RAPID RISK ASSESSMENT

Genetic evolution of influenza A(H7N9) virus in China – implications for public health

Sixth update, 9 March 2017

Conclusions and options for response

Since the notification of a novel reassortant influenza A(H7N9) virus on 31 March 2013, 1 258 laboratory-confirmed cases of human infection with avian influenza A(H7N9) virus have been reported. This is the fifth winter season in the northern hemisphere with human cases caused by A(H7N9) infections. During this wave, the number of human cases has been higher than in previous waves and accounts for 37% of the human cases reported so far. This is most likely due to greater environmental contamination in live bird markets and increased circulation of the virus among poultry.

In February 2017, a new A(H7N9) virus with mutations in the haemagglutinin gene - indicating high pathogenicity in poultry - was detected in two patients from Guangdong and one patient from Taiwan with a travel history to Guangdong, as well as in environmental and poultry samples. However, this new virus has been detected in only three out of 460 human cases confirmed in the current epidemic wave and in one province only. It is unclear at the moment if the newly-emerged, highly-pathogenic avian influenza (HPAI) virus A(H7N9) will replace the low pathogenic virus or if both will co-circulate in the bird population. Although the genetic changes in A(H7N9) may have implications for poultry in terms of pathogenicity, surveillance and control strategies, to date, there is no evidence of increased transmissibility to humans or sustainable human-to-human transmission.

Evidence presented at the recent WHO influenza vaccine composition meeting showed both the newly emerged and some of the currently circulating A(H7N9) viruses to be genetically and antigenically distinct from current A(H7N9) candidate vaccine viruses. To address this, new A(H7N9) candidate vaccine viruses were proposed.

In addition, the HPAI A(H7N9) strain in these three patients presented with a mutation in the neuraminidase (NA) gene associated with reduced susceptibility to neuraminidase inhibitors. Mutations related to resistance to neuraminidase inhibitors have possibly emerged during the antiviral treatment of the three patients.

The continued transmission of A(H7N9) to humans in China poses the risk that sporadic imported cases may be detected in Europe. The following options for prevention and control of the infection should be considered:

- people travelling to China should avoid direct exposure to poultry and refrain from visiting live poultry markets or backyard farms;
- travellers who have visited affected areas and develop respiratory symptoms and fever upon their return should consult a physician and mention their recent travel history to enable early diagnosis and treatment.

In addition, travellers who have visited affected areas should avoid entering farms for the entire duration of the 10-day incubation period (and during the symptomatic period in the event that they develop symptoms) in order to prevent a possible virus introduction to poultry in the EU. The possibility of humans infected with A(H7N9) returning to the EU/EEA cannot be excluded. However, the risk of the disease spreading within Europe via humans is still considered low, as there is no evidence of a sustained human-to-human transmission.

Suggested citation: European Centre for Disease Prevention and Control. Genetic evolution of A(H7N9) virus in China – implications for public health. Sixth update, 9 March 2017. Stockholm: ECDC; 2017.

Source and date of request

Request from France's Ministry of Health on 24 February 2017 and internal ECDC decision on 28 February 2017 following an upsurge in cases in China since December 2016, the report of a virus change from low pathogenic to highly pathogenic in poultry and the report of a mutation associated with drug resistance in viruses isolated from human cases.

Public health issue

In this document, ECDC summarises the epidemiological and virological information on animal and human infections with avian influenza A(H7N9) viruses and assesses the risks of:

- increased transmissibility of the HPAI A(H7N9) virus among poultry, captive birds and wild birds
- increased transmissibility of the new virus to humans
- increased transmissibility of the new virus among humans
- increased pathogenicity of the new virus in humans
- the virus acquiring antiviral drug resistance
- spread of the A(H7N9) virus beyond Chinese borders
- the emergence of new reassortants in humans.

In addition, the document covers the implications of the detection of HPAI A(H7N9) virus for vaccine development.

This rapid risk assessment builds on the fifth update of the ECDC rapid risk assessments on avian influenza published on 27 January 2017 [1] and on the recent public health development 'Mutation of avian influenza A(H7N9): now highly-pathogenic for poultry but risk of human-to-human transmission remains low' dated 24 February 2017 [2].

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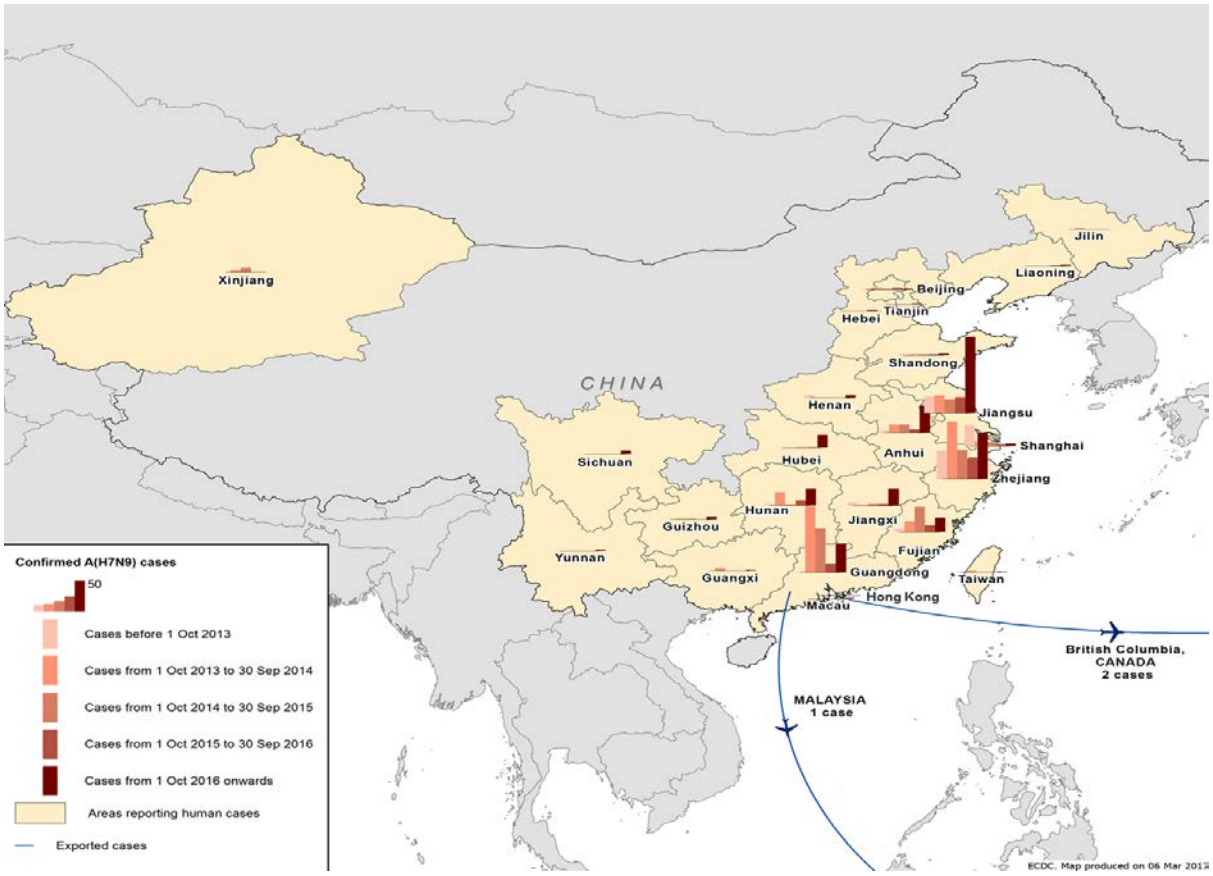
ECDC acknowledges the valuable contributions of all experts. All experts have submitted Declarations of Interest. ECDC has reviewed these and finds that none of them represent conflicts of interest with the comments and suggestions the experts have made. It should be noted that opinions expressed by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

Event information

Update on human cases infected in China

In March 2013, Chinese authorities announced the identification of a reassortant A(H7N9) influenza virus in patients in eastern China. According to WHO, as of 24 February 2017, 1 258 laboratory-confirmed cases had been reported in China (taking into account the 35 additional cases referred to during a WHO virtual press conference on 1 March 2017), including two cases reported from Canada (2) in 2015 and one case from Malaysia (1) in 2014, that had been infected in China (Figure 1, Table 1) [3].

Figure 1. Distribution of confirmed A(H7N9) human cases by place of reporting in China or with recent travel history to China, week 7/2013 to week 7/2017 (N=1 223)



Numbers according to WHO report dated 14 February 2017 [3].

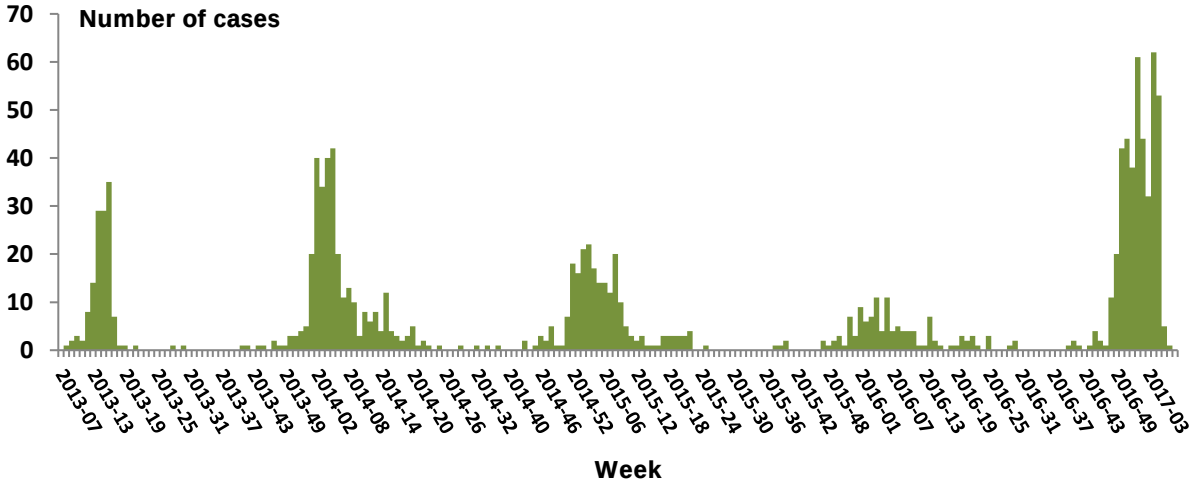
Table 1. Number of reported cases due to A(H7N9) infection by place and time of reporting

Place of reporting	First wave (2/2013–9/2013)	Second wave (10/2013–9/2014)	Third wave (10/2014–9/2015)	Fourth wave (10/2015–10/2016)	Fifth wave (10/2016–24/02/2017) Four months	Total
Zhejiang	46	93	47	33	75	294
Guangdong	1	108	72	14	47	242
Jiangsu	27	29	22	26	125	229
Fujian	5	17	41	11	23	97
Anhui	4	14	14	6	45	83
Hunan	3	21	2	8	27	61
Shanghai	34	8	6	3	4	55
Jiangxi	5	1	3	3	27	39
Hubei			1	1	21	23
Hong Kong		10	3	3	4	20
Shandong	2	2	2	2	4	12
Beijing	2	3	1	3	1	10
Xinjiang		3	7			10
Henan	4				4	8
Guizhou		1	1		4	6
Sichuan					6	6
Guangxi		4			1	5
Taiwan	1	3			1	5
Hebei	1			3		4
Liaoning				1	2	3
Jilin		2				2
Macau					2	2
Tianjin				2		2
Yunnan					2	2
Canada			2			2
Malaysia		1				1
Total	135	320	224	119	425*	1 223

**According to the teleconference held at WHO on 1 March 2017, there have been 460 cases during the fifth peak. http://terrance.who.int/mediacentre/presser/WHO-RUSH_H7N9_and_other_avian_influenzas_VPC_01MAR2017.mp3*

The A(H7N9) outbreak in China shows a seasonal pattern peaking in January and February, with sporadic cases reported during weeks 20–40 (Figure 2). In this assessment, cases reported between week 41 of one year and week 40 of the subsequent year are considered to belong to one epidemic wave. The first wave in spring 2013 (weeks 7/2013–40/2013) included 135 cases, the second 320 cases, the third 224 cases and the fourth 121 cases. A fifth wave started in October 2016 (week 41/2016), with 460 cases [4] reported as of 24 February 2017 and this wave has had a higher number of reported cases than any of the previous epidemic waves (Figure 2, Table 1 and 2). In addition, during the current epidemic wave cases have been reported from previously unaffected provinces, indicating a geographical spread of the epidemic (Figure 1, Table 1).

Figure 2. Distribution of reported human influenza A(H7N9) cases in China by week, week 7/2013 to week 7/2017 (N=1 223).



The week of reporting is used when the week of onset is unknown

Seven clusters with limited human-to-human transmission, mainly consisting of two cases each, have been investigated during the current wave. Two clusters involve transmission among patients admitted to the same hospital ward, while the five other clusters involve transmission among family members. For several family clusters, common exposure to poultry cannot be ruled-out. Similar clusters were also identified during previous waves, and there are no indications of sustained chains of human-to-human transmission [5,6].

On 19 February 2017, China's Center for Disease Control and Prevention reported two new human infections in Guangdong with an influenza A(H7N9) virus strain for which gene sequencing analysis revealed mutations in the haemagglutinin (HA) gene that resulted in the insertion of basic amino acids at the cleavage site of this protein, known to confer increased pathogenicity in chickens [7,8].

The first case was a 43-year-old female with symptom onset on 29 December 2016 who recovered. She had been exposed to poultry, but had also cared for her sister who was hospitalised with pneumonia caused by infection with influenza A(H7N9). The second case was a 57-year-old male with symptom onset on 5 January 2017. He died on 18 February, having reported poultry exposure prior to the onset of symptoms. None of the 105 close contacts of these two cases developed symptoms during the two weeks of observation [9]. On 4 February 2017, Taiwan Centers for Disease Control reported one laboratory-confirmed case of human infection with influenza A(H7N9). The patient, a 69-year-old male, travelled to Guangdong Province in China between September 2016 and January 2017. He developed fever and chills on 23 January while in China and was hospitalised upon his return to Taiwan where he died one month later. The virus isolated from this patient showed the same multi-basic amino acid insertions at the cleavage site of the HA, consistent with increased pathogenicity in chickens [10].

A similar mutation had been reported earlier in a confirmed case during the current epidemic wave, resulting in three cases so far in the fifth epidemic wave presenting with the mutation. This is the first description of human infections related to a highly-pathogenic A(H7N9) avian influenza (HPAI) virus*. Such A(H7N9) HPAI viruses had been detected during the same time period in Guangdong in a small subset of environmental and poultry specimens.

* 1. 'Avian influenza' means an infection of poultry or other captive birds caused by any influenza A virus: a) of the subtypes H5 or H7; or b) with an intravenous pathogenicity index (IVPI) in six-week old chickens greater than 1.2.

2. 'Highly pathogenic avian influenza (HPAI)' means an infection of poultry or other captive birds caused by: a) avian influenza viruses of the subtypes H5 or H7 with genome sequences codifying for multiple basic amino acids at the cleavage site of the haemagglutinin molecule similar to that observed for other HPAI viruses, indicating that the haemagglutinin molecule can be cleaved by a host ubiquitous protease; or b) avian influenza viruses with an intravenous pathogenicity index in six-week old chickens greater than 1.2;2.

3. 'Low pathogenic avian influenza (LPAI)' means an infection of poultry or other captive birds caused by avian influenza viruses of subtypes H5 or H7 that do not come within the definition in paragraph 2.

In addition, WHO reports that the viruses isolated from the three reported cases showed an amino acid substitution in the neuraminidase gene known to be associated with reduced sensitivity to neuraminidase inhibitors [10,11]. However, the three patients received antiviral treatment with neuraminidase inhibitors before samples were collected which could have induced the antiviral resistance in the patients as observed before in other patients [9,10].

The proportion of resistant viruses in this wave remains similar to that detected in the previous ones. Among the 1 258 cases notified since the beginning of this epidemic in 2013, at least 476 have died (case-fatality ratio=38%). The observed case fatality ratio does not appear to have changed during the fifth wave. These estimates are based on the currently available information and might change as deaths among current and recent cases occur and are reported.

Table 2. Distribution of reported A(H7N9) cases* and fatalities by epidemic wave, weeks 2/2013 to 2/2017

	First wave (2/2013–9/2013)	Second wave (10/2013–9/2014)	Third wave (10/2014–9/2015)	Fourth wave (10/2015–10/2016)	Fifth wave (10/2016–2/2017) Four months	Total number of cases (2/2013–2/2017)
Cases	135	319	223	121	460	1 258
Deaths	43	134	98	45	156**	476
CFR (%)	32%	42%	44%	37%	34%	38%

** Source: WHO [4]*
*** Source: WHO collaborating Centre Beijing, China CDC, personal communication*

Animal infections and environmental detection

On the 18 February 2017, the Veterinary Bureau of the China Animal Disease Control Centre notified the World Organisation for Animal Health (OIE) of the detection of an A(H7N9) HPAI virus in birds sampled on 10 January 2017 at live bird markets in Guangdong, as mentioned previously [12]. These findings have not been described in other regions so far.

The conversion of LPAI A(H7N9) into HPAI virus has been already described in the previously published ECDC Public Health development [2]. The virus was isolated in seven environmental samples from live bird markets and three human case samples related to Guangdong Province [13]. Following the OIE notification, on 18 February 2017 the Ministry of Agriculture in China published an emergency notice to strengthen national A(H7N9) surveillance, prevention and control [14]. As previously described, the detection of A(H7N9) has increased substantially during this wave in the poultry and environmental specimens tested from live bird markets and poultry farms [1]. Figure 3 shows geographical locations where human cases were reported, as well as locations of positive poultry and environmental samples. For some cases, exposure may have occurred in a different geographical area.

On 7 March 2017, the US Department of Agriculture confirmed the detection of a North American wild bird lineage influenza A(H7N9) strain in poultry from a farm in Tennessee [15]. The eight segments of this virus are different from the viruses circulating in China, therefore constituting an unrelated development.

Figure 3. Distribution of human cases of influenza A(H7N9) and positive avian and environmental samples, China, 1 October 2015 to 27 February 2017

Source: Food and Agriculture Organization of the United Nations (FAO), Emergency Prevention System for Transboundary Animal Diseases (EMPRES), Rome, Italy [14]

Virological information

Evolution to highly pathogenic avian influenza virus

Initially, as reported in the fifth update of the ECDC rapid risk assessments on avian influenza [1], evidence from genetic analysis of viruses infecting humans during the fifth wave did not reveal an altered pathogenicity risk profile when compared to viruses from previous waves. Since the emergence of A(H7N9), different evolution patterns have been observed with the emergence of two main lineages currently circulating in different regions in China: the Yangtze River Delta and the Pearl River Delta lineages [10,13]. In January 2017, A(H7N9) viruses were detected in humans, environmental and poultry specimens from the Guangdong province, with genetic sequences suggestive of their evolution from low pathogenic to highly pathogenic avian viruses in poultry [10,11]. Such genetic changes consisted of insertion mutations at the cleavage site of the haemagglutinin (HA) gene, also called the multi-basic cleavage site (MBCS) of the HA. The MBCS in the HA can be cleaved by ubiquitously expressed host proteases. This cleavage facilitates systemic virus replication and can result in mortality of up to 100% in chickens [7,8].

The evolution of avian influenza viruses from low to high pathogenicity is associated with increased virulence and the ability to spread in multiple organs of infected birds, in addition to their respiratory and intestinal tract. So far, there is no evidence that the observed mutation in A(H7N9) viruses at the MBCS of the HA has had an effect on increased pathogenicity of the HPAI virus compared to the LPAI virus infecting humans. Moreover, previous studies have shown that in vitro insertion of an MBCS in the HA of human influenza A(H3N2) virus does not increase pathogenicity in ferrets [15]. For HPAI A(H5N1) the cleavage site is a major pathogenicity factor in mammals including humans [16,17]. However, studies on H5 HPAI viruses have shown that in some cases such highly pathogenic viruses might even have reduced airborne transmissibility [18,19], shorter infectious periods and lower virus titres than LPAI viruses [20,21]. Efficient airborne transmission has been proven to be associated with the acquisition of other mutations, rather than only the MBCS of HA [22].

Further evolution processes of the viruses are ongoing and whole genome sequencing of the A/Taiwan/1/2017 strain revealed a number of other variations, previously found to be associated with the pathogenesis and transmissibility of the virus to animal models [10].

Antiviral resistance

Antiviral drug resistance in viruses from the fifth wave was similar to that already reported in previous waves. Since the first transmission events of A(H7N9) viruses to humans, reduced susceptibility to neuraminidase (NA) inhibitors has been described in several cases after the start of oseltamivir treatment [23-25]. In addition, a few isolates showed drug resistance to oseltamivir but sensitivity to peramivir [26]. The three viruses with the insertion mutations at the cleavage site isolated from human cases in January 2017 carried a substitution in their neuraminidase gene associated with reduced susceptibility to neuraminidase inhibitors [29]. The samples were obtained after the initiation of treatment with neuraminidase inhibitors, suggesting that the mutation might have occurred during the treatment [9,10,29]. Short-term treatment with NA inhibitors has previously been shown to be associated with the emergence of resistance in A(H7N9) viruses [28,29]. Previous studies on the R292K mutation have shown that a high-level resistance may develop without loss of replicative ability, virulence and transmissibility [30].

Disease background

Clinical aspects and treatment

The median incubation period of A(H7N9) viruses in infected humans has been estimated to be six days (range: 1 to 10 days) [31]. Fever and cough have been the most common symptoms, while vomiting and diarrhoea have appeared in a smaller proportion of cases [31-33]. Paediatric A(H7N9) patients tend to present with clinically milder disease [32-34]. Some milder cases were also identified through extended testing of outpatients with influenza-like symptoms, suggesting that A(H7N9) presents with a broad clinical spectrum. A high frequency of comorbidities in infected patients has also been reported [31,33]. The presence of at least one chronic underlying condition has been demonstrated as a risk factor for A(H7N9) infection [35]. The case fatality ratio has remained around 40% over the years (Table 2). There are limited numbers of human infections by viruses carrying the insertion mutations at the cleavage site and it is too early to identify possible (dis-)similarity with cases infected with viruses without these mutations.

WHO recommends antiviral treatment with a neuraminidase inhibitor as early as possible for patients with suspected or confirmed A(H7N9) infection, but does not recommend routine post-exposure antiviral chemoprophylaxis for close contacts [38]. The US CDC has published interim guidance on the use of antivirals for treatment of A(H7N9) infection [39,40] and for chemoprophylaxis of close contacts [39]. They recommend oseltamivir or inhaled zanamivir for close contacts of a confirmed or probable influenza A (H7N9) case, depending on the risk of exposure. For high risk exposure (e.g. household or close family members) chemoprophylaxis should be administered while for moderate risk exposure (e.g. healthcare worker having higher-risk contact with cases) chemoprophylaxis could be considered.

Given the severity of the disease, the fact that human-to-human transmission cannot be excluded in some clusters, that no vaccine is available against A(H7N9) in EU/EEA Member States, and that the safety profile of the antiviral drugs of choice is favourable, it is likely that the benefits of post-exposure chemoprophylaxis for close contacts with neuraminidase inhibitors outweigh the risks. Evidence of benefits and effectiveness of prophylaxis and treatment remain limited. However, it is important to monitor the occurrence of viruses resistant to antivirals, particularly in patients under treatment with NA inhibitors.

Vaccines against avian influenza A(H7N9) infections in humans

Vaccines against A(H7N9) have been developed and others have been approved for clinical trials by the China Food and Drug Administration (CFDA) [42]. Evidence presented at the WHO influenza vaccine composition meeting in March 2017 showed both the recent highly pathogenic and some of the currently circulating low pathogenic A(H7N9) viruses to be genetically and antigenically distinct from current candidate vaccine viruses. To address this, new LPAI and HPAI A(H7N9) candidate vaccine viruses were proposed. For HPAI viruses the new proposed candidate vaccine virus (CVV) will be a A/Guangdong/17SF003/2016-like virus [43].

Disease surveillance and prevention

Surveillance and public health control measures in humans

All novel influenza strains and human infections with A(H5N1) are notifiable diseases under EU legislation and the International Health Regulations* (IHR), through the Early Warning and Response System (EWRS) and the IHR notification system [44,45]. 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 [46]. Infectious disease protocols for case investigations are available from the Consortium for the Standardization of Influenza Sero-epidemiology (CONSISE) [47] and national authorities. Agreed protocols for clinical investigations have been prepared by the International Severe Acute Respiratory and Emerging Infections Consortium (ISARIC) [48]. Contacts of confirmed cases should be followed-up and tested. International recommendations for the use of post-exposure prophylaxis differ (see 'Clinical aspects and treatment' above).

In order to minimise the risk of infection, EU citizens travelling to or living in China should minimise their exposure to animals in live poultry markets or slaughter areas, avoid contact with live or dead poultry or their products, and practice good hand hygiene when visiting places with birds or poultry. Contact with surfaces potentially contaminated with droppings from poultry or other animals should also be avoided [49]. This should also include adequate food safety practices.

EU/EEA Member States and the European Commission should consider relevant options for preparedness and communication. Such options can include, but are not limited to, measures to:

- decrease human exposure (especially for populations at risk of exposure, such as animal handlers or hospital caregivers)
- continue influenza surveillance in poultry and wild birds for avian influenza viruses
- ensure availability of vaccines and vaccine strains for humans
- ensure availability and rapid deployment of antivirals (including use of antivirals not yet available on EU markets)
- sensitise healthcare systems and ensure surge capacity is available at healthcare facilities.

Surveillance and control measures in birds

The surveillance and control of pathogenic avian influenza viruses in poultry and wild birds is laid down in EU legislation detailed in Council Directive 2005/94/EC and Commission Decision 2010/367/EU. In addition, official notifications have to be reported according to the Terrestrial Animal Health Code of the World Organisation for Animal Health (OIE).

A known risk factor for infection with influenza A(H7N9) for humans is poultry handled at live bird markets or in backyard farms [35]. Wild birds act as reservoirs for the H7 and N9 genes of influenza viruses, while live bird markets seem to serve as the location of amplification of the virus in birds [48,49]. In December 2016 and January 2017, according to FAO and the Chinese authorities, several cities in affected areas temporarily closed live bird markets, poultry wholesale markets, and farmers' poultry markets, or suspended all live poultry trade either for the season or until further notice - e.g. in Guangdong, Jiangsu, Shanghai, Anhui and Zhejiang [14,52]. In Zhejiang and Guangdong provinces, live poultry trade is currently prohibited and slaughtering is centralised [14,52]. A Chinese investigation team identified a greater contamination of the environment with A(H7N9) viruses and higher exposure levels as the reason and driver behind the increase in human cases reported since December 2016 [52].

* Case definitions for the four diseases requiring notification in all circumstances under the International Health Regulations (2005) are available at http://www.who.int/ihr/Case_Definitions.pdf

This greater contamination of the environment might be due to the higher numbers of infected poultry as well as a larger distribution of infected poultry across different provinces.

Following the detection of HPAI A(H7N9) viruses, the Ministry of Agriculture in China published an emergency notice to strengthen national A(H7N9) prevention and control. Consequently, in addition to the existing measures, additional measures were implemented in Guangdong Province, such as closure of the markets for cleaning purposes, emergency monitoring of poultry and flocks, and the culling of flocks if the HPAI virus is detected [9].

The risk of avian influenza viruses being transported from China to Europe through legal trade in poultry is negligible. EU regulations do not permit importation of live poultry, day-old chicks, hatching eggs or 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.

Diagnostics of influenza A infections in humans

People in the EU presenting with severe respiratory or influenza-like infection and a history of travel to the affected areas in China with potential exposure to poultry or live bird markets will require careful investigation, management and infection control. Adequate samples for influenza tests should be rapidly taken and processed from patients with relevant exposure history within 10 days of symptom onset. Sequencing of such samples should be encouraged. Repeated sampling should be considered in cases with relevant exposure history, rapid progression of symptoms or severe symptoms, as many cases reported from China initially have RT-PCR-negative samples from the upper airways and only after disease progression and ability to collect specimens from the lower respiratory tract can the diagnosis be confirmed. Influenza A specimens which cannot be sub-typed should be rapidly referred to national influenza centres. Early or presumptive treatment with neuraminidase inhibitors should always be considered for suspect or confirmed cases, in line with relevant national and international recommendations. Contacts of confirmed cases should be followed up for symptoms and tested. International recommendations for the use of post-exposure prophylaxis differ (see 'Clinical aspects and treatment' above).

With routine diagnostic laboratory assays, the 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 unsubtypeable influenza A if no specific A(H7) diagnostic test is performed. It is a 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 to a WHO Collaborating Centre for characterisation, as was done in China for the first influenza A(H7N9) isolates. The European Reference Laboratory Network for Human Influenza (ERLI-Net) laboratories have rapidly developed and verified their capabilities for detecting the novel influenza A(H7N9) influenza virus [53]. 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 [54].

ECDC threat assessment for the EU

Influenza A(H7N9) remains a widespread zoonotic disease in several provinces in China. The virus is transmitted sporadically to humans exposed to infected poultry, or contaminated environments (e.g. live bird markets) and rarely from human to human.

The reporting of human cases of influenza A(H7N9) in China has followed a seasonal pattern, with peaks in winter months and sporadic cases in the summer. The second and fifth waves, in 2014 and 2017 respectively, have had a significantly larger amplitude than the other waves, both in terms of the number of cases and geographical spread. This may suggest that the virus has become more widespread in its domestic bird reservoir, which, in turn, has led to increased human exposure to the virus. As expected, the age and sex distribution has remained comparable throughout the waves.

It is too early to know if the highly pathogenic virus will replace the low pathogenic virus or whether they will co-circulate and how the observed variations might affect the transmissibility and viral shedding in birds. Increased transmissibility and/or viral shedding could result in more infections in poultry, which would consequently increase the likelihood of human exposure. It is also unknown if HPAI A(H7N9) viruses will be able to spill over to migratory birds.

The newly emerged mutations leading to high pathogenicity in poultry triggered the need to reassess the risks associated with the pathogenicity, transmissibility between birds and to and among humans.

Risk of increased HPAI H7N9 transmissibility among poultry, captive birds and wild birds

The data are too limited to assess whether infection with the new strains results in increased viral shedding and transmissibility among birds, which would result in a wider spread of the virus and more infections in birds. HPAI A(H7N9) viruses have been detected only in one small location while the vast majority of the viruses during the fifth wave have been LPAI A(H7N9) viruses.

Risk of increased HPAI H7N9 transmissibility to humans

Human cases have been observed during the fifth wave in 20 provinces of China. Only three of the 460 cases were infected with the HPAI A(H7N9) strain, all in the Guangdong province. If the HPAI A(H7N9) strain spreads and increases the number of infected poultry, the risk of exposure and therefore the transmission to humans might increase. However, the fact that poultry will be symptomatically ill or rapidly die will be likely have an impact on human exposure, the magnitude of which is difficult to anticipate.

Risk of increased HPAI H7N9 transmissibility among humans

To date, only few clusters with possible human-to-human transmission of the non HPAI A(H7N9) viruses and no clusters of the HPAI A(H7N9) viruses have been reported. There is currently no evidence that the transmissibility among humans has changed. ECDC concurs with the WHO assessment that the likelihood of sustained human-to-human transmission is low [9].

Risk of increased HPAI H7N9 pathogenicity in humans

The multi-basic amino acid insertion at the cleavage site of HA, consistent with the evolution from low to high pathogenicity, refers to increased pathogenicity only in poultry. The data from the three human cases (two of which were fatal) infected with A(H7N9) viruses highly pathogenic for poultry is too limited for an overall assessment of the situation related to humans.

Risk of established drug resistance

The three patients reported with HPAI A(H7N9) infections received antiviral treatment prior to the sample collection, which suggests that the resistance mutation may have been acquired following the antiviral drug uptake. Samples before the initiation of antiviral drug treatment are not available. According to the Global Initiative on Sharing All Influenza Data (GISAID), only one environmental sample from 2014 showed such indications for antiviral resistance.

During the fifth wave, the proportion of resistant viruses was 7–9% which is similar to the rates during previous waves [13]. Continued genetic testing pre- and post-treatment is needed to exclude the possibility of a wider circulation of viruses with NA-resistant mutations in humans.

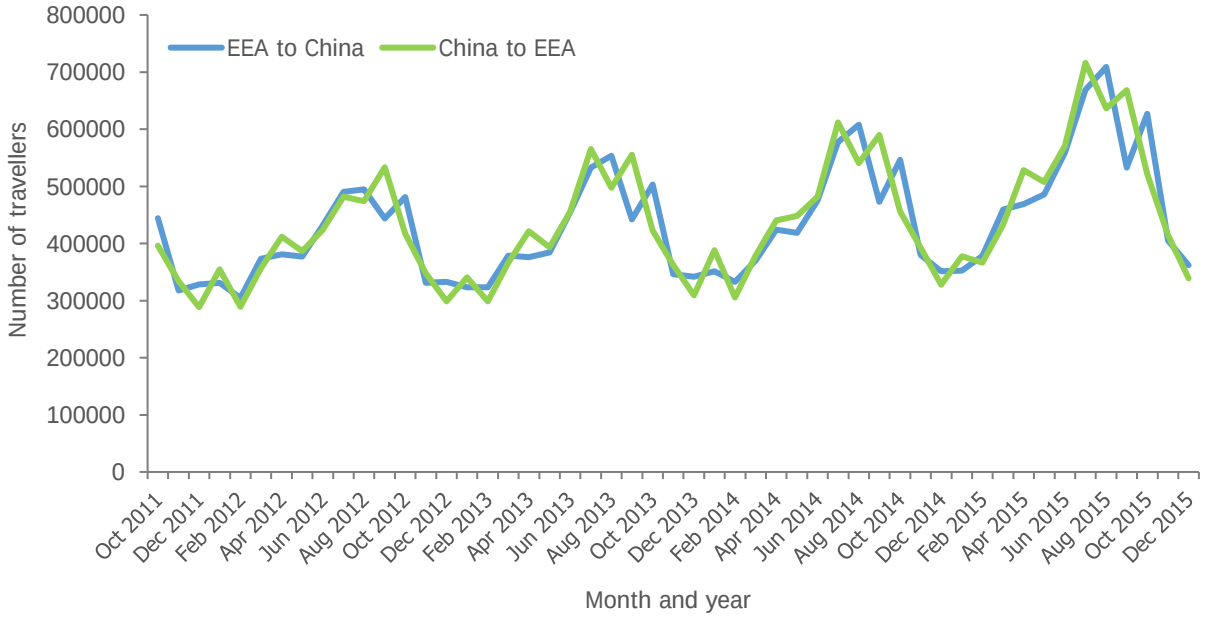
What are the implications for vaccine development?

Vaccines have been developed against the previously circulating A(H7N9) viruses and clinical trials are ongoing. Evidence presented at the recent WHO influenza vaccine composition meeting showed both the recent highly pathogenic and some of the currently circulating low pathogenic A(H7N9) viruses to be genetically and antigenically distinct from the current A(H7N9) candidate vaccine viruses. To address this, new A(H7N9) candidate vaccine viruses were proposed [43]. Sequences have already been shared with the GISAID and a few viruses containing these new mutations have been shared with all WHO Collaborating Centres and other partners to improve diagnostics and the development of candidate vaccines [55].

What is the risk of spread of the virus beyond Chinese borders?

The significant number of cases in both poultry and humans in China represents a risk for the spread of the virus beyond China to Central Asia and Europe. Currently, the likelihood of detecting human cases in Europe is related to the number of individuals exposed in China travelling to Europe (Table 3).

Table 3. Distribution of international air travellers from EU/EEA countries to and from China, by month, October 2011 to December 2015



Source: International Air Transport Association (IATA)

Risk of emergence of new reassortants in humans

As other avian influenza viruses are circulating in the bird population in China, the likelihood of reassortment of those viruses in animals is high, with a risk of transmission to humans. With the seasonal influenza season currently ongoing, the risk of reassortment between seasonal and avian influenza viruses in humans is possible. In several patients, co-infections of A(H7N9) with seasonal influenza viruses have already been observed, either with A(H1N1)pdm09, A(H3N2) or B viruses. Moreover, a nosocomial cluster of a co-infection of A(H7N9) and a seasonal A(H1N1)pdm09 influenza virus has been observed in two patients with severe underlying immunocompromised conditions [54].

The increasing circulation of the virus, resulting in more human and animal exposures, heightens the risk of reassortment events and the risk of viruses emerging with higher human transmission potential, thereby increasing the likelihood of a pandemic strain emerging.

Risk to public health in the EU/EEA and to EU/EEA citizens

The increasing geographic spread and intensity of A(H7N9) virus exposure in China heightens the risk of the virus being introduced through infected travellers returning to Europe, although over the past five seasons no introduction of the virus into Europe has been observed and the transmission of this virus has been confined to China. The continuous circulation of A(H7N9) in poultry in China poses a risk that people having had contact with poultry in China might introduce the virus to EU poultry farms. If HPAI viruses are able to spill over to the migratory bird population the risk of them being introduced into Europe via migratory birds may increase.

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