RAPID RISK ASSESSMENT

Human infection with avian influenza A viruses, China

24 February 2014

Main conclusions

On 31 March 2013, 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 identification of 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 18 February 2014, there have been 354 laboratory-confirmed cases of A(H7N9) reported in China (with a case–fatality rate of 32%). In addition, the virus has been detected in one asymptomatic case in Beijing. A case has been reported in Malaysia of a Chinese tourist travelling by air. In recent weeks there has been a notable increase in the number of human cases, which may indicate a larger wild or domestic bird reservoir, an increase in the number of exposed individuals, enhanced transmissibility of the virus, a seasonal transmission pattern or a combination of these factors.

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 remains a cause for concern due to the pandemic potential. However, the most likely current scenario for China is that these outbreaks remain zoonotic outbreaks in which the virus is transmitted sporadically to humans in close contact with the animal reservoir, similar to the influenza A(H5N1) situation.

Influenza A(H5N1) has been circulating in poultry in China for almost two decades, causing occasional human cases (654 globally, of which 46 cases in China). In early 2014, a case likely infected in Beijing was detected by and reported from Canada.

Three human cases of influenza A(H10N8) virus have been reported in Jiangxi province in China. The first human case was reported by the Chinese authorities on 17 December 2013, in a 73-year-old female with multiple underlying medical conditions, who was admitted to hospital on 30 November 2013, and died on 6 December 2013. According to local authorities, the patient had visited a local live-poultry market. Since then two more cases have been detected, of which one has died.

In May 2013, a human case of influenza A(H6N1) was detected in Taiwan.

While likely human-to-human transmission of A(H7N9) and A(H5N1) in clusters of reported cases has been documented in a few instances, there is no indication of sustained human-to-human transmission. A few mild A(H7N9) cases have been detected.

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The most plausible underlying scenario for A(H7N9) is similar to that for A(H5N1), i.e. one of a zoonotic avian influenza that is circulating in poultry in parts of south-eastern China and occasionally causing human cases.

The severe nature of human infections and the persistence of A(H7N9) and A(H5N1) in poultry represents a significant long-term threat to humans, either through zoonotic transmission or potentially through developing pandemic capacity. Both scenarios should be prepared for.

The detection of new human cases of A(H10N8) and A(H6N1) likely reflects enhanced surveillance activities in China and Taiwan.

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 and contact with live poultry in China.

The recent importation of A(H5N1) from China to Canada and A(H7N9) from China to Malaysia in travellers highlights the possibility of travel-related cases being detected also in Europe. This should be prepared for. However, sporadic cases imported from China would not alter ECDC's current risk assessment.

Source and date of request

ECDC internal decision, 13 February 2014.

Public health issue

This document aims to:

- summarise the epidemiological, virological and environmental information about human infections with avian influenza A viruses in China of subtypes H7N9, H5N1, H10N8, and H6N1;
- assess the risk to public health in the EU/EEA and to EU/EEA citizens;
- anticipate development scenarios and provide options for prevention and control in the EU/EEA.

This Rapid Risk Assessment builds on earlier Rapid Risk Assessments on avian influenza, notably on A(H7N9) and A(H5N1).

Consulted experts

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External experts consulted and acknowledgements

The following experts contributed to the present update: Marco Cavaleri, European Medicines Agency; Per Have, European Food Safety Authority; John McCauley, WHO Collaborating Centre for Reference and Research on Influenza, London, UK; Sylvie van der Werf, Pasteur Institute, France; Diane Gross, WHO Regional Office for Europe; Maria Pittman, Alberto Laddomada, and Francesco Berlingieri, Directorate-General for Health and Consumers, Unit G2: Animal Health, European Commission.

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 represents a conflict 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. [1]

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.

1 Event information

The epidemiological, virological and environmental information regarding human infections with avian influenza A viruses of subtypes H7N9, H5N1, H10N8 and H6N1 in China since January 2013 is summarised below.

1.1 Human epidemiology

Influenza A(H7N9)

In March 2013, Chinese authorities announced the identification of a novel reassortant A(H7N9) influenza virus in patients in eastern China. As of 18 February 2014, 354 laboratory-confirmed cases have been reported: Zhejiang (135), Guangdong (69), Shanghai (42), Jiangsu (40), Fujian (20), Hunan (13), Jiangxi (5), Henan (4), Anhui (8), Beijing (4), Shandong (2), Hebei (1), Guangxi (3), Guizhou (1), Hong Kong (5) and Taiwan (2). In addition, the virus has been detected in one asymptomatic case in Beijing.

Most cases have developed severe respiratory disease. At least 112 cases are known to have died (case–fatality ratio=32%) [2]. The average age is 55.5 years, ranging from two to 91 years; 238 (68%) of 350 patients with documented gender are male, resulting in a M/F sex ratio of 2.1.

The outbreak has had two peaks separated by more than five months during which just two cases were reported (Figure 1). The first peak comprised 135 cases, the second peak, as of 18 February, 220 cases. Both peaks occurred during the cold season in China. The age and sex distributions do not differ significantly between the two peaks. In the first peak, of the 130 cases with known age and sex, 70% (91) were male and 30% (39) were female while during the second peak, 67% (147) of the 220 cases with known age and sex were male and 33% (73) were female.

In the first peak period, 43 of 135 cases died while, in the second peak, 69 of 219 cases died, resulting in a CFR of 32% in both periods together. These estimates are based on the information available at the time of notification and it must be considered that the CFR among recent cases could rise as their disease progresses and final outcomes are reported. While the data are scarce for the first peak regarding the date of hospitalisation and severity, during the second peak, 218 of 219 patients have been hospitalised and, of these, 191 have been reported to be in either severe or critical condition at the time of notification. Only a few mild A(H7N9) cases have been detected.

The map in figure 2 illustrates the emergence of the cases in the two peaks of the disease. Since 15 October 2013, 219 cases were reported from Zhejiang (89), Guangdong (68), Fujian (15), Jiangsu (13), Shanghai (8), Hunan (10), Anhui (4) Beijing (2), Guangxi (3), Guizhou (1), Taiwan (1) and Hong Kong (5).

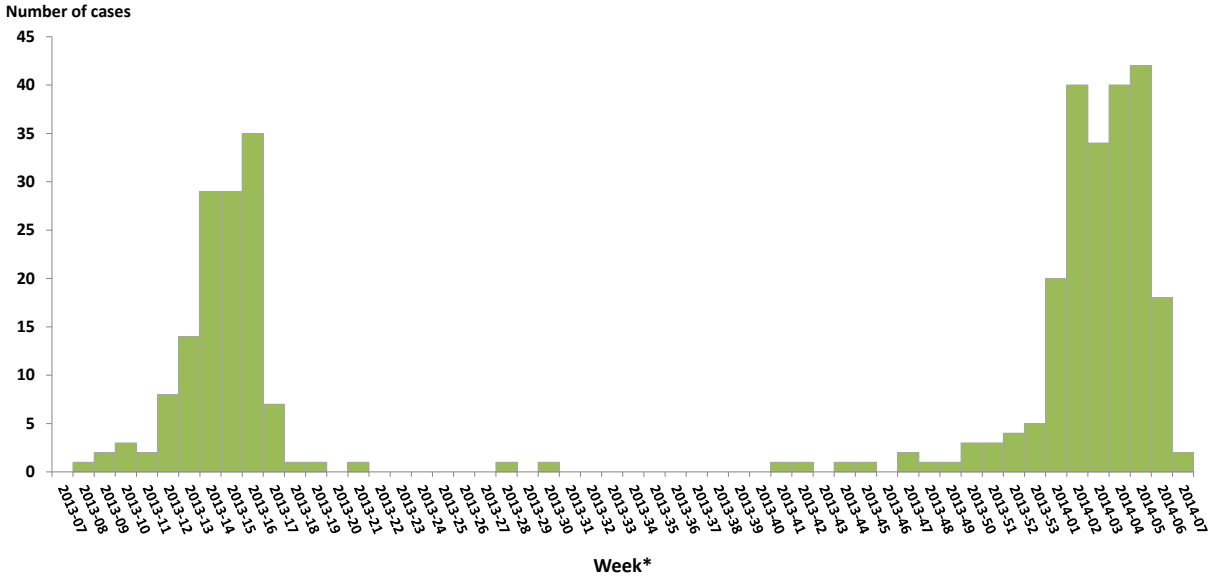
A few small clusters were detected but almost all cases have occurred sporadically, without epidemiological links between them. While occasional human-to-human transmission in the clusters cannot be ruled out, there has been no confirmed sustained human-to-human transmission.

One exported case from China was reported. A 67-year-old female from Guangdong Province, China, travelled to Malaysia on 3 February as part of a tour group of 17 people. She was admitted to hospital in Malaysia on 7 February and subsequently diagnosed with A(H7N9) infection.

Most human A(H7N9) cases have reported contact with poultry or live-bird markets.

On 21 February, Chinese media are quoting health authorities in Jilin province having reported a first human case of A(H7N9) in the city of Changchun. Jilin province is not adjacent to the currently affected provinces in China (Figure 2) and bordering North Korea and Russia to the east, Heilongjiang to the north, Liaoning to the south, and Inner Mongolia to the west. The 50-year-old patient is reported to have been engaged in poultry farming and to have been exposed to dead poultry.

Figure 1. Distribution of confirmed A(H7N9) cases by week*, weeks 7/2013 to 7/2014, China (n=354)



**Where week of onset is unknown, the week of reporting has been used.*

Figure 2. Distribution of confirmed A(H7N9) cases by place of reporting, weeks 8/2013 to 8/2014, in China (n=354)

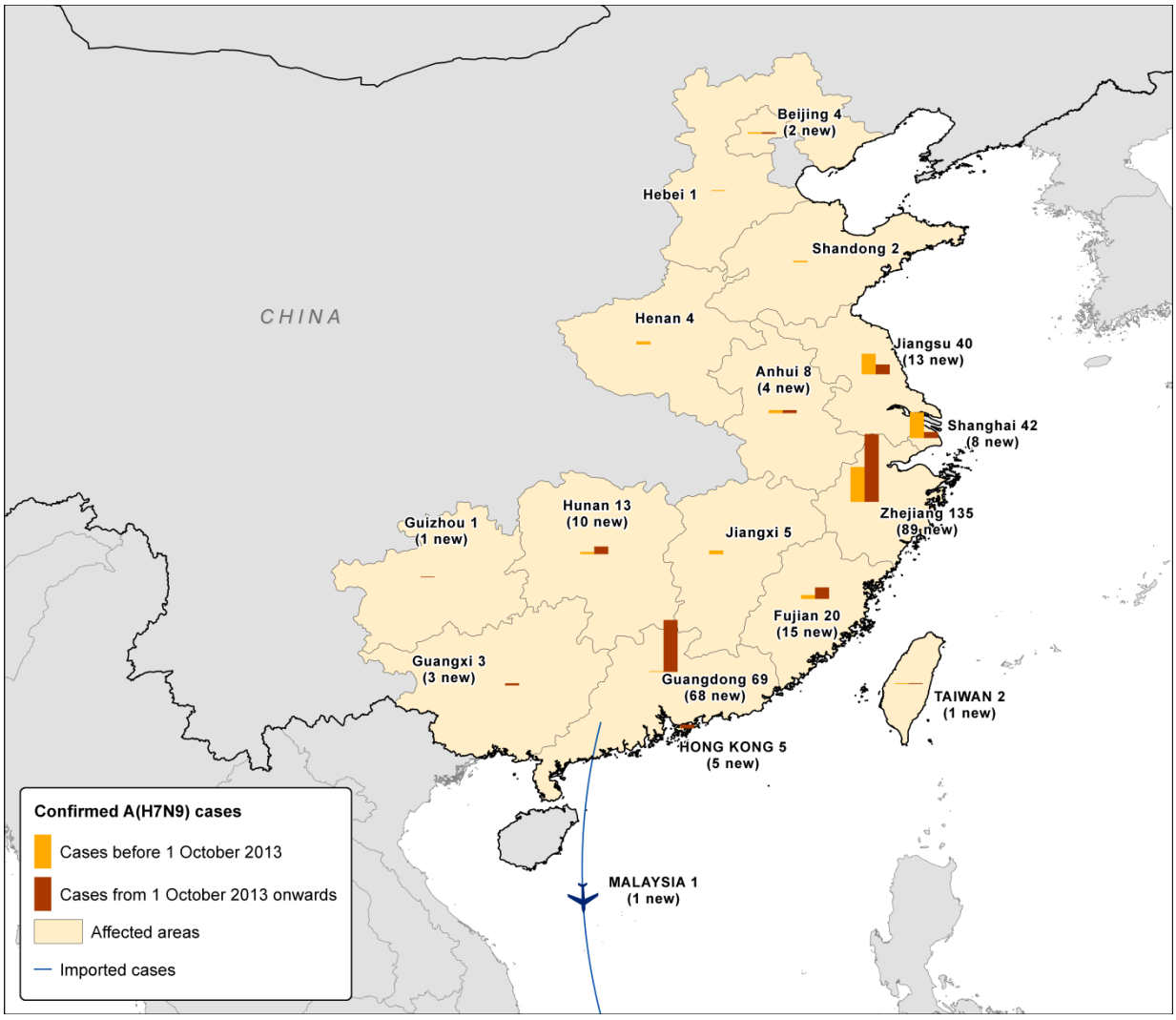
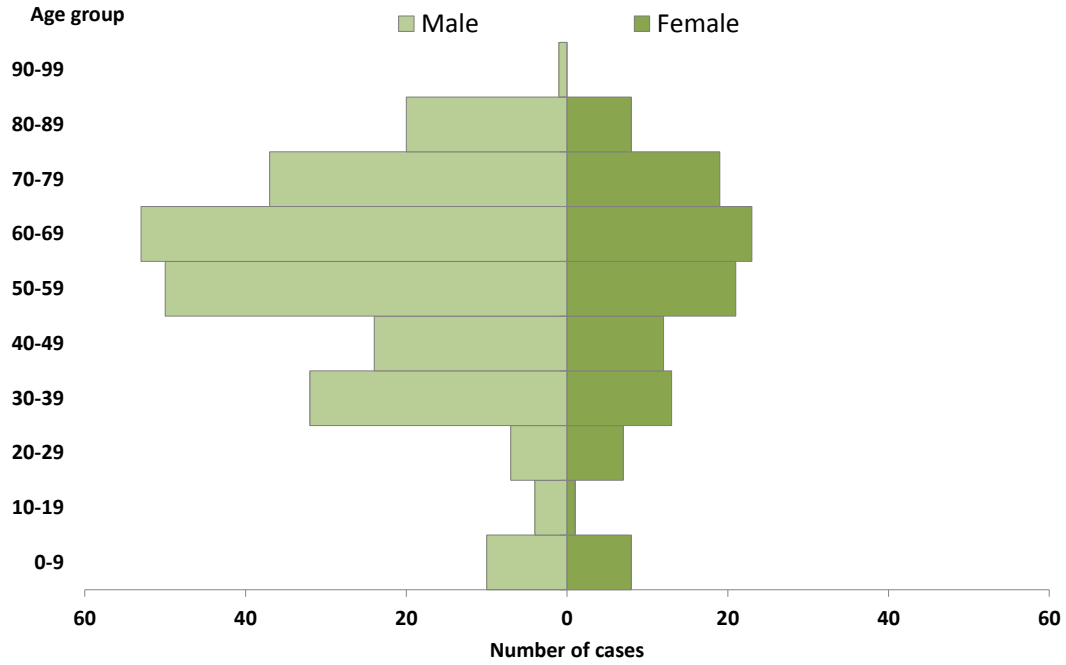


Figure 3. Distribution of confirmed A(H7N9) cases by age and sex, 31/3/2013–18/2/2014, China (n=349*)



** Five cases with age or gender missing have been excluded.*

Influenza A(H5N1)

The first human case of avian influenza A(H5N1) in China was reported in 2003 (Figure 4). Before that, in 1997, an outbreak of 18 cases had been reported by Hong Kong [2A]. Since 2003, 46 cases have been reported in China: 8 cases (5 fatal) in 2005, 13 (8 fatal) in 2006, 5 (3 fatal) in 2007, 4 cases (all fatal) in 2008, 7 cases (4 fatal) in 2009, 2 cases (1 fatal) in 2010, 1 case (fatal) in 2011, 2 cases (1 fatal) in 2012, 2 cases (both fatal) in 2013 and 1 case in 2014 (Table 1, Figure 5). There is no seasonal pattern to the 46 cases in China.

Table 1. Distribution of A(H5N1) cases by country and year, February 2003 to 18 February 2014

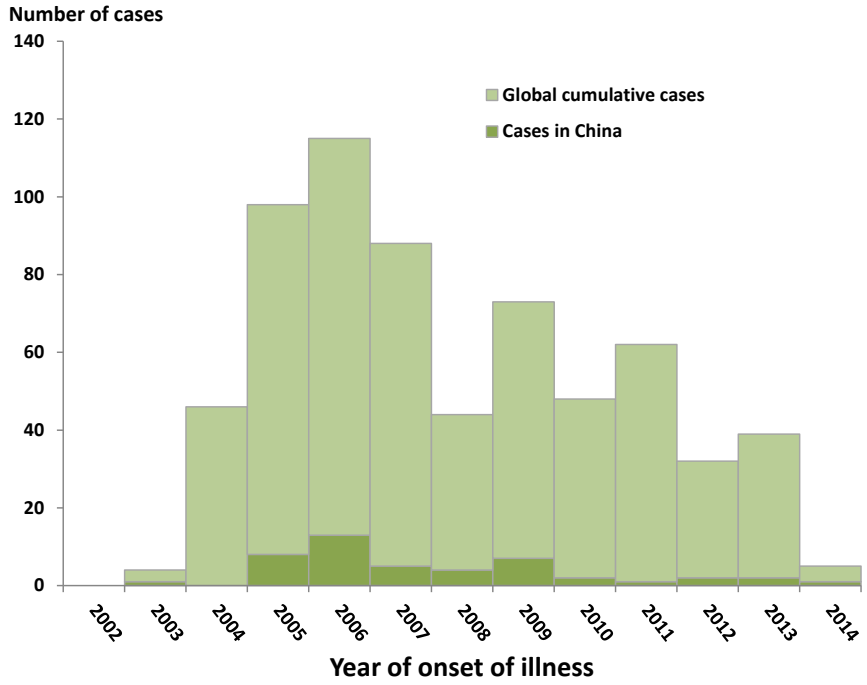
Reporting country	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	Total
Azerbaijan				8									**8**
Bangladesh						1			2	3	1		**7**
Cambodia			4	2	1	1	1	1	8	3	26	2	**49**
Canada											1		**1**
China	*1*		*8*	*13*	*5*	*4*	*7*	*2*	*1*	*2*	*2*	*1*	***46***
Djibouti				1									**1**
Egypt				18	25	8	39	29	39	11	4		**173**
Indonesia			20	55	42	24	21	9	12	9	3		**195**
Iraq				3									**3**
Laos					2								**2**
Myanmar					1								**1**
Nigeria					1								**1**
Pakistan					3								**3**
Thailand		17	5	3									**25**
Turkey				12									**12**
Vietnam	3	29	61		8	6	5	7		4	2	2	**127**
Total	**4**	**46**	**98**	**115**	**88**	**44**	**73**	**48**	**62**	**32**	**39**	**5**	**654**

Source of data: WHO. http://www.wpro.who.int/emerging_diseases/AvianInfluenza/en/

One recent case was a person from Canada who visited Beijing, China, from 6 to 27 December 2013, and returned to Canada on 27 December 2013 [3]. The person, who travelled with a healthy companion, was symptomatic during travel with malaise and feeling feverish. This is the first case of human infection with avian influenza A(H5N1) virus reported in Canada and the first confirmed human case in the Americas.

Since the re-emergence of avian influenza A(H5N1) in 2003, there have been 654 cases including 388 deaths (CFR=59%). Of the 46 cases in China, 22 were female (48%) and 24 were male (52%). Fourteen of the 22 female cases have died (CFR=64%) and 16 of the 24 male cases have died (67%). The mean age for the cases is 28 years (Figure 6).

Figure 4. Cumulative number of confirmed human cases for avian influenza A(H5N1) reported to WHO, 2003–2014, as of 14 February 2014, globally, including China



Since 2003, 46 laboratory-confirmed cases have been reported in China: Hunan (6), Anhui (5), Guangdong (5), Fujian (4), Guangxi (4), Guizhou (4), Beijing (3), Sichuan (3), Hubei (2), Jiangsu(2), Xinjiang (2), Hong Kong (1), Jiangxi (1), Liaoning(1), Shandong (1), Shanxi (1) and Zhejiang (1).

Figure 5. Distribution of confirmed A(H5N1) cases by place of reporting, 2003 to 18 February 2014, China (n=46)

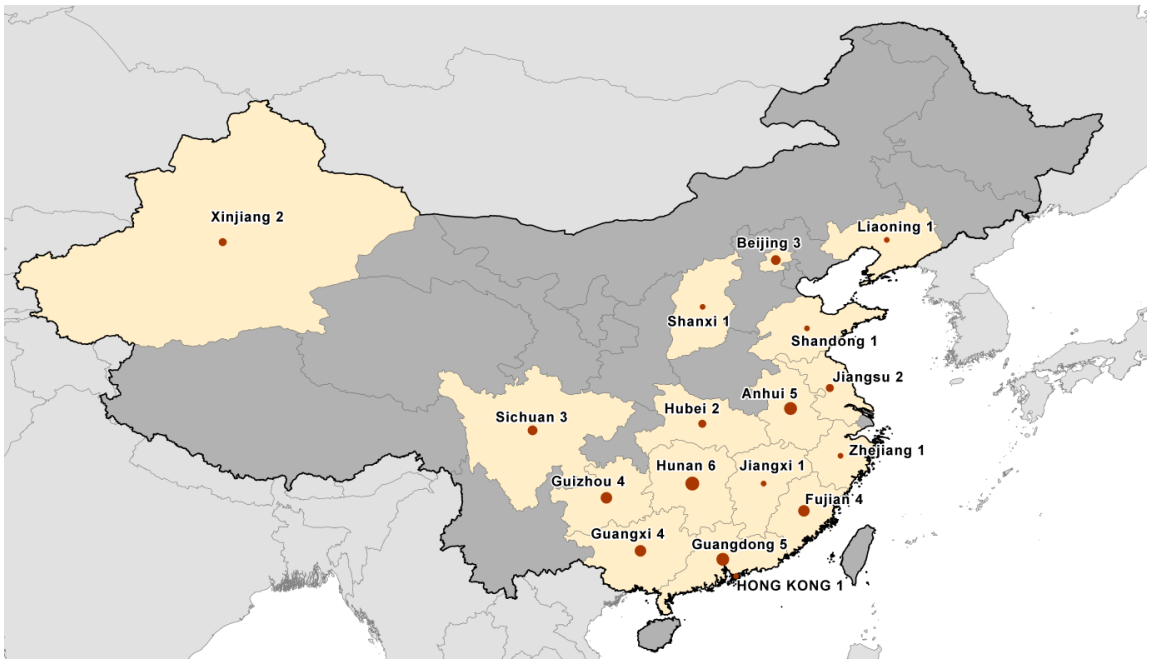


Figure 6. Cumulative number of confirmed human cases of avian influenza A(H5N1) in China, 2003–2014 as of 14 February 2014, by age and sex

Influenza A(H10N8)

As of 21 February 2014, three human cases of influenza A(H10N8) virus have been reported in Jiangxi province in China. The first human case was reported by the Chinese authorities on 17 December 2013 in a 73-year-old female with multiple underlying medical conditions who was admitted to hospital on 30 November 2013 and died on 6 December 2013. According to local authorities, she had recently visited a local live-poultry market [4–7] prior to illness onset.

She had initial symptoms of cough and chest tightness, followed by fever two days after illness onset. She was admitted to hospital on day 4 of illness with fever and pneumonia. She developed multi-organ failure, deteriorated rapidly and died nine days after illness onset.

On 29 January 2014, the second human case of influenza A(H10N8) was reported. The case was a 55-year-old female who visited a local live-poultry market on 4 January 2014 and had no exposure to similar cases before the onset of symptoms, which later developed into severe pneumonia. However, the patient was reported on 30 January to be in a stable condition [8].

The third human case of influenza A(H10N8) in Jiangxi province was reported on 13 February 2013. The case was a 75-year-old man from Nanchang who developed fever and fatigue on 4 February and was admitted to hospital on the same day. His lung infection worsened on 5 February and he died on 8 February. There is currently no information available about whether this patient was exposed to live poultry or had underlying medical conditions [9,10].

Influenza A(H6N1)

In May 2013, the first human case of influenza A(H6N1) was in Taiwan. The case was a healthy 20-year-old woman who developed shortness of breath and persistent fever and was diagnosed with an acute lower respiratory tract infection after detection of bilateral infiltrates on radiographic examination of her thorax. She was admitted to hospital care for a few days and was treated with antiviral and antibiotic medication, after which she was discharged. A subsequent radiograph was clear of infiltrates [11]. Tracing of 36 contacts and 12 healthcare workers involved in treatment of the patient did not identify additional cases.

2 Disease background

2.1 Clinical aspects, spectrum of disease and treatment

Influenza A(H7N9)

The median incubation period has been estimated at six days (range of 1–10 days) [12].

Fever and cough have been the most common symptoms, with vomiting and diarrhoea appearing in a smaller proportion of cases [13]. Conjunctivitis, a common finding with previous H7 human infections [14], was not a reported feature of the A(H7N9) infections in China.

Of 139 laboratory-confirmed A(H7N9) cases identified between 25 March and 1 December 2013, 99% were hospitalised [12], 125 (90%) presented with pneumonia or respiratory failure. Seventy-nine (73%) of 108 patients with available data had underlying medical conditions; 65 (63%) of 103 cases with available data were admitted to an intensive care unit because of severe lower respiratory tract disease; 47 (34%) of the 139 cases died in hospital of acute respiratory distress syndrome (ARDS) or multi-organ failure; 1% of 2 675 close contacts of the 139 patients developed respiratory symptoms during the seven-day surveillance period. Throat swabs from these contacts, which were collected a median of one day (range of 0–8 days) after illness onset, were all negative for A(H7N9) on real-time RT-PCR. Some mild cases have also been identified through expanded testing of outpatients with influenza-like illness [15], suggesting that A(H7N9) presents with a wide clinical spectrum.

Yu et al. have estimated the symptomatic case–fatality risk to be between 160 (63–460) and 2 800 (1 000–9 400) per 100 000 symptomatic cases [16], suggesting that A(H7N9) is not as severe as A(H5N1) [17] but is more severe than pandemic A(H1N1)pdm2009 [18].

A serological study in China found that 25 (6%) of 396 poultry workers in affected areas were seropositive for antibodies against A(H7N9), with haemagglutinin inhibition (HI) titres of ≥80, versus none of the 1 129 serum samples tested from the general population [19].

Studies of H7N9 viruses isolated from humans suggest that they are resistant to adamantane antiviral agents but susceptible to neuraminidase inhibitors [20–22]. However, in several severely ill patients, a R292K mutation in the viral neuraminidase, which is associated with highly reduced sensitivity to neuraminidase inhibitors, had been found to occur in H7N9 viruses after the start of oseltamivir treatment [23].

WHO recommends antiviral treatment with a neuraminidase inhibitor as soon as possible for patients with suspected or confirmed A(H7N9) infection [24].

WHO does not recommend routine post-exposure antiviral chemoprophylaxis for close contacts of confirmed influenza A(H7N9) cases, although the initiation of empiric post-exposure antiviral treatment may be considered in certain circumstances, mainly in people with underlying medical conditions [24]. Considering the severity of the disease, the fact that limited, non-sustained, human-to-human transmission cannot be excluded in some clusters, and that no H7N9 vaccine is available, we expect for EU/EEA Member States in the current zoonotic scenario, that the possible benefits of post-exposure chemoprophylaxis of close contacts with neuraminidase inhibitors outweigh the risks. However, evidence of benefit is limited. In these cases, use of treatment doses (75mg oseltamivir twice daily, for five days), might decrease the risk of antiviral resistance developing [25].

The US CDC has also published interim guidance on the use of antivirals for treatment of A(H7N9) infection [26] and for chemoprophylaxis of close contacts [27]. They recommend oseltamivir or inhaled zanamivir to close contacts of a *confirmed or probable* influenza A(H7N9) case according to risk of exposure. Two doses per day for 5 or 10 days (dependent on extent of exposure) should be provided based on the desire to prevent antiviral resistance. For high-risk exposure groups (household or close family member) chemoprophylaxis should be administered, while for moderate-risk exposure groups (healthcare workers with higher-risk contact to case) chemoprophylaxis could be considered.

Influenza A(H5N1)

The incubation period for A(H5N1) infection has been estimated to be up to seven days, although it is usually 2–5 days after the last known exposure to sick or dead poultry. Longer periods have, however, been suggested [28].

A study of 26 laboratory-confirmed A(H5N1) cases identified in China between October 2005 and April 2008 found that the clinical course was characterised by initial fever and cough, with rapid progression to lower respiratory disease [29]. Upper respiratory tract symptoms of rhinorrhoea and sore throat were less common in China than observed elsewhere. Many of the 26 cases had respiratory failure, ARDS and multi-organ failure. Seventeen (65%) of the cases died.

WHO has published guidance on the clinical management of human infection with A(H5N1) virus, as well as risk-stratified considerations for the use of chemoprophylaxis [30,31].

2.2 Animal infections and environment detection

Influenza A(H7N9)

Active surveillance among animals for A(H7N9) is ongoing in China, where public health authorities sample chickens, waterfowl, captive-bred pigeons, quail 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 [32].

Influenza A(H7N9) has been detected in animal and environmental samples in China. The virus has been detected in ducks, pigeons and chickens, but not in pigs [33]. In April 2013, 88 samples tested positive for influenza A(H7N9). 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 [34]. 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 [35,36].

Although the virus has been detected in several poultry species, chickens appear the most susceptible to infection. Samples from the environment, particularly from live-poultry markets, were tested positive for influenza A(H7N9) in 2013 and 2014 [37,38]. Goose meat has tested positive for influenza A(H7N9) and a positive sewage sample was identified at the same wet market; the market was subsequently closed and disinfected [39].

Since March 2013, influenza A(H7N9) outbreaks have been notified to OIE or reported to FAO from Anhui, Fujian, Guangdong, Guangxi, Hebei, Henan, Hunan, Jiangsu, Jianxi, Shandong, Shanghai and Zhejiang.

Influenza A(H7N9) sequences have been uploaded to GISAID, including from samples from the environment, chickens, ducks and pigeons. The virus has been detected and sequenced from a healthy tree sparrow in Shanghai city in May 2013 [40]. Further information about influenza A(H7N9) detections in China can be found at the Global Animal Disease Information System EMPRES-i [41].

Influenza A(H5N1)

Since January 2013, influenza A(H5N1) outbreaks have been notified to OIE or reported to FAO from Tibet, Chongqing, Guizhou, Hubei, Hunan, and Xizang. In addition one positive black-headed gull was detected in Hong Kong in early 2013.

A significant difference between A(H5N1) and A(H7N9) avian influenza viruses is the low 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.

Influenza A(H10N8)

Antibodies against influenza H10 and N8 or A(H10N8) viruses have been found in different bird species around the world, mostly migrating birds and water fowl [42-45]. Before the occurrence of the human cases, only two A(H10N8) viruses with low pathogenicity in chickens have been reported in China: one environmental isolate from a water sample in Hunan province, China, in 2007, and one from a duck at a live-poultry market in Guangdong Province in southern China in January 2012 [43,46].

Viruses from wild birds might have been transmitted to poultry sold at live-bird markets [43]. These seem to be important places where avian influenza viruses spread between the different poultry species, and are a source of human infections [47,48].

All subtypes

The major source of infection with influenza H7N9, H5N1, H10N8 and H6N1 for humans is likely to be poultry or birds handled in the live-bird markets, although the epidemiological evidence for this on non-H5 strains is limited. While wild birds are the reservoir for H7 and N9 genes of influenza viruses [49,50], live-bird markets seem to amplify and maintain the infection: wild birds mixing with poultry may lead to increased environmental contamination with the virus [51]. In 2013, the Ministry of Agriculture reported that 'stamping-out' control measures were implemented in poultry markets and some markets were temporarily closed. These closures were associated with a decrease in the number of human cases of A(H7N9) in those localities [52,53]. 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. Some provinces have announced permanent closure of live poultry markets in 2014. It is unclear whether the authorities in China are able to comprehensively implement such measures, and it remains possible that unauthorised and informal trade will continue to take place.

2.3 Virological information

Influenza A(H7N9)

The novel influenza A(H7N9) viruses are the first low pathogenicity viruses that have been documented to have caused severe human disease. The 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 [1,54,55]. 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. 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 humans in southern China currently increasing [56,57], there is an increased risk for reassortment of the seasonal influenza viruses with the A(H7N9) viruses in co-infected humans.

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 viruses typically only replicates efficiently in the upper respiratory tract) [21], although pigs appear refractory to infection. 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 [58]. Additional human adaptation of the influenza A(H7N9) virus might need to take place for these viruses to transmit efficiently from human to human [59].

The WHO Collaborating Centre in Beijing has confirmed that influenza A(H7N9) virus is sensitive to oseltamivir and zanamivir in phenotypic tests [20]. However, Arg292Lys substitutions in the NA associated with reduced susceptibility to neuraminidase inhibitors have been documented in several treated cases and tend to lead to poor clinical outcome when identified [23].

Influenza A(H5N1)

Outbreaks of A(H5N1) have occurred in poultry in different parts of Asia since 1997 [60]. The causative agent for the highly pathogenic infections in poultry was identified as an H5N1 reassortant virus for which all the gene components were originally from different avian influenza viruses [61]. The major virulence factors have been identified as the HA multibasic cleavage site [60] and the distribution of HA-activating proteases in the host [62]. Several of the virus genes and gene products contribute to the overall pathogenicity of the A(H5N1) viruses [63]. Although some adaptation to humans has occurred, A(H5N1) viruses have remained poorly transmitted among humans. A(H5N1) viruses target mainly human lower respiratory tract cells [64]. Disease severity of A(H5N1) is not dependent on the predicted tropism of the virus for tissues of the lower respiratory tract and it could be that these viruses use a yet unidentified receptor for entry into the cells of the human upper respiratory tract [65].

Influenza A(H10N8)

The virus from the first human case of A(H10N8) was designated as A/Jiangxi-Donghu/346/2013(H10N8), henceforth, JX346. Phylogenetic analysis of the retrieved sequences suggested that the haemagglutinin gene of JX346 was closely related to A(H10N3) from a duck, the neuraminidase gene related to A(H10N8) and A(H3N8) from mallard/avian origin and the six internal genes originated through reassortment of A(H9N2) strains circulating in poultry. The data suggest that the virus arose by reassortment events in domestic birds. The haemagglutinin gene shows no indications for a multibasic cleavage site, suggesting low pathogenicity in poultry, but contains other genetic markers for mammalian adaptation and virulence. Potential resistance to adamantanes was suggested, but the virus was sensitive to oseltamivir and zanamivir. In the epidemiological investigation, JX346 did not successfully spread to close contacts [4].

2.4 Diagnostics of avian influenza infections in humans

Based on sequence analysis, it is expected that the generic RT-PCR assays for influenza A virus based on highly conserved viral gene sequences, e.g. in the M-gene, will detect the A(H7N9), A(H5N1), A(H10N8) and A(H6N1).

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 Collaborating Centre for Reference and Research on Influenza (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, non-seasonal, influenza viruses to a WHO CC for further characterisation.

In May 2013, ECDC, WHO CC, 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/NICs. Twenty-seven of 29 responding countries considered their generic influenza A virus detection assay to be appropriate for the novel influenza A(H7N9) virus [66]. 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. Influenza reference laboratories were offered positive control virus RNA to evaluate their assays through the WHO Global Influenza Surveillance and Response System (GISRS)[*]. 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 [66].

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, which would have been later confirmed correctly at the WHO CC (unpublished data).

With the diagnostic laboratory assays, the novel A(H7N9) 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. 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 [67].

Most EU national reference laboratories are capable of detecting A(H5N1) and H5 samples are tested in annual external quality assessment schemes organised by the WHO CC [68]. Information regarding human influenza reference laboratories' detection capability for H10N8 and H6N1 is being currently collected using the ECDC Flu Laboratory Capability tool (FluLabCap). For an overview of the methods available through the laboratories in the influenza surveillance system please refer to the ECDC website[†].

Support to national influenza laboratories for the shipment of samples to the WHO CC in London is provided through GISRS. Additional support is available through the Joint Action on Quality Assurance Exercises and Networking on the Detection of Highly Infectious Pathogens (QUANDHIP Joint Action)[‡] funded by the European Commission. 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 [69].

2.5 Vaccines against avian influenza infections in humans

Influenza candidate vaccine virus strains are usually developed in a few laboratories that are part of the WHO 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 the various influenza vaccine manufacturers.

A list of zoonotic candidate influenza viruses including A(H5N1), A(H7N9), A(H9N2), and A(H3N2)v available or under development as well as reagents for vaccine standardisation can be found on the WHO website [70, 70A]).

Influenza A(H5N1) vaccines. EMA Guidelines to vaccine manufacturers on vaccines produced from viruses with the potential to cause a pandemic and intended for use outside of the core dossier context were already published in 2007 [71]. Since then three H5N1 vaccines have acquired EU authorisation: Prepandemic Influenza Vaccine (H5N1) (surface antigen, inactivated, adjuvanted), Novartis Vaccine and Diagnostics (2010); Pandemic Influenza Vaccine H5N1 (whole virion, inactivated), Baxter (2009); and Prepandrix (split virion, inactivated, adjuvanted) from GSK (2008) [72–74].

Influenza A(H7N9) candidate 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

[*] World Health Organization. 'Global influenza virological surveillance'. Available from: http://ecdc.europa.eu/en/activities/surveillance/EISN/laboratory_network/Pages/laboratory_surveillance_influenza.aspx

[†] 'Laboratory surveillance of influenza' Available from: http://ecdc.europa.eu/en/activities/surveillance/EISN/laboratory_network/Pages/laboratory_surveillance_influenza.aspx

[‡] Project: Quality Assurance Exercises and Networking on the Detection of Highly Infectious Pathogens. Available from http://www.quandhip.info/Quandhip/EN/Home/Homepage_node.html

reassortment technique are ongoing. Other approaches such as development of virus-like particles or culturing wild-type influenza A(H7N9) viruses for inactivation are being developed in parallel.

As of 21 February 2014, several clinical trials using different variants of influenza A(H7N9) candidate vaccines 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 in trials conducted in the United States. 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. To the best of our knowledge, no clinical trials are being conducted or planned in the European Union or in Canada.

Development of influenza candidate vaccines is ongoing in China, and clinical trial results are expected later this year.

Published or submitted results from Phase 1 studies are available for candidate vaccines produced by Novavax [55] and Novartis [55]. In addition, Microgen has published Phase 1 results for a live attenuated H7N3 vaccine showing cross-reactive antibodies against H7N9 [75].

In a Phase 1 observer-blinded, placebo-controlled clinical trial, researchers from Novavax provided monovalent A/Anhui/1/2013 (H7N9) virus-like particle (VLP) avian influenza antigen recombinant to adults over 18 years of age in two doses (intramuscularly) with and without 30 or 60 units of the saponin-based ISCOMATRIX adjuvant [55]. 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 responses in the group that received the highest dose (5µg of HA with 60 units of adjuvant), resulted in 80% seroconversion detected by an HAI assay and 97% seroconversion detected by an NAI assay. However, Novavax does not routinely produce influenza vaccines for human use and has no licensed influenza vaccine product.

In another Phase 1 clinical trial based on a vaccine candidate developed by Novartis on their cell culture platform evaluated in 400 healthy adults between the ages of 18 and 64 [76] 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.

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

ECDC is not aware of any developments regarding influenza A(H10N8) or A(H6N1) vaccines.

2.6 Infection control measures in healthcare

WHO has produced guidance on infection control in healthcare facilities for A(H5N1) and laboratory biorisk management for A(H7N9) [77,78]. These guidelines are broadly applicable to management of all human cases of avian influenza and related samples.

3 Human and animal surveillance in Europe

3.1 Surveillance for respiratory infections in humans

All novel influenza strains are notifiable diseases in the EU under EU legislation and the International Health Regulations (IHR) through the Early Warning and Response System and IHR, respectively [79]. 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 [80].

Evidence of the effectiveness of contact tracing on board airlines in limiting spread of infection is limited and should only be considered upon a risk assessment on a case-by-case basis [81]. Human infections with A(H5N1) are notifiable according to Decision 1082/2013/EU*. Case definitions for A(H5N1) have been set out in Commission Decision 2008/426/EC [82].

No specific case definitions have been defined for H10N8 or H6N1 internationally or within the EU.

Infectious disease protocols for case investigations are available from the Consortium for the Standardization of Influenza Seroepidemiology (CONSISE) [83] and national authorities. Agreed protocols for clinical investigations have been prepared by the International Severe Acute Respiratory and Emerging Infections Consortium (ISARIC) [84].

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

EU animal health legislation [85] 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, which, in turn, submits the required notifications to the European Commission and the other Member States. EU animal health legislation requires that EU Member States carry out surveillance in poultry and wild birds [86] in order to detect the circulation of avian influenza viruses under approved programmes, according to harmonised guidelines [87]. EU animal health legislation [88] 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 [86] in order to detect the circulation of avian influenza viruses as outlined by harmonised EU guidelines [87].

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) using the influenza A(H7N9) viruses from China. Laboratory 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 capability to detect A(H5N1) among poultry in the EU is maintained at a good level through the above-mentioned active surveillance programmes and in particular through passive surveillance and early detection systems in areas with a heightened risk for avian influenza introduction [89]

The OIE international standards address avian influenza surveillance measures (Chapter 10.4 of the OIE Terrestrial Animal Health Code 2013). In addition, 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 providing data to reduce uncertainty [90]. Other surveillance guidelines and laboratory protocols are available [91].

National reference laboratories for avian influenza have the capability to determine all influenza HA subtypes. The focus is on the detection of H5/H7 subtypes in the context of the mandatory surveillance programmes, as these viruses have the potential to mutate to become highly pathogenic and are subject to veterinary control measures. However, annual external quality assessments amongst EU national laboratories are designed to ensure detection of all influenza A virus subtypes. Importantly, national reference laboratories have in any case to submit all haemagglutinin viruses to the EU reference laboratory for detailed analysis.

* Decision No 1082/2013/EU of the European Parliament and of the Council of 22 October 2013 on serious cross-border threats to health and repealing Decision No 2119/98/EC. Official Journal L 293, 05/11/2013 P. 1–15.

4 Discussion

At the beginning of the A(H7N9) 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 the animal reservoir, and
- Scenario B: a pandemic scenario with a movement towards efficient human-to-human transmission [92].

Currently, scenario A is the most likely in China, and therefore worldwide. However, with the regular influenza season now ongoing in southern China and elsewhere in the northern hemisphere, there is a potential risk for co-infection and the development of new reassortant viruses with the possibility of increased capacity for transmission in the human population.

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 42/2013, a notable increase has been detected (Figure 1). This increase in the number of cases may indicate a larger wild or domestic bird reservoir, an increase in the number of exposed individuals, enhanced transmissibility of the virus, a seasonal transmission pattern, increased awareness and surveillance, or a combination of these factors.

Intervention strategies such as temporary closures of live-poultry markets, seem to have had an impact on the number of infections in the spring of 2013. However, it is not yet proven that this was more than a temporal association, and even if there is a causal relationship, alternative and safer poultry processing may not be feasible in many parts of China. Chinese New Year, on 31 January 2014, increased the potential for human exposure to both A(H7N9) and seasonal influenza viruses due to increased travel within China, thereby increasing the risk of reassortment in humans.

Rigorous epidemiological investigations are urgently needed and are currently being conducted in China in order to identify risk behaviours, other risks, and predisposing factors for avian influenza A(H7N9) infection. It is noteworthy that a 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 [93]. There may also be a role for influenza A(H7N9) vaccines for poultry in affected areas, though careful consideration of benefits, risks and conditions are required for this. 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 [94].

There are reasons for further concern over human infections with influenza A(H7) viruses in general [95]. This reassortant virus, as well as the A(H10N8), harbours the internal genes derived from avian influenza A(H9N2) viruses, for which laboratory studies with animals have suggested that they have pandemic potential [96]. Low pathogenicity avian influenza A(H9N2) virus infections in humans, infrequently reported since 1998, have usually resulted in uncomplicated influenza illness, but at least one case of lower respiratory tract disease in an immunocompromised adult has been reported [70A, 97]. The current influenza A(H7N9) viruses are considered to have pandemic potential [98].

Considering the spread of influenza A(H5N1) over national and geographic borders in and outside Asia, it is noteworthy 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 is a marked difference in age and sex distribution between A(H7N9) and A(H5N1) cases. A(H7N9) cases tend to be older with a predominance among males.

The human cases infected with influenza A(H10N8) and A(H6N1) were detected and reported through active hospital-based or syndromic surveillance by the Chinese and Taiwanese health authorities. This is a sign that the surveillance systems are functioning well. It is possible that increased vigilance due to the A(H7N9) outbreak is leading to detection of previously undetected rare avian influenza cases and this is likely to continue to occur in the future.

Considering the severity of the disease, the fact that limited human-to-human transmission cannot be excluded in some clusters, that no vaccine is available against A(H7N9), and the favourable safety profile of the anti-viral drugs of choice, it is likely that the benefits of post-exposure chemoprophylaxis of close contacts with neuraminidase inhibitors outweigh the risks when used in Europe. However, evidence of benefits and effectiveness of treatment remains very limited.

5 ECDC threat assessment for the EU

The A(H7N9) transmission pattern indicates a persistent zoonotic reservoir, and the continued and increasing transmission of this novel reassortant avian influenza virus capable of causing severe disease in humans in one of the most densely populated areas in the world remains a cause for concern due to the potential for a pandemic virus to develop. However, the most likely current scenario for China is that these outbreaks remain local zoonotic outbreaks 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 likely that the spread of the virus is associated with the time of the year but it is far from clear what the mechanism is for this possible seasonal characteristic.

It is commendable that the Chinese authorities quickly notified the outbreak of A(H7N9) to WHO under the International Health Regulations. The continued communication of results from their outbreak investigations has facilitated the assessment of the risk to human health in Europe, as elsewhere. Additional information on probable routes of transmission and risk factors would be highly valuable for further risk assessments.

The recent fatal case of influenza A(H5N1) imported to Canada and the case of A(H7N9) from China that was detected in Malaysia provide support to the notion that sporadic imported cases of avian influenzas might also be seen in Europe. However, the risk of the disease spreading to Europe via humans in the near future is 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 avian influenza viruses developing into viruses that transmit 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 is critical for assessing this risk and instruments like the Influenza Risk Assessment Tool (IRAT) can play a role.

Increased transmission of H7N9 viruses between humans remains a possible scenario. European countries should continue to prepare for the eventuality of future pandemics, including one caused by avian influenza. Preparedness activities should include the precautionary development of early human vaccine candidates and increased monitoring of animal influenzas at the animal–human interface [99–102].

The risk of avian influenza viruses being transported to Europe in 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. Legal and illegal export of poultry products to several African countries does appear to take place.

The risk of the avian influenza 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) [103–105]. The hypothesis that poultry in the affected area has been infected by wild birds has not been confirmed but neither can it be excluded.

6 Options for reducing the risk to human health in Europe

The measures that have the potential to reduce the risk to human health in Europe from the transmission of avian influenza A viruses in China can be divided into five categories. They are interventions that are likely to: (1) reduce transmission in China; (2) reduce the risk of importation of viruses to Europe (either in an infected human or in infected birds); (3) reduce the risk of transmission in the event that an imported case would be detected in Europe (including therapeutic and prophylactic treatment and infection control measures); (4) increase timely diagnosis of imported cases in Europe; and (5) speed up the development of effective vaccines.

Reduce the risk of transmission to humans in China

There is some empirical evidence that the closure of live poultry markets can reduce transmission to humans, but the fact that the animal reservoir of virus and the mode of transmission to humans have not been identified present important challenges for effective control. The offer of international technical support to China should be considered for:

- rigorous epidemiological and epizoological studies to identify the animal reservoir, transmission patterns and risk factors for infection;
- measures to control transmission or mitigate the impact of the epidemic.

Reduce the risk of importation of avian influenza A viruses from China to Europe

- Strict control measures on importation of poultry products and birds from China to continue.
- Attention to be paid to legal and illegal commerce of poultry products from China to Africa.
- Advice to EU citizens travelling to or living in China to minimise exposure to live poultry markets.
- Travel restrictions are not likely to be effective control measures.

Reduce the risk of transmission from cases imported to Europe

- Evidence of the effectiveness of contact-tracing of passengers potentially exposed on board airlines in limiting spread of infection is limited, and should only be considered upon a risk assessment on a case-by-case basis.
- See Section 2.1 'Influenza A(H7N9)', for specific guidance on A(H7N9) post-exposure chemoprophylaxis.
- National and local pandemic plans should be reviewed in light of the experiences of the 2009 pandemic and with respect to potential introduction of A(H7N9) into EU poultry or human populations.

Increase the capacity for timely diagnosis of imported cases and cases resulting from local transmission in Europe

- Laboratory capability of influenza laboratories in EU/EEA to detect H10N8 and H6N1 to be reviewed.
- Laboratory EQAs for A(H10N8) and A(H6N1) to be considered in the future among the ERLI-Net laboratories.

Development of vaccines

- Efforts to ensure possibilities for A(H7N9) vaccine development and production capability and capacity worldwide and in Europe.

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