TECHNICAL REPORT

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

September 2023

Summary

Following the autumn bird migration, avian influenza virus outbreaks are expected to occur and spread geographically across the EU/EEA. The transmission of avian influenza viruses to wild, domesticated and farmed mammals will be likely to continue. Whenever avian influenza viruses are present in wild birds and mammals, the possibility of transmission to humans cannot be excluded, particularly for those who are directly exposed while not wearing protective equipment.

During the winter months when seasonal influenza viruses are circulating in the population, testing and sub-typing approaches for avian influenza virus need to be proportionate to the epidemiological situation and the capacities of reference laboratories. Therefore, **a risk-based targeted approach** is proposed **in areas with ongoing avian influenza outbreaks in poultry and detections in wild birds and other animals**, focussing on outbreaks and severe respiratory or unexplained neurological disease.

To identify human infections with avian influenza virus, the following approach is proposed:

- People admitted to hospitals with respiratory symptoms should be asked about exposure to sick or dead birds, wild or other animals in the two weeks prior to symptom onset or before admission (if symptom onset date cannot be defined). They should be tested based on an exposure risk assessment by the clinician. Specimens from hospitalised patients with very severe influenza virus infections could be considered for sub-typing, particularly if they are believed to be part of a nosocomial outbreak.
- Consideration should be given to testing hospitalised patients with unexplained viral encephalitis/meningoencephalitis for seasonal influenza virus. Specimens positive for type A virus should be further sub-typed for seasonal influenza viruses to rule out avian influenza virus.
- Clusters of severe respiratory infections requiring hospitalisation should be investigated and tested for avian and other influenza viruses if routine testing for respiratory pathogens is inconclusive.
- Wastewater surveillance could be considered as an additional monitoring system locally in affected areas, however, so far there is very limited experience and evidence of wastewater surveillance being used to identify low-level circulation of zoonotic influenza virus infections in the population.

In general, any influenza A-positive sample for which routine sub-typing using PCR has been attempted with an inconclusive result or which is negative for seasonal influenza viruses A(H1)pdm09 and A(H3), should be sent to national reference laboratories and to the WHO Collaborating Centre.

Suggested citation: European Centre for Disease Prevention and Control. Targeted surveillance to identify human infections with avian influenza virus, EU/EEA – 22 September 2023. Stockholm: ECDC; 2023.

Stockholm, September 2023.

ISBN: 978-92-9498-657-3; Catalogue no: TQ-04-23-933-EN-N; DOI: 10.2900/044902

Scope of this document

This document describes a risk-based targeted approach to identifying possible avian influenza virus infections through established routine respiratory virus surveillance systems during the winter season 2023/24. It complements 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]. This document also complements the previous guidance Enhanced surveillance of severe avian influenza virus infections in hospital settings in the EU/EEA (europa.eu) for the summer period 2023 (weeks 21–39) [2].

Target audience

This document is intended for public health authorities in the EU/EEA; public health professionals who work on surveillance of respiratory viruses; clinical societies giving guidance for the testing of severely ill patients, particularly in hospital settings, and for clinicians in order to raise awareness of possible human cases of avian influenza.

Background

Avian influenza A(H5N1) clade 2.3.4.4b viruses continue to circulate in wild birds across Europe, with ongoing spill-over events in poultry farms and sporadic infections among various wild, domesticated and farmed mammals, such as foxes, cats and mink.

To date, no human infections have been identified in the EU/EEA, despite many individuals being exposed to infected animals[1].

During the summer months, large outbreaks were observed in colony-breeding birds. These outbreaks, involving mass mortality, mostly affected gulls at their breeding sites. As the year progresses, with the autumn bird migration, wild birds are returning to their over-wintering sites. As observed in previous years, a change in the epidemiological situation is expected, with more detections in central and southern Europe. Therefore, human exposure to infected, sick or dead wild birds and exposure to infected, sick or dead mammals will probably continue, given the wider geographical distribution of infected wild birds.

To prevent spill-over events in commercial and backyard farms and to reduce the risk of human exposure, increased vigilance is advised (see Avian influenza overview April – June 2023 (europa.eu). People exposed to infected sick or dead birds and other animals should be monitored (active or passive surveillance) for 10–14 days from their last exposure in order to identify the occurrence of symptoms and initiate testing as soon as possible [3].

During the course of the COVID-19 pandemic, surveillance systems were adapted to integrate COVID-19 and other respiratory viruses into routine monitoring of seasonal influenza viruses. Together with WHO, ECDC published operational considerations for respiratory virus surveillance in Europe that describe how to further strengthen and design surveillance systems for respiratory viruses to fulfil different surveillance objectives [1].

Surveillance of avian influenza in humans during the winter season 2023/24

Sentinel surveillance systems in primary and secondary care are considered important for monitoring the seasonal epidemic of respiratory viruses in the EU/EEA. Although not designed for early identification of a newly emerging virus such as avian influenza in the general population, hospital-based monitoring of severe infections with respiratory viruses, combined with event-based surveillance of severe respiratory infection clusters in healthcare settings, is an important tool for early signal detection.

To identify severe sporadic human infections with avian influenza virus, without overburdening healthcare and diagnostic laboratories unnecessarily during the influenza season, we propose a **risk-based targeted approach focussing on areas where outbreaks of avian influenza in birds or detections in mammals** are reported. The sections below outline the proposed approach for the different surveillance sectors.

[1] Detections of H5 viral particles in two Spanish workers involved in culling activities during an outbreak of avian influenza at a poultry farm were considered contaminations and not true productive infections.

Targeted surveillance related to risk settings and identification of severe respiratory disease clusters

Clinicians should be aware of the need to ask patients with severe respiratory disease about exposure to dead animals, primarily in areas where outbreaks in poultry and detections in wild birds and mammals have been reported. In the event of suspected avian influenza exposure and possible infection, testing should first be carried out for seasonal influenza viruses, with sub-typing of influenza type A positive specimens. Those specimens that are influenza type A positive but negative for seasonal influenza viruses should then be tested and characterised for avian influenza. If possible, those specimens should be sent to national influenza centres for further analysis and sub-typing.

In addition, people exposed to sick or dead animals as well as people (should they occur in the EU) with possible or confirmed avian influenza infection (including pets) who are unprotected should be followed up by public health authorities and/or should self-monitor for 10–14 days following exposure. If relevant symptoms (respiratory, gastroenteric, neurological, non-specific fever-like or fatigue) are observed, those affected should be advised to approach the relevant healthcare provider for the initiation of testing.

There are settings where people may possibly not be aware of the presence of avian influenza in sick or dead animals,. In these settings people might be less likely to wear personal protective equipment. Such settings need to be assessed in the context of whether there has been confirmation of avian influenza virus in the animals, and the likely level of exposure. Such settings can include:

- backyard and hobby farms, with limited biosecurity measures where wild birds can have contact with chickens or other birds and where different animal species are kept in close proximity;
- fur (mink) farms with low biosecurity measures where wild birds can enter the premises;
- urban and rural areas where sporadic dead (carnivore) mammals (foxes, etc.) are found;
- coastal areas or areas with water bodies where wild birds and single or multiple dead marine mammals (seals, dolphins, etc.) are found;
- households or shelters with infected pets.

The threshold to initiate testing in such settings when there is evidence of avian influenza outbreaks in animals in the vicinity should be low. In such settings, testing of asymptomatic persons as a precautionary measure should be considered, depending on the risk of exposure, or as part of an outbreak investigation. Testing could also be considered as part of a study to assess asymptomatic transmission, particularly when there was unprotected contact with infected mammals.

Cluster identification through event-based surveillance in healthcare settings with severe respiratory disease

Event-based surveillance plays an important role in the early detection of events related to communicable diseases and it complements traditional indicator-based surveillance systems. Formal and informal reporting of, and/or monitoring (e.g. through media reports) for clusters of respiratory infection, or other events indicative of avian influenza activity, can be a valuable adjunct to other routine national surveillance systems.

In the EU/EEA, event-based surveillance covers notifications through the Early Warning and Response System (EWRS), EpiPulse, and Event Information Site for the International Health Regulations (IHR 2005), as well screening of publicly available information.

In addition to monitoring of restricted systems – EWRS, EpiPulse and EIS (IHR) – ECDC's epidemic intelligence group performs regular and systematic screening of publicly available information, including media and social media screening, looking for any reports on avian and swine influenza virus infections in humans. As part of strengthened surveillance, epidemic intelligence is looking for clusters of severe respiratory diseases identified in healthcare settings (e.g. similar exposure history, family clusters and information about patients with atypical or unexplained neurological symptoms during the influenza season). Any relevant information detected is further validated and monitored for a period of time to inform EU/EEA counterparts of the event through the (restricted) daily and (restricted and/or public) weekly Communicable Disease Threats Reports (CDTR).

Surveillance for human avian influenza virus infections in primary care

For the season 2022/23, EU/EEA countries reported that around 90 000 specimens were tested in sentinel systems and nearly 2 million specimens in non-sentinel systems, underlining the large number of tests performed across routine healthcare systems for seasonal influenza virus.

Existing sentinel surveillance systems for acute respiratory infection (ARI) or influenza-like illness (ILI) in the EU/EEA provide a basis for monitoring human avian influenza cases. In the EU/EEA countries, selected specimens from patients that fulfil the case definition for acute respiratory infection (ARI) or influenza-like illness (ILI) are sent to national reference laboratories from primary care sentinel sites to be further tested for influenza. This testing includes sub-typing/lineage determination, as well as viral characterisation and antiviral resistance testing. Most of the specimens testing positive for influenza type A viruses are sub-typed (A(H1N1)pdm09 or A(H3N2) - see also https://flunewseurope.org/PrimaryCareData/SentinelVirologicalDetections).

Other non-sentinel surveillance systems for influenza are generally less suitable for monitoring human avian influenza cases. In such systems, influenza virus testing is largely conducted in primary care or hospital diagnostic laboratories. The majority of these tests in non-sentinel settings rely on commercial assays, point-of-care testing or high throughput testing for several respiratory viruses. This generally only includes testing for influenza type A or B and does not provide information about sub-types or lineages (see Flu News Europe|Virus characteristics). Although influenza type A virus detections that are negative for A(H1N1)pdm09 or A(H3N2) in sentinel specimens will be further analysed and identified as sporadic human infections with zoonotic influenza viruses, there will generally be no additional sub-typing of non-sentinel specimens, and therefore possible human infections with zoonotic viruses might remain undetected.

Therefore, although sub-typing of influenza type A virus positive specimens during an epidemic season is feasible for sentinel specimens, such an approach is unlikely to be feasible for non-sentinel systems, in the absence of any clear change in the epidemiological situation, due to the additional costs, capacity limitations and effort required to adapt them. Outside the sentinel system, clinical assessment, based on clinical symptoms and suspicion of exposure to possibly infected animals in an affected geographical area, is the most important factor for initiating testing of patients with respiratory symptoms.

Hospital surveillance for severe human avian influenza virus infections

All recent detections of avian influenza viruses of clade 2.3.4.4b in humans causing symptomatic infections have shown a severe or fatal disease course. Patients have shown symptoms of upper and lower respiratory tract infection, but also atypical non-respiratory symptoms, such as neurological symptoms [4-8]. Rapid progressions to severe pneumonia, sepsis with shock, acute respiratory distress syndrome, or encephalitis and even fatal outcomes have been reported.

Hospital-based surveillance is considered to be an important setting for identifying sporadic human infections with avian influenza virus. It should be noted that seasonal influenza viruses are going to circulate during the influenza season (weeks 40/2023–20/2024) and are likely to cause substantial burden with many severely-ill people requiring hospital admission. A **risk-based targeted approach,** as described below, is therefore recommended for hospitalised patients, since sub-typing of all positive type A virus detections in all hospitalised patients is **not** considered feasible or proportionate (see also www.flunewseurope.org).

To identify severe human infections with avian influenza virus in hospitalised patients during the influenza season, we propose the following approach in **areas where avian influenza is detected in animals or causing mortality in wild birds or mammals**:

- People admitted to hospitals with severe respiratory symptoms should be asked about history of exposure to birds (e.g. wild birds or poultry) or other animals (dead or alive) in the two weeks prior to onset of symptoms or admission (when the date of symptom onset is unknown);
- Specimens from hospitalised patients with very severe influenza virus infections could be considered for sub-typing, particularly if believed to be part of a nosocomial outbreak;
- Hospitalised patients with unexplained neurological symptoms, e.g. unexplained viral encephalitis/ meningoencephalitis, should be tested for seasonal influenza virus and type A virus positive specimens sub-typed. Specimens that are influenza type A positive but negative for seasonal influenza viruses should be tested and characterise for avian influenza;
- Clusters of severe respiratory infections requiring hospitalisation should be investigated and testing for avian and other influenza viruses should be considered if routine testing for respiratory pathogens is inconclusive.

In general, samples positive for influenza type A virus but negative for seasonal influenza viruses A(H1)pdm09 and A(H3), or with an unidentifiable sub-type should be sent to the national influenza reference laboratories for further analysis and H5 testing.

According to the WHO guidelines for the clinical management of severe illness from influenza virus infections [9] and the ECDC expert opinion on neuraminidase inhibitors for prevention and treatment of influenza [10], clinical specimens for testing should be collected as quickly as possible and antiviral treatment could even start before clinical diagnosis and influenza confirmation.

Virus characterisation of unsub-typeable influenza A viruses

Virus characterisation of unsub-typeable influenza A viruses to identify zoonotic influenza infections has been described in a previous document Testing and diagnosis of avian influenza (europa.eu) [3]. There are specialised laboratory techniques (often multiplex assays) targeting the avian influenza virus haemagglutinin genes to identify the avian influenza sub-type. Whole Genome or Sanger sequencing can also be used for that purpose. If a laboratory lacks the capacity to perform specific influenza A sub-type identification, it should send the specimens to a national influenza centre, WHO Collaborating Centre (WHO CC) and/or to a WHO H5 Reference Laboratory. Unsub-typeable influenza A virus specimens and positive H5 virus specimens should be shared with national influenza centres (NICs) and the WHO CC for typing and further characterisation which will include antigenic characterisation, whole genome sequencing and antiviral drug resistance testing. Positive material can include human clinical specimens, extracted RNA, virus cultures or egg allantoic fluid.

Molecular surveillance

Avian influenza specimens from detections in wild bird or mammals and from outbreaks in farmed animals are shared with the EU reference laboratory for avian influenza viruses and with World Organisation for Animal Health (WOAH) reference laboratories for virus characterisation and sequencing. Data are uploaded to GISAID to share with a wider community of animal and public health experts in order to analyse and assess the situation and evolution of the viruses.

All specimens taken from people involved in culling/cleaning activities during outbreaks or from suspected human cases testing positive for avian influenza need to be sequenced and further characterised. Information about the virus sequence should be provided to a public database (e.g. the GISAID sequence platform and/or the European Nucleotide Archive (ENA).

Emerging new reassortant viruses need to be identified as early as possible to assess the risk and implement control measures. Reassortant viruses with gene segments deriving from different species (e.g. from avian and seasonal influenza) might have the ability to readily transmit between humans and have properties for which the human population has no immunity.

Wastewater surveillance for avian influenza virus detection

During the COVID-19 pandemic, testing of wastewater for SARS-CoV-2 in different sites across regions and countries has shown promising results for identifying an increase in virus copy numbers ahead of other clinical or virological surveillance indicators and this could be useful for early adjustment of public health measures and guidance.

This approach was also applied when MPOX emerged in the EU/EEA. Wastewater surveillance has been suggested as a complement to integrated respiratory virus surveillance, also for other respiratory viruses such as seasonal influenza viruses.

Wastewater monitoring could be a potential additional system useful for the early identification of circulating avian influenza virus infections locally in an affected area with ongoing outbreaks of avian influenza. However, so far there is very limited experience and evidence of wastewater surveillance to identify low level circulation of zoonotic influenza virus infections in the population so this approach would be more on an experimental level e.g. targeted to sewage of hospitals.

Proposed time frame

This document complements the previous guidance Enhanced surveillance of severe avian influenza virus infections in hospital settings in the EU/EEA (europa.eu) for the summer period 2023 (weeks 21–39). The new document covers the seasonal epidemic period during the winter 2023/24 (weeks 40/2023–20/2024) to address the change in the epidemiological situation linked to infected wild birds following autumn bird migration, the increase in season influenza infections and the related increase in specimens required for seasonal influenza virus testing.

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 [3].

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 [11]. This includes any relevant information that may 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 be carried out 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. In addition, The European Surveillance System (TESSy) should be used for the longer-term monitoring using record type INFLZOO and INFLZOOAGGR.

The number of people tested for avian influenza viruses against H5 can be reported in an aggregate form to INFLZOOAGGR.

Clusters of severe respiratory diseases identified in healthcare settings (e.g. with similar exposure history or family cluster) and patients with atypical or unexplained neurological symptoms during the influenza season should be reported to EpiPulse.

Additional resources

Latest situation update of the avian influenza situation in the EU/EEA: Surveillance and disease data for zoonotic influenza (europa.eu)

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 Public health resource pack for countries experiencing outbreaks of influenza in animals 9789240076884-eng.pdf (who.int)

US 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.

Acknowledgements

Contributing ECDC experts: Cornelia Adlhoch, Edoardo Colzani, Ole Heuer, Angeliki Melidou, Grazina Mirinaviciute.

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