

Swine-origin triple reassortant influenza A(H3N2) viruses in North America

29 November 2011

Conclusions and recommendations

Following recent infections in children in North America with a swine-origin triple reassortant influenza A(H3N2) virus that includes a genetic component from the pandemic 2009 virus, and with probable human-to-human transmission of these viruses, ECDC has come to the following preliminary opinion:

- These viruses are known to be found in pigs in North America but they have not been found in pigs in Europe (EU/EEA countries). However, surveillance for influenza in pigs is weak in both North America and Europe, and surveillance for infections in humans in close contact with pigs is notably weak in Europe. Hence all such statements on the epidemiology of swine influenzas must be treated with caution.
- Most of the US cases experienced only mild disease. Those hospitalised had underlying conditions and all patients recovered completely.
- These viruses are susceptible to the neuraminidase inhibitors (oseltamivir and zanamivir) though the current A(H3N2) component of seasonal influenza vaccines is unlikely to provide protection. Older people are likely to have some protection from exposure to earlier vaccines.
- It is considered by the United States Centers for Disease Control (CDC) that there had already been some very limited human-to-human transmission of these and similar viruses in the US.
- Unlike in March 2009 (the start of the pandemic) there are no reports of numbers of unexplained influenza infections elsewhere in the Americas. Hence it is unlikely that these US cases represent outliers for a larger phenomenon.
- Overall, therefore, the immediate direct threat to human health in Europe is low.
- ECDC staff are following the situation closely and are in direct contact with the WHO, the US CDC and relevant experts in EU Member States.
- There is a need to ensure that these infections could be detected through diagnostic testing in European national influenza laboratories.
- There are strong public health arguments for more active virological surveillance of pig herds in Europe (and North America) including active surveillance of infections in humans that are in direct or indirect contact with pigs.
- Equally justified are more formal approaches to assessing emerging influenza viruses for their pandemic potential and such virological risk assessments should continue to be developed.
- Unusual influenza viruses should continue to be referred to National Influenza Centres and on to the WHO Collaborating Centre in Europe, along with relevant clinical and epidemiological data.

SOURCE AND DATE OF REQUEST

Request from the Directorate-General for Health and Consumers, supported by Member States at the EU Health Security Committee, 24 November 2011.

PUBLIC HEALTH ISSUE

Implication for Europe of recent human infection and limited probable human-to-human transmission in the United States with triple reassortantⁱ swine-origin influenza S-OtrA(H3N2) viruses with a unique gene segment combination including the M gene from the 2009 A(H1N1)ⁱⁱ pandemic viruses.

The objectives of this rapid risk assessment are:

- to identify immediate risks to human health in Europe;
- to give guidance on how Europe should respond; and
- to consider how the longer term risks of pandemic emergence from these viruses can be approached.

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RECENT DEVELOPMENTS IN THE UNITED STATES

As of 23 November 2011, eighteen human infections with swine-origin triple reassortant influenza A(H3N2) viruses have been identified in the USA since 2009 [1]. Infections with other triple reassortant swine influenza viruses have been reported in humans for some time due to swine-to-human transmission but with very limited onward spread to other humans [2].

In 2011 a virological change has been observed with the addition of the matrix (M) gene from the 2009 A(H1N1) viruses to these viruses [1]. The ten most recent US cases were all infections with S-OtrH3N2 viruses containing the matrix (M) gene from the pandemic 2009 influenza A(H1N1) virus [1,3]. These viruses are considered reassortant viruses between a swine-origin influenza A(H3N2) virus circulating among North American swine and a pandemic A(H1N1) virus. All ten cases were reported in 2011 and have been from four states: Pennsylvania (three cases), Maine (two), Indiana (two), and most recently Iowa (three) [3–4]. Most of the cases have resulted in mild infection. There have been three hospitalisations but two of these were children with underlying medical conditions and they recovered.

On 20 November 2011, the CDC reported investigations concerning three cases of swine-origin triple reassortant influenza A(H3N2) (S-OtrH3N2) virus infection with the A(H1N1) matrix gene in children in two counties in Iowa [3]. None of the children were hospitalised, and each has recovered from a mild episode of febrile respiratory illness. All three were in contact with one another, and none had a known recent exposure to swine. No additional human infections with this virus have been detected in Iowa to date. No evidence of sustained human-to-human transmission of this S-OtrH3N2 virus has been found and no additional transmission by these three children has

ⁱ Reassortment means the mixing of the genetic material of two or more virus species into new combinations, usually following co-infection of a host animal or human.

ⁱⁱ The influenza viruses that caused the 2009 pandemic are now designated A(H1N1)pdm09 (<http://www.who.int/wer/2011/wer8643.pdf>). However, since these are now seasonal viruses and no other human adapted A(H1N1) viruses have been found in the last Northern and Southern seasons in this risk assessment they will generally be referred to as A(H1N1) in text for brevity. Swine influenza viruses are generally designated as S-O to indicate swine origin.

been identified. Surveillance is ongoing but the CDC consider that there has been limited human-to-human transmission and has published convincing additional information to support this view [4].

The viruses from these three patients are resistant to amantadine and rimantadine but according to their genetic sequence they are susceptible to the neuraminidase inhibitor drugs oseltamivir and zanamivir. Because these viruses carry a unique combination of genes, little information is currently available regarding the potential of these viruses to transmit efficiently in swine, humans, or between swine and humans.

Independent approaches by ECDC to relevant national and international agencies found no indications of unusual outbreaks (for example, unusually large or out of season) of respiratory viral infections in the Americas, which indicates that this situation is not like that in Mexico and the south-western United States in 2009 when a few reported cases in the USA represented much larger outbreaks elsewhere [5, 6].

DISEASE BACKGROUND INFORMATION

Animal infection and disease

Swine influenza is an acute viral infection of the respiratory tract in pigs. The mortality in pigs is low and recovery usually occurs within 7–10 days. An infected pig may have rapid onset fever, loss of appetite, laboured abdominal breathing and coughing but subclinical infections are common. The infections are considered endemic in pigs in Europe, and elsewhere in the world [7]. Serological surveys indicate that a significant proportion of all pigs are infected during their lifetime. Unlike human influenza in temperate countries there is no seasonal pattern for influenza among pigs [8, 9].

However, surveillance of influenza in pigs remains incomplete and patchy even in Europe and the USA, mostly because swine influenza has little significance for food production and food safety. There is little relevant legislation and swine producers are reluctant to allow voluntary testing. Swine influenza is not a notifiable animal disease in the EU and there is no extensive surveillance. The most relevant EU data come from research work in a limited number of countries supported by the European Commission (Directorate-General for Research and Innovation) such as in [FLUPIG](#), [ESNIP2](#) and [ESNIP3](#). The latter has the objective of tracking changes in the virology and epidemiology of infection in pigs. This includes the infection of the pigs with human influenza viruses such as A(H1N1). Given the limitations of surveillance in Europe, statements on the epidemiology and virology of swine influenza in Europe can only be preliminary. The swine influenza subtypes currently circulating in pigs in Europe are known to include A(H1N1)ⁱ, A(H3N2)ⁱⁱ and A(H1N2) [6, 8]. Recently, a reassortant pandemic A(H1N1) influenza virus has been identified circulating among pigs in Germany [10].

The epidemiology and virology of swine influenza viruses in Europe and the United States seem to be quite different. The triple reassortant viruses, S-OtrA(H3N2), seen in pigs and humans in the USA have not been found in Europe to date. The main swine influenza viruses circulating in US pig herds in recent years have been swine triple reassortant A(H1N1) viruses, A(H3N2) and A(H1N2) viruses [8].

An important point is that there is little if any movement of live pigs between continents. Indeed it is not legal for live pigs to be imported from the USA to Europe. Hence there is little risk of spread of the American viruses to pigs in Europe. This is in contrast to the situation, for example, of the transmission of avian influenza through movement of wild birds and trade in domestic poultry [11]. It is considered that there is no risk to humans of acquiring infections with swine influenza from consumption of food.

Human infection and disease

Infection with swine influenza virus has occasionally been detected in humans since the 1950s [12]. Because of weaknesses in surveillance, statements on how common these infections are in humans must be made with caution [12].

Human disease is usually clinically similar to disease caused by infections with human influenza viruses. Complications have only rarely been reported in the literature, although they have occurred even in otherwise healthy adults [12]. However, such reports will tend to be biased towards more severe disease. In the most complete and best described series from the United States, all 31 identified cases have recovered [2].

Cases of swine influenza in humans usually occur after a history of exposure to pigs with direct, close or indirect contact [11]. Of the 31 cases reported in the US between December 2005 and 22 November 2011, 11 had a history of exposure to pigs; for one case exposure was unknown. Twenty-three cases occurred in children (persons

ⁱ These are swine influenzas not human influenzas.

18 years or younger) and eight in adults [2]. Single generation person-to-person transmission has been reported but not longer chains of transmission [2].

An exception is a well known 1976 outbreak of swine influenza among young essentially healthy adult military recruits at a basic-training centre in New Jersey (Fort Dix). This was caused by a swine-origin A(H1N1) virus and resulted in at least 230 infections, 13 of whom experienced severe disease, and one death of a previously healthy man. After intense local transmission over a one-month period that virus was then never observed again [13]. Hence the pandemic 2009 A(H1N1) virus is so far the only swine-origin virus that has shown the capacity to spread rapidly between humans [6].

There have been only five recent reports of human infection with swine-origin influenzas in Europe. In late 2008, a middle-aged woman in Spain who worked with pigs suffered a mild self-limiting influenza-like illness, was infected with a swine-origin influenza virus A(H1N1). This was completely unrelated to the pandemic A(H1N1)pdm09 virus that emerged in 2009 [14, 15].

In September 2011, a very similar swine influenza virus A(H1N1) was identified in an 18-month-old boy from Lower Saxony, Germany. The genetic characterisation of the HA, NA, NP and NS genes showed that the virus is typical of the A(H1N1) Eurasian swine lineage. This virus is known to be endemic within European pig herds and is unrelated to the A(H1N1)pdm09 influenza virus or the earlier human seasonal A(H1N1) virus [10,16].

In Switzerland three adult males working with pigs have been reported with swine-origin A(H1N1) virus infections over the period 2009 to 2011 with similar viruses being found in the pigs they were working with (L. Kaiser; personal communication).

Serological surveys undertaken in North America among persons working with pigs have shown that they quite often have evidence of prior infection with swine influenza viruses. Interpretation of sero-prevalence data can be difficult due to cross-reactivity (i.e. infection with a seasonal influenza virus might be misinterpreted as indicating prior swine influenza infection). There are few contemporary serological data from humans for Europe [17].

Laboratory diagnosis

Diagnostic RT-PCR for generic influenza A virus will detect these viruses as human influenza A. However, the subtype-specific RT-PCR for either H3 or N2 of human influenza A viruses will most probably have a decreased sensitivity or will result in no detection of the SO-A(H3N2) viruses. Probes directed against other genes, e.g. the nucleoprotein gene as was used during the early phase of the 2009 pandemic caused by the A(H1N1)pdm09 virus, will enable preliminary differentiation between human seasonal H3N2 viruses and these zoonotic H3N2 viruses. Therefore, swine-origin specific subtype RT-PCR, antigenic characterisation, and partial or full genome sequencing are the most appropriate techniques to distinguish between the human and these new zoonotic origin influenza viruses. The European influenza reference laboratories (National Influenza Centres) are aware of the detection challenges and a number are updating their detection protocols to be able to make this distinction. However, it is not clear what the strategies are across national laboratories in the EU/EEA countries

The National Influenza Centres in France and the WHO Collaborating Centres in Atlanta, US and London, UK have been analysing the genetic sequences on these viruses. They essentially agree that it is very likely that the current seasonal vaccine would not protect against infection should these viruses appear in humans in Europe. However, the phylogenetic analysis of these viruses also suggests that those infected or vaccinated in the past with strains with antigenic characteristics similar to the strain (H3N2) may have some degree of protection against this virus. This possible cross-protection could be verified by sero-epidemiological surveys to assess the prevalence of antibodies' cross-reactive potential protection by age group [18]. This observation is consistent with the notably young ages of many of the cases in the United States [3–4].

Human public health importance of swine influenza

The public health importance of swine influenza is twofold. Firstly there is the direct risk of infection for those coming into close contact with pigs or through limited human-to-human transmission. Triple reassortant swine influenza viruses with avian, human and swine genes have been circulating in pigs in the US, and have been transmitted to humans. This is now also the case for the triple reassortant viruses with the additional A(H1N1) M-gene [1]. However, none of these reassortant viruses has been able to maintain themselves in the human population and, in addition, there have been no large clusters of infection. The second risk is of reassortment to produce a novel virus (possibly a strain with pandemic potential), either in the pig or in the human host, by co-infection with a human and a swine strain. The pandemic A(H1N1)pdm09 influenza virus is so far the only swine-origin virus that has shown the capacity to spread readily and extensively between humans. However, it demonstrates that this is a possibility.

ECDC RAPID RISK ASSESSMENT FOR THE EU

It is important to emphasise that the viruses circulating in pigs in North America seem to be quite different from those reported in pigs in Europe. Swine influenza A(H3N2) viruses predominate in North America as triple reassortant viruses while the H3N2 viruses that are endemic in swine in some regions of Europe are antigenically and genetically different [6,7]. Reports of swine-origin viruses in humans in North America occur most years and since 'novel influenza A viruses' are a nationally notifiable disease in the US, laboratories that detect a possible novel influenza A virus are required to investigate the case and rapidly send laboratory specimens to the CDC for testing [2]. By contrast, reports of swine viruses in humans in Europe are rare: there have been only two published reports since 2008 (one in Spain and one in Germany) plus the three cases from Switzerland that have yet to appear in the literature [14–16].

However, it must be noted that the discovery of the Spanish and German cases in humans was almost accidental, so it is likely that the numbers of human infections are underestimated. Following the emergence of the 2009 pandemic from pigs in Mexico there is a strong public health case for increased active ascertainment of human infections with swine viruses in Europe [15]. Finally it should be noted that human influenza viruses from the 2009 pandemic may be circulating in pig herds in Europe, giving rise to the possibility of reassortment as demonstrated recently in Germany in which case these infections may not be detectable by conventional testing [10].

The risk of the emergence of a pandemic virus based on the American triple reassortant swine viruses with or without the A(H1N1) M gene cannot be known. This is only one of a number of potential pandemic influenza viruses. Others include A(H9), A(H2) and A(H5N1) viruses. An international initiative recently started with the aim of judging which candidate viruses are most likely to warrant the development of pandemic preparedness tool-kits that include both diagnostic components and early vaccine development [19]. That initiative is not yet developed enough to justify its application to S-OtrH3N2 viruses but they would be early candidates for consideration. In Europe this initiative is being supported by the European Food safety Authority [20].

CONCLUSIONS AND RECOMMENDATIONS

The viruses in question have not been seen in pigs in Europe (EU/EEA) but there has been swine-to-human transmission in Europe with European viruses. However, there are no reports of anything but mild self-limiting illness and no ongoing transmission. The clinical picture is in stark contrast to avian influenza A(H5N1) infections [11].

Surveillance for infections in humans in contact with pigs is not as robust in Europe as in the US and there are strong public health reasons for strengthening surveillance of animal infections on both continents. Human influenza viruses from the A(H1N1) pandemic may be circulating in pigs and reassortant viruses from pigs have also been described recently. This is in addition to integrated virological, clinical and epidemiological surveillance of human infections in various healthcare settings (community, primary care, hospitals including intensive care units).

It is important to ensure that there is at least national capacity for detecting these viruses in EU/EEA countries and ECDC should work with the Community Network of Reference Laboratories (CNRL) to determine what methods are being used. Depending on the results of that exercise it may be worthwhile to issue guidance on recommended options for potential sampling and testing.

Another area requiring rapid work is determining what to call these and other new influenza viruses, since whilst a virological terminology such as S-OtrA(H3N2) plus an A(H1N1) M gene and A(H1N1)pdm09 may be essential for technical discussions, it does not facilitate communication.

It is impossible to comment on the pandemic potential of the current swine influenza viruses but formal virological risk assessments on the pandemic potential of emerging viruses like these are under development.

It is possible that these triple reassortant infections will appear in Europe, particularly if there is more human-to-human transmission, which could lead to imported cases. Hence Member States should continue to work with WHO and ECDC-CNRL to ensure there is diagnostic capacity at least at the national level in EU/EEA countries.

Finally, the situation highlights the importance of early and rapid referral of unusual influenza viruses, along with relevant clinical and epidemiological data, to National Influenza Centres and on to the WHO Collaborating Centre in Europe.

Relevant EU swine influenza websites:

ESNIP2 - European Surveillance Network for Influenza in Pigs 2: <http://www.esnip.ugent.be/>

ESNIP3 - European Surveillance Network for Influenza in Pigs 3: <http://www.esnip3.eu/>

FLUPIG - Pathogenesis and transmission of influenza in pigs: <http://www.flupig.ugent.be/>

CONTACT: support@ecdc.europa.eu

References

1. Centers for Disease Prevention and Control Swine-Origin Influenza A (H3N2) Virus Infection in Two Children --- Indiana and Pennsylvania, July--August 2011 CDC Morbidity and Mortality Weekly Report, September 9, 2011 / 60(35); 1213-1215
2. Centers for Disease Control and Prevention (CDC) Reported human Infections with Swine Origin Influenza Viruses (SOIV) in the United States since 2005 November 22nd 2011 http://www.cdc.gov/flu/swineflu/soiv_cases.html
3. Centers for Disease Control and Prevention November 22nd 2011 Iowa Reports Novel Influenza Infections in Three Children http://www.cdc.gov/media/haveyouheard/stories/iowa_influenza.html
4. Centers for Disease Control and Prevention (CDC) Limited Human-to-Human Transmission of Novel Influenza A (H3N2) Virus — Iowa, November 2011 MMWR November 23, 2011 / 60(Dispatch);1-3 http://www.cdc.gov/mmwr/preview/mmwrhtml/mm60d1123a1.htm?s_cid=mm60d1123a1_e
5. WHO Influenza like illness in the United States of America November 24th 2011 http://www.who.int/csr/don/2011_11_24/en/index.html
6. WHO Report of the Review Committee on the Functioning of the International Health Regulations (2005) and on Pandemic Influenza A (H1N1) 2009 (Fineberg Report) Final submitted to the World Health Assembly 2011 http://apps.who.int/gb/ebwha/pdf_files/WHA64/A64_10-en.pdf
7. Kyriakis C.S., Brown I.H., Foni E., Kuntz-Simon G., Maldonado J., Madec F., Essen S.C., Chiapponi C., Van Reeth K. - Virological Surveillance and Preliminary Antigenic Characterization of Influenza Viruses in Pigs in Five European Countries from 2006 to 2008. *Zoonoses Public Health*, 2011: 58, 93-101.
8. Olsen CW, Brown I, Easterday BC, Van Reeth K. Swine influenza. In: Straw B.E., Zimmerman J.J., D'Allaire S., Taylor D.J., eds. *Diseases of Swine*, 9th edition, Iowa State University Press, Ames, Iowa, 2006: 469-82.
9. Van Reeth K, Brown IH, Dürrwald R, Foni E, Labarque G, Lenihan P, et al. Seroprevalence of H1N1, H3N2 and H1N2 influenza viruses in pigs in seven European countries in 2002–2003. *Influenza and other respiratory viruses*. 2008;2(3):99-105.
10. Starick E, Lange E, Fereifuni S, Bunzenthel C, Hoveler R, Kuczka A et al. Reassorted pandemic (H1N1) 2009 influenza A virus discovered from pigs in Germany. *J Gen Virol* 2011; 92: 1184-8.
11. Van Reeth K. Avian and swine influenza viruses: our current understanding of the zoonotic risk. *Vet Res*. 2007;38(2):243-60.
12. Myers KP, Olsen CW, Gray GC. Cases of swine influenza in humans: a review of the literature. *Clin Infect Dis*. 2007;44(8):1084-8.
13. Neustadt RE, Fineberg HV. *The swine flu affair: decision making on a slippery disease*. Washington: US Department of Health, Education and Welfare 1978
14. Adiego Sancho B, Omeñaca Terés M, Martínez Cuenca S, Rodrigo Val P, Sánchez Villanueva P, Casas I, Pozo F, Pérez Breña P. Human case of swine influenza A (H1N1), Aragon, Spain, November 2008. *Euro Surveill*. 2009;14(7):pii=19120. Available online: <http://www.eurosurveillance.org/ViewArticle.aspx?ArticleId=19120>
15. Van Reeth K, Nicoll A. A human case of swine influenza virus infection in Europe – implications for human health and research. *EuroSurveill*. 2009;14(7):pii=19124. Available from: <http://www.eurosurveillance.org/ViewArticle.aspx?ArticleId=19124>
16. ECDC Public Health Development. [True swine influenza in humans: recent different findings in the United States and Europe \(Germany\)](#). 28 October 2011.
17. Gerloff NA, Kremer JR, Charpentier E, Sausy A, Olinger CM, Weicherding P, et al. Swine influenza virus antibodies in humans, western Europe, 2009. *Emerg Infect Dis* [serial on the Internet]. 2011 Mar [date cited]. <http://dx.doi.org/10.3201/eid1703100581>
18. CDC. Serum cross-reactive antibody response to a novel influenza A (H1N1) virus after vaccination with seasonal influenza *Mmwr*. 2009 May 22;58(19):521-4.
19. WHO Antigenic and genetic characteristics of zoonotic influenza viruses and development of candidate vaccine viruses for pandemic preparedness and Standardization of terminology of the pandemic A(H1N1)

2009 virus Weekly Epidemiological Record 21 October 2011, vol. 86, 43 (pp 469–480)
<http://www.who.int/wer/2011/wer8643.pdf>

20. ECDC. Public Health Development. Virological Risk Assessment of Pandemic Potential - EFSA Call for proposals 18th July 2011. Available at:
http://ecdc.europa.eu/en/activities/sciadvise/Lists/ECDC%20Reviews/ECDC_DispForm.aspx?List=512ff74f%2D77d4%2D4ad8%2Db6d6%2Dbf0f23083f30&ID=1156