell-culture-propagated cultivar of A/Stockholm/6/2014, a clade 3C.3a virus, was also used. This antiserum recognised all 12 test viruses at titres within fourfold of the titre of the antiserum with the homologous virus, 10 (83%) within twofold.

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 subclades and genetic subgroups have been adopted. Amino acid substitutions that define these subclades and 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

[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

- 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 in this subclade, with recent collection dates, 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.

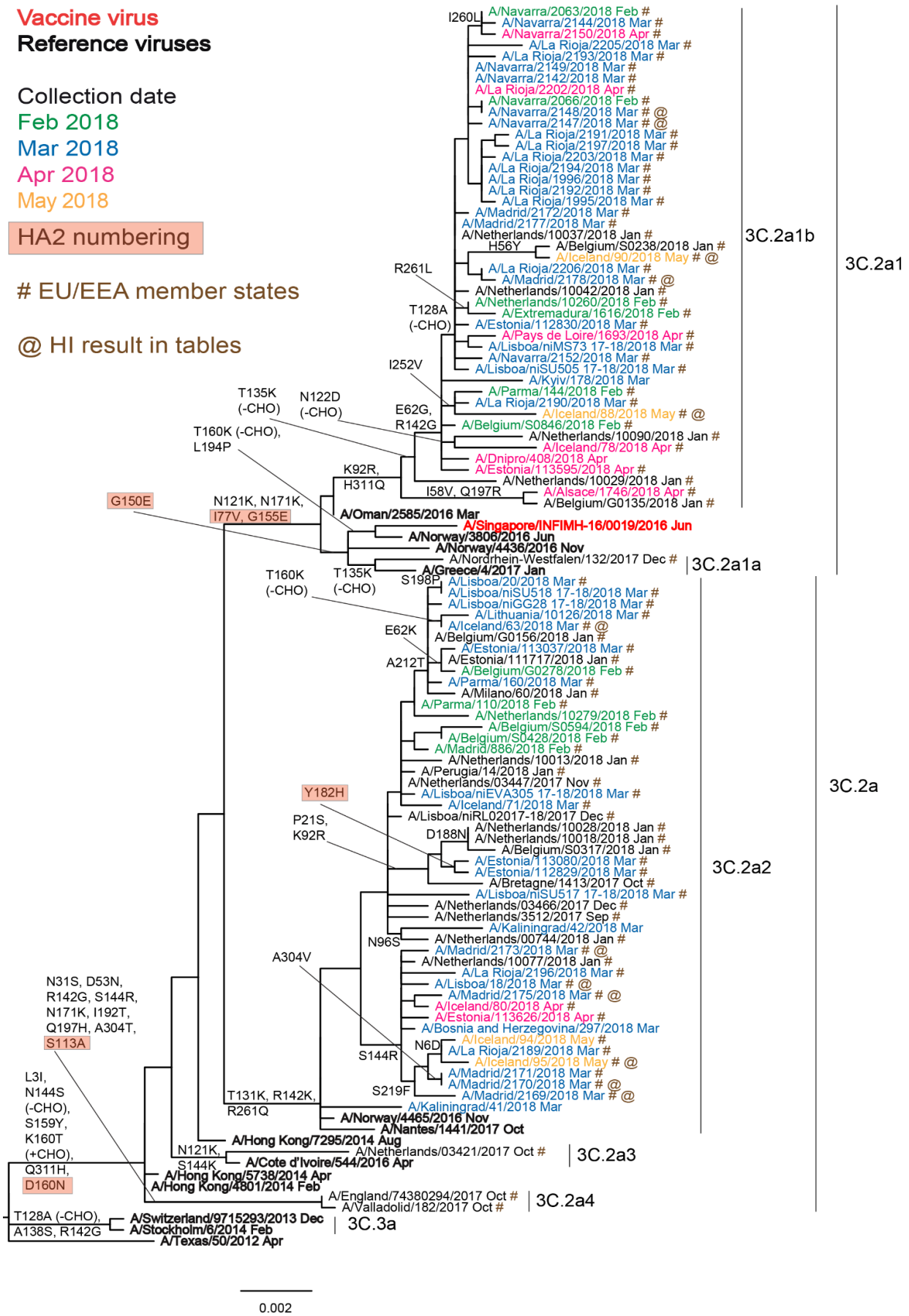
Table 4-1. Antigenic analysis of A(H3N2) viruses by HI

Viruses	Other information		Collection date	Passage history	Haemagglutination inhibition titre: Post-infection ferret antisera							
		Passage history			A/Stock 6/14	A/HK 5738/14	A/HK 4801/14	A/Bretagne 1413/17	A/Oman 2585/16	A/Nor 4436/16	A/Greece 4/17	A/Sing 0019/16
		Ferret number			SIAT F14/14*1	MDCK F30/14*1	Egg F41/15*1	SIAT F01/18*1	SIAT NIB F50/16*1	SIAT F03/17*1	SIAT F27/17*1	Egg 10^{-4} F41/17*1
		Genetic group			3C.3a	3C.2a	3C.2a	3C.2a2	3C.2a1	3C.2a1	3C.2a1a	3C.2a1
REFERENCE VIRUSES												
A/Stockholm/6/2014		3C.3a	2014-02-06	SIAT1/SIAT2	320	160	160	160	320	320	320	160
A/Hong Kong/5738/2014		3C.2a	2014-04-30	MDCK1/MDCK2/SIAT3	160	160	160	160	320	320	160	320
A/Hong Kong/4801/2014	isolate 1	3C.2a	2014-02-26	E6/E2	80	320	2560	640	640	320	640	2560
A/Bretagne/1413/2017		3C.2a2	2017-10-09	MDCK1/SIAT4	160	160	320	1280	320	320	320	160
A/Singapore/INFIMH-16-0019/2016		3C.2a1	2016-06-14	E5/E1	40	40	320	80	160	160	160	1280
TEST VIRUSES												
A/Navarra/2148/2018		3C.2a1b	2018-03-05	SIAT1	160	160	40	40	160	160	320	80
A/Madrid/2175/2018		3C.2a2	2018-03-06	SIAT1	160	160	160	160	160	320	320	80
A/Navarra/2147/2018		3C.2a1b	2018-03-06	SIAT1	160	80	40	40	160	160	320	80
A/Madrid/2178/2018		3C.2a1b	2018-03-08	SIAT1	160	160	80	40	160	160	320	80
A/Madrid/2173/2018		3C.2a2	2018-03-12	SIAT1	320	160	160	160	320	320	320	160
A/Madrid/2170/2018		3C.2a2	2018-03-12	SIAT1	320	320	160	320	320	320	320	160
A/Madrid/2169/2018		3C.2a2	2018-03-15	SIAT1	320	160	160	320	320	320	320	160
A/Lisboa/18/2018		3C.2a2	2018-03-19	SIAT1/SIAT1	160	40	40	80	160	160	160	80
A/Iceland/63/2018		3C.2a2	2018-03-20	MDCK1/SIAT1	160	80	160	640	160	320	160	160
A/Iceland/88/2018		3C.2a1b	2018-05-09	MDCK1/SIAT1	80	40	80	40	80	80	160	160
A/Iceland/90/2018		3C.2a1b	2018-05-13	MDCK1/SIAT1	80	40	40	40	160	80	160	40
A/Iceland/95/2018		3C.2a2	2018-05-20	MDCK1/SIAT1	160	80	160	320	160	160	160	160
							Vaccine NH 2017-18					Vaccine SH 2018 NH 2018-19

* 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

A total of 701 influenza type B-positive specimens with collection dates after August 2017 have been received, with 623 being ascribed to a lineage: 88 B/Victoria-lineage and 535 B/Yamagata-lineage (Table 2).

Influenza B – Victoria lineage

Twenty-four tissue-culture-propagated test viruses have been antigenically characterised by HI assay since the June 2018 report (Tables 5-1 and 5-2). 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, with only the antiserum raised against B/Malta/636714/2011 recognising two test viruses at titres within fourfold of the homologous titre. 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 eighteen test viruses at titres within twofold of those with the homologous viruses while the other six viruses were poorly recognised. 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), recognised 6, 6 and 5 viruses, respectively, none of which had 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 vaccines: it recognised only two test viruses within twofold and 15 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. Previously, we also reported that they were also antigenically distinct from those with a deletion of three amino acids in HA1 [4].

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); they also fall 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. A major group seen in Europe, the Americas, Asia and Oceania have HA genes encoding an HA with deletion of residues 162 and 163 of HA1 (1A(Δ2) in Figure 3). These viruses have additional substitutions **D129G, I180V** in **HA1** and **R151K** in **HA2**. Eighteen of the recently characterised test viruses carry the **HA1** double deletion (1A(Δ2) in Tables 5-1, 5-2 and Figure 3). Less common are viruses with HA genes encoding a deletion of three amino acids K162, N163 and D164 (1A(Δ3)) which have been detected primarily in the Far East, many of which share the substitutions I180T and K209N in HA1, though other viruses with similar deletions have been detected elsewhere.

Influenza B – Yamagata lineage

HI results for 68 B/Yamagata-lineage test viruses analysed since the June 2018 report are shown in Tables 6-1 to 6-3. The 405 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 seasons and trivalent vaccines for the southern hemisphere 2018 season [2], recognised 67 test viruses at titres within fourfold of the titre of the antiserum with the homologous virus and 66 (97%) within twofold. An antiserum raised against the cell-culture-propagated cultivar of B/Phuket/3073/2013 similarly recognised all test viruses at titres within fourfold of the homologous titre of the antiserum and 66 (97%) within twofold. 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 63 (93%) test viruses, respectively, at titres within fourfold of the homologous titres, with 66 (97%) and 36 (53%) being recognised within twofold. An antiserum raised against a recently circulating clade 3 cell-culture-propagated virus, B/Mauritius/1791/2017, recognised 67 test viruses at titres within fourfold of the homologous titre and 66 within twofold.

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 39 (57%), 63 (93%) and 33 (49%) test viruses, respectively, were recognised at titres within fourfold of the titres of the antisera with their homologous viruses.

The 67 genetically characterised test viruses all carried HA genes in genetic clade 3 (Tables 6-1 to 6-3). 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 D232N [introducing a potential N-linked glycosylation site]), is occurring but with no obvious antigenic effects (Tables 6-1 to 6-3).

Table 5-1. Antigenic analysis of influenza B/Victoria-lineage viruses by HI

Viruses	Other information		Collection date	Passage history	Haemagglutination inhibition titre									
					Post-infection ferret antisera									
		Passage history			B/Bris 60/08 Egg	B/Bris 60/08 Egg	B/Malta 636714/11 Egg	B/Sth Aus 81/12 Egg	B/HK 514/09 MDCK	B/Ireland 3154/16 MDCK	B/Nord-West 1/16 MDCK	B/Nor 2409/17 MDCK	B/Colorado 06/17 MDCK	B/Colorado 06/17 Egg
		Ferret number			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]
		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	320	320	320	160	40	40	<	20	80
B/Malta/636714/2011		1A	2011-03-07	E4/E1	2560	320	320	320	160	40	40	<	40	80
B/South Australia/81/2012		1A	2012-11-28	E4/E2	2560	640	320	640	160	40	40	<	40	80
B/Hong Kong/514/2009		1B	2009-10-11	MDCK1/MDCK2	2560	80	160	40	160	80	80	<	20	<
B/Ireland/3154/2016		1A	2016-01-14	MDCK1/MDCK4	2560	20	40	20	40	80	40	<	10	<
B/Nordrhein-Westfalen/1/2016		1A	2016-01-04	C2/MDCK2	1280	10	40	10	20	40	80	<	<	<
B/Norway/2409/2017		1A(Δ2)	2017-04-27	MDCK1/MDCK2	40	<	<	<	<	10	<	40	80	40
B/Colorado/06/2017		1A(Δ2)	2017-02-05	MDCK1/MDCK2	40	<	<	<	<	10	<	40	80	40
B/Colorado/06/2017		1A(Δ2)	2017-02-05	E5/E1	1280	80	80	40	10	<	<	40	160	160
TEST VIRUSES														
B/Norway/347-2/2018		1A(Δ2)	2018-01-14	MDCK2	160	<	10	20	<	20	10	80	160	80
B/Norway/416/2018		1A	2018-01-16	MDCK1	2560	20	40	20	40	80	40	<	<	<
B/Norway/1205/2018		1A	2018-02-13	MDCK1	2560	40	80	40	80	160	40	<	10	<
B/Paris/986/2018		1A(Δ2)	2018-02-19	MDCK1/MDCK1	80	<	10	10	<	20	<	40	160	40
B/Norway/1540/2018		1A	2018-02-21	MDCK2	2560	40	80	20	80	80	80	<	10	<
B/La Rioja/2182/2018		1A(Δ2)	2018-03-08	SIAT1/MDCK2	160	<	10	10	<	20	<	40	160	20
B/Norway/2020/2018		1A(Δ2)	2018-03-09	MDCK1	80	<	10	10	<	10	10	40	80	40
B/Madrid/2180/2018		1A(Δ2)	2018-03-09	MDCK1	80	<	10	10	<	20	<	40	160	40
B/Madrid/2179/2018		1A(Δ2)	2018-03-12	MDCK1	80	<	10	10	<	10	<	40	160	40
B/Lyon/1492/2018		1A(Δ2)	2018-03-30	MDCK2/MDCK1	80	<	10	10	<	10	<	40	160	40
B/Norway/2513/2018		1A(Δ2)	2018-04-06	MDCK1	160	<	10	10	<	10	10	40	160	80
						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

Table 5-2. Antigenic analysis of influenza B/Victoria-lineage viruses by HI

Viruses	Other information	Collection date	Passage history	Haemagglutination inhibition titre: Post-infection ferret antisera										
				B/Bris 60/08 Egg	B/Bris 60/08 Egg	B/Malta 636714/11 Egg	B/Sth Aus 81/12 Egg	B/HK 514/09 MDCK	B/Ireland 3154/16 MDCK	B/Nord-West 1/16 MDCK	B/Nor 2409/17 MDCK	B/Colorado 06/17 MDCK	B/Colorado 06/17 Egg
	Passage history			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]
	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	320	640	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	320	320	640	320	40	40	<	40	80
B/Hong Kong/514/2009	1B	2009-10-11	MDCK1/MDCK2	2560	40	160	80	160	80	80	<	10	<
B/Ireland/3154/2016	1A	2016-01-14	MDCK1/MDCK4	2560	10	80	40	80	160	160	<	<	<
B/Nordrhein-Westfalen/1/2016	1A	2016-01-04	C2/MDCK2	2560	10	40	40	40	80	80	<	<	<
B/Norway/2409/2017	1A(Δ2)	2017-04-27	MDCK1/MDCK2	80	<	<	<	<	<	20	40	160	40
B/Colorado/06/2017	1A(Δ2)	2017-02-05	MDCK1/MDCK2	80	<	<	<	<	<	10	40	160	40
B/Colorado/06/2017	1A(Δ2)	2017-02-05	E5/E1	640	40	80	80	20	<	<	20	160	160
TEST VIRUSES													
B/Lisboa/miSU094-17-18/2017	1A	2017-12-19	SIAT1/MDCK1	2560	<	<	40	80	80	160	<	<	<
B/Lisboa/miSU099-17-18/2017	1A	2017-12-20	SIAT1/MDCK1	2560	10	80	40	80	160	160	<	<	<
B/Finland/815/2018	1A	2018-01-03	MDCK1/MDCK1	2560	40	40	80	80	80	80	<	<	<
B/Finland/840/2018	1A(Δ2)	2018-01-09	MDCK1/MDCK1	160	<	10	20	<	10	<	80	160	40
B/Perugia/16/2018	1A(Δ2)	2018-01-15	MDCK3/MDCK1	160	<	<	<	<	<	10	40	160	40
B/Finland/843/2018	1A(Δ2)	2018-01-17	MDCK1/MDCK1	160	<	10	10	<	10	<	40	160	40
B/Milano/105/2018	1A(Δ2)	2018-01-23	MDCK3/MDCK1	160	<	<	<	<	<	<	40	80	20
B/Finland/856/2018	1A(Δ2)	2018-01-24	MDCK1/MDCK1	160	<	10	20	<	10	<	40	80	40
B/Belgium/G0144/2018	1A(Δ2)	2018-01-24	MDCKx/MDCK1	80	<	<	<	<	<	10	40	80	40
B/Belgium/S0540/2018	1A(Δ2)	2018-01-30	MDCKx/MDCK1	80	<	<	<	<	<	10	40	80	40
B/Belgium/G0188/2018	1A(Δ2)	2018-01-31	MDCKx/MDCK1	160	<	<	<	<	<	10	40	160	40
B/Lisboa/miSU460-17-18/2018	1A(Δ2)	2018-02-12	SIAT1/MDCK1	80	<	<	<	<	<	10	40	80	20
B/Lisboa/miSU519-17-18/2018	1A(Δ2)	2018-03-05	SIAT1/MDCK1	80	<	<	<	<	<	10	20	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

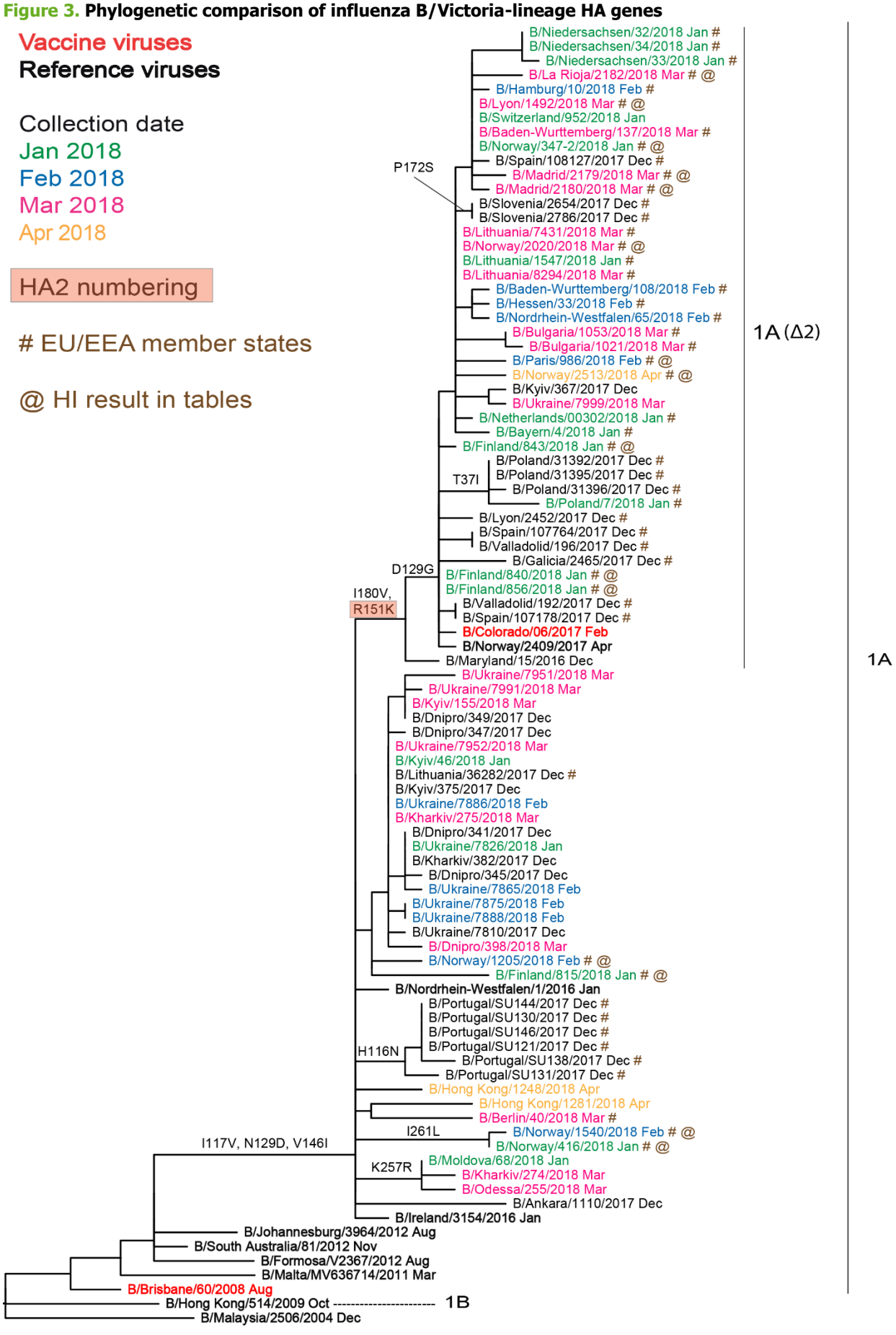


Table 6-1. Antigenic analysis of influenza B/Yamagata-lineage viruses by HI

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	40	40
B/Massachusetts/02/2012		2	2012-03-13	MDCK1/C2/MDCK3	640	320	80	640	160	80	80	160	40
B/Massachusetts/02/2012		2	2012-03-13	E3/E3	640	160	10	640	80	160	40	80	10
B/Wisconsin/1/2010		3	2010-02-20	E3/E2	1280	80	20	320	160	160	80	320	80
B/Stockholm/12/2011		3	2011-03-28	E4/E1	1280	40	10	320	80	160	40	80	40
B/Phuket/3073/2013		3	2013-11-21	MDCK2/MDCK2	2560	320	80	320	320	160	320	160	320
B/Phuket/3073/2013		3	2013-11-21	E4/E3	1280	40	<	160	80	80	40	80	40
B/Mauritius/1791/2017		3	2017-09-20	MDCK1/MDCK4	1280	80	20	160	80	80	80	80	160
TEST VIRUSES													
B/Linkoping/2/2018		3	2018-01-06	MDCK0/MDCK1	2560	160	40	160	160	80	160	160	160
B/Paris/912/2018		3	2018-02-09	MDCK1/MDCK1	2560	160	20	80	80	80	80	80	80
B/Trollhattan/1/2018		3	2018-02-18	MDCK1/MDCK1	2560	80	20	80	80	40	80	80	160
B/Paris/988/2018		3	2018-02-19	MDCK1/MDCK1	2560	320	20	160	160	80	160	160	160
B/Pays de Loire/1233/2018		3	2018-02-27	MDCK1/MDCK1	2560	320	40	160	80	80	160	80	160
B/Dijon/1292/2018		3	2018-02-28	MDCK1/MDCK1	2560	160	20	160	80	40	80	80	160
B/Aragon/1910/2018		3	2018-03-01	SIAT1/MDCK1	2560	160	40	160	80	80	160	80	160
B/Extremadura/1834/2018		3	2018-03-01	SIAT1/MDCK1	2560	80	20	80	80	40	80	80	80
B/Aragon/1910/2018		3	2018-03-01	E1/E1	640	10	<	40	40	20	10	20	10
B/Extremadura/1833/2018		3	2018-03-02	SIAT1/MDCK1	2560	160	20	160	80	80	80	80	160
B/Alsace/1276/2018		3	2018-03-05	MDCK1/MDCK1	2560	160	20	160	80	40	80	80	160
B/Navarra/2146/2018		3	2018-03-05	MDCK1	2560	160	20	160	80	40	80	80	160
B/Basse Normandie/1345/2018		3	2018-03-06	MDCK1/MDCK1	2560	160	40	160	80	80	160	80	160
B/Navarra/2145/2018		3	2018-03-06	MDCK1	2560	160	20	160	80	80	160	80	160
B/La Rioja/2181/2018		3	2018-03-07	SIAT1/MDCK1	2560	160	40	160	160	80	160	160	160
B/Poland/15599/2018		3	2018-03-08	MDCK1/MDCK1	2560	320	80	320	320	160	320	320	320
B/Pays de Loire/1355/2018		3	2018-03-08	MDCK1/MDCK1	2560	160	20	160	160	80	160	80	160
B/Poland/15952/2018		3	2018-03-12	MDCK1/MDCK1	2560	320	40	160	160	80	160	160	160
B/Poland/15938/2018		3	2018-03-13	MDCK1/MDCK1	2560	160	<	80	80	40	80	80	80
B/Stockholm/3/2018		3	2018-03-13	MDCK0/MDCK1	2560	320	40	80	160	80	160	80	160
B/La Rioja/2183/2018		3	2018-03-13	SIAT1/MDCK1	2560	160	20	160	80	80	160	160	160
B/Dijon/1517/2018		3	2018-03-14	MDCK1/MDCK1	2560	160	40	160	160	80	80	80	160
B/Navarra/2143/2018		3	2018-03-14	MDCK1	2560	80	20	160	80	40	80	80	160
B/Bretagne/1441/2018		3	2018-03-15	MDCK1/MDCK1	2560	160	40	160	160	80	160	80	160
B/Nord Pas de Calais/1448/2018		3	2018-03-16	MDCK1/MDCK1	2560	160	10	160	160	40	160	80	160
B/Lorraine/1506/2018		3	2018-03-19	MDCK1/MDCK1	2560	160	40	160	160	80	160	80	160
B/Nord Pas de Calais/1492/2018		3	2018-03-19	MDCK1/MDCK1	2560	160	40	160	160	80	160	160	160
B/Alsace/1499/2018		3	2018-03-20	MDCK1/MDCK1	2560	160	40	160	160	80	160	160	320
B/La Rioja/2185/2018		3	2018-03-22	SIAT1/MDCK1	2560	160	20	160	80	40	80	80	160
B/La Rioja/2184/2018		3	2018-03-23	SIAT1/MDCK1	2560	160	20	160	80	40	80	80	160
B/Poland/18971/2018		3	2018-03-26	MDCK1/MDCK1	5120	640	640	320	640	320	640	320	640
B/Jonkoping/1/2018		3	2018-03-26	MDCK0/MDCK1	2560	160	40	80	160	80	160	80	160
B/Navarra/2151/2018		3	2018-04-03	MDCK1	1280	80	10	80	80	40	40	40	40
B/Trollhatttan/2/2018		3	2018-04-12	MDCK1/MDCK1	2560	160	20	160	160	80	160	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	F06/15*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	1280	640	40	160	160	20	80	40	40		
B/Massachusetts/02/2012	2	2012-03-13	MDCK1/C2/MDCK3	1280	320	40	640	320	80	80	160	40		
B/Massachusetts/02/2012	2	2012-03-13	E3/E3	1280	80	10	640	160	160	40	80	10		
B/Wisconsin/1/2010	3	2010-02-20	E3/E2	1280	40	10	320	160	160	80	160	80		
B/Stockholm/12/2011	3	2011-03-28	E4/E1	1280	40	<	160	80	80	40	80	40		
B/Phuket/3073/2013	3	2013-11-21	MDCK2/MDCK2	2560	160	80	320	320	160	320	160	320		
B/Phuket/3073/2013	3	2013-11-21	E4/E3	1280	40	<	160	160	80	40	80	40		
B/Mauritius/1791/2017	3	2017-09-20	MDCK1/MDCK4	2560	80	20	80	160	40	80	80	160		
TEST VIRUSES														
B/Finland/821/2017	3	2017-12-11	MDCK1/MDCK1	2560	160	80	160	160	80	160	160	320		
B/Finland/846/2018	3	2018-01-17	MDCK1/MDCK1	2560	40	20	160	160	40	80	80	160		
B/Finland/926/2018	3	2018-02-19	MDCK1/MDCK1	2560	80	20	160	160	40	160	80	160		
B/Finland/934/2018	3	2018-03-12	MDCK1/MDCK1	2560	40	40	160	320	80	160	160	320		
B/Finland/939/2018	3	2018-03-26	MDCK1/MDCK1	2560	40	20	80	80	40	80	40	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 6-3. 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/15/2018		3	2018-01-17	SIAT1/MDCK1	2560	160	80	160	320	80	160	160	320
B/Lisboa/niGG16-17-18/2018		3	2018-01-30	SIAT1/MDCK1	2560	80	40	160	160	40	80	80	160
B/Lisboa/niMS65-17-18/2018		3	2018-01-31	SIAT1/MDCK1	2560	160	160	160	320	80	320	160	320
B/Lisboa/18/2018		3	2018-01-31	SIAT1/MDCK1	2560	160	160	320	320	80	160	160	320
B/Perugia/25/2018		3	2018-01-31	MDCK3/MDCK1	1280	40	10	40	80	20	40	40	40
B/Lisboa/27/2018		3	2018-02-05	SIAT1/MDCK1	2560	80	80	160	160	80	80	160	160
B/Lisboa/niMS68-17-18/2018		3	2018-02-08	SIAT1/MDCK1	2560	160	80	320	320	80	160	160	160
B/Lisboa/19/2018		3	2018-02-08	MDCK1/MDCK1	1280	80	10	80	80	20	40	40	80
B/Milano/199/2018		3	2018-02-12	MDCK4/MDCK1	1280	40	20	160	80	40	80	80	80
B/Parma/117/2018		3	2018-02-13	MDCK2/MDCK1	2560	80	40	160	160	40	80	80	160
B/Iceland/42/2018			2018-02-15	MDCK1/MDCK1	2560	80	20	160	80	40	40	80	160
B/Parma/119/2018		3	2018-02-17	MDCK2/MDCK1	1280	40	<	40	40	20	40	20	40
B/Iceland/44/2018		3	2018-02-18	MDCK1/MDCK1	5120	160	80	320	320	80	160	160	320
B/Lisboa/niSU481-17-18/2018		3	2018-02-20	SIAT1/MDCK1	2560	160	80	160	160	80	160	160	160
B/Lisboa/25/2018		3	2018-02-23	SIAT1/MDCK1	2560	160	40	160	160	80	160	160	320
B/Sassari/16/2018		3	2018-02-26	MDCK2/MDCK1	1280	80	20	80	80	40	40	40	80
B/Sassari/17/2018		3	2018-02-27	MDCK2/MDCK1	1280	80	40	80	160	40	80	80	80
B/Friuli Venezia Giulia/89/2018		3	2018-02-28	MDCK2/MDCK1	1280	40	20	80	80	40	40	80	80
B/Parma/131/2018		3	2018-03-08	MDCK2/MDCK1	1280	80	20	40	80	20	40	40	80
B/Lisboa/niSU525-17-18/2018		3	2018-03-12	SIAT1/MDCK1	2560	160	160	160	320	80	160	160	160
B/Iceland/61/2018		3	2018-03-14	MDCK1/MDCK1	1280	80	20	160	80	40	80	80	160
B/Parma/132/2018		3	2018-03-19	MDCK2/MDCK1	2560	160	80	160	160	40	160	80	160
B/Iceland/66/2018		3	2018-03-23	MDCK1/MDCK1	1280	40	20	160	80	40	80	80	80
B/Iceland/70/2018		3	2018-03-27	MDCK1/MDCK1	2560	80	20	160	160	40	160	80	160
B/Iceland/76/2018		3	2018-04-10	MDCK1/MDCK1	1280	80	20	160	80	40	80	80	160
B/Iceland/83/2018		3	2018-04-19	MDCK1/MDCK1	2560	80	40	160	160	40	160	160	160
B/Iceland/87/2018		3	2018-05-08	MDCK1/MDCK1	1280	80	20	160	80	40	80	80	80
B/Iceland/93/2018		3	2018-05-16	MDCK1/MDCK1	2560	80	40	160	320	40	160	160	160
B/Iceland/96/2018		3	2018-05-23	MDCK1/MDCK1	1280	80	40	160	160	40	80	80	160
												Vaccine[#]	

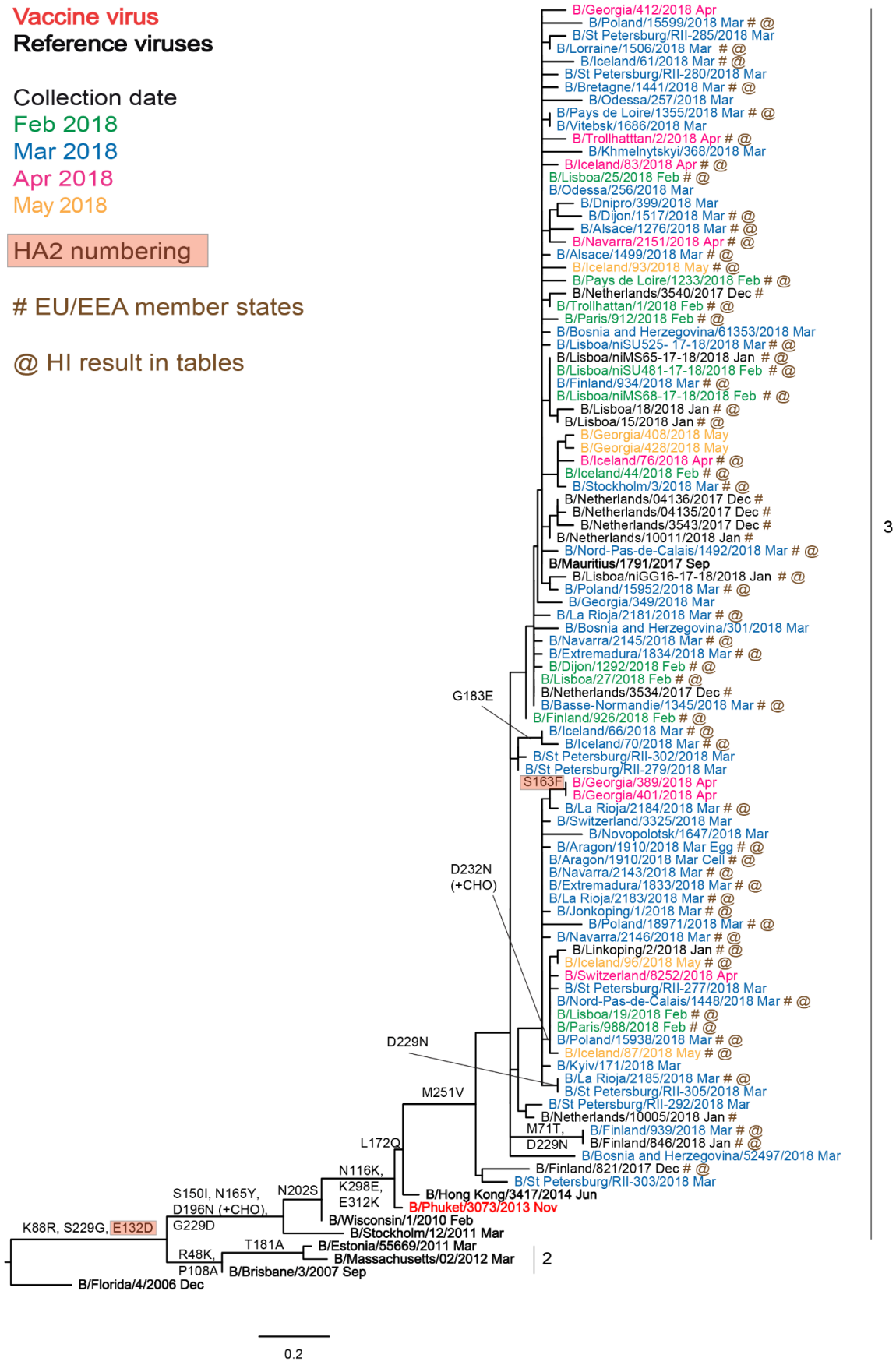
* Superscripts refer to antiserum properties (< relates to the lowest dilution of antiserum used):

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

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—25/2018, 3 869 viruses had been characterised genetically and ascribed to a genetic clade:

- 812 A(H1N1)pdm09 were subclade 6B.1, represented by A/Michigan/45/2015, and two were clade 6B, represented by A/South Africa/3626/2013
- 650 were A(H3N2) clade 3C.2a represented by A/Hong Kong/4801/2014, 448 were subclade 3C.2a1 represented by A/Singapore/INFIMH-16-0019/2016, 11 were clade 3C.3a represented by A/Switzerland/9715293/2013, and nine 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
- 1 782 were B/Yamagata-lineage clade 3 represented by B/Phuket/3073/2013, and one was B/Yamagata-lineage clade 2 represented by B/Massachusetts/02/2012
- A number of viruses (three A(H1N1)pdm09, 35 A(H3N2), one B/Victoria lineage, 20 B/Yamagata lineage) were not ascribed to genetic clades listed in reporting categories for the 2017–18 season; reporting countries have been contacted for clarification.

Antiviral susceptibility

The WIC conducted phenotypic testing for susceptibility to oseltamivir and zanamivir on 1 109 viruses, with collection dates from week 40/2017: 309 A(H1N1)pdm09, 328 A(H3N2), 74 B/Victoria-lineage, and 398 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 culture-pagated cultivar contained the NA T325N substitution and showed RI by oseltamivir.

As of week 30/2018 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; 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 [5] 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 H7N9 viruses can be found on the WHO website [6]. Increased numbers of cases were reported over the course of the following seasons; more 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 [7]. A revised ECDC rapid risk assessment [8] for these A(H7N9) viruses was posted on 11 February 2015 and most recently updated on 3 July 2017 [9]. WHO posted an analysis of information on A(H7N9) viruses on 10 February 2017 [10]. 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 [11], with the latest human case having occurred early in February 2018 [12]. On 14 February 2018, China notified WHO of the first recorded case of human infection with an avian H7N4 virus [13].

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 the A(H5N6) viruses that previously infected humans in China [11]. So far, no cases of human infection by A(H5N1) viruses have been reported to WHO in 2018 as of 20 July 2018 [14]. ECDC published an updated rapid risk assessment on the situation in Egypt on 13 March 2015 [15] and an epidemiological update on 10 April 2015 [16]. On 18 November 2016, ECDC published a rapid risk assessment related to outbreaks of highly pathogenic avian influenza H5N8 viruses in Europe [17]. 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 23 March 2018 and can be found on the ECDC website [18].

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 15 Aug 2018]
and
https://crick.ac.uk/media/409431/crick_feb2018_report_for_the_web.pdf [accessed 15 Aug 2018]

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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