ECDC INTERIM RISK ASSESSMENT

# Human cases of influenza A(H1N1)v

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## Public health issue

Implication for Europe of the new influenza A(H1N1) virus[1]

## Disease background information

A new influenza A virus was identified by the United States CDC in April this year in samples from two Californian children and retrospectively in cases in Mexico (CDC 2009a, Fraser 2009, CDC 2009b).

The new virus and the disease it caused were initially called 'swine flu'. The basic genetic structure of the virus has been described and this information is available through publicly accessible websites (Trifonov 2009, Nava 2009). The virus has a number of genetic elements from two different types of swine influenza, but also elements originally from avian and human influenzas that were incorporated into other swine influenza viruses (Nava 2009). However, it is unclear if the specific reassortment leading to the new virus took place in pigs or humans.

In recent years occasional swine influenza infections in humans have been detected through surveillance of humans, especially in North America. Particular swine influenza viruses with avian, human and swine genes have previously been circulating in pigs in the US, and have occasionally been transmitted to humans (Olsen 2006, Newman 2008). However, those infections have not transmitted efficiently from human to human. In contrast, this new novel virus is not only infecting humans and causing some disease but it is also transmitting efficiently from

1 This technical nomenclature A(H1N1)v has been adopted by the WHO Global Influenza Surveillance Network http://www.who.int/csr/resources/publications/swineflu/ivr153_20090608_en.pdf

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human to human[2]. There are now tens of thousands of cases confirmed from at least four continents (including many hundreds from Europe) with a number of attributable deaths[3]. The virus therefore meets WHO's criteria for a pandemic influenza strain and should be regarded as a human influenza (WHO 2009a).

ECDC prefers to use the term *influenza A(H1N1)v* (where *v* indicates *variant*), which has been chosen by WHO's Global Influenza Surveillance Network and helps distinguish the virus from seasonal influenza A(H1N1) viruses and A(H1N1) swine influenza viruses. A name for the disease caused by the virus has yet to be determined by WHO but the term 'swine flu' is inaccurate for what is now a human influenza.

There are several recent examples where influenza viruses of animal origin have occasionally transmitted to humans. Some have also transmitted occasionally from human to human. The most obvious example being the avian A(H5N1) influenza 'bird flu' which has been circulating in East and Southeast Asia for more than a decade, and which still causes deaths in the region. However human-to-human transmissions of A(H5N1) and other avian influenza have been very limited (ECDC 2006). Influenza A(H1N1)v is the first animal influenza for some years to have adapted sufficiently to be referred to as a human influenza.

# ECDC risk assessment

There is always a series of important unknowns when a new influenza virus emerges and becomes a pandemic, what ECDC calls the 'known unknowns' (ECDC 2007, ECDC 2009, Lipsitch 2009, WHO 2009b). The previous risk assessment listed a number of these. Many of these are still unknown, but more data are becoming available, especially from North America, through the authorities in Canada, Mexico and USA. Analyses from these data need to be relied on for now, though at a later stage data from Europe and other countries will be used as infection spreads.

## For any future pandemic virus – what can and cannot be assumed?

What probably can be assumed:

**Known knowns**

- Modes of transmission (droplet, direct and indirect contact)
- Broad incubation period and serial interval
- At what stage a person is infectious
- Broad clinical presentation and case definition (what influenza looks like)
- The general effectiveness of personal hygiene measures (frequent hand washing, using tissues properly, staying at home when you get ill)
- That in temperate zones transmission will be lower in the spring and summer than in the autumn and winter

What cannot be assumed:

**Known unknowns**

- Antigenic type and phenotype
- Susceptibility/resistance to antivirals
- Age-groups and clinical groups most affected
- Age-groups with most transmission
- Clinical attack rates
- Pathogenicity (case-fatality rates)
- 'Severity' of the pandemic
- Precise parameters needed for modelling and forecasting (serial interval, $R_o$)
- Precise clinical case definition
- The duration, shape, number and tempo of the waves of infection
- Will new virus dominate over seasonal type A influenza?
- Complicating conditions (super-infections)
- The effectiveness of interventions and counter-measures including pharmaceuticals
- The safety of pharmaceutical interventions

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[2] The virus is not genetically related to the single human swine flu infection detected in a human in Europe of late http://www.eurosurveillance.org/ViewArticle.aspx?ArticleId=19120 (Personal communication to ECDC A Hay WHO Influenza Collaborating Centre, May 2009)

[3] Information is being updated regularly on the WHO (http://www.who.int/csr/disease/swineflu/en/index.html) and ECDC (http://www.ecdc.europa.eu/en/Health_topics/novel_influenza_virus/2009_Outbreak/) dedicated webpages.

# Basic epidemiology

**Age and sex:** The observed age distribution is unusual and different from seasonal influenza, being skewed towards younger age groups (Investigative Team 2009). There is a marked underrepresentation of infections in older people (over 64 years old) even among those being hospitalised (Investigative Team 2009, Thompson 2004). This is more than can be explained by initial case finding focusing on returning travellers in the age group of 20–29 year-olds, and secondary spread in schools (Investigative Team 2009, ECDC 2009). There are also some laboratory results from serology consistent with this as they indicate that older people may be less affected due to some enduring immunological memory of an earlier influenza A(H1N1) infection with a similar phenotype (CDC 2009d). Males and females are equally affected (WHO 2009c).

**Method and ease of transmission — effective reproductive number:** The virus seems to spread in the same way as other human influenza: by droplets from coughing and sneezing and direct and indirect contact with respiratory secretions from infected persons (Brankston 2007). To date there is no evidence from North America suggesting unusual transmission routes and no reason to suggest transmission through food (WHO 2009). There have already been estimates of the effective reproductive rate (R), which all lie between 1 and 2 (with some outliers); the range 1.4 to 1.6 being most probable (Fraser 2009). This is higher than the value observed for seasonal influenza but in line with previous pandemics (Hall 2007, ECDC 2007). However, effective reproductive number will be a more important parameter that $R_0$, and that is being monitored in a number of countries.

# Disease characteristics

**Clinical attack rate:** Reports of this differ. One publication from Mexico suggested high attacks rates with over 30% of children infected by presumed A(H1N1)v in one area (Fraser 2009). However, in the United States, at a time of year when influenza incidence would be expected to be declining, attack rates have been lower at around 7–10%, at the population level in affected areas, and 20%, in confined outbreaks. Whilst the reasons may be different, this figure is not very different from seasonal influenza (CDC 2009e). Given the time of year that transmission was taking place in the USA, this does not necessarily represent the final cumulative clinical attack rate, which is usually higher for pandemic than seasonal viruses. No serological data are yet available. As is the case with other human influenza infections, there will probably be many mild and asymptomatic cases (ECDC 2009).

**Spectrum of disease — clinical features:** This is beginning to be described. The only notable features that differ to date from seasonal influenza are some reports of more gastroenteric symptoms than are common for seasonal influenza (Investigative Team 2009), and preliminary reports that the incubation period may have a longer tail than usually observed. The results to date are: median 3–4 days, range 1–7 days (WHO 2009c). There are no reports of gastrointestinal symptoms on their own without other more usual signs of influenza (Investigative Team 2009). There are some indications of asymptomatic cases from contact tracing in Europe (ECDC 2009). However, it will be some time before it is known what proportion of infected people develop disease. That will have to be assessed from future serological studies.

**Hospitalisation and risk groups for severe disease case fatality ratio:** In one published study from California of 553 probable and confirmed infections with A(H1N1)v, 30 (5%) people were hospitalised because of needing care. Nineteen of the 30 patients had underlying chronic conditions which have been in decreasing frequency: asthma or chronic obstructive airways disease, diabetes, immuno-compromise, chronic cardiovascular disease (not simple hypertension), chronic renal failure, seizure disorder and malignancy.

**Case Fatality Ratio** It is difficult to estimate case fatality ratio (CFR) with any accuracy at this stage. In Mexico, case ascertainment has favoured detecting patients with more severe illness so that a report of 97 deaths among 5 337 confirmed cases gives a misleadingly high case fatality ratio of 1.8%. An indirect method gave a value of 0.4% (Fraser 2009), while estimates for the United States give a figure for 0.2% (CDC unpublished data). This is close to what is seen for seasonal influenza.

# Features of the virus

**Susceptibility to antivirals:** Based on genetic evidence, all the indications are that the neuraminidase inhibitors oseltamivir and zanamivir will be effective treatment, but that the virus will be resistant to adamantenes (amantadine). There is some concern that genetic reassortment could take place with circulating oseltamivir-resistant viruses.

**Pathogenicity of the virus:** There are as yet no reports of known genetic markers associated with severe disease, and initial animal challenges show that though the virus does cause disease, the results are considerably less severe than, for instance, for the highly pathogenic influenza A(H5N1).

**Immunity:** Laboratory studies are being undertaken and they are showing some cross-reactivity in sera from older people. Epidemiological data from the US also indicate that older age groups may be less affected. Virus of the same subtype, A(H1N1), has been responsible for seasonal influenza during several years, but that subtype is quite different from the current one. Most of the genes of the novel virus are similar to genes that have developed in pigs — independently of human H1N1 viruses — probably since 1918 (CDC 2009d).

# Severity

Many national authorities consider it important to have an assessment of the 'severity' of a pandemic so as to determine a proportionate response (WHO 2009c). However, it is difficult to classify pandemics, as the experience of people, organisations and societies may differ because severity can vary from country to country and even from place to place within a country. It can also change over time and there are important social and societal factors including the vulnerability of populations, capacity for response, the available healthcare and the level of advance planning and preparedness. Severity can also be seen either from the individual angle: people who are infected experience a severe disease (even though they may be few), or from a societal angle: many people are away from work and critical services are threatened (even though the disease may be relatively mild).

It is difficult at this stage to comment on severity in EU Member States when there has been so little experience in Europe. It is especially difficult to place the impact and effect of this pandemic virus into the mild, moderate and severe categories preferred by WHO. However, what is known so far from the North American and limited European experience is as follows:

- **Hospitalisation and case fatality ratio.** From the United States' experience about 7% of the confirmed cases have been hospitalised and the case fatality ratio is 0.2%. These figures are little different from what is seen for seasonal influenza in that country, while the limited information to date for Europe suggests that they may be even lower. Because of the seeming underrepresentation of older people among those infected the total number of deaths in Europe may be less than for a moderate influenza season like 2008–9.
- **Number of people being ill with respiratory illnesses at any one time.** This correlates to the pressure on the health services to deal with these patients. The limited experience from North America suggests that this is manageable as long as the public are not alarmed into coming forward and there are not other epidemics of illness taking place.
- **Critical services functioning.** So far, there have been no reports of the peak prevalence of people off ill or caring for others as causing any problems.
- **Certain groups experiencing severe illness or dying unexpectedly.** Here there have been unexpected findings as there is both an underrepresentation of older people and three groups who are suffering more than would be expected with seasonal flu, namely people under age 65 with chronic but treatable illnesses, pregnant women and very young children. These three groups are overrepresented in those falling ill and dying in the United States.

Given this experience, it would seem that most well-prepared European Member States should be able to cope with this pandemic in its present. However, it must be remembered that historically pandemic viruses are quite capable of worsening their impact over time (this happened in 1918–19 and 1968–69 in some European countries) and so severity will need to be monitored, especially given the possibility of the virus acquiring genetic material associated with pathogenicity or antiviral resistance for humans.

# Data from Europe

At present, about one third of the cases in Europe have acquired the infection in their own country (mainly in Spain and the UK). Initially most of these endogenous cases were secondary to someone who has travelled to North America, but there are also increasing reports of tertiary and community transmission, notably from the UK (ECDC 2009, HPA 2009).

Also in Europe the cases are young, median age, being 25 years in those who acquired the infection during travel, and 13 years in those domestically infected. Only 2% of cases are above 60. The distribution of symptoms is very similar to what is described from the USA, with the proportion of patients reporting gastrointestinal symptoms (24%) being higher than for seasonal influenza. One difference is that in Europe more than a third of patients were hospitalised, but this was often for isolation purposes rather than for any clinical need. No deaths have been reported from Europe.

In addition to close surveillance of cases in the EU, ECDC will continue to closely monitor the situation in Mexico, US and Canada. It is from these countries and the Southern Hemisphere that further information for the parameters listed above will come — in addition to the information from the European Union. ECDC will continuously provide information through its website and update this risk assessment as needed. For rapid updates, please see the Situation Reports published on the website (www.ecdc.europa.eu) every day.

## The current ECDC threat assessment for Europe

The current ECDC threat assessment for Europe is that the new influenza A(H1N1)v virus will continue to spread. Though it seems that most of those infected in the US and in Europe experience a mild and self-limiting infection, this picture is still unclear as there has not been enough transmission to judge the effects, especially in those more at risk. The indications from North America is that there are significant differences from seasonal influenza with an underrepresentation of older people and a prominent representation of adults under age 60 with chronic ill health, pregnant women, very obese persons and very young children among those with more severe disease. If confirmed this will have important implications for early treatment and vaccination policies.

Also pandemic viruses are unpredictable, and can change their characteristics as they evolve. Even pandemics usually slow down in summer, only to pick up in autumn, and the virus may then come back, perhaps in a more aggressive form as happened in 1918–19 and 1968–69.

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