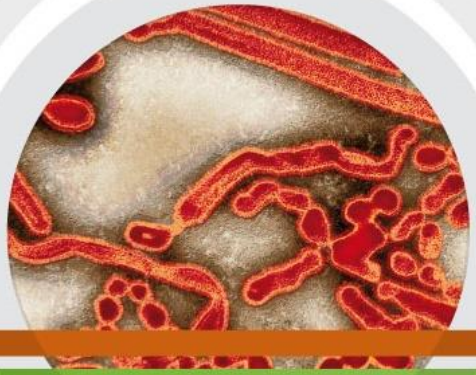

SURVEILLANCE REPORT

Influenza virus characterisation

Summary Europe, October 2018

Summary

This is the first report for the 2018–19 influenza season. As of week 44/2018, only 540 influenza detections across the WHO European Region have been reported. Detections were made up of 88.4% type A viruses, with A(H1N1)pdm09 prevailing over A(H3N2), and 15.6% type B viruses, with the few (5) ascribed to a lineage being B/Yamagata.

Since week 40/2018, no EU/EEA countries have shared influenza-positive specimens with the London WHO CC, the Francis Crick Worldwide Influenza Centre (WIC). Therefore, this report provides phylogenetic analyses of the HA genes of globally collected seasonal influenza viruses with recent collection dates (1 June 2018 or later) that international laboratories had submitted to the GISAID EpiFlu database by 7 November 2018.

All 162 A(H1N1)pdm09 viruses with recent collection dates had HA genes that fell within subclade 6B.1, defined by HA1 amino acid substitutions S84N, S162N and I216T, represented by the vaccine virus A/Michigan/45/2015. Additionally, all 162 carried substitutions of S74R, S164T and I295V, with a number of subgroups being defined by additional substitutions (e.g. S183P or T120A). Previous HI analyses using post-infection ferret antisera raised against A/Michigan/45/2015 have shown the great majority of such viruses to be antigenically similar to the vaccine virus.

Of the 99 A(H3N2) viruses with recent collection dates, 95 have HA genes falling in clade 3C.2a, and four viruses fall in clade 3C.3a. The clade 3C.2a viruses fell within subclades 3C.2a3 (n = 2), 3C.2a2 (n = 28; represented by the southern hemisphere 2019 egg-propagated vaccine virus, A/Switzerland/8060/2017) and 3C.2a1 (n = 65; represented by the northern hemisphere 2018–19 vaccine virus, A/Singapore/INFIMH-16-0019/2016), with 64 of the latter falling in subgroup 3C.2a1b. Based on previous HI analyses performed with post-infection ferret antisera raised against the two vaccine viruses, those raised against the subclade 3C.2a1 virus induced responses that gave cross-subclade reactivity while those raised against the subclade 3c.2a2 virus gave more subclade-specific reactivity.

All 70 B/Victoria-lineage viruses with recent collection dates had HA genes that encoded HA1 amino acid substitutions of I117V, N129D and V146I and fell within a subclade of clade 1A (the B/Brisbane/60/2008 clade). However, 13 and 43 of these, respectively, fell in groups defined by deletions of three (Δ162-164) or two (Δ162-163) amino acids in HA1. Previous HI analyses with panels of post-infection ferret antisera have shown these three groups of viruses to be antigenically distinguishable; a Δ162-163 virus, B/Colorado/06/2017, has been recommended for use in trivalent vaccines for the upcoming northern and southern hemisphere influenza seasons.

HA genes of the 81 B/Yamagata viruses with recent collection dates fell within the B/Phuket/3073/2013 vaccine virus clade (clade 3) and encoded HA1 amino acid substitutions of L172Q and M251V, and some had additional substitutions. Previous HI analyses with post-infection ferret antisera raised against B/Phuket/3073/2013 have shown such viruses to be antigenically similar to the vaccine virus which has been recommended for use in quadrivalent vaccines for the upcoming northern and southern hemisphere influenza seasons.

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.

Suggested citation: European Centre for Disease Prevention and Control. Influenza virus characterisation, summary Europe, October 2018. Stockholm: ECDC; 2018.

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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 2018–19 season (weeks 40-44/2018). As is usual for this time of the year, a low number (540) of detections have been reported, with type A (84.4%) predominating over type B (15.6%) viruses, which is the usual pattern, unlike the 2017–18 season when type B predominated over type A at the start of the season and throughout most of it. Of the type A viruses subtyped (n = 208) and the type B viruses ascribed to a lineage (n = 5), A(H1N1)pdm09 (n = 120) are prevailing over A(H3N2) (n = 88) viruses and all type B viruses have been B/Yamagata-lineage; these relative proportions are comparable to those summarised in the September 2018 characterisation report[1]. Overall, the ratio of type A to type B detections is significantly increased compared with the 2017–18 season (0.8:1 to 5.4:1), and of the A subtyped viruses, a small increase in the proportion of A(H1N1)pdm09 has been seen (57.7% in 2018–19 compared with 50.6% in 2017–18).

Since week 40/2018, no shipments of specimens have been received at the Crick Worldwide Influenza Centre (WIC) from EU/EEA countries. As a consequence, no antigenic characterisation data have been generated for viruses in EU/EEA countries. This report contains haemagglutinin (HA) phylogenetic analyses for seasonal influenza viruses with the most recent collection dates that have been deposited in the GISAID EpiFlu database (as of 7 November 2018). These viruses are predominantly from southern hemisphere countries and the USA; the phylogenetic analyses serve to illustrate the recent global situation as an indicator of what may emerge in the WHO European Region.

Table 1. Influenza virus detections in the WHO European Region from the start of reporting for the 2018–19 season (weeks 40-44/2018)[a]

	Cumulative number of detections			Totals*		Totals for 2017-18 season*		
Virus type/subtype/lineage	Sentinel sources	Non-sentinel sources	Totals	%	Ratios	Number	%	Ratios
Influenza A	**25**	**431**	**456**	**84.4**	**5.4:1**	**106 003**	**44.1**	**0.8:1**
A(H1N1)pdm09	14	106	120	57.7		23 121	50.6	
A(H3N2)	6	82	88	42.3	0.7:1	22 568	49.4	1:1
A not subtyped	5	243	248			60 314		
Influenza B	**6**	**78**	**84**	**15.6**		**134 618**	**55.9**	
Victoria lineage	0	0	0			301	1.9	
Yamagata lineage	2	3	5	100.0	All	15 701	98.1	52.2:1
Lineage not ascribed	4	75	79			118 616		
Total detections (total tested)	**31 (2 492)**	**509 (52 360)**	**540 (54 852)**			**240 621 (903 182**		

*** Percentages are shown for total detections (types A & B [in bold type], and for viruses ascribed to influenza A subtype and influenza B lineage). Ratios are given for type A:B [in bold type], A(H3N2):A(H1N1)pdm09 and Yamagata:Victoria lineages.**

Influenza A(H1N1)pdm09 virus analyses

All 162 viruses with collection dates from 1 August 2018 for which HA gene sequences were submitted to the EpiFlu database of GISAID, fall within clade 6B.1, the A/Michigan/45/2015 vaccine virus clade [1] but carry additional amino acid substitutions of S74R, S164T and I295V (Figure 1). The structure of the phylogeny is very similar to that presented in the September 2018 characterisation report, which focused on viruses circulating in the period March to July 2018, with a number of genetic subgroups defined by specific amino acid substitutions having emerged. The great majority of viruses in the various subgroups have remained antigenically similar to A/Michigan/45/2015 as shown in the September 2018 and earlier characterisation reports.

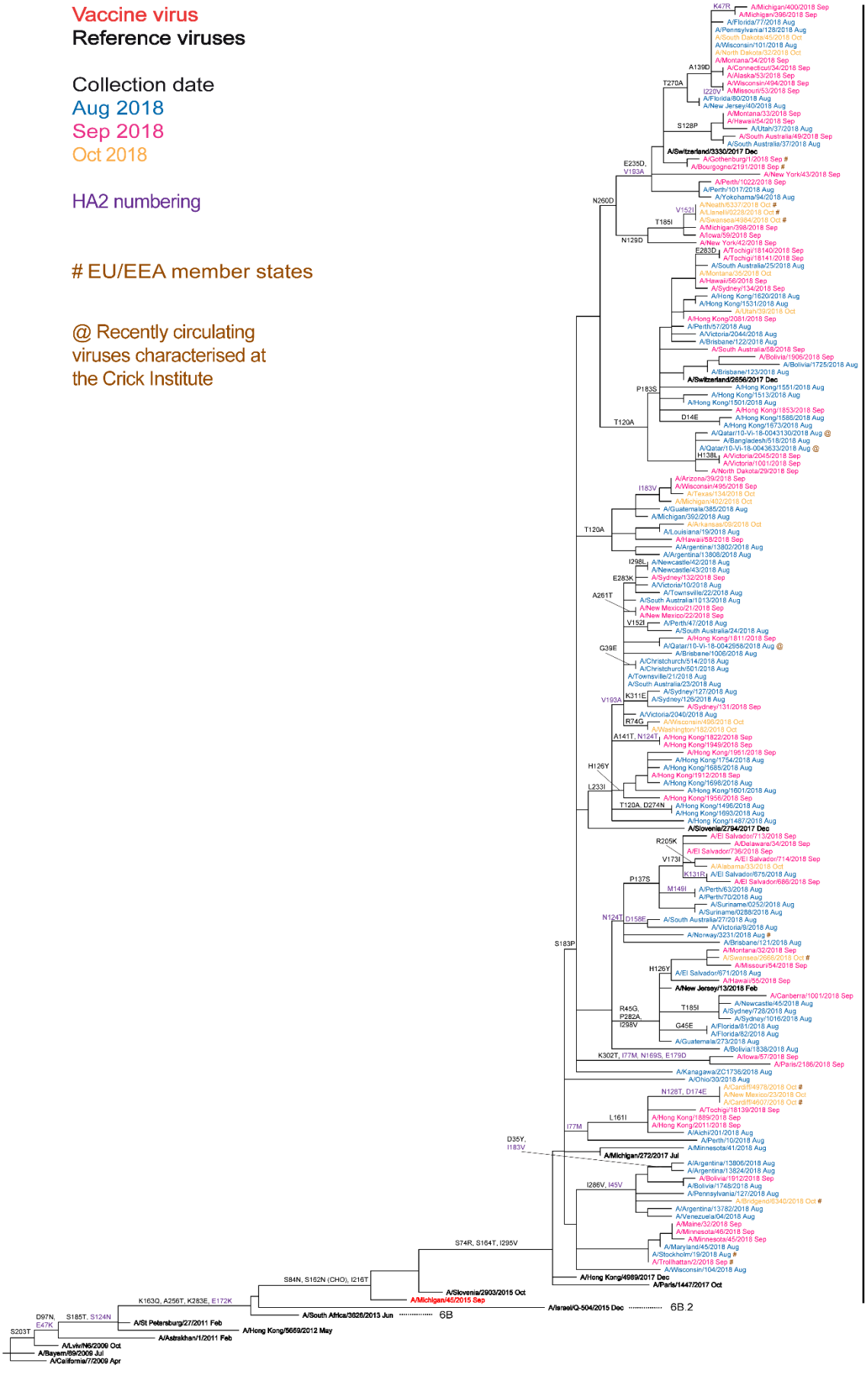
Of the 12 viruses from EU/EEA countries (one from France, one from Norway, three from Sweden, and seven from Wales) featured in Figure 1:

- one falls in a subgroup defined by **I286V** in **HA1** with **I45V** in **HA2**;
- two fall within a subgroup defined by **L161I** in **HA1** with **I77M**, **N128T** and **D174E** in **HA2**;
- one falls within a subgroup defined by **R45G**, **H126Y**, **S183P**, **P282A** and **I298V** in **HA1**;
- one falls within a subgroup defined by **S183P** in **HA1** and **N124T** in **HA2**;
- three fall within a subgroup defined by **N129D**, **S183P**, **T185I**, **N260D** in **HA1** and **V152I** in **HA2**; and
- two fall within a subgroup defined by **S183P**, **E235D**, **N260D** in **HA1** and **V193A** in **HA2**.

Globally, based on Figure 1, the proportions of viruses falling within subgroups defined by **S183P**, **L233I** in **HA1** and **V193A** in **HA2** or **T120A** and **P183S** (a reversion) in **HA1**, together with subgroup 2 (identified above) appear to be increasing.

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

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



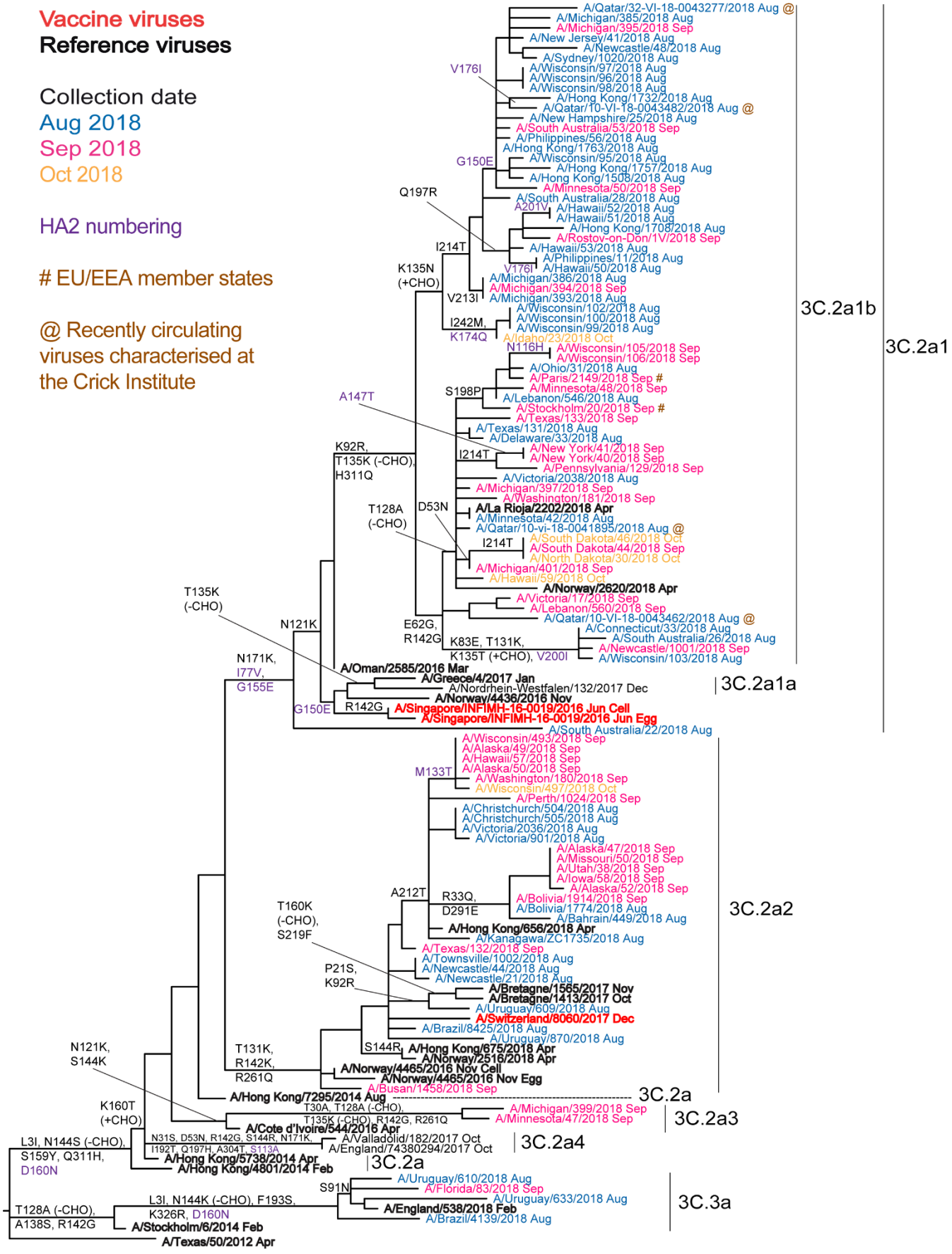
Influenza A(H3N2) virus analyses

A phylogenetic analysis of the 99 HA genes of A(H3N2) viruses with recent collection dates (after 1 August 2018; 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 with 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 (a former vaccine virus)
- Subclade 3C.2a1: Those in clade 3C.2a plus: **N171K** in **HA1** and **I77V** and **G155E** in **HA2,** most also carry **N121K** in **HA1**, e.g. A/Singapore/INFIMH-16-0019/2016 (2018-19 northern hemisphere vaccine virus)
- Subgroup 3C.2a1a: Those in subclade 3C.2a1 plus **T135K** in **HA1**, resulting in the loss of a potential glycosylation site, and also **G150E** in **HA2**, e.g. A/Greece/4/2017
- Subgroup 3C.2a1b: Those in subclade 3C.2a1 plus **K92R** and **H311Q** in **HA1**, e.g. A/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 and A/Switzerland/8060/2017 (2019 southern hemisphere vaccine virus)
- Subclade 3C.2a3: Those in clade 3C.2a plus **N121K** and **S144K** in **HA1**, e.g. A/Cote d'Ivoire/544/2016
- Subclade 3C.2a4: Those in clade 3C.2a plus **N31S, D53N, R142G, S144R, N171K, I192T, Q197H** and **A304T** in **HA1** and **S113A** in **HA2**, e.g. A/Valladolid/182/2017
- 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 (a former vaccine virus).

The great majority of recently circulating viruses have HA genes that continue to fall into genetic groups within clade 3C.2a (n = 95), notably the 3C.2a2 (n = 28) subclade and the 3C.2a1b (n = 64) subgroup, with a low number of viruses falling in clade 3C.3a (n = 4; Figure 2). In contrast to the phylogeny presented in the September 2018 characterisation report, which focused on viruses collected from March to July 2018, where subclade 3C.2a2 viruses were more numerous than subgroup 3C.2a1b viruses, Figure 2 indicates that viruses in subgroup 3C.2a1b were more numerous than those in subclade 3C.2a2 for the period August to October 2018. The two viruses from EU/EEA countries, A/Paris/2149/2018 and A/Stockholm/20/2018, both fall in subgroup 3C.2a1b. 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].

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



Influenza B virus analyses

Influenza B – Victoria lineage

No B/Victoria-lineage HA gene sequences from EU/EEA countries or the wider WHO European Region, for viruses with collection dates from 1 June 2018, have so far been deposited in the EpiFlu database of GISAID, and only small numbers were deposited from elsewhere (Figure 3). However, the 70 recently circulating viruses of this lineage continue to have HA genes that fall in the B/Brisbane/60/2008 clade (clade 1A; Figure 3), with all falling 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, Oceania and South Africa have HA genes encoding an HA with deletion of residues **K162** and **N163** of **HA1** (1A(Δ2) in Figure 3). These viruses have additional substitutions of **D129G** and **I180V** in **HA1**, and **R151K** in **HA2**. This group of viruses is more prevalent than the subcluster viruses that show no deletions. Less common are viruses with HA genes encoding a deletion of three **HA1** amino acids, **K162**, **N163** and **D164** (1A(Δ3) in Figure 3), which have been detected primarily in the Far East and Africa (with no detections in the WHO European Region at the time of this report), many of which carry additional substitutions of **I180T** and **K209N** in **HA1**. Other members of the 1A(Δ3) group carry the **HA1** substitution **K136E**, often with additional HA1 substitutions of **K52N** and **E198G** (within the **197-199** glycosylation site), notably for a batch of viruses from Cote d'Ivoire that have been characterised by WHO CC London. It was noted in the September 2018 characterisation report, and earlier ones, that the clade 1A viruses without deletions, the 1A(Δ2) and 1A(Δ3) groups, and the 1A(Δ3) viruses with the **HA1 K136E** substitution, are antigenically distinct from one another. Following the emergence and spread of viruses in the 1A(Δ2) group, a representative, B/Colorado/06/2017, was recommended for use in trivalent influenza vaccines for both the 2018–19 northern hemisphere [3] and 2019 southern hemisphere [4] seasons.

Influenza B – Yamagata lineage

One EU/EEA country (Sweden) deposited a B/Yamagata-lineage HA gene sequence from a virus, B/Stockholm/4/2018, with a collection date after 1 August 2018 in the GISAID EpiFlu database (Figure 4). The 60 HA gene sequences deposited for viruses with collection dates from 01 August 2018, together with 21 sequences determined by WHO CC London for viruses from Africa and the Middle East collected in June and July of 2018, fall in genetic clade 3 (the B/Wisconsin/1/2010–B/Phuket/3073/2013 clade) as has been the case, worldwide, for all HA genes from viruses collected since 01 August 2017. Compared to the vaccine virus, B/Phuket/3073/2013, all recently circulating viruses have fallen 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 N217D** or **D229N** or **D232N** [introducing a potential N-linked glycosylation site]), can be seen amongst the most recently circulating viruses characterised (Figure 4). It has been noted in the September 2018 characterisation report – and previous ones – that none of these amino acid substitutions have any obvious antigenic effects based on haemagglutination inhibition (HI) assays using post-infection ferret antisera raised against egg-propagated B/Phuket/3073/2013 which has been recommended for inclusion in quadrivalent vaccines for the 2017–18 [1] and 2018–19 [3] northern hemisphere, the 2019 [4] southern hemisphere seasons, as well as trivalent vaccines for the southern hemisphere 2018 season [2].

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

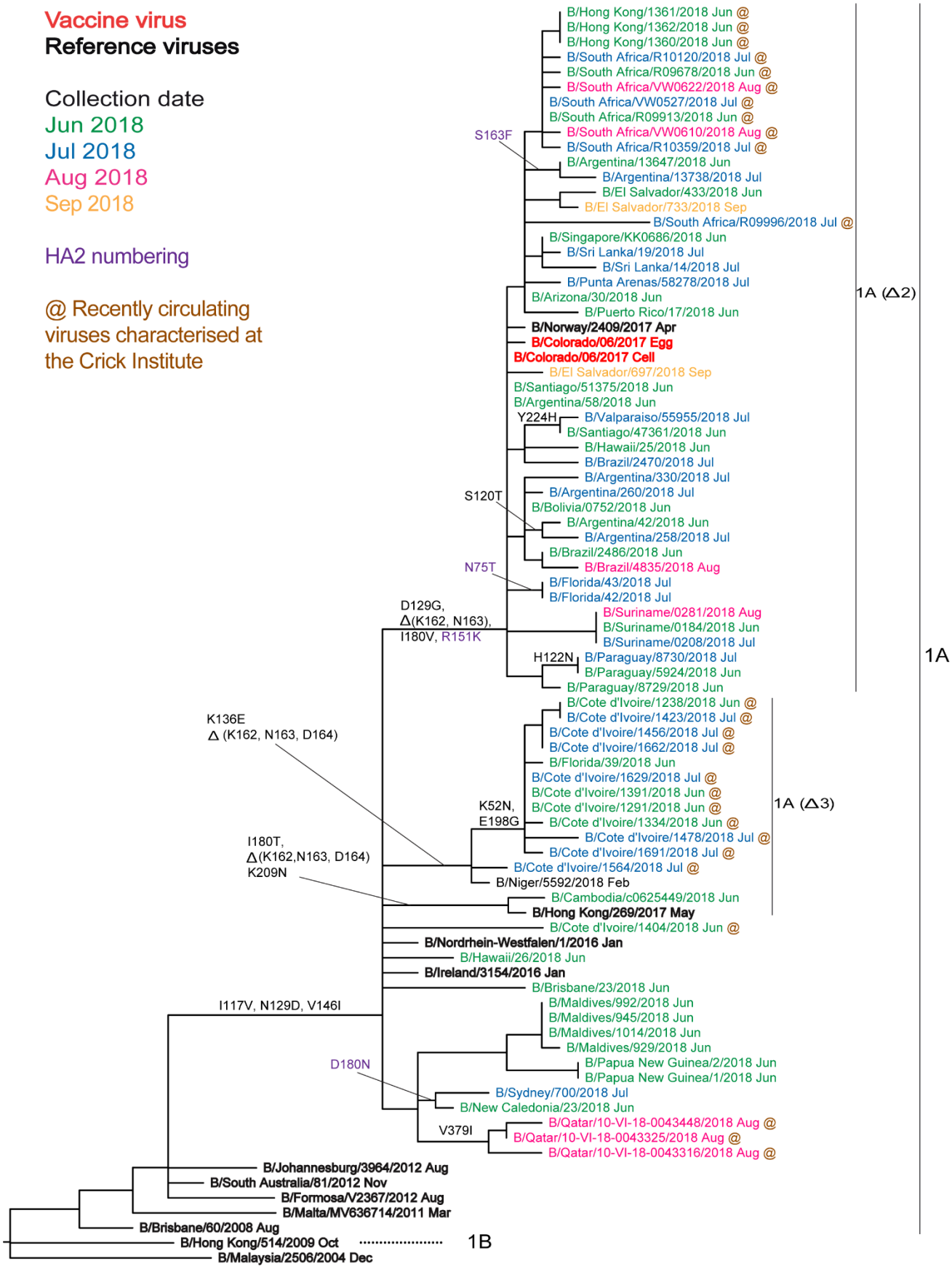
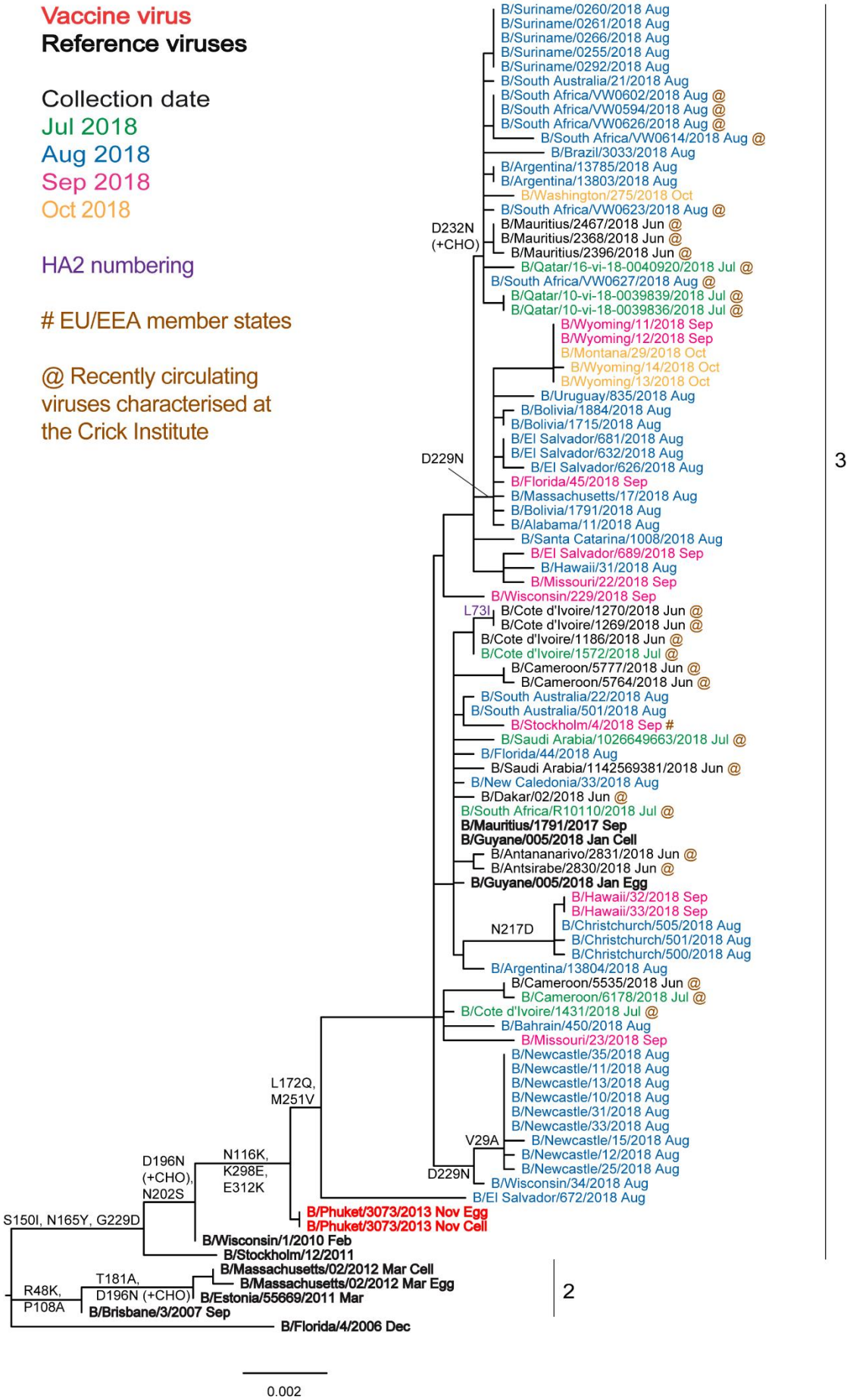


Figure 4. Phylogenetic comparison of influenza B/Yamagata-lineage HA genes



Summaries of data submitted to TESSy

Genetic characterisation

For the 2018–19 season, as of week 44/2018, 12 viruses have been characterised genetically. All were A(H1N1)pdm09 viruses belonging to the A/Michigan/45/2015 vaccine virus (6B.1) clade.

Antiviral susceptibility

For the 2018–19 season, as of week 44/2018, 12 A(H1N1)pdm09 viruses have been tested for susceptibility to neuraminidase inhibitors. None showed evidence of reduced susceptibility to the inhibitors.

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 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 [7]. WHO posted an analysis of information on A(H7N9) viruses on 10 February 2017 [8]; a summary and assessment of influenza viruses at the human-animal interface on 21 September 2018 indicates that A(H7N9) avian influenza viruses continue to be detected by agricultural authorities in China but at lower levels than before [9], with the latest human case having occurred early in February 2018 [10]. 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 [11].

Influenza A(H5) virus

The most recent monthly risk assessment of influenza at the human–animal interface was published by WHO on 21 September 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; a new human case of influenza A(H5N6) virus infection was detected in August 2018 [9]. By 21 September 2018, no cases of human infection by A(H5N1) viruses had been reported to WHO in 2018 [12]. On 18 November 2016, ECDC published a rapid risk assessment related to outbreaks of highly pathogenic avian influenza H5N8 viruses in Europe [13]. As described above, the EU Reference Laboratory for Avian Influenza, in collaboration with ECDC and the European Food Standards Agency, published the latest overview of avian influenza on 23 March 2018, which can also be found on the ECDC website [11].

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) WHO Geneva, 19–21 February 2018, and 2) CDC Atlanta, 24–26 September 2018, can be found at:

https://www.crick.ac.uk/sites/default/files/2018-07/crick_feb2018_report_for_the_web.pdf

and

https://www.crick.ac.uk/sites/default/files/2018-10/September%202018%20interim%20report_opt.pdf.

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 most viruses from non-EU/EEA countries were recovered from the EpiFlu database of GISAID; those that were generated by WHO CC London are indicated (@). We gratefully acknowledge the authors, originating and submitting laboratories of the sequences from the EpiFlu database of GISAID which were downloaded for use in the preparation of this report (all submitters of data may be contacted directly via the GISAID website), along with all laboratories who submitted sequences directly to WHO CC London.

References

1. World Health Organization. Recommended composition of influenza virus vaccines for use in the 2017–2018 northern hemisphere influenza season. Wkly Epidemiol Rec. 2017 Mar 17;92(11):117-128. http://apps.who.int/iris/bitstream/10665/254756/1/WER9211.pdf
2. World Health Organization. Recommended composition of influenza virus vaccines for use in the 2018 southern hemisphere influenza season. Wkly Epidemiol Rec. 2017 Oct 20;92(42):625-648. http://apps.who.int/iris/bitstream/10665/259275/1/WER9242.pdf
3. World Health Organization. Recommended composition of influenza virus vaccines for use in the 2018–2019 northern hemisphere influenza season. Wkly Epidemiol Rec. 2018 Mar 23;93(12):133-152. http://apps.who.int/iris/bitstream/handle/10665/260550/WER9312.pdf
4. World Health Organization. Recommended composition of influenza virus vaccines for use in the 2019 southern hemisphere influenza season. Wkly Epidemiol Rec. 2018 Oct 19;93(42):553-576. http://apps.who.int/iris/bitstream/handle/10665/275475/WER9342.pdf
5. World Health Organization. Emergencies preparedness, response – Human infection with influenza A(H7N9) virus in China. 1 April 2013 [internet]. Geneva: WHO; 2013 [accessed 9 Nov 2018]. Available from: http://www.who.int/csr/don/2013_04_01/en/index.html
6. World Health Organization. Influenza – Avian influenza A(H7N9) virus [internet]. Geneva: WHO; 2017 [accessed 9 Nov 2018]. Available from: http://www.who.int/influenza/human_animal_interface/influenza_h7n9/en/
7. World Health Organization. Emergencies preparedness, response –Human infection with avian influenza A(H7N9) virus – China [internet]. Geneva: WHO; 2017 [accessed 9 Nov 2018]. Available from: http://www.who.int/csr/don/26-october-2017-ah7n9-china/en/
8. World Health Organization. Analysis of recent scientific information on avian influenza A(H7N9) virus. 10 February 2017 [internet]. Geneva: WHO; 2017 [accessed 9 Nov 2018]. Available from: http://www.who.int/influenza/human_animal_interface/avian_influenza/riskassessment_AH7N9_201702/en
9. World Health Organization. Influenza at the human-animal interface. Summary and assessment, 21 July to 21 September 2018. Geneva: WHO; 2018. Available from: http://www.who.int/influenza/human_animal_interface/Influenza_Summary_IRA_HA_interface_21_09_2018-revised.pdf
10. World Health Organization. Influenza at the human–animal interface. Summary and assessment, 26 January to 2 March 2018. Geneva: WHO; 2018. Available from: http://www.who.int/influenza/human_animal_interface/Influenza_Summary_IRA_HA_interface_02_03_2018.pdf
11. European Centre for Disease Prevention and Control, European Food Safety Authority, European Union Reference Laboratory for Avian influenza. Avian influenza overview, November 2017 – February 2018. Parma and Stockholm: EFSA and ECDC; 2018. Available from: https://ecdc.europa.eu/sites/portal/files/documents/avian-influenza-overview-nov-2017%E2%80%93Febr-2018.pdf
12. World Health Organization. Cumulative number of confirmed human cases for avian influenza A(H5N1) reported to WHO, 2003–2018. Geneva: WHO; 2018. Available from: http://www.who.int/influenza/human_animal_interface/2018_09_21_tableH5N1.pdf
13. European Centre for Disease Prevention and Control. Outbreak of highly pathogenic avian influenza A(H5N8) in Europe – 18 November 2016. Stockholm: ECDC; 2016. Available from: https://ecdc.europa.eu/sites/portal/files/media/en/publications/Publications/risk-assessment-avian-influenza-H5N8-europe.pdf