RAPID RISK ASSESSMENT

Severe respiratory disease associated with a novel influenza A virus, A(H7N9) - China

3 April 2013

Main conclusions and recommendations

On 31 March, the Chinese authorities announced the identification of a novel influenza A virus, A(H7N9), in three seriously ill people in two provinces. Two male cases in Shanghai without any epidemiological link aged 87 and 27 years old became ill with respiratory infections in mid to late February and both have died. In Anhui Province, a 35-year-old woman became ill on 9 March and is now in critical condition. The three cases presented with acute high fever onset, cough and respiratory tract infection symptoms. After five to seven days, the patients developed severe pneumonia, progressing rapidly into acute respiratory distress syndrome. The influenza A viruses from the three cases were non-subtypeable and were sent to the WHO Influenza Collaborating Centre at the Chinese Center for Disease Control and Prevention (CDC). They were sequenced and found to be almost identical. China CDC posted an announcement on its website (31 March) and lodged the genetic information on the publicly accessible GISAID website. It identified genes from both A(H7N9) and A(H9N2) viruses, thus indicating a novel reassortant avian influenza A virus. No similar viruses have been seen before and they differ genetically from A(H7) and A(H9) viruses that have been detected in Europe and elsewhere worldwide. This is the first time that human infection with influenza A(H7N9) virus has been identified. It is also the first time that human infection with a low pathogenic avian influenza A virus has been associated with a fatal outcome.

The Chinese CDC reports that most close contacts of the confirmed cases from Shanghai and Anhui have not shown similar symptoms so far. However, there are reports of a small family cluster of severe disease around the first case. There are no links between the three cases and no obvious association with bird die-offs (which may not have any relevance, since this is a low-pathogenic avian influenza virus and will not cause any poultry die-offs). Chinese authorities have notified the event to WHO under the International Health Regulations (IHR) for assessment. Local investigations are underway in China and it is too early to anticipate the outcome of these as additional patients with severe respiratory disease are under investigation.

Erratum:

This risk assessment was amended on 5 April 2013 to remove three references to animal surveillance.

Main conclusions and recommendations continued

Threat assessment

Such severe disease involving a novel reassortant influenza virus, in the context of an unknown animal source and mode of transmission is a significant public health event requiring notification under the terms of the International Health Regulations (IHR). As such it was notified through the IHR system by the Chinese authorities. The risk of disease spread to Europe is considered low at this stage though individual cases coming from China cannot be ruled out.

Recommendations for the EU/EEA

There is no need for any change in case finding strategy that was developed in relation to human infections with highly pathogenic avian influenza A (H5N1) virus. This new event stresses the importance of considering the possibility of zoonotic influenza due to novel influenza A viruses in persons presenting with severe acute respiratory disease who have recently been in countries where there are animal influenza A viruses circulating, and have recently caused severe respiratory disease in humans which includes China.

It will be important that EU/EEA countries:

- Remind clinicians and laboratory specialists to consider the possibility of human infection with novel influenza A viruses such as A(H7N9) and A(H5N1) in persons presenting with severe acute respiratory disease who have, in the last ten days, been in China and other countries where there are have been animal influenza A viruses circulating known to have recently caused severe respiratory disease in humans.
- Clinicians should also be reminded of standard guidance for infection control and contact tracing around such cases.
- Similarly, standard guidance should be applied for vigorously investigating clusters of severe respiratory infections and such infections in health care workers who have been caring for patients with severe acute respiratory disease.
- Particular emphasis should be put upon laboratories rapidly referring non sub-typeable influenza A viruses to the WHO Collaborating Centre for Reference and Research on Influenza in London.
- Patients under investigation for suspected infection with avian influenza A viruses such as H7N9 or H5N1 may need to be notified to national authorities but do not need to be reported to ECDC before confirmation.
- Any confirmed case being diagnosed in the EU/EEA area should be reported to national authorities, through the Early Warning and Response System (EWRS) and to WHO under the International Health Regulations (2005). Reporting through EWRS qualifies as IHR notification and avoids double reporting.

Source and date of request

ECDC internal decision, 1 April 2013.

Public health issue

The aim of this document is to summarise the limited information currently available on this important development, to give some initial guidance for European countries supplementing that from WHO and to highlight some priorities for further investigation.

Consulted experts

ECDC internal response team

Paloma Carrillo-Santisteve, Massimo Ciotti, Denis Coulombier, Caroline Daamen, Assimoula Economopoulou, Johan Giesecke, Peter Kreidl, Angus Nicoll, Rene Snacken, Cindy Schenk and Bertrand Sudre,.

External experts consulted and acknowledgements

The following individuals provided information and comments: Caroline Brown, WHO Regional Office for Europe, Copenhagen; Olav Hungnes, FHI, Oslo, Norway; John McCauley, WHO Collaborating Centre for Reference and Research on Influenza, London, UK; Adam Meijer and Marcel Jonges, RIVM, Bilthoven, the Netherlands; Malik Peiris, Hong Kong University, Hong Kong SAR, China; Tim Uyeki, US Centers for Disease Control and Prevention, Atlanta, USA; Thedi Ziegler, THL, Finland.

ECDC is very grateful for the expert input from the persons above. They were consulted as individuals on the basis of their expert knowledge and experience rather than as representatives of their institutions or countries. A Declaration of Interest has been requested from all experts, but has not yet been received from all of them. It should therefore be noted that responsibility for the content of this risk assessment rests with ECDC rather than with these individuals.

ECDC acknowledge that this analysis has been possible only with the viruses and molecular data provided in the publicly accessible GISAID[1] database by the WHO Collaborating Centre for Influenza at the Chinese Center for Disease Control and Prevention[2].

[1] The Global Initiative on Sharing All Influenza data (GISAID) http://platform.gisaid.org/epi3/frontend#c6798

[2] Chinese Center for Disease Control and Prevention http://www.chinacdc.cn/en/

Event background information

On 31 March the Chinese Authorities (the National Health and Family Planning Commission, previously the Ministry of Health) announced the identification of a novel influenza A virus infection, A(H7N9) in three seriously ill people in two Chinese provinces[3][1] .

Two cases in Shanghai were men aged 87 and 27 years who became ill in mid to late February and later died (on 4 and 10 March). A third case is a 35-year-old woman from Anhui Province who became ill on 9 March. As of 1 April 2013, she is in critical condition in Nanjing (Jiangsu Province). A summary of information about officially confirmed cases is below in Table 1.

The three cases presented with acute high fever onset, cough and respiratory tract infection symptoms at the early stage of the disease. After approximately seven days, the patients developed severe pneumonia progressing rapidly into acute respiratory distress syndrome.

The viruses were confirmed as A(H7N9) infection by RT-PCR, virus isolation and then sequencing by the Chinese CDC in Beijing. The three virus strains isolated from the three cases were found to be almost identical. China CDC posted an announcement in English on the CCDC website on 31 March [2] and lodged the genetic information on the GISAID website.

There is no evidence of an epidemiologic link between cases. Moreover, there are no reported links with bird die-offs or animals although the young male patient in Shanghai was a butcher. Also as this is a low pathogenicity virus for poultry it is possible that there will be no die-off events such as often occurs with highly pathogenic influenza. The third case had exposure history to poultry before the onset of symptoms. Over eighty close contacts are currently being followed-up. None of these have had symptoms apart from two members of the family of Case 1 (in the table below). These are two sons of the 87 year old case aged 69-year-old and 55-year-old. It is reported that they were admitted to a hospital between 14 and 24 February with pneumonia. The 69-year-old recovered but the 55-year-old died later in February from respiratory failure. The cause of their illnesses is still under investigation[4,5]

There are investigations underway locally and in other parts of China. The Jiangsu Provincial Health Department has set up an avian flu prevention and control work leading group organizing prevention and response activities, notably around Nanjing city in Jiangsu Province. The Health authorities in Shanghai have ordered hospitals to strengthen monitoring and supervision of respiratory illness cases[6]. Standard advice is being given on personal hygiene, avoiding contact with dead livestock and symptomatic persons seeking medical attention. With these investigations, a number of patients are being tested for possible A(H7N9) infection and while no additional cases have been officially confirmed as of 2 April 2013 it seems likely that more will follow and be confirmed as confirmatory testing has been distributed to the provinces in China.

Some other authorities in the Asia Region are adding A(H7N9) to their pre-existing guidance on detecting A(H5N1) cases from China or occurring within country. This includes Thailand that has set-up nationwide surveillance for H7N9 bird-flu virus[7]Hong Kong[8] and Taiwan's Centers for Disease Control[9]

[3] Hong Kong Ministry of Health Press release: notification of three human cases of H7N9 in Shanghai and Anhui Province http://www.info.gov.hk/gia/general/201303/31/P201303310295.htm

[4] Chinese CDC report: http://www.chinacdc.cn/tzgg/201303/t20130331_79281.htm

[5] Treyfishs's H5N1 Pandemic information news [internet] http://swineflumagazine.blogspot.se/

[6] AFP news report [internet] 1 April 2013 http://au.news.yahoo.com/thewest/a/-/world/16483906/shanghai-boosts-checks-after-bird-flu-deaths/

[7] The Nation (Thailand) media report [internet] 1 April 2013 http://www.nationmultimedia.com/breakingnews/Alert-for-H7N9-birdflu-virus-after-deaths-in-China-30203140.html

[8] The Strait Times media report [internet] 1 April 2013 http://www.straitstimes.com/breaking-news/asia/story/hong-kong-issues-warning-new-bird-flu-strain-20130401

[9] Focus Taiwan news channel media report [internet] 31 March 2013 http://focustaiwan.tw/news/aall/201303310020.aspx

Disease background information

Virological information

The China CDC has posted summary information on its website as well as detailed genetic sequence data on the publicly accessible GISAID web-site.

The virus is an avian influenza A reassortant of A(H7N9) from which the haemagglutinin and the neuraminidase genes have their origin, and A(H9N2) from which the other six gene segments are derived. This makes it different from previously observed avian influenza A(H7N9) viruses including those reported in birds in Europe. There are none of the known genetic markers associated with high pathogenicity in poultry. This will need to be confirmed through further laboratory testing. Pathogenicity in poultry does not necessarily indicate pathogenicity in humans. Based on the presence of the marker S31N for adamantane resistance in the M gene of all three viruses, it is anticipated that the viruses will be resistant to the adamantanes (amantadine and rimantadine), though these medications are not used now in Europe. Although in one virus the R292K amino acid substitution in the neuraminidase that confers resistance to oseltamivir in H3N2 virus has been identified, the sensitivity to oseltamivir and zanamivir is now being confirmed by the WHO Collaborating Centres as a priority using a phenotypic test but the likelihood is that sensitivity to neuraminidase inhibitors will be confirmed.

The new virus will be detected as an influenza A virus by assays using the conserved M-Genes but then when sub-typing is performed will appear as an un-subtypeable influenza A virus using currently available primers and probes by RT-PCR (e.g. negative for H1, H3, H5). It is standard practice that influenza A viruses with such designation are sent rapidly to a WHO Collaborating Centre as happened here with the WHO Beijing Centre. In Europe that is the WHO Influenza Centre in London.

Table 1. Information on confirmed novel A(H7N9) cases as of 1400 CET 2 April 2013

Case Number.	1	2	3
Date of onset	19 February 2013	27 February 2013	9 March 2013
Age (years)	87	27	35
Sex	M	M	F
Occupation	Not stated	Pork butcher	Not stated
Risk exposure	Not stated	Not stated	exposure history to poultry
Probable place of infection	No travel in the preceding two weeks	No travel in the preceding two weeks	No travel in the preceding two weeks
Date reported	31 March 2013	31 March 2013	31 March 2013
Outcome	Death	Death	Critical condition (2013/03/31) TTT: Nanjing, Jiangsu
Date of death	4 March 2013	10 March 2013	
Time to death (days)	14	12	NA
Location	Shanghai	Shanghai	Chuzhou City (Anhui Province) Around 220km from Shanghai
Official source	China CDC Posting	China CDC Posting	China CDC Posting
Initial source of information	Press release HK MoH	Press release HK MoH	Press release HK MoH
Follow-up	Flutracker post[10] China news[11]	Flu tracker post China news	Flu tracker post China news
Additional Information	Family members: 69-year-old and 55-year-old sons hospitalised at the same time are under investigation (69-year recovered 55-year-old died from respiratory failure)		

Case-finding strategy and surveillance

For Europe, there is no need for a change in the case-finding strategy developed in relation to A(H5N1). Current guidance is to consider the possibility of animal influenza in persons presenting with severe acute respiratory disease who have recently been in countries where there are animal influenza viruses circulating that have recently caused severe respiratory disease in humans. That includes China and a few other countries.[12] However, it will be important that EU/EEA countries remind clinicians and laboratory specialists of this guidance, along with the standard guidance of vigorously investigating clusters of severe respiratory infections and such infections in health care workers who have been caring for patients with severe acute respiratory disease. Particular emphasis should be put upon rapidly referring un-subtypable influenza A virus to the WHO Collaborating Centre in London.

[10] Flutrackers website [internet] 1 April 2013 http://www.flutrackers.com/forum/

[11] China News website [internet] 1 April 2013 http://www.chinanews.com/jk/2013/04-01/4694628.shtml

[12] Countries recently (2012 and 2013) reporting A(H5N1) human cases are Bangladesh, China Cambodia, Egypt, Indonesia, Laos and Viet Nam http://www.who.int/influenza/human_animal_interface/EN_GIP_20130312CumulativeNumberH5N1cases.pdf

Epidemiological characteristics

At this stage of the investigations in China it is too early to speculate over which animals the viruses are coming from, routes of transmission, the possibility of human-to-human transmission, the incubation period and risk of infection. The reservoir and routes of transmission to humans are all under investigation by the Chinese authorities and have yet to be determined. While influenza A(H5N1) presents one potential model (very severe human disease but very limited human-to-human transmission) other recent reassortant animal influenza A viruses present other models. For example, A(H3N2)v virus (mostly mild human disease and limited human to human transmission) and A(H1N1)pdm09 virus (mostly very mild human disease but high levels of transmission) indicate other possibilities. There is one small cluster of severe respiratory disease under investigation in Shanghai (Case 1). However, this could equally be due to a common animal or environmental source as limited human-to-human transmission. It is also unclear whether the three cases represent a high severity of most infections, e.g. like A(H5N1) virus or whether there are in fact other milder cases as yet undiagnosed. The strong influenza surveillance system in China is not reporting any overall increase in influenza virus detection or atypical pneumonia cases in the most recently reporting period, although even this is hard to interpret at a time when rates of influenza virus transmission are expected to be falling. However, transmission would have to be quite advanced for those systems to show a signal.

Pandemic Risk

Pandemic risk cannot be determined in any meaningful way at present. Previous A(H7) infections in humans have tended to be mild [3–7]. The exception is one death during a large outbreak in the Netherlands involving highly pathogenic A(H7N7) [8–9]. The death in the Netherlands case was associated with an E627K substitution in PB2 of the H7 influenza virus [8]. The same E627K substitution has been associated with high virulence, host range adaptation and airborne transmission in H5 viruses though the significance of its presence here is yet to be clarified [10–12]. It may be significant that the three H7N9 viruses also have this E627K substitution. Whether this substitution has the same effect in the H7N9 virus as in the H5 and H7 viruses remains to be confirmed in the laboratory. Additionally there is reason for concern over human infections with A(H7) viruses in general [13]. This is an A(H7N9)-A(H9N2) reassortant, and laboratory studies of A(H9N2) viruses with animals have suggested those viruses have pandemic potential [14]. LPAI H9N2 virus infections of humans have usually resulted in uncomplicated influenza illness, but one case of lower respiratory tract disease in an immunocompromised adult has been reported [15].

There is much that could be determined about these new viruses but international authorities, including WHO, the US CDC and ECDC will now be concentrating on the limited number of parameters of the greatest public health and clinical importance using tools like the Influenza Risk Assessment Tool [16–18].

ECDC threat assessment for the EU

A threat assessment for the EU is difficult to undertake at present. Influenza infection with a novel and unexpected reassortant influenza A(H7N9) virus has been associated with severe disease in three humans in two provinces in China and two of these have died. A cluster of infections around one of the cases is being investigated and more cases are emerging. The source of this novel influenza A virus and the mode of transmission are yet to be determined. This is the first time that human infection with influenza A (H7N9) virus has been identified. It is also the first time that human infection with a low pathogenic avian influenza A virus has been associated with a fatal outcome, explaining its significance under the terms of the International Health Regulations (2005) and the Chinese authorities rapid notification for assessment through the IHR system. The risk of international disease spread to Europe is probably low though it is quite possible that individual cases of people with severe respiratory infection which could be due to this A(H7N9) will come to Europe as happened with possible A(H5N1) cases. Certainly it will be important for countries and laboratories to be ready to assess and handle such cases as they do for other severe acute respiratory infections. A degree of preparedness already exists since at the last WHO vaccine strain selection meeting (February 2013) H7 is under consideration as a pandemic candidate and vaccine candidate strains have been developed as a response to previous human cases in Europe and North America, although North American viruses are different from Eurasian viruses. These candidate strains may not efficiently cross protect against the novel A(H7N9) strain but the fact that they are moving towards development does indicate a degree of preparedness globally [19].

Recommendations for the EU/EEA

There is no need for any change in case finding strategy that was developed in relation to A(H5N1).

This new event stresses the importance of considering the possibility of animal influenzas in persons presenting with severe acute respiratory disease who have recently been in countries where there are animal influenza viruses circulating that can cause severe respiratory disease in humans which includes China.

It will be important that EU/EEA countries:

- Remind clinicians and laboratory specialists to consider the possibility of animal influenzas in persons presenting with severe acute respiratory disease who have in the last ten days been in China and other countries where there are animal influenza viruses circulating that can cause severe respiratory disease in humans.[13]
- Clinicians should also be reminded of standard guidance for infection control and contact tracing around such cases.[14]
- Similarly, standard guidance should be applied for vigorously investigating clusters of severe respiratory infections and such infections in health care workers who have been caring for patients with severe acute respiratory disease.
- Particular emphasis should be placed on rapidly referring un-subtypable influenza A virus to the WHO Collaborating Centre based in Europe.
- Patients under investigation may need to be notified to national authorities according to national guidelines but do not need to be reported internationally before confirmation.
- Any confirmed case being diagnosed in the EU/EEA area should be reported to national authorities, through the Early Warning and Response System (EWRS) and to WHO under the International Health Regulations (2005). Reporting through EWRS qualifies as IHR notification and avoids double reporting.

[13] Countries recently (2012 and 2013) reporting A(H5N1) human cases are Bangladesh Cambodia, China, Egypt, Indonesia, Laos and Viet Nam http://www.who.int/influenza/human_animal_interface/EN_GIP_20130312CumulativeNumberH5N1cases.pdf

[14] See WHO Guidelines and National Guidelines such as those of the UK Health Protection Agency http://www.hpa.org.uk/Topics/InfectiousDiseases/InfectionsAZ/PandemicInfluenza/Guidelines/

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