



## RAPID RISK ASSESSMENT

# Circulation of drifted influenza A(H3N2) viruses in the EU/EEA

22 December 2014

### Main conclusions and recommendations

Surveillance data gathered since 1 October 2014 indicate that in the first ten weeks of the 2014–15 influenza season, viruses in EU/EEA countries have been predominantly A(H3N2) rather than A(H1N1)pdm09 and type B viruses. In previous seasons, influenza A(H3N2) viruses were associated with more severe disease than A(H1N1) and type B viruses; they were also associated with several outbreaks in long-term care facilities.

The recently published US CDC health alert network notification on antigenically drifted influenza A(H3N2) viruses is the first signal from a northern hemisphere country that circulating viruses will include strains that are antigenically distinct from the A(H3N2) vaccine virus, A/Texas/50/2012, which was recommended by WHO for the northern hemisphere 2014–15 season at the February 2014 strain selection meeting.

Very few influenza virus characterisations have been conducted to date in EU/EEA countries, and the majority of them have been genetic rather than antigenic. The genetic information reported so far suggests the following:

- Influenza A(H3N2) viruses circulating in EU/EEA countries this season will be antigenically distinct from the northern hemisphere A(H3N2) vaccine virus.
- Early indications are that circulating A(H1N1)pdm09 viruses are antigenically similar to the vaccine virus.
- Too few type B viruses have been characterised to date to comment on the likely effectiveness of the B/Massachusetts/2/2012 vaccine component.

These observations indicate that the 2014-15 influenza season may be associated with a greater number of cases with more severe disease, given the higher proportion of A(H3N2) strains among isolates typed to date and the early evidence of drift that is likely to be associated with reduced vaccine effectiveness.

Despite the expected low vaccine effectiveness (VE) of the A(H3N2) vaccine virus component in the vaccines administered for protection in the 2014–15 influenza season, the current tri- and quadrivalent vaccines are likely to provide protection against infection by other currently circulating influenza viruses. Even with low VE of the A(H3N2) vaccine virus components, the vaccine may ameliorate or shorten the duration of influenza disease in infected individuals and is likely to reduce the number of severe outcomes and mortality. Influenza vaccination remains the most effective measure to prevent illness and possibly fatal outcomes.

The circulating viruses are susceptible to the antiviral drugs oseltamivir and zanamivir. Physicians should therefore always consider treatment or post-exposure prophylaxis with antivirals when treating influenza-infected patients and exposed individuals in risk groups.

Influenza vaccine coverage among the elderly and the risk groups in most parts of Europe is low. However, the benefits of vaccination are considerable in protecting these population groups, even if vaccine effectiveness against one of the circulating viruses may turn out to be low.

## Source and date of request

ECDC Internal Decision, 11 December 2014.

## Public health issue

On 3 December 2014, the US CDC issued a health advisory notice regarding the circulation of drifted influenza A(H3N2) viruses in the USA [1]. According to the notice, about half of influenza A(H3N2) viruses currently circulating in the USA are antigenically different from the A(H3N2) vaccine virus component recommended for the 2014–15 influenza season in the northern hemisphere.

This rapid risk assessment focuses on the following question:

- Is there evidence of circulating influenza A(H3N2) viruses in EU/EEA countries being antigenically different from the current A(H3N2) vaccine virus component, and does this have implications for prophylaxis strategies?

## Consulted experts

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External reviewers: Rod Daniels (WHO Collaborating Centre, London, UK), Adam Meijer (RIVM, the Netherlands) and WHO Regional Office for Europe.

## Event background information - USA

On 3 December 2014, the Centers for Disease Prevention and Control (CDC) Health Alert Network published a health advisory highlighting that:

- only 48% of the circulating influenza A(H3N2) viruses which had been antigenically characterised during the ongoing season (collected between 1 October and 22 November 2014) were similar to the virus used in the current seasonal vaccine; and that
- 52% of the circulating influenza A(H3N2) viruses had antigenically 'drifted' away from the current vaccine strain.

By 6 December 2014, CDC had characterised 197 influenza A(H3N2) viruses (received since 1 October 2014), 133 (67.5%) of which were significantly different (drifted) from the northern hemisphere vaccine strain, A/Texas/50/2012 [2,3].

Most of the drifted viruses are antigenically similar to the A(H3N2) strain selected this year for the southern hemisphere vaccine (A/Switzerland/9715293/2013). According to the report for vaccine recommendations for the southern hemisphere, the drifted viruses belong to two different genetic subclades of clade 3C A(H3N2) viruses, but are antigenically indistinguishable and similar to A/Switzerland/9715293/2013 [4]. These drifted strains have become more dominant among the influenza samples in the USA since March 2014, and CDC assumes that these strains will continue to circulate throughout the 2014–15 season in the USA. All of the viruses tested so far in the USA have shown susceptibility to oseltamivir and zanamivir.

In previous seasons, an 'antigenic drift' implied decreased vaccine effectiveness for a particular component of the tri- or quadrivalent vaccine [5,6]. To date, there is no evidence for 'antigenic drift' in the A(H1N1)pdm09 or influenza B components of the vaccine. However, the CDC reported that by 6 December 2014, 31% of characterised influenza B viruses belonged to the B/Victoria-lineage, which is not included in the trivalent vaccine for the northern hemisphere.

The CDC recommends that influenza vaccination should continue to be offered to those who have not yet been vaccinated.

CDC also reminds clinicians of the benefits of influenza antiviral medication. The CDC guidance on influenza antiviral drugs remains unchanged [7].

# Background information

## Influenza vaccines

Vaccination is the most effective means of preventing infection by seasonal influenza viruses.

Currently, seasonal influenza viruses are represented by two influenza type A subtypes described by their haemagglutinin (HA/H) and neuraminidase (NA/N) constituents (H1N1 and H3N2) and two type B lineages (Victoria and Yamagata).

Vaccines are commonly trivalent, formulated with recommended representatives of the two type A subtypes and one type B lineage. Quadrivalent vaccines containing representatives of the two type A subtypes and both type B lineages are becoming increasingly available. However, only a few EU Member States are able to offer quadrivalent vaccines in their national immunisation programmes this winter season, namely countries which provide quadrivalent, live attenuated influenza vaccine to children and adolescents. Immunity develops following either infection or vaccination, usually by a single subtype or lineage, with little cross-reactivity occurring.

While both influenza A subtypes and both type B lineages co-circulate every year, the extent to which each subtype circulates varies between and within seasons. Immunity developed against type A viruses is subtype-specific, while that against type B viruses can provide some cross-lineage protection. The immunity developed can provide some protection against viruses circulating in subsequent years, but the viruses evolve continuously under immune pressure and accumulate amino acid substitutions in their HA surface glycoproteins, the main targets for neutralising antibodies, leading to antigenic drift. Single amino acid substitutions – or a combination of substitutions – can cause antigenic drift of a magnitude that allows escape from existing immunity. Therefore, the influenza A(H3N2), A(H1N1) and type B viruses recommended for use in vaccines have to be reviewed by the WHO strain selection meeting, organised biannually and changed as required. For type A viruses, new vaccines may also be recommended when humans become infected with viruses from other sources, notably birds or swine (zoonotic events), that carry different H and N components (H<sub>x</sub>[x = 1–16] N<sub>y</sub>[y = 1–9]) – a process known as antigenic shift, when a virus enters an immunologically naïve population and can potentially cause a pandemic.

The WHO consultation and information meeting on the composition of influenza virus vaccines provides recommendations on the composition of the new influenza vaccines for the following influenza seasons [3,4]. The meetings are organised in February and September for the northern and the southern hemispheres, respectively. An advisory group of experts analyses influenza virus surveillance data generated by the WHO Global Influenza Surveillance and Response System (GISRS). The recommendations are used by regulatory agencies and pharmaceutical companies to develop, produce and license influenza vaccines.

The September 2014 influenza vaccine consultation meetings resulted in the recommendation of a change to two of the vaccine components, the A(H3N2) and B viruses, for use in the 2015 southern hemisphere season [4]. The data reviewed at the time of the decision showed that two new genetic clades of A(H3N2) viruses (clades 3C.2a and 3C.3a) had emerged containing antigenic drift viruses that were poorly inhibited by post-infection ferret antisera raised against cell- and egg-propagated cultivars of the vaccine virus, A/Texas/50/2012 [4].

Vaccine effectiveness (VE) data for 2012–13 and 2013–14 influenza seasons in Europe have suggested variable VE, from low to moderate, for the A(H3N2) component of the influenza vaccines used [5]. It has also been suggested that immunity (antibody titres) against the A(H3N2) vaccine component might wane in some individuals, to very low levels, by three months post-vaccination [8].

## Characterisation of influenza viruses in the EU/EEA countries and reporting in The European Surveillance System (TESSy)

Influenza viruses are characterised antigenically, genetically, and for their antiviral susceptibility. The results of antigenic characterisation are of primary importance in determining how similar circulating viruses are to their corresponding vaccine virus. These results also inform recommendations relating to vaccine viruses for upcoming influenza seasons. Genetic characterisation gives an indication of the molecular evolution of the virus in comparison to the vaccine virus and identifies amino acid substitutions associated with antigenic drift, thereby complementing antigenic characterisation. Antiviral susceptibility testing does not contribute to determining the similarity of circulating viruses to the vaccine viruses but provides crucial information when assessing public health measures, notably when there is significant antigenic drift compared to one or more of the vaccine viruses.

For the 2013–14 season, 18 of the 29 EU/EEA countries provided antigenic characterisation data [9]. The genetic characterisations were reported by 15 EU/EEA Member States. It is likely that the same countries will continue to report antigenic and genetic characterisation data in season 2014–15.

The EU/EEA Member States and countries of the WHO European Region notify information on influenza virus detections together with data on clinical influenza-like illness and/or acute respiratory infection to TESSy on a

weekly basis [9]. Data are presented during the influenza season (week 40 through week 20 of the following year) in a weekly bulletin entitled *Flu News Europe* (<http://www.FluNewsEurope.org>), produced by ECDC and the WHO Regional Office for Europe [10].

A representative subset of the influenza-positive specimens is characterised antigenically and/or genetically by the WHO-recognised National Influenza Centre (NIC) in each Member State. In addition, the NICs send recently collected samples for in-depth analysis to the WHO Collaborating Centre (CC), London, usually at least twice during the course of a season, to inform both the February and September vaccine composition.

## Observations made during the 2013–14 influenza season

During the 2013–14 season, no obvious antigenic drift away from any of the vaccine components was observed. Consequently, the WHO vaccine recommendation for the 2014–15 season remained unchanged compared with the previous season.

As of 17 June 2014, a total of 1 764 virus isolates have been antigenically characterised, with only six A(H1N1)pdm09 and three A(H3N2) viruses being not attributed to any reporting category. Sixty per cent of the viruses were A(H1)pdm09 A/California/7/2009 (H1N1)-like and 37% A(H3) A/Texas/50/2012 (H3N2)-like [9].

Of the 1183 genetically characterised viruses, 535 were A(H3N2) viruses, and all 535 were reported as belonging to the A(H3) clade representative A/Perth/16/2009 – A/Texas/50/2012 subgroup (3C) [9].

## Observations made during the 2014–15 season

Most viruses that have been characterised to date by laboratories reporting to the European Surveillance System (TESSy) as A(H1N1)pdm09 are similar to those recommended for inclusion in the [current vaccines recommended by WHO](#). Regarding A(H3N2), the genetic, and to some extent, antigenic characterisation, results indicate a situation in Europe similar to that reported by CDC for week 49/2014 [2], with the majority of A(H3N2) viruses being significantly different antigenically from the current component of the seasonal influenza vaccine [10].

Of the genetically characterised A(H3N2) viruses, 26 (five A/Texas/50/2012 subgroup 3C.1 and twenty-one A/Samara/73/2013 3C.3) are in genetic groups containing viruses that have antigenic properties similar to the vaccine virus, but 50 (44 A/Hong Kong/5738/2014 3C.2a and six A/Switzerland/9715293/2013 3C.3a) are in genetic groups containing viruses that show antigenic drift from the vaccine virus. In summary, 66% of the genetically characterised A(H3N2) viruses are in subgroups containing antigenic drift variants compared to A/Texas/50/2012 (the vaccine component for the northern hemisphere 2014–2015 season) [10].

Including data of week 50, none of the influenza viruses (70 A(H3N2); 17 A(H1N1) and 1 B virus) analysed for susceptibility to neuraminidase inhibitors oseltamivir and zanamivir have shown phenotypic or genotypic evidence for reduced inhibition.

Influenza activity in Europe is still low, and most Member States have only recently made their first influenza virus detections for the season. Antigenic characterisation relies on isolation of viruses, so there is always a delay in the reporting of antigenic characterisation data to ECDC, the WHO Regional Office for Europe, and the WHO CC in London.

To date, the WHO CC in London has received only four A(H3N2) specimens for characterisation from the European NICs, and no conclusions can be drawn based on so few viruses.

However, the current virological information available in TESSy would indicate a situation in Europe similar to that reported by the US CDC for week 48/2014 where the majority of A(H3N2) viruses have shown significant antigenic drift compared to the vaccine virus [1].

## ECDC threat assessment for the EU

Early results of characterisation of the circulating influenza viruses in the USA, where the current season has progressed further than in Europe, may be also indicative for the rest of the season in Europe.

Early virological information from Europe indicates that the majority of the influenza A(H3N2) viruses characterised to date show mismatch with the A(H3N2) component of the northern hemisphere vaccine, which is in use in EU/EEA Member States.

All circulating influenza A(H1N1)pdm09 viruses characterised genetically and antigenically in the EU/EEA match the current vaccine strains. However, it is still early in the season, and too few influenza B viruses have been characterised to reach any conclusions.

Viruses of each type and subtype analysed so far show susceptibility to neuraminidase inhibitors, oseltamivir and zanamivir.

Vaccine effectiveness estimates using laboratory confirmations of influenza virus infections from Europe during the 2013–14 season as a proxy suggest low to moderate effectiveness against the A(H3N2) component of the vaccine. Further, reduced effectiveness against one of the three (trivalent vaccine) or four (quadrivalent vaccine) influenza strains included in the current seasonal vaccine is possible.

These observations indicate that the 2014–15 influenza season may be associated with a greater number of cases with more severe disease, given the higher proportion of A(H3N2) strains among isolates typed to date and the early evidence of drift that is likely to be associated with reduced vaccine effectiveness.

Influenza vaccination remains the most effective measure to prevent illness and possibly fatal outcomes. In the EU, up to 40 000 people die prematurely during an average influenza season. Protecting those who are at risk of severe outcomes of influenza should remain the number-one priority of vaccination programmes, particularly the elderly and those vulnerable due to pre-existing illnesses or risk factors. An estimated 49% of the EU population (249 million people, based on 2014 population estimates) would benefit from a seasonal influenza vaccine.

In 2009, the Council of the European Union recommended that influenza vaccination coverage should be increased to > 75% among 'older age groups' and 'other risk groups'. Only two Member States, the United Kingdom and the Netherlands, have achieved this target in recent years.

The antiviral agents, oseltamivir and zanamivir, have been granted marketing authorisation for prevention (post-exposure prophylaxis) and treatment of influenza in the EU. In most EU countries, these antiviral drugs are easily available, but remain an underutilised tool against influenza. These agents are mainly effective if used immediately (< 48h) following the onset of symptoms of influenza.

In terms of prevention, after vaccination, post-exposure prophylaxis is probably the most effective way of protecting the elderly and people in risk groups against serious influenza illness. Treatment of cases and post-exposure prophylaxis for risk groups continues to be the primary indication for the use of antivirals.

ECDC will convene an expert panel in February 2015 to review the evidence currently available on the effectiveness of antivirals in public health use.

ECDC will review the epidemiological, virological and clinical evidence once the influenza season in Europe has started in order to produce a 'seasonal risk assessment'.

## Conclusions

Surveillance data gathered since 1 October 2014 indicate that in the first ten weeks of the 2014–15 influenza season, viruses in EU/EEA countries have been predominantly A(H3N2) rather than A(H1N1)pdm09 and type B viruses. In previous seasons, influenza A(H3N2) viruses were associated with more severe disease than A(H1N1) and type B viruses; they were also associated with several outbreaks in long-term care facilities [11,12].

The recently published US CDC health alert network notification on antigenically drifted influenza A(H3N2) viruses is the first signal from a northern hemisphere country that circulating viruses will include strains that are antigenically distinct from the A(H3N2) vaccine virus, A/Texas/50/2012, which was recommended for the northern hemisphere 2014–15 season by WHO in February 2014.

Following the WHO recommendations for vaccine viruses to be used in the 2015 southern hemisphere influenza season, ECDC and the WHO Regional Office for Europe commented on the seasonal influenza vaccine composition in October 2014 and suggested that the northern hemisphere vaccine may not offer optimal protection against the circulating A(H3N2) and B/Yamagata viruses in the 2014–15 influenza season in temperate countries [13,14].

Very few influenza virus characterisations have been conducted to date in EU/EEA countries, and the majority of them have been genetic rather than antigenic. The genetic information reported so far suggests the following:

- Influenza A(H3N2) viruses circulating in EU/EEA countries this season will be antigenically distinct from the northern hemisphere A(H3N2) vaccine virus.
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- Too few type B viruses have been characterised to date to comment on the likely effectiveness of the B/Massachusetts/2/2012 vaccine component.

These observations indicate that the 2014-15 influenza season may be associated with a greater proportion of cases with more severe disease, given the higher proportion of A(H3N2) strains among isolates typed to date and the early evidence of drift that is likely to be associated with reduced vaccine effectiveness.

Despite the expected low vaccine effectiveness of the A(H3N2) vaccine virus, the current tri- and quadrivalent vaccines are likely to provide protection against infection against other currently circulating influenza viruses. Even with low vaccine effectiveness of the A(H3N2) vaccine virus components, the vaccine may ameliorate or shorten the duration of influenza disease in infected individuals and is likely to reduce the number of severe outcomes and mortality, therefore the recommendations for vaccination must be maintained.

The circulating viruses are susceptible to the antiviral drugs oseltamivir and zanamivir. Physicians should therefore always consider treatment or post-exposure prophylaxis with antivirals when treating influenza-infected patients and exposed individuals in risk groups.

Influenza vaccine coverage among the elderly and the risk groups in most parts of Europe is low. However, the benefits of vaccination are considerable in protecting these population groups, even if vaccine effectiveness against one of the circulating viruses may turn out to be low.

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