Risk assessment of seasonal influenza, EU/EEA, 2016–2017

Update, 25 January 2017

Conclusions and options for response

Most countries with high influenza activity have reported appreciable numbers of cases with severe outcomes. These case numbers place a high burden on hospitals. Increased excess winter mortality from all causes has been observed in some, but not all, EU countries, concurrent with the circulation of influenza. While peaks of influenza activity have been reached in some countries, e.g. Portugal and Italy (where transmission rates and associated severe cases have decreased), others, e.g. France, Greece, Spain and the United Kingdom (Scotland), are still experiencing increasing influenza activity (ILI/ARI rates) and excess deaths. EU Member States falling in the latter category should critically assess the healthcare resources necessary to provide care to influenza patients at risk of developing severe disease in order to minimise severe outcomes and consider addressing any gap in resources as a matter of urgency.

It is also of critical importance that all EU Member States collect and can share information that enables rapid risk and impact assessments to be undertaken. This includes surveillance of laboratory-confirmed influenza cases admitted to intensive care units and mortality monitoring, as well as sharing these data with ECDC and EuroMOMO. Any EU Member State that has not implemented laboratory-confirmed influenza monitoring in hospitals and is not submitting virus-based data should consider doing so, as this would improve the real-time assessment of the current influenza season and future epidemics or pandemics.

Continued vaccination of the elderly and other at-risk individuals at this time is unlikely to have a major impact in those EU Member States that have reached the peak of influenza activity, as full immunity is not developed until two weeks post vaccination. However, efforts to vaccinate these groups should be continued in other Member States. Efforts to improve vaccination coverage should start immediately after the current season, particularly for the elderly, other at-risk groups, healthcare workers and children – if nationally recommended for the 2017–2018 season.

Given the low vaccination coverage in most EU Member States and the suboptimal effectiveness of influenza vaccines, timely administration of neuraminidase inhibitors, ideally within 48 hours of symptom onset, for probable or laboratory-confirmed cases of influenza infection should be considered for vaccinated and non-vaccinated patients in at-risk groups. In addition, prophylaxis in high-risk contacts should always be considered [1].

Source and date of request

ECDC internal decision, 16 January 2017.

Public health issue

Update of rapid risk assessment on seasonal influenza (24 December 2016) in light of additional epidemiological and virological data indicating a severe impact on the seasonal increase of influenza cases, with stresses on the healthcare system, excess mortality and suggestions of suboptimal vaccine effectiveness.

Consulted experts

External experts (in alphabetical order): M. Brytting, R. Daniels, A. Larrauri, B. Lina, R. Pebody, K. Prosenc, W. van der Hoek

ECDC (in alphabetical order): C. Adlhoch, E. Broberg, A. Melidou, P. Penttinen, R. Snacken

Disease background information

The ongoing influenza season started early in eleven EU countries on week 46/2016, with an overall 13% of sentinel specimens testing positive for influenza in EU/EEA countries (Figure 1) [2]. By week 49/2016, clinical indicators (ILI/ARI rates) were still at baseline level or just starting to increase while influenza detection rates continued to rise in sentinel settings. From the beginning of the season, the vast majority (98%) of type A viruses were subtype A(H3N2) belonging to clade 3C.2a, which is the same clade as the vaccine strain A/Hong Kong/4801/2014, with most falling in an emerging subclade, 3C.2a1, represented by A/Bolzano/7/2016, which has been antigenically well matched with the vaccine component [3]. First estimates in Finland [4] and Sweden [5] suggested a suboptimal vaccine effectiveness (VE) against laboratory-confirmed infection in people aged 65 years and older. Based on the experiences of 2011–2012 and 2014–2015, with A(H3N2) virus predominating, severe outcomes were anticipated, particularly in the elderly. Since week 51/2016, there have been indications of disease severity with high hospitalisation rates and excess mortality from all causes in some, but not all, EU countries.

The main objectives of this update are to estimate the extent of observation of these severe cases and to evaluate the intensity of severe outcomes in EU countries for the rest of the season, in particular in people above 65 years of age, in comparison to previous seasons dominated by A(H3N2) viruses.

Figure 1. Weekly proportions of primary care sentinel specimens testing positive for influenza in the EU/EEA, seasons 2011–2012 to 2016–2017*
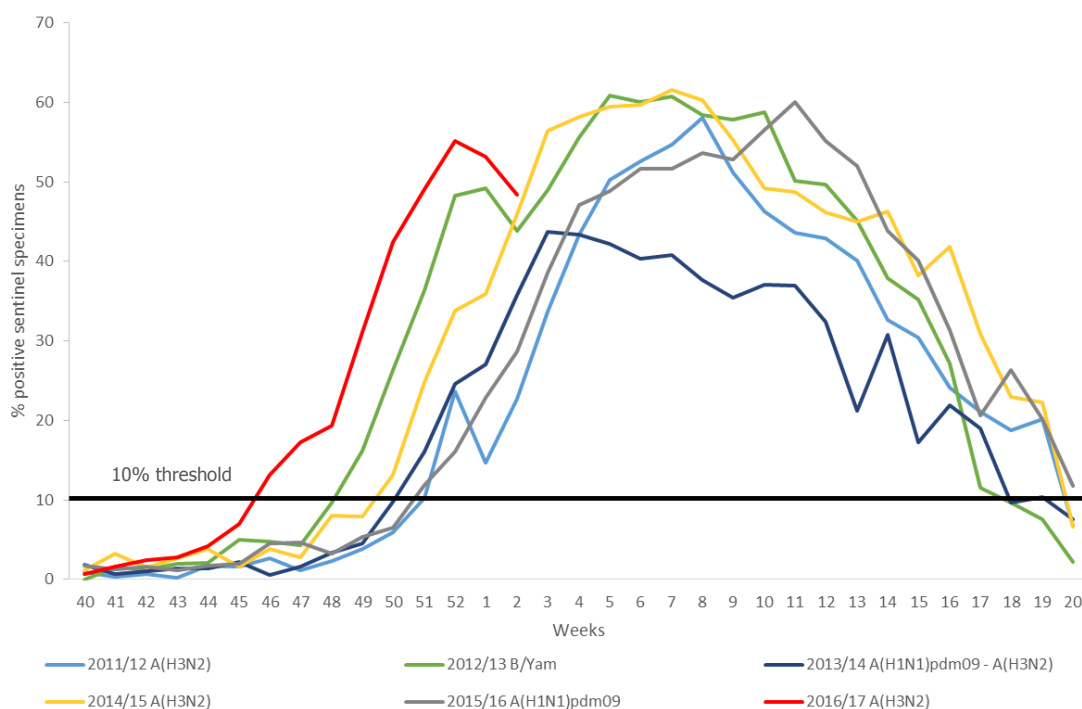
* Week 53 during season 2015–2016 excluded.

Event background information

Data sources

This risk assessment is based on the weekly clinical (influenza-like illnesses (ILI) and acute respiratory infections (ARI)), epidemiological and virological data from primary and secondary healthcare settings, routinely collected and reported to ECDC by public health institutes and national influenza centres through the European Influenza Surveillance Network (EISN) and the European Reference Laboratory Network for Human Influenza (ERLI-Net). Additional information was gathered from peer-reviewed literature, national weekly bulletins, serological surveys, ECDC epidemic intelligence, and EuroMOMO (European monitoring of excess mortality for public health action).

Primary care situation in EU/EEA countries

By week, 2/2017, 23 EU/EEA countries reported widespread geographic influenza activity. All countries reported >10% of specimens testing positive for influenza (Figure 2).

Figure 2. Proportions of primary care sentinel specimens testing positive for influenza in EU/EEA countries, weeks 40–2/2017
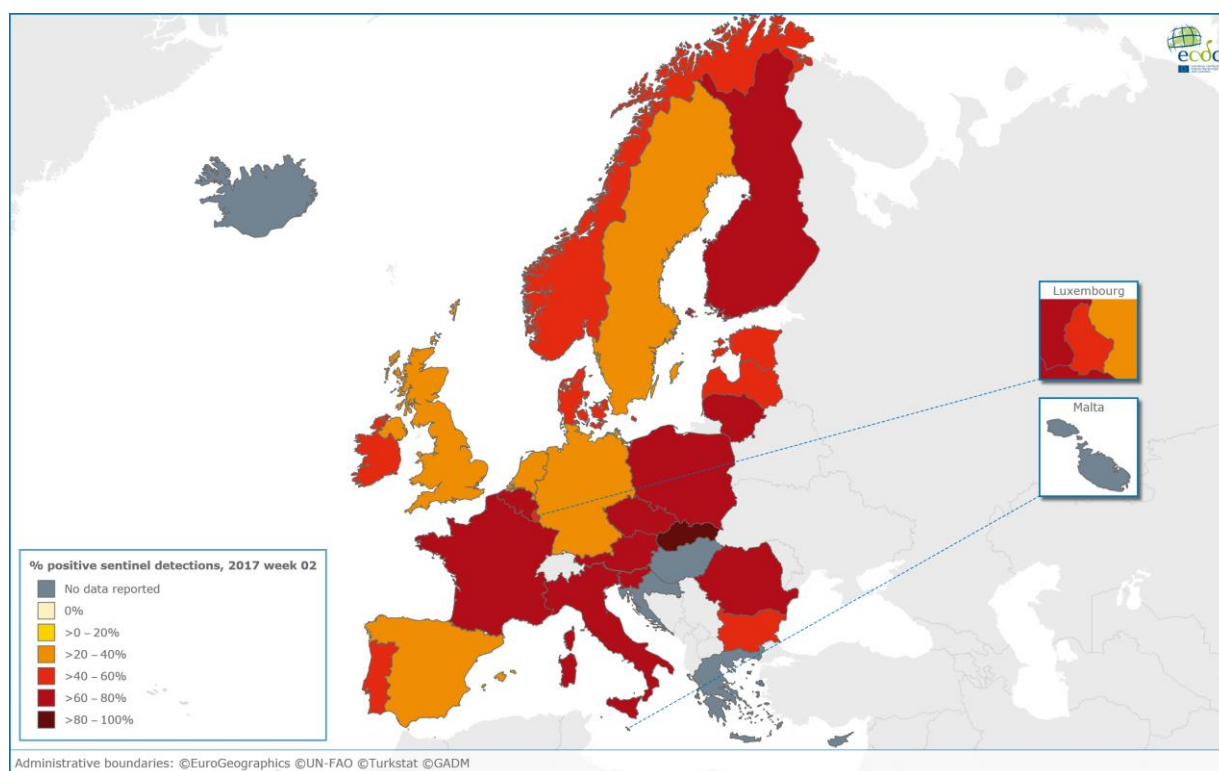

Note: Latvia, Romania and Slovakia tested <10 specimens

The proportion of positive specimens in the region seems to have peaked during week 52/2016. However, a reporting delay can influence the estimates (Figure 3). By week 2, ILI/ARI rates were still increasing in most EU/EEA countries. In Bulgaria, Italy, Ireland, Norway and Slovakia, clinical activity seemed to have peaked but a surveillance artefact due to holidays cannot be excluded. The peak in the weekly detections rate for ILI and influenza seems to have passed in Finland and Sweden.

The seasonal influenza epidemic is in full swing across the EU/EEA, with some countries having peaked already while others are still reporting increasing trends. In week 2/2017, 98% of the circulating viruses in the community were type A viruses; only 2% were type B viruses. A(H3N2) represented 98% of type A viruses in all countries. Of the few type B viruses detected, 36 were ascribed to a lineage, with 63% belonging to the B/Yamagata lineage.

Figure 3. Weekly numbers and proportions of primary care sentinel specimens testing positive for influenza, by type and subtype, EU/EEA, 2016–2017
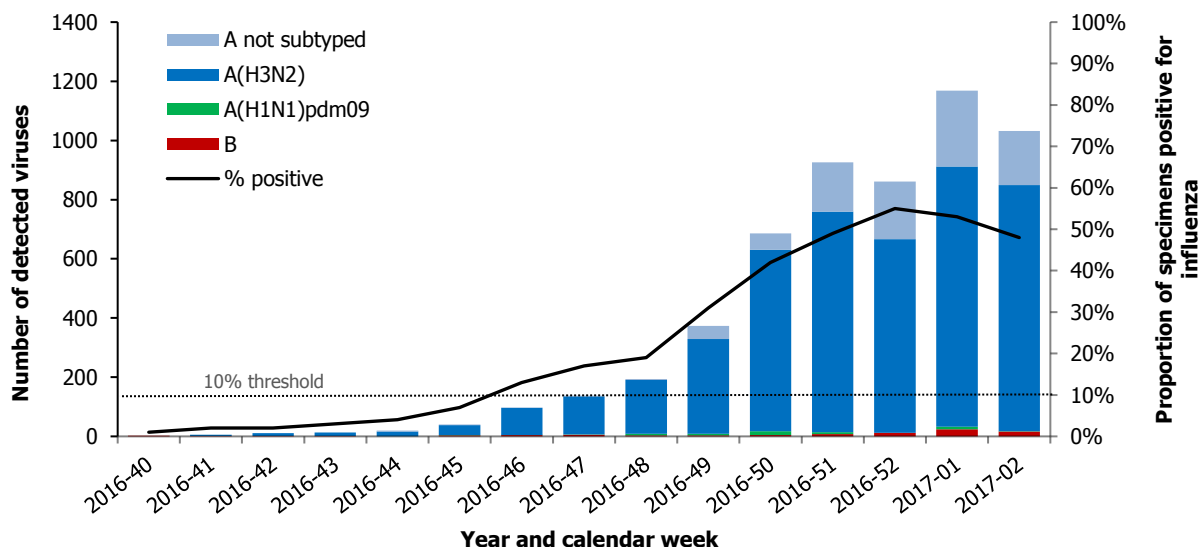
## Secondary care situation in EU/EEA countries

Between weeks 40/2016 and 2/2017, eight countries (the Czech Republic, Finland, France, Ireland, Romania, Spain, Sweden and the UK) reported hospitalised laboratory-confirmed influenza cases. Of the 2 996 reported cases, 1 457 were admitted to intensive care units (ICUs) and 1 539 to other wards. The vast majority (98%) of hospitalised cases were infected by influenza type A viruses, and 445 (86%) of the 518 subtyped viruses were A(H3N2) viruses. ICU cases show a trend towards an increase in the age of patients, with 25% in the age group 40–64 years and 68% in the age group 65 and older (Figure 4).

Figure 4. Distribution of confirmed influenza cases admitted to ICUs, by virus types/subtypes and age group, EU/EEA, weeks 40/2016–1/2017
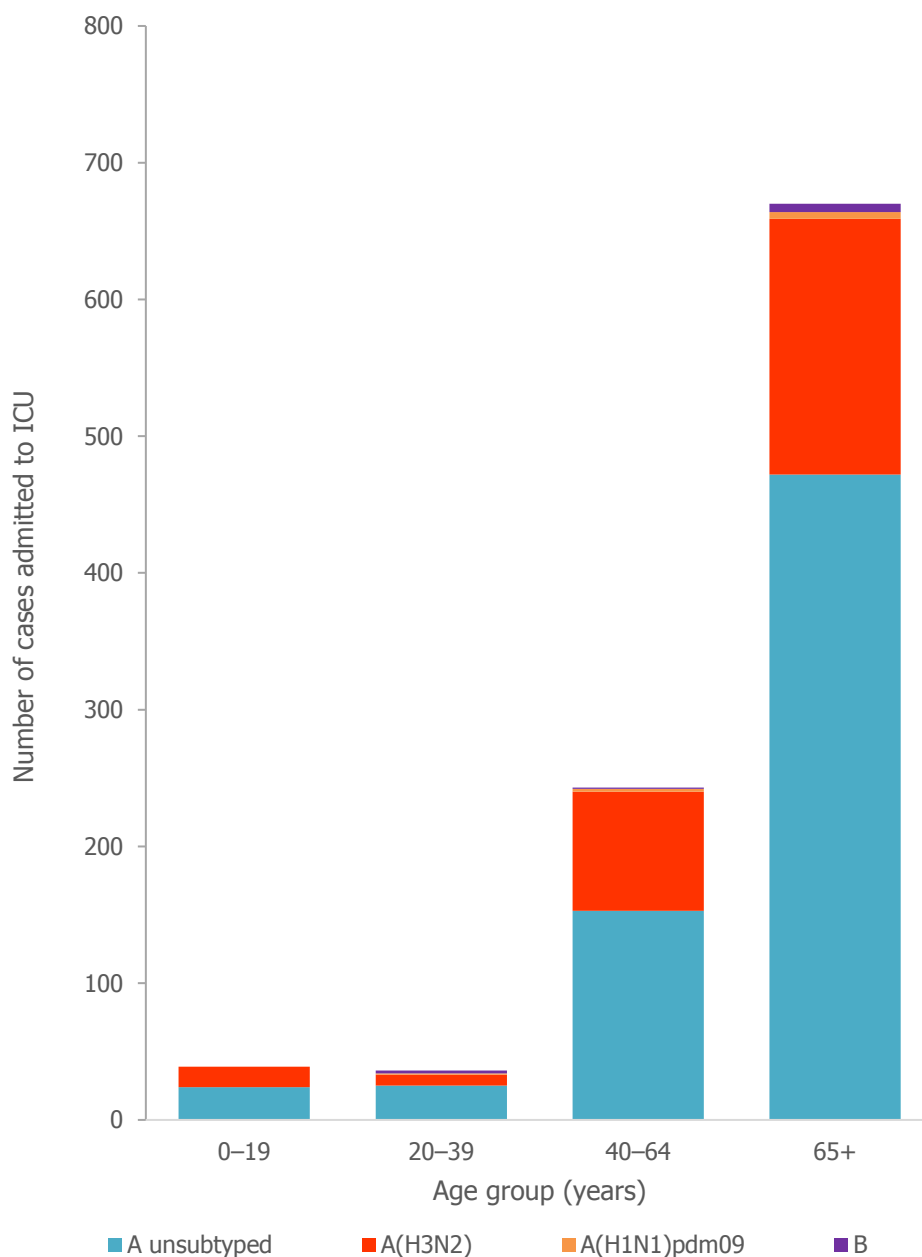
The peak in the weekly number of cases admitted to ICU remains in the range of values reported during the 2014–2015 season, which was also dominated by A(H3N2) viruses (Figure 5). During the 2014–2015 season, the proportion of people aged 65 years or older was lower (49%) and more (37%) middle aged people (40–64 years of age) were admitted to ICUs than during the current season (68% and 25%, respectively). However, in the 2014–2015 season, a higher proportion of A(H1N1)pdm09 and type B viruses was detected in ICU patients, notably among people younger than 65 years of age. Although the number of cases being admitted to ICUs seems to be decreasing, a reporting delay may be influencing this. ICU data have to be interpreted with caution, as these are absolute numbers with possibly different denominators in different seasons.

Figure 5. Number of influenza cases admitted to ICUs by type and subtype in eight EU/EEA countries, seasons 2012–2013 to 2016–2017
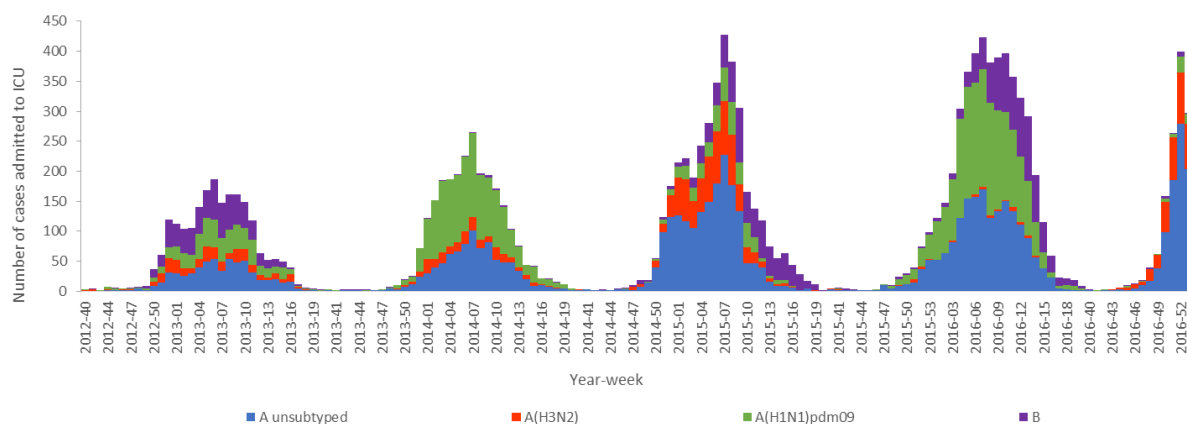
Until week 2/2017, 221 fatal cases have been reported from hospital settings in seven countries (the Czech Republic, Finland, France, Ireland, Romania, Spain and Sweden); 125 of these cases were reported from ICUs, and 96 cases were in other wards. Of the 221 cases, influenza A(H3N2) was detected in 100 patients (45%); 119 (54%) influenza A viruses were unsubtyped, and two patients (1%) had a B virus infection. The majority (184/220, 84%) of the fatal cases were older than 65 years of age, among them 54 between 70 and 79 years of age; 105 patients were 80 years and older.

During the 2014–2015 season, 604 fatal cases were reported from hospitals in seven countries (Finland, France, Ireland, Romania, Spain, Sweden and Slovakia); 427 of these cases were in ICUs, and 177 from other wards. Of the fatal cases, 104 (17%) cases were due to B virus infection, and 500 cases (83%) were due to influenza A infection, with 186 typed as A(H3N2) and 80 as A(H1N1)pdm09. Of the fatal cases, 398 (66%) were older than 65 years of age, and 172 cases (29%) were between 40 and 64 years of age.

During week 2/2017, national reports and data from epidemic intelligence indicated unusual pressures on health care services in several EU/EEA countries. For example, in France the situation was considered critical and required an intervention at the political level, and all hospitals were asked to delay non-urgent surgical operations [6]. In the UK, in week 1, 84 outbreaks in care homes were reported, with high hospital and ICU admissions rates for influenza cases, although the numbers did not reach the levels seen in 2015–2016 [7]. In both countries, the highest hospitalisation and mortality rates were observed in the very elderly (80 years and above).

Starting in week 51/2016, the EuroMOMO project reported increasing excess weekly mortality from all causes in people aged 65 years and above in Portugal, Italy, France, Greece, Italy, Spain and the United Kingdom (Scotland) [8]. After taking into account the early start of the season, the pooled excess mortality appears to be comparable to the previous A(H3N2)-dominated season in 2014–2015. In some countries, however, the excess mortality this season could exceed that in the 2014–2015 season. No excess all-cause mortality has yet been observed in some countries, e.g. in the UK.

Virus characteristics

Virus characteristics are reported to TESSy through aggregate or strain-based reporting by the Member States. The genetic testing is based on sequencing, and in strain-based data collection a reference to a sequence identifier can be reported. In aggregate reporting, phylogenetic group by reference strain is indicated. The antigenic characterisation is based mainly on haemagglutination inhibition testing, and antigenic group by reference strain is reported through aggregate or strain-based data collection.

For specimens collected since week 40/2016, genetic characterisation of 700 viruses has been reported through aggregate (n=197) and strain-based (n=503) reporting (Table 1). Among 650 A(H3N2) viruses, 203 (31%) fall in the vaccine component clade (3C.2a), and 447 (69%) in the new 3C.2a1 subclade. Viruses in these two clades are antigenically similar. Only two (<1%) viruses falling in the clade of the previous vaccine virus, 3C.3a, have been reported. All seven A(H1N1)pdm09 viruses fell in clade 6B, with five falling in subclade 6B.1 like the virus recommended for southern hemisphere 2017 vaccines: viruses in these genetic groupings remain antigenically similar to the 2016–2017 northern hemisphere vaccine virus, A/California/7/2009. Of the 41 influenza B viruses genetically characterised, one third were of the B/Victoria-lineage, included in the northern hemisphere 2016–2017 and southern hemisphere 2017 trivalent influenza vaccines, and two thirds were of the B/Yamagata-lineage included in quadrivalent vaccines (Table 1).

Eighty-five viruses were antigenically characterised, and 40 of those reported through strain-based reporting (Table 1). Of a total of 75 A(H3N2) viruses, the majority (n=72, 96%) were antigenically similar to the current vaccine component A/Hong Kong/4801/2014. One A(H1N1)pdm09 virus was characterised as being similar to the vaccine component. Of the nine antigenically characterised influenza B viruses, three were characterised as B/Victoria-lineage viruses similar to the vaccine component, while six were of the B/Yamagata-lineage, which is included in quadrivalent vaccines.

Table 1. Influenza viruses attributed to genetic and antigenic groups, weeks 40/2016–2/2017

Phylogenetic group	Number of viruses
A(H1N1)pdm09 A/Michigan/45/2015 (subgroup 6B.1)[b]	5
A(H1N1)pdm09 A/South Africa/3626/2013 (subgroup 6B)	2
A(H3N2) A/Bolzano/7/2016 (subgroup 3C.2a1)	447
A(H3N2) A/Hong Kong/4801/2014 (subgroup3C.2a)[a, b]	203
A(H3N2) A/Switzerland/9715293/2013 subgroup (3C.3a)	2
B/Brisbane/60/2008 (Victoria lineage clade 1A)[a, b]	13
B/Phuket/3073/2013 (Yamagata lineage clade 3)[c]	28
Antigenic group	**Number of viruses**
A(H1)pdm09 A/California/7/2009 (H1N1)-like[a]	1
A(H3) A/Hong Kong/4801/2014 (H3N2)-like[a, b]	72
A(H3) A/Switzerland/9715293 (H3N2)-like	3
B/Brisbane/60/2008-like (B/Victoria/2/87 lineage)[a, b]	3
B/Phuket/3073/2013-like (B/Yamagata/16/88-lineage)[c]	6

[a] Vaccine component for northern hemisphere 2016–2017 season

[b] Vaccine component for southern hemisphere 2017 season

[c] Vaccine component of the quadrivalent vaccine for both northern and southern hemispheres

In total, 907 viruses were reported to TESSy using the strain-based reporting system. Among the data reported were 249 influenza virus HA sequences from seven EU countries (Austria, Germany, Finland, the Netherlands, Norway, Spain and Sweden): 242 (97%) were derived from A(H3N2) viruses, and sequences were retrieved from GISAID. Phylogenetic analysis of the HA1 coding sequences reported to TESSY revealed that 70 (29%) A(H3N2) viruses belonged to subclade 3C.2a, represented by A/Hong Kong/4801/2014 and 172 (71%) belonged to subclade 3C.2a1, represented by A/Bolzano/7/2015 (Figure 6) – similar proportions as reported by phylogenetic groups in Table 1.

Viruses falling within subclade 3C.2a are defined by the characteristic amino acid substitutions L3I, N144S (results in loss of a glycosylation site), F159Y, K160T (results in the majority of viruses gaining a glycosylation site), N225D and Q311H in HA1. The 3C.2a1 subclade viruses also carry N171K substitution in HA1 with I77V and G155E substitutions in HA2, e.g. A/Bolzano/7/2016, often with N121K in HA1, e.g. A/Scotland/63440583/2016, while new subgroups have emerged, characterised by addition amino acid substitutions, e.g. T135K (results in loss of a glycosylation site) or I140M (Figure 6).

Vaccination status was reported for 339 patients with H3N2, and HA sequence information was included for 149 of those. Out of those 149, only 32 were vaccinated, the rest unvaccinated. Twenty-three out of those 32 had 3C.2a1, several of which also carried additional HA1 amino acid substitutions. Antigenic analyses are required to determine whether any of these amino acid substitutions alter virus antigenicity, possibly causing vaccine failure in these patients.

ECDC threat assessment for the EU

Primary care data showed an early onset of the seasonal epidemic with a high rate of sentinel specimens testing-positive for influenza despite relatively low ILI/ARI rates. The season has been dominated by a nearly exclusive circulation of A(H3N2) viruses, and it appears that not all countries have reached their epidemic peaks. Data from secondary care and EuroMOMO indicate high pressure in healthcare settings, with severe cases admitted to ICUs, mostly patients aged 65 years and older. The almost exclusive circulation of A(H3N2) viruses is likely to increase the proportional burden of disease experienced by the elderly compared with 2014–15, when A(H1N1)pdm09 and B viruses also circulated in greater numbers and affected younger age groups.

Weekly excess mortality above normal seasonal levels, particularly in the elderly aged 65 years and older, has been comparable to previous A(H3N2)-dominated seasons. In some countries, weekly peak mortality has exceeded the weekly maximum of the 2014–2015 A(H3N2)-dominated season when an estimated 217 000 premature deaths among the 94 million elderly aged 65 years and older occurred in the EU [11].

Although two thirds of the A(H3N2) viruses characterised at this stage of the season belong to a new genetic subclade (subgroup 3C.2a1), this subclade has been, until now, reported as antigenically similar to the vaccine virus (showing no more than a fourfold reduction in haemagglutination inhibition titre with post-infection ferret antisera raised against the vaccine virus, compared to the homologous titre). However, genetic analyses show that A(H3N2) viruses are continuing to evolve, with some forming clusters defined by new HA1 amino acid substitutions in antigenic sites.

Most EU Member States report vaccination coverage of less than 50% for the elderly, other at-risk groups, and healthcare workers, so the majority of target groups is not effectively immunised. Furthermore, preliminary estimates of vaccine effectiveness in the elderly from Sweden and Finland this season show that the vaccine effectiveness has been suboptimal, though similar to other A(H3N2)-dominated seasons. Additional studies are needed to better estimate overall effectiveness.

Figure 6. Phylogenetic comparison of influenza A(H3N2) HA genes
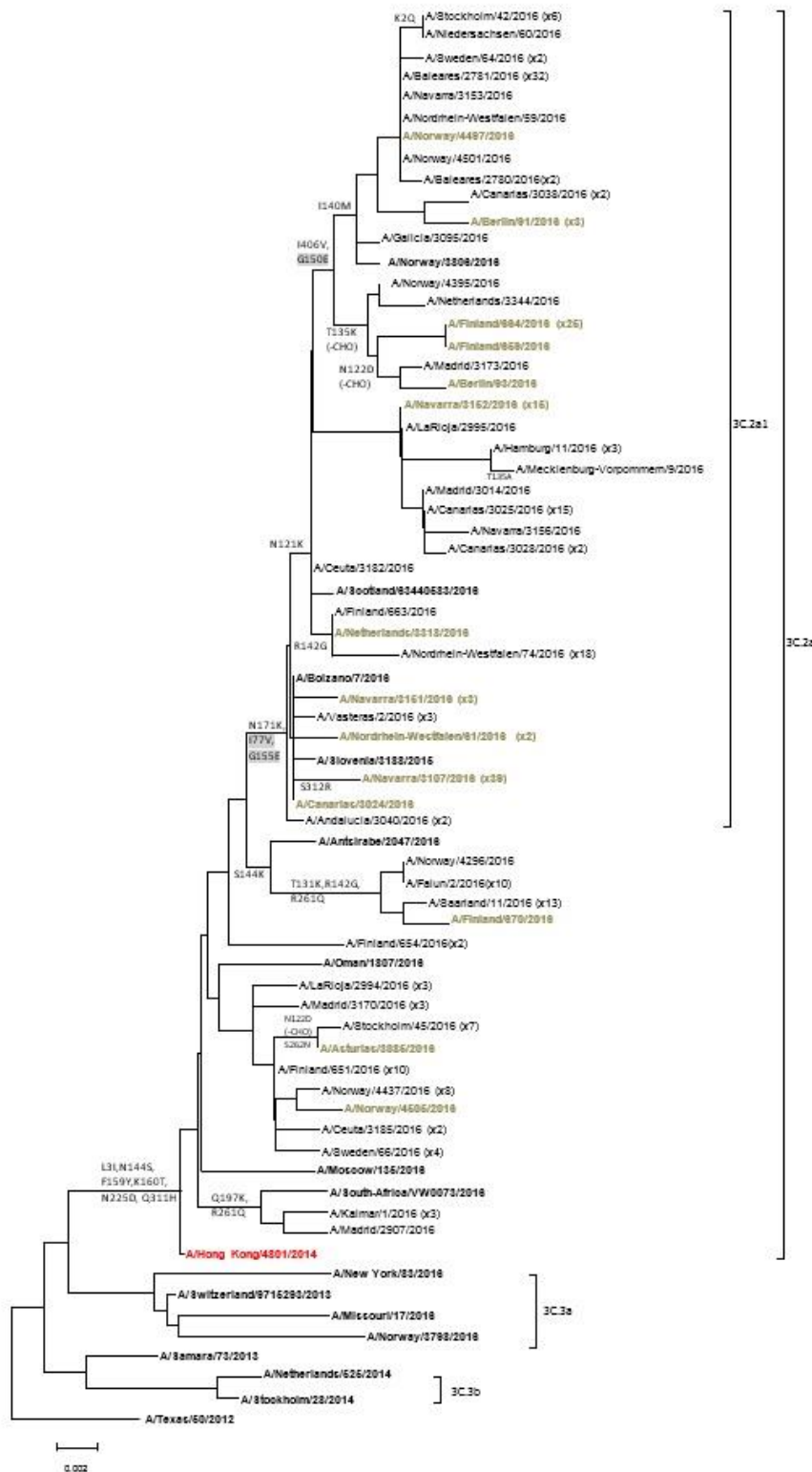
Using MEGA software version 7.0, the tree was constructed with the Neighbor-Joining method, using Kimura-2 parameter-corrected distances and bootstrapped with 1000 replicates [9, 10]. Illustrated in red is the vaccine virus for the 2016–2017 northern hemisphere influenza season, in black WHO CC reference viruses and in brown viruses that originated from vaccinated patients. Characteristic substitutions are mentioned, HA2 substitutions are shown in grey shading.

ECDC acknowledges the authors and the originating/submitting laboratories of the sequences from GISAID's Epiflu database (http://platform.gisaid.org/epi3) on which this analysis is based.

References

[1]   European Centre for Disease Prevention and Control. Expert opinion on neuraminidase inhibitors for prevention and treatment of influenza. ECDC: Stockholm; 2016. Available from: http://ecdc.europa.eu/en/publications/publications/neuraminidase-inhibitors-flu-consultation.pdf

[2]   European Centre for Disease Prevention and Control. Risk assessment of seasonal influenza, EU/EEA, 2016/2017–24 December 2016. Stockholm: ECDC; 2016. Available from: http://ecdc.europa.eu/en/publications/Publications/Risk-assessment-seasonal-influenza-2016-2017.pdf

[3]   World Health Organization. WHO recommendations on the composition of influenza virus vaccines [homepage on the internet]. Geneva: WHO; 2016 [cited 22 Jan 2017]. Available from: http://www.who.int/influenza/vaccines/virus/recommendations/en/

[4]   National Institute for Health and Welfare, Finland. Influenssa leviää nyt – rokotuksen ehtii ottaa vielä [homepage on the internet]. Helsinki: THL; 2017 [cited 22 Jan 2017]. Available at: https://www.thl.fi/en/web/infektiotaudit/-/influenssa-leviaa-nyt-rokotuksen-ehtii-ottaa-viela

[5]   Smittskydd Stockholm. Säsongstatistik för influensa 2016/2017 [homepage on the internet]. Stockholm: Smittskydd Stockholm; 2017 [cited 22 Jan 2017]. Available from: http://www.vardgivarguiden.se/behandlingsstod/smittskydd/dokument/statistik/influensa/sasongen-2016-2017/

[6]   Santé publique France. Grippe – bulletin hebdomadaire. Semaine 1, 11 Jan 2017. Paris: Santé publique France; 2017. Available from: http://invs.santepubliquefrance.fr/content/download/133367/477911/version/216/file/Bulletin_grippe_S01.pdf

[7]   Public Health England. PHE weekly national influenza report, 12 Jan 2017–Week 02 report. London: PHE; 2017. Available from: https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/583109/Weekly_national_influenza_report_week_02_2017.pdf

[8]   European monitoring of excess mortality for public health action [homepage on the internet]. Mortality monitoring in Europe mortality bulletin, week 1–2017. Copenhagen: EuroMOMO; 2017 [cited 20 Jan 2017]. Available from www.euromomo.eu.

[9]   Kimura M. A simple method for estimating evolutionary rate of base substitutions through comparative studies of nucleotide sequences. J Mol Evol. 1980 Dec;16(2):111-20.

[10]   Kumar S, Stecher G, Tamura K. (2016). MEGA7: Molecular Evolutionary Genetics Analysis version 7.0 for bigger datasets. Mol Biol Evol. 2016 Jul;33(7):1870-4.

[11]   European monitoring of excess mortality for public health action. Excess mortality in Europe in the winter season 2014/15, in particular amongst the elderly. Copenhagen: EuroMOMO; 2015. Accessible from: http://www.euromomo.eu/methods/pdf/winter_season_summary_2015.pdf