RAPID RISK ASSESSMENT

Risk assessment of seasonal influenza - Update, EU/EEA, 2016-2017

24 January 2017

Conclusions and options for response

Most countries with high influenza activity have reported severe outcomes resulting in 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 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 are able to share, information that enables rapid risk and impact assessments to be undertaken. This includes surveillance of laboratory-confirmed influenza-cases admitted in intensive care units, and mortality monitoring with sharing of data with ECDC and EuroMoMo. Any EU member states that have not implemented such monitoring should consider doing so, as this would improve the real-time assessment of the ongoing influenza season and of future epidemics and pandemics.

Continued vaccination of the elderly and other at-risk individuals at this time is unlikely to have a major impact in the majority of EU countries during the current peak of influenza activity, as full immunity is not developed until 2 weeks post-vaccination. Efforts to improve vaccination coverage among the elderly, at-risk groups, healthcare workers and children in countries where recommended for the 2017-2018 season should start immediately after the ongoing season is over.

Given the low vaccination coverage in most EU Member States and partial effectiveness of influenza vaccines, timely administration of neuraminidase inhibitors, ideally within 48hrs 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 of high risk contacts should be always considered.

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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 of the season, with stresses on the healthcare system, excess mortality and suggestions of suboptimal vaccine effectiveness.

Consulted experts (In alphabetical order)

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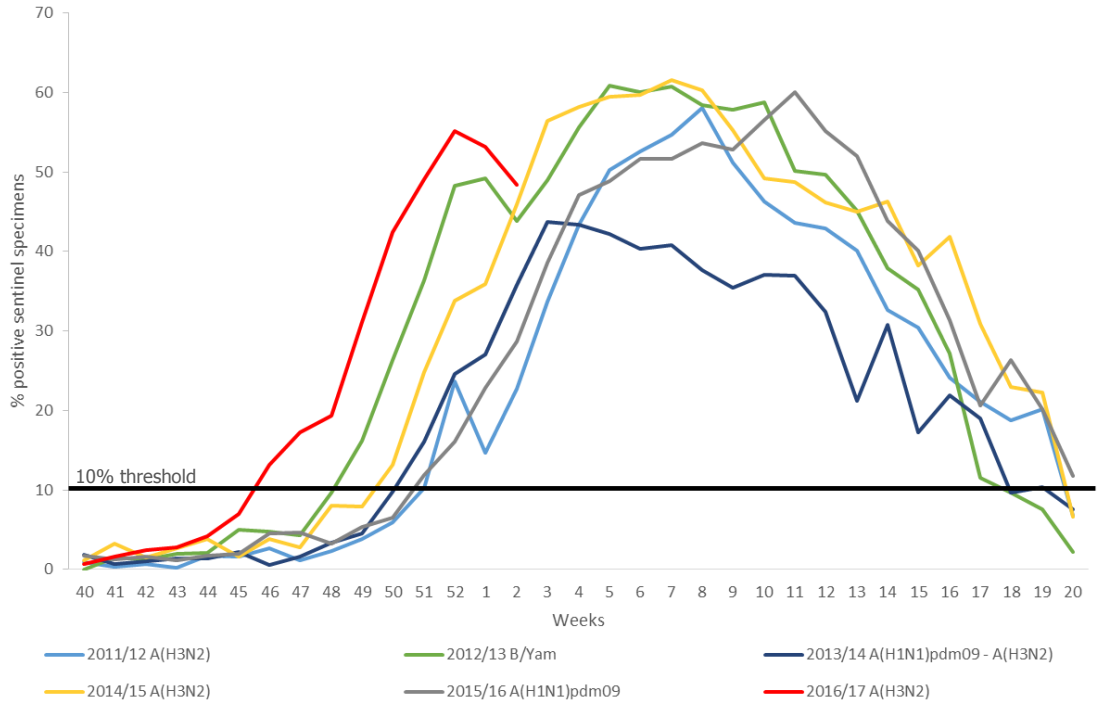
Disease background information

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) [1]. 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 [2]. First estimates in Finland [3] and Sweden [4] 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 EU/EEA, seasons 2011–2012 to 2016–2017*



* Week 53 during season 2015–2016 excluded.

Event background information

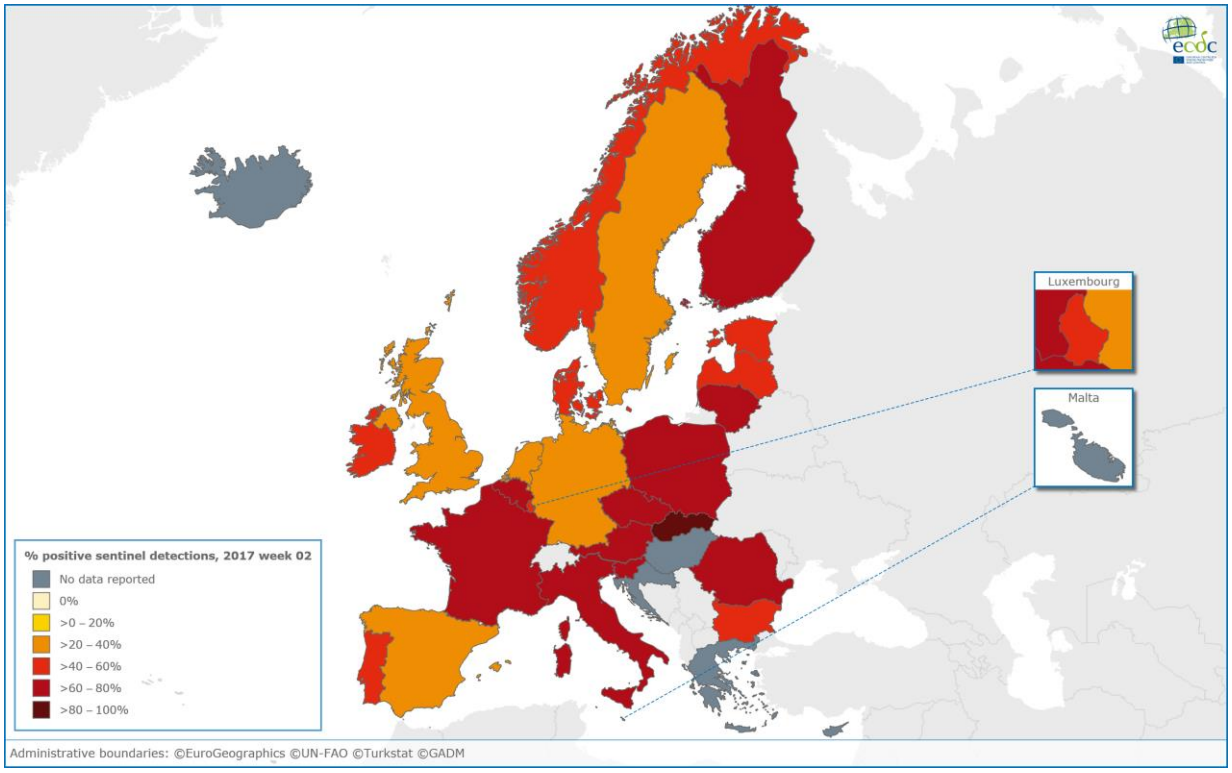
Data sources

This risk assessment is based on the weekly clinical (influenza-like illnesses (ILI) and acute respiratory infections (ARI)), epidemiologic and virologic data from primary and secondary healthcare settings, routinely collected and reported by public health institutes and national influenza centres to ECDC 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, data collected through ECDC epidemic intelligence and results from the European Monitoring of Excess Mortality for Public Health Action (EuroMOMO).

Primary care situation in EU/EEA countries

By week, 02/2017, 23 EU/EEA countries reported widespread geographic influenza activity. All countries reported >10% of specimens testing positive for influenza (Figure 2).

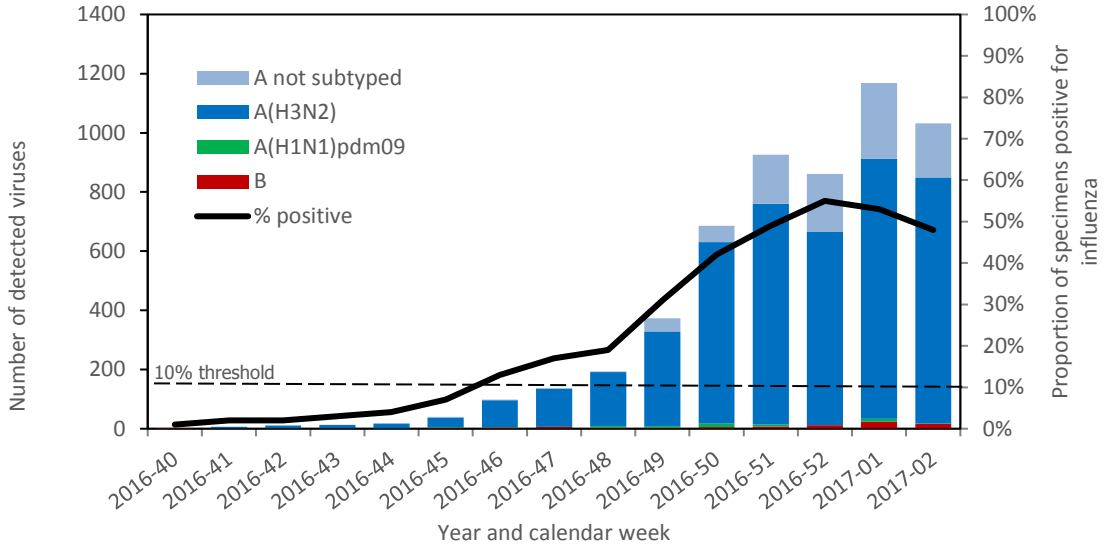
Figure 2. Proportions of primary care sentinel specimens testing positive for influenza in EU/EEA countries, week 02/2017.



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 of ILI and influenza weekly detections rate seemed to be passed in Finland and Sweden. This indicates that the seasonal influenza epidemic is in full swing across the EU/EEA region with some countries having peaked already while others are still reporting increasing trends. In week 02/2017, proportions of circulating viruses in the community were 98% of type A viruses vs. 2% 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% being B/Yamagata lineage.

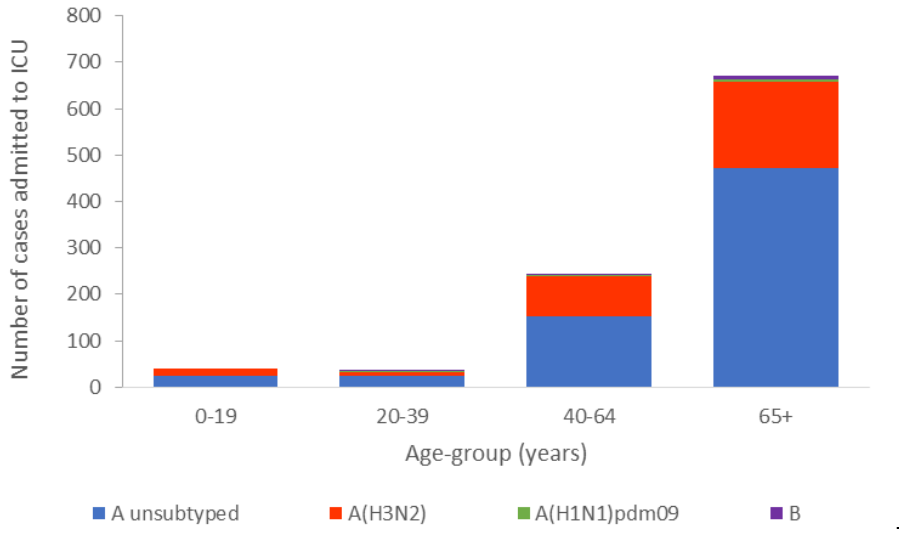
Figure 3. Weekly numbers and proportions of primary care sentinel specimens testing positive for influenza by type and subtype in the EU/EEA region, 2016–2017



Secondary care situation in EU/EEA countries

Between weeks 40/2016 and 02/2017, eight countries (the Czech Republic, Finland, France, Ireland, Romania, Spain, Sweden and the UK) have reported hospitalised laboratory-confirmed influenza cases. Of 2 996 cases reported, 1 457 cases were admitted to intensive care units (ICU) and 1 539 to other wards. The vast majority (98%) of hospitalised cases were infected by influenza type A viruses and 445 (86%) of 518 subtyped were A(H3N2) viruses. Numbers of ICU cases show increases in age of admitted patients with 25% in the age group 40-64 and 68% in the age group 65 and older (Figure 4).

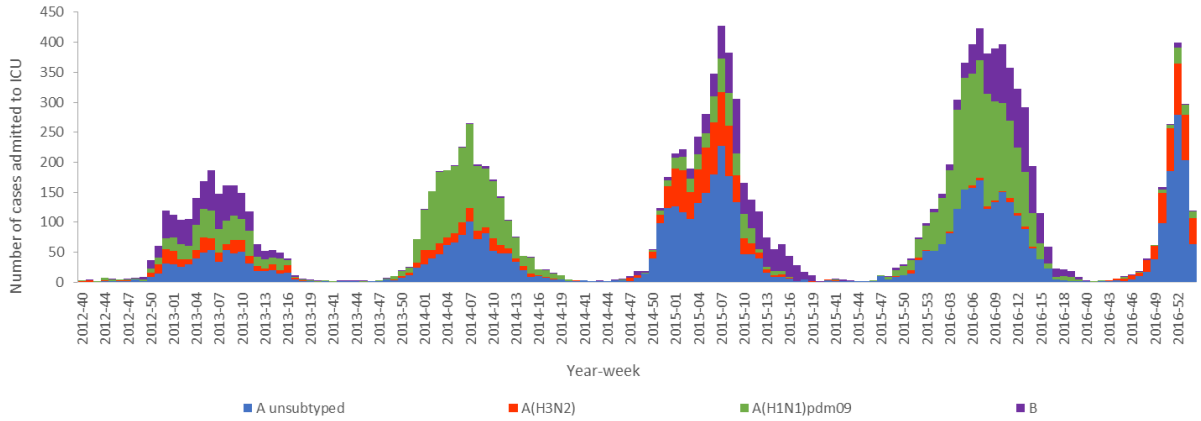
Figure 4. Distribution of confirmed influenza cases admitted to ICU by virus types and subtypes and age group, EU/EEA region, weeks 2016-40 to 2017-01



The peak in the weekly number of cases admitted to ICU remains in the range of values reported during the 2014-2015 season, when A(H3N2) viruses also dominated(Figure 5). During the 2014-2015 season the proportion of people aged 65 years or older was lower (49%) and more (37%) middle aged (40- 64 years) people were admitted to ICU than during the current season with 68% and 25%, respectively. However, in the 2014–2015 season a higher proportion of A(H1N1)pdm09 and type B viruses were detected in ICU patients notably among people younger than 65 years of age. Although the number of cases being admitted to ICU seems to be decreasing a

reporting delay may be influencing this. The 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 ICU by type and subtype in eight EU/EEA countries, seasons 2012–2013 to 2016–2017



Until week 02/2017, 221 fatal cases have been reported from hospital settings from seven countries (Czech Republic, Finland, France, Ireland, Romania, Spain and Sweden), 125 from ICUs and 96 from other wards. Of the 221 cases, influenza A(H3N2) was detected in 100 patients (45%) and 119 (54%) influenza A viruses were unsubtyped virus 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 being between 70 and 79 years old and 105 patients being 80 years and older.

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

During week 02/2017, 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, needing a political level intervention, and all hospitals were asked to delay non-urgent surgical operations [5]. In the UK, in week 1, 84 outbreaks in care homes were reported, with hospital and ICU flu high admissions rates, although not yet reaching the peak levels seen in 2015-2016 [6]. In both countries, the highest hospitalisation and mortality rates were observed in the very elderly (80 years and above).

Starting from week 51/2016, increasing weekly excess winter mortality from all causes in people aged 65 years and more have been observed in Portugal, Italy, France, Greece, Italy and United Kingdom (Scotland) by the EuroMOMO project [7]. 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 however, in some countries, 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 characterization 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). Additionally, antigenic characterisation was attempted for A(H3N2) 38 viruses. Among total of 113 A(H3N2) viruses, the majority (n=72, 64%) were antigenically similar to the current vaccine component A/Hong Kong/4801/2014. Thirty-eight (34%) A(H3N2) viruses were reported as not attributed to category from Germany from weeks 47/2016 to week 02/2017. While this may be an indication of antigenic changes in circulating A(H3N2) viruses, it may result from widely reported difficulties in interpreting haemagglutination inhibition (HI) results for A(H3N2) viruses. 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 to 02/2017

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
A(H3) not attributed to category	38
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

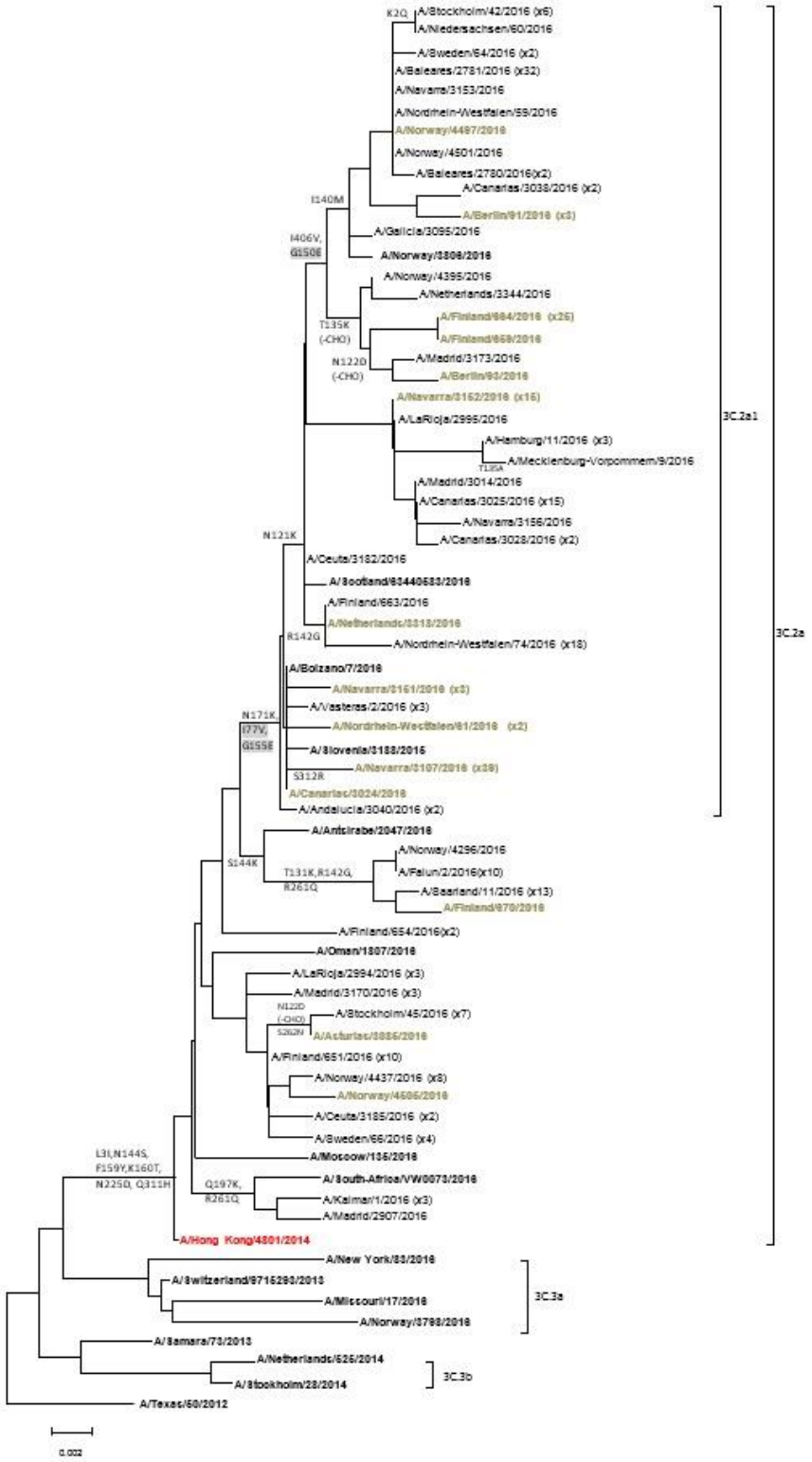
In total, 907 viruses were reported to TESSy using the strain-based reporting system. Among the data reported were 249 influenza virus HA sequences from seven EU countries (Austria, Germany, Finland, the Netherlands, Norway, Spain and Sweden): 242 (97%) were derived from A(H3N2) viruses and sequences 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 infected with A(H3N2) viruses, HA sequence information being available for 149; 76 had been vaccinated. HA sequence information from 32 vaccinees was reported and 23 were infected with viruses belonging to clade 3C.2a1, a number of which carry 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 infected patients.

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 [8, 9]. 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 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 indicates high pressure in health care settings with severe cases admitted to ICU mostly being 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 to 2014-15, when A(H1N1)pdm09 and B viruses also circulated in greater numbers and affected younger age groups.

Excess weekly mortality, 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 amongst the 94 million elderly aged 65 years and older occurred in the EU [10].

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 four-fold 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. Further antigenic characterisation data are needed in light of one Member State reporting 38 A(H3N2) viruses not attributed to category, though this could be attributed to the current difficulties in HI testing of A(H3N2) viruses.

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

Conclusions and options for response

Most countries with high influenza activity have reported severe outcomes resulting in 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 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.

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Continued vaccination of the elderly and other at-risk individuals at this time is unlikely to have a major impact in the majority of EU countries during the current peak of influenza activity, as full immunity is not developed until 2 weeks post-vaccination. Efforts to improve vaccination coverage among the elderly, at-risk groups, healthcare workers and children in countries where recommended for the 2017-2018 season should start immediately after the ongoing season is over.

Given the low vaccination coverage in most EU Member States and partial effectiveness of influenza vaccines, timely administration of neuraminidase inhibitors, ideally within 48hrs 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 of high risk contacts should be always considered [11].

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