RISK ASSESSMENT

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

17 August 2012

Summary, assessment and conclusions

Following recent increased reporting of human infections in the US with an influenza A(H3N2) variant virus of swine origin (A(H3N2)v), ECDC has updated its risk assessment:

Summary of event

- Thirteen cases of human infections with a novel influenza A(H3N2) variant were reported in six States across the US between July 2011 and April 2012. From April to 9 August 2012, over 150 cases were reported from nine States, with most of the cases in Indiana and Ohio.
- Ninety-three percents of cases are under 18 years. No serious complications or deaths have been reported. Most cases report direct contact with swine or attendance at agricultural fairs. Only limited, non-sustained, human-to-human transmission has been reported.
- Serological studies show that younger children are more susceptible. The current seasonal influenza vaccines are unlikely to provide protection.
- CDC expects that cases will continue to be detected including some due to human-to-human transmission.
- On a precautionary basis an influenza A(H3N2)v reassortant vaccine strain has been developed for use in production of influenza A(H3N2)v vaccines if needed. Clinical trials evaluating the immunological response and safety of such vaccine candidates are planned in the next few months.

Risk assessment for the EU

- No swine influenza A(H3N2)v viruses have been found in European pigs.
- No influenza A(H3N2)v virus infections have been reported among humans in the EU.
- European travellers exposed to pigs in the US are at some risk of developing the disease.

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Conclusions and recommendations

The swine-origin influenza A(H3N2)v viruses do not currently pose a serious risk to human health in general and Europe in particular. Should increased pathogenicity and/or transmissibility be acquired this assessment will be revised as well as further developments presented on the ECDC web-site.

1. **Europe needs to be prepared for detecting these infection should they emerge in humans**

ECDC and its laboratory collaborators in national laboratories, the WHO Influenza Collaborating Centre and the Community Network of Reference Laboratories (CNRL) is taking action to ensure that reference laboratories in Europe can detect these novel viruses. However, to ensure that novel influenza A infections can be detected in European primary diagnostic laboratories further capacity building will be needed.

2. **From a human health perspective, it remains essential to obtain timely information on the circulation of influenza viruses among pigs in the EU.**

Monitoring emerging animal influenza viruses for their pandemic potential is essential and continues to be a priority in Europe. Unusual influenza viruses and viruses which cannot be subtyped should be referred to national influenza reference laboratories and to the WHO Collaborating Centre in Europe, along with relevant clinical and epidemiological data. This ECDC assessment will be revised if pigs in the EU are found to be, or at risk of becoming infected with this triple reassortant influenza A(H3N2) variant virus.

Source and date of request

Original request for a risk assessment from the Directorate-General for Health and Consumers and supported by Member States in the EU Health Security Committee, 24 November 2011. Please see original risk assessment here [1a]. A first update of the original risk assessment was prepared in December 2011 [1b]. Further information on the topic has been provided in the following ECDC publications; Scientific Advance (January 2012) [55], Public Health Development (August 2012) [1c] and Epidemiological Update (August 2012) [1d].
Decision to prepare a second update of the original risk assessment followed an internal decision at the daily round table meeting of ECDC, 9 August 2012.

Public health issue

Implication for Europe of increased reported number of human cases of infections with swine-origin influenza A(H3N2) variant viruses [(H3N2)v] in the United States.

The objectives of this update of the risk assessment are:

- to update risks to human health in Europe given the increased number of human cases reported in the US
- to give guidance on diagnosis of the new viruses
- to give guidance on how Europe should respond concerning possible treatment and preventive measures should infections occur
- to consider the longer term risk of pandemic emergence from these influenza A(H3N2)v viruses

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* The views in this document do not necessarily represent the views of the WHO Regional Office for Europe.

Recent developments in the United States

Human infections with influenza A(H3N2)v viruses of swine origin have been reported in the United States since July 2011. During the period July 2011 to April 2012, 13 such cases were reported from six States (Indiana, Iowa, Maine, Pennsylvania, Utah and West Virginia). Between July and 9 August 2012, there were a further 153 cases, including reports from three additional States (Hawaii, Illinois, and Ohio), bringing the total to 166 cases from nine US states [2]. Indiana (n=122) and Ohio (n=31) have reported most cases. Demographic information available for 138 of 153 reported cases show the following; 128 (93%) occurred in persons <18 years, and 10 (7%) occurred in adults [3]. The median age was seven years. Most H3N2v patients for whom information was available reported contact with swine or having attended an agricultural fair where swine were present. However, some limited human-to-human transmission has been reported in households and in a childcare setting [4].

Most of the reported human cases with influenza A(H3N2)v infections have resulted in symptoms similar to uncomplicated seasonal influenza, such as fever, cough, pharyngitis, rhinorrhea, myalgia and headache. Vomiting and diarrhoea have also been reported in some paediatric cases. Milder clinical illness is possible. Influenza A (H3N2)v infections can therefore not be distinguished in their clinical features from seasonal influenza A or B virus infections.

In most cases, the duration of illness appears to be three to five days. Viral replication, pathogenesis and transmission in humans have not been studied. Three hospitalisations occurred in 2011, two in children with underlying medical conditions and all three recovered fully. Between 12 July and 9 August 2012, two individuals were hospitalised and both have had an uneventful recovery. Although no deaths have been reported [3] underlying conditions (e.g. asthma) have been exacerbated. CDC considers that the same individuals at increased risk of complications from seasonal influenza are likely to be at risk of complications due to the influenza A(H3N2)v virus infection.

Though some human-to-human transmission has been reported, there is no known evidence of sustained human-to-human transmission of these influenza A(H3N2)v viruses since most cases have been associated with direct exposure to swine [2].

In the United States, CDC suggests that the key to diagnosing influenza A (H3N2)v virus infection in a patient is to elicit an epidemiological link to recent swine exposure in the week prior to illness onset (direct contact – e.g. raising pigs, feeding pigs, cleaning pig waste or indirect contact – e.g. visiting a pig farm or walking through a swine barn). A case definition for a probable influenza A(H3N2)v case has been developed in the US for a patient with influenza-like illness and an epidemiological link to recent swine exposure [5]. In guidance issued by CDC, US clinicians are requested to notify local public health departments regarding probable cases and obtain relevant diagnostic samples for testing in a state public health laboratory.

Swine influenza viruses do not commonly infect humans. However, sporadic human infections with influenza viruses that normally circulate in swine and not people, such as H1N1v, H3N2v and H1N2v, have previously been detected in the United States [6,7]. The CDC currently reports these cases in its weekly national influenza surveillance report, FluView.

There is no systematic influenza surveillance in pigs in the USA, although efforts are being made to address this issue [6,8]. In addition to the current weekly case counts, virological characterisation is performed through genetic sequencing and has determined that the new influenza A(H3N2)v reassortant viruses contain the influenza A(H1N1)pdm09 Matrix (M) gene [5]. Further characterisation shows that the influenza A(H3N2)v viruses are likely to be susceptible to the neuraminidase inhibitor drugs oseltamivir and zanamivir but resistant to amantadine and rimantadine [5].

Little information is currently available regarding the potential of these viruses to transmit efficiently in humans, between swine and humans or other animal species known to be susceptible to influenza. However, in ferrets A(H3N2)v viruses have shown the capacity for efficient replication and transmission and these mammals are considered good models for how influenza behaves in humans [9]. This underscores the need for continued public health surveillance, especially as regards further human-to-human transmission.

Serological data from the United States and Canada suggest that children under 10 years lack immunity to influenza A(H3N2)v viruses and therefore are likely to be most susceptible [2, 10]. Adolescents and younger adults may have cross-protective antibodies, but some are expected to be susceptible. Middle-aged and older adults have lower levels of cross-protective antibodies and may therefore be more susceptible. The results of serological studies are in line with the age pattern observed in affected cases, i.e. younger individuals being more affected. There are no indications in the serological studies that seasonal influenza vaccination during the last two seasons provides any protection against the influenza A(H3N2)v infections [2,10]. Therefore, as a precaution, an A(H3N2)v reassortant vaccine strain has been developed for use in the production of H3N2v vaccines, if necessary. Clinical trials evaluating the immunological response and safety of such vaccine candidates are planned in the next few months [12].

Epidemic intelligence work and independent approaches by ECDC to relevant national and international agencies in other regions found no indications of unusual outbreaks of respiratory viral infections. This indicates that the situation is not similar to that in Mexico and the south-western United States in 2009 when a few reported cases in

the USA represented much larger outbreaks elsewhere and the start of the influenza A 2009 H1N1 pandemic [13,4]. No cases of influenza A(H3N2)v infections have been reported in humans in the EU/EEA Member States.

Background information

Swine influenza

Swine influenza is an acute viral infection of the respiratory tract in pigs with swine influenza A viruses. Mortality in pigs is low and recovery usually occurs within seven to ten days. An infected pig may suffer rapid onset fever, loss of appetite, laboured abdominal breathing and coughing but subclinical infections are common. Infections are considered endemic in pigs in Europe, and elsewhere in the world [14]. Serological surveys indicate that a significant proportion of pigs are infected during their lifetime. Unlike human influenza in temperate countries there is no apparent seasonal pattern for influenza among pigs [15,16,17].

A voluntary anonymous system of surveillance in swine has recently been developed in the United States. At present, information on human infections due to influenza A(H3N2)v viruses is providing useful complementary information.

Swine influenza is not a notifiable animal disease in the European Union and there is no formalised disease surveillance in humans. EU data are only available from research studies supported by the European Commission (Directorate-General for Research and Innovation) and conducted in a limited number of countries (e.g. under the FLUPIG and ESNIP3 projects). The objective of the ESNIP3 project is to follow changes in the disease epidemiology of swine influenza infection in pigs and screen for virological changes.

The triple reassortant variant viruses previously detected in the United States are H1N1v, H3N2v and H1N2v [5,17]. In the US, the circulation of A(H3N2)v in pigs seems to be endemic and active, since over 95% of the samples taken randomly at fairs in different counties across several states were positive for the virus [19]. It is quite possible that the influenza A(H3N2)v and other variant viruses are circulating in pigs in other parts of the Americas where animal influenza surveillance is weaker.

The swine influenza A subtypes currently known to be circulating in pigs in Europe are quite different from those circulating in the USA. They are known to include A(H1N1)[*], A(H3N2)[ii], A(H1N2) and A(H1N1)pdm09 [17]. Reassortants among these swine influenza virus lineages have occasionally been reported in Europe [15,20,21-25].

Hence, the epidemiology and virology of swine influenza viruses in Europe and the United States are significantly different. The triple reassortant viruses A(H3N2)v seen in pigs and humans in the United States have not been found in Europe. 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 [14]. The triple reassortant H3N2 viruses were first noted in swine in North America in 1998. Their HA and NA proteins are derived from human seasonal A(H3N2) viruses circulating in the mid-1990s. Since 2010, triple reassortant swine A(H3N2) viruses have started to reassort with genes from the A(H1N1)pdm09 virus [26]. The European swine A(H3N2) viruses are derived from descendants of the 1968 'Hong Kong' pandemic human virus, but they have evolved further through genetic reassortment with the 'avian-like' H1N1 swine influenza virus, presumably during the mid-1980s. This has resulted in A(H3N2) viruses with human-like HA and NA genes and avian-like internal genes [27-29].

The novel influenza A(H3N2)v viruses have so far not been identified in either humans or pigs in Europe. However, the potential risk of introducing these viruses to Europe through infected pigs or humans cannot be ruled out. Surveillance of influenza A(H3N2)v viruses in Canada has so far not identified any A(H3N2)v infected pigs. Related influenza virus reassortants have recently been identified in Canada [30]. The spread of swine influenza viruses is therefore more controlled than, for example transmission of avian influenza through movement of wild birds and trade in domestic poultry [31]. It is also important to note that there is no risk of contracting swine influenza from consumption of pork or pork products.

The risk posed by the human cases of A(H3N2)v viruses is related to the fact that the A(H1N1)pdm09 virus has become established globally in domestic pigs (originating from an as yet unidentified source). The A(H3N2)v were generated by several instances of reassortments between A(H1N1)pdm09 and enzootic swine influenza viruses in dually infected pigs [32-33]. A significant number of such reassortants (involving both H1 and H3 viruses) has already been described over the last three years from both United States [2], Europe [25] and Asia [34-35] and the A(H3N2)v is just one example of a reassortant that has become established in US swine herds. Thus, the presence of A(H1N1)pdm09 in pigs constitutes a major public health risk for the emergence of new influenza strains with pandemic potential [36]. This strain is able to provide one or more genes to new reassortants that can increase transmissibility to humans of any subtype occurring in pigs, including H1, H3, H5 or H9 [37].

[*] These are swine influenzas not human influenzas.

Swine influenza infections in humans

Infection with swine influenza A viruses have occasionally been detected in humans since the 1950s [38]. Due to weak or non-existent surveillance systems in large parts of the world, statements on how common these variant infections are in humans must be made with caution [38-39].

Cases of swine influenza in humans occur after a history of exposure to pigs with direct, close or indirect contact [31]. The capacity of variant influenza A viruses to cause sustained transmission in humans has been rare in history. One exception was the well-known 1976 outbreak of swine influenza among young, essentially healthy adult military recruits at a training centre in New Jersey (Fort Dix). This outbreak was caused by a swine-origin A(H1N1) virus and resulted in at least 230 infected cases. Thirteen cases experienced severe disease, and one death occurred in a previously healthy man. After intense local transmission over a one-month period, this virus was never observed again in humans but continued to circulate in pigs [40]. The second exception is the influenza A(H1N1)pdm09 virus that so far is the only swine-origin virus to have shown the capacity to spread rapidly among humans and which is still circulating in the human population three years later [14].

Reports of swine-origin influenza A viruses in humans in the United States occur almost on an annual basis. Infections caused by 'novel influenza A viruses' are notifiable diseases in the United States and laboratories that detect possible novel influenza A viruses are required to investigate the case and rapidly send laboratory specimens to the CDC for testing [6,41].

There are only five recent reports of human infection with swine-origin influenza A infections in Europe. In late 2008, a middle-aged woman in Spain who worked with pigs suffered a mild, self-limiting influenza-like illness and was found to be infected with a swine-origin influenza virus A(H1N1). This was unrelated to the influenza A(H1N1)pdm09 virus that emerged in 2009 [38,41].

In September 2011, a similar swine influenza virus A(H1N1) was identified in an 18-month-old boy from Lower Saxony, Germany [43]. The genetic characterisation of the HA, NA, NP and NS genes showed that the virus was 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 [43,44]. In Switzerland, during the period 2009 to 2011, three adult males working with pigs were diagnosed as having swine-origin A(H1N1) virus infections, with similar European viruses identified in the pigs they were working with (L. Kaiser; personal communication).

It should 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 earlier work by ECDC and the Community Network of Reference Laboratories for human influenza in Europe (CNRL), national laboratories are ensuring that the European influenza reference laboratories have the ability to detect novel influenza A viruses should they appear in referred specimens in Europe (see Laboratory Diagnosis below).

In 1993, the European H3N2 swine influenza virus was isolated from a one-year-old girl and a two-year-old boy in the Netherlands [44]. The children, who were living in the same geographically distinct region, developed mild respiratory symptoms. The father of the boy had regular contact with his pigs through his occupation. A similar H3N2 swine influenza virus was isolated from a 10-month-old girl in Hong Kong in 1999 [45].

Serological surveys undertaken in North America among personnel working with pigs have shown that some have evidence of antibodies reactive with swine influenza viruses [46,47]. Interpretation of seroprevalence data is difficult due to the possibility of serum cross-reactivity within an influenza virus subtype between swine and human influenza viruses (i.e. it is not clear whether antibodies result from infection with swine influenza virus or related human influenza viruses). There is a lack of contemporary serological data from humans available for Europe [48] but during the 2009 influenza A H1N1 pandemic it has been suggested that approximately 50% of the serologically confirmed cases were asymptomatic [49] and the novel A(H3N2)v infection may exhibit a similar pattern.

Laboratory diagnosis

Diagnostic RT-PCR for generic influenza A virus targeting influenza A M gene will detect these viruses as human influenza A. However, the subtype-specific RT-PCRs used for H3 (or N2) of human influenza A viruses may not be suitable for reliable detection of the A(H3N2)v viruses, or discriminating the A(H3N2)v viruses from current human A(H3N2) viruses. The detection based on H3 or N2 needs to be verified for each particular method separately. The nucleoprotein (NP) gene of the A(H3N2)v is from the North American classical swine influenza lineage. Probes directed against the NP gene, as 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. So far, swine-origin specific subtype RT-PCR, antigenic characterisation, and partial or full genome sequencing are the most appropriate techniques for distinguishing between the human and the new zoonotic-origin influenza viruses.

Together with the Community Network of Reference Laboratories for human influenza in Europe (CNRL) and WHO Regional Office for Europe, ECDC is working on a laboratory detection guidance for the European influenza reference laboratories (National Influenza Centres). The reference laboratories are aware of the detection challenges. However, it is not clear what strategies are used in national primary diagnostic laboratories in the EU/EEA countries for subtyping activities, for example. It is quite likely that with the current diagnostic real-time

(rt) RT-PCR detection systems, a variant virus would be detected as influenza A or even H3 positive in a diagnostic laboratory but would not be distinguished from the seasonal A(H3N2) viruses. Furthermore, not all commercially available rapid influenza diagnostic tests will detect the A(H3N2)v viruses at all [3]. Therefore, it is important that the Member States ensure that algorithms for forwarding unusual influenza A virus detections (e.g. in patients exposed to pigs or sick poultry) to the national reference laboratory are in place.

CDC real-time PCR assay (CDC Flu rRT-PCR Dx Panel) detects the A(H3N2)v as influenza A (with the M gene as target). The following markers can be used for further subtyping of the A(H3N2)v: NP gene of swine origin viruses (including A(H1N1)pdm09), seasonal A(H3N2) haemagglutinin gene (H3) and negative detection of A(H1N1)pdm09 haemagglutinin gene (H1). In EU/EEA countries, the majority (18 of 27 laboratories; 67%) of the influenza reference laboratories have already updated their protocols to swine-specific primers and probes targeting the NP gene (11 of 27 laboratories; 41%), or A(H3N2)v specific H3 RT-PCR (7 of 27 laboratories; 26%) to distinguish the seasonal A(H3N2) viruses from the variant viruses [62]. Based on the CDC Flu rRT-PCR Dx Panel as regards H3N2v for public health laboratories, specimens may be reported as 'presumptive positive for influenza A(H3N2)v virus' when a specimen tests positive for influenza A, H3 and pdm09 markers and negative for influenza B, A(H1) and H1pdm09 markers [50]. CDC rtRT-PCR panel is not a point-of-care test available to clinicians. Confirmation is currently based on sequence analysis at the WHO Collaborating Centres. Therefore, all influenza A(H3)v positive and all influenza A positive but A(H3) negative samples should be referred to the WHO Collaborating Centre. Among others, the National Influenza Centres in France and the WHO Influenza Collaborating Centres in Atlanta, US and UK have been analysing the genetic sequences of 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, especially if individuals with no prior A(H3N2) virus infections are infected. However, the phylogenetic analysis of these viruses also suggests that those infected or vaccinated in the past with strains that have antigenic characteristics similar to the strain (H3N2) may be afforded some degree of protection against this virus [11, 51]. This possible cross-protection could be verified by sero-epidemiological surveys to assess the prevalence of antibody cross-reactive potential protection by age group [10,52]. Current data suggest that the most susceptible groups for the A(H3N2)v infection are children under 10 years and people aged around 40–60 years [10,52]. This observation is consistent with the young ages of many of the cases in the United States [2,13], although the age distribution may be biased by the high number of children exposed to pigs during various summer fairs in the US. In addition, using immunoinformatics, a very recent study suggests possible pre-existing CD4+ T cell immunity in the human population to the swine-origin triple reassortant influenza A (H3N2) variant viruses that emerged in 2011 [53].

Significance of the influenza A(H3N2)v viruses to public health

The significance of swine influenzas to public health in general is twofold. Firstly, there is the direct risk of influenza infection for individuals 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 particularly relevant for the influenza A(H3N2)v viruses. The increase in cases in parts of the USA is unusual, although this may reflect increased awareness and testing by clinicians. Secondly, there is a risk of reassortment and development of novel influenza A viruses (possibly a strain with pandemic potential) in dually infected individuals. Reassortments may develop in dually infected pigs or humans, by co-infection with a human influenza strain and a swine influenza strain. Infections with three influenza A strains also occur, resulting in the triple reassortant strains, and perhaps even involving avian viruses. 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 among humans, confirming the pandemic potential of such viruses. Given the number of circulating influenza A strains affecting animals throughout the world with different pathogenicity, it is important to characterise circulating strains and perform formal multi-dimensional virological risk assessments, such as the IRAT [54] and the EU FluRisk projects [63]. This will help prioritise the development of human diagnostics and vaccines, as is the case in the USA with international input (55). It is reassuring that to date there have been no further reported changes in the A(H3N2)v viruses observed in the USA.

ECDC risk assessment for the EU

There is currently no known risk of infection with the influenza A(H3N2)v viruses in EU/EEA Member States since the virus is not considered to be circulating among pigs in the EU/EEA and no human cases have been reported in the EU.

It should be noted that influenza A(H3N2)v virus infections cannot be distinguished by clinical features from seasonal influenza.

As transmission of the disease in the United States is mainly related to direct contact with infected pigs, travellers to the affected States in the USA who have contact with pigs in farms or visit agricultural exhibitions may be at risk of being infected. If influenza-like symptoms develop in an individual with an epidemiological link to swine exposure in the United States in the week prior to onset of illness, clinicians should consider and sample for the influenza A(H3N2)v viruses. Travellers to the affected States should avoid exposure to pigs, especially if they are at higher risk of influenza complications. Risk groups for more severe influenza disease (adults and children with underlying conditions) are expected to be similar to those for seasonal influenza [56]. Both direct contact (raising

pigs, cleaning pig waste), indirect exposure to pigs (visiting pig farm, walking through a swine barn at a county fair, etc) or close contact (within two meters) with a person who is ill and was recently exposed to pigs.

These viruses cannot be acquired from food products.

Human influenza viruses from the 2009 influenza A H1N1 pandemic are circulating in swine in at least some European countries. Reassortants between influenza A(H1N1)pdm09 and other European swine influenza virus lineages have been reported in Italy, Germany and the United Kingdom [21,24,44]. Infections caused by these reassortants may not be detected by conventional testing. Therefore should there be any clinical or epidemiological suspicion (such as flu-like illness in a person who has recently had contact with pigs) clinicians should contact one of the European influenza reference laboratories (National Influenza Centres).

The risk of the emergence of a pandemic virus with sustained transmission among humans based on the influenza A(H3N2) variant viruses is unknown at present. This is only one of a number of potential pandemic influenza viruses. Others include the influenza A(H2), A(H5), A(H7) and A(H9) viruses. An international initiative – the International Risk Assessment Tool (IRAT) – was recently launched with the aim of judging which candidate viruses are most likely to warrant the development of pandemic preparedness tool-kits including both diagnostic components and early vaccine development [57]. The initiative is not yet sufficiently developed to justify its application to influenza A(H3N2)v viruses. In Europe, it is being supported by the European Food Safety Authority and implemented through the limited Flurisk project [58].

Conclusions and recommendations

The increasing numbers of human cases of A(H3N2) variant virus infections in the United States are a matter of concern. However, it is unclear whether or not the increase represents heightened awareness on the part of clinicians and public health experts. It could be that there are increasing numbers of infections in the US pig population, but this is hard to judge since there is only anonymous voluntary surveillance for influenza in pigs in the USA. Given this fact, and the ability to detect mild and asymptomatic human cases with sensitive diagnostic tools, attention should focus on epidemiological changes, looking for increasing human-to-human transmission and other changes in the behaviour of the virus rather than the number and distribution of cases. It is reassuring that there are such investigations underway, led by the US CDC which expects to observe an increase in the numbers of directly infected and human-to-human cases in the coming weeks. The study protocols used in such investigations need to be formalised and this is being investigated through the Consortium to Standardise Influenza Seroepidemiology (CONSISE) which includes ECDC and a number of other public health bodies [59].

Most of the A(H3N2) variant virus infected individuals in the ongoing outbreak are reported to be under 18 years of age. First results from serological testing suggest that cross-protective antibodies from exposure to earlier circulating H3N2 viruses may confer some protection, and that those most susceptible to infection are children and older adults.

There are no human cases of the A(H3N2) variant virus infections reported in the EU/EEA and these viruses have not been identified in pigs in Europe (EU/EEA). Limited swine-to-human transmission of European swine influenza viruses have been reported in Europe, resulting in mild self-limiting illness, but it is considered that there is likely to be significant under-ascertainment. Therefore, the lack of reports on human-to-human transmission of swine influenza in Europe should be viewed with caution. Reassuringly, the clinical picture of swine influenza infection in humans is in stark contrast to one avian influenza A(H5N1) infection. Swine influenza infection appears instead to be similar to other types of animal influenza that are occasionally transmitted to humans [31].

Surveillance of infections in humans that have contact with pigs is not as robust in Europe as in the United States. There are strong public health reasons for strengthening surveillance of animal influenza infections on both continents, and in other parts of the world. Human influenza viruses from the influenza A(H1N1)pdm09 are circulating in pigs and reassortant viruses from pigs have also been described recently. This surveillance should be an addition to integrated virological, clinical and epidemiological surveillance of human infections in various healthcare settings (community, primary care and hospitals including intensive care units). Following the emergence of the 2009 pandemic there is a strong public health case for increased active ascertainment of human infections with swine viruses in Europe. Clinicians should therefore always bear this in mind if they see influenza-like symptoms in patients known to have had contact with pigs. In such cases samples should be taken and sent to a laboratory alerting the staff there to the risk factors.

It is important to ensure that there is at least capacity in one national centre for detecting these viruses in EU/EEA countries. ECDC and the Community Network of Reference Laboratories (CNRL) have worked to assess and strengthen laboratory capacity in Europe for detecting influenza A(H3N2)v, should it appear in persons in Europe. Results from laboratory efforts indicate that the variant viruses would be detected in most EU countries, although some laboratories may not be able to subtype and identify the viruses as variant [60-61]. ECDC is working together with CNRL to issue a guidance for detection of A(H3N2)v viruses. Updates to sampling and testing protocols are under development.

Clinical management of A(H3N2)v virus infections, as recommended by CDC, is similar to management of seasonal influenza A or B virus infections.[4] Persons who are at higher risk of influenza complications should avoid exposure to pigs, and to persons who are ill following exposure to pigs. If exposure to pigs cannot be avoided, persons at higher risk

of influenza complications should consider wearing appropriate personal protective equipment. This latter recommendation by CDC is relevant for European travellers who may come into contact with pigs.

The current human influenza A(H3N2) component included in seasonal influenza vaccines is considered unlikely to provide any protection to the A(H3N2)v viruses. As a precaution an (H3N2)v reassortant vaccine strain has been developed for use in production of H3N2v vaccines if needed. Clinical trials evaluating the immunological response and safety of such vaccines are planned for in the next few months in the United States. This should not be taken as an indication that A(H3N2)v will become a pandemic virus in the way A(H1N1)pdm09 did. Rather it is a reasonable precautionary step, so that in the unlikely event of an A(H3N2) pandemic many of the initial development steps will have already been completed. The current A(H3N2)v viruses have been characterised and shown to be stable. However, they would represent a risk to human health in Europe if they became transmissible between humans in the USA as they could then very easily move to Europe, as A(H1N1)pdm09 did in 2009. In this case the risks to health would be reduced by the timely development of human vaccines for Europe, although there is no case for the deployment of such vaccines at present beyond essential early trials [40].

It is possible that these variant virus infections will appear in Europe, particularly if there is more human-to-human transmission or travellers visiting US agricultural exhibitions, which could lead to imported cases. Hence Member States should continue to work with WHO and ECDC-CNRL and to collaborate with animal health laboratories to ensure there is diagnostic capacity at least at the national level in EU/EEA countries.

It is currently impossible to assess the pandemic potential of the current swine influenza viruses but formal virological risk assessments on the pandemic potential of emerging viruses such as these are being developed through tools like the CDC Influenza Risk Assessment Tool and the EU Flurisk Project [55, 63].

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 then onto the WHO Collaborating Centre in Europe.

Relevant websites on swine and influenza

WHO Global Influenza Surveillance and Response System (GISRS)
http://www.who.int/influenza/gisrs_laboratory/en/

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/

FLURISK: http://www.izsvenezie.it/index.php?option=com_content&view=article&id=1203&Itemid=629

Main CDC sites on A(H3N2): http://www.cdc.gov/flu/swineflu/influenza-variant-viruses-h3n2v.htm

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