


GUIDANCE



# Investigation protocol for human exposures and cases of avian influenza in the EU/EEA

2023

**ECDC TECHNICAL REPORT**

# **Investigation protocol for human exposures and cases of avian influenza in the EU/EEA**



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## Abbreviations

AAR	After action review
AIV	Avian influenza virus
ARI	Acute respiratory infection
BSL	Biosafety level
Ct	Cycle threshold value
EC	European Commission
EFSA	European Food Safety Authority
ENA	European Nucleotide Archive
EU-OSHA	European Agency for Safety and Health at Work
EURL	European Union Reference Laboratories
ERLInet	European Reference Laboratory for influenza network
EWRS	Early Warning Reporting System
EpiPulse	European surveillance portal for infectious diseases
FFP	Filtering face piece
GISAID	Global Initiative on Sharing All Influenza Data
GISRS	Global Influenza Surveillance and Response System
ILI	Influenza-like illness
IPC	Infection prevention and control
LRT	Lower respiratory tract
NITAG	National Immunisation Technical Advisory Groups
OSH	Occupational safety and health
PEP	Post-exposure prophylaxis
PPE	Personal protective equipment
RT-PCR	Reverse transcriptase- polymerase chain reaction
RADT	Rapid antigen detection test
SARI	Severe acute respiratory infection
TESSy	The European Surveillance System
URI	Upper respiratory tract infection
UTM	Universal transport medium
URT	Upper respiratory tract
VTM	Viral transport medium
WGS	Whole genome sequencing
WHO	World Health Organization

## Summary

This protocol 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. It is based on what is known from the animal-to-human and (non-sustained) human-to-human transmission events observed previously. In this protocol we recommend a **precautionary approach** for managing potential, possible or confirmed cases and their contacts.

## Guidance for individuals exposed to infected animals

- Individuals who are occupationally or otherwise exposed to birds or mammals infected with avian influenza virus (AIV) while taking appropriate preventive precautions (such as appropriately using personal protective equipment (PPE)) should monitor their symptoms for a minimum of 10 and up to 14 days after the last exposure and test if they develop symptoms. Testing of asymptomatic exposed individuals should be considered on a case-by-case basis according to the level of exposure.
- Given the uncertainties related to mammal-to-mammal transmission, individuals who have been exposed to infected mammals while unprotected (e.g. pets in the household) should ideally get tested as soon as possible, as a precautionary measure.
- **Antivirals** should be considered as post-exposure prophylaxis for individuals exposed to infected animals.

## Management of human cases

- Human avian influenza cases should **self-isolate** for 14 days but may cease isolation earlier if symptoms resolve and they have two consecutive negative RT-PCR tests after Days 7–8.
- **Antivirals** should be considered early for treatment of patients with confirmed AIV infection.

## Guidance for individuals exposed to human cases<sup>1</sup>

- Contact tracing and contact management should be coordinated by public health authorities.
- No contact tracing activities need to be initiated for **contacts of potential cases** (i.e. those exposed to infected animals without protection, but with no symptoms or laboratory confirmation yet) before test results are available.
- **Contacts of probable human avian influenza cases** should be identified and actively monitored for symptoms for 10–14 days, even before the test result of the index case becomes available. If any of the contacts develop symptoms, they should self-isolate and get tested. If the index case is negative and AIV infection is ruled out, then contact tracing activities can end.
- **Contacts of confirmed human avian influenza cases** are of particular concern and any potential human-to-human transmission needs to be monitored and studied closely due to the potential increase of pandemic risk. Close contacts of confirmed human cases should be advised to remain at home for 14 days from the last known exposure (self-quarantine) and be tested as soon as possible, so that further contact tracing can commence. If the contacts develop symptoms, they should be retested and self-isolate.
- **Antivirals** should be considered as post-exposure prophylaxis for individuals exposed confirmed human cases.

## Data sharing, preventive measures and risk communication

- All avian influenza viruses from human cases should be sequenced and the sequences should be shared in public databases as soon as possible (e.g. Global Initiative on Sharing All Influenza Data (GISAID), European Nucleotide Archive (ENA)).
- Clinical specimens from human cases should be sent to the National Influenza Centre/National Reference Laboratory for Influenza in each country and to the World Health Organization (WHO) Collaborating Centre for further characterisation.
- Laboratory-confirmed cases need to be **reported** to WHO under the International Health Regulations (IHR) (2005) and according to EU regulations, they are notifiable to the Early Warning Reporting System (EWRS), EpiPulse and the European Surveillance System (TESSy).
- Strong collaboration between animal and human sectors and involvement of authorities for occupational safety and health (in settings where workers are involved) is paramount for an effective case investigation and response to a zoonotic event such as a case of avian influenza in humans.

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<sup>1</sup> For case definitions, see pages 8 and 9.

- Individuals who are occupationally exposed to animals infected with avian influenza can be offered **vaccination against seasonal influenza** to minimise the risk of reassortment between avian and human seasonal influenza strains. National Immunisation Technical Advisory Groups (NITAGs) can be consulted for specific vaccination recommendations.
- Other **preventive measures** should focus on minimising exposure, ensuring correct use of appropriate PPE and hygiene measures, reducing environmental contamination and enhancing biosafety and biosecurity measures, as necessary.
- Public health authorities should communicate about the risk to the public and raise awareness of the possibility of human infection by avian influenza. In collaboration with occupational safety authorities, they should also raise awareness among employers concerning safety procedures on farms.

## Scope of this document

This protocol outlines the key steps for case investigation in response to human cases of AIV infection in the European Union and European Economic Area (EU/EEA). It provides guidance for case detection, investigation of other potential cases, testing, contact tracing, case reporting and notification, risk communication and preventive measures. The objective of this document is to provide guidance for the investigation and control of a potential avian influenza outbreak in humans. Investigation findings can be used to inform risk assessments.

This protocol aims to complement ECDC's document '[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]. It also builds on other relevant documents previously published by ECDC [2,3]. WHO, the US Centers for Disease Control (US CDC) and national authorities (e.g. in the United Kingdom (UK)) have also published protocols for investigation of human cases of zoonotic influenza and other respiratory virus infections [4-12].

## Target audience

This protocol provides guidance on how public health authorities in EU/EEA countries can investigate and respond to potential, probable and confirmed human cases of avian influenza. It is intended as a reference for public health authorities in human sectors dealing with surveillance of respiratory viruses. It aims to provide guidance for case investigation, contact tracing and management of individuals – including healthcare workers – who have had contact with human cases of avian influenza and preventive measures.

## Background and actions during a case investigation

Timely case investigation and contact tracing are critical parts of an effective response to an avian influenza case in humans. These inform actions to reduce morbidity and mortality, as well as to prevent transmission between people. Thorough investigations will identify presumptive transmission events from animals to people and the likely source of infection, determine the most likely modes of transmission and identify risk factors associated with transmission and development of disease. The findings of case investigations are essential for risk assessment and implementation of appropriate control measures to stop further transmission. They also inform a wider assessment of the pandemic risk. Timely sharing of information in a One Health approach is crucial and a strong collaboration between the human health sector (including occupational health) and the animal health sector is paramount for any investigation.

This protocol is based on what is known from the instances of animal-to-human and (non-sustained) human-to-human transmission observed previously. In this document, we recommend a **precautionary approach** for events involving human exposure to infected animals, recognising that this may need to be adapted when more information becomes available. Preventive measures and risk communication are also described.

Case investigation objectives and associated actions can include the following:

- Determining who was infected (potentially or confirmed), what they were infected with, and when this happened.
- Contact identification and management: identifying and tracing contacts, recommending self-quarantine and following up contacts.
- Identifying the source of infection (human, animal and/or environmental sources).
- Identifying the most probable modes of transmission.
- Determining other key epidemiological and clinical characteristics of cases, as well as virological characteristics.
- Communication, collaboration, and data sharing:
  - timely sharing of findings and exchange of information to facilitate decision-making at the local and national levels;
  - timely sharing of findings at the international level, including exchange of information and sharing of virus sequences.
- Risk assessment: using investigation findings to assess the risk and advise on public health measures.



## Categorising the exposure

Transmission of AIV to humans is a rare event and the human cases reported until now have been sporadic [13,14]. As extensively discussed in ECDC's document '[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], infections can occur through a variety of transmission routes and exposures, including:

- direct or close contact with infected animals or their body fluids, tissues or droppings;
- ingestion and inhalation of aerosolised virus; or
- exposure to a contaminated environment.

Nevertheless, it should be emphasised that the avian influenza viruses currently circulating in birds in Europe do not easily transmit from infected birds or animals to humans. Therefore, not all exposures, even if unprotected and at a high level, will automatically lead to human infection. On the contrary, infection is expected to remain a rare event unless there are significant changes to the virus receptor binding properties and adaptation to humans.

The likelihood of infection with AIV varies according to the duration and type of interaction between the human and infected animal, but also includes other factors related to the virus and the host. Other aspects that can have an impact on the likelihood of infection include technical and organisational protective measures in workplaces, the level of personal protection, the viral load in the area of exposure and the infectious dose. There are uncertainties in relation to the infectious dose, actual duration of exposure, distance from the source and other environmental, virological and host characteristics (e.g. genetics) that can affect the likelihood of infection by AIV. Some studies have indicated that detection of viral RNA in respiratory specimens from a person may not necessarily indicate a true AIV infection [15].

To categorise the level of exposure to AIV, the nature and extent of the contact with the infectious agent should be taken into account (based on an assessment of the duration, type, and location of the exposure), the specific activities involved, the viral load received and the animal species encountered. As the level of exposure is likely to vary according to different situations, activities and environmental conditions, it needs to be assessed on a case-by-case basis, as described in Table 1. The following categorisation is suggested to identify individuals with a moderate/high level of exposure to infected animals or human cases, in order to monitor their health and direct public health measures accordingly. Considerations to be taken into account for the identification of potential human cases of avian influenza, according to the different settings and the population groups at risk of infection, can be found in ECDC's document '[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].

## Exposure to infected animals

### Exposure levels, according to activity/occupation and level of protection

**High level of exposure:** the exposure level may be high if an individual has direct or indirect contact with an infected animal, their secretions or their environment (e.g. dust) without following the appropriate technical and organisational protective measures (as outlined in detail in the section 'Implementation of preventive measures'), without using PPE or without properly using PPE<sup>2</sup> [16,17]. Such activities include slaughtering, butchering, and handling sick animals and may be most common in occupations such as veterinarians, workers with close occupational exposure to animals, individuals involved in the cleaning of affected premises after culling operations or cleaning areas contaminated with animal faeces or secretions (e.g. during clean-up and disposal activities or in backyard settings with low biosafety and biosecurity), as well as volunteers or other staff handling wild animals or their carcasses. Exposure to infected droplets or dust particles is also possible in the environments where these activities take place. Lower environmental temperatures, higher humidity, and less exposure to sunlight (UV) can facilitate the survival of AIV in the environment for longer periods of time. Laboratory workers handling positive AIV specimens without adequate protective measures, including appropriate PPE, also have a high level of exposure.

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<sup>2</sup> For tasks such as culling, decontamination or cleaning, the recommended PPE for activities involving animals infected with highly pathogenic avian influenza viruses is determined at the national level (usually through legally binding texts) and occupational safety and health authorities should be consulted. This PPE usually includes eye protection, FFP3 with exhalation valve or an equivalent powered air-purifying respirator (PAPR), a water-resistant full body suit, protective gloves, and appropriate shoe protection (galoshes).

**Moderate level of exposure:** the exposure level may be moderate if an individual spends time in contaminated environments but is not directly in contact with sick animals or their secretions, faeces, or other body parts. This category covers inspectors or observers, as well as farm workers and veterinarians who are not directly involved in culling, disposal of carcasses, or cleaning operations. These individuals are present in the vicinity of infected animals or in the infected environments, possibly without taking appropriate measures to reduce exposure. Exposure to infected droplets or dust particles is also possible in these environments.

**Low level exposure:** the exposure level may be low if an individual from the general public incidentally encounters (without contact) a sick animal or its carcass (without contact), or when workers in animal-related industries do not directly come in contact with the animals or their environments. Workers that have taken adequate protection measures and correctly used the appropriate PPE can also be classified as low-level exposures. However, it should be noted that a breach in PPE or improper use of PPE cannot be excluded with certainty by history alone, and it is important to assess whether there is ongoing risk of exposure after PPE is removed (e.g. for workers living close to their place of occupation). In addition, experience from the UK's enhanced surveillance study in poultry farms showed that A(H5) virus was detected in nasopharyngeal swabs of exposed individuals using PPE [18].

## Duration of exposure

A shorter duration of exposure usually results in a lower level of exposure and lower likelihood of infection. Prolonged exposure, especially in confined spaces, will significantly increase the level of exposure [19].

## Location of exposure

There is a higher likelihood of exposure to a high viral load of avian influenza from infected or contaminated sources in indoor spaces with poor ventilation due to the accumulation of viral particles. However, the level of exposure can be significantly reduced by avoiding aerosol production (e.g. through high-pressure water cleaning or sweeping) and using appropriate PPE.

There is still a substantial level of exposure from infected or contaminated sources in indoor spaces with good ventilation. This can be significantly reduced using appropriate technical and organisational measures (e.g. limiting access to authorised personnel), appropriate hygiene and decontamination measures and correctly using appropriate PPE where needed (please refer to the section on 'Implementation of preventive measures').

Outdoor contained spaces (e.g. a backyard coop) in close contact with infected or contaminated sources pose a moderate to low likelihood of exposure to high viral loads depending on the size of the space, the type of activity and the level of spray/dust/aerosol generation it entails, and the number of animals present. This can be significantly reduced when using appropriate PPE.

There is a lower likelihood of exposure to high viral loads for individuals in outdoor open spaces having no direct contact with infected animals/environments due to the reduced concentration of viral particles in the air.

## Type of exposure

There are several types of exposure that can increase the level of exposure to AIV:

- **Inhalation:** inhaling virus particles present in the environment (e.g. during aerosol generating activities such as culling) or infected dust particles.
- **Direct contact:** touching or slaughtering/butchering infected animals.
- **Indirect contact:** touching objects or surfaces contaminated with the virus and then touching face/mouth/eyes.
- **Mucosal exposure:** mucosal surfaces (e.g. of the respiratory and gastrointestinal tracts) coming into contact with virus particles. The eye mucosa (the cornea, conjunctiva and ocular mucosae) also play an important role as an entry point for viruses [20–22].
- **Ingestion:** consuming contaminated food or drink. This has been shown to be an efficient mode of infection in animals – e.g. carnivores consuming dead bird carcasses – but there is limited evidence available on this route of infection for humans.

## Infectious dose

There is limited information available on the infectious dose of AIV required to produce infection in animals and humans. However, in general, exposure to a high viral load (e.g. direct contact with secretions or body fluids of animals showing symptoms) and highly contaminated environments (e.g. where there is a large amount of animal secretions) indicate higher level of exposure, due to the increased likelihood of encountering a sufficient infectious dose to facilitate transmission and subsequent infection.

## Animal species

- **Infected wild birds:** wild birds are primary reservoirs for AIV and can shed a large amount of virus, resulting in a high risk of transmission.
- **Poultry:** infected domesticated birds can have high viral loads; their proximity to humans and high density in the setting increases the level of exposure.
- **Wild mammals:** it is not common for humans to have close contact with infected wild mammals and any interaction would usually be for a short duration and in an open space, suggesting a low level of exposure. The level of exposure becomes higher when handling infected mammals (e.g. removing dead carcasses), especially if the appropriate PPE is not correctly used. Some mammals (such as mink, ferrets and seals) are susceptible to both human seasonal influenza and AIV, increasing the risk of virus reassortment.
- **Farmed mammals (e.g. mink):** the increased proximity and duration of interaction with humans increases the level of exposure from farmed mammals. Some mammals (such as mink or pigs) are susceptible to both human seasonal influenza and AIV, increasing the possibility of virus reassortment. Individuals who are occupationally exposed may be better protected when handling infected animals, as they may be more likely to take preventive measures, such as wearing appropriate PPE. There is, however, a time window from initial infection until the outbreak is suspected/confirmed when specific measures may not be implemented and PPE may not be used, leaving workers unprotected.
- **Domesticated mammals (pets):** it is possible that pets (e.g. dogs and cats) could become infected with AIV. The proximity and duration of contact between the pets and their owners can increase the level of exposure, particularly as PPE are not used. In the recent situation in Poland, when cats were infected by AIV, there were no reports of cat owners developing symptoms or testing positive [23].

## Exposure to infected humans

### Exposure levels, according to activity/occupation and level of protection

**High exposure level:** the exposure level may be high for close contacts of a patient with laboratory-confirmed AIV infection (e.g. household members, carers for the patient, seasonal workers or farm workers who are sharing living areas at agricultural premises, or healthcare workers performing aerosol-generating procedures without adequate protection). Limited human-to-human transmission that is not sustained has been reported in close contact scenarios (e.g. between household or family members and in healthcare settings in very few instances in China [24,25]). Care needs to be taken when healthcare workers are in contact with infected individuals (e.g. when aerosol-generating procedures are performed). In these situations, guidance should be provided on the use of rooms with appropriate ventilation, the use of appropriate PPE and following proper infection prevention and control (IPC) measures to reduce the risk of transmission.

**Moderate level exposure:** the exposure level may be moderate for co-workers of a symptomatic human AIV infection case sharing the same workspace, particularly if the workspace is enclosed, but not having such prolonged close contact as with high-level exposure.

**Low level exposure:** the exposure level may be low for those who have an incidental encounter (without contact) with an infected person, or for workers in the health sector not directly/indirectly in contact with the infected individuals or their environments (e.g. hospital administration staff). Exposed individuals, including healthcare workers, protected by adequate measures and correctly using appropriate PPE can be considered to have a low level of exposure.

### Duration and location of exposure

The level of exposure would be high for an individual who was <1m from a symptomatic AIV-infected patient (coughing, sneezing) for a prolonged period (>15 min). This is a precautionary consideration, based on evidence of airborne transmission of respiratory viruses, and therefore may need to be reconsidered if more information becomes available regarding human infections with AIV and its specific strains. Similar considerations apply here to those for 'exposure to infected animals' in terms of the location of exposure (indoors versus outdoors).

### Type of exposure

- **Inhalation:** inhaling virus particles present in the environment (e.g. healthcare workers involved in aerosol-generating procedures in a hospital setting) or infected dust particles from the environment.
- **Direct contact:** caring for an AIV-infected person.
- **Indirect contact:** touching objects or surfaces contaminated with the virus and then touching face/mouth/eyes.
- **Ocular exposure:** the eyes coming into contact with virus particles (the cornea and ocular mucosa can be exposed to aerosol and/or droplets, e.g. during aerosol-generating procedures).

**Table 1. Case-by-case assessment of the level of exposure to avian influenza**

Exposure level	Activities and occupations	Type of exposure	Location of exposure	Indoor/outdoor space	Duration of exposure	Viral load	Recommended actions
<b>High-level exposure</b>	<ul style="list-style-type: none"> <li>Occupations or activities that involve direct/indirect contact with an infected animal or its secretions (e.g. inhalation of infected droplets or dust) or close contact allowing for inhalation or ocular exposure to virus droplets without correct use of appropriate preventive measures or with breach of PPE.</li> <li>Activities with direct exposure to infected animals, such as slaughtering, butchering, and handling sick animals (e.g. veterinarians/workers with close occupational exposure to animals, individuals involved in cleaning affected premises after culling operations, individuals cleaning areas contaminated with animal faeces or secretions during clean-up and disposal activities, individuals working in backyard holding areas accessible to wild animals, volunteers or other staff handling wild animals or their carcasses, or laboratory workers handling positive AIV specimens without adequate protection) without use of appropriate protective measures (e.g. PPE) or with breach of PPE. The risk of close contact from inhalation of dust/droplets from contaminated clothes/equipment should also be taken into account.</li> <li>Close contacts (e.g. household members, caretakers, seasonal workers or farm workers who are sharing living areas in agricultural premises, healthcare workers caring for a patient with laboratory-confirmed AIV infection without use of appropriate measures (including PPE or with breach of PPE) or other contacts having encounters with human cases for &gt;15 min and &lt;1m away.</li> </ul>	<ul style="list-style-type: none"> <li>Direct</li> <li>Indirect</li> <li>Ocular</li> <li>Mucosal</li> <li>Inhalation</li> </ul>	Areas with confirmed AIV outbreaks (e.g. fur farms).	<ul style="list-style-type: none"> <li>Indoor spaces with poor ventilation</li> </ul>	Prolonged exposure (>15 min)	High (based on density of infected animals)	Handle as potential case: monitor for symptoms, test, consider post-exposure prophylaxis.
<b>Moderate-level exposure</b>	<ul style="list-style-type: none"> <li>Individuals present in infected environments but not directly in contact with sick animals or their secretions, faeces or other body parts (e.g. observers), as well as workers in the occupational groups that include those at high risk of exposure (e.g. farm workers, veterinarians) who do not directly handle infected animals, but who are in their vicinity/in infected environments, often without use of appropriate measures.</li> <li>Co-workers of a symptomatic human AIV infection case sharing the same workspace, particularly if enclosed, but not having such prolonged close contact as with a high-level exposure.</li> </ul>	<ul style="list-style-type: none"> <li>Direct</li> <li>Indirect</li> <li>Ocular</li> <li>Mucosal</li> </ul>	Areas with known presence of AIV	<ul style="list-style-type: none"> <li>Indoor spaces with good ventilation</li> <li>Outdoor contained spaces</li> </ul>	Intermediate duration of exposure	Intermediate (based on density of infected animals)	Handle as potential case: monitor for symptoms, test, consider post-exposure prophylaxis
<b>Low-level exposure</b>	<ul style="list-style-type: none"> <li>Incidental encounters with sick animals/carcasses or workers in animal-related industries not directly in contact with the animal/environment.</li> <li>Exposed individuals protected by adequate measures and correctly using appropriate PPE (e.g. healthcare workers), as well as residents in areas with known presence of AIV without direct or indirect contact with sick or dead animals.</li> <li>Incidental encounters with a human case without direct or indirect contact with the human case. For potential contacts during flights, the exposure level should be assessed on a case-by-case basis [26].</li> </ul>	<ul style="list-style-type: none"> <li>Indirect</li> <li>Ocular</li> <li>Ingestion</li> </ul>	Areas with potential, unconfirmed AIV exposure	Outdoor spaces with AIV infections in the area	Brief exposure	Low or unknown	Monitor for symptoms, instruct to seek medical attention if symptoms develop

*PPE: personal protective equipment.*

# Clinical and public health investigation of potential, probable and confirmed human cases of avian influenza virus infection

## Indicators for initiation of an investigation

Initiation of an investigation into a probable human infection with an AIV can involve a variety of elements, including the assessment of exposure history, clinical presentation, and laboratory findings. It is essential to recognise early indicators of a human AIV infection to limit any potential further spread and mitigate potential public health implications.

### Exposure history

The main reason for initiating a case investigation is exposure to infected animals or humans. This protocol indicates the need for investigation or consideration of investigation for potential human infection in the following situations:

- Contact (direct, indirect, ocular or through inhalation) with potentially infected animals in areas where an AIV outbreak is confirmed, such as poultry or fur farms, or areas with recent mass mortality events in animals, when adequate preventive measures have not been taken.
- Direct/indirect contact with an AIV-infected live or dead animal (wild, farmed or pets) or its secretions, especially when adequate preventive measures have not been taken.
- Owners of pets with confirmed AIV infection.
- Identification of present or past infection with AIV through testing/screening activities, in a person exposed to laboratory-confirmed infected animals (e.g. occupational exposure).
- Close contact with a confirmed human avian influenza case.

Other scenarios in which investigation of exposed individuals should be considered, depending on the level of exposure, include:

- workers on poultry farms with AIV outbreaks;
- workers on backyard and hobby farms, with low biosafety and biosecurity measures, where infected wild birds can have contact with domesticated birds and where different animal species are kept in close proximity;
- workers on fur farms with low biosafety and biosecurity measures, where infected wild birds can enter the premises;
- workers on fur farms with AIV outbreaks;
- individuals with a history of relevant contact in urban or rural areas where sporadic, single, dead (carnivore) mammals (foxes, etc.) are found;
- individuals with a history of relevant contact in coastal or other areas (e.g. wetlands, lakes) where single or multiple dead marine mammals (seals, dolphins, etc.) or wild sea birds are found;
- individuals in households or shelters with pets manifesting symptoms of mass mortality (cats or dogs after direct contact with infected wild birds or eating contaminated meat/food).

### Clinical presentation

The effects of AIV infections in humans range from asymptomatic infection to mild or severe disease. Human infections with AIV can present with mild respiratory illness, with influenza-like symptoms of the upper respiratory tract (fever, sore throat, difficulty breathing and cough), but can also include more pronounced signs of acute respiratory infection (ARI), or severe acute respiratory infection (SARI). Conjunctivitis has been commonly reported in patients, as well as bleeding from the nose or gums and gastrointestinal symptoms such as diarrhoea, vomiting and abdominal pain [27]. Atypical symptoms, e.g. involving the central nervous system, could also be related to AIV infection in mammals (including humans) and influenza diagnosis should be considered in the differential diagnosis for patients with encephalitis, meningoencephalitis or encephalopathy of unknown aetiology. In more severe cases, a rapid progression to severe pneumonia, sepsis with shock, acute respiratory distress syndrome, encephalitis, varying degrees of encephalopathy and even death have been reported [28,29].

Clinical presentations of particular concern, even in the absence of a known history of exposure to AIV, are:

- very severe influenza virus infections requiring hospitalisation and intensive care (to be initially tested for seasonal influenza A subtypes);
- hospitalised patients with severe neurological symptoms, lacking an aetiological agent, particularly in areas where AIV infection has been reported in farmed animals but also if increased mortality is reported in wild animals;
- a cluster of severe respiratory illness or unexplained fatalities, especially among individuals with similar exposure.

## Laboratory findings

Laboratory findings that should prompt an investigation for AIV:

- Detection with RT-PCR of AIV in respiratory samples such as oropharyngeal or nasopharyngeal swabs.
- Detection with rapid antigen tests or RT-PCR of influenza A in a person with exposure to AIV-infected animals.
- Serological evidence of recent AIV infection (although this cannot be a rapid mechanism of detection).
- AIV isolation from respiratory or other clinical specimens (although this cannot be a rapid mechanism of detection).

## Surveillance data

Public health surveillance can reveal trends or identify cases that warrant further testing for AIV. Investigation should follow if an AIV infection is detected in a human specimen, e.g. in the following instances:

- Increase in hospitalisations or deaths due to pneumonia, atypical presentations (e.g. encephalitis) or influenza-like illness, especially outside of the typical seasonal influenza period.
- Unusual or non-seasonal patterns of respiratory illness detected through syndromic surveillance.
- Reports of human AIV or influenza A detections that cannot be subtyped to a seasonal strain (H1pdm09 or H3) ('un-subtypeable') from national/international surveillance systems.

The scenarios outlined above may indicate a potential infection or outbreak of human AIV infection and, depending on the scenario, would require either further assessment or immediate and thorough investigation. Not all triggers will lead to confirmation of an AIV outbreak, but timely identification and investigation of potential AIV infections can mitigate the public health impact and prevent wider spread of the virus. When more information becomes available on the AIV strain, potential risk groups will need to be redefined. However, for the initial potential human infection, and given the above indicators, there should be a low threshold for initiation of investigations.

## Assembling an investigation team

Once a potential trigger has been identified, a multidisciplinary investigation team needs to be assembled. Outbreak investigation and control should be led and coordinated by public health professionals. The team should include experts in epidemiology and public health, as well as clinicians, laboratory staff, and practitioners in the fields of IPC, occupational health and risk communication. Animal health experts (including veterinary and laboratory experts) are also required to investigate the zoonotic event and decide on control measures in animal populations, as well as potential food safety measures. If available, and depending on requirements, the team can be expanded to include modellers, logisticians, statisticians, and environmental health experts. Relevant national/regional/local authorities, human and veterinary health authorities, hospitals and laboratories should be informed of the investigation. The laboratories and clinicians involved should be alerted of the investigation in a timely manner so that they are prepared to receive specimens and patients.

## Development of a case definition

The proposed case definitions are solely for use during the outbreak investigation and not for reporting purposes according to IHR or [Regulation 2022/2371 on serious cross-border threats to health](#), where any AIV detection in a human in the EU/EEA should be communicated through the EWRS and EpiPulse platforms. The case definition should be adapted to the setting of the outbreak (e.g. a healthcare setting), and consider the exposure history, laboratory test results and clinical presentation.

Challenges distinguishing between true infections and contaminations following detections of A(H5) in people exposed to infected animals or contaminated environments have been described and not all investigations will result in a clear conclusion. The guidance below outlines the contexts and results to take into account during the outbreak investigation.

For the purposes of a case investigation of individuals exposed to infected animals, the following potential outbreak case definitions could be considered, and be adapted as needed (see also Box.1):

**A potential case** may be defined as any person with history of exposure to infected animal cases who does not have symptoms or laboratory confirmation. Assessment of the level of exposure (moderate/high) is warranted for categorising an exposed person as a potential case (see the section 'Categorising risk of exposure' above), and determining the time of exposure (if exposure occurred in the previous two weeks).

**A probable case** may be defined as a person with history of exposure to infected animals AND a positive AIV laboratory test result, but no symptoms OR a person who is symptomatic pending laboratory confirmation OR a person who is asymptomatic/very mildly symptomatic with a positive AIV laboratory test result with high Ct value (e.g. Ct>32), but no virus isolation and no serological evidence of infection. The latter could be a case of contamination of the mucosa rather than true productive infection, especially if the sample for the initial RT-PCR test was obtained during the first 1–2 days after exposure. In that case, no sequence or only partial sequence data can be retrieved. When testing asymptomatic individuals as part of screening/enhanced surveillance activities in farms, a positive sample obtained at least two days (48 hours) after the last exposure would need to be considered as a probable infection.

**A confirmed case** may be defined as a person with or without known history of exposure that has a positive AIV laboratory test result with a low Ct value (e.g. Ct<32) that retested positive (preferably at a national influenza reference laboratory), and who has developed symptoms. Symptoms can be ARI, ILI, SARI, conjunctivitis, neurological presentation (e.g. encephalitis) or atypical presentations. Virus isolation and/or a positive serological test – i.e. a specific antibody response (four-fold or greater rise or single high titre), can also be considered as a laboratory diagnosis of infection, even in the absence of symptoms. In confirmed cases, partial or full sequence data should be sought. If laboratory results are suggestive of true productive infection (i.e. low Ct value RT-PCR result that has been confirmed and/or whole genome sequence and/or serological evidence of acute infection and/or successful virus isolation) and no symptoms have yet developed, the case can be considered confirmed. However, it should be noted that this scenario of an asymptomatic case that has a low Ct value and repeatedly tests positive with RT-PCR, suggesting a true infection, with a possibility of cultivating the virus and sequencing its whole genome, has very rarely been reported [18]. Specimens of this type that could be sequenced have almost always originated from symptomatic patients so far.

### Box 1. Overview of the case definitions for outbreak investigation

#### Potential case

(+) History of exposure to infected animals  
No symptoms  
No laboratory confirmation.

#### Probable case

(+) History of exposure to infected animals  
No symptoms  
(+) AIV test  
OR  
No symptoms or mild symptoms  
(+) AIV test with high Ct (e.g. Ct>32), no virus isolation, no or partial sequencing, no seroconversion  
OR  
(+) History of exposure to infected animals  
Symptoms  
No laboratory confirmation yet (awaiting test results).

#### Confirmed case

(+/-) History of exposure to infected animals  
(+/-) symptoms: ILI, ARI, SARI, conjunctivitis, encephalitis  
(+) AIV test with low Ct (e.g. Ct<32), and (+) re-test in the reference laboratory, and/or seroconversion/virus isolation/whole genome sequencing.

The table in Annex 1 summarises the possible situations (including exposure, symptoms, laboratory test results) in different settings and the respective response measures.

## Laboratory investigation

Laboratory investigation is essential to confirm or exclude AIV infection (Annex 2).

All probable and confirmed cases of avian influenza in humans should undergo full laboratory investigation, as outlined below.

Potential cases of avian influenza should monitor for symptoms (as discussed in the section 'Management of individuals exposed to infected animals') and systematic testing of these groups exposed to infected animals should be considered on a case-by-case basis, depending on the risk of exposure. For example, those following adequate protective measures (including correctly wearing appropriate PPE, which is usually the case for those occupationally exposed) are considered to have a low-level of exposure, unless there are breaches in protective

measures. Systematic testing of potential cases may also be undertaken as part of an outbreak investigation (e.g. to assess risk factors for infection) or in a study to assess asymptomatic transmission (please see the section on 'contact tracing'). In the event of a positive case being detected, confirmation should ideally be undertaken at a designated national influenza reference laboratory.

Laboratory investigation requires timely sample collection from cases and their contacts, the proper storage and shipment of clinical specimens to a designated laboratory and the use of appropriate laboratory diagnostic methods to detect and identify AIV. The gold standard for detection and identification of AIV from respiratory samples is RT-PCR, but laboratory testing can also involve antigen testing, virus isolation, sequencing and/or serological testing. Rapid diagnosis together with characterisation of virus isolates at the relevant WHO Collaborating Centre and national influenza reference laboratories will facilitate early detection of cases, implementation of IPC measures, proper management of patients, and assessment of the risk. In-depth virus characterisation is important for monitoring the development of resistance to antivirals, informing vaccine composition decisions and candidate vaccine virus development, and evaluating/validating laboratory methods.

More information on the diagnostic specimen collection from humans, storage of specimens and shipment to the laboratory, AIV diagnosis and differentiation of true infections from environmental contamination, sequencing and further characterisation can be found in Annex 2 and in ECDC's document: ['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].

## Testing approaches

All probable and confirmed human cases and contacts of confirmed human cases (see the previous section on 'case definition development') should be tested, and the need for testing of potential cases should be considered on a case-by-case basis. Laboratory investigation should be considered in the following situations:

### Testing symptomatic individuals

- All individuals exposed to infected animals who develop symptoms compatible with AIV infection should be tested immediately.
- Testing for seasonal influenza should also be considered for those who are occupationally exposed to infected animals, especially mammals (e.g. mink farm workers) if they develop symptoms.
- Hospitalised patients with unexplained neurological symptoms (e.g. unexplained viral encephalitis/meningoencephalitis) should be tested for influenza A and positive samples should be subtyped).
- Samples positive for influenza type A virus but negative for A(H1N1)pdm09 and A(H3N2)/un-subtypeable for seasonal influenza viruses should be tested for AIV.
- Clusters of severe respiratory infections negative for other respiratory pathogens should be investigated.

Figure 1 describes the timeline of specimen collection and **testing of symptomatic individuals** exposed to AIV in the days after symptom onset.

### Testing asymptomatic individuals

- Asymptomatic individuals exposed to infected animals, where appropriate protective measures have not been taken, should be assessed on a case-by-case basis, depending on the level of exposure, and tested.
- Testing asymptomatic individuals (e.g. occupationally exposed individuals adhering to protective measures) can be considered as a precautionary measure, as part of an outbreak investigation (e.g. to assess risk factors for infection) or a study to assess asymptomatic transmission.
- In the epidemiological situation of confirmed outbreaks in mammal farms (e.g. mink farms), more intensified weekly testing could be considered to identify any transmission to a worker (using rapid antigen tests or RT-PCR). If a person tests positive for influenza, further contact with the animals should be strictly avoided. Confirmation by RT-PCR, followed by subtyping for type A positive specimens and sequencing, should be required.
- If the RT-PCR test generates a borderline positive test (e.g. high Ct>32), the specimen should be retested and, if necessary, a new sample should be collected for RT-PCR testing.
- If the RT-PCR test generates a positive test, always retest to confirm AIV detection. Confirmation of positive results should ideally be performed at a national influenza reference laboratory.

Figure 2 describes the timeline of specimen collection from **asymptomatic individuals** in the days after exposure.

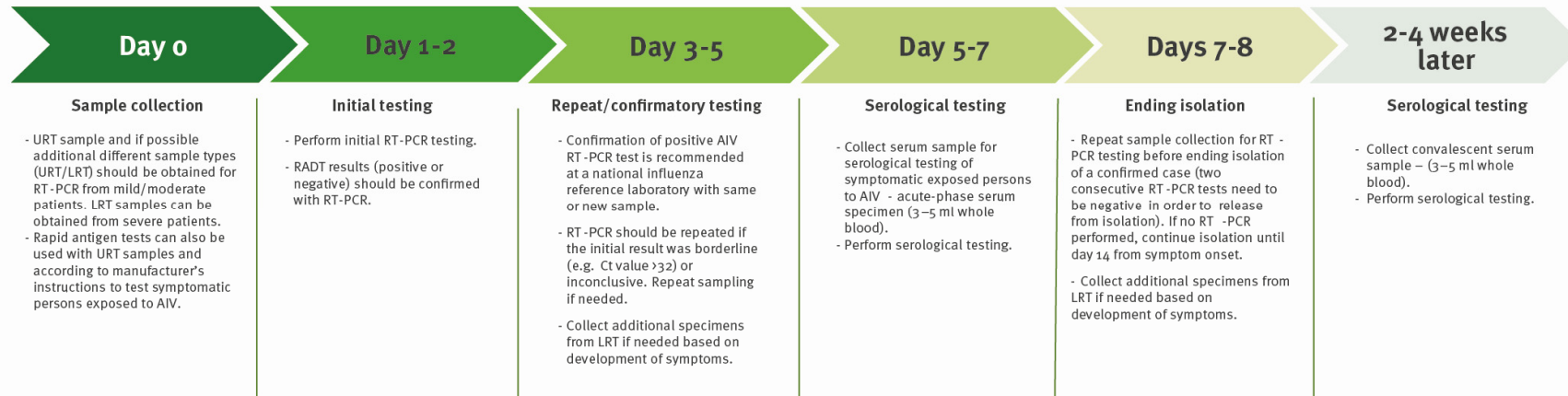
## Reporting of test results

- Develop a line list to keep record of all laboratory results and ensure results are reported and communicated to the case investigators, clinicians and public health professionals, as per national guidelines.
- Laboratory-confirmed human infections with AIV and other novel influenza strains are notifiable under the IHR and at the European level, in line with EU Regulation 2022/2371 on serious cross-border threats to health [30]. This includes any relevant information that may be useful for coordinating a response, such as the type and

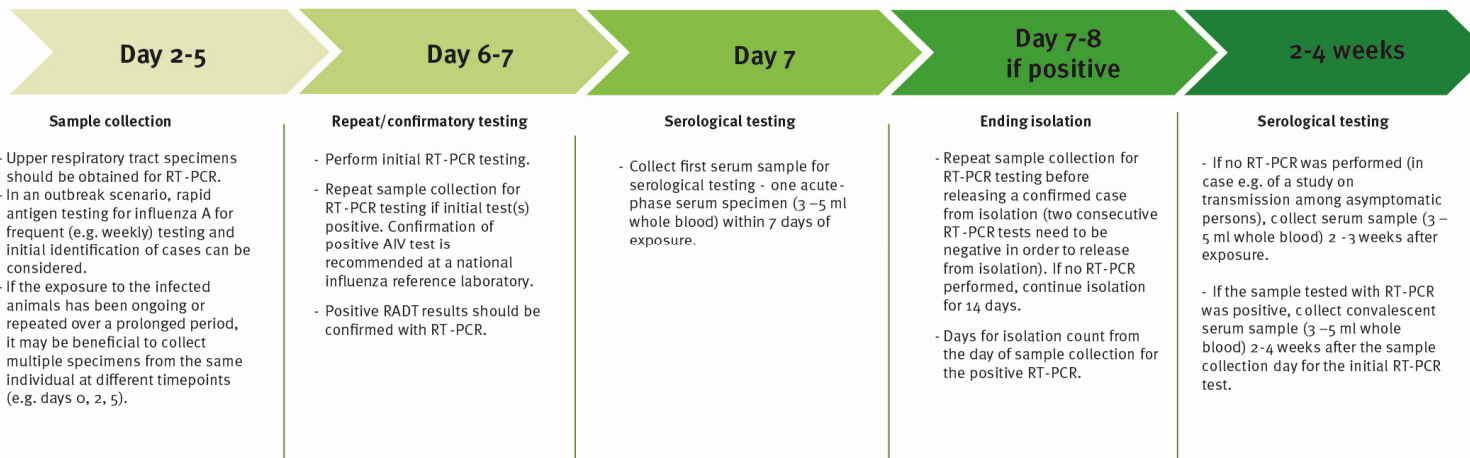


origin of the agent, date, and place of incident or outbreak and the detection and confirmation methods. Reporting should be carried out within 24 hours of the laboratory diagnosis. The Early Warning and Response System (EWRS) should be used for high-level early warning of a human case and to communicate measures implemented. The European Surveillance Portal for Infectious Diseases (EpiPulse), operated by ECDC, should be used for the epidemiological monitoring and assessment of human infections with AIV, and for sharing epidemiological situation updates. In addition, TESSy, which is integrated into EpiPulse, should be used for case-based reporting in a structured way in the event of an outbreak involving multiple cases. All laboratory-confirmed human cases, irrespective of whether there is suspicion of environmental contamination, should be reported. Any updated case information during the investigation progress should be communicated retrospectively.

**Figure 1. Timeline of specimen collection and testing of symptomatic individuals exposed to AIV in the days after symptom onset**



**Figure 2. Timeline of specimen collection from asymptomatic individuals exposed to AIV in the days after exposure**



*\* If the person tests negative in all of the initial tests and they are asymptomatic, then no further testing is needed unless they develop symptoms. The person needs to continue monitoring for symptoms for 10–14 days from the last exposure.*

## Management of individuals exposed to infected animals and contacts of human cases

Management of individuals exposed to infected animals and contacts of human cases is an essential public health measure to mitigate an AIV outbreak, in conjunction with active case finding and testing. The purpose of early identification and management of exposed individuals is to detect and notify potential animal-to-human and human-to-human transmission in a timely manner, and to limit onward transmission through prompt and targeted control measures. The most important goal for investigations involving human cases of AIV infection is to assess the potential for, and guide the prevention of human-to-human transmission. WHO has published guidance with key resources and information on the topic [31].

The identification, assessment and follow-up of exposed people should be performed by trained public health personnel. Protocols should include dedicated forms for the collection and updating of data (e.g. in REDCap), including guidance for the protection of personal data. Contact information and epidemiological information, including time since last exposure, should be kept in a line list and exposed individuals should be informed of the risk to them and others and the recommended public health measures. It is worth noting that, in the case of occupational exposure (as the zoonotic influenza virus subtypes described here are classified as Group 3 biological agents according to the [Directive 2000/54/EC on the protection of workers from risks related to exposure to biological agents at work](#) [32]), employers need to keep a record of exposed workers in accordance with occupational safety and health regulations.

## Management of individuals exposed to infected animals

At present, the information available on the incubation period of AIV infection in humans is very limited and infections from viruses of older clades might be different. Based on the limited available evidence from human infections, the incubation period of A(H5N1) is estimated to be up to seven days, usually 2–5 days after last known exposure [33–35]. Longer incubation periods of up to 17 days have been reported [36]. Based on this and due to the lack of evidence for the currently circulating A(H5) virus, which has also been presenting with delayed onset of clinical symptoms in infected animals, ECDC advocates for a conservative approach. This involves extending the monitoring period to 14 days, with a minimum period of 10 and up to 14 days of monitoring. As more information on the actual virus strain involved in the investigation and its incubation period becomes available, the monitoring/quarantine duration may need to be adapted.

The following proposal can be used to decide on measures and develop a case definition for outbreak investigation purposes (Table 2). The proposal classifies levels of exposure and investigation results, to adjust response and control measures accordingly. The proposed case definitions are solely for use during the outbreak investigation and not for reporting purposes. Reporting should be done in accordance with EU regulations to EWRS or IHR, where any AIV detection in a human would have to be reported.

**Individuals who have had occupational or other protected exposure to infected animals** (e.g. poultry farm workers, workers at animal conservation centres or shelters who are adequately protected) should be passively monitored, but if feasible can be actively monitored<sup>3</sup> (especially when there is exposure to infected mammals) for influenza compatible symptoms for 10–14 days after last exposure (and during the exposure period, if there is prolonged exposure). If symptoms develop, they should immediately self-isolate, inform public health authorities, seek medical care and test.

In the event of symptom development and self-isolation advice, employers should set out clear procedures clarifying how workers should self-isolate, the duration of isolation and any health surveillance or testing they should undergo. Employers should seek advice from the occupational health services and/or an occupational physician on any measures and also recommend health surveillance for any other potentially infected workers. Workers should be able to follow public health recommendations for self-isolation and subsequently return to work safely. The confidentiality of sensitive medical data should be respected and maintained. If a worker is found to have an infection or illness as a result of exposure, health surveillance or testing should be offered to other workers.

Testing of asymptomatic individuals should be considered as a precautionary measure on a case-by-case basis depending on the level of exposure (e.g. if there is a breach in PPE) or as part of an outbreak investigation or a study to assess asymptomatic transmission. Retesting of positive cases and serological testing can be considered to differentiate between true productive infection and contamination of mucosa through exposure to a contaminated environment. In the event of occupational exposures, employers should enable workers to be tested, as recommended by occupational safety and health authorities, public health authorities or the occupational health service or physician.

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<sup>3</sup> 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.

**Occupationally or otherwise exposed individuals who are not adequately protected** when exposed to infected animals (e.g. owners of infected pets in the household, forest workers, hunters or others in work places in contact with animals where preventive measures have not been taken) should be actively monitored for symptoms for 10–14 days. If symptoms develop, they should immediately self-isolate (and be allowed to do so by their employer), inform public health authorities, seek medical care and get tested. Workers who may have been exposed and infected should inform their healthcare providers, so that measures can be taken at the healthcare premises.

Testing should be considered on a case-by-case basis according to the level of exposure. Given the uncertainties related to mammal-to-mammal transmission, all those with close contact to infected mammals without appropriate preventive measures should ideally get tested as soon as possible. If the person exposed to an infected animal without protection (a potential case) remains asymptomatic and RT-PCR is negative, monitoring of symptoms should continue for 10–14 days.

Antiviral post-exposure prophylaxis (PEP) with oseltamivir, zanamivir or baloxavir can be considered for individuals with unprotected exposure to an infected animal. The decision to initiate PEP with antivirals should be based on careful clinical assessment, taking into consideration the type of exposure (with or without PPE, type of contact, duration and time of last exposure) [37] and known infection status of the animals. It should also consider whether the person is at higher risk of complications from influenza and the susceptibility of antivirals against the circulating AIV strains. If antiviral PEP is initiated, an adaptation of the PEP dose of neuraminidase inhibitors to once daily (compared to the twice daily dose for treatment), could be considered to avoid the development of antiviral resistance. The recommendation to increase the dose is based on limited data and could be considered based on clinical assessment [38,39].

Communication with exposed individuals is important for successful follow-up. Information regarding avian influenza and how to manage it should be provided in multiple languages if farm workers belong to a group of foreign or migrant workers.

## Case treatment and management

Healthcare facilities need to be ready to manage human avian influenza cases, prevent nosocomial spread and provide appropriate supportive care and treatment, as necessary. For efficient management of potential, probable and confirmed cases of human AIV infection, the elements set out below need to be considered by the sectors involved.

### Probable and confirmed cases

#### For probable cases

- If a potential avian influenza case develops symptoms (respiratory, gastrointestinal, or neurological) and/or has a positive laboratory result for AIV (yet to be confirmed), then they should be considered as a probable case; it is recommended that these individuals are isolated until the disease is ruled out. Testing, self-isolation and contact mapping (identification of contacts of the probable case) should be promptly initiated. Antiviral treatment should be initiated as soon as possible for all symptomatic patients (as discussed below under 'Clinical issues').
- Rapid antigen detection tests (RADTs) can be used as a first line test (e.g. in animal outbreak settings) to rapidly test all symptomatic exposed individuals and aid decisions on isolation. All positive and negative RADT tests from symptomatic individuals should be confirmed with molecular tests (RT-PCR) as soon as possible.

#### For confirmed cases

- If a symptomatic exposed person tests positive for AIV and positivity is confirmed with a second RT-PCR test (preferably at a national influenza reference laboratory), they should be isolated and follow guidance for management of cases. Contact tracing should commence (with testing and self-quarantine of contacts as discussed below). Antiviral treatment should be initiated as soon as possible.

### Clinical aspects

- Provide information and raise awareness among healthcare workers, including those in veterinary professions and animal care and laboratory staff. This should include providing guidance on how to make the initial assessment of symptoms, taking exposure history and epidemiological links into consideration [40].
- Train staff on how to collect samples for AIV detection (for rapid antigen testing, molecular diagnostics and serological tests) and other tests, as needed. Samples should be treated as highly infectious.
- The A(H5) clade 2.3.4.4b AIVs currently in circulation are widely susceptible to all three categories of influenza antiviral drugs: neuraminidase inhibitors oseltamivir and zanamivir, M2 blockers amantadine and rimantadine and PA inhibitors such as baloxavir [41]. Resistance to antivirals has only been observed sporadically, apart from higher resistance levels to M2 blockers observed in viruses detected in mink in the EU/EEA [42]. For symptomatic patients, treatment with antivirals should be initiated according to national protocols, once samples have been collected. For patients with severe, progressive or complicated illness, oseltamivir and intravenous zanamivir treatment is recommended [43-46]. For patients with uncomplicated mild to moderate

illness with symptom onset within 48 hours, oseltamivir, zanamivir or baloxavir can be used [44,47–50]. Antiviral drugs are most effective if administered early (24–48 hours from onset of symptoms); therefore, treatment may be started before laboratory confirmation for patients with compatible clinical presentation, but later onset of treatment has also shown some benefits in those severely ill with influenza infection [51]. In the case of seasonal influenza and in elderly hospitalised patients, antivirals can reduce the risk of in-hospital death even if given up to seven days after onset of symptoms [51].

- For asymptomatic individuals, antiviral PEP with oseltamivir, zanamivir or baloxavir may be considered. The decision to initiate PEP with antivirals should be based on a careful assessment, taking into consideration the type of exposure (with or without PPE), duration of exposure, timing of exposure (ideally less than 48 hours, but can be up to seven days post exposure), known infection status of the animals the person was exposed to, whether the person is at higher risk of complications from seasonal influenza and the susceptibility of antivirals against the circulating AIV strains. This time frame may need to be adapted if more information becomes available on the incubation period of the virus in humans.
- Asymptomatic patients who are not treated with antiviral medications should be monitored for progression to disease for 10–14 days after last exposure.

## Infection prevention and control aspects for healthcare settings

- Inform the hospital infection control team and/or occupational health department.
- Ensure a procedure is in place for when a potential case is transferred to a facility. Limit visitors and transfer/movement of patients within the treating facility as much as possible. IPC precautions should stay in place during patient transport within healthcare facilities, as respiratory secretions are infectious and can be one of the main sources of infection in healthcare settings.
- Cases should be managed as highly infectious, aiming to prevent severe illness and death according to national protocols and considering guidelines for the clinical management of severe illness from influenza virus infections [41].
- Cases who need to be hospitalised should preferably be placed in an isolation room with an anteroom and negative pressure or, if not available, in a single room with anteroom and own toilet. Access should be limited to the staff that need to perform tasks.
- Staff caring for cases should be trained in putting on, using, taking off and properly disposing of PPE. Recommended PPE include a well-fitted FFP2 respirator (or higher, e.g. FFP3 or PAPR), gown, gloves and goggles, which should be used for prolonged contact in close proximity to the patient, including the performance of aerosol-generating procedures.
- Staff (multiple levels) involved in caring for cases should be monitored for fever and development of symptoms in accordance with the contact tracing guidance. They may be included in studies for seroconversion.
- Clinical waste connected to the care of a case should be assessed, depending on risk, and handled in accordance with healthcare facility policies and local regulations.
- Cleaning staff should be appropriately trained, informed and equipped, particularly if these tasks have been sub-contracted. Cleaning and disinfection play a key role in reducing the risk of transmission in healthcare settings. Regular cleaning and disinfection products work effectively against orthomyxoviruses; a solution of 0.05% to 0.1% hypochlorite can be used for disinfection purposes.
- Appropriate IPC measures should be taken for laboratory staff and those handling and transporting samples.
- Inform and train patient and family of procedures for IPC (isolation, use of PPE, hygiene, follow-up, etc.) [52].

## Hospital management

- Ensure that relevant procedures are in place with agreed IPC guidance, as well as a trained team of staff. Appropriate PPE must also be available in adequate quantities.
- Information on the patient's illness and necessary precautions should ideally be shared with the facility beforehand so that they can prepare its screening and triaging system.

## Public health aspects

- Notify the local/regional/national/international public health authorities according to national guidelines.
- For management purposes, develop a line list and add cases to the line list.

## Ending isolation of confirmed avian influenza cases

Based on available evidence from AIV and seasonal influenza virus infections in humans, the infectious period can start 1–2 days before symptom onset and usually lasts up to one week after symptom onset. However, long term shedding has been reported (e.g. from children, elderly or immunocompromised individuals) and the exact infectious period of an AIV infection in humans is not clearly defined. This can vary considerably depending on a number of factors including the person's overall health, age and immune response. Therefore, at this stage we are cautious with advice on the duration of isolation and note that the recommendations may change when more information on the infectious period of the AIV strain becomes available.

The following generic guidance can be provided:

- A confirmed case can end isolation after two consecutive negative RT-PCR tests with a one-day interval in-between. It is recommended that the earliest a test should be performed is on Days 7 and 8 from symptom onset.
- If no RT-PCR can be performed to end isolation, the patient can end isolation 14 days after symptom onset or from the sample collection date for the original diagnostic test.
- When long-term shedding is indicated (e.g. in immunocompromised patients that have prolonged RNA shedding with low Ct values) the decision to discontinue isolation should also include an assessment of the clinical and immune status of the case. This is one of the scenarios that presents the highest risk for human adaptation of the virus and particular care must be taken in the assessment of risk when such cases end isolation while the RT-PCR result remains positive. Treatment options to help eliminate infection should be considered.
- Before discharge/ending isolation, inform and train the patient on personal hygiene and PPE. The patient should practise good hand hygiene and wear a surgical face mask until 14 days have passed from the onset of symptoms.
- If applicable, arrange follow-up appointment for collection of convalescent serum after discharge/ending isolation.

More information on IPC and preparedness in healthcare settings applicable to respiratory viruses can be found in ECDC's document '[Infection prevention and control and preparedness for COVID-19 in healthcare settings](#)' [53] and more information on occupational safety and health measures for those exposed at work can be found in document '[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].

## Management of contacts of human cases

Transmission of AIV to and among humans remains rare, although environmental measurements and experimental data have indicated the potential for airborne transmission of A(H5N1) and A(H9N2) [19,25,54,55]. Based on the data currently available, most human infections have been connected to exposure to high viral loads without the use of PPE, and most human-to-human infections have been limited to very close contacts of the index case. Therefore, a contact person is defined as someone exposed to a probable or confirmed human avian influenza case and limited to members of the same household, carers of the patient or healthcare workers performing aerosol-generating procedures without appropriate PPE, or other close contacts (defined as remaining <1m away from a symptomatic patient (who is coughing, sneezing) for a prolonged period (>15 min)). A contact can also be a seasonal worker or farm worker who shares living areas at agricultural premises. The duration and distance is based on evidence of airborne transmission of respiratory viruses and therefore may need to be reconsidered if more information becomes available on the specific avian influenza strain.

Active case finding should commence in areas/regions where one or more cases have been confirmed. To avoid any delays until the laboratory result confirming a case becomes available, identification of contacts of probable cases should ideally begin before the confirmation of the index case. Therefore, specimens from the case(s), from suspected infection sources (e.g. animals, environment) and from contacts should be collected promptly. Contact tracing and contact management should be coordinated by public health authorities.

The following generic guidance can be provided (see also Table 2):

**Contacts of potential human avian influenza cases** (i.e. contacts of people exposed to infected animals without protection, where there are no symptoms or laboratory confirmation) do not require contact tracing activities to be initiated by public health authorities before their test results are available.

**Contacts of probable human avian influenza cases** should be identified and actively monitored for symptoms for 10–14 days, even before the test result of the index case becomes available. If any of the contacts develop symptoms, they should immediately self-isolate and get tested. Testing of all contacts should commence as soon as possible if the index case is confirmed as having AIV, to facilitate further contact tracing. If the index case is negative and AIV infection is ruled out, then contact tracing activities can end. If the index case is confirmed, quarantine of close contacts should commence even if the test result of the contacts is negative (see below). Repeated testing should be carried out if any of the contacts develops symptoms.

**Contacts of confirmed human avian influenza cases** are of particular concern to public health authorities and any potential human-to-human transmission needs to be monitored and studied closely due to the potential increased pandemic risk. Therefore, close contacts of confirmed human avian influenza cases should be defined according to the level of exposure (i.e. household member, caretaker, healthcare worker of a patient with laboratory-confirmed AIV infection without use of appropriate PPE or with breach of PPE) and should be advised to remain at home 14 days from the last known exposure (self-quarantine) and be tested as soon as possible to allow for further contact tracing (Table 1). They should not go to work, limit physical contact with other people, use an FFP2 respirator (or, if unavailable, a surgical face mask) when contact is necessary, and practise rigorous respiratory etiquette and hand hygiene. They should preferably sleep in a separate room from other household members and avoid sharing household items (utensils, glasses, etc.). Public health authorities should actively monitor close contacts daily for development of symptoms compatible with AIV infection. Contacts can be followed up through daily phone calls or monitoring visits. Since human AIV infections are rare, and the total number of

potential close contacts is also likely to be small, stricter monitoring will probably be feasible for public health authorities. However, close contacts may need support to be able to comply with self-quarantine and, in some instances, authorities may decide to admit these individuals to a simple isolation room at a healthcare facility until AIV infection is ruled out. RADTs can be used to rapidly test all symptomatic contacts of a confirmed human case, but all positive and negative RADT tests should be confirmed with molecular tests (RT-PCR) as soon as possible. Patients who take antiviral PEP and test negative with RT-PCR on Day 10 may be released from quarantine early, but it should be noted that evidence is still lacking to support alternative approaches.

The following actions are recommended, depending on the exposure and progress of symptoms:

- If the contact develops avian influenza compatible symptoms, self-isolation is recommended, public health authorities should be notified, and the contact should be tested. Antiviral treatment can be considered and initiated as soon as possible (ideally within 48 hours of symptom onset).
- If the contact remains asymptomatic and AIV infection is ruled out for the index human case, then monitoring can end.
- If the contact remains asymptomatic and the index human case has laboratory-confirmed AIV infection, self-quarantine and monitoring of symptoms should continue for 10–14 days after last exposure. Antiviral PEP with oseltamivir, zanamivir or baloxavir [56] may be considered for exposed individuals [56]. The decision to initiate PEP with antivirals should be based on careful assessment, taking into consideration the level of exposure risk (type, with or without PPE, duration, time of exposure), whether the person is at greater risk of complications from influenza, and the susceptibility of circulating avian influenza strains to antivirals. PEP should be considered even before test results become available if there is indication of a moderate-to-high level of exposure.
- If antiviral PEP is initiated, neuraminidase inhibitors can be administered once a day, rather than twice a day as used for treatment, in order to avoid development of antiviral resistance (based on limited data) [38,39].
- Healthcare workers treating patients with confirmed AIV infection should monitor every day for signs of illness for 10–14 days following exposure and patients should be managed as a probable case if they develop compatible symptoms during this period. Healthcare workers should wear an FFP2 respirator (or, if unavailable, a surgical face mask) when in contact with other patients or other people for 10–14 days after last exposure. In the event of frequent contact with cases, regular screening of healthcare workers using RADTs and/or RT-PCR can be considered.

**Table 2. Guidance for the management of individuals exposed to infected animals and contacts of potential, probable or confirmed human cases of AIV**

Exposed individuals/contacts of cases	Exposure/contact category	Antiviral treatment/post-exposure prophylaxis*	Monitoring of symptoms for 10–14 days**	Testing	Self-isolate for 14 days ***	Self-quarantine for 10–14 days ****	Initiate contact tracing
Exposed individuals to AIV-infected animals	Adequately protected occupational groups who are exposed to AIV-infected animals	No	Yes, actively if feasible (e.g. in mammal outbreaks) or passively.	No, but regular testing of workers on mink farms can be considered.	NA	No	No
	Asymptomatic individuals occupationally or otherwise exposed to AIV-infected animals without adequate protection (potential case).	Should be considered	Yes, actively.	Yes, on a case-by-case basis (assess risk of exposure).	NA	No	No
	Individuals who are asymptomatic, very mildly symptomatic and/or have inconclusive RT-PCR (probable case) who are occupationally or otherwise exposed to AIV-infected animals.	Should be considered	Yes, actively.	Yes	NA	Yes, until AIV is ruled out	Initiate identification of contacts, inform about monitoring of symptoms.
	Symptomatic individuals with positive RT-PCR (confirmed case) with or without exposure to AIV-infected animals.	Should be considered	NA	NA	NA	Yes	Yes, immediate identification of contacts, monitoring of symptoms, testing and quarantine.
Human contacts of probable or confirmed human cases	Close contact of confirmed human case (e.g. household contact).	Should be considered	Yes, actively.	Yes	NA	Yes	Initiate
	Other asymptomatic human contacts of confirmed human cases (based on a risk assessment, considering duration of exposure, type of contact, setting).	Should be considered	Yes, actively.	Yes	NA	Should be considered, based on risk assessment.	Initiate
	Asymptomatic healthcare worker in contact with confirmed avian influenza case.	Should be considered	Yes, actively.	Yes, on a case-by-case basis (assess risk of exposure).	NA	No, but wear an FFP2 or surgical face mask for 14 days.	Should be considered, depending on the exposure.
	Human contact of probable human case.	Should be considered	Yes, actively.	Not until index case is laboratory confirmed.	NA	No	Yes

\* The decision to initiate PEP with antivirals should be based on careful clinical assessment, taking into consideration the level of exposure risk (type of exposure, with or without PPE, duration, and time of last exposure), as well as whether the person is at greater risk of complications from influenza and the susceptibility of antivirals against the circulating avian influenza strains.

\*\* Active follow-up refers to public health authorities contacting the exposed individuals every day, or as frequently as possible, while passive follow-up refers to individuals reporting to public health authorities, either at set intervals or only if they develop symptoms.

\*\*\* A confirmed case can end isolation 14 days after symptom onset (or 14 days after day of sample collection of first positive test) or after two consecutive negative RT-PCR tests with a one-day interval between tests. The earliest these tests can be performed is on Days 7 and 8 after symptom onset.

\*\*\*\* Close contacts of confirmed human cases should self-quarantine for 14 days. Patients that take antiviral PEP and have a negative RT-PCR test on Day 10 can be considered for early release, although it should be noted that evidence is still lacking to support alternative approaches.



# Epidemiological investigation and data collection

The collection of clinical, epidemiological and laboratory data from cases is vital for a successful case investigation. Good quality data will facilitate the investigation and it is important that all relevant necessary information from the case investigation is collected.

## Data collection

The necessary steps for data collection are set out below.

- Prepare a case investigation form.
- Consider different methods for data collection, including telephone or face-to-face interviews, record review, case investigation forms, case follow-up, etc.
- Data can be collected from the patients, their families and caregivers and should also be extended to healthcare workers, co-workers, neighbours etc. (please refer to the 'contact tracing' section).
- The source of the infection and the potential for further transmission needs to be investigated. This could include assessment of the individual's home, workplace, healthcare facility and/or other environments for evidence of AIV, as well as broader surveillance measures in the community or area.
- Collect data for each case on exposure, demographics (e.g. age, sex, nationality, ethnicity, occupation), clinical information (e.g. symptoms, date of symptom onset, pre-existing medical conditions), suspected risk factors (exposure to food and travel history), and information on treatment.
- Compile a line list of affected individuals, summarising the case data (including information on age, sex, symptom onset date, duration of symptoms, location, epidemiological links, specimens collected and laboratory results). According to occupational and safety health legislation, employers have record-keeping obligations.

## Descriptive analysis of epidemiological data

Descriptive analysis of the epidemiological data related to the time, place and personal characteristics of the cases will need to be performed. The analysis of the epidemiological features of the outbreak is crucial to identify risk factors, enable proper management of the cases and guide the implementation of control measures [3]. Laboratory findings, as well as any animal or environmental study findings should be taken into consideration. The descriptive findings, together with analytical study results and further studies, will enhance understandings of the outbreak and provide the evidence base to guide risk assessment and direct control measures during the early stages.

## Identify and control the potential source of infection

The descriptive analyses should aim to:

- investigate all potential exposures that could have resulted in the infection/contamination of the index case, including possible human-to-human transmission;
- consider animal and environmental investigation findings;
- prevent further events by identifying any persistent exposure sources (e.g. in infected birds/mammals);
- take actions to reduce human exposure; and
- notify relevant stakeholders and agencies in the human, occupational safety and health and animal health sectors.

Refer to 'Contact tracing and management' for the list of different types of exposures that need to be considered.

## Determine the extent of the outbreak

The investigation of potential exposure in relation to the index case should determine whether this exposure represents:

- a point source event (such as handling or slaughtering a sick bird) or
- a persistent exposure in the community (e.g. working with poultry).

This is important to consider when attempting to identify other exposed contacts and community members.

## Determine the population at risk

The population at risk needs to be determined, especially the likelihood of an isolated incident versus other members of the community sharing this exposure.

The descriptive analyses can include the parameters set out below.

## Description of the time

Generating plots of cases by date of symptom onset and describing the epidemic curve can provide insight into the potential transmission mode of the infection. The characteristics of the epidemic curve may indicate:

- point source or continuous/persistent exposure event, depending on when cases are clustered or spread in time;
- potential human-to-human transmission when cases exposed to other human cases appear after a delay corresponding to the incubation period.

## Description of the place

Describing the characteristics of place can provide insight into the spread of the potential exposure and disease transmission characteristics. This can involve the mapping of the attack rate by place, using a spot map or area map.

## Description of the person

Describing the characteristics of a person, such as sex, age or occupation, can provide insight into the exposure and risk factors. The investigation should estimate epidemiological indicators such as:

- number of people meeting the case definition;
- sex ratio;
- attack rate among household members and/or co-workers in the event of occupational exposure;
- case-fatality ratio; and
- transmission coefficient if human-to-human transmission is suspected.

## Further studies

Further complementary studies, such as case-control studies, WGS or seroprevalence surveys, in vitro transmissibility studies and other virological studies should be considered to enhance understanding of the virus (Annex 5).

## Animal health, and occupational health and safety collaboration

Strong collaboration between the animal and human sectors is paramount for an effective case investigation and response to a zoonotic event such as an avian influenza case in humans. The authorities responsible for occupational safety and health (e.g. the regional labour inspectorate) should be involved in settings with workers and this is important for the implementation of any response measures. Animal health and environmental investigations need to complement the activities on the public health side. If the potential/probable/confirmed human avian influenza case had contact with infected animals, further investigation and appropriate control measures should be coordinated with the animal health authorities, as outlined in legislation. Close collaboration and timely exchange of findings is crucial for an effective response.

The necessary information from the animal side should include confirmation of infection in the animal source, identification of the virus and virus sequence(s), markers for adaptation/resistance in the animal virus, spread of the virus in animals, animal species affected, measures implemented on the animal health side, type of studies conducted and/or planned, challenges and barriers to obtaining results, and planned risk communication.

# Implementation of control measures

## Implementation of preventive measures

More information on IPC and preparedness for COVID-19 in healthcare settings can be found in the ECDC document '[Infection prevention and control and preparedness for COVID-19 in healthcare settings](#)' [53] and more information on occupational safety and health measures for those exposed at work can be found in the ECDC document '[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]. WHO has also published a guidance with key resources and information on the topic [31].

### Minimising exposure

The general public should minimise contact with animals or potentially contaminated surfaces in areas with known outbreaks (e.g. farms). Since exposure is likely in workplaces where animal contact cannot be avoided, occupational safety and health measures should be taken at such premises and enhanced where occupational cases have been identified. There is a comprehensive body of legislation defining the obligations of employers and framing the measures to be taken.

Employers should periodically revise their workplace risk assessment and ensure that all necessary technical, organisational, maintenance and hygiene measures are taken to prevent the infection of workers. These measures need to be taken in consultation with the health and safety committee, if available, or workers' representatives. Measures include the avoidance of aerosol and dust creation/dispersion, ventilation, separation of work and personal clothing, and measures to prevent contamination of worker accommodation. Employers must keep a record of any workers that may have been exposed to the viruses and offer health surveillance, as appropriate. The workplaces concerned include farms, animal breeding centres, zoos and slaughterhouses. However, workers in laboratories, healthcare and waste management facilities, or those who may be in contact with wild animals could also be exposed.

When there is a suspected outbreak, the workplace risk assessment should be revised, taking into account all occupational risks, including the increased physical load on workers from applying additional measures and wearing PPE. Appropriate measures should then be taken. To reduce the risk of infection with zoonotic influenza viruses, workers should be protected from direct physical contact with sick or dead animals or their remains (e.g. sick birds, poultry carcasses, poultry faeces or litter, surfaces and water that might be contaminated with poultry excretions in the case of infected or dead birds, or pigs, bodily fluids and faeces or litter in the case of pigs or wild boar).

Preventive measures include limiting the number of workers potentially in contact with infected animals, areas and objects; physically separating and limiting access to contaminated areas; strictly avoiding the production of aerosols and dust; enhanced ventilation; specific cleaning and disinfection procedures and, where technical and organisational measures are insufficient, the use of appropriate PPE (see footnote 2 on page 3). Potentially contaminated areas must also be separated from clean areas (black-white areas).

Working and living areas should be strictly separated. For example, if seasonal workers live on the farm premises, it should be possible for them to decontaminate themselves before entering the accommodation. Good hand hygiene is important (proper use of gloves, hand washing, and hand sanitisers) and helps prevent infection and keep the virus from spreading. The employer should provide facilities for hand washing and appropriate disinfection products and ensure decontamination where there is a risk of infection. Showering at the worksite or at a nearby decontamination station at the end of the work shift, and leaving all contaminated clothing and equipment at work should be recommended and facilitated by the employer.

Workers must receive training and instructions on appropriate working practices, the application of the technical, organisational and decontamination measures, the use of PPE, and how to put on, use, take off, and dispose of it. Employers should ensure that there are proper waste storage and disposal facilities in closed containers. Workers should be informed of any emergency measures and know to whom they should report any incident that could cause the spread of the virus. Workers should follow the employer's health and safety rules, apply preventive measures and wear or use all the required equipment.

In the event of positive cases among workers in a specific workplace, employers should take measures to protect other workers from becoming infected, and facilitate self-isolation and testing. This issue should also be addressed when workers use common areas and housing at the employer's premises.

When tasks are sub-contracted to other employers (e.g. culling, clean-up or disinfection) it should be ensured that preventive measures are coordinated and all workers are adequately protected.

## Personal protective equipment

People who come into contact with potentially infected animals should always use appropriate PPE. Training in the use of PPE should be offered to workers who may be exposed in connection with their work. At workplaces, employers need to make appropriate PPE available if other means of prevention are not sufficiently protective. The nature of the PPE to be used will depend on the workplace risk assessment and the preventive measures that have been determined in consultation with workers or their representatives. Employers need to ensure that PPE is appropriately stored or disposed of and that work and personal clothing can be kept separate. Workers should be trained on how to put on and take off PPE appropriately and how to dispose of it. Means should be provided for the adequate disposal of contaminated PPE or cleaning of contaminated work clothing.

## Hygiene measures

All those in contact with potentially infected animals should practise frequent and thorough hand hygiene, either by washing hands with soap and water and/or by using alcohol-based hand sanitisers. At workplaces, employers should provide facilities for workers to decontaminate (for example by showering, washing or disinfecting hands, depending on the circumstances). It should be ensured that working clothes and normal clothes are kept apart and that living and break areas are not contaminated.

## Reducing environmental contamination

Rapid culling, cleaning and disinfection of affected premises helps reduce the contamination of the environment and the risk of further spread of the viruses to humans. Removal of dead animals in the environment will also help to limit the spread of the virus (e.g. across breeding bird colonies) and reduce the environmental contamination. However, employers should restrict access to the areas where these tasks are performed to those who are doing the culling, cleaning or decontamination, as appropriate, and they should also minimise the number of workers exposed.

## Biosafety and biosecurity measures

Adherence to high biosafety and biosecurity standards is vital to prevent the introduction of any virus to animals being kept or farmed and to reduce the likelihood of humans being exposed to infected animals.

## Management of asymptomatic farm workers or people exposed to infected animals

Refer to the section 'Management of individuals exposed to infected animals' above.

## Testing of exposed workers

Refer to the sections 'Testing approaches' and 'Management of individuals exposed to infected animals' above.

## Testing asymptomatic individuals

Refer to the sections 'Testing approaches' and 'Management of individuals exposed to infected animals' above.

## Antiviral drugs

Refer to the sections 'Management of exposed individuals to infected animals', 'Case treatment and management' and 'Management of contacts of human cases'.

## Seasonal influenza vaccination

Individuals who are exposed to AIV-infected animals through their work can be offered immunisation against seasonal influenza to minimise the risk of reassortment between avian and human seasonal influenza strains. NITAGs can be consulted for specific vaccination recommendations. It is important to combine vaccination with comprehensive preventive strategies (e.g. offering low threshold testing for seasonal and avian influenza viruses and implementing other preventive measures, as necessary).

## Vaccination against avian influenza virus A(H5)

Immunisation against AIV A(H5) for individuals who are occupationally exposed to infected animals could be considered, once a vaccine is available, to minimise the risk of disease in humans, potential virus recombination and appearance of human-adapted mutations. At present, the only A(H5N1) vaccine available in the EU is being updated to include an AIV strain to match the circulating virus/clade and it is expected to be authorised in 2024.

## Risk communication and community engagement

Risk communication and community engagement during the response to a disease outbreak are essential to protect individuals and communities and should be carefully planned, focusing on three key principles: use of a trusted voice or representative as a spokesperson; provision of clear, actionable advice; and tailoring of messages and communication methods to the communities' needs. The communication strategy should be intersectoral and include both occupational health and safety authorities and animal health authorities.

Countries need to develop effective risk communication and community engagement strategies to ensure that the public and relevant stakeholders are aware of the situation, the risks associated with avian influenza and the measures being taken to prevent its spread. General recommendations are set out below.

- Communicate the risk and actions to minimise exposure of the public to infection sources (e.g. animals infected with AIV). Be the first with the information: tell the public about a case as soon as you know and do not wait to release information that has already become a rumour. Communicate clearly and often.
- Community engagement should be prioritised to better understand community concerns, needs and suggestions, as well as to address rumours, misinformation, or misunderstandings. By actively seeking and incorporating feedback, health authorities can gain valuable insights, address gaps in the response, and tailor interventions to better meet community needs. Engagement should be attempted, depending on the situation, with representatives/leaders of the workers (culling, farm workers, hunters, etc.), farming communities, pet owners, etc.
- Do not over-reassure or say that the situation is under control if it is not. Say what you know and what you are doing about it. Tell the public what they can do (e.g. staying away from dead animals).
- Ensure that messages reach the risk groups they are intended for (e.g. by disseminating them at the affected workplaces or in the affected regions). Use multiple communication channels to reach the population at risk and ensure that the chosen channels are accessible and widely used by the target population. In an occupational context, cooperation on communication should be sought with the social partners of the sectors concerned (i.e. the organisations representing workers and employers.)
- Avoid technical jargon and use plain language that is easily understood by the population at risk. Use visuals, pictograms and illustrations whenever possible to enhance comprehension. Communication material in other languages may be needed as farm or culling workers may belong to an immigrant population. The relevant communication material should be agreed with occupational safety and health authorities.
- Increase awareness of human cases of avian influenza. Clearly explain preventive measures to mitigate health risks, including those to be taken by employers in the event of occupational exposure, such as technical and organisational measures, personal protective measures, recognition of symptoms and what to do if they occur.
- In addition to disseminating information, consider how the risk communication strategy might provide channels for receiving information as well (i.e. listening aspect), to enable better community engagement and gather feedback on how messages are received. Examples of such activities include organising hotlines, monitoring social media and organising community meetings where community members can provide feedback on their needs and the response to the crisis.

More specifically, the following information should be communicated in a timely manner when there is a human case or even proactively when there are outbreaks of avian influenza in animals and risk of human exposure:

### Messages to the general public and groups at risk to reduce human exposure

- Inform the public of the risk of AIV infection and the modes of transmission to humans. This could include a recommendation for the general population to avoid close contact with sick/dead animals. This information could also help increase awareness of human cases of avian influenza.
- Advise the public that they should avoid contact with animals that are sick/dead, even if the cause of infection is unknown, including wild animals, and encourage them to report dead wild animals and request their removal by contacting local wildlife or veterinary authorities.
- Advise and inform people who have been exposed to infected animals or human cases on how to practice proper personal hygiene (e.g. wash hands frequently, use appropriate PPE as needed and seek medical help if they develop symptoms). Occupational health and safety authorities should be involved in any guidance developed for potentially exposed workers, and such guidance should address employer's obligations and the measures recommended.
- Explain that follow-up and monitoring of exposed individuals will be performed for 10–14 days after exposure to infected animals, and/or environmental contamination. Communicate clear instructions to identified contacts in terms of their period of monitoring, hygiene measures, mask wearing etc. and what to do if they develop symptoms. Translations or cultural mediators may be needed to communicate guidance properly (e.g. culling workers may be sub-contracted from another country).

## Risk assessment during outbreak investigation

The main objective of an outbreak investigation for AIV infections is to identify human cases and prevent human-to-human transmission. Based on the findings of the investigation and the public health implications, investigators should provide recommendations and outline their rationale for IPC measures, involving occupational safety and health authorities in the event of occupational exposure.

Findings need to be linked to the risk assessment process. The case investigation should aim to assess the likelihood of transmission to humans and whether there is evidence of increased viral adaptation, enabling human-to-human transmission. It is important to note that risk assessments reflect the knowledge and information available at a specific point in time and should be repeated when more information becomes available until the event is concluded. In general, the situation will need to be assessed on a regular basis in terms of efficacy and/or the need for modifications of the proposed interventions. This assessment should include enhanced surveillance and other public health interventions (e.g. hospital and laboratory preparedness, risk communication, etc.). In the event of a small cluster of cases exposed to the same source with no sustained human-to-human transmission, the investigation should continue for 14 days after the last case was detected, to be able to fully assess the risk of severe disease associated with an infection.

Describing the animal and human cases/clusters and assessing the potential for limited or sustained human-to-human transmission is critical to enable the alert level to be raised as needed. The human-to-human transmission described to date has only been sporadic, with no sustained chains of transmission. While this gives rise to the expectation that future mammal-related outbreaks are more likely to result in limited (rather than sustained) human-to-human transmission, prompt and stringent investigation of all events is required to detect any indication of sustained human-to-human transmission.

For the situational risk assessment, public health authorities need to consider multiple factors, as set out below.

- **Epidemiological links and common exposure:** determine the most likely infection source and mode of transmission (direct exposure to infected animals, contaminated environment or a confirmed human case). Human cases may have been in contact with a confirmed case but may also have had common exposure to sick/dead animals or contaminated environment. In this situation, it may be difficult to confirm human-to-human transmission and exclude direct infection from the same source.
- **Locations of exposure:** identify the areas where the patient worked and/or travelled while symptomatic, potentially spreading the virus, and identify close contacts.
- **Clinical severity:** assess and document the severity of symptoms of infected individuals and the clinical outcome.
- **Timing:** consider the period between exposure and symptom onset in human cases (e.g. if the delay is longer than one incubation period, human-to-human transmission cannot be excluded).
- **Potential human-to-human transmission:** identify any potential cases who develop symptoms after contact with a confirmed human avian influenza case and have no history of other exposure to infected animals (e.g. a healthcare worker, laboratory personnel handling positive specimens, relatives taking care of a confirmed case).
- **Sporadic cases with no known exposure:** identify any positive human cases detected clinically in patients with severe respiratory infection that have no known exposure to sick animals or positive cases picked up by routine surveillance activities. With such cases, low-level human-to-human transmission in the community should be considered. Additional epidemiological investigations are required.
- **Indications from sequencing and phylogenetic analysis of avian influenza viruses:** it is important to analyse the genetic profile of the virus to identify mammalian adaptation mutations that can increase the ability of the virus to infect and transmit between humans, cause more severe disease, or have resistance to antivirals. All of these factors will have significant implications for a country's response. Sequencing can also be used to determine potential chains of transmission, as well as vaccine decisions.

The following situations should trigger enhanced surveillance and response measures at the national and/or EU/EEA level and indicate a higher-risk event:

- circulation of seasonal influenza viruses in mammals;
- confirmed spill-over from infected mammal to human, which has not been observed so far, indicating a new intra-mammal-species barrier jump;
- evidence of limited human-to-human transmission (e.g. case series among family members) or more general human-to-human transmission (e.g. multiple cases of AIV with no known exposure history or AIV detections in samples from sentinel sources);
- clusters of human cases or an outbreak of AIV infection;
- accumulation of mammalian adaptation mutations and/or other relevant mutations, particularly those in the HA gene related to a receptor switch from avian-like to human-like;
- circulation of reassortant viruses with gene segments derived from different species (e.g. from avian and seasonal influenza) but also any other influenza virus from animals (e.g. swine) that might have acquired the ability to transmit between humans with properties the population has no immunity against.

Indications of a lower-risk event:

- detection of one or a few sporadic cases with history of direct exposure to contaminated environments or infected animals, with no further human cases identified among contacts within 10–14 days of the investigation being initiated and therefore, no evidence of human-to-human transmission;
- suspicion of environmental contamination of the mucosa rather than true infection;
- no mutations of concern identified through sequencing.

With a lower-risk event, the situation still needs to be continuously monitored, especially if there are ongoing animal outbreaks in the area. Public health awareness is always paramount.

## Evaluation and closure of the investigation

Upon completion of the investigation and implementation of control measures, it is necessary to conduct an assessment to record the success of the response and pinpoint areas that could benefit from improvement. Once the case(s) has recovered, and if no further case(s) is identified among contacts within 14 days of the investigation being initiated, the investigation can close, as there is no longer a risk of further transmission and all necessary response actions have been taken. If there are newly identified cases among contacts within 14 days of the last case detection, the investigation should continue or a new investigation should be initiated as needed. After-action reviews (AARs) are useful tools for the identification of what went well and what needs to be improved in the planning. ECDC guidance is available on conducting shorter or longer AARs [52,57]. AARs should ideally be conducted within three months of the investigation being closed. It is important to relay updates and findings to all stakeholders who participated in the investigation, ensuring that they are kept involved and informed of the progress and outcome of the investigation.

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# Annex 1. Possible situations in different settings and response measures

An overview of the response measures suggested for different settings is given in Table 1A. Descriptions of the possible situations are set out below.

## Possible situations

**A:** Occupationally exposed individual with appropriate protection, but moderate/high level of exposure cannot be excluded (e.g. due to breach in PPE). Asymptomatic or with very mild symptoms, usually identified through enhanced surveillance activities (e.g. cases in the United Kingdom and Spain [18,58]).

**B:** Occupationally exposed person with appropriate protection, but moderate/high level of exposure cannot be excluded (e.g. due to breach in PPE) Mild symptoms are present.

**C:** Occupationally exposed person with appropriate protection, but moderate/high level of exposure cannot be excluded (e.g. due to breach in PPE). No symptoms and no test.

**D:** Occupationally exposed person with appropriate protection, but moderate/high level of exposure cannot be excluded (e.g. due to breach in PPE) or otherwise exposed person with severe disease.

**E:** Occupationally exposed person with appropriate protection, but moderate/high level of exposure cannot be excluded (e.g. due to breach in PPE) or otherwise exposed person with severe disease.

**F:** Asymptomatic, occupationally exposed person with appropriate protection, but moderate/high level of exposure cannot be excluded (e.g. due to breach in PPE) or otherwise exposed person.

**G:** Symptomatic person otherwise exposed to infected animals or their environment without protective measures.

**H:** Asymptomatic person otherwise exposed to infected animals or their environment without protective measures.

**I:** Asymptomatic person otherwise exposed to infected animals or their environment without protective measures (e.g. to pets in a household) with no testing available.

**J:** Symptomatic person otherwise exposed to infected animals without protective measures and no testing available.

**K:** Person with mild disease and no known exposure (identified through ILI/ARI sentinel surveillance system or random laboratory detection).

**L:** Person with severe disease and no known exposure (identified through hospitalisation/SARI patient testing).

**Table 1A. Possible situations in different settings and response measures**

	Possible situations												
	Occupational settings			Occupational or other settings			Other settings (unprotected exposure)				Healthcare settings (unknown exposure)		
	A	B	C	D	E	F**	G	H	I	J	K	L	
<b>Factors</b>	Exposure	+	+	+	+	+	+	+	+	+	+	+	
	Protective measures (e.g. PPE)	(+)	(+)	+	(+/-)	(+/-)	(+/-)	-	-	-	-	unknown	unknown
	Symptoms	- or very mild	+	-	+	+	-	+	-	-	+	+	+
	Hospitalisation	-	-	-	+	+	-	-	-	-	-	-	+
	First PCR result (day 1-2 after exposure)	+	NA	NA	NA	NA	NA	+	+	NA	NA	NA	NA
	First PCR result (day 1-2 after symptom onset)	N/A	+	NA	+	-URT	+		+	NA	NA	+	+
	Ct<32	N/A			+		+						+
	Ct>2***	+			NA			+	+				
	Retest PCR (day 3-5)	-	+	NA	+	+LRT	+	-	-	NA	NA	+	+
	Genomic sequence	- or partial	+ or partial	NA	+ or partial	+/-partial	+ or partial	-	- or partial	NA	NA	NA	+
Virus isolation	-	+ or NA	NA	+ or NA	+/-	+/-	-	-	NA	NA	NA	+	
Serology	- or NA	+ or - or NA	NA	+ or - or NA	+ or - or NA	+ or - or NA	- or NA	- or NA	NA	NA	NA	+ or - or NA	
<b>Cases</b>		Probable case (can be true infection or contamination)	Confirmed case	No	Confirmed case	Confirmed case	Confirmed case	Probable case (True infection or contamination)	No	Potential case	Probable case	Yes	Yes
	Isolation	Yes, until AIV is excluded	Yes	No	Yes	Yes	Yes	Yes until AIV is excluded	No	No	Yes	Yes	Yes
<b>Measures</b>	Monitoring of symptoms	Yes	Yes, for progress to severe disease	Yes	NA	NA	Yes, for development of symptoms	Yes	Yes	Yes	Yes	NA	NA
	Identification of contacts	Yes	Yes	No	Yes	Yes	Yes	Yes	No	No	Yes	Yes	Yes
	PCR testing of contacts	Not until AIV for index case is confirmed	Yes	No	Yes	Yes	Yes	Not until AIV for index case is confirmed	No	No	Not until AIV for index case is confirmed	Yes	Yes
	Monitoring symptoms of contacts	Yes, until AIV of index case excluded	Yes	No	Yes	Yes	Yes	Yes, until AIV of index case excluded	No	No	Yes	Yes	Yes
	Quarantine of contacts	No	Yes	No	Yes	Yes	Yes	No	No	No	No	Yes	Yes
	Antiviral treatment	No	To be considered	NA	To be considered	To be considered	To be considered	No	No	No	To be considered	To be considered	To be considered
	Antiviral prophylaxis*	To be considered	To be considered	No	To be considered	To be considered	No	To be considered	To be considered	To be considered	To be considered	To be considered	To be considered

§ According to proposed case definition for outbreak investigations and not for reporting purposes to EWRS or IHR (as is the requirement for every avian influenza virus detection in a human).

(+) Use of PPE, but breach cannot be excluded.

\* The decision to initiate PEP or antiviral treatment should be based on a careful clinical assessment, taking into consideration the level of exposure (type of exposure, with or without PPE, duration and time of last exposure), as well as whether the person is at greater risk of complications from influenza and the susceptibility of antivirals against the circulating avian influenza strains.

\*\* This possible situation of an asymptomatic case that has a low Ct value and tests repeatedly positive with RT-PCR suggests a true productive infection with the possibility of cultivating the virus and sequencing its whole genome has not been observed so far.

\*\*\* Ct values are indicative of viral copy numbers and RT-PCR results with high Ct values at detection limit (also those with Ct>32). Specimens with high Ct values should be retested (same sample, as well as retrieving additional specimens from the person) and ability to generate full versus partial sequences provides additional information, as well as success or failure in cultivating to identify infectious viral particles.

## Annex 2. Laboratory aspects of the investigation

### Diagnostic specimen collection from humans

- Ensure safe, correct and timely sample collection (Figures 1 and 2). Specimens should be considered highly infectious and sampling should be done according to biosafety and biosecurity regulations. Appropriate technical and organisational measures should be taken and PPE used where necessary (refer to Annex 3 for more information on biosafety regulations). Respiratory and blood samples should be collected by trained personnel. Self-swabbing could also be considered if appropriate training is provided.
- Appropriate sample types for respiratory pathogens are oropharyngeal swabs, bronchioalveolar washes, conjunctival washes, or tracheal aspirates. Specimens from nasopharyngeal swabs are acceptable, but they may contain a low quantity of the virus in patients with primarily lower respiratory tract infection (LRT) (e.g. those with severe disease). LRT specimens may be the most suitable in cases of pneumonia. With mechanically ventilated patients, the best specimens from the respiratory tract are throat, nasal cavity, bronchioalveolar lavage and endo-tracheal aspirates. For the investigation of an avian influenza case, it is recommended that clinical specimens are collected in viral transport medium (VTM) or universal transport medium (UTM) to ensure viability of the virus for subsequent isolation and further characterisation. If there are restricted transportation and Biosafety Level (BSL)3 capacity issues, swabs can be also transported in 'inactivation buffer' that is not suitable for viral culture but would increase testing capacity. Serum samples from patients in acute and convalescent phase should also be collected when possible.
- Before collecting specimens, it is important to ensure that the relevant diagnostic laboratories are informed and that specimens can be taken, stored, and shipped safely, taking the appropriate occupational safety and health preventive measures and at the appropriate biosafety level.
- Additional data collection should include the date, time and condition of samples when received.

### Storage of specimens and shipment to the laboratory

- Ensure safe packaging, storage and transport of the specimens according to biosafety and biosecurity regulations (Annex 3). This will also ensure viability of the pathogen for isolation and further characterisation purposes, although a viable virus is not needed for molecular diagnostic techniques.
- Identify which laboratories in the country can safely handle and rapidly perform diagnostic tests for AIV and make logistical arrangements for the transport of specimens to the designated laboratories during the preparation phase of the investigation.
- Only cultures of highly pathogenic avian influenza virus are considered as Category A (shipping name 'Infectious Substance affecting human') and are assigned to UN2814 ([Annex 5-G](#)). Clinical samples should be considered Category B (shipping name: 'Biological substance, Category B') and are assigned to UN 3373 [59].
- Inform the designated diagnostic laboratory of the courier information and expected arrival time, number of specimens, type of specimens and key epidemiological information.

More information on the diagnostic specimen collection and storage for zoonotic influenza virus infections in humans can be found in ECDC's document: '[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].

### Molecular testing

Molecular tests that detect influenza A viruses will most likely detect the avian influenza A strain but will not be able to identify and subtype the specific strain.

- Use appropriate molecular detection tests that can identify seasonal influenza strains (A(H1N1)pdm09 and A(H3N2)) and AIV AH5 as a minimum; if there is lack of capacity in the country to diagnose H5 virus, ECDC and the WHO Regional Office for Europe should be contacted to assist with shipment of specimens to WHO reference laboratories.
- Use appropriate reference/control material for RT-PCR testing (contact ECDC if you need support).
- Analyse samples according to validated protocols for AIV diagnosis using appropriate biosafety protocols (Annex 3).
- If necessary, prepare clinical samples/RNA for shipment according to national guidelines and biosafety protocols (Annex 3).
- Send any influenza A sample that cannot be subtyped as H1pdm09 or H3 ('un-subtypeable') to the national influenza reference laboratory that is a member of the European Reference Laboratory Network for Influenza (ERLInet) and WHO's Global Surveillance and Response system (GISRS) without delay.
- Confirmatory/repeat RT-PCR AIV testing should be carried out in a specialised laboratory (national influenza centre/national influenza reference laboratory).

Annex 1 summarises the scenarios (including exposure, symptoms and laboratory test results) in the different settings and the respective response measures.

## Sequencing and further virus characterisation

Whole genome sequencing (WGS) and analysis of WGS data is important for case investigations and necessary to inform decisions related to the outbreak. It is also important for assessing the pathogen characteristics, diagnostic assay performance and antiviral drug susceptibility. Partial genome sequencing (Sanger) of haemagglutinin, neuraminidase and other genes, if possible, can also be useful, although sequencing the whole viral genome would be more informative. The genetic constitution of the AIV needs to be assessed for mutations linked to adaptation to the human host, in particular host specificity, antigenicity, transmissibility, virulence, receptor binding, replication efficiency and antiviral drug susceptibility.

If there are confirmed human cases of AIV infection:

- perform sequencing of all positive cases;
- submit sequence data as soon as possible to GISAID, ENA and other public databases;
- ensure sequencing capacity can be upscaled to allow for proper monitoring of the epidemiological situation if necessary; and
- send specimens/genetic material/virus isolate to the WHO Collaborating Centre/WHO H5 Reference Laboratory for further analysis and virus characterisation.

To support sequencing capacity building in the EU/EEA, ECDC – in collaboration with the Health Emergency preparedness and Response Authority (HERA) – can offer direct sequencing and bioinformatics support and has executed national sequencing infrastructure projects. ECDC also provides access to centralised laboratory support services for EU/EEA countries, including genetic and antigenic characterisation of respiratory viruses.

## AIV diagnosis and differentiation of true infections from environmental contamination

In 2023, there were A(H5) detections in Spain, the UK and elsewhere from asymptomatic/very mildly symptomatic people with positive H5 laboratory test results, but high Ct values. These detections, especially when the sample is collected within the first few days after exposure to infected birds (with no or partial sequencing, no virus isolation and no serological evidence of infection), are probably indicative of a contamination of the mucosa rather than true productive infection [15,18,58]. To distinguish whether a positive specimen is due to environmental contamination or a true systemic infection, the parameters set out below can be considered.

**Symptom assessment:** presence of symptoms points towards a true infection. Many respiratory pathogens cause similar symptoms, such as fever, cough, and difficulty breathing. Evaluating these symptoms can be a first step in identifying an infection. AIV infection can cause a range of symptoms in humans, as described above. Multiplex kits to test for other viral infections, as well as influenza A subtyping RT-PCR tests, can be used to differentiate between different viral infections with similar symptomatology, especially when seasonal influenza viruses are circulating. In asymptomatic cases, the likelihood of a contamination due to environmental exposure is higher.

**Rapid antigen testing:** rapid antigen detection tests (RADTs) can be used with upper respiratory tract (URT) specimens according to the manufacturer's instructions as a first-line test (e.g. in an animal outbreak setting) to rapidly test those exposed to infected animals or contacts of a confirmed human case. Self-sampling can be considered after proper training. However, none of these tests can differentiate between human or zoonotic influenza virus subtypes and validation would be needed to verify whether the RADTs are suitable for detecting AIV [60,61]. More information on RADTs can be found in ECDC's document: '[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].

**Repeated/confirmatory testing:** repeated/confirmatory testing should be carried out if the positive case is asymptomatic. If the individual is simply contaminated from environmental exposure, the body's immune system may clear the virus prior to causing a systemic infection and a follow-up test with a new sample may be negative. Positive samples from symptomatic cases should also be confirmed at a national reference laboratory before they can be considered as confirmed. As mentioned above, positive rapid antigen tests should always be confirmed with RT-PCR as soon as possible.

**Repeated sampling:** new specimens would need to be obtained if results are inconclusive. If the RT-PCR test generates a borderline positive test (e.g. high Ct value >32) or there is a positive result from an asymptomatic farm worker, a new sample should be collected for RT-PCR testing. Positive samples obtained either during the period of exposure or within 48 hours of exposure (Days 0–2) may be due to oro-/nasopharyngeal contamination rather than true infection. Repeated sampling/testing with samples in subsequent days can be useful to



differentiate between true infection and environmental contamination, taking into account the day of the first negative sample after testing positive. The threshold for what is considered a high Ct value can vary, depending on the methodology used.

**Evaluate the timing of sample collection of positive/negative samples:** in the event of environmental contamination of the mucosa, the first samples (e.g. taken on Day 2 after exposure) may be positive, while samples collected later (e.g. Day 5 after exposure) may test negative. In the case of true infection, the opposite is more likely (i.e. initially the samples test negative and later they test positive, depending on the incubation period of the virus).

**Testing different sample types:** a variety of different sample types should be obtained and tested. At a minimum, specimens from the URT should be collected and, if possible or needed, also from the lower respiratory tract (LRT) depending on symptom progression (i.e. in cases of severe disease, LRT samples should also be collected).

**Virus culture:** this involves growing the virus in cell culture in a BSL3 laboratory from patient samples. This can confirm the presence of the virus and therefore an active infection and allow for further study of the virus (i.e. through WGS). In the UK, no virus could be isolated from the samples taken from cases identified through enhanced surveillance in asymptomatic poultry farm workers [18]. However, cell culture is a laborious technique that requires time and a high biosafety level and is therefore not suitable for a routine diagnostic laboratory or if timely results are required for the early detection of cases.

**Viral load assessment:** when using techniques such as RT-PCR, a higher viral load (e.g. Ct<32) could indicate an active infection rather than contamination; however, confirmation with subsequent samples is always needed to draw any conclusions as this is a qualitative assessment that relies heavily on other parameters (e.g. sample type, sample collection, methodology used).

**Viral sequencing/WGS:** sequencing can provide information on pathogenicity and transmission dynamics, which could help determine whether the virus is more likely to have caused a human infection. The lower viral load in samples that originate from contamination due to environmental exposure can prohibit WGS efforts and generate no or partial genome sequences, but this is not always the case (e.g. sequencing was successful for the two UK poultry farm cases with a high likelihood of contamination by the environment that were not deemed true infections) [62].

**Serology:** serological tests can detect antibodies against AIV, indicating a recent, past or ongoing infection. More information on serological assays, their usefulness and limitations can be found in ECDC's document: '[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].

**Epidemiological information:** this involves collecting information about the person's level of exposure (please see relevant sections of this document).

It is important to note that the tests should be carried out by trained personnel and often multiple tests are needed to confirm the infection status of a person. It is important to follow the guidelines established by public health authorities and to use validated tests and reference/control material. Confirmation of a positive test at the national influenza centre/national reference laboratory for influenza is always recommended.

## Annex 3. Biosafety and biosecurity guidance and regulations

The following WHO guidance documents and EU Directives describe the relevant biosafety regulations that may apply. In the EU/EEA, national regulatory authorities are responsible for establishing the biosafety regulations that apply in each country:

- [WHO laboratory biosafety manual, 4<sup>th</sup> edition](#) [63].
- [WHO Biorisk management: laboratory biosecurity guidance](#) [64].
- [Directive 2000/54/EC on the protection of workers from risks related to exposure to biological agents at work](#) [32] and national legislation implementing it (refer to the [EU OSHA](#) resources for further information).
- [WOAH \(OIE\) Manual of Diagnostic Tests and Vaccines for Terrestrial Animals, 2018](#) [65].
- [Directive 89/656/EEC on the minimum health and safety requirements for the use by workers of personal protective equipment at the workplace](#) [66].
- [Regulation \(EU\) 2016/425 on personal protective equipment](#) [67].
- [Directive 2008/98/EC on waste](#) [68].
- [Directive 2008/68/EC on the inland transport of dangerous goods](#) [69].

Samples from patients meeting clinical and epidemiological criteria that suggest possible infection with a highly pathogenic AIV should be handled using at least BSL-2 for diagnostic purposes (any clinical specimen should only be handled outside of a BSL-2 biosafety cabinet for molecular testing after adding lysis buffer or otherwise inactivating the specimen). Clinical samples should be considered as Category B (shipping name: 'Biological substance, Category B') and are assigned to UN 3373 [59] for shipping purposes. BSL-3 practices should be implemented for virus isolation and culture as a minimum. Sample manipulation must be performed within a class-II (or higher) biosafety cabinet [1]. Further occupational health and safety requirements may apply (e.g. record-keeping requirements). Highly pathogenic avian influenza viruses (e.g. in a culture) are considered as Category A (shipping name 'Infectious Substance affecting human') and are assigned to UN2814 ([Annex 5-G](#)) for shipping purposes.

## Annex 4. Confidentiality and ethics

The protection of privacy, confidentiality and the ethical treatment of individuals is paramount to the conduct of effective and responsible case investigations. This includes the handling and use of medical data in an occupational context. All personnel involved in avian influenza case investigations should be adequately trained to adhere to the following confidentiality and ethics guidelines:

- unique identifiers can be assigned to each case to anonymise individual identities during data processing and storage;
- access to databases or files containing case data will be strictly controlled and only authorised personnel should be permitted access;
- data transfers should be conducted securely;
- unauthorised disclosure of confidential case information should be strictly prohibited;
- all cases or their legal guardians should be required to provide informed consent, where there should be clear and comprehensive explanation of the purpose of the investigation and the privacy issues;
- confidentiality of case information should be maintained and informed consent for data collection and testing should be obtained.

Case data should be retained securely for the period defined by local regulations or institutional guidelines.

## Annex 5. Cooperation and coordination

### Coordination among different stakeholders

An effective outbreak investigation will require coordination among different levels of the health system, from the central coordination/administration departments of the country's Ministry of Health to the regional health structures and laboratories. Response to an outbreak will require coordination and collaboration among different stakeholders that can include, but is not limited to, ministries of health, ministries of agriculture, public health agencies, healthcare providers, animal health agencies and other relevant organisations, national reference laboratories, subregional diagnostic laboratories, public/private hospitals and clinics, primary care units, etc. A coordinated response can help ensure that resources are deployed in an efficient manner and that response efforts are aligned.

### Coordination between the human and animal health sectors

The animal health sector is in charge of preventing and controlling outbreaks of disease in animals, including avian influenza. Sharing of information on human cases with the animal health sector is important so that the animal sector can target their response activities. Therefore, EU/EEA countries need to ensure that they:

- establish clear and transparent communication routes between human and animal health sectors in the country, which is vital for an efficient national response to an event of public health interest; and
- emphasise the importance of information exchange between animal and human health sectors on poultry outbreaks and surveillance in humans and animals.

### International cooperation

International cooperation is essential to pandemic preparedness and response. Countries should collaborate with each other to share information, resources and expertise in order to ensure an effective global response to a potential avian influenza pandemic.

In order to ensure that the evolution of the virus can be studied and diagnostics and vaccines adapted accordingly, it is important to share virus isolates, clinical specimens and/or genetic material with the WHO Reference Laboratories and/or Collaborating Centres (for avian influenza WHO H5 Reference Laboratories). WHO can assist with shipment of samples to these WHO laboratories. Virus isolates, clinical specimens and/or genetic material should be prepared for virus/sample sharing in accordance with biosafety regulations.

Timely sequence sharing is paramount. Consensus sequences should be deposited in public databases (e.g. GISAID or Genbank). If available, raw sequencing data should be deposited in the European Nucleotide Archive (ENA). WHO has produced guidance describing the communication and publication of analysis results and how to share influenza viruses/specimens with the potential to cause human influenza pandemics [70].

The Istituto Zooprofilattico Sperimentale delle Venezie, Italy, designated as EURL for Avian Influenza in the animal health sector, is assisting actively in the diagnosis of highly pathogenic avian influenza outbreaks in EU/EEA countries by carrying out confirmatory diagnosis. It also ensures that national reference laboratories in these countries are correctly implementing harmonised and up-to-date diagnostic protocols for avian influenza [71].

The Global Influenza Surveillance and Response System (GISRS) also plays a critical role in global surveillance for respiratory pathogens and zoonotic influenza viruses from human cases. GISRS is a collaborative network of national influenza centres, including the European Reference Laboratories for Influenza Network (ERLInet), and other institutions that work together to monitor the emergence and spread of influenza viruses, including AIV [72]. The WHO Reference Laboratories are the WHO Collaborating Centres for Influenza, Crick Institute in London, UK and the WHO H5 Reference Laboratory, Pasteur Institute, Paris, France.

## Annex 6. Complementary studies for evidence generation and addressing knowledge gaps

Research will need to focus on our understanding of the virological characteristics (e.g. incubation period, duration of infectiousness), transmission patterns, immunity, severity, clinical features, and risk factors for infection from avian influenza viruses.

Additional complementary studies should be performed to obtain more information and create an evidence base for informed public health decisions. Such studies should ideally use standardised epidemiological, molecular, and serological methods and standards to enable comparability and to ultimately inform evidence-based decisions, both at national and international level.

Depending on the situation, these additional complementary studies can include (list is not exhaustive):

- Validation studies of diagnostic tests, including rapid antigen tests, point-of-care tests and existing RT-PCR methods for detection of the virus.
- Standardisation of serological assays.
- Determining the extent of asymptomatic transmission.
- Determining the extent of mammal-to-mammal transmission of the AIV strain.
- Determining the extent of mammalian adaptation.
- Determining the stability of the virus in the environment.
- Assessment of suitability of candidate vaccine viruses and antigenic similarity with the AIV strain.
- Sero-incidence studies among close contacts of patients to document the incidence of new infection using paired sera.
- Seroprevalence studies among people in the affected area (e.g. with possible occupational risk or residents of an area experiencing bird or animal and/or human outbreaks.) Such surveys should include collection of appropriate epidemiological data to assess risk factors for infection.
- Case-control or cohort studies to evaluate risk factors for infection.
- The first X cases (where the number for X depends on each country's protocol) and contact investigation protocol (e.g. transmission of the virus in first X cases or household transmission investigation protocols).
- Protective effectiveness of previous seasonal influenza infection or vaccination against AIV infections.
- Vaccine effectiveness against infection or severe disease (once vaccine is deployed).
- Systematic evaluation of the safety and efficacy of antivirals or other treatment regimens.
- Monitoring of antiviral drug susceptibility.
- Assessment of risk factors in healthcare workers.
- Defining correlates of protection.
- Level of pre-existing protective immunity from previous exposure to other zoonotic influenza strains.
- Studies on virological characteristics, infectious period and dose, incubation period, and reproduction number ( $R_0$ ).
- Genotype to phenotype: studies to better understand how the genotypic data translate to the viral phenotype are needed to better assess the impact of the emergence of different mutations.

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