THREAT ASSESSMENT BRIEF

First identification of human cases of avian influenza A (H5N8) infection

24 February 2021

Summary

On 20 February 2021, Russian authorities reported the detection of influenza A(H5N8) virus infection in seven poultry workers in an outbreak of highly pathogenic avian influenza (HPAI) A(H5N8) virus on a poultry farm in the south of Russia. All seven human cases were reported to be mild or asymptomatic. HPAI A(H5N8) viruses have been circulating in European bird populations since 2014, causing large outbreaks and affected several million of birds and poultry. More than 10 000 exposure events of people have been estimated between 2016 and 2018. Since October 2020, around 1 700 outbreaks in poultry holdings and wild bird findings due to A(H5N8) and other reassorted A(H5Nx) viruses have been reported to the animal disease notification system (ADNS) from the European Union (EU), the European Economic Area (EEA) and neighbouring countries. In the same period, seven EU/EEA countries reported a total of 1 888 people exposed to infected birds (e.g. during culling activities) to the European Food Safety Authority (EFSA). No transmission to humans has been reported from EU/EEA countries or any other country globally related to A(H5Nx) viruses since the first introduction to Europe in 2014. This is the first report providing direct virological evidence of a zoonotic transmission of highly pathogenic avian influenza A(H5N8) virus from birds to humans. There has been no evidence of human-to-human transmission.

This assessment is based on very limited data and there is therefore considerable uncertainty regarding the conclusions reached. The risk of infection related to avian influenza influenza A (H5N8) virus for the general public is assessed as **very low**, and for occupationally exposed people as **low**.

The virus remains purely avian-adapted and no markers for mammalian adaptation, pathogenicity for humans or altered susceptibility to existing antivirals have been observed. The disease severity has been described as asymptomatic or mild, so the impact based on severity is very low.

People at risk are mainly those in direct contact/handling diseased or dead birds or poultry (e.g. farmers, veterinarians and labourers involved in culling and rendering). Wearing personal protective equipment when exposed to infected birds will minimise the risk of transmission. Local health authorities may consider monitoring exposed people for a minimum of 10 days in order to detect possible related influenza-like symptoms or conjunctivitis and initiate diagnostic testing as soon as possible after onset of symptoms. People exposed to birds likely to be infected should be instructed to report any symptoms to local health services. Sampling material from symptomatic people should be taken immediately for diagnostic and confirmatory purposes.

Any human infection with avian influenza viruses is notifiable within 24 hours through the Early Warning and Response System (EWRS) and the International Health Regulations (IHR) notification system. The continued surveillance of avian influenza virus in wild birds and poultry in Europe, combined with timely generation and sharing of complete viral genome sequences, are crucial.

Suggested citation: European Centre for Disease Prevention and Control. First identification of human cases of avian influenza A (H5N8) infection. 24 February 2021. ECDC: Stockholm; 2021.

Event background

Situation background

On 20 February 2021, media reported that Rospotrebnadzor, Russia's Federal Service for Surveillance on Consumer Rights Protection and Human Wellbeing, had confirmed the first detection of avian influenza virus A(H5N8) in humans [1,2]. The seven reported cases were employees of a poultry farm in the south of Russia, where an outbreak of A(H5N8) occurred in December 2020, and were reported to have had mild symptoms. The World Health Organization (WHO) informed that all human cases were asymptomatic and investigations are ongoing to better understand and assess the situation [1]. No evidence of human-to-human transmission has been reported.

However, a previous report from Russia described serological evidence of poultry workers testing positive in haemagglutination inhibition (HI) and microneutralization assays [3]. Of 760 tested paired sera, 28 showed antibodies to A/rook/Chany/32/2015 (H5N1) and 60 had antibodies against A/chicken/Sergiyev Posad/38/2017 (H5N8) in HI tests, only 40% of the HI positive samples were also positive in a neutralization assay. Both paired sera were positive so that a time of exposure and seroconversion could not be determined in relation to local A(H5N8) outbreaks. In a study in Egypt following the introduction and spread of the influenza A (H5N8) virus among the poultry population, no indication of antibodies to A(H5N8) were observed in people [4].

Highly pathogenic avian influenza (HPAI) A(H5N8) viruses have been circulating in Europe in wild birds, since 2014, causing large outbreaks in poultry farms and mortality in wild birds with many millions of birds affected in the EU/EEA and globally [5-7]. Several reassortment events have been described with other low pathogenic viruses causing new virus types [8-13]. Such reassorted viruses have been detected in wild and captive birds and caused outbreaks in poultry holdings over the course of this last winter season in many European countries [11] (Annex, Table 1).

Since 2014, many millions of birds have died or needed to be culled, requiring exposure of workers to A(H5N8)-infected birds. Between 2016 and 2018, it was estimated that over 10 000 exposure events of people during outbreaks in EU/EEA and Israel [14]. When the first HPAI A(H5N8) outbreak was detected in poultry within this epidemic season, seven countries reported a total of 1 888 people exposed to infected birds (e.g. during culling activities) [11] [and unpublished data]. Poland accounts for 78%, with a total of 1 318 exposed people. Data on the number of exposed persons were not available for 12 affected countries. The highest number of exposures of people during HPAI outbreaks was related to turkeys and chickens (Annex, Figure 1). Despite the high number of outbreaks and extensive exposure, no human cases related to avian influenza A(H5Nx) viruses detected in Europe have been reported in the EU/EEA and also globally so far.

Outbreaks of avian influenza viruses

Since the beginning of October 2020, 23 countries in the EU/EEA, Switzerland, Ukraine and the United Kingdom have reported around 1 700 outbreaks of HPAI viruses in poultry holdings, captive birds and wild birds to the animal disease notification system (ADNS) (Annex Table 1) [15]. Reassortant viruses of A(H5N1), A(H5N3), A(H5N4), A(H5N5) and A(H5N8) subtypes, as well as A(H5Nx) viruses lacking the neuraminidase type, have been identified in these outbreaks. Between 8 December 2020 and 23 February 2021, seven low-pathogenic avian influenza (LPAI) virus outbreaks were also notified in the poultry sector and in captive birds in Europe.

A joint report by ECDC, EFSA and the EU reference laboratory for avian influenza (EURL) describing the situation on avian influenza in the EU/EEA will be published on 1 March 2021. A previous report was published in December 2020 [11]. An overview of previous quarterly published joint reports can be found here [16].

Sequence analysis

Analyses of the genetic characteristics of HPAI viruses of the A(H5) subtype circulating in Europe were performed by EURL. The complete genome sequences of 90 European HPAI A(H5) viruses of clade 2.3.4.4b were deposited in the GISAID EpiFlu database by Member States (accessed on 21 February 2021) [17]. The characterised viruses were collected between 16 October 2020 and 4 February 2021 from wild and domestic birds. The topology of the HA phylogenetic tree shows that the European HPAI A(H5N8), A(H5N5) and A(H5N1) viruses group together and also group with HPAI A(H5) viruses, which have been identified in Iraq, Kazakhstan and in the Russian Federation since May 2020.

The virus sequence from one of the human cases identified in December 2020 in Russia uploaded to GISAID showed a close relationship to the A(H5N8) detected in birds in the same period and in the same geographic region, Astrakhan [18,19]. These viruses group together with A(H5N8) viruses currently circulating in Europe.

To date, no evidence of fixation of mutations associated to adaptation to mammalian species previously described as associated to zoonotic/pandemic potential has been observed in the sequences analysed of viruses circulating in

the EU/EEA, Russia or other neighbouring countries. Analyses performed so far have shown that the virus has maintained the characteristics typical of viruses adapted to avian species [20]. However, analyses indicate a high propensity of the current epizootic H5 strains to reassort, which resulted in a high genotypic variability. Specifically, five subtypes – A(H5N1), A(H5N3), A(H5N4), A(H5N5) and A(H5N8) – and six distinct genotypes – two A(H5N8), one A(H5N1) and three A(H5N5) – which originated from multiple reassortment events with LPAI viruses circulating in wild birds in Europe, Asia and Africa have been detected in Europe and Russia.

Risk assessment question

What is the risk of infection related to avian influenza A(H5N8) virus to the general population and the occupationally exposed?

ECDC risk assessment

This assessment is based on very limited data and there is therefore considerable uncertainty regarding the conclusions reached.

Avian influenza A(H5N8) viruses have caused large outbreaks in birds and poultry since 2014, with estimates suggesting over 10 000 exposure events of people in the EU/EEA during the outbreaks in 2016-2018 [14]. Since 2019 alone, nine countries reported 2 210 exposures of people during culling and related activities, but no transmission to humans (data reported to EFSA) [11-13,21-24]. Despite this high number of exposure events and ongoing large and widespread outbreaks, no documented transmission to humans has ever been reported in the EU/EEA or globally.

The assessment of risk is based on the following information:

- Transmission of avian influenza viruses from birds to humans is a rare event.
- Only seven human cases have now been reported despite widespread global circulation of A(H5N8) since 2014.
- The seven human cases were occupational workers in an A(H5N8)-virus-affected poultry farm, who likely had close contact with infected birds.
- All seven human cases have been reported as mild or asymptomatic.
- No human-to-human transmission has been reported.
- No markers for mammalian adaptation, pathogenicity for humans or altered susceptibility to existing antivirals have been observed in avian influenza viruses currently detected in EU/EEA in wild birds and poultry outbreaks. The A(H5N8) viruses remain poorly adapted to humans.

*The risk to the general public is assessed as **very low**:*

No human-to-human transmission has been described, and the likelihood of infection is therefore related only to exposure to infected wild birds or poultry, which is very low for the general population.

In relation to the severity of the disease, the human cases have all been asymptomatic or mild, and the impact based on severity is therefore very low, although case numbers are low.

The limited information hampers any further assessment on the impact on a population with no likely pre-existing immunity to A(H5) viruses, should the virus transmit between humans.

*The risk to occupationally exposed workers is assessed as **low**:*

No human-to-human transmission has been described, and the likelihood of infection is therefore related to direct exposure to infected wild birds or poultry or contaminated environment. Personal protection equipment as required for people exposed to infected or dead birds, e.g. involved in culling activities, following the outbreak confirmation of HPAI viruses in many countries reduces the risk of transmission. Viruses remain purely avian-adapted without markers for mammalian adaptation. The likelihood of infection is therefore assessed as low.

In relation to the severity of the disease, the human cases have all been asymptomatic, and the impact based on severity is therefore very low, although case numbers are low.

Other A(H5Nx) viruses have shown high severity and mortality, so that the evolution of these viruses need to be closely monitored and any human-to-human transmission identified and reported as early as possible to implement public health control measures.

The molecular data on available sequences do not indicate a pattern for increased transmission to humans. However, the high frequency of reassortment events related to the clade 2.3.4.4 A(H5N8) viruses might pose a risk for A(H5N8) viruses to acquire features for increased transmission to and between humans.

Further information of the viruses and detailed case data (e.g. age, gender, date of sampling (swabs and serum) tests performed and results, date of results, outcome) are needed to better assess the situation and, for example, understand why and which tests have been taken of the asymptomatic workers to confirm an infection. Should data on mutations in the virus genome become available and such mutations with indication for human transmissibility or pathogenicity identified, a reassessment will be performed.

Options for response

Monitoring and public health prevention and control measures

Zoonotic transmission to humans from infected birds can occur either directly or through environmental contamination. Protective measures have been recommended in accordance with national guidelines for HPAI. A previous analysis identified that the majority of human exposures during avian influenza outbreaks were related to outbreaks in commercial farms with large (>10 000) number of birds [14].

People at risk are mainly those in direct contact/handling diseased birds or poultry, or their carcasses (e.g. farmers, veterinarians and labourers involved in culling and rendering). Workers should wear personal protective equipment (face mask, goggles/face shield/protective glasses, gloves and gown/overall) when HPAI is detected or suspected in order to avoid unprotected direct contact with sick or dead birds, carcasses, faeces as well as potentially contaminated environments.

It is important to remain vigilant, identify any possible early transmission events to humans and ensure active surveillance of exposed workers at the affected holdings for human health complaints, particularly during and after culling operations. People in direct contact with birds or poultry with avian influenza virus infection should be identified and monitored for a minimum of 10 days in order to detect possible related influenza-like symptoms, such as fever and cough or conjunctivitis, to initiate diagnostic testing as soon after symptom onset as possible. Local health authorities may consider actively monitoring these groups. All people exposed to likely infected birds should be instructed to report any symptoms to local health services.

People in the EU presenting with severe respiratory or influenza-like infection and a history of exposure to poultry or wild birds require careful investigation, management and infection control. Appropriate samples for influenza tests should be taken rapidly and processed from patients with relevant exposure history within 10 days preceding symptom onset. If positive specimens cannot be subtyped, those should be shared with the national reference laboratory (National Influenza Centres; NICs).

Avian influenza viruses circulating in the EU/EEA have not shown any resistance to antivirals such as neuraminidase inhibitors. Early or presumptive treatment with neuraminidase inhibitors should always be considered for confirmed cases, in line with relevant national and international recommendations. Antiviral prophylaxis could also be considered depending on the local risk assessment (i.e. intensity of exposure). Considering that no vaccine is available on the market against A(H5N8) and the favourable safety profile of the antiviral drugs of choice, it is likely that the benefits of post-exposure chemoprophylaxis of close contacts with neuraminidase inhibitors outweigh the risks [25]. However, it should be noted that evidence of the benefits and effectiveness of prophylaxis and treatment remains limited.

Wearing personal protective equipment and providing antiviral prophylaxis has previously been shown to limit transmission of HPAI A(H5N6) virus during large outbreaks in South Korea in 2016-2017 among exposed workers involved in culling activities, where no acute infection in any of the 4 633 workers monitored has been identified [26].

Contacts of confirmed cases should be followed up, tested and offered post-exposure prophylaxis as recommended by relevant national/international guidelines. Study protocols for investigations of human cases are available from the Consortium for the Standardization of Influenza Sero-Epidemiology (CONSISE) [27]. WHO has published a protocol to investigate non-seasonal influenza and other emerging acute respiratory diseases [28].

Healthcare workers managing symptomatic exposed or possible cases should follow standard contact and respiratory precautions, depending on the local risk assessment.

An overview of the protective measures implemented in the EU/EEA between 2014 and 2017 following the first A(H5N8) introduction and outbreaks has been described previously [29,30] and is available on ECDC's webpage.

Diagnosis

With routine diagnostic laboratory assays, human infection with A(H5Nx) viruses should be detected as positive for influenza A virus, and negative for influenza B, A(H1), A(H1)pdm09 and A(H3) viruses, and therefore classified as un-subtypeable influenza A virus if no-specific A(H5) diagnostic test is performed. Such un-subtypable influenza A virus isolates or clinical samples that cannot be subtyped should be sent to NICs, and further to a WHO Collaborating Centre for Reference [31,32].

Sharing of sequences and isolates

Continued surveillance of avian influenza virus in wild birds and poultry in Europe, combined with timely generation and sharing of complete viral genome sequences, are crucial. These efforts have led to the detection of novel reassortant viruses in the EU/EEA. Continued monitoring together with in-depth analyses to identify and

monitor virus evolution and genetic mutations, resulting in changes in viral properties that are relevant for animal and public health, are of utmost importance. This information will enable laboratories to adapt the diagnostic tests systems.

The timely characterisation of viruses and the sharing of sequence information remain crucial for virus vaccine development. Sharing of sequence data through the GISAID EpiFlu sequence database as well as virus isolates with WHO Collaborating Centres are important for public health assessment, improvement of diagnostics and the development of candidate vaccines [17,32].

Reporting

Human infections with avian influenza viruses and other novel influenza strains are notifiable under EU legislation EU Decision 1082/2013/EU [33] and the International Health Regulations (IHR) through the Early Warning and Response System (EWRS) and the IHR notification system [34]. The Commission Implementing Decision (EU) 2017/253 of 13 February 2017 lays down the procedures for the notification of alerts under the EWRS related to cross-border health threats [35]. Reporting has to be performed within 24 hours. Immediate notification is required according to the IHR case definition for human influenza caused by a new subtype [36]:

"State Parties to the IHR (2005) are required to immediately notify WHO of any laboratory confirmed case of a recent human infection caused by an influenza A virus with the potential to cause a pandemic. Evidence of illness is not required for this report. An influenza A virus is considered to have the potential to cause a pandemic if the virus has demonstrated the capacity to infect a human and if the haemagglutinin gene (or protein) is not a variant or mutated form of those, i.e. A/H1 or A/H3, circulating widely in the human population. An infection is considered recent if it has been confirmed by positive results from polymerase chain reaction (PCR), virus isolation, or paired acute and convalescent serologic tests. An antibody titre in a single serum is often not enough to confirm a recent infection and should be assessed by reference to valid WHO case definitions for human infections with specific influenza A subtypes."

Vaccines

The most important intervention in preparing for the pandemic potential of influenza viruses is the development and use of human vaccines - therefore antigenic, genetic and epidemiologic data, are constantly monitored and assessed by WHO [37]. No licenced vaccine for A(H5N8) is currently available. An overview of recommended candidate vaccine viruses (CVVs) and status of development lists 33 different CVVs for different A(H5) clades as available and eight additional CVVs for the most recently circulating viruses under development [38].

The Vector institute in Russia has reported development of an A(H5N8) vaccine [39].

Source and date of request

Internal ECDC decision, 22 February 2021.

Consulted experts

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Disclaimer

ECDC issues this risk assessment document based on an internal decision and in accordance with Article 10 of Decision No 1082/13/EC and Article 7(1) of Regulation (EC) No 851/2004 establishing a European centre for disease prevention and control (ECDC). In the framework of ECDC's mandate, the specific purpose of an ECDC risk assessment is to present different options on a certain matter. The responsibility on the choice of which option to pursue and which actions to take, including the adoption of mandatory rules or guidelines, lies exclusively with the EU/EEA Member States. In its activities, ECDC strives to ensure its independence, high scientific quality, transparency and efficiency.

This report was written with the coordination and assistance of an Internal Response Team at the European Centre for Disease Prevention and Control. All data published in this risk assessment are correct to the best of our knowledge at the time of publication. Maps and figures published do not represent a statement on the part of ECDC or its partners on the legal or border status of the countries and territories shown.

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Annex

Table 1. Number of highly pathogenic avian influenza outbreaks in Europe, by country, virus subtype and affected sub-population, 5 October 2020-16 February 2021

Country	Captive birds		Poultry				Wild birds						Total
	A(H5Nx)	A(H5N8)	A(H5Nx)	A(H5N1)	A(H5N5)	A(H5N8)	A(H5Nx)	A(H5N1)	A(H5N3)	A(H5N4)	A(H5N5)	A(H5N8)	
Austria											1	2	3
Belgium	1		1		1		8					11	22
Bulgaria						4							4
Croatia						1							1
Czechia						5	1					5	11
Denmark		2				2	6		1		2	120	133
Estonia												1	1
Finland						1						3	4
France			5			452	5		1			7	470
Germany		3			1	55	23	1	36	1	18	537	675
Hungary						6						1	7
Ireland						1			1			26	28
Italy						1		5			1	12	19
Latvia												4	4
Lithuania						1	2					2	5
Netherlands		10		1		9	4	5			1	40	70
Norway	1											13	14
Poland						43					1	14	58
Romania						1	4				3		8
Slovakia		1			1						4		6
Slovenia											1	5	6
Spain												3	3
Sweden	1				1	3					2	10	17
Switzerland										2 2			2
Ukraine			9			3							12
United Kingdom**		2		1		15	3	2			3	85	111
Northern Ireland*						1			1				2
Total	3	18	15	2	4	604	56	13	40	3	37	901	1 696

** Northern Ireland reported data to the ADNS starting from 1 January 2021. **The United Kingdom reported data to the ADNS up to 31 December 2020. Data source: ADNS (16.02.21) [15].*

Figure 1. Number of exposed people by affected bird species (N=2 043) in nine EU/EEA countries, 1 January 2019 to 11 February 2021