September 2018

Summary of influenza virus characterisation data reported by national influenza centres to The European Surveillance System (TESSy) for weeks 40/2017 to 20/2018

Summary

This report summarises influenza surveillance data from the WHO European Region (weeks 40/2017 to 20/2018). Surveillance data were collected by the national influenza centres and reported to the TESSy (The European Surveillance System) database at the European Centre for Disease Prevention and Control (ECDC).

Within the period of reporting, 203 511 influenza virus detections – 43% for influenza A and 57% for influenza B – were reported in the WHO European Region (48 countries and Kosovo[*]).

The subtype was not determined for 55 016 (63%) influenza A viruses; 14 212 viruses (16% overall and 44% of the subtyped A viruses) were subtyped as A(H1N1)pdm09, and 17 787 viruses (20% overall and 55% of the subtyped A viruses) were subtyped as A(H3N2). For 101 910 (87%) of the reported influenza B virus detections the lineage was not determined; 14 325 influenza B viruses (12.2% overall, 98% of the B viruses assigned to a lineage) belonged to the B/Yamagata lineage, and 261 (<1% overall, 2% of the B viruses assigned to a lineage) were reported as B/Victoria lineage. Of the total detections, 4 442 viruses from 22 countries were antigenically characterised, and 4 359 viruses from 24 countries were genetically characterised. The vaccination status of 4 334 patients was reported, and 675 (15.5%) influenza detections were from vaccinated patients.

The majority (1 357, 91%) of the 1 488 antigenically characterised A(H1N1)pdm09 viruses were reported as A/Michigan/45/2015, the current season's vaccine virus, while 131 (9%) did not fall into a reportable category in TESSy. Of the 918 genetically characterised A(H1N1)pdm09 viruses, 913 (99%) belonged to genetic subgroup 6B.1, represented by A/Michigan/45/2015, and <1% of viruses fell in the 6B subgroup, represented by A/South Africa/3626/2013, or were not assigned to a reportable group.

Of the 325 antigenically characterised A(H3N2) subtype viruses, 161 (49.5%) were A/Hong Kong/4801/2014-like, 103 (32%) were A/Singapore/INFIMH-16-0019/2016-like, 10 (3%) were A/Switzerland/9715293/2013-like, and 51 (16%) were not assigned to a reportable category. Among the 1 240 genetically characterised A(H3N2) viruses, 708 (59%) fell in the vaccine virus component A/Hong Kong/4801/2014 clade 3C.2a, while 475 (39%) fell in genetic subclade 3C.2a1, represented by A/Singapore/INFIMH-16-0019/2016. Less than 1% (n=9) of the viruses fell in clade 3C.3, represented by A/Samara/73/2013 and 13 (~1%) fell in clade 3C.3a, represented by A/Switzerland/9715293/2013. Influenza A(H3N2) viruses within clade 3C.2a and subclade 3C.2a1 are genetically diverse and a number of virus clusters have emerged. Therefore, five (3%) of the viruses were reported as 'subgroup not listed'.

Low numbers of B/Victoria-lineage viruses were detected and 50 (44%) of the 113 antigenically characterised viruses were characterised as B/Brisbane/60/2008-like, while 59 (52%) were like a virus with a 2-amino acid deletion in haemagglutinin (Δ162-163), B/Norway/2409/2017, which is antigenically distinct from the vaccine virus. One virus was characterised as B/Hong Kong/269/2017-

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[*] This designation is without prejudice to positions on status and in accordance with UNSCR 1244 (1999) and the ICJ Opinion on the Kosovo Declaration of Independence.

like, and three viruses were not assigned to a reportable category. Of the genetically characterised B/Victoria-lineage viruses (n=159), 82 (52%) were assigned to the B/Brisbane/60/2008 clade and 76 (46%) to the B/Norway/2409/2017 group. One B/Victoria-lineage virus was not assigned to a clade.

The majority (2 447, 97%) of antigenically characterised viruses of the B/Yamagata-lineage were characterised as B/Phuket/3073/2013-like, three (<1%) of the viruses were characterised as B/Massachusetts/02/2012-like, and 66 (3%) were not assigned to a reportable category. Of the 2 201 genetically characterised B/Yamagata viruses, 2 021 (99%) were assigned to the B/Phuket/3073/2013 clade (clade 3), one was assigned to the B/Massachusetts/02/2012 clade (clade 2), and 20 (1%) were reported as not falling into a reportable clade.

Neuraminidase inhibitor susceptibility was assessed for 3 693 viruses (1 174 A(H1N1)pdm09, 982 A(H3N2), and 1 537 type B). Two (<1%) type B viruses showed evidence of reduced inhibition (RI) by oseltamivir and zanamivir, and two (<1%) type B viruses showed RI by oseltamivir. Nineteen (1.6%) A(H1N1)pdm09 viruses showed evidence of highly reduced inhibition (HRI) by oseltamivir, and two showed RI by zanamivir. Two (<1%) A(H3N2) viruses showed evidence of RI by oseltamivir and zanamivir.

Introduction

Influenza vaccines are safe, effective and the principal measure for preventing influenza and reducing the impact of epidemics [1]. Influenza viruses frequently undergo genetic and antigenic changes. Therefore, based on global surveillance data, review and recommendation of influenza viruses for inclusion in vaccines has to be undertaken every year. Since 1973, WHO has published formal recommendations for the composition of influenza vaccines based on the information provided by the WHO Global Influenza Surveillance and Response System (GISRS) [2]. WHO updates its recommendations for the composition of the vaccine twice annually in order to target the viruses expected to be the most frequently circulating in the coming northern and southern hemisphere influenza seasons [3]. Twice a year, in February for the northern hemisphere and in September for the southern hemisphere, WHO convenes the consultation on the composition of influenza virus vaccines (VCM) [4,5].

The laboratory network responsible for the virological surveillance of influenza in the WHO European Region is part of GISRS and consists of national influenza laboratories in 50 countries of the Region, a WHO Collaborating Centre for Reference and Research on Influenza (at the Francis Crick Institute Worldwide Influenza Centre, London, United Kingdom (WHO CC London)), a WHO Essential Regulatory Laboratory (ERL) at the National Institute for Biological Standards and Control, Potters Bar, United Kingdom, and three WHO H5 reference laboratories in France, the Russian Federation and the United Kingdom [6-8]. National influenza laboratories in 43 of the countries in the WHO European Region are recognized by WHO as National Influenza Centres (NICs), and laboratories in 30 countries of the European Union/European Economic Area (EU/EEA) participate in the European Reference Laboratory Network for Human Influenza (ERLI-Net) coordinated by ECDC, the European Centre for Disease Prevention and Control [9].

NICs provide information on circulating influenza viruses by testing clinical specimens obtained from surveillance systems in their countries (outpatient and inpatient healthcare settings) for the presence of influenza virus by type (A and B) and subtype (A(H3N2) and A(H1N1)pdm09) or lineage (B/Victoria or B/Yamagata). Initial identification of virus type and subtype can be performed on influenza-positive clinical specimens, and a subset of viruses was derived from them using reagents provided by WHO through GISRS and the International Reagent Resource (IRR). NICs also conduct preliminary antigenic characterisation of viruses, using strain-specific post-infection ferret antisera raised against vaccine viruses and reference viruses provided by WHO CC London, and genetic characterisation through sequencing. Furthermore, susceptibility to neuraminidase inhibitor (NAI) antiviral agents is assessed by phenotypic and/or genotypic tests. On a weekly basis, NICs are encouraged to submit their characterisation results to TESSy, The European Surveillance System database hosted at ECDC.

Purpose

The purpose of this report is:

- to summarise reports on antigenic and genetic data provided to TESSy by NICs in the WHO European Region during the 2017–2018 influenza season;
- to monitor the diversity and circulation of viruses, their geographic occurrence and frequency;
- to provide feedback to NICs, through analysis of their antigenic and genetic characterisation results in the context of data from the whole region.

Methods

Data sources

NICs received clinical specimens from sentinel and non-sentinel surveillance sources for virological analysis. Forty eight of the 53 Member States of the WHO European Region and EU/EEA countries regularly report epidemiological and virological influenza surveillance data to ECDC and WHO/Europe from primary care sentinel sites and 26 (49%) report hospital surveillance non-sentinel data. Sentinel

specimens were obtained through systematic sampling of clinical cases of influenza-like illness and/or acute respiratory infection (ILI/ARI) seen by sentinel primary healthcare practitioners. The catchment population of these sentinel physicians formed the population under surveillance. Patients with ILI/ARI (or a subset of these patients) were swabbed in accordance with a defined sampling protocol. In addition, non-sentinel detections of influenza viruses were reported to ECDC, originating from inpatients and outpatients, from outbreak investigations or enhanced surveillance. A more detailed overview of country-specific surveillance systems can be found elsewhere [10].

The detection of influenza A and B viruses, subtyping of influenza A(H1N1)pdm09 and A(H3N2) viruses, and, in some instances, type B lineage determination were performed with real-time RT-PCR techniques. Weekly detection data were reported to ECDC in aggregate format.

NICs cultured influenza viruses, from a subset of influenza-positive clinical specimens, in MDCK, MDCK-SIAT or other cell lines and/or embryonated chicken eggs [11]. Virus recovery was commonly assessed by agglutination of red blood cells (RBCs), most commonly from turkey, guinea pig or humans. A haemagglutination inhibition (HI) assay was used for antigenic characterisation of recovered influenza viruses using post-infection ferret antiserum raised against a vaccine/reference influenza virus (supplied by WHO CC London) to inhibit virus agglutination of RBCs [12]. A virus isolate was considered antigenically similar to a reference virus if the HI titre with the respective post-infection ferret antiserum differed by no more than fourfold (usually a decrease), in a twofold dilution series, from the HI titre of the antiserum with the reference virus itself. To consider an isolate antigenically different from a reference virus, the HI titre had to show a decrease of eightfold or more. For antigenic characterisation of A(H3N2) viruses, some NICs conducted HI assays in the presence of oseltamivir to prevent haemagglutination by the N2 neuraminidase, and/or performed virus neutralization assays. Antigenic characterisations could be reported to TESSY under nine different representative influenza virus categories: one for A(H1N1)pdm09, three for A(H3N2) subtypes, three for B/Victoria lineage and two for the B/Yamagata lineage. In addition, 'not assigned to category' was available for each subtype and lineage to accommodate viruses that either did not match one of the preset major antigenic groups or did not yield a conclusive HI assay result.

NICs also conducted genetic characterization of viruses through sequencing. To report a virus as belonging to a specific genetic group, the phylogenetic and amino acid sequence analyses must meet the following criteria: a) in phylogenetic analysis of the HA gene, the virus should cluster within the clade represented by the indicated vaccine/reference virus, and b) it should neither contain many nor critical amino acid substitutions when compared to viruses recognized as belonging to the specific group with which it associates. WHO CC London provided the list of reference viruses to be used for the purpose of genetic analysis in October 2017, together with reporting categories for influenza virus characterisation related to the HA gene (genetic) and the encoded glycoprotein product (antigenic) (ECDC, TESSy influenza virus characterisation guidelines for the northern hemisphere influenza season, 2017–2018; available upon request). GISAID accession numbers were reported. Sequences were either obtained through sequencing at the NICs or at the WHO Collaborating Centres. Weekly virus characterisation data were reported to ECDC in aggregate and/or strain-specific format by date of sampling. In cases of duplicate reporting, only the strain-specific data were taken into consideration.

NAI antiviral susceptibility data were produced by the NICs using genotypic (limited SNP detection by RT-PCR or pyrosequencing, or full NA gene sequence analysis) and/or phenotypic analysis (drug-specific IC_{50} determination), and results were reported to TESSy. For genotypic analysis, susceptibility was determined by checking for amino acid substitutions associated with reduced/highly reduced inhibition (RI/HRI) by NAIs oseltamivir or zanamivir [13]. Phenotypic susceptibility was assessed by determining IC_{50} values representing the concentration of oseltamivir or zanamivir needed to inhibit virus neuraminidase activity by 50%. For influenza A viruses, inhibition was classified as normal inhibition (NI) if a reported value was <tenfold increased above the median IC_{50} value after removal of obvious outliers. Reduced inhibition (RI) required a 10- to 100-fold increase above the median IC_{50} and highly reduced inhibition (HRI) >100-fold above the median IC_{50}. For influenza B viruses the corresponding values were: <5-fold increase above median (NI); 5- to 50-fold increase above median (RI) and >50-fold increase above median (HRI) [14]. Median values and fold-changes were calculated by virus (sub)type, antiviral drug, IC_{50} assay method and submitting laboratory.

Data analysis

All seasonal influenza HA sequences for A(H1N1)pdm09, A(H3N2), B/Victoria, and B/Yamagata from 2017–2018 were downloaded from the EpiFlu database of the Global Initiative for Sharing All Influenza Data (GISAID). An ECDC in-house software application was used to process the sequence data for each subtype separately as follows: all entries for TESSy-reported HA sequences were compared with the GISAID datasets; TESSy entries that matched a GISAID accession number were kept, and the HA sequences of those matches were extracted to a separate file. HA sequences were excluded if the sequences were unreleased, if there were errors in the accession number, or if a mismatch between the name of the virus in the TESSy report and GISAID was detected. Alignment was performed with MAFFT v7 by first aligning the reference sequences and then adding the available test sequences. Alignment was trimmed to include only the HA1 coding region. RAxML v8.2.7 was used to construct a phylogenetic tree with 10 bootstraps and a maximum likelihood search. The tree was rooted on the oldest reference sequence with treesub (https://github.com/tamuri/treesub). PAML baseml v4.9f was used to perform ancestral reconstruction of the HA1 sequences for all internal nodes of the tree. Treesub was used to annotate the tree branches with amino acid substitutions, based on the root sequence. The nodes were coloured according to month (January, February, March, April, May, June, July, August, September, October, November, December), and the tree was exported in NEXUS format. PDF trees were edited and annotated using FigTree and PDF Illustrator. HA amino acid sequence alignments were used to inspect amino acid substitutions in BioEdit.

Data that were added to TESSy by NICs by 2 July 2018 – the reporting deadline for week 20 data – were accessed and summarised. The data for weeks 40/2017–20/2018 were included in this analysis.

Results

From week 40/2017 to week 20/2018, 203 511 influenza detections across the WHO European Region were reported from sentinel and non-sentinel surveillance sources in 48 countries and Kosovo (Figures 1 and 2). Influenza type B viruses (116 496, 57%) have prevailed over type A (87 015, 43%). Of 31 999 subtyped influenza A viruses, 17 787 (56%) were A(H3N2) and 14 212 (44%) were A(H1N1)pdm09 viruses. The lineage of 14 586 B viruses was determined: 261 (2%) fell in B/Victoria and 14 325 (98%) in B/Yamagata lineages (Figures 1 and 2).

Figure 1. Cumulative number and proportion of influenza virus detections by subtype and lineage, WHO European Region, weeks 40/2017−20/2018

B(Vic), 261 <1%

B(Yam), 14325, 7%

A(no subtype), 55016, 27%

B(no lineage), 101910, 50%

A(H1)pdm09, 14212, 6.9%

A(H3), 17787, 8.7%

N=203 511
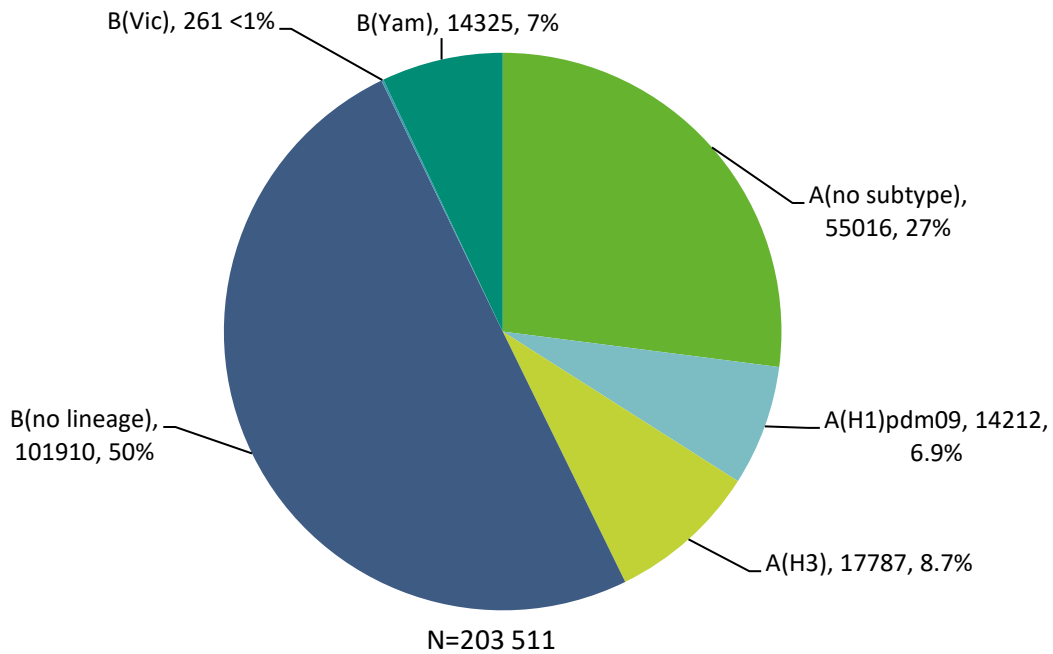
Figure 2. Number of specimens by surveillance system and source, mode of reporting for antigenic and genetic characterisation data, WHO European Region, weeks 40/2017–20/2018. Number of sequence data by subtype

Sentinel detections, n=20 327
- A, not subtyped, n=1 309
- A(H1)pdm09, n=3 712
- A(H3), n=2 324
- B, no lineage, n=6 684
- B/Victoria, n=185
- B/Yamagata, n=6 113

Non-sentinel detections, n=183 184
- A, not subtyped, n=53 707
- A(H1)pdm09, n=10 500
- A(H3), n=15 463
- B, no lineage, n=95 226
- B/Victoria, n=76
- B/Yamagata, n=8 212

Aggregate characterizations, n=8 801
- Antigenic, n=4 442
- Genetic, n=4 359

Strain-based reports, n=8 817 viruses
- Antigenic, n=3 699
- Genetic, n=3 929
- Antiviral susceptibility, n=3 693

HA sequence available, n=2 846
- A(H1)pdm09, n=668
- A(H3), n=878
- B/Victoria, n=103
- B/Yamagata, n=1 197

Known vaccination status (with HA sequence)
- Total n=4 334 (2 051)
- Vaccinated, n=675 (376)
- Not vaccinated, n=3 659 (1 675)

Table 1. Number of viruses characterised antigenically (AG) and genetically (GEN) as reported to TESSy (both aggregate and strain-based reports), by country and week of sampling, WHO European Region, weeks 40/2017–20/2018

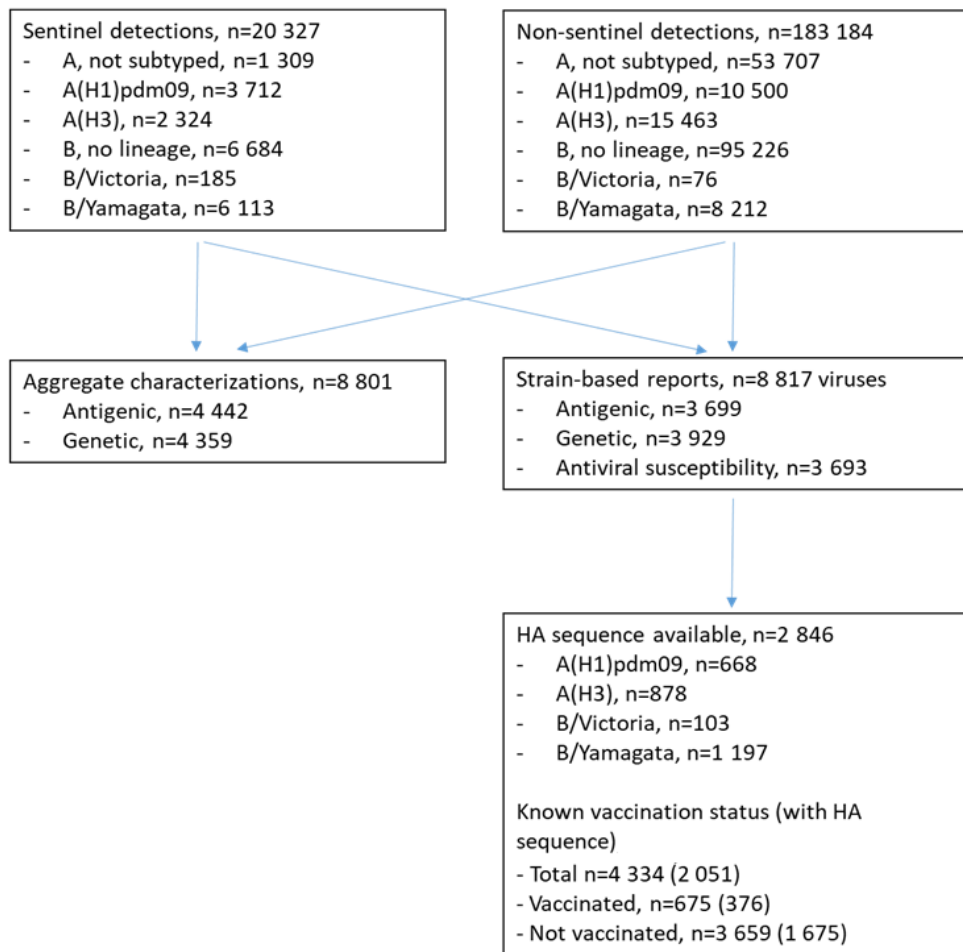| Country		2017 40	41	42	43	44	45	46	47	48	49	50	51	52	2018 01	02	03	04	05	06	07	08	09	10	11	12	13	14	15	16	17	18	19	20	ALL
Austria	AG													7	4	9	3	4	10	7	10	1	5	6	1										67
	GEN												2	7	4	14	7	10	18	10	23	7	8	8	1										119
Belgium	AG																																		0
	GEN	1								3	2	4	6		4	12		2	2	7	6														49
Hungary	AG								2		1	2																							5
	GEN								2		1	2																							5
Lithuania	AG															2	16	40	11	16	2			6											93
	GEN																																		0
Czech Republic	AG														1	1																			2
	GEN														1	2	1	3	2	4															13
Denmark	AG								1		2	6	6		4	1																			20
	GEN	1	1		2	1	1		1	4		15	19	23	38	10	33	19																	168
Finland	AG																																		0
	GEN		1				2	4	4	7	3	4	4	3	9	7	11	7	11	13	16	7	7	15	5	6	5	4	1	2					158
France	AG		2	2	1	2	3	2	5	9	7	22	26	31	26	16	19	27	18	15	29	34	23	17	20	19	13	4	3						395
	GEN	2	5	3	1	2	4	2	7	10	10	27	35	38	34	25	27	36	21	17	32	39	29	29	24	21	14	7	4						505
Germany	AG			1	1		2	1	5	6	4	11	15	20	48	86	137	161	181	122	212	187	171	193	127	86	50	29	8	3	2	1			1870
	GEN	1	1	2		1	2	2	5	6	6	8	12	5	8	12	11	20	15	14	15	17	9	16	13	6	8	7	3	3		2			230
Greece	AG														2	2	17	13	7	6				4	5	1									61
	GEN														2		2	5	21	11	7	12	2		5	5	2		2						78
Ireland	AG		2							2	3	4	10		21	22	5	3	3	1	2	1			1										87
	GEN	2	4	1	2		1	4		3	6	5	13	18	40	40	24	22	15	14	12	8	5	5	2	1		1							248
Italy	AG														7		2	2			8	6	3	4	2										34
	GEN							1	6	8	14	9	21		25	1	1	1	1	2	7	4	7	3	7	1	5								124
Kazakhstan	AG						2				1		2	2	2		3	1			7	3	4	4											33
	GEN						2				1		2	2	2		3	1			7	3	4	4											33
Kyrgyzstan	AG																																		0
	GEN																																		0
Latvia	AG							1			3	2	1	3		5	2	4	11	19	12	8	14	15	6	1	6				4				117
	GEN																																		0
Luxembourg	AG																																		0
	GEN										1				2	4	3	5	4	4	3	3		3	2	2	4	1							41
Montenegro	AG																																		0
	GEN																																		0
Netherlands	AG					1	1			1	1	1	6	7	5	2	2	1																	28
	GEN	2	1	3		2	2			2	4	5	12	10	12	9	19	24	20	14	16	14	19	23	25	10	9	8	4	5					274
Norway	AG																																		0
	GEN	6	4	7	8	11	13	10	10	17	16	10	20	7	15	22	2	19	7		10	8	2	28	4	12	1	11	4	13					297
Portugal	AG									2	1	9	7	12	14	7	5	6	6	3	2	1	3	1	2										81
	GEN							5	4	3	10	28	19	21	24	20	18	9	12	9	8	4	4	3	3										204
Republic of Moldova	AG																																		0
	GEN																																		0
Romania	AG										1	4			1	1	1	4	14	16	10	17	7	12	3	3	1	1							96
	GEN											2			1	2	4	5	10	7	6	9	5	10	4	4	1	1							71
Russian Federation	AG			1	1	1	1	2					1	4	1	8	17	29	33	54	77	111	132	74	90	58	50	60	35	15	14	5	2	1	877
	GEN			1	1	2							3	1	3	6	9	4	7	5	1	2													45
Slovakia	AG							1			1		3	1		2	7	12	43	39	49	30	33	17	13	11	6	4	3		1				276
	GEN																																		0
Slovenia	AG	1								1	2	3		4	7	8	7				1	1	1	3	8					2					49
	GEN	1								1	3	3	6	11	5	10	11	1		1	4	1			1										59
Spain	AG			1		1		1	3	2	5	7	4		10	6	12	10	5	7	7	4													85
	GEN		2	3	3	2	6	8	21	32	33	54	77	95	119	125	108	92	67	51	63	40	33	36	22	19	2	7	7		1			1	1129
Sweden	AG																																		0
	GEN	5	2	1	2	2	7	13	12	5	10	9	21	19	6	5	4	15	21	24	12	9	10	8	6	12	5	2	5	1					253
Switzerland	AG		1				1		1	3	3	14	13	9	11	20	3	5	12	6	4	4	5	5	3	5	5	4	1						138
	GEN		1				1		1	3	4	6	12	10	7	13	6	7	5	8	6	6	6	5	5	3	4	5	1	1					126
Ukraine	AG									1	4	6	5	3		1																			20
	GEN									1	4	6	5	3		1																			20
Tajikistan	AG																																		0
	GEN																																		0
United Kingdom	AG										1	1				1	4											1							8
	GEN	5	3	2	4	2	2	11	12	16	4	2	8		10	2	1	2	2		2	2	3	10				1							110
ALL	AG	1	5	4	4	4	11	5	14	31	28	82	104	125	165	195	232	285	378	309	458	424	410	352	281	192	131	106	57	19	21	6	2	1	4442
	GEN	26	25	22	22	24	44	61	78	118	121	200	279	312	372	338	302	310	239	220	268	194	159	207	136	97	58	60	34	27	1	4	0	1	4359

Antigenic group reporting

By week 20/2018, 22 countries had reported antigenic characterisations to TESSy (Tables 1 and 2). Germany and the Russian Federation contributed the vast majority of the data, 42% and 20%, respectively. France contributed 9% of antigenic characterisations, Slovakia 6%, Latvia 3%, Switzerland 3% and other contributing countries between 0.04 and 2% each.

Among the 4 442 antigenically characterised viruses, 1 813 (41%) were influenza A and 2 629 (59%) were influenza B (Table 2 and Figure 3). Of the influenza A viruses antigenically characterised, 1 488 (82%) were A(H1N1)pdm09 viruses, and of those, 1 357 (91%) were reported as A/Michigan/45/2015-like, while 131 (9%) were not assigned to a category. Of the 325 (18% of all characterised A viruses) antigenically characterised A(H3N2) subtype viruses, 161 (49.5%) were A/Hong Kong/4801/2014-like, 103 (31.7%) were A/Singapore/INFIMH-16-0019/2016-like, 10 (3.1%) were

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A/Switzerland/9715293/2013-like, and 51 (15.7%) were not assigned to a category. Subsets of these viruses were sent to WHO CC/London for further characterisation.

Out of 2 629 influenza B viruses that were antigenically characterised, 113 (4%) belonged to the B/Victoria lineage, 59 (52%) were characterised as B/Norway/2409/2017-like, 50 (44%) were characterised as B/Brisbane/60/2008-like, one was characterised as B/Hong Kong/269/2017-like, and three were not assigned to a category. All 2 516 (96%) remaining influenza B viruses antigenically characterised belonged to the Yamagata lineage; 2 447 (97%) were characterised as B/Phuket/3073/2013-like, 3 (<1%) were characterised as B/Massachusetts/02/2012-like and 66 (2.6%) were not assigned to a category.

Figure 3. Antigenic characterisation data by subtype as reported to TESSy (data combined from aggregate and strain-based reports), WHO European Region, weeks 40/2017– 20/2018
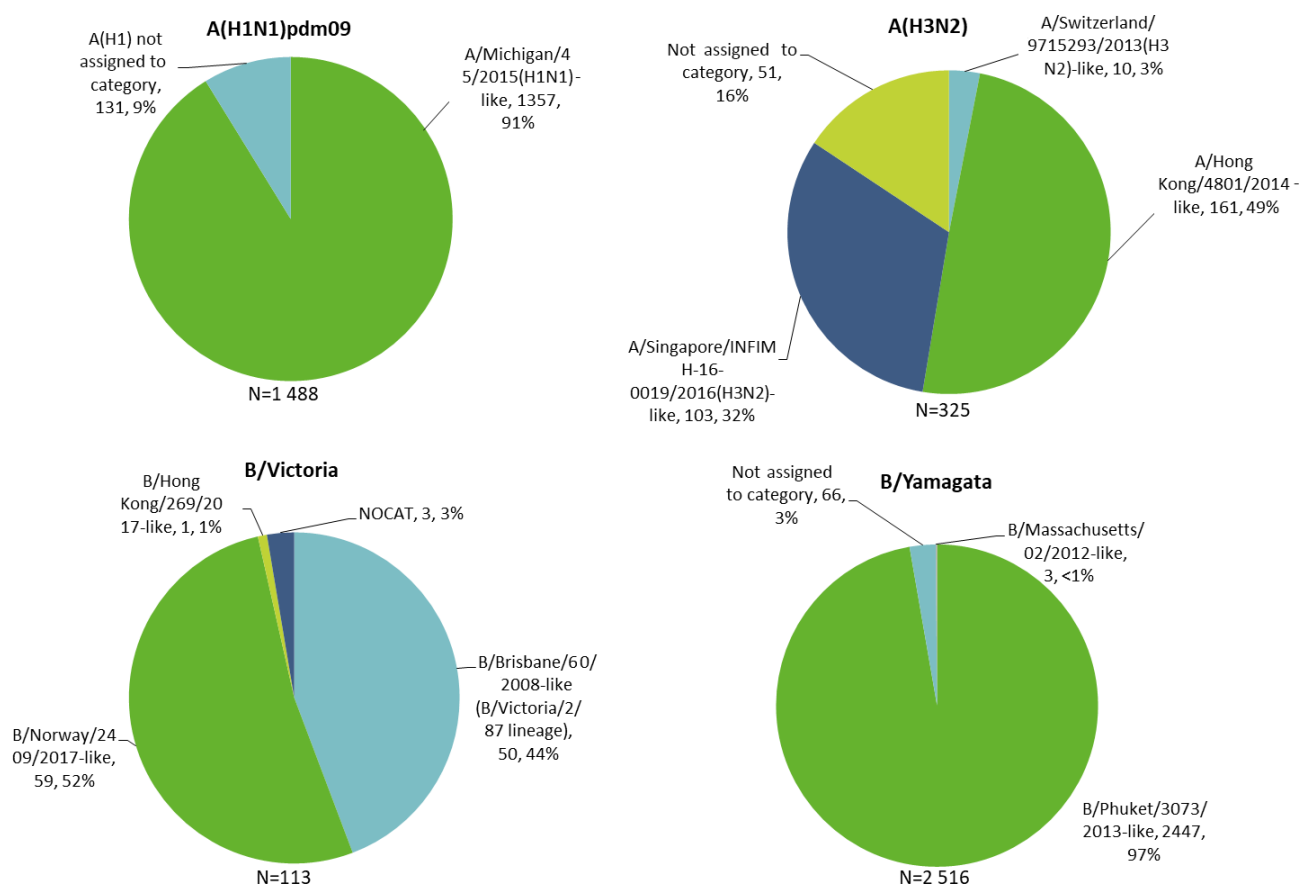
Table 2. Antigenic characterisation data by reporting category as reported to TESSy (data combined from aggregate and strain-based reports), by country, WHO European Region, weeks 40/2017–20/2018

Countries	Austria	Czech Republic	Denmark	France	Germany	Greece	Hungary	Ireland	Italy	Kazakhstan	Lithuania	Latvia	Netherlands	Portugal	Romania	Russian Federation	Slovakia	Slovenia	Spain	Switzerland	Ukraine	United Kingdom	Total by category
A/Michigan/45/2015(H1N1)pdm09 [a]	20	1	0	80	694	20	0	17	15	9	8	50	3	18	33	279	52	16	0	38	0	4	**439**
A(H1N1)pdm09 Not Categorised	6	0	0	125	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	**0**
A/Hong Kong/4801/2014 (H3N2) [b]	0	0	0	4	0	0	0	0	0	9	1	1	0	2	0	129	3	0	0	12	0	0	**146**
A/Switzerland/9715293/2013 (H3N2)	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	9	0	0	**9**
A/Singapore/INFIMH-16-0019/2016 (H3N	0	0	0	30	0	0	0	0	0	0	2	10	0	1	0	52	0	6	0	1	1	0	**60**
A(H3N2) Not Categorised	0	0	0	31	0	0	0	8	0	0	5	0	0	7	0	0	0	0	0	0	0	0	**7**
B/Yamagata-B/Phuket/3073/2013 [d]	40	1	20	113	1128	41	5	59	17	8	53	56	4	47	63	406	216	25	67	73	1	4	**901**
B/Yamagata-B/Massachusetts/02/2012	1	0	0	2	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	**0**
B/Yamagata Not Categorised	0	0	0	38	0	0	0	0	0	0	0	0	21	6	0	0	0	0	0	1	0	0	**28**
B/Victoria-B/Brisbane/60/2008 [a]	0	0	0	2	8	0	0	0	0	6	0	0	0	0	0	10	5	0	0	1	18	0	**16**
B/Victoria-B/Norway/2409/2017 [e]	0	0	0	0	10	0	0	0	2	0	24	0	0	0	0	0	0	2	18	3	0	0	**23**
B/Victoria-B/Hong Kong/269/2017	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	**1**
B/Victoria Not Categorised	0	0	0	0	0	0	0	3	0	0	0	0	0	0	0	0	0	0	0	0	0	0	**0**

[a] *Vaccine component for both northern (2017–2018 season) and southern (2018 season) hemispheres*

[b] *Vaccine component for the northern hemisphere 2017–2018 season*

[c] *Vaccine component for the southern hemisphere 2018 season and northern hemisphere 2018–2019 season*

[d] *Vaccine component of quadrivalent vaccines for use in northern hemisphere 2017–2018 season and southern hemisphere 2018 season*

[e] *Deletion of K162 and N163 in the HA1 subunit of the haemagglutinin and antigenically different from the vaccine component, vaccine component for the northern hemisphere 2018–2019 season.*

Genetic group reporting

With regard to specimens collected since week 40/2017, TESSy received genetic characterisation data of 4 359 viruses, reported by 24 countries (Tables 1 and 3). The largest contributors of the genetic data were Spain (26%) and France (12%). The rest of the countries each contributed between 0.1% and 6.8% of the data. The viruses characterised genetically fell within 11 available reporting categories (Table 3 and Figure 4). In addition to these categories, 'not assigned to clade' was available for each subtype and lineage, and 'subgroup not listed' was available for each subtype. Among the genetically characterised viruses, 2 158 (49.5%) were influenza A; 2 201 (50.5%) were influenza B viruses.

Of the 918 A(H1N1)pdm09 viruses (42.5% of influenza A viruses), 915 were assigned to a predefined clade. Of those, 913 fell in the A/Michigan/45/2015 subgroup (6B.1) and two fell in the A/South Africa/3626/2013 subgroup (6B). Two A(H1N1)pdm09 viruses belonged to a subgroup that was not listed; one was reported as not falling into a clade.

Among 1 240 A(H3N2) viruses (57.5% of influenza A viruses), 1 205 were assigned to a clade. 708 (58.7%) fell in the A/Hong Kong/4801/2014 clade (3C.2a), and 475 (39.4%) viruses fell in subclade 3C.2a1 with viruses defined by HA1 amino acid substitutions N171K, often with N121K, like A/Singapore/INFIMH-16-0019/2016. Nine viruses (<1%) fell in clade 3C.3, represented by A/Samara/73/2013, and 13 (~1%) fell in clade 3C.3a, represented by A/Switzerland/9715293/2013. Viruses in the first two groups are antigenically similar, but both clade and subclade are evolving rapidly, with the emergence of several virus clusters defined by additional amino acid substitutions in the haemagglutinin. This underlines the necessity of continued monitoring of antigenic characteristics. Thirty-five (3%) A(H3N2) viruses were reported as 'subgroup not listed'.

Of the 2 201 B viruses genetically characterised, the majority were assigned to the B/Yamagata lineage (2 042, 93%). Of the B/Yamagata lineage viruses, 2 021 (99%) were assigned to the B/Phuket/3073/2013 clade (clade 3), one was assigned to the B/Massachusetts/02/2012 clade (clade 2) and 20 were reported as not falling into a clade.

All of the B/Victoria lineage viruses that were assigned to a clade (158, 7% of B viruses) were assigned to clade 1A (Table 3 and Figure 4). Of these, 82 (51%) were assigned to the B/Brisbane/60/2008 group and 76 (48%) to the B/Norway/2409/2017 group. The latter carries the HA1 double amino acid deletion, Δ162-163, characteristic of a new antigenically distinct subgroup of viruses, and the proportion of B/Victoria-lineage viruses falling in this subgroup increased as the season progressed (Table 4 and Figure 5). One B/Victoria virus was not assigned to a clade.

Of the viruses that were characterised genetically, accession numbers for HA sequences in the GISAID EpiFlu database were provided and the sequences were included in phylogenetic analyses: 668 (73%) A(H1N1)pdm09, 878 (71%) A(H3N2), 1 197 (59%) B/Yamagata, and 103 (65%) B/Victoria.

Figure 4. Genetic characterisation data by subtype as reported to TESSy (data combined from aggregate and strain-based reports), WHO European Region, weeks 40/2017– 20/2018.
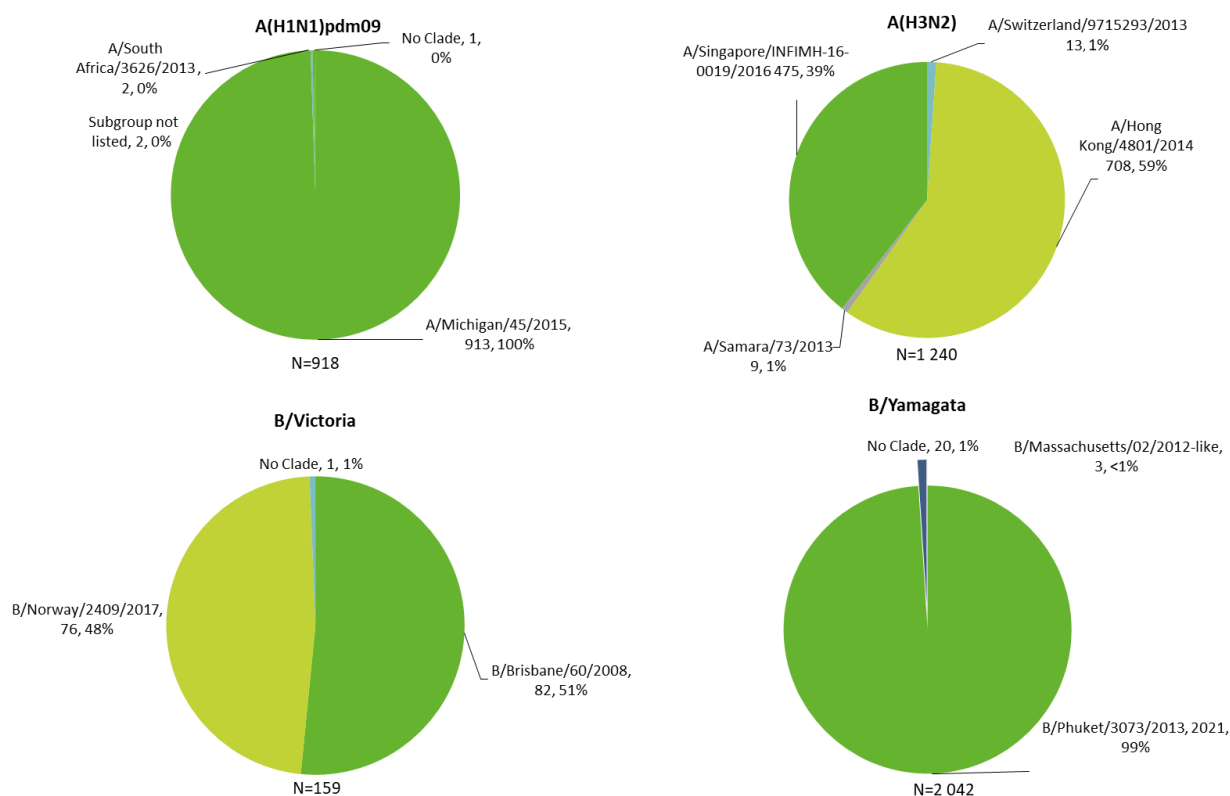
Figure 5. Proportion of B/Brisbane/60/2008 and B/Norway/2409/2017 genetic groups by week , weeks 40/2017–20/2018
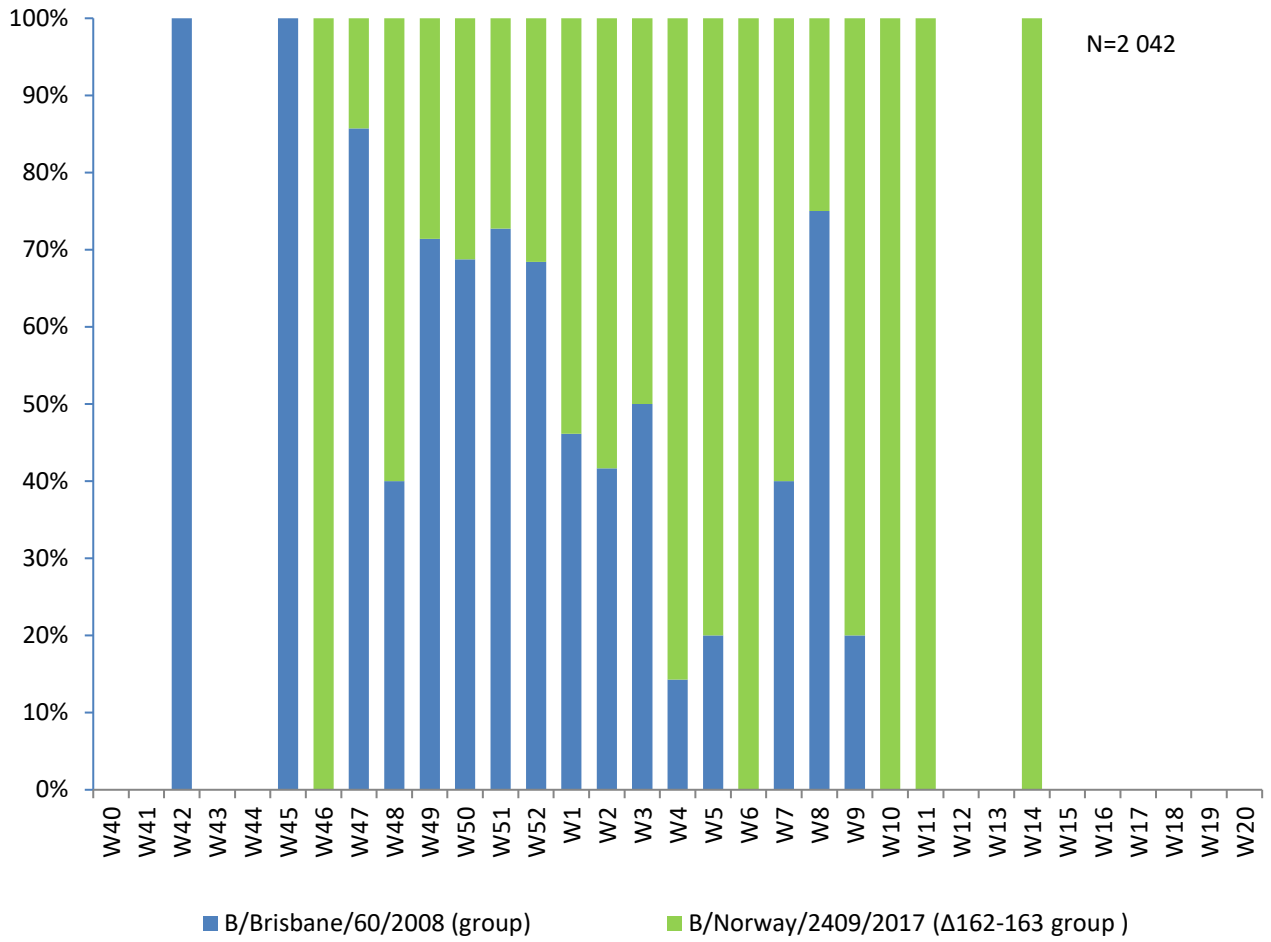
Table 3. Genetic characterisation data by category as reported to TESSy (data combined from aggregate and strain-based reports), by country, WHO European Region, weeks 40/2017–20/2018

Countries	Austria	Belgium	Czech Republic	Denmark	Finland	France	Germany	Greece	Hungary	Ireland	Italy	Kazakhstan	Luxembourg	Netherlands	Norway	Portugal	Romania	Russian Federation	Slovenia	Spain	Sweden	Switzerland	United Kingdom	Ukraine	Total by category
A/Michigan/45/2015 (H1N1)pdm09[a]	31	19	13	19	4	218	72	21	0	25	55	9	16	60	66	46	19	9	19	102	47	35	8	0	**831**
A/South Africa/3626/2013 (H1N1)pdm09	0	0	0	0	0	2	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	**2**
A(H1N1)pdm09 Subgroup Not Listed	0	0	0	0	0	2	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	**2**
A(H1N1)pdm09 No Clade	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	**1**
A/Hong Kong/4801/2014 (H3N2)[b]	12	9	0	32	45	34	46	0	0	66	11	9	0	48	88	26	0	9	19	135	54	13	52	0	**655**
A/Perth/16/2009grA/Samara/73/2013 (H3N2)	0	0	0	0	0	9	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	**9**
A/Perth/16/2009grA/Switzerland/9715293/2013 (H3N2)	0	0	0	0	0	2	0	0	0	4	0	1	1	0	0	0	0	0	0	0	3	0	2	0	**13**
A/Singapore/INFIMH-16-0019/2016 (H3N2)[c]	4	3	0	11	23	0	7	0	0	15	2	0	4	23	44	11	7	5	2	253	30	4	26	1	**457**
A(H3N2) Subgroup Not Listed	0	0	0	0	0	30	0	0	0	0	0	0	0	0	0	0	5	0	0	0	0	0	0	0	**35**
A(H3N2) No Clade	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	**0**
B/Victoria-B/Norway/2409/2017[e]	1	5	0	0	7	0	6	0	0	4	0	0	1	0	6	0	0	0	2	42	0	2	0	0	**70**
B/Victoria-B/Hong Kong/269/2017	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	**0**
B/Victoria-B/Brisbane/60/2008[a]	0	0	0	0	4	1	0	0	0	0	0	6	0	3	11	25	0	2	0	11	0	1	0	18	**82**
B/Victoria No Clade	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	**1**
B/Yamagata-B/Massachusetts/02/2012	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	**1**
B/Yamagata-B/Phuket/3073/2013[d]	71	13	0	106	75	185	99	57	5	134	56	7	19	140	82	96	40	20	17	586	119	71	22	1	**1831**
B/Yamagata No Clade	0	0	0	0	0	20	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	**20**

[a] *Vaccine component for both northern (2017–2018 season) and southern (2018 season) hemispheres*

[b] *Vaccine component for the northern hemisphere 2017–2018 season*

[c] *Vaccine component for the southern hemisphere 2018 season and northern hemisphere 2018–2019 season*

[d] *Vaccine component of quadrivalent vaccines for use in northern hemisphere 2017–2018 season and southern hemisphere 2018 season*

[e] *Deletion of K162 and N163 in the HA1 subunit of the haemagglutinin and antigenically different from the vaccine component, vaccine component for the northern hemisphere 2018–2019 season.*

Comparison of antigenic and genetic characterisation reporting

Genetic and antigenic characterisations were reported to TESSy for every week of the reporting period, i.e. weeks 40/2017 to 20/2018 (Table 4).

Antigenic analyses showed a good representation of influenza A and B viruses (41% influenza A and 59% influenza B viruses) in relation to influenza detection data (43% influenza A and 57% influenza B viruses). More influenza A(H1N1)pdm09 viruses than influenza A(H3N2) viruses were antigenically characterised, possibly due to the predominance of A(H1N1)pdm09 in some countries and difficulties associated with HI analyses of A(H3N2) viruses. Influenza B virus lineages were also characterised (4% B/Victoria and 96% B/Yamagata) in line with detections (2% B/Victoria and 98% B/Yamagata).

Genetic analyses showed similar representation of A and B viruses (49.5% and 50.5%, respectively), in contrast to detection data (43% and 57%, respectively). However, for influenza type A viruses, the proportions of subtyped viruses (43% A(H1N1)pdm09 and 57% A(H3N2)) were similar to virus detection proportions (44% and 56%, respectively). By contrast, proportions of characterised influenza B virus lineages (7% B/Victoria and 93% B/Yamagata) were somewhat disparate compared to virus detection proportions (2% and 98%, respectively), probably due to the low number of detected B/Victoria lineage viruses and the need to assess the proportion of the recently emerged Δ162-163 subgroup.

Antigenic and genetic information for the same virus can only be compared if reporting is strain-based. Eighteen countries reported strain-based data to TESSy. In many instances, the genetic characterisation data did not coincide with the antigenic characterisation data. Of 356 strain-based reports for A(H1N1)pdm09 viruses that were both antigenically and genetically characterised, 225 were reported as A/Michigan/45/2015-like in both reports. The remainder were not reported due to a reporting error that was corrected by the country after the compilation of data for this report. Of the 80 strain-based reports for A(H3N2) viruses that were both antigenically and genetically characterised, 17 were reported as A/Hong Kong/4801/2014, three were reported as A/Singapore/INFIMH-16-0019/2016 and eight were reported as 'subgroup not listed' or 'no category' in both reports. Six viruses were antigenically characterised as A/Hong Kong/4801/2014 and genetically as A/Singapore/INFIMH-16-

0019/2016; for seven viruses, the opposite was reported. The remaining viruses were reported as 'no antigenic category'; genetically, they were characterised as A/Hong Kong/4801/2014 or A/Switzerland/9715293/2013. The countries were contacted, and representative samples were sent to WHO CC/London.

Of the 41 B/Victoria viruses that were both antigenically and genetically characterised, 26 were B/Brisbane/60/2008-like and seven were B/Norway/2409/2017-like in both categories, but two viruses were antigenically characterised as B/Brisbane/60/2008 and genetically as B/Norway/2409/2017. An additional two viruses were reported with the opposite mismatch. Three were reported as having 'no antigenic category', but were genetically characterised as B/Norway/2409/2017; one was reported as 'no genetic clade', but was antigenically characterised as B/Brisbane/60/2008.

Of the 471 B/Yamagata viruses that were both antigenically and genetically characterised, 388 were characterised as B/Phuket/3073/2013 in both reports; two were genetically characterised as B/Phuket/3073/2013, but antigenically as B/Massachusetts/02/2012; one was reported with the opposite mismatch. One virus was antigenically reported as B/Massachusetts/02/2012, but genetically reported as 'no clade'; two viruses were antigenically reported as 'no category' and genetically reported as 'no clade'; 63 were genetically characterised as B/Phuket/3073/2013, but antigenically reported as 'no category', while 14 were reported with the opposite mismatch (despite falling in clade 3 by phylogenetic analysis) due to a reporting error.

Table 4. Antigenic and genetic characterisation data as reported to TESSy (data combined from aggregate and strain-based reports) by week of sampling, WHO European Region, weeks 40/2017–20/2018

		ANTIGENIC														GENETIC																				
YEAR	WEEK	A/Michigan/45/2015 (H1N1)pdm09	A(H1N1)pdm09 No Category	A/Singapore/INFIMH-16-0019/2016 (H3N2)	A/Switzerland/9715293/2013 (H3N2)	A/Hong Kong/4801/2014 (H3N2)	B/Victoria-B/Norway/2409/2017	A(H3N2) No Category	B/Victoria-B/Brisbane/60/2008	B/Victoria-B/Hong Kong/269/2017	B/Victoria No Category	B/Yamagata-B/Phuket/3073/2013	B/Yamagata-B/Massachusetts/02/2012	B/Yamagata No Category	TOTAL ANTIGENIC	A/Dakar/04/2014 (H1N1)pdm09	A/Israel/Q-504/2015 (H1N1)pdm09	A/Michigan/45/2015 (H1N1)pdm09	A/South Africa/3626/2013(H1N1)pdm09	A(H1N1)pdm09 No Clade	A(H1N1)pdm09 Subgroup Not Listed	A/Singapore/INFIMH-16-0019/2016 (H3N2)	A/Hong Kong/4801/2014 (H3N2)	A/Perth/16/2009grA/Samara/73/2013 (H3N2)	A/Perth/16/2009grA/Switzerland/9715293/2013 (H3N2)	A(H3N2) Subgroup Not Listed	A(H3N2) No Clade	B/Victoria-B/Brisbane/60/2008	B/Victoria-B/Hong Kong/514/2009	B/Victoria-B/Norway/2409/2017	B/Victoria-B/Hong Kong/269/2017	B/Victoria No Clade	B/Yamagata-B/Phuket/3073/2013	B/Yamagata-B/Massachusetts/02/2012	B/Yamagata No Clade	TOTAL GENETIC
2017	40			1											1			5				5	11							2			3			26
	41	2				2								1	5			4				2	13			1							5			25
	42	1	1									2			4			5				5	4					2					6			22
	43	1	1			1						1			4			4				4	9										5			22
	44	1				2								1	4			3				7	8					1					5			24
	45	2	2			2		2				1		2	11			10				12	10					2					10			44
	46	1	1			2								1	5			6				11	21			1				4			18			61
	47	1	4			2						5		2	14			9				8	21			2		6		1			31			78
	48	2	7	1		1	1		1			17		1	31			16				20	17			1		2		3			59			118
	49	6	5	2						2		13			28			17				11	23			2		5		2			61			121
	50	9	17	2	1	2	1	2	4			41		3	82			47				17	32	2		1		11		5			85			200
	51	18	18	1	1	1	1	1	7			45		11	104			56				21	47			3		16		6			129		1	279
	52	22	21	1		4	1		7		1	60		8	125			67				25	35			1		13		6			163		2	312
2018	1	28	20	1		4	4	2	2			97	1	6	165			77				26	38	1		2		6		7			215			372
	2	48	14	4	2	4	1	2	2			116	1	1	195			66				35	49	1		3		5		7			171	1		338
	3	60	13	1		7	3		4			140		4	232			54				26	45			1		5		5			166			302
	4	106	3	4	1	6	7	2	4		1	149		2	285			74	1	1		32	35			1		1		6			158		1	310
	5	97		11	1	3	11	4	4			243		4	378			54				24	28	1		1		2		8			121			239
	6	89	1	7		12	9	2	2			184	1	2	309			47				16	43			2				1			110		1	220
	7	139	1	19		6	10	9			1	273			458			67	1			34	41	1		3		2		3			116			268
	8	140	1	19	1	16	6	3	3			234		1	424			43				23	28			2		1		3	1	1	89		3	194
	9	132	1	16	1	24	3	6	1	1		224		1	410			27			1	24	26	2		1		1		1	4		69	1	2	159
	10	130		6	1	12	1	4	1			197			352			48			1	31	36					5			4		76		6	207
	11	115		2		13	7					142		2	281			30				17	30	2		1					1		53		2	136
	12	81			1	1	3	3				100		3	192			25				16	18			1							36		1	97
	13	57		2		5	1					59		7	131			15				3	11	1		1							27			58
	14	31		2		4	3	1				65			106			13				11	15	1		3					2		15			60
	15	20				12						22		3	57			10				3	9			1							11			34
	16	5				4						10			19			14				4	4										5			27
	17	9		1		4						7			21																		1			1
	18	3				3									6							2											2			4
	19					2									2																					0
	20	1													1			1																		1
	ALL	1357	131	103	10	161	59	51	50	1	3	2447	3	66	4442	0	0	913	2	1	2	475	708	9	13	35	0	82	0	76	0	1	2021	1	20	4359

Genetic and phylogenetic analysis of HA sequences

There were 2 846 HA sequences reported to TESSy for which accession numbers from the GISAID EpiFlu database were provided. Countries that contributed the reported HA sequences are shown in Table 5. Patient vaccination status was reported for 2 051 of the viruses with EpiFlu accession numbers for HA genes; 376 (18.3%) viruses were recovered from vaccinated patients.

Table 5. Number of HA sequences with EpiFlu database accession numbers reported to TESSy, by subtype and country, WHO European Region, weeks 40/2017–20/2018

Country/ HA sequences	A(H1N1)pdm09	A(H3N2)	B/Victoria	B/Yamagata
Austria	31	16	1	71
Belgium	19	12	5	13
Finland	4	29	9	24
France	223	75	2	205
Germany	72	38	6	99
Hungary	-	-	-	5
Ireland	25	85	4	134
Italy	41	11	-	51
Luxembourg	15	5	-	
Netherlands	42	45	2	127
Norway	16	37	4	24
Romania	19	13	-	39
Russian Federation	4	5	2	3
Slovenia	19	21	2	17
Spain	85	351	48	253
Sweden	47	87	-	119
Ukraine	-	1	18	1
United Kingdom	6	41	-	12
Total number of HA sequences	**668**	**878**	**103**	**1 197**

Influenza A viruses

A(H1N1)pdm09

By week 20/2018, 668 HA gene sequences from A(H1N1)pdm09 viruses were deposited in the GISAID EpiFlu database and reported to TESSy; 662 were retrieved and included in a phylogenetic analysis.

All of the viruses fell in genetic subclade 6B.1, including the vaccine virus A/Michigan/45/2015, which is defined by the substitutions S84N, S162N (introducing a new potential glycosylation site) and I216T in HA1 (Figure 6). Within this subgroup, the majority of viruses (644, 96%) cluster into a genetic subgroup defined by the HA1 amino acid substitutions S74R, S164T (which alters the glycosylation motif at residues 162 to 164) and I295V in their HA1. Genetic clusters within clade 6B.1 included 251 viruses carrying the amino acid substitution T120A and 156 viruses with amino acid substitution S183P. Two or more viruses carried one of the amino acid substitutions T72S, P137S, I149V, S183P, L233I, E235K or D, V250A, N260D, I267T. Eighteen (2%) of the circulating viruses carried the amino acid substitution D222G or N or K in their HA1. There were no subgroup 6B.2 viruses identified.

Of the 469 viruses that were derived from patients with known vaccination status, 57 were from vaccinated patients (12.1%).

Figure 6. Phylogenetic comparison of influenza A(H1N1)pdm09 HA genes[*]

Colour coding indicates the northern hemisphere 2017–2018 vaccine virus in red, reference strains in black, and TESSy-reported sequences according to the virus collection month (January, February, March, April, May, June, July, August, September, October, November, December). 'VACCINFULL' and 'NOVACC' indicate viruses that were derived from patients with known vaccination status, vaccinated and non-vaccinated, respectively.

A(H3N2)

By week 20/2018, 878 HA gene sequences from A(H3N2) viruses deposited in in the GISAID EpiFlu database and reported to TESSy; all were retrieved and included in the genetic analysis.

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[*] Due to their complexity, Figures 6–9 are not included; they are, however, available for download from the ECDC website.

Of the viruses analysed, 868 belonged to the 3C.2a genetic clade. Of the clade 3C.2a viruses, 378 (43.5%) belonged to the genetic subclade 3C.2a1. Ten (<1%) of the reported sequences fell in the 3C.3a clade represented by A/Switzerland/9715293/2013 (Figure 7). Viruses in clade 3C.2a have predominated since the 2014–2015 season and continued to predominate among the A(H3N2) viruses during the 2017–2018 season in the WHO European Region.

Clade 3C.2a viruses are defined by L3I, N128T (gain of potential glycosylation site), N144S (loss of potential glycosylation site), N145S, F159Y, K160T (gain of potential glycosylation site), P198S, F219S, N225D and Q311H in HA1. Different genetic groups within clade 3C.2a have emerged; the most populated subclade, 3C.2a2 (453 viruses, 52%), was defined by amino acid substitutions T131K, R142K and R261Q in HA1; subclade 3C.2a3 (34 viruses, 4%) was defined by N121K and S144K in HA1, with additional subgroups of viruses carrying HA genes that encoded N122D (potential loss of a glycosylation site) and S262N in HA1, or the substitution R261Q in HA1; subclade 3C.2a4 (three viruses, <1%) was defined by N31S, D53N, R142G, S144R, N171K, I192T, Q197H, A304T in HA1 (Figure 6).

Subclade 3C.2a1 viruses encode additional N121K and N171K substitutions in HA1. Within subclade 3C.2a1, two genetic groups have emerged, namely 3C.2a1a (4 viruses, 1%) with T135K (loss of potential glycosylation site) in HA1, and 3C.2a1b (374 viruses, 99%) defined by K92R and H311Q substitutions in HA1, often combined with I58V, or R142G and E62G, and T135K (loss of potential glycosylation site) in HA1 (Figure 6).

Amino acid substitutions often occurred in one or more of the five HA antigenic sites (sites A, B, C, D, and E) and involved N-linked glycosylation motifs in HA [15,16]. Substitutions at residues 62, 78, 91, 121, 122, 128, 131, 135, 140, 142, 144, 150, 159, 160, 171, 193, 197, 212, 219, 252, 262, 309 and 326 in HA1 were observed at several places in the phylogeny.

Of the 572 viruses that originated from patients with known vaccination status, 159 (27.8%) were from vaccinated patients. Of the vaccinated patients, 85 (53.5%) were infected with clade 3C.2a viruses (excluding subclade 3C.2a1), 66 (41.5%) with subclade 3C.2a1 viruses, two (1.2%) with clade 3C.3a viruses, and six (3.8%) viruses were reported as 'subgroup not listed'.

Figure 7. Phylogenetic comparison of influenza A(H3N2) HA genes*

Colour coding indicates the northern hemisphere 2017–2018 vaccine strain in red, reference strains in black, and TESSy-reported sequences according to the virus collection date by month (January, February, March, April, May, June, July, August, September, October, November, December). 'VACCINFULL' and 'NOVACC' indicate viruses that were derived from patients from known vaccination status, vaccinated and non-vaccinated, respectively.

Influenza B viruses

B/Victoria-lineage

By week 20/2018, 103 B/Victoria-lineage HA sequences were deposited in the GISAID EpiFlu database and reported to TESSy. Of these, 101 were retrieved and included in the phylogenetic analysis.

All B/Victoria lineage viruses belonged to genetic clade 1A. All of the sequences carried additional amino acid substitutions of I117V and N129D or N129G in HA1 compared to B/Brisbane/60/2008. Sixty-six HA sequences (65%) belonged to a newly emerged subclade of viruses carrying two amino acid deletions at positions 162 and 163 in HA1 (Δ162-163), represented by B/Norway/2409/2017. The Δ162-163 viruses carried additional substitutions N129G and I180V in HA1, sometimes also combined with N126S or E128K. These viruses originated from Austria, Belgium, Germany, Ireland, Finland, France, Slovenia and Spain. None of the reported viruses carried the three amino acid deletion at positions 162, 163 and 164 (Δ162-164) in HA1, identified in viruses like B/Hong Kong/269/2017. Two or more viruses, not belonging to the new subclade, carried one of the following HA1 amino acid substitutions: V87A, A154T, I175V, M251L, I261L (Figure 8).

Of the 68 viruses that were derived from patients with known vaccination status, four were from a vaccinated patient (5.9%). The HA sequence of three of these viruses carried the Δ162-163 deletion.

Figure 8. Phylogenetic comparison of influenza B/Victoria-lineage HA genes*

Colour coding indicates the northern hemisphere 2017–2018 vaccine strain in red, reference strains in black, and TESSy-reported sequences according to the virus collection date by month (January, February, March, April, May, June, July, August, September, October, November, December). 'VACCINFULL' and 'NOVACC' indicate viruses that were derived from patients from known vaccination status, vaccinated and non-vaccinated, respectively.

B/Yamagata-lineage

There were 1 197 B/Yamagata HA sequences deposited in the GISAID EpiFlu database and reported to TESSy. Of these, 1 189 were retrieved and included in phylogenetic analysis.

All of the viruses fell in clade 3 represented by B/Phuket/3073/2013, the vaccine virus recommended for inclusion in quadrivalent influenza vaccines for the 2017–2018 northern hemisphere season (Figure 8). All viruses fell in a subgroup defined by the amino acid substitutions L172Q and M251V in HA1. There were 77 viruses with S229N substitution and 48 viruses with D232N in HA1. More than two viruses carried one of the following HA1 amino acid substitutions: P31Q, R50K, Q122R, N165H, V176I, T181A, G183E and K253S (Figure 9).

Of the 942 viruses that were derived from patients with known vaccination status, 156 (16.6%) were from vaccinated patients.

Figure 9. Phylogenetic comparison of Influenza B/Yamagata-lineage HA genes*

Colour coding indicates the northern hemisphere 2017–2018 vaccine strain in red, reference strains in black, and TESSy-reported sequences according to the virus collection date by month (January, February, March, April, May, June, July, August, September, October, November, December). 'VACCINFULL' and 'NOVACC' indicate viruses that were derived from patients from known vaccination status, vaccinated and non-vaccinated, respectively

Antiviral susceptibility

During weeks 40/2017 to 20/2018, neuraminidase inhibitor susceptibility was assessed for 3 693 viruses (1 174 A(H1N1)pdm09, 982 A(H3N2) and 1 537 type B). Two type B viruses carried the neuraminidase (NA) amino acid substitution D197N and showed evidence of reduced inhibition (RI) by oseltamivir and zanamivir, and two type B viruses showed RI by oseltamivir only. Nineteen A(H1N1)pdm09 viruses carried the NA amino acid substitution H275Y and showed evidence of highly reduced inhibition (HRI) by oseltamivir; two showed RI by zanamivir only. Two A(H3N2) viruses carried NA amino acid substitution R292K and showed evidence of RI by oseltamivir and zanamivir.

Conclusion

A total of 203 511 influenza virus detections and 4 442 antigenic and 4 359 genetic characterisations were reported to TESSy from the WHO European Region; the reporting period covered weeks 40/2017 to 20/2018. Influenza virus types A and B were co-circulating, with a higher proportion of type B viruses, notably from the beginning to the peak of the season. Different proportions of circulating influenza virus types and influenza A subtypes were observed between countries in the European Region. B/Yamagata-lineage viruses greatly outnumbered those of the B/Victoria-lineage. Patterns of circulation may have differed due to regional differences but may have also been influenced by different proportions of sentinel and non-sentinel sources (please see maps and country-specific tables at www.flunewseurope.org).

The main antigenic categories reported by subtype were A(H1N1)pdm09 A/Michigan/45/2015-like, A(H3N2) A/Hong Kong/4801/2014-like, A(H3N2) A/Singapore/INFIMH-16-0019/2016-like, A(H3N2) A/Switzerland/9715293/2013-like, B/Brisbane/60/2008-like or B/Norway/2409/2017-like (Victoria lineage), and B/Phuket/3073/2013- or B/Massachusetts/02/2012-like (Yamagata lineage). The main genetic categories reported by subtype were A(H1N1)pdm09 A/Michigan/45/2015 (subgroup 6B.1), A(H3N2) A/Hong Kong/4801/2014 (clade 3C.2a), B/Norway/2409/2017 (almost at equal proportions

with B/Brisbane/60/2008 (Victoria-lineage clade 1A)), and B/Phuket/3073/2013 (Yamagata-lineage clade 3).

Regarding similarity of circulating viruses to the 2017–2018 northern hemisphere vaccine components, viruses reported to TESSy showed that the predominant lineage for influenza B viruses was B/Yamagata, which was a component of quadrivalent vaccines, but not trivalent vaccines. Influenza B/Victoria lineage viruses were detected in low numbers, but a substantial proportion of these were antigenically distinguishable from the vaccine virus, B/Brisbane/60/2008. For A(H3N2) viruses, although the majority (49.5%) of the viruses were reported as vaccine component A/Hong Kong/4801/2014-like, 31.6% were A/Singapore/INFIMH-16-0019/2016-like (recommended for inclusion in trivalent vaccines for the northern hemisphere 2018–2019 season) and 3% were A/Switzerland/9715293/2013-like. The majority of A(H1N1)pdm09 viruses that circulated were reported antigenically as A/Michigan/45/2015-like and all fell in genetic subgroup 6B.1, represented by A/Michigan/45/2015.

Two new B/Victoria-lineage groups have emerged in both hemispheres, with deletions in the HA gene. In the first group, the HA gene encodes deletion of residues 162 and 163 of HA1. The second group, which encodes deletion of residues 162, 163 and 164 of HA1, detected in China, Hong Kong and other Asian countries, was not detected in the WHO European Region sequences reported to TESSy. As both groups are antigenically distinct from the vaccine virus and from each other, it is crucial to monitor the circulation of these viruses. Currently, more than half of the genetically characterised B/Victoria-lineage viruses belonged to the Δ162-163 group and were reported by eight countries. There was a trend of increasing frequency of the Δ162-163 group as the season progressed (Figure 5).

It is important to analyse virus characterisation results in the light of virus detection data. Proportions of detected influenza types matched relatively well with the proportions of antigenically and genetically characterised viruses. In terms of the distribution of influenza B lineages, the proportion of genetically characterised viruses of the Victoria lineage was higher compared to their overall detections. Some specimen selection bias based on different selection criteria, the choice of further genetic and antigenic analyses, and the variable circulation of influenza A virus subtypes and influenza B virus lineages in different countries may have contributed to the slight discrepancies.

A few limitations should be considered. Only 28 (57%) of the 49 countries reporting influenza detection data contributed virus characterisation data. The proportions of subtypes and lineages among antigenically and genetically characterised viruses may therefore not apply to the whole WHO European Region. The genetic analysis was based on the HA1 coding region of the HA gene and does not extend to changes in other virus genes. Incorrectly submitted HA sequence accession numbers and sequences related to these were excluded from analysis. Furthermore, the antigenic data currently reported to TESSy do not include antigenic titres, so no direct analysis of antigenic properties was possible.

Despite the indicated limitations of influenza surveillance in the WHO European Region, influenza virus detection and virus characterisation data remain crucial for the selection of viruses to be sent to a WHO CC for detailed analyses. These analyses inform the decision-making process that eventually leads to a recommendation at the biannual WHO meeting on the composition of influenza virus vaccines.

Contributors and acknowledgements

Disclaimer

The data were extracted from the TESSy database on 2 July 2018. Errors in the database at this point in time will most likely have affected the analysis.

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