TECHNICAL REPORT

Enhanced influenza surveillance to detect avian influenza virus infections in the EU/EEA during the inter-seasonal period

20 June 2024

Summary

Highly pathogenic avian influenza A(H5N1) viruses continue to be widespread in wild bird populations across the European Union/European Economic Area (EU/EEA). Viruses circulating in wild birds have spilled over to both wild and domestic/farmed animals, leading to outbreaks in poultry and other animal farms.

Transmission to humans can occur when avian influenza is circulating in animals, especially when people are directly exposed without wearing appropriate levels of protective equipment, with an estimated low-to moderate risks for individuals exposed. During the summer months, seasonal influenza virus activity tends to be very limited, resulting in few cases of seasonal influenza infection and even fewer cases of hospitalisation and severe disease.

Ideally, all influenza positive specimens from sentinel sources should be typed and subtyped, augmented by year-round surveillance of influenza and other respiratory viruses. Sentinel surveillance systems are important for the monitoring of respiratory viruses in the EU/EEA, but these systems are not designed and are not sufficiently sensitive to identify a newly emerging virus such as avian influenza in the general population early enough for the purpose of implementing control measures in a timely way.

To identify sporadic severe human infections with avian influenza virus in hospital settings, the following approach is proposed:

- People admitted to hospitals with respiratory symptoms or other symptoms compatible with avian influenza virus infection should be asked about exposure to birds (wild birds or poultry) or other animals (dead or alive) in the two weeks before symptom onset or, if not available, before admission.
- Patients admitted to the hospital due to respiratory or other influenza related symptoms should be considered for influenza A/B testing.
- Testing for influenza virus of hospitalised patients with unexplained viral encephalitis/ meningoencephalitis in whom a causative agent cannot be identified should be considered.
- All influenza A-positive samples from hospitalised patients should be subtyped for seasonal influenza viruses A(H1)pdm09 and A(H3).
- Samples positive for influenza type A virus but negative for A(H1)pdm09 or A(H3) should immediately be sent to national influenza reference laboratories for further testing, subtyping and genetic analysis. Member States should ensure they have sufficient laboratory capacity to meet this need and future demands.

Raising awareness among all primary care workers and communicating the epidemiological situation is important in order to not miss or delay diagnosis of potential human cases. Raising awareness in primary care providers including consideration of specific enquiring about animal exposure would be a good practice: people who seek medical care during the summer period with respiratory or other symptoms compatible with avian influenza virus infection be asked about history of exposure to dead or sick animals within the two weeks before symptom

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onset, especially when there are ongoing outbreaks among animals in the area. Primary care clinicians should be educated on symptoms compatible with avian influenza infections and testing of symptomatic persons with a history of exposure should follow a risk-based approach according to the level of exposure as proposed in the published ECDC guidance documents 'Investigation protocol of human cases of avian influenza virus infections in EU/EEA' and 'Testing and detection of zoonotic influenza virus infections in humans in the EU/EEA, and occupational safety and health measures for those exposed at work'.

ECDC encourages national public health authorities to provide messaging to the general public to avoid close contact with or touching of sick or dead birds (especially seabirds and wildfowl) and dead wild mammals.

Scope of this document

This document describes how to strengthen surveillance in primary and secondary care for the identification of avian influenza virus infections in the EU/EEA, including severely affected patients suspected to be infected with avian influenza, during the summer period. This document aims to complement the guidance on testing and detection of zoonotic influenza virus infections in humans in the EU/EEA, and occupational safety and health measures for those exposed at work [1] and the investigation protocol of human cases of avian influenza virus infections in EU/EEA [2]. Jointly with the World Health Organization (WHO) Regional Office for Europe, ECDC published operational considerations for respiratory virus surveillance in Europe that describe how to strengthen and design surveillance systems for respiratory viruses to fulfil different surveillance objectives. This document provides an update of the surveillance guidance document 'Enhanced surveillance of severe avian influenza virus infections in hospital settings in the EU/EEA' published in 2023 [3].

What is new in this document

Compared to the 2023 document on 'Enhanced surveillance of severe avian influenza virus infections in hospital settings in the EU/EEA', this report has been updated to cover relevant aspects of wastewater and primary care surveillance [3]. It has also been updated to include other mammalian species that have since been affected by A(H5N1) (e.g. cattle). In this version, ECDC also suggests that the history of exposure can take into account exposure to animals that occurred within two weeks since the symptom onset, which would reflect the incubation period of the virus, if this information is available; using the hospital admission date also remains an option. In addition, the reference to the new ERVISS platform has been added and recently published ECDC documents have been cited.

Target audience

This document is intended for public health authorities in the EU/EEA that deal with surveillance of respiratory viruses, for clinical societies giving guidance for testing of patients with respiratory symptoms in primary and secondary care, and for clinicians to raise awareness for possible human cases due to avian influenza. This document is also intended for all One Health practitioners whose work involves the identification and management of highly pathogenic avian influenza.

Background

Avian influenza has caused large outbreaks in wild birds and poultry in Europe in recent years, with 2.3.4.4b currently the dominant circulating A(H5N1) clade. Despite exposure to infected sick and dead birds and other animals, no human infections have been identified in the EU/EEA to date. The detections of H5 viral RNA in two Spanish workers involved in culling activities during an outbreak of avian influenza at a poultry farm are considered contamination events and not true infections [4,5]. Nevertheless, with the extensive circulation of avian influenza viruses in bird populations, sporadic transmission to humans exposed to infected animals, their products or their environment cannot be ruled out, especially if appropriate levels of personal protective equipment are not used.

To support public health investigations related to avian influenza outbreaks, a document on testing and detecting zoonotic influenza virus infections in humans in the EU/EEA and occupational safety and health measures for those exposed at work was published in 2022 [1]. ECDC has also published a protocol that sets out measures for the follow-up and management of individuals exposed to infected animals and human cases of avian influenza, and for the public health management of possible and confirmed human cases [2].

ECDC suggests that people exposed to avian influenza virus are identified rapidly, particularly those occupationally exposed, e.g. in culling activities [1,2]. Those people should be monitored (through active or passive surveillance) for 10 to 14 days following their last exposure to identify the occurrence of symptoms and initiate testing as soon as possible [2].

In addition to those at-risk groups more likely to be exposed occupationally or recreationally described in the published documents [1,2], other people might have direct unprotected contact and be exposed to avian influenza viruses, e.g. when mortality events in wild birds such as gulls occur. Monitoring of these events is extremely challenging, if not unfeasible, for health authorities. In such situations, sporadic transmission to humans can occur and people could become infected with avian influenza virus.

Avian influenza circulation and detection in wild birds with spill-over to mammal populations, as well as outbreaks in poultry farms, can show different epidemiological characteristics during summer and winter months depending on the migratory bird season, e.g. movement and residence in summer breeding sites or migration and overwintering during colder winter months. Highly pathogenic avian influenza A(H5N1) viruses continue to be widespread in wild bird populations across the EU/EEA. Viruses circulating in wild birds can spill over to both wild and domestic animals, leading to outbreaks in poultry and occasional cases or outbreaks in mammals.

Considerations for primary care settings

ECDC published, jointly with WHO, operational considerations for respiratory virus surveillance in Europe that describe how to strengthen and design surveillance systems for respiratory viruses to fulfil different surveillance objectives [6].

Sentinel surveillance systems are particularly important for the monitoring of respiratory viruses in the EU/EEA, but these systems are not designed and are not sufficiently sensitive to provide early identification of a newly emerging virus such as avian influenza in the general population and to implement control measures.

Despite this, the sentinel system provides reliable information from sentinel sites on pathogens circulating that can complement the surveillance of newly emerging pathogens. It is important that all influenza positive specimens from sentinel sources are typed (A/B) and subtyped (H1pdm09/H3/Hx). Surveillance of influenza and other respiratory viruses should be performed throughout the entire year.

ECDC encourages national public health authorities to raise awareness among all primary care workers and communicate the epidemiological situation, both of which are important to reduce the likelihood of delayed or missed diagnoses in humans. Specific questioning about animal exposure would be a good practice to implement in primary care settings: people who seek medical care during the summer period with respiratory or other symptoms compatible with avian influenza virus infection can be asked about history of exposure to dead or sick animals within the two weeks before symptom onset, especially when there are ongoing outbreaks in the area.

ECDC encourages national public health authorities to provide messaging to the general public to avoid close contact with or touching of sick or dead birds (especially seabirds and wildfowl) and dead wild mammals. This messaging should be enhanced during periods of high H5N1 activity.

Testing of symptomatic persons with a history of exposure should follow a risk-based approach according to the level of exposure and as described at the ECDC case investigation protocol guidance [2]. The main considerations on the follow-up of exposed persons and testing are described below.

Strengthened hospital surveillance for severe human avian influenza virus infections

Based on limited evidence from the EU/EEA and globally on circulating avian influenza viruses of clade 2.3.4.4b, the symptoms of avian influenza virus infections in humans can range from asymptomatic infection to severe disease. People with avian influenza virus infection can show symptoms of the upper and lower respiratory tract infection, but also atypical non-respiratory symptoms, such as conjunctivitis or neurological symptoms. Human cases can display conjunctivitis as the only symptom or together with other symptoms. In more severe cases, a rapid progression to severe pneumonia, sepsis with shock, acute respiratory distress syndrome, or encephalitis with fatal outcome have been reported. It is important to increase awareness about A(H5N1) among clinicians so that testing for influenza A and subtyping for H5 is undertaken in patients with the above symptoms, especially after exposure to at risk animals.

According to the WHO guidelines for the clinical management of severe illness from influenza virus infections [7] and the ECDC expert opinion on neuraminidase inhibitors for prevention and treatment of influenza [8], clinical specimens for testing should be collected as quickly as possible and antiviral treatment could commence once samples have been taken and prior to influenza confirmation.

Options for One Health mitigation measures in the human and animal sectors to reduce the potential of transmission to humans as well as the drivers and critical steps for a pandemic due to avian influenza are discussed in the joint ECDC/EFSA technical report 'Drivers for a pandemic due to avian influenza and options for One Health mitigation measures' [9]. In order to protect human health, a strong collaboration between the animal and human sectors is critical.

Assumptions and considerations:

- Human infection with avian influenza virus following unprotected direct contact with infected birds, mammals, or contaminated environment cannot be excluded.
- Data from human cases with avian influenza virus infection show that those identified with true productive infection mostly develop severe disease progression requiring hospital admission and care.
- Seasonal influenza viruses of subtypes A(H1N1)pdm09 and A(H3N2) are more likely to circulate at a very low level outside the influenza season during the summer months (weeks 21–39) (see also www.erviss.org) and consequently there should be very few severe human infections with seasonal influenza viruses to be admitted to hospitals.
- Most commercial test systems used in hospital settings to test patients with respiratory symptoms only detect and differentiate influenza type A and B viruses but they do not identify the subtype of influenza A viruses, e.g. A(H1N1)pdm09 or A(H3N2) for seasonal influenza viruses. Additional haemagglutinin specific RT-PCR assays are needed to determine the subtype.
- Any A(H5N1) or another avian influenza virus infection would likely be detected as influenza type A positive[1] and they would be missed if no subtyping, or specific testing requested based on suspicion of the treating clinician, was performed.
- Avian influenza A(H5N1) caused encephalitis and meningoencephalitis in a wide number of different infected mammalian species. Patients with viral infection of the brain with unknown aetiology would most likely not be considered for influenza virus testing.

To identify sporadic **severe** human infections with avian influenza virus in **hospital settings**, we propose the following approach for consideration:

- People admitted to hospitals with respiratory symptoms or other symptoms compatible with avian influenza virus infection (as discussed above) should be asked about history of exposure to birds (e.g. wild birds or poultry) or other animals (dead or alive) within the two weeks before symptom onset or, if this is not available, before hospital admission.
- Patients admitted to the hospital due to respiratory or other influenza related symptoms should be considered for influenza A/B testing.
- Consider testing for influenza virus of hospitalised patients with unexplained viral encephalitis/ meningoencephalitis in whom a causative agent cannot be identified. It is important to note that these will most likely not be picked up through routine respiratory virus surveillance. In case of an emergence of an A(H5N1) strain that exhibits mutations that would allow the virus to bind to human receptors, consideration should be given for routine immediate examination of those cases for A(H5) following risk assessment.
- All influenza A-positive samples from hospitalised patients should be subtyped for seasonal influenza viruses A(H1pdm09) and A(H3). In case hospital laboratories do not have the assays in place to subtype influenza A viruses, specimens could also be shared with the national reference laboratories, national influenza centres, or other designated laboratories that can perform subtyping of influenza A viruses, after consulting with them.
- Samples positive for influenza type A virus but negative for A(H1)pdm09 or A(H3) should immediately be sent to the national influenza reference laboratories for further analysis and H5 testing.

A validation of existing assays (at least in silico checking the primers/probes) and/or participation to external quality assessment might be good to perform if validated commercial assays are not already in use. Please contact ECDC at ecdc.influenza@ecdc.europa.eu for more information about laboratory support activities.

Proposed time frame

The time frame to have extended subtyping for hospitalised patients with influenza A virus infection in place is proposed from June to early October (i.e. influenza interseason period, weeks 21–39), when a small number of human patients with seasonal influenza virus infection are expected to be hospitalised and exposure to infected sick and dead wild birds or other animals might be more likely than in winter months when birds migrate to their overwintering sites. A risk-based approach taking into account the epidemiological situation was suggested during the 2023/24 influenza season [10].

Follow-up of people exposed to animals infected with avian influenza and targeted testing

Although human infections from currently circulating 2.3.4.4b A(H5N1) influenza viruses remain rare despite widespread transmission among animals, sporadic human cases among exposed individuals can be expected. Active monitoring and testing of exposed persons to infected animals is recommended for early detection of human cases and to assess the possibility of human-to-human transmission.

[1] Some M or NS gene-based generic influenza type A/B protocols might miss H5 and give a false negative result for influenza type A.

ECDC has published an 'Investigation protocol for human exposures and cases of avian influenza in the EU/EEA', which sets out measures for the follow-up and management of individuals exposed to infected animals and human cases of avian influenza, and for the public health management of possible and confirmed human cases of avian influenza. People exposed to infected animals should be followed up to identify early transmission from animals to humans, as well as between humans.

The protocol recommends that follow-up should last between 10 to 14 days after last exposure. This could involve active or passive follow-up. Active follow-up refers to public health authorities contacting the exposed individuals daily/frequently, while passive follow-up requires individuals to report to public health authorities daily/frequently or only if they develop symptoms.

If individuals develop symptoms, which could range from fever, conjunctivitis, and diarrhoea to respiratory, neurological, or other atypical symptoms, immediate testing should be undertaken, and the individuals should isolate. Those who have been in close contact with confirmed cases should also be tested and monitored to prevent further spread and to track transmission. Testing of asymptomatic individuals who have been exposed may be conducted on a case-by-case basis, taking into account the level of exposure. A lower threshold for testing asymptomatic exposed persons linked with an avian influenza outbreak should be considered in case there are circulating A(H5N1) strains with mutations that would allow binding to human receptors indicating increased human adaptation.

Given the uncertainties related to mammal-to-mammal transmission and according to the epidemiological situation, a low threshold for testing persons exposed to potentially infected mammals can be considered. Serological testing can be applied in the context of avian influenza outbreaks in the area and as follow-up studies to evaluate the seroconversion upon exposure; such studies can support the overall risk assessment for zoonotic transmission.

More information on testing and detection of zoonotic influenza virus infections in humans in the EU/EEA, and occupational safety and health measures for those exposed at work can be found at the joint ECDC/EFSA/EU-OSHA/EURL operational guidance 'Testing and detection of zoonotic influenza virus infections in humans in the EU/EEA, and occupational safety and health measures for those exposed at work'.

Wastewater surveillance

There is currently limited experience in wastewater surveillance to detect low-level circulation of zoonotic influenza virus infections in the human population [11,12]. As part of the pandemic preparedness efforts of the European Commission, the Health Emergency Preparedness and Response Authority (HERA) in cooperation with the European Commission's Joint Research Centre (JRC) has taken on the topic of wastewater surveillance for public health by two initiatives, the EU Wastewater Observatory for Public Health and the Global Consortium for Wastewater and Environmental Surveillance for Public Health (GLOWACON). Moreover, HERA and JRC have initiated the Joint Action EU-WISH (EU-Wastewater Integrated Surveillance for Public Health), which is working towards implementation of wastewater surveillance for public health in the EU/EEA. According to the latest JRC report (27 May 2024) on implementation of avian influenza surveillance in wastewater, 12 EU/EEA countries are conducting preliminary studies on wastewater surveillance of avian influenza.

Reporting

Requirements for immediate reporting to national and international public health authorities (via the Early Warning and Response System and International Health Regulations) are outlined elsewhere [1,2].

Laboratory-confirmed human infections with avian influenza and other novel influenza strains are notifiable under the International Health Regulations and through the Early Warning and Response System, in line with EU Decision 2022/2371 on serious cross-border threats to health and repealing Decision 1082/2013/EU [13]. This includes any relevant information that might be useful for coordinating a response, such as the type and origin of the agent, date, and place of incident or outbreak and the detection and confirmation methods. Reporting should occur within 24 hours of the laboratory diagnosis. The European Surveillance Portal for Infectious Diseases (EpiPulse) operated by ECDC should be used for the epidemiological monitoring and assessment of human infections with avian influenza, and for sharing epidemiological situation updates with EWRS. The European Surveillance System (TESSy) should additionally be used for reporting using record type INFLZOO for case-based data and INFLZOOAGGR for aggregated data.

Prevention and response measures

Options for One Health mitigation measures in the human and animal sectors to reduce the potential of transmission to humans as well as the drivers and critical steps for a pandemic due to avian influenza are discussed in the joint ECDC/EFSA technical report 'Drivers for a pandemic due to avian influenza and options for One Health mitigation measures'. In order to protect human health, strong collaboration between the animal and human sectors is critical.

Infection prevention and control measures and communication in primary and secondary care settings

Implementation of early infection prevention and control precautions, proper education/training of healthcare staff, – especially in the appropriate use of personal protective equipment – risk communication, and follow-up measures, which are outlined in the publications listed below, are paramount when an avian influenza virus infection in a person is identified. Proper education, information-sharing and communication to healthcare workers (in both primary and secondary care) regarding potential cases of avian influenza in humans should include comprehensive information, the current epidemiological situation, symptoms compatible with avian influenza and testing protocols according to exposure levels, as well as prevention and response measures.

More information on the preparedness measures that countries have implemented and laboratory capacities and capabilities to detect and characterise zoonotic influenza viruses can be found in two ECDC survey reports: 'Survey report on laboratory capacity for molecular diagnosis and characterisation of zoonotic influenza viruses in human specimens in EU/EEA and the Western Balkans' and 'EU/EEA country survey on measures applied to protect exposed people during outbreaks of highly pathogenic avian influenza'.

Links to additional resources

Latest situation update of the avian influenza situation in the EU/EEA: Avian influenza overview December 2023–March 2024 (europa.eu)

Investigation protocol for human exposures and cases of avian influenza in the EU/EEA (europa.eu)

Drivers for a pandemic due to avian influenza and options for One Health mitigation measure

Targeted surveillance to identify human infections with avian influenza virus during the influenza season 2023/24, EU/EEA

Testing and detection of zoonotic influenza virus infections in humans in the EU/EEA, and occupational safety and health measures for those exposed at work

Annual Epidemiological Reports: Annual Epidemiological Reports on avian influenza (europa.eu)

ECDC webpages: Avian influenza (europa.eu)

Operational considerations for respiratory virus surveillance in Europe

Infection prevention and control and preparedness for COVID-19 in healthcare settings Editorial on avian influenza in Eurosurveillance – May 2023: Avian influenza, new aspects of an old threat

ECDC contact tracing: https://www.ecdc.europa.eu/en/covid-19-contact-tracing-public-health-management

ECDC toolkit: https://www.ecdc.europa.eu/en/avian-influenza-humans/preparedness/toolkit-investigation-cases

WHO Protocol to investigate non-seasonal influenza and other emerging acute respiratory diseases: https://apps.who.int/iris/handle/10665/275657

WHO Protocol for the investigation of acute respiratory illness outbreaks of unknown etiology: https://www.afro.who.int/publications/protocol-investigation-acute-respiratory-illness-outbreaks-unknown-etiology

WHO guidelines for investigation of human cases of avian influenza A(H5N1): https://apps.who.int/iris/handle/10665/69416

CDC Investigate an Outbreak: https://www.cdc.gov/urdo/outbreak.html

Epipulse: EpiPulse - the European surveillance portal for infectious diseases (europa.eu)

TESSy: The European Surveillance System

Communicable disease threats reports

Survey report on laboratory capacity for molecular diagnosis and characterisation of zoonotic influenza viruses in human specimens in EU/EEA and the Western Balkans

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