



### **GUIDES AND TOOLS**

Surveillance and targeted testing for the early detection of zoonotic influenza in humans during the winter period in the EU/EEA

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## **Summary**

This document gives recommendations to EU/EEA Member States on testing, typing and subtyping to identify zoonotic influenza virus infections in humans during the influenza season, 2024–2025 in the European Union/European Economic Area (EU/EEA). The recent detection of a human case of avian influenza A(H5N1) in Missouri, United States through the state's surveillance system for seasonal influenza emphasises the importance of influenza virus typing, subtyping and further virus characterisation.

#### Raising awareness among healthcare workers (in primary and secondary care)

- In areas where outbreaks of avian influenza in birds or mammals have occurred, there is a possibility that there
  may be human cases of zoonotic influenza infection with unknown exposure and therefore public health authorities
  should encourage laboratories and hospitals/clinicians to consider increasing testing for influenza, typing and
  subtyping.
- Raising awareness should include communicating the local epidemiological situation, including avian influenza in birds and animals, to healthcare workers (including primary care workers) in the region.
- In order not to miss or delay diagnosis of potential human zoonotic influenza cases, healthcare workers should ask patients about any symptoms compatible with zoonotic influenza infection and their history of exposure to animals, particularly in the context of any ongoing avian influenza outbreaks in birds or mammals.

#### Testing of exposed persons to infected animals with zoonotic influenza

- Persons exposed to zoonotic influenza should be monitored for 10–14 days from last day of exposure.
- If exposed individuals develop symptoms, they should self-isolate and be tested immediately.
- Asymptomatic individuals who have been exposed to zoonotic influenza may be tested on a case-by-case basis, taking into account the level of exposure and the epidemiological context.

#### Testing, typing and subtyping for influenza in hospital settings

- Patients admitted to hospital with respiratory symptoms or other symptoms compatible with avian influenza virus infection should be asked about their history of exposure to animals potentially infected with avian influenza or other sick/dead animals.
- Patients admitted to hospital due to respiratory or other influenza-related symptoms should be tested for influenza A/B infection in accordance with a clinical decision, including subtyping. Decisions on who to test and type/subtype should take into account the epidemiological situation (e.g. avian influenza outbreaks in the area) and the risk of exposure and be linked to a national risk assessment. As the avian influenza epidemiological situation is dynamic, ECDC is continuously re-assessing the risk and will update the risk assessment as necessary in the quarterly ECDC/EFSA avian influenza monitoring report.

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- It is recommended that all hospitalised patients with unexplained viral encephalitis/meningoencephalitis in whom an alternative causative agent cannot be identified should be tested for influenza virus. Isolates from patients who test positive for influenza A should then be subtyped to rule out zoonotic influenza.
- Severely ill patients with unexplained illness who have had prior animal exposure should be considered for influenza virus testing and further typing/subtyping if they test positive for influenza A.
- Clusters of severe respiratory infections requiring hospitalisation should be investigated, and patients should be tested for zoonotic influenza if routine testing/subtyping for respiratory pathogens is inconclusive, or if they test positive for influenza A which cannot be subtyped.

#### Influenza testing in specimens from sentinel ILI/ARI/SARI surveillance sources

 Ideally, all sentinel influenza-positive specimens from both primary and secondary care sentinel sources should be typed and subtyped.

#### Influenza testing in specimens from other sources (including non-sentinel)

If there are known avian influenza outbreaks in birds or mammals in the area, even in the absence of known
exposure to infected animals, laboratories/clinicians are encouraged to increase typing and subtyping of
influenza-A positive cases.

#### Wastewater surveillance

- Wastewater surveillance is currently emerging as a novel surveillance tool to detect low-level circulation of avian influenza viruses due to outbreaks in birds or mammals, with studies mainly originating from the national system in the US.
- In the EU/EEA, wastewater surveillance for influenza is currently being conducted in six EU/EEA countries (see reference 38), and additional countries have expressed interest in contributing to wastewater surveillance activities related to avian A(H5N1) influenza viruses.
- Wastewater surveillance can be used as a potential complementary system useful for the early identification of the presence of circulating avian influenza viruses in specific areas.

# **Objective of surveillance and scope of this document**

The objective of surveillance proposed here is to identify possible zoonotic influenza virus infections in a timely manner by means of targeted testing using established routine respiratory virus surveillance systems during periods of seasonal influenza circulation. This document describes a risk-based targeted approach for such surveillance. It addresses the global epidemiological situation, calls for public health authorities to raise awareness among healthcare workers (in primary and secondary care) and emphasises the challenges in identifying zoonotic influenza virus infections in humans. It gives advice on testing of individuals exposed to animals infected with zoonotic influenza, testing, typing and subtyping for influenza in hospital settings and testing of specimens from sentinel ILI/ARI/SARI surveillance and other sources. In addition, it includes ocular exposure as a potential route of transmission from animals to humans. It also sets out considerations on the use of wastewater surveillance for avian influenza in the EU/EEA.

## **Target audience**

This document is intended for public health authorities in the EU/EEA; public health professionals who work on surveillance of respiratory viruses; clinicians, who can help to raise awareness of possible human cases of avian influenza; clinical societies who provide guidance for healthcare workers, and clinics and laboratories who perform testing, particularly in hospital settings.

## **Previous guidance**

The European surveillance systems have been adapted to integrate COVID-19 and other respiratory viruses into routine monitoring of seasonal influenza viruses. Together with the World Health Organization (WHO), ECDC published operational considerations for respiratory virus surveillance in Europe in 2022 that describe how to strengthen and improve the design of surveillance systems for respiratory viruses to fulfil different surveillance objectives [1]. Furthermore, ECDC has published guidance documents on enhanced surveillance of severe avian influenza virus infections in hospital settings in the EU/EEA [2], 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 [3], and previous guidance on targeted surveillance to identify human infections with avian influenza virus during the influenza season 2023/24, EU/EEA [4]. In addition, the existing case definitions, infectious period, definition of exposure, antiviral prophylaxis and preventive measures are discussed in the ECDC case investigation protocol [5]. This document updates and complements the previous guidance documents.

# Situation with zoonotic influenza in Europe and worldwide

HPAI A(H5N1) virus of clade 2.3.4.4b has spread extensively among wild birds across the globe, leading to outbreaks in domestic birds, as well as infection in several terrestrial and marine mammals. In 2024, HPAI (H5N1) was detected for the first time in dairy cattle in the United States, resulting in an ongoing outbreak, with dairy farms affected across multiple states [6].

Sporadic cases of infection with zoonotic influenza viruses have been reported in humans worldwide. The majority of human infections with avian influenza viruses have been associated with unprotected exposure to poultry, live poultry markets, or contaminated environments. In addition, there have been recent human cases of A(H5N1) following exposure to dairy cattle infected with HPAI A(H5N1) virus. There have also been occasional detections of zoonotic influenza infections, without known exposure to infected animals or their environments, through routine surveillance systems for seasonal influenza [7,8].

Since 2020, there has been widespread circulation of highly pathogenic avian influenza (HPAI) A(H5N1) virus in wild birds in Europe, causing outbreaks in domestic poultry and, occasionally, spillovers to wild and domestic mammals, with suggested onward transmission in certain settings [9-12]. In 2024, there have been fewer detections of HPAI viruses in wild and domestic birds in Europe than in recent years, with HPAI viruses circulating at low levels. Between June and September 2024, the main category of wild birds affected were colony-breeding seabirds, resulting in the majority of detections of HPAI A(H5N1) in wild and domestic birds being located along the coastline of the Atlantic Ocean, North Sea and Baltic Sea. During the same period, there were no new detections of HPAI virus in mammals reported in Europe. However, detections of HPAI in birds may increase with the autumn migration of wild birds [13].

There have been no infections of avian influenza reported among humans in the EU/EEA, despite the extensive circulation of avian influenza in wild birds, poultry and some mammals in recent years, with frequent opportunities for human exposure. Detections of A(H5) viral particles in two Spanish workers involved in culling activities during an outbreak of avian influenza at a poultry farm were due to suspected environmental contamination rather than true infection [14].

Given the extensive circulation of avian influenza viruses in animal populations, transmission from infected animals to humans remains a rare event. To date, there has been no evidence of sustained human-to-human transmission [13].

Detections of avian A(H5N1) influenza viruses of clade 2.3.4.4b in humans causing symptomatic infections have shown variable symptoms, from mild to severe or even fatal disease course. Patients have shown symptoms of upper and lower respiratory tract infection, but also non-respiratory symptoms, such as conjunctivitis, gastrointestinal and neurological symptoms [6,15-21]. Rapid progression to severe pneumonia, sepsis with shock, acute respiratory distress syndrome, or encephalitis, and even fatal outcomes have been reported. Recent findings of encephalitis/meningoencephalitis with high viral loads in the brain samples of mammals (seals, foxes, porpoises, dolphins, black bears, etc.) infected with A(H5N1) or A(H5N8) viruses suggest the possibility of avian influenza infection in patients presenting with atypical symptoms such as encephalitis, neurological affection and unclear aetiology [3].

Further information on the epidemiological situation and avian influenza cases worldwide can be found in the 'Avian influenza overview' report, published on a quarterly basis by ECDC and the European Food Safety Authority (EFSA) [13]. Furthermore, ECDC's 'Communicable Disease Threats Report' provides regular weekly updates on human cases of zoonotic influenza worldwide [22].

Influenza A(H1) and A(H3) viruses are endemic in swine populations in Europe and globally [23], and these viruses circulate continuously in intensive production systems [24].

Zoonotic infections with influenza viruses of swine origin are referred to as variant (v) viruses. All human cases with disease onset reported so far this year have been outside of Europe. From 20 February to 23 September 2024, one human case of A(H1N1)v and four A(H1N2)v infections were detected in the US and one A(H1N1)v identified in Viet Nam, five A(H3N2)v virus infections in humans were detected in the US and one in Canada [23]. In Europe, sporadic transmission of influenza variant viruses of swine origin to humans has previously been reported [8,25-27]. For human infections with swine influenza viruses, most cases have been mild, resembling seasonal influenza, mainly presenting with fever, cough, pharyngitis, rhinorrhoea and myalgia, and only a few cases have required hospitalisation, mainly linked to other pre-existing medical conditions. A few cases have been reported with serious illness, presenting with severe acute respiratory infection and requiring extracorporeal membrane oxygenation (ECMO) [28,29].

With the extensive circulation of zoonotic influenza viruses in animal populations worldwide, sporadic transmission to humans is likely to continue in settings where people have unprotected exposure to infected animals or their environment. Monitoring and genetic characterisation is important to identify viruses with mutations or reassortments that could lead to increased transmission to and among humans.

To prevent human infections, measures should be taken to reduce the risk of human exposure to zoonotic influenza viruses (see [13,30]).

## Awareness-raising among healthcare workers

Awareness of zoonotic influenza infections among healthcare workers should be raised. With an avian influenza virus, infected people can show symptoms of upper and lower respiratory tract infection, ranging from very mild to severe. However, avian influenza infection can also present as atypical non-respiratory symptoms (e.g. conjunctivitis or neurological symptoms). Human cases may display conjunctivitis as the only symptom, or a number of different symptoms.

Raising awareness among healthcare workers (including primary care workers) should include communicating on the local epidemiological situation in the area, including the situation regarding avian influenza in birds and animals. The importance of enquiring about history of exposure to animals potentially infected with avian influenza or other sick/dead animals should be emphasised, particularly if there are ongoing avian influenza outbreaks in birds or mammals in the area, based on national risk assessment. This will ensure that diagnosis of potential human avian influenza cases is not missed or delayed. This is especially important in hospital settings, when there are cases of severe respiratory disease, or other cases involving avian-influenza-compatible symptoms.

In the context of outbreaks in birds or mammals in the area, there is a possibility of avian influenza infection with unknown exposure, and therefore public health authorities should communicate to hospitals/clinicians the importance of increasing testing, and to laboratories the need to increase typing and subtyping. As the avian influenza epidemiological situation is dynamic, ECDC is continuously re-assessing the risk and will update the risk assessment, as necessary, in the quarterly ECDC/EFSA avian influenza monitoring report [13].

## Follow-up and targeted testing of individuals exposed to animals infected with zoonotic influenza

ECDC has published an Investigation protocol for human exposures and cases of avian influenza in the EU/EEA [5], 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. This has been also discussed in the context of all zoonotic influenza viruses (including swine) in the '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' [3].

According to the case investigation protocol, people exposed to sick or dead animals and those with possible or confirmed zoonotic influenza infection (should this occur in the EU) need to be followed up by public health authorities and/or self-monitor for 10–14 days following the last exposure. If relevant symptoms consistent with avian or other zoonotic influenza virus (e.g. respiratory, gastroenteric, conjunctivitis, neurological, non-specific fever, or fatigue) are observed, immediate testing should be initiated and the individuals should self-isolate. Asymptomatic individuals who have been exposed may be tested on a case-by-case basis, taking into account the level of exposure and the epidemiological situation.

In the event of suspected zoonotic influenza virus exposure and possible infection, testing should first be carried out for influenza viruses A and B, with sub-typing of influenza type A positive specimens. Those specimens that are influenza type A positive, but negative for seasonal influenza viruses should be sent to national influenza centres (NIC) for zoonotic influenza sub-typing and virus characterisation, including sequencing. Positive zoonotic influenza cases should also be sent to the NIC for confirmation.

In certain settings, people may not be aware of the presence of avian influenza in sick or dead animals and therefore they might be less likely to wear personal protective equipment. Such settings need to be assessed to determine whether there has been confirmation of avian influenza virus in the animals, and the likely level of exposure. These 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.

Examples of populations at risk of being occupationally or recreationally exposed to avian or swine influenza virus scan be found in the previous 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' [3]. It would be good practice to test people with occupational exposure to swine who develop respiratory symptoms during the influenza season (including typing/subtyping) in order to rule out seasonal, swine or other zoonotic influenza infections. Seasonal influenza vaccination is not expected to protect against zoonotic influenza infections, however, seasonal vaccination can be recommended to those who may be occupationally exposed to zoonotic influenza, in accordance with national guidelines, to reduce the possibility of reassortment.

It should be noted that in the event of a potential swine influenza infection, PCR subtyping assays might indicate A(H1) or A(H3) swine influenza virus detection as a seasonal A(H1)pdm09 or A(H3) infection, respectively, and therefore sequencing would be required to distinguish between seasonal and swine influenza viruses. More information on testing and detection of zoonotic influenza virus infections in humans in the EU/EEA can be found in the previously published document [3].

# Surveillance of avian or other zoonotic influenza in humans during the winter season

#### Recommendations

- Specimens that are positive for influenza type A, but negative for seasonal influenza viruses should be sent to the national influenza reference laboratory, sub-typed for zoonotic influenza (including A(H5)) and, if zoonotic influenza is confirmed, characterised (including sequencing).
- Ideally, all sentinel influenza-positive specimens from both primary and secondary care sources should be typed and subtyped.
- If there are zoonotic influenza outbreaks in animals in the area, even in the absence of known exposure to infected animals, laboratories/clinicians are encouraged to decrease the threshold for testing and increase typing and subtyping of influenza-A positive cases.

The sections below outline the proposed approach for the different surveillance sectors to facilitate the early detection of avian influenza virus infections. This approach would also be applicable for other zoonotic influenza viruses. To identify sporadic human infections with avian influenza virus, without overburdening healthcare and diagnostic laboratories during the influenza season, a targeted, risk-based approach is proposed, focussing on areas where outbreaks of avian influenza in birds or detections in mammals have been reported.

## Hospital surveillance for severe human avian or other zoonotic influenza virus infections

The hospital 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 expected to circulate during the influenza season and will probably cause a substantial burden, with many severely-ill people requiring hospital admission. A targeted, risk-based approach, as described below, is therefore recommended for hospitalised patients with relevant symptoms, where it is not feasible or proportionate to sub-type all positive type A virus detections in all patients, irrespective of the epidemiological situation.

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 has been detected in animals:

- People admitted to hospitals with respiratory or other influenza-related symptoms should be asked about their history of exposure to animals potentially infected with avian influenza or other sick/dead animals in the two weeks prior to onset of symptoms or (when the date of symptom onset is unknown) before admission. The history of exposure and the epidemiological situation can be taken into account when deciding which positive flu samples to further (sub)type.
- Potential routes of exposure, other than respiratory, should also be taken into consideration (e.g. ocular).
- Patients admitted to hospital due to respiratory or other influenza-related symptoms should be tested for influenza A/B infection, in accordance with a clinical decision, including subtyping of specimens, either on site or through referral to NIC. Decisions on who to test and type/subtype should take into account the epidemiological situation (e.g. avian influenza outbreaks in the area), and the risk of exposure to infected animals or their environment.
- Severely-ill patients with unexplained illness who have had prior animal exposure should be considered for zoonotic influenza virus testing.
- Hospitalised patients with unexplained neurological symptoms (e.g. viral meningitis/encephalitis/meningoencephalitis or multi-organ failure) in whom an alternative agent could not be identified should be tested for seasonal influenza virus and type-A-virus-positive specimens should be subtyped, either onsite or through referral to NIC.
- Unusual clusters of severe respiratory infections requiring hospitalisation (e.g. with atypical clinical
  presentation, inconclusive testing results, patient demographics) should be investigated and tested for
  avian/zoonotic influenza if routine testing for respiratory pathogens is inconclusive (including influenza A
  subtyping).
- Specimens that are positive for influenza type A, but negative for seasonal influenza viruses should be sent to the national influenza reference laboratory and sub-typed for zoonotic influenza. If positive, they should be further characterised, including sequencing.

According to WHO's 'Guidelines for the clinical management of severe illness from influenza virus infections' [31] and ECDC's 'Expert opinion on neuraminidase inhibitors for prevention and treatment of influenza' [32], clinical specimens for testing should be collected as quickly as possible and antiviral treatment can even be started before clinical diagnosis and influenza confirmation.

### **Cluster identification through event-based surveillance**

Event-based surveillance plays an important role in the early detection of events related to communicable diseases, complementing traditional indicator-based surveillance systems. Formal and informal reporting of, and/or monitoring (e.g. through media reports) for unusual clusters of respiratory infection, or other events indicative of avian or other zoonotic 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 the Event Information Site of the International Health Regulations (IHR 2005), as well as screening of publicly-available information. Member States should use these channels to inform the international community and institutes of any unusual infectious disease events or clusters.

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).

## Testing, typing and subtyping to identify zoonotic influenza cases in specimens from sentinel and non-sentinel sources

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 unusual severe respiratory infection clusters in healthcare settings, is an important tool for early signal detection.

Existing sentinel surveillance systems for acute respiratory infection (ARI) or influenza-like illness (ILI) in the EU/EEA provide a basis for monitoring human 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 [33]. This testing includes sub-typing/lineage determination, viral characterisation and antiviral resistance. For the season 2023/24, EU/EEA countries reported that around 106 000 specimens were tested in sentinel systems and 2 040 000 specimens in non-sentinel systems, underlining the large number of tests performed across routine healthcare systems for seasonal influenza virus.

Ideally, all sentinel influenza-positive specimens from both primary and secondary care sources should be typed and subtyped. According to the 'Activity section' of <u>ERVISS</u> [34], most of the sentinel specimens testing positive for influenza type A viruses are sub-typed (A(H1N1)pdm09 or A(H3N2). Influenza type A virus detections that are negative for A(H1N1)pdm09 or A(H3N2) in sentinel specimens should always be further analysed as they could be identified as sporadic human infections with zoonotic influenza viruses. It is worth noting that the Netherlands recently detected human infections with Eurasian avian-like swine influenza virus A(H1) through routine respiratory surveillance systems [35].

Influenza virus testing in samples from non-sentinel sources is largely conducted in primary care or hospital diagnostic laboratories. Most of the 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 on sub-types or lineages (see <u>erviss.org</u>). There will generally be no additional sub-typing of non-sentinel specimens, and therefore possible human infections with zoonotic viruses might remain undetected. If there are known avian influenza outbreaks in birds or mammals in the area, even in the absence of known exposure to infected animals, laboratories/clinicians are encouraged to increase typing and subtyping of influenza-A positive cases in a subset of specimens from non-sentinel sources.

Clinical assessment, based on clinical symptoms and suspicion of exposure to possibly infected animals in an affected geographical area, remains the most important factor for initiating testing of patients with respiratory symptoms.

More information on testing and detection of zoonotic influenza can be found in the previous guidance [3].

## **Confirmation of zoonotic influenza cases and further characterisation**

Virus characterisation of un-subtypeable influenza A viruses to identify zoonotic influenza infections has been described in a previous document [3]. There are specialised laboratory techniques (often multiplex assays) targeting the avian influenza virus haemagglutinin genes to identify the avian/zoonotic influenza sub-type. Whole Genome or Sanger sequencing can also be used for this 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 (NIC) that will share them with the WHO Collaborating Centre (WHO CC) and/or the WHO H5 Reference Laboratory. Specimens that are positive for zoonotic influenza should also be sent to the NIC/NRL for confirmation. Unsub-typeable influenza A virus specimens and positive A(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 for identifying potential mammalian adaptation or other significant mutations increasing the zoonotic potential of the virus, and monitoring of antiviral drug susceptibility.

Positive material can include human clinical specimens, extracted RNA, virus cultures or egg allantoic fluid. Sequence data should be uploaded to GISAID sequence platform and/or the European Nucleotide Archive (ENA) 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 avian/zoonotic influenza-positive specimens should be sequenced and sequences submitted as soon as possible to GISAID, ENA and/or other public databases. It should be noted that sequencing may also be necessary to differentiate between seasonal A(H1)pdm09 and swine A(H1) influenza viruses in A(H1)-positive specimens from patients with known exposure to potentially infected swine. For more information on testing and detection of swine influenza viruses please refer to our previous 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' [3].

Emerging new reassortant viruses or evolved human-adapted zoonotic influenza viruses that may have the ability to transmit between humans and properties for which the human population has no immunity (e.g. HA and NA segments originating from animal influenza viruses) need to be identified as quickly as possible to assess the risk and implement control measures.

### Wastewater surveillance for avian influenza virus detection

Wastewater surveillance is currently emerging as a novel surveillance tool to detect low-level circulation of avian influenza viruses due to outbreaks in birds or mammals, with studies mainly originating from the US national system [36-38]. According to the latest JRC Monthly Bulletin, wastewater surveillance for influenza is currently being conducted in six EU/EEA countries, and additional countries have expressed an interest in contributing to wastewater surveillance activities for A(H5N1) [39]. Wastewater monitoring can be a potential valuable complementary system which is useful for the early identification of circulating avian influenza viruses in an affected area with ongoing outbreaks of avian influenza. However, it will not be possible to distinguish between human and animal avian influenza virus infections. Detection of A(H5) in wastewater could therefore be an indicator of infection in animals resulting from animal-related inputs from farm waste, plants processing animal products or wild birds [38]. As a result, the sampling source needs to be well-defined and well-understood (e.g. land-use, input sources that each WW plant receives, environmental factors), and results need to be interpreted with caution. Wastewater surveillance has been implemented in some countries to complement routine respiratory virus surveillance, including human respiratory viruses such as seasonal influenza viruses and SARS-CoV-2, and could possibly be used for early adjustment of public health measures and guidance. It should be noted that most wastewater surveillance systems currently lack the ability to differentiate between seasonal and zoonotic influenza A viruses. During the upcoming influenza season, when seasonal influenza A viruses are expected to be in high circulation, interpretation of wastewater surveillance results will be challenging.

As part of the European Commission's pandemic preparedness efforts, the Health Emergency Preparedness and Response Authority (HERA) is working on wastewater surveillance for public health in cooperation with the European Commission's Joint Research Centre (JRC) through two initiatives, the EU Wastewater Observatory for Public Health and the Global Consortium for Wastewater and Environmental Surveillance for Public Health (GLOWACON). In addition, the Joint Action EU-WISH (EU-Wastewater Integrated Surveillance for Public Health) has also been set up to work towards implementation of wastewater surveillance for public health in the EU/EEA. [39]

## **Reporting of data**

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[40]. 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 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, for detections of avian influenza A viruses in wastewater, and for sharing epidemiological situation updates with EWRS. In addition, The European Surveillance System (TESSy) should be used for routine reporting of surveillance data for seasonal influenza and TESSy record types INFLZOO/INFLZOOAGGR should be used for the reporting of zoonotic influenza.

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.

## Link to additional resources

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

Annual Epidemiological Reports: <u>Annual Epidemiological Reports on avian influenza (europa.eu)</u> ECDC webpages: <u>Avian influenza (europa.eu)</u>

Considerations for infection prevention and control practices in relation to respiratory viral infections in healthcare settings (europa.eu)

Editorial on avian influenza in Eurosurveillance – May 2023: <u>Avian influenza, new aspects of an old threat</u> Preparedness information for avian influenza: <u>Preparedness information for avian influenza (europa.eu)</u>

WHO public health resource pack for countries experiencing outbreaks of influenza in animals <u>9789240076884-eng.pdf (who.int)</u>

US CDC 'Investigate an Outbreak': <u>Investigate an Outbreak | Unexplained Respiratory Disease Outbreaks (URDO) |</u> <u>CDC</u>

Epipulse: EpiPulse - the European surveillance portal for infectious diseases (europa.eu) TESSy: <u>The European Surveillance System</u>.

## **Acknowledgements**

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## References

- European Centre for Disease Prevention and Control (ECDC)/World Health Organization Regional Office for Europe (WHO/Europe). Operational considerations for respiratory virus surveillance in Europe. Stockholm: ECDC; 2022. Available at: <u>https://www.ecdc.europa.eu/en/publications-data/operational-considerationsrespiratory-virus-surveillance-europe</u> [Accessed: 1 Sep 2024]
- European Centre for Disease Prevention and Control (ECDC). Enhanced surveillance of severe avian influenza virus infections in hospital settings in the EU/EEA. Stockholm: ECDC; 2023. Available at: <u>https://www.ecdc.europa.eu/en/publications-data/enhanced-surveillance-severe-avian-influenza-virusinfections-hospital-settings</u> [Accessed: 2 October 2024]
- European Centre for Disease Prevention and Control (ECDC). 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. Stockholm: ECDC; 2022. Available at: <u>https://www.ecdc.europa.eu/en/publications-data/zoonotic-influenzavirus-infections-humans-testing-and-detection</u> [Accessed: 2 October 2024]
- European Centre for Disease Prevention and Control (ECDC). Targeted surveillance to identify human infections with avian influenza virus during the influenza season 2023/24, EU/EEA. Stockholm: ECDC; 2023. Available at: <u>https://www.ecdc.europa.eu/en/publications-data/avian-influenza-infections-surveillance-eu-eea</u> [Accessed: 2 October 2024]
- European Centre for Disease Prevention and Control (ECDC). Investigation protocol of human cases of avian influenza virus infections in EU/EEA. Stockholm: ECDC; 2023. Available at: <u>https://www.ecdc.europa.eu/en/publications-data/avian-influenza-investigation-protocol-human-cases</u> [Accessed: 2 October 2024]
- Webby RJ, Uyeki TM. An Update on Highly Pathogenic Avian Influenza A(H5N1) Virus, Clade 2.3.4.4b. J Infect Dis. 2024 Sep 23;230(3):533-42. Available at: <u>https://www.ncbi.nlm.nih.gov/pubmed/39283944</u>
- US Centers for Disease Control and Prevention (US CDC). CDC Confirms Human H5 Bird Flu case in Missouri. Atlanta: CDC; 2024. Available at: <u>https://www.cdc.gov/media/releases/2024/s0906-birdflu-case-missouri.html</u> [Accessed: 4 October 2024]
- 8. Cogdale J, Kele B, Myers R, Harvey R, Lofts A, Mikaiel T, et al. A case of swine influenza A(H1N2)v in England, November 2023. Euro Surveill. 2024 Jan;29(3)
- European Food Safety Authority (EFSA), European Centre for Disease Prevention Control (ECDC), European Union Reference Laboratory for Avian Influenza, Fusaro A, Gonzales JL, Kuiken T, et al. Avian influenza overview December 2023–March 2024. EFSA Journal. 2024;22(3):e8754. Available at: <u>https://efsa.onlinelibrary.wiley.com/doi/abs/10.2903/j.efsa.2024.8754</u>
- 10. Agüero M, Monne I, Sánchez A, Zecchin B, Fusaro A, Ruano MJ, et al. Highly pathogenic avian influenza A(H5N1) virus infection in farmed minks, Spain, October 2022. Eurosurveillance. 2023;28(3):2300001. Available at: <a href="https://www.eurosurveillance.org/content/10.2807/1560-7917.ES.2023.28.3.2300001">https://www.eurosurveillance.org/content/10.2807/1560-7917.ES.2023.28.3.2300001</a>
- Lindh E, Lounela H, Ikonen N, Kantala T, Savolainen-Kopra C, Kauppinen A, et al. Highly pathogenic avian influenza A(H5N1) virus infection on multiple fur farms in the South and Central Ostrobothnia regions of Finland, July 2023. Eurosurveillance. 2023;28(31):2300400. Available at: https://www.eurosurveillance.org/content/10.2807/1560-7917.ES.2023.28.31.2300400
- 12. Domańska-Blicharz K, Świętoń E, Świątalska A, Monne I, Fusaro A, Tarasiuk K, et al. Outbreak of highly pathogenic avian influenza A(H5N1) clade 2.3.4.4b virus in cats, Poland, June to July 2023. Eurosurveillance. 2023;28(31):2300366. Available at: <u>https://www.eurosurveillance.org/content/10.2807/1560-7917.ES.2023.28.31.2300366</u>
- 13. European Food Safety Authority (EFSA), European Centre for Disease Prevention and Control (ECDC), European Union Reference Laboratory for Avian Influenza, Alexakis L, Buczkowski H, Ducatez M, et al. Avian influenza overview June–September 2024. European Food Safety Agency Journal. 2024. Available at: <u>https://www.ecdc.europa.eu/en/publications-data/avian-influenza-overview-june-september-2024</u>
- Aznar E, Casas I, González Praetorius A, Ruano Ramos MJ, Pozo F, Sierra Moros MJ, et al. Influenza A(H5N1) detection in two asymptomatic poultry farm workers in Spain, September to October 2022: suspected environmental contamination. Eurosurveillance. 2023;28(8):2300107. Available at: <u>https://www.eurosurveillance.org/content/10.2807/1560-7917.ES.2023.28.8.2300107</u>
- World Health Organization (WHO). Human infection caused by avian influenza A(H5) Ecuador. Geneva: WHO; 2023. Available at: <u>https://www.who.int/emergencies/disease-outbreak-news/item/2023-DON434</u> [Accessed: 2 October 2024]
- World Health Organization (WHO). Human Infection caused by Avian Influenza A (H5N1) Chile. Geneva: WHO; 2023. Available at: <u>https://www.who.int/emergencies/disease-outbreak-news/item/2023-DON461</u> [Accessed: 2 October 2024]
- Uyeki TM, Milton S, Abdul Hamid C, Reinoso Webb C, Presley SM, Shetty V, et al. Highly Pathogenic Avian Influenza A(H5N1) Virus Infection in a Dairy Farm Worker. N Engl J Med. 2024;390(21):2028-9. Available at: <u>https://www.nejm.org/doi/full/10.1056/NEJMc2405371</u>

- US Centers for Disease Control and Prevention (US CDC). CDC A(H5N1) Bird Flu Response Update September 13, 2024. Atlanta: CDC; 2024. Available at: <u>https://www.cdc.gov/bird-flu/spotlights/h5n1-response-09132024.html</u> [Accessed: 4 October 2024]
- 19. The Government of the Hong Kong Special Administrative Region. CHP closely monitors human case of avian influenza A(H5N1) in Mainland. Hong Kong: CHP; 2022. Available at: https://www.info.gov.hk/gia/general/202211/30/P2022113000354.htm [Accessed: 8 Oct 2024]
- 20. Pulit-Penaloza JA, Brock N, Belser JA, Sun X, Pappas C, Kieran TJ, et al. Highly pathogenic avian influenza A(H5N1) virus of clade 2.3.4.4b isolated from a human case in Chile causes fatal disease and transmits between co-housed ferrets. Emerg Microbes Infect. 2024 Dec;13(1):2332667.
- 21. Drehoff CC, White EB, Frutos AM, Stringer G, Burakoff A, Comstock N, et al. Cluster of Influenza A(H5) Cases Associated with Poultry Exposure at Two Facilities - Colorado, July 2024. MMWR Morb Mortal Wkly Rep. 2024 Aug 29;73(34):734-9.
- 22. European Centre for Disease Prevention and Control (ECDC). Weekly threats reports (CDTR) Communicable disease threats reports Stockholm: ECDC; 2024. Available at: <u>https://www.ecdc.europa.eu/en/publications-and-data/monitoring/weekly-threats-reports</u> [Accessed: 2 October 2024]
- 23. World Health Organization (WHO). Genetic and antigenic characteristics of zoonotic influenza A viruses and development of candidate vaccine viruses for pandemic preparedness Geneva: WHO; 2024. Available at: <a href="https://cdn.who.int/media/docs/default-source/vcm-southern-hemisphere-recommendation-2025/202409">https://cdn.who.int/media/docs/default-source/vcm-southern-hemisphere-recommendation-2025/202409</a> zoonotic recommendations final.pdf?sfvrsn=20be903a 3 [Accessed: 3 October 2024]
- 24. Lagan P, Hamil M, Cull S, Hanrahan A, Wregor RM, Lemon K. Swine influenza A virus infection dynamics and evolution in intensive pig production systems. Virus Evolution. 2024;10(1) Available at: <u>https://doi.org/10.1093/ve/veae017</u>
- 25. Parys A, Vandoorn E, King J, Graaf A, Pohlmann A, Beer M, et al. Human Infection with Eurasian Avian-Like Swine Influenza A(H1N1) Virus, the Netherlands, September 2019. Emerg Infect Dis. 2021 Mar;27(3):939-43.
- 26. World Health Organization (WHO). Influenza A H1N1 Germany. Geneva: WHO; 2022. Available at: <u>https://www.who.int/emergencies/disease-outbreak-news/item/2022-DON384</u> [Accessed: 3 October 2024]
- 27. World Health Organization (WHO). Influenza A(H1N1) variant virus Spain. Geneva: WHO; 2024. Available at: <u>https://www.who.int/emergencies/disease-outbreak-news/item/2024-DON503</u> [Accessed: 3 October 2024]
- Fraaij PLA, Wildschut ED, Houmes RJ, Swaan CM, Hoebe CJ, de Jonge HCC, et al. Severe acute respiratory infection caused by swine influenza virus in a child necessitating extracorporeal membrane oxygenation (ECMO), the Netherlands, October 2016. Eurosurveillance. 2016;21(48):30416. Available at: <u>https://www.eurosurveillance.org/content/10.2807/1560-7917.ES.2016.21.48.30416</u>
- 29. Adlhoch C, Penttinen P. Letter to the editor: Just a coincidence? Two severe human cases due to swine influenza (SIV) A(H1N1)v in Europe, October 2016. Eurosurveillance. 2017;22(10):30478. Available at: <a href="https://www.eurosurveillance.org/content/10.2807/1560-7917.ES.2017.22.10.30478">https://www.eurosurveillance.org/content/10.2807/1560-7917.ES.2017.22.10.30478</a>
- European Food Safety Authority (EFSA), European Centre for Disease Prevention and Control (ECDC), Melidou A, Enkirch T, Willgert K, et al. Drivers for a pandemic due to avian influenza and options for One Health mitigation measures. EFSA Journal. 2024;22(4):e8735. Available at: <u>https://efsa.onlinelibrary.wiley.com/doi/abs/10.2903/j.efsa.2024.8735</u>
- 31. World Health Organization (WHO). Guidelines for the clinical management of severe illness from influenza virus infections. Geneva: WHO; 2022. Available at: <a href="https://iris.who.int/handle/10665/352453">https://iris.who.int/handle/10665/352453</a>
- 32. European Centre for Disease Prevention and Control (ECDC). Expert Opinion on neuraminidase inhibitors for prevention and treatment of influenza (Feb 2016). Stockholm: ECDC; 2016. Available at: <a href="https://www.ecdc.europa.eu/en/publications-data/expert-opinion-neuraminidase-inhibitors-prevention-and-treatment-influenza-feb">https://www.ecdc.europa.eu/en/publications-data/expert-opinion-neuraminidase-inhibitors-prevention-and-treatment-influenza-feb</a>
- 33. European Commission. Commission Implementing Decision (EU) 2018/945 of 22 June 2018 on the communicable diseases and related special health issues to be covered by epidemiological surveillance as well as relevant case definitions. Official Journal of the European Union: 6 July 2018;L 170/1. Available at: <a href="https://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:32018D0945">https://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:32018D0945</a>
- 34. European Centre for Disease Prevention and Control (ECDC). The European Respiratory Virus Surveillance Summary (ERVISS). Stockholm: ECDC; 2024. Available at: <u>https://erviss.org/</u> [Accessed: 21 Aug 2024]
- 35. Eggink D, van den Brink S, Dingemans J, van der Vries E, Fouchier R, Kroneman A, et al. Human infections with Eurasian Avian-like swine influenza virus A(H1) in The Netherlands coincidentally detected in routine respiratory surveillance systems. In: Siebenga JJ, van Gennip E, Vriens R, editors. Paradigm Shifts for Global One Health Book of Abstracts. Wageningen: Wageningen University & Research; 2024. p. 49-.
- Adams C, Bias M, Welsh RM, Webb J, Reese H, Delgado S, et al. The National Wastewater Surveillance System (NWSS): From inception to widespread coverage, 2020–2022, United States. Sci Total Environ. 2024 2024/05/10/;924:171566. Available at: https://www.sciencedirect.com/science/article/pii/S0048969724017078
- 37. Wolfe MK, Duong D, Shelden B, Chan EMG, Chan-Herur V, Hilton S, et al. Detection of Hemagglutinin H5 Influenza A Virus Sequence in Municipal Wastewater Solids at Wastewater Treatment Plants with Increases in

Influenza A in Spring, 2024. Environmental Science & Technology Letters. 2024 2024/06/11;11(6):526-32. Available at: <u>https://doi.org/10.1021/acs.estlett.4c00331</u>

- Louis S, Mark-Carew M, Biggerstaff M, Yoder J, Boehm AB, Wolfe MK, et al. Wastewater Surveillance for Influenza A Virus and H5 Subtype Concurrent with the Highly Pathogenic Avian Influenza A(H5N1) Virus Outbreak in Cattle and Poultry and Associated Human Cases - United States, May 12-July 13, 2024. MMWR Morb Mortal Wkly Rep. 2024 Sep 19;73(37):804-9. Available at: <a href="https://www.ncbi.nlm.nih.gov/pubmed/39298357">https://www.ncbi.nlm.nih.gov/pubmed/39298357</a>
- European Commission Joint Research Centre (JRC) EU Wastewater Observatory for Public Health. Ispra: EU; 2024. Available at: <u>https://wastewater-observatory.jrc.ec.europa.eu/media/bulletin\_files/08\_Sep\_2024\_Bulletin\_120924\_cXebnL4.pdf</u> [Accessed: 2 October 2024]
- European Parliament/Council of the European Union. Regulation (EU) 2022/2371 of the European Parliament and of the Council of 23 November 2022 on serious cross-border threats to health and repealing Decision No 1082/2013/EU. Brussels: European Parliament and Council of the European Union; 2022. Available at: <u>http://data.europa.eu/eli/reg/2022/2371/oj</u> [Accessed: 2 October 2024]