UPDATED RAPID RISK ASSESSMENT

Human infection with a novel avian influenza A(H7N9) virus, China

Third update

27 January 2014

Main conclusions

On 31 March 2013, the Chinese authorities reported the identification of a novel reassortant influenza A(H7N9) virus isolated from three unlinked fatal cases of severe respiratory disease in eastern China, two in Shanghai and one in Anhui province. This was the first time human infections with avian influenza virus A(H7N9) were identified; this event also marked the first fatal human infections caused by a low pathogenicity virus of avian origin.

Since then, human cases have continued to be reported from China. As of 27 January 2014, 251 laboratory-confirmed cases, including 56 deaths (22.3%), have been reported from twelve provinces in China and two municipalities (Beijing and Shanghai). Taiwan reported two cases imported from Jiangsu, and Hong Kong reported three cases imported from Guangdong. In the last weeks there has been a notable increase in the number of cases, which may indicate an enlargement of the reservoir, an increase in the number of exposed individuals, enhanced transmissibility of the virus, a seasonal transmission pattern, or a combination of these factors.

While occasional human-to-human transmission in clusters of reported cases cannot be ruled out, there is no indication of sustained human-to-human transmission. A few mild cases have been detected. Almost identical viruses have been isolated in poultry and environmental samples taken from live animal markets in several provinces that have reported human cases.

The most plausible underlying scenario is of a zoonotic avian influenza that is circulating in poultry in parts of south-eastern China. The severe nature of the disease and the genetic features of the virus present a threat to humans because of the human pandemic potential. The persistence of this virus in poultry represents a significant long-term threat either as a zoonosis or perhaps a pandemic virus. Both eventualities should be prepared for.

At present, the most immediate threat to EU citizens is to those living in China or visiting the country. It is advised to avoid live bird markets.

A possible scenario foresees travel-related, imported cases in Europe. This should be prepared for. However, cases imported from China would not alter ECDC's risk assessment.

Developments since the second update of ECDC's Rapid Risk Assessment (8 May 2013)

Between weeks 20 and 41/2013, only a few cases of human influenza A(H7N9) were reported. Starting in week 42/2013, the number of reported cases increased steadily, with significant increases in the last three weeks. The case-fatality ratio has been 9.4% since week 42/2013. There is no sustained human-to-human transmission, although a few small family clusters were reported in February and March 2013. The geographic distribution has expanded to eleven neighbouring provinces and two municipalities; further imported cases were reported from Taiwan and Hong Kong (SAR).

International groups working with the Chinese authorities have completed in-country assessments of the situation. WHO and the World Organization for Animal Health (OIE) have also responded to the situation.

Samples of the virus have been distributed to international WHO Collaborating Centres for Reference and Research on Influenza, in Europe and elsewhere, allowing further investigation. In Europe, diagnostic testing capacity is established in national influenza centres and public health laboratories.

Selection of viruses suitable for vaccine development has started, including in Europe. Six clinical trials have been initiated in Australia, Canada and the United States to assess safety and immunogenicity. Studies are currently conducted in healthy adults and include adjuvanted and unadjuvanted candidate vaccines. Trials will elucidate whether one or two doses will be needed. Preliminary scientific data point toward the need for two doses, which would be expected given the virus-naïve population.

Source and date of request

ECDC internal decision, 13 January 2014.

Public health issue

The aim of this document is to summarise all available facts on the novel avian influenza A(H7N9) and assess the situation as of 27 January 2014, focusing on new developments since the ECDC rapid risk assessment of 3 April 2013 [1], updated 12 April 2013 and 8 May 2013 [2,3]. This document assesses the risk associated with the outbreak of avian influenza A(H7N9) to public health in the EU/EEA and the risk to EU/EEA citizens in order to anticipate future developments.

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External experts consulted and acknowledgements

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ECDC acknowledges the valuable contributions of all experts. All experts have submitted Declarations of Interest. ECDC has reviewed these and finds that none of them represent conflicts of interest with the comments and suggestions the experts have made. It should be noted that opinions expressed by individual experts do not necessarily represent the opinion of their institutions.

A number of the analyses in this document would not have been possible without the virological and molecular data made available in the GISAID database [8].

We are also grateful to the WHO Collaborating Centre for Reference and Research on Influenza at the Chinese Center for Disease Control and Prevention; the Harbin Veterinary Research Institute; the Ministry of Agriculture, China; and the Hangzhou Center for Disease Control and Prevention, Mingshi, Hangzhou, China.

Event information

Human epidemiology

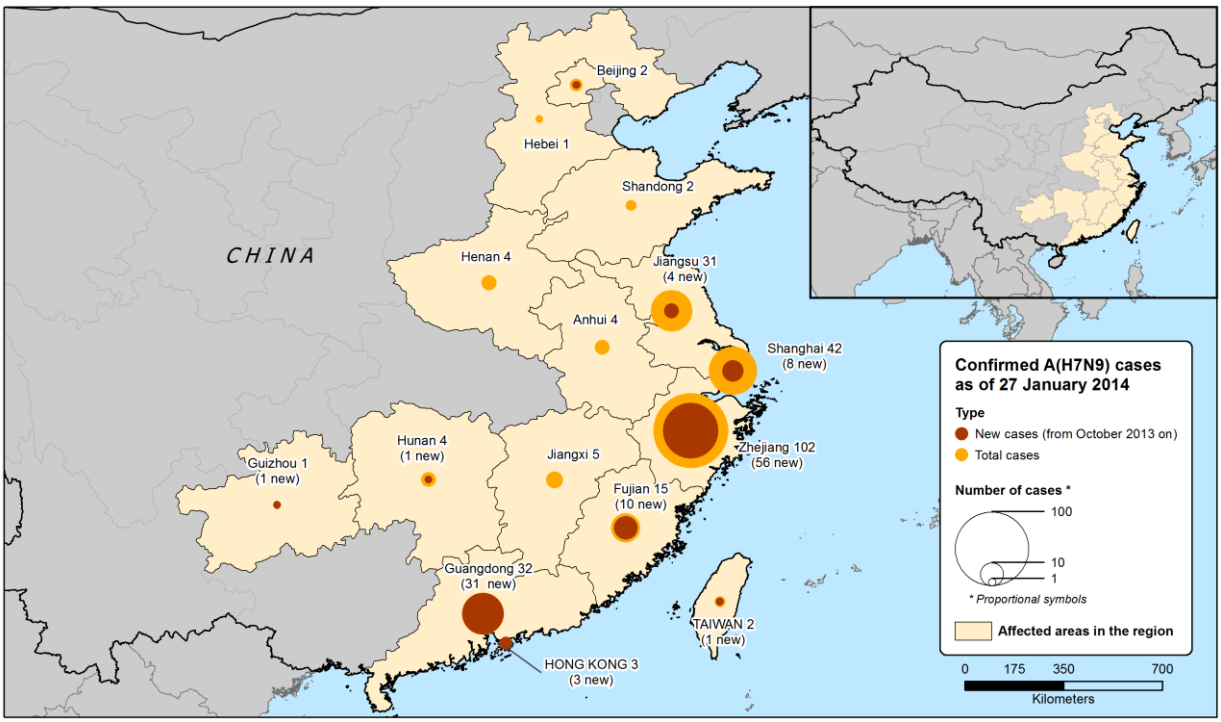
On 31 March 2013, the Chinese authorities announced the identification of a novel influenza A(H7N9) virus infection in three seriously ill people who subsequently died. These cases occurred in the Chinese provinces of Shanghai and Anhui [1]. The Chinese CDC rapidly made tests for avian influenza A(H7N9) available and distributed them via a network of over 400 provincial and local CDC influenza laboratories, major hospitals and research agencies. Data are now being published weekly, and the epidemiological information presented below mostly represents what was available on 27 January 2014, 12 noon (including cases confirmed by local authorities not yet acknowledged by WHO).

As of 27 January 2014, 251 cases of human infection with influenza A(H7N9) have been reported from Zhejiang (102 cases), Shanghai (42), Jiangsu (31), Guangdong (32), Fujian (15), Jiangxi (5), Henan (4), Anhui (4), Hunan (4), Hong Kong (3), Beijing (3), Shandong (2), Taiwan (2), Hebei (1) and Guizhou (1). In addition, the virus has been detected in one asymptomatic case in Beijing (not included in the current case count). Most cases have developed severe respiratory disease. Fifty-six patients have died, although final outcomes are not routinely reported after the initial notification [11,12].

After several months of only detecting sporadic cases, a series of new cases have been reported from nine Chinese provinces/municipalities and Taiwan since week 42/2013 (Figure 1). Since October 2013, 116 cases have been reported: Taiwan (1 case), Hong Kong (3), Zhejiang (56), Guangdong (31), Jiangsu (4), Shanghai (8), Beijing (1), Fujian (10), Hunan (1) and Guizhou (1).

Poultry density is very high in the affected areas, and the extensive poultry trade is considered likely to have contributed to the distribution of the novel avian virus [13].

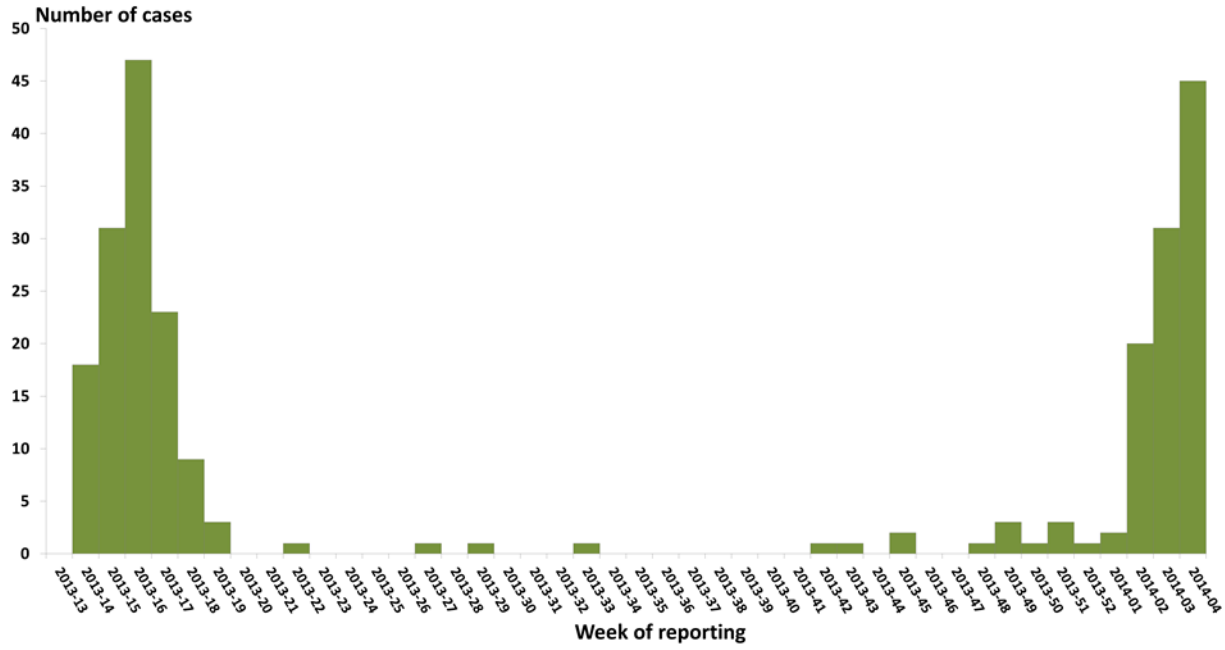
Figure 1. Distribution of cumulative number of human cases of avian influenza A(H7N9), by province and date, China, week 14/2013 to week 5/2014 (n=251)



Note: This figure includes 251 cases confirmed by local authorities; some of these cases have not yet been acknowledged by WHO.

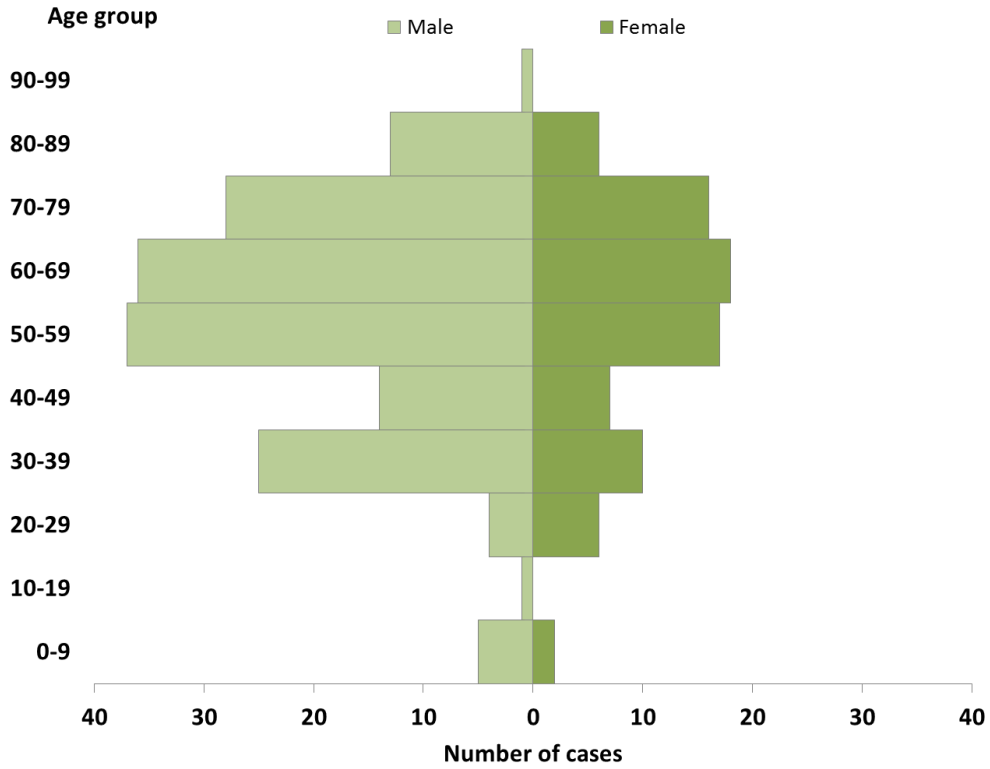
The dates of symptom onset for cases range from 19 February 2013 to 20 January 2014. The epidemic curve by week of reporting (Figure 2) indicates there was a peak in week 16/2013, followed by a decrease of cases through week 19/2013. Between week 20/2013 and 44/2013, only sporadic single cases were reported. Since week 42/2013, the number of cases of confirmed influenza A(H7N9) have increased (Figure 2).

Figure 2. Distribution of avian influenza A(H7N9) cases by week of reporting, as of 27 January 2014 (n=251)



Note: Some of the cases included have not yet been acknowledged by WHO.
Five cases reported in week 5/2014 were not included (data still incomplete by 27 January 2014).

Figure 3. Distribution of confirmed avian influenza A(H7N9) cases by age and gender, weeks 14/2013 to 5/2014, China (n=246*)



** Five cases were excluded because age or gender was unknown.*

Of the 251 confirmed cases, 56 (22.3%) are known to have died, although outcome information is not systematically available to ECDC.

The overall age of the cases ranges from three to 91 years, with a median age of 56 years. The age group between 10 and 19 years of age is least affected. More men are infected than women: among the 246 confirmed cases where age and gender is known, 164 cases are male (67%) and 82 female (33%). The majority of the confirmed cases required hospitalisation.

Close to 3 000 contacts were followed up, and only four contacts are reported to have developed symptoms. These four cases were part of several small family clusters identified in February and March 2013: In Shanghai, two family clusters (two confirmed cases, one suspected A(H7N9) case) were identified. One of these persons recovered but the other two died from respiratory failure. The Shanghai cluster also included a husband and wife, both confirmed cases. A third family cluster was identified in Jiangsu, with one confirmed and one suspected case. Both cases were hospitalised in critical condition. In the first two clusters, it was not possible to determine if there was limited person-to-person transmission or whether the infected persons were exposed to a common source [14,15].

Exposure information is available for 82 confirmed cases, suggesting that 63 (77%) of the cases have been exposed to live animals. There is, however, no information available on the number of exposed Chinese citizens by age group.

The closure of live poultry markets in late spring appears to have had an effect on the number of cases reported from the affected areas.

Clinical aspects, spectrum of disease, and treatment

It is difficult to estimate the incubation period at present due to a lack of data. The first published analysis indicates a median incubation period of six days for all patients, with a range of one to 10 days [15].

Most of the cases have presented with influenza-like illness, with a minority reporting diarrhoea or vomiting [9]. Unlike other avian influenza A(H7) infections, initial conjunctivitis has not been a reported feature [15].

Of the first 111 patients evaluated by Gao et al., 85 (77%) were admitted to an intensive care unit (ICU); of these patients, 54 had been admitted directly to the ICU, and 31 had been admitted during hospitalisation. Moderate to severe acute respiratory distress syndrome (ARDS) was the most common complication (79 patients), followed by shock (29 patients), acute kidney injury (18 patients), and rhabdomyolysis (11 patients) [16].

The estimated case-fatality risk is 36% on admission to hospital among the first 123 cases and between 0.16–2.8% of the symptomatic cases in the community [17].

Serological studies were conducted among Chinese poultry workers and healthcare workers. In the first study, 126 healthy healthcare workers and 615 healthy non-healthcare workers were tested for the presence of H7N9 antibodies: one of the serum samples from either group contained a high level of H7-specific antibodies [18]. In another study, 6% (25/396) of poultry workers had elevated titres for antibodies specific for avian-origin H7N9 virus versus none of 1 129 samples tested in the general population [19].

The current treatment practices do not differ from treatment of other severe influenza disease. WHO recommends immediate empirical treatment of symptomatic individuals exposed to A(H7N9) with neuraminidase inhibitors. Chemoprophylaxis of asymptomatic exposed individuals is not recommended [20]. The US CDC has also published interim guidance on the use of antivirals for A(H7N9) [21].

Animal infections and environment detection

Active surveillance is ongoing in China, where public health authorities sample chickens, waterfowl, captive-bred pigeons, quails and wild birds. Additionally, environmental samples are collected at wholesale live bird markets, live bird trading areas (stalls) at farmers' markets, large-scale poultry farms, village/backyard poultry holdings, poultry slaughterhouses, wild migrating bird habitats, and other locations. The Chinese Ministry of Agriculture has notified the World Organization for Animal Health (OIE) about the detection of some genetically similar influenza A(H7N9) isolates from birds [22].

In April 2013, 88 samples tested positive for the virus. The 88 positive samples were identified from approximately 900 000 samples collected from different surveillance sites around the country and were analysed by national and provincial avian influenza reference laboratories in China [23]. Results from the national monitoring of influenza H7N9 conducted by the Chinese Ministry of Agriculture in December 2013 included 18 positive samples (virus genome) out of 200 tested (9.0%) from four sampling sites in Zhejiang, and two positive samples (genomic) out of 2 521 tested (0.08%) from 151 sampling sites in Guangdong [24,25].

The virus has been detected in ducks, pigeons and chickens, but it has not been detected in pigs [26]. Also, samples from the environment, particularly from live poultry markets, were tested positive for influenza A(H7N9) in

2013 and 2014 [27,28]. Goose meat has also tested positive for influenza A(H7N9). A positive sewage sample was identified at the same wet market; the market was subsequently closed and disinfected [29].

Since December 2013, influenza A(H7N9) sequences have been uploaded to GISAID, including samples from the environment, chickens, ducks and pigeons. Further information about influenza A(H7N9) detections in China can be found at the Global Animal Disease Information System EMPRES-i [30].

A significant difference between influenza A(H5N1) and A(H7N9) avian influenza viruses is the reduced pathogenicity of the H7N9 virus in poultry. H5N1 is highly pathogenic in poultry and can be detected by flock die-offs. H7N9 does not severely affect poultry, and it is likely that influenza A(H7N9) can circulate silently in poultry and other bird populations. The human cases may be the first indication of infections in birds.

The major source of infection for humans seems to be poultry handled in the poultry market, while wild birds are the reservoir for H7 and N9 genes of influenza viruses [31,32]. Live bird markets seem to amplify the infection: wild birds mixing with poultry can lead to environmental contamination [33]. The Ministry of Agriculture reported that 'stamping-out' control measures were implemented in poultry markets; also, some markets were temporarily closed. These closures were associated with a decrease in the number of human cases in those localities [14,34]. Following the occurrence of new cases, at least one provincial government closed live poultry markets in 2014. Other control measures have been reported to the OIE by the Chinese Ministry of Agriculture.

Virological information

The outbreak virus is a reassortant avian influenza A virus in which the six RNA segments encoding the internal proteins are closely related to avian A(H9N2) viruses recently isolated from poultry in China [8,35,36]. The segment encoding haemagglutinin (HA) belongs to the Eurasian A(H7) avian influenza virus lineage, and the segment for neuraminidase (NA) is most similar to avian H11N9 and H7N9 viruses. However, the nearest matches found for the HA and NA are considerably less closely related than for the six internal-gene RNA segments. This gene constellation makes the outbreak strain different from previously isolated avian influenza A(H7N9) viruses, including those reported in birds in Europe. A combination of active surveillance, screening of virus archives, and evolutionary analyses has shown that the A(H7) viruses probably transferred from domestic duck to chicken populations in China on at least two different occasions and then reassorted with poultry influenza A(H9N2) to generate the influenza A(H7N9) strain that has been affecting humans; it also generated 'a related previously unrecognised H7N7 lineage', which has been shown experimentally to infect mammals [37]. The reservoir for this novel virus remains unknown, but the virus has been detected in domestic birds in live markets in eastern China. With the seasonal influenza virus circulation in southern China currently increasing [38,39], there is an increased risk for reassortment of the seasonal influenza viruses with the A(H7N9) viruses.

The novel influenza A(H7N9) is classified as a low pathogenic avian influenza (LPAI) since the intravenous pathogenicity index indicates that infections in chickens are subclinical [40]. Low or zero pathogenicity in poultry does not necessarily indicate low pathogenicity in humans. The novel influenza A(H7N9) viruses are the first low pathogenicity viruses to have caused severe human disease.

The novel influenza A(H7N9) virus can infect other mammals as well. Experimental studies have demonstrated replication in ferrets and mice and in the upper and lower respiratory tracts of non-human primates (seasonal influenza typically only replicates efficiently in the upper respiratory tract) [41]. Influenza A(H7N9) viruses replicated to a higher level in the respiratory tracts of ferrets than seasonal influenza A(H3N2) viruses. Transmission of influenza A(H7N9) has shown so far to be less efficient than transmission of seasonal influenza A(H1N1)pdm09 in the same ferret model. One experimental study has shown transmissibility between ferrets by respiratory droplets [42]. Additional human adaptation of the influenza A(H7N9) virus might need to take place for these viruses to transmit efficiently from human to human [43].

The WHO Collaborating Centre in Beijing has confirmed that influenza A(H7N9) virus is sensitive to oseltamivir and zanamivir in phenotypic tests [9]. However, Arg292Lys substitutions in the NA associated with resistance to neuraminidase inhibitors have been documented in several treated cases and tend to lead to poor clinical outcome when identified [44].

Diagnostics of avian influenza A(H7N9) infections in humans

Based on sequence analysis, it is expected that the generic RT-PCR assays for influenza A virus, which is based on highly conserved viral gene sequences, e.g. in the M-gene, will detect the novel viruses. Diagnostic and reference laboratories in the EU should therefore continue to use their current generic RT-PCR assays for influenza A virus for screening and testing of possible cases if those tests are based on highly conserved internal gene sequences and have been confirmed *in silico* to fit the sequence of the influenza A(H7N9) virus. Clinically validated assays that specifically detect influenza A(H7N9) viruses are already available in several European countries. The diagnostic and reference laboratories should pay special attention to the detection algorithms and assays.

In May 2013, ECDC, the World Health Organization Collaborating Centre for Reference and Research on Influenza (WHO CC) in London, and the WHO Regional Office for Europe conducted an *in silico* assessment of novel influenza A(H7N9) detection capabilities in 32 national influenza reference laboratories, mostly WHO National Influenza Centres participating in the WHO Global Influenza Surveillance and Response System (GISRS), covering 29 countries. Twenty-seven of 29 responding countries considered their generic influenza A virus detection assay to be appropriate for the novel influenza A(H7N9) virus. Twenty-two countries reported having containment facilities suitable for its isolation and propagation. Laboratories in 27 countries had applied specific H7 real-time RT-PCR assays, and 20 countries had N9 assays in place. Through GISRS, influenza reference laboratories were offered positive control virus RNA to evaluate their assays; the WHO CC in London supplied 34 laboratories in 22 countries. Twenty-four laboratories in 19 countries validated good performance of their generic influenza A virus detection, H7 and N9 subtyping assays. Survey results showed that European Reference Laboratory Network for Human Influenza (ERLI-Net) laboratories rapidly developed and verified their capabilities for detecting the novel influenza A(H7N9) influenza virus [45].

In autumn 2013, ERLI-Net distributed an external quality assessment RT-PCR detection panel which included an influenza A(H7N9) sample. Thirty-three of the 36 participating EU/EEA laboratories in 29 countries detected the virus correctly as influenza A(H7); the remaining three identified the virus as 'influenza A un-subtypeable' (unpublished data). The latter laboratories would have sent the specimens to the WHO Collaborating Centre at the National Institute for Medical Research in London for confirmatory testing, where they would have been correctly identified as H7 at that time. These results confirm the good capability of the ERLI-Net laboratories to detect influenza A(H7N9) viruses in Europe.

With the diagnostic laboratory assays, the novel viruses should be detected as positive for influenza A virus, and negative for influenza B, A(H1), A(H1)pdm09, A(H3) and A(H5) viruses. Hence, influenza A(H7N9) viruses are expected to be classified as un-subtypeable influenza A if no specific A(H7) diagnostic test is performed. Laboratories with experience in influenza A(H7) subtyping will be able to subtype the novel viruses with their H7 primers and probes. If there is a lack of experience, the precise procedures used in national EU/EEA primary diagnostic laboratories for the detection and subtyping of influenza viruses are readily available.

Without proper subtyping, current diagnostic RT-PCR detection systems would likely identify an influenza A(H7N9) virus as 'influenza A' but would fail to distinguish it from seasonal A viruses. It is therefore critical that all specimens sent to diagnostic laboratories are supplied with adequate clinical information and a complete list of influenza strains that need to be subtyped.

It is standard procedure in diagnostic laboratories to send influenza A virus isolates or clinical samples that cannot be subtyped to the national reference laboratory (National Influenza Centres; NICs) and further to a WHO CC for characterisation, as was done in China for the first influenza A(H7N9) isolates. In Europe, the WHO CC in London receives un-subtypeable isolates from abroad and from European NICs. All EU/EEA Member States are urged to send un-subtypeable A viruses and subtyped influenza A(H7) viruses to a WHO CC for further characterisation.

To assist European laboratories in verifying and ensuring their diagnostic capabilities with regard to avian influenza A(H7N9) virus, ECDC, ERLI-Net and the WHO Regional Office for Europe have released a technical briefing note on Diagnostic preparedness in Europe for detection of avian influenza A(H7N9) viruses [46].

Support to national influenza laboratories for the shipment of samples to the WHO Collaborating Centre for Reference and Research on Influenza in London is provided through the WHO Global Influenza Surveillance and Response System. Additional support is available through the European-Commission-funded Joint Action on Quality Assurance Exercises and Networking on the Detection of Highly Infectious Pathogens (QUANDHIP Joint Action). WHO has produced guidance on how to handle clinical material (at BSL-2) and virus propagation (at BSL-3), which is needed both in diagnostic laboratories and in laboratories developing vaccine strains [47].

Vaccines against avian influenza A(H7N9) infections in humans

Influenza candidate vaccine virus strains are usually developed in a few laboratories that are part of the WHO Global Influenza Surveillance and Response System (GISRS). Candidate vaccine virus strains that are developed either by researchers or manufacturers are freely shared with all stakeholders; this is ensured by WHO regulations and contracts between the US government and the various influenza vaccine manufacturers.

A limited number of manufacturers (e.g. AstraZeneca, Baxter, Novartis and Novavax) can develop candidate vaccine virus strains in their own facilities; this requires a high biosafety level for growing wild-type influenza A(H7N9) virus strains or the use of techniques not dependent on growth.

WHO Geneva has established biosafety level (BSL) guidelines to be used for the development and production of human influenza A(H7N9) vaccines [48]. In addition, WHO Geneva conducts regular telephone conferences with regulatory agencies throughout the world to facilitate the evaluation and authorisation of new candidate vaccines should the need arise to assess the capacities of vaccine manufacturers for H7N9 vaccines.

New candidate vaccine viruses based on the published genetic sequences of influenza A(H7N9) virus and using reverse genetics technology have been developed by several WHO collaborating laboratories, including the WHO Essential Regulatory Laboratory National Institute for Biological Standards and Control (NIBSC) in the EU. Attempts to develop candidate vaccine virus strains, using the classical reassortment technique, are ongoing. Other approaches such as development of virus-like particles or culturing wild-type influenza A(H7N9) viruses for inactivation are developed in parallel.

As of 13 January 2014, six clinical trials using different variants of influenza A(H7N9) candidate vaccine virus strains have been listed at the website ClinicalTrials.gov. Available candidates are based on either live or inactivated influenza viruses. Unadjuvanted and adjuvanted (MF59, AS03) inactivated candidate vaccine virus strains will be compared. All vaccine candidates will be tested in smaller trials involving healthy adults (~18–65 years) for immunogenicity and safety, following administration of two doses three weeks apart. Trials will elucidate whether one or two doses will be needed.

First study results are available from a candidate vaccine virus strain produced by Novavax [49]. In a phase-1 observer-blinded, placebo-controlled clinical trial, researchers provided monovalent A/Anhui/1/2013 (H7N9) virus-like particle (VLP) avian influenza antigen recombinant to adults above 18 years age in two doses (intramuscularly) with and without 30 or 60 units of the saponin-based ISCOMATRIX adjuvant. This vaccine combines haemagglutinin (HA) and neuraminidase (NA) of A/Anhui/1/13 with the matrix 1 protein (M1) of A/Indonesia/5/05. The study involved 284 participants and was conducted in Australia (Queensland, South Australia and Western Australia). The VLP vaccine with adjuvant was associated with increased local and systemic reactions. No body temperatures exceeded 38.5 °C. Immune response in the group that received the highest dose (5µg of HA with 60 units of adjuvant) resulted in 80% seroconversion (detected by HAI assay) and 97% seroconversion (NAI assay). However, Novavax does not routinely produce influenza vaccines for human use and has no licensed influenza vaccine product.

Novartis has conducted a phase-1 clinical trial based on a vaccine candidate developed on their cell culture platform in 400 healthy adults between the age of 18 and 64 [50]. Results have so far only been presented in a press release dated 14 November 2013, stating that after two doses of MF-59 adjuvanted 15µg of HA vaccine, 85% of the vaccinated individuals developed a protective immune response while in the unadjuvanted 15µg HA group only 6% achieved a protective response. The full study has been submitted to a peer-reviewed journal for publication.

Two phase-1 clinical trials are currently recruiting study participants:

- Safety and immunogenicity of a live attenuated influenza H7N9/A/Anhui/13 influenza virus vaccine provided in 1–2 doses, followed by an inactivated subvirion H7N9 vaccine on day 98 in healthy adults 18–49 years of age (n=48), with the US National Institute of Allergy and Infectious Diseases as sponsor (study start: October 2013; estimated primary outcome completion date: March 2014). The study is conducted in an isolation unit in an inpatient clinic at the University of Rochester, USA.
- Immunogenicity and safety study of GlaxoSmithKline (GSK) Biologicals' placebo-controlled adjuvanted and unadjuvanted influenza vaccines GSK3206641A and GSK3206640A, administered in adults 18–64 years of age (n=420), with GlaxoSmithKline as sponsor (study start: November 2013; estimated primary outcome completion date: February 2014). The study is conducted in the US (Florida, Georgia, Idaho, Pennsylvania, Washington) and Canada (Nova Scotia, Ontario, Quebec).

Other clinical trials have started but are not currently recruiting participants. Of interest are 'mix-and-match' studies that mix unadjuvanted H7N9 candidate vaccines from different manufacturers with MF59 and AS03 adjuvants. These studies are sponsored by the US National Institute of Allergy and Infectious Diseases.

Development of influenza candidate vaccine virus strains is also ongoing in China, and clinical trials are expected later this year. To the best of our knowledge, no clinical trials are being conducted or planned in the European Union.

The EU Vaccine Task Force on Influenza (European Commission, European Medicines Agency, European Food Standards Authority, and ECDC) has been meeting regularly since the onset of the H7N9 outbreak to consider the issues and discuss briefing from WHO and NIBSC. The main regulatory work at the EU level will be conducted by European Medicines Agency and the European Commission.

Human and animal surveillance in Europe

Surveillance for respiratory infections in humans

ECDC has developed an interim case-finding algorithm and a case definition for disease surveillance and the reporting of patients infected by the avian influenza A(H7N9) virus in EU/EEA Member States [4].

Infectious disease protocols for case investigations are available from the Consortium for the Standardization of Influenza Seroepidemiology (CONSISE) [51] and national authorities. Agreed protocols for clinical investigations have been prepared by the International Severe Acute Respiratory and Emerging Infections Consortium (ISARIC) [7].

Surveillance and control of low and high pathogenic influenza in poultry and other captive birds in the EU

EU animal health legislation [52] requires the control of outbreaks in poultry and other captive birds of highly pathogenic and low pathogenic avian influenza viruses of the H5 and H7 subtypes. Suspected and confirmed presence of infection in poultry and other birds must be immediately notified to the competent animal health authority. EU Member States should carry out surveillance programmes in poultry and wild birds [53] in order to detect the circulation of avian influenza viruses as outlined by harmonised EU guidelines [54].

The EU reference laboratory for avian influenza in Weybridge, United Kingdom, in collaboration with EU national reference laboratories for avian influenza, has confirmed the predicted utility of EU-recommended PCR protocols for the detection of the influenza A(H7N9) virus (both H7 and M gene assays) based on sequence comparison of the influenza A(H7N9) viruses from birds in China. Preliminary data indicate that the H7 antigens used in the mandatory European serological survey in poultry for H5/H7 viruses are suitable for the detection of antibodies to influenza A(H7N9), at least as a detection method at flock level.

The Food and Agriculture Organization of the United Nations has published guidelines for risk-based surveillance strategies to investigate the presence of infection along the bird market chain, with the purpose of informing the control strategies and provide data to reduce uncertainty [55]. Other surveillance guidelines and laboratory protocols are available [56].

Discussion

At the beginning of the outbreak, as part of the risk assessment and strategic planning related to the emergence of avian influenza A(H7N9) in China, ECDC considered two major scenarios: Scenario A, a zoonotic epidemic with sporadic transmission of the virus to humans in close contact with an animal reservoir; and Scenario B, a pandemic scenario with a movement towards efficient human-to-human transmission [57].

Currently, the most likely scenario in China, and therefore worldwide, is that this event remains a localised, widespread zoonotic outbreak in which the virus is transmitted sporadically to humans in close contact with the animal reservoir. However, with the regular influenza season now ongoing in southern China and elsewhere in the northern hemisphere there is a potential risk for co-infections and the development of new reassortants with the possibility of increased capacity to transmit among human populations.

During 2013, a peak of human influenza A(H7N9) cases was observed in week 16/2013, with a subsequent decrease of cases after week 20. Since week 42, a notable increase has been detected (Figure 2). This increase in the number of cases may indicate an enlargement of the reservoir, an increase in the number of exposed individuals, enhanced transmissibility of the virus, a seasonal transmission pattern, or a combination of these factors.

Intervention strategies, e.g. temporary closures of life poultry markets, seemed to have had an impact on the number of infections in spring 2013, and alternative and safer routes of poultry processing may not be possible in many parts of China. Chinese New Year, which falls on 31 January this year, will dramatically increase the potential for human exposure to both A(H7N9) and seasonal influenza viruses, increasing the risk of reassortment in humans: Hundreds of millions of Chinese are returning to their villages over the festive season in what is believed to be the world's largest annual human migration.

Rigorous epidemiological investigations are urgently needed and are currently conducted in China in order to identify risk behaviours, other risks, and predisposing factors for avian influenza A(H7N9) infection.

It is noteworthy that the joint Chinese-WHO inspection team concluded that only a long-term cross-sectoral control programme will be able to defeat or at least contain this serious influenza threat [58]. There may also be a role for influenza A(H7N9) vaccines for poultry in affected areas.

If the A(H7N9) virus manages to spread widely in poultry without detection and becomes highly pathogenic in poultry, food security in China might become a significant concern [59].

Considering the spread of influenza A(H5N1) over national and geographic borders in and outside Asia, it is nothing short of surprising that neighbouring Asian countries have not reported more cases of influenza A(H7N9). It is possible that additional countries will be affected in the coming months.

There are reasons for further concern over human infections with influenza A(H7) viruses in general [60]. This reassortant virus harbours the internal genes derived from avian influenza A(H9N2) viruses for which laboratory studies with animals have suggested that they have pandemic potential [61]. LPAI A(H9N2) virus infections in humans have usually resulted in uncomplicated influenza illness, but at least one case of lower respiratory tract disease in an immunocompromised adult has been reported [62]. The current influenza A(H7N9) viruses are considered to have pandemic potential [63].

ECDC threat assessment for the EU

The continued and increasing transmission of a novel reassortant avian influenza virus capable of causing severe disease in humans in one of the most densely populated areas in the world is a cause for concern due to the pandemic potential. However, the most likely scenario for China is that this remains a local (but widespread) zoonotic outbreak in which the virus is transmitted sporadically to humans in close contact with the animal reservoir, similar to the influenza A(H5N1) situation.

It is commendable that the Chinese authorities quickly notified the event to WHO under the International Health Regulations. The continued communication of outbreak investigations has facilitated the assessment of the risk to human health from this outbreak in Europe as elsewhere. It is essential that this continues.

The first human infection with influenza A(H7N9) virus was identified in March 2013, and this was the first time that human infection with a low pathogenic avian influenza A virus has been associated with a fatal outcome. After a period of several months with only few cases detected, the Chinese authorities have detected new cases with increasing frequency since October 2013. This indicates a persistent reservoir and transmission pattern which might have seasonal characteristics.

The recent fatal case of influenza A(H5N1) imported to Canada provides support to the notion that imported cases of influenza A(H7N9) might also be seen in Europe. However, the risk of the disease spreading to Europe via humans in the near future is still considered low. People in the EU presenting with severe respiratory infection *and* a history of potential exposure in the outbreak area will require careful investigation in Europe.

To date, there is no epidemiological evidence that avian influenza can be transmitted to humans through the consumption of cooked food, notably poultry meat and eggs.

There is insufficient evidence to quantify the risk of influenza A(H7N9) developing into a virus that transmits from human to human, thereby increasing the risk of an influenza pandemic. Close monitoring of the outbreak epidemiology, clinical features and the genetic characteristics of the virus will be critical for assessing this risk; instruments like the Influenza Risk Assessment Tool (IRAT) can play a role [64,65].

The risk of increased transmission of H7N9 viruses between humans is not negligible. European countries should continue to prepare for the eventuality of future pandemics, including one caused by A(H7N9). Preparedness activities should include the precautionary development of early human vaccine candidates and increased monitoring of animal influenzas at the animal–human interface [66-69].

The risk of influenza A(H7N9) virus being transported to Europe in viraemic poultry through legal trade is negligible. EU regulations do not permit importation of live poultry, day-old chicks and hatching eggs and other birds (captive birds such as parrots, finches and ornamental birds) from China. The only poultry commodities

authorised for import from China into the EU are sterilised meat products, heat-treated poultry meat from Shandong, and heat-treated egg products. Given the very heat-labile nature of all influenza viruses, these commodities are not considered to pose a risk of influenza virus transmission to consumers.

The risk of the avian influenza A(H7N9) viruses arriving in Europe with migratory birds cannot be quantified. ECDC and the European Food Safety Authority (EFSA) have performed multiple independent risk assessments in the past regarding avian influenza that also cover pathways for avian influenza A(H7N9) [64,70,71]. The hypothesis that poultry in the affected area has been infected by wild birds has not been confirmed but neither can it be excluded. Surveillance in wild birds for this novel virus has not been initiated in the EU/EEA.

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