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GUIDE & TOOLS

Scenarios for pre-pandemic zoonotic influenza preparedness and response in the EU/EEA

4 December 2025

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Abbreviations

CVV	Candidate vaccine virus
EC	European Commission
EFSA	European Food Safety Authority
EMA	European Medicines Agency
ERVI-Net	European respiratory virus network
EU	European Union
EU/EEA	European Union/European Economic Area
EU-OSHA	European Agency for Safety and Health at Work
EURL	European Union Reference Laboratory
FAO	Food and Agriculture Organization of the United Nations
FFX	First few X-cases
GISRS	Global Influenza Surveillance and Response System
HA	Hemagglutinin
HCW	Healthcare worker
HERA	Health Emergency Preparedness and Response Authority
HPAI	Highly pathogenic avian influenza
HTHT	Human-to-human transmission
IPC	Infection prevention and control
LHTHT	Limited human to human transmission
LPAI	Low pathogenic avian influenza
MP	Matrix protein
NA	Neuraminidase
NP	Nucleoprotein
PA	Polymerase acidic protein
PB1	Polymerase basic protein 1
PB2	Polymerase basic protein 2
PEP	Post-exposure prophylaxis
PPE	Personal protective equipment
PrEP	Pre-exposure prophylaxis
RPE	Respiratory protective equipment
SCBTH	Serious Cross-Border Threats to Health
WHO	World Health Organization
WOAH	World Organisation for Animal Health

Executive summary

The aim of this framework is to guide a scalable public health response to influenza of zoonotic origin in EU/EEA countries and provide options for preparing and responding to different possible pre-pandemic scenarios. The European Food Safety Authority (EFSA) reported unprecedented levels of HPAI A(H5N1) circulation in wild birds across Europe during the 2025 autumn migration, highlighting the need for strengthened preparedness and coordinated public health action [1,2].

We have defined 14 scenarios based on specific epidemiological and virological factors, including animal origin, characteristics of human cases (number and exposure context), severity signals, that are then further defined based on the presence of virus mammalian adaptation, antiviral resistance and mismatch with available pre-pandemic vaccines and/or candidate vaccine viruses. The document provides a detailed guide and a simple **downloadable Excel tool** for defining and scoring the different scenarios based on early triggers, promoting transparency and coherence across countries, integrating a One Health perspective, through focusing on the public health side of the response measures; it describes the baseline/escalating public health actions that should be in place/ implemented to ensure a timely and effective response.

Baseline actions in surveillance, laboratory preparedness and other public health interventions should always be in place in the current epidemiological situation in the EU/EEA. If there are human cases in the EU/EEA, escalating actions will apply depending on the scenario characteristics and will be further defined according to the assessment of the risk assessment; examples of escalating actions are described for every public health domain: interventions, surveillance, laboratory preparedness and additional studies/research. This guidance aims to strengthen countries' preparedness and capacities for the early detection and assessment of potential pandemic threats from zoonotic influenza viruses. The scenario framework is intended to inform appropriate public health actions, adaptable to evolving scientific evidence and the changing epidemiological context.

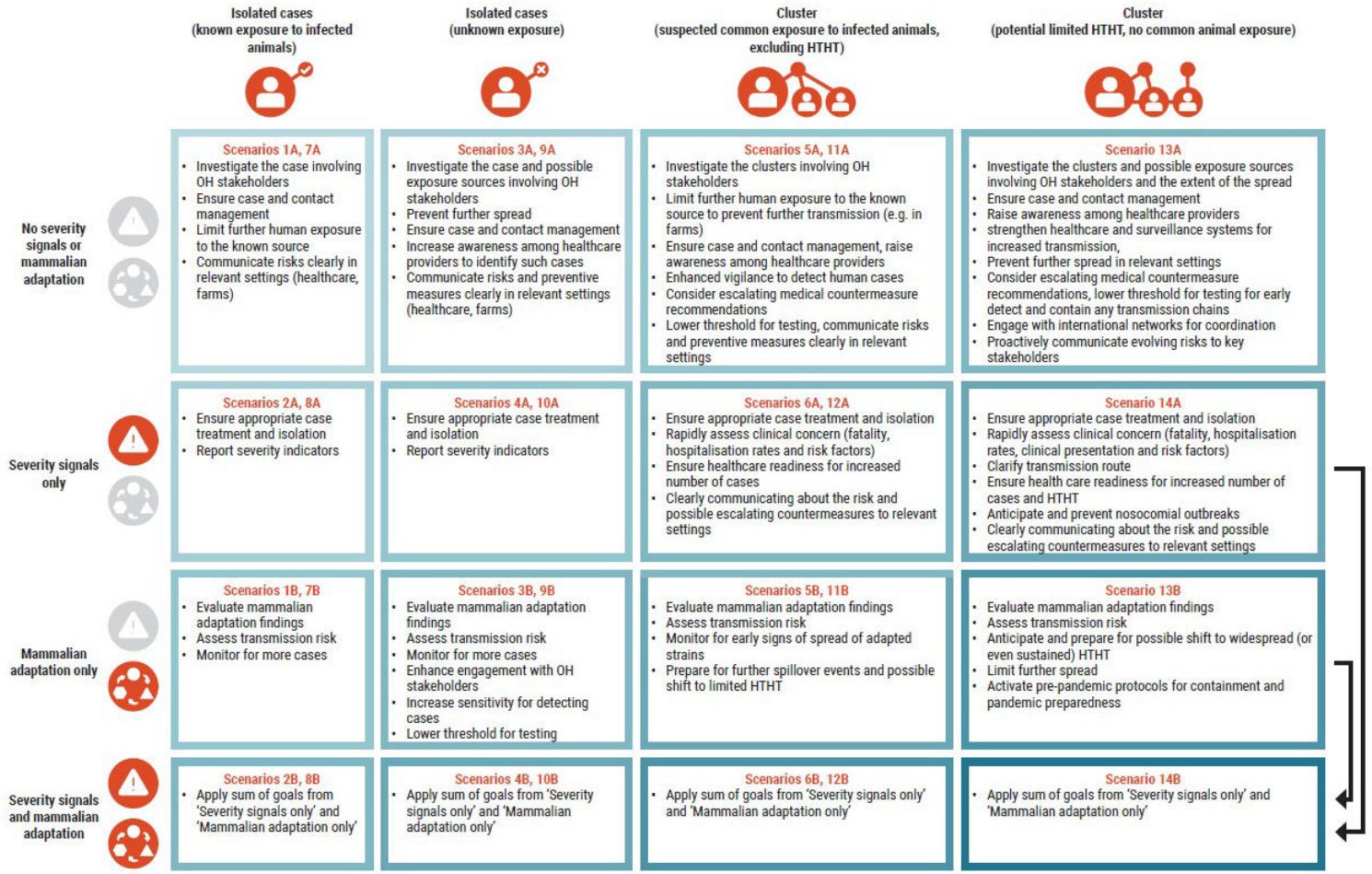
The framework is intended for EU/EEA national public health authorities, in particular those involved in preparedness plan updating, risk assessors and managers, and policy-makers in EU/EEA countries. It is also relevant to clinical and laboratory stakeholders involved in zoonotic influenza surveillance, risk communication, and outbreak response.

Recommended actions

For each scenario, the framework proposes recommended public health actions across preparedness, surveillance, diagnostics, case investigation and management and One Health coordination and communication, as well as additional studies that may be needed. For each public health measure, we recommend a set of baseline and escalating-level actions, also taking into consideration the potential for antiviral drug resistance or vaccine mismatch and the origin of the event (affected country/area inside or outside the EU/EEA). We have also summarised and linked to guidance from ECDC and other international bodies as well as EU regulations relevant to each public health measure to support consistent and evidence-based implementation.

The scenarios and the priority goals for escalating public health actions for each scenario are summarised in Figure 1 below.

Figure 1. Scenarios and priority goals for escalating public health actions



Colour grading illustrates the increasing scenario score and need for a graduated public health response in more concerning scenarios.

Key considerations

- The scoring system accounts for increased concern that may warrant escalating public health actions for scenarios with the following characteristics: virus origin in mammals or unknown sources, cases with unknown exposure, clusters of cases, severe infections and/or presence of genetic markers associated with mammalian adaptation.
- Public health actions should be adapted based on evolving evidence about the virus characteristics, human exposure routes, and the epidemiological context within or outside the EU/EEA. A risk assessment should always be performed to inform decisions on appropriate public health measures.
- Heightened alert actions within the EU/EEA may also be triggered for scenarios occurring outside the EU/EEA if they involve mammalian adaptation or signals of potential human-to-human transmission.
- A precautionary approach is recommended where uncertainty exists, especially regarding the extent of mammalian adaptation and the potential for human-to-human transmission of zoonotic viruses under investigation.

Introduction

The persistent global circulation of avian influenza viruses – particularly A(H5N1) – among wild birds, poultry, and increasingly mammals, raise concerns about the risk of zoonotic spillover and the potential for these viruses to evolve in ways that enable sustained human-to-human transmission [3,4]. The European Food Safety Authority (EFSA) reported unprecedented levels of HPAI A(H5N1) circulation in wild birds across Europe during the 2025 autumn migration, highlighting the need for strengthened preparedness and coordinated public health action [1,2]. While human cases remain sporadic, the current epidemiological situation reinforces highlights the need for a framework to respond to possible human cases within the EU/EEA. Based on experience from previous zoonotic spillover and pandemics and applying the current evidence on influenza virus genetic and phenotypic characteristics, ECDC developed a scenario-based framework to inform public health response in EU/EEA countries.

This pre-pandemic scenario framework for zoonotic influenza serves as a tool to support EU/EEA countries in translating early signals of zoonotic influenza activity into proportionate and timely public health actions. By outlining scalable interventions across scenarios of increasing concern - based on epidemiological and virological signals – the framework is designed to guide preparedness planning, early response, and coordinated decision-making. It enables countries to align response measures and decide when to activate elements of national pandemic preparedness plans in the face of potentially evolving threats such as avian influenza A(H5N1). By presenting scenarios and associated actions within a common framework, this guidance also serves as a structured communication tool to help countries identify and articulate preparedness gaps. This facilitates the comparison and assessment of shared challenges across the EU/EEA.

Robust and adaptive preparedness planning is essential to ensure that countries are equipped to respond efficiently and effectively to human cases, outbreaks or a potential pandemic caused by a zoonotic influenza virus. Preparedness and response to emergencies involve multiple actors at different levels.

At the national level, public health and veterinary authorities oversee respectively human and animal surveillance and outbreak control, with local health services and laboratories playing an important role in the implementation of measures on the field. Globally, the World Health Organization (WHO), the Food and Agriculture Organisation (FAO) and the World Organisation for Animal Health (WOAH) provide global coordination, risk assessment and reporting according to the International Health Regulations (IHR), supported by networks such as the Global Influenza Surveillance and Response System (GISRS) for data- and virus-sharing. At the national level, relevant stakeholders at all levels should be involved in the planning, informed and ready to act, applying a One Health approach [5].

Union prevention, preparedness and response plan for health crises

In line with Regulation (EU) 2022/2371 [6], the European Commission has developed a Union-wide plan for prevention, preparedness, and response. This plan sets out operational measures to support EU/EEA countries in preparing for and responding to serious cross-border health threats. It also defines the roles and responsibilities of each actor – that is, the policy-makers, crisis managers, EU institutions and agencies, EU/EEA countries, and other stakeholders involved in EU health-crisis governance – consistent with their respective mandates [7-9].

Scope and objectives

This pre-pandemic scenario framework aims to support EU/EEA countries in anticipating and responding to early threat signals from zoonotic influenza viruses. While the document has been developed in the context of avian influenza outbreaks, it can be considered for extracting public health actions relevant to responding to human infections from other zoonotic influenza viruses, taking into account the national and supranational risk assessment. The document outlines proportionate public health measures across a range of possible scenarios, and aims to support the further development of national preparedness plans in line with the EU Serious Cross-Border Threats to Health (SCBTH) Regulation [6].

This guidance aims to strengthen countries' preparedness and capacities for early detection, assessment and response to pandemic threats. While ECDC actions in support to the countries will be presented, other aspects related to EU and global preparedness and response-related mechanisms, including the declaration of a Public Health Emergency at Union level, are beyond the scope of this document as they are covered elsewhere [7]. The document also summarises and links to EU Regulations, ECDC and other international guidance relevant to each public health measure to support consistent and evidence-based implementation.

At its core, the framework presents tiered scenarios to guide stepwise and proportionate public health responses. It does not replace established risk assessment methodologies which assess the risk for specific populations by combining the *likelihood* of infection with the potential *impact* of disease, but serves a different, complementary purpose: it supports early-stage situational awareness and operational planning by characterising the evolving threat landscape. While these pre-pandemic scenarios are informed specifically by defined epidemiological and virological factors, formal risk assessment tools that assess different types of risks (e.g. risk of infection, risk of severe disease, pandemic risk) – such as the pathogen-agnostic ECDC risk assessment tool [10] or influenza-specific tools like the WHO Tool for Influenza Pandemic Risk Assessment (TIPRA) [11,12] and US CDC's Influenza Risk Assessment Tool (IRAT) [13,14] – may incorporate a broader range of contextual considerations, such as population immunity or healthcare system capacity, to reach their conclusions. This document is also not intended to cover aspects of animal health measures to mitigate the risk of importation of animals or animal products or viruses that are circulating in animals outside the EU/EEA. For those aspects, other documents can be consulted [15-20].

Finally, the scope of this document excludes pandemic-phase planning [21,22]. The escalating scenario scores do not represent a linear continuum towards a pandemic, nor are they designed to assess the likelihood or potential impact of a pandemic.

Target audience

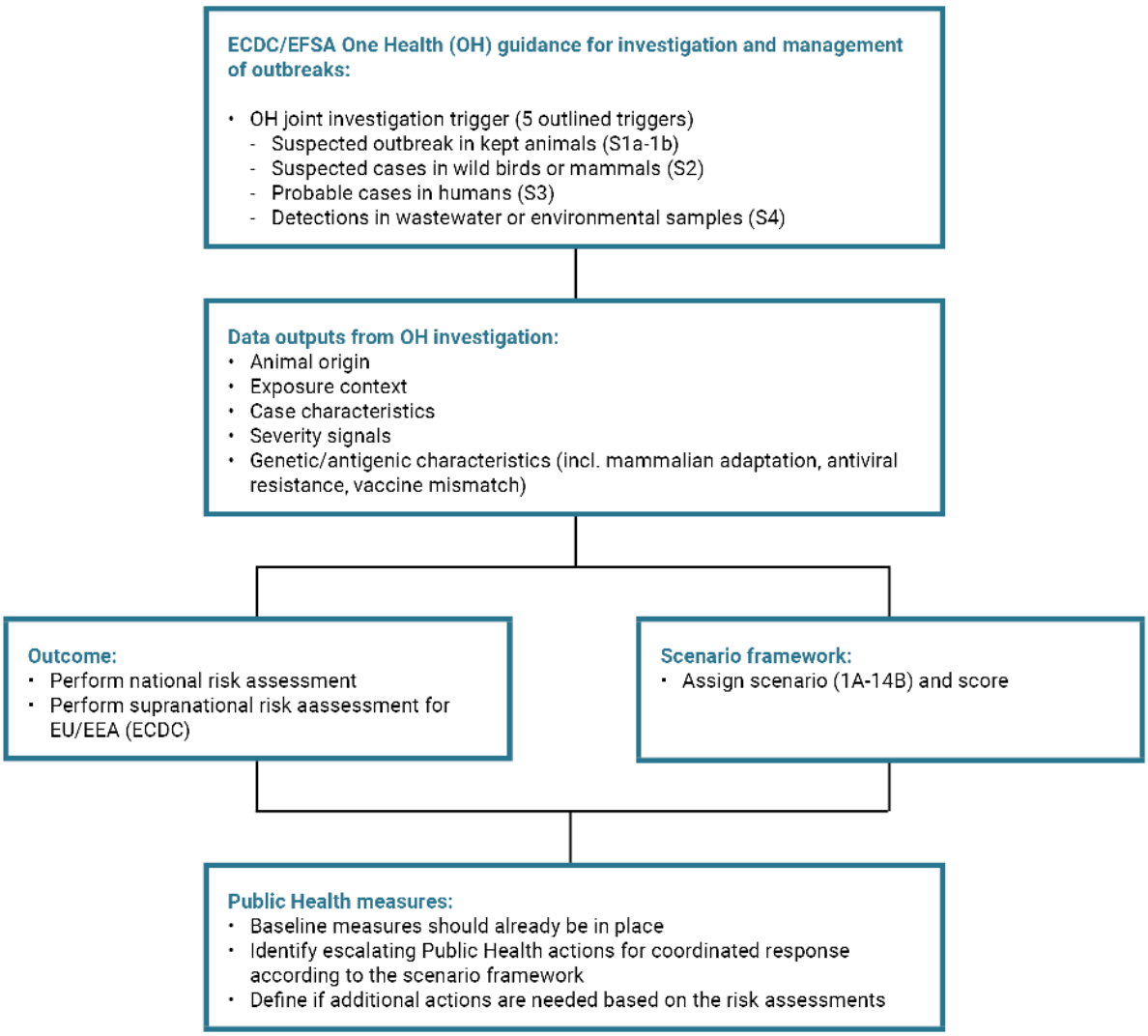
The framework is intended for EU/EEA national public health authorities, those involved in preparedness plan updating, risk assessors and managers, and policy-makers in EU/EEA countries. It is also relevant to clinical and laboratory stakeholders involved in zoonotic influenza surveillance, risk communication, and outbreak response.

One Health approach

A coordinated One Health approach is essential when responding to zoonotic influenza viruses, particularly in an evolving epidemiological situation. While this document does not detail specific One Health mechanisms, these are outlined in the jointly published ECDC/EFSA guidance 'Coordinated One Health investigation and management of outbreaks in humans and animals caused by zoonotic avian influenza viruses' [5] and further elaborated in other joint ECDC/EFSA outputs [23,24]. The One Health guidance [5] describes the investigation and management of zoonotic avian influenza triggered by different outbreak scenarios (e.g. an outbreak in animals, an environmental finding, or a human case) and focuses on the organisation of cross-sectoral work for joint investigations and case/outbreak management.

On the other hand, the current framework expands on the epidemiological and virological characteristics defined through the aforementioned joint investigations and sets out the baseline and escalating public health actions that should already be in place or further implemented after these investigations. The two documents are therefore complementary: the One Health guidance [5] identifies possible triggers for initiation of investigations and describes *how joint One Health investigations are organised in different outbreak scenarios (strategies and tools)*, while this framework defines *which public health measures to escalate* based on the signals and outcomes/data outputs of those investigations (Figure 2).

Figure 2. Linking One Health investigation and its data outputs with scenario-based public health actions



Defining and scoring the scenarios

To provide a structured approach for assessing and responding to zoonotic influenza threats with pandemic potential, different scenarios were defined. Four ECDC Experts in Respiratory Viruses were consulted for the definition of different early epidemiological and virological factors that indicate a changing situation and that are commonly assessed when human cases arise. The baseline scenario is considered as the global epidemiological situation as seen as of October 2025 and described under 'Definitions for scenario classification and scoring' in Annex 1.

The scenario-based categorisation is structured around the following factors:

1. Animal origin (birds, mammals);
2. Case and exposure context (number and clustering of human cases, known/unknown exposure);
3. Severity signals;
4. Genetic markers for mammalian adaptation (scenario subcategories A and B);
5. Limitations in available pharmaceutical measures (antiviral resistance -R, vaccine mismatch -V).

Fourteen scenarios were defined based on possible combinations of the above factors further defined (A/B) based on the existence of genetic markers for mammalian adaptation. The global situation is taken into account in defining the baseline scenario that we are currently into and also in the situation when there is risk of importation (please refer to the section National actions when there is a risk of zoonotic influenza virus importation).

The described framework does not estimate the *likelihood* of a scenario occurring; for example, mammalian adaptation is more likely to arise from virus circulation in farmed mammals than in poultry, or if an avian influenza virus spreads in swine populations that may favour reassortment events. Escalating scenarios reflect the possible accumulation of factors that may precede a pandemic, with a specific focus on those aspects that are relevant to the different public health measures, but do not estimate the *likelihood* of any given scenario progressing to a pandemic, or the *impact* of a pandemic should one occur.

Each of the defined scenarios in this framework were then scored using a composite algorithm that integrates the key epidemiological and virological indicators described above.

Each domain category is assigned a numerical value based on its potential to signal increased risk for sustained human-to-human transmission and impact to public health. The specific score values for each domain category were determined by unanimous consensus among four ECDC experts and calculated via a process of iteration (Annex 1a), working sequentially from scenarios associated with the highest potential for human-to-human transmission - such as those involving clusters of cases with unknown sources of exposure – to those with lower potential, including isolated cases emerging following confirmed exposure to an infected animal. The scoring system was independently validated by the experts and stress-tested using real-world cases, such as recent A(H5N1) human infections in the United States and Asia, to evaluate performance and ensure appropriate differentiation between scenario levels. The scoring system was finalised following a process of peer review by additional ECDC experts and following written consultation with the European Respiratory Virus Disease Network (ERVI-Net) and the European Food Safety Authority (EFSA).

Based on the scoring, the total scenario score (maximum of 15) is the sum of values assigned to categories in three domains: 1) onward human-to-human transmission potential; 2) virological adaptation to mammals; and 3) severity potential. Two additional factors – antiviral resistance and pre-pandemic vaccine mismatch – are included as qualitative scenario modifiers (-R and -V), guiding specific public health actions but not contributing numerically to the score (Annex 1a). The total scenario score is the sum of values assigned for each category across three domains. Please refer to the section 'Definitions for scenario classification and scoring' in Annex 1b for an explanation of how to define each category.

The scoring system was designed to assign higher scores to scenarios with higher risk of human-to-human transmission and/or greater potential public health impact, considering the following characteristics: virus origin in mammals or unknown sources, clusters of cases, unknown exposure, severe infections, presence of genetic markers associated with mammalian adaptation. Higher scores also reflect scenarios that exhibit signs of increased infection severity, as these may warrant additional public health actions (e.g. reinforced infection prevention and control (IPC) measures). While the presence of milder cases does not exclude the possibility of pandemic evolution, such an assessment falls outside the scope of this document, which focuses exclusively on the corresponding public health measures.

The resulting score reflects the composite estimate of the level of public health concern with regards to the corresponding need for escalation of response measures. For each scenario a score *range* is presented, to reflect the uncertainty associated with early assessment, in particular the assessment of virus mammalian adaptation (Figure 3).

The scoring system primarily serves as a structured tool for making comparative assessments between emerging scenarios within and between countries and supports a harmonised approach for public health decision-making and escalating public health actions at national and supra-national levels. The framework links scenario-specific actions to the scenarios, using overlapping bands for scenario scores rather than fixed values, to account for uncertainty during early outbreak stages, particularly when virological assessments are ongoing or incomplete. Scoring also allows comparison of simultaneous outbreaks with differing virological features. Overall, the scenario framework and scoring system promote consistency and early action, providing a shared reference for countries and enabling coordination with supranational partners such as the European Commission and EU agencies like ECDC, EFSA, EMA, EU-OSHA and WHO.

When information is unknown or unavailable, we suggest following a precautionary approach and assigning a higher score that can be modified retrospectively. While the scoring system is designed to accommodate challenges such as limited information (e.g. unknown animal origin), some countries may still be unable to complete all elements of the scoring – particularly where specialised resources, such as bioinformatic capacity, are limited. ECDC support services are available via access to internal microbiology capacity and laboratory network support. In addition, ECDC carries out its own independent assessment. Comparison between ECDC's scoring and national assessments can be part of the scenario evaluation, helping to identify potential gaps and inform scenario-specific preparedness and response recommendations.

IMPORTANT! The detailed scenario scoring algorithm is described in Annex 1a.

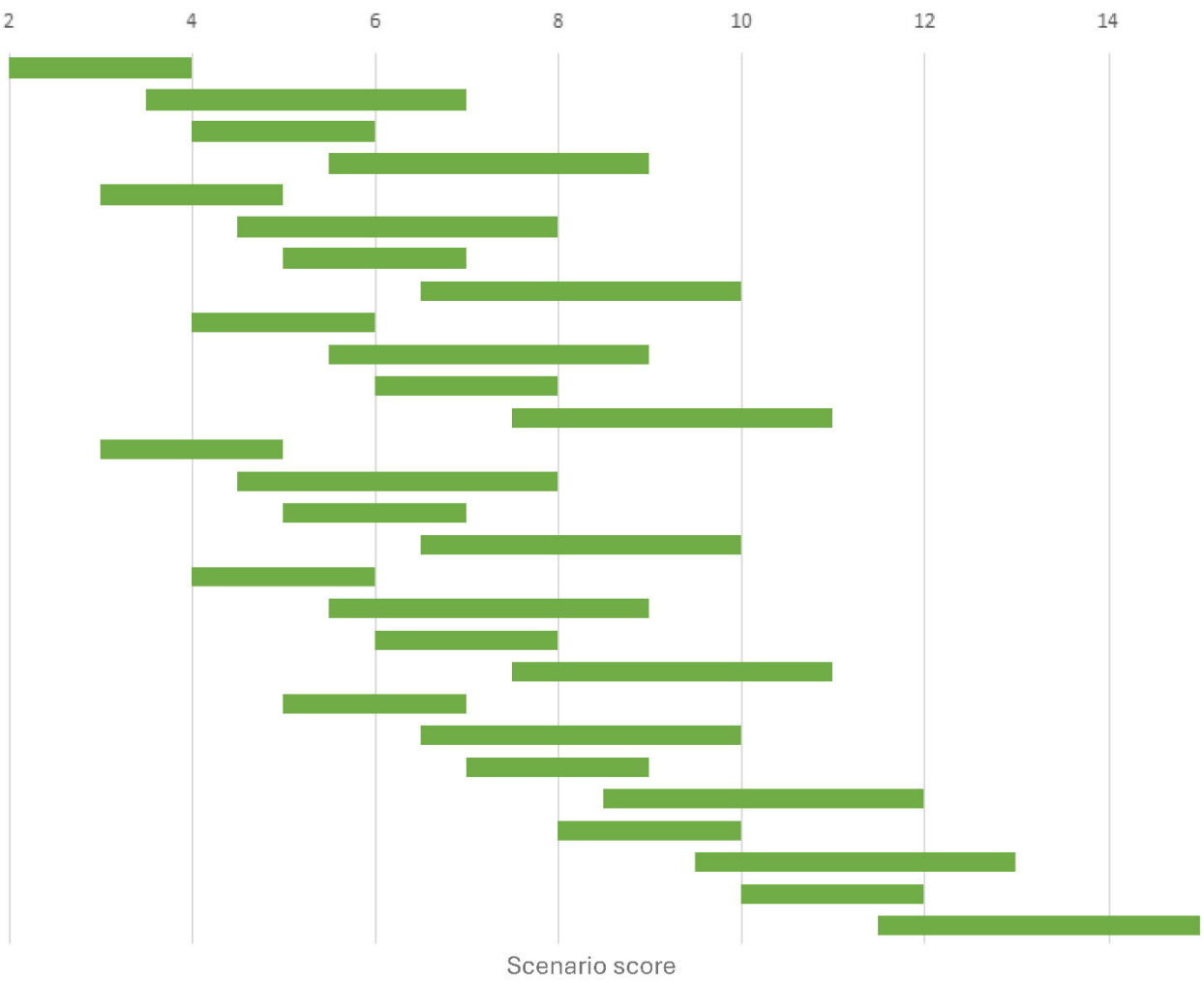
IMPORTANT! Details on the Definitions (i.e. what is the baseline scenario, how to define the affected area, virus origin, cluster of cases, exposure context and how to interpret severity signals and mammalian adaptation) are described in detail in Annex 1b.

IMPORTANT! A downloadable Excel tool is provided to support with the definition and scoring of the scenarios.

Figure 3. Scenarios and their scoring outcomes

The scenario scoring and factors are described in the method section.

Animal origin	Cases in humans	Severity signal	Mammalian adaptation potential	#
Birds	Isolated cases (known exposure)	No	A	1A
			B	1B
		Yes	A	2A
			B	2B
	Isolated cases (unknown exposure)	No	A	3A
			B	3B
		Yes	A	4A
			B	4B
	Clusters (suspected common exposure, excluding HTHT)	No	A	5A
			B	5B
		Yes	A	6A
			B	6B
Mammals or unknown	Isolated cases (known exposure)	No	A	7A
			B	7B
		Yes	A	8A
			B	8B
	Isolated cases (unknown exposure)	No	A	9A
			B	9B
		Yes	A	10A
			B	10B
	Clusters (suspected common exposure, excluding HTHT)	No	A	11A
			B	11B
		Yes	A	12A
			B	12B
N/A	Limited HTHT (no common animal exposure)	No	A	13A
			B	13B
		Yes	A	14A
			B	14B



Determining key baseline and escalating actions

A review of published national preparedness and response plans was conducted to identify key national and supranational public health actions relevant for preparing and responding to zoonotic influenza infections for each scenario.

Public health actions were finalised following a process of peer review by additional ECDC experts (from the Respiratory Viruses, Emergency Preparedness and Response, AMR and Healthcare Associated Infections, Communication sections) and following consultation with the European Respiratory Virus Disease Network (ERVI-Net), ECDC's National Focal Points for Preparedness and Response, ECDC's Advisory Forum, European Medicines Agency (EMA), EFSA and the European Agency for Safety and Health at Work (EU-OSHA). The document has been shared with SANTE and HERA to ensure alignment with ongoing initiatives at EU level.

Public health actions were divided into the following categories:

- **Baseline-level actions**, which are relevant to the current baseline scenario (described in the 'Definitions for scenario classification and scoring' in Annex 1b) and should be actively implemented by all EU/EEA countries.
- **Escalating-level actions**, which should be applied across the different scenarios depending on the scenarios' epidemiological and virological characteristics. Escalating-level actions are defined for consideration in the affected country or area and in areas with similar risk in the EU/EEA, based on the national risk assessment. The geographical area considered affected for public health actions may need to be adjusted depending on the scenario, conclusions of the risk assessment and epidemiological investigation. Escalating-level actions may also be applicable if an imported case is detected.
- **Heightened alert-level actions**, which are relevant to scenarios where there is a risk of importation to the EU/EEA due to clusters with significant mammalian adaptation detected and/or potential limited HTH transmission outside the EU/EEA.

The lists of proposed baseline and escalating actions follow a precautionary approach, informed by existing knowledge from past events of animal-to-human and limited, not sustained human-to-human transmission. As new evidence emerges about the characteristics of the virus causing the outbreak in animals and/or humans and the epidemiological context, the recommendations may need to be updated or refined. Similarly, if the situation de-escalates – for example, if circulation of avian influenza viruses in birds and other animals decreases significantly – recommendations may be revised downward to reflect the lower level of concern. Supranational and national risk assessments should be used to update and refine public health actions and inform decisions as needed.

National-level baseline and escalating actions

This section outlines key national-level public health baseline and escalating actions that can be implemented in response to emerging zoonotic influenza threats. Together, the baseline and escalating activities provide a list for relevant scalable preparedness and response actions that can be considered across the different pre-pandemic scenarios. Baseline actions should always be in place as long as there is widespread circulation of zoonotic influenza viruses in animals and sporadic human cases even outside the EU/EEA; a definition of the baseline scenario is provided in Annex 1b.

Potential escalating actions are recommended for the different scenarios and are defined for the affected EU/EEA countries/areas or areas in similar risk, based on the national risk assessment. The main goals/objectives in each scenario are described in Figure 1 in the Executive summary.

The actions are categorised into four main domains below:

- Preparedness and public health interventions;
- Surveillance activities and case/outbreak investigations in humans;
- Laboratory preparedness, activities and functions; and
- Research and additional studies.

IMPORTANT! The downloadable Excel tool can be used to extract the relevant public health actions for each domain for each scenario.

IMPORTANT! A list of all baseline and escalating actions is presented in Annex 2 (separate table for each domain, Tables A2.1 – A2.4).

IMPORTANT! In Annex 3 (Tables A3.1 – A3.9), the escalating actions for each domain have been mapped to each of the scenarios based on the current knowledge; in the event of human cases in the EU/EEA, a risk assessment should be used to determine the most appropriate actions; additional actions may be warranted according to the situation.

While presented in separate sections in this document, the actions across the different domains are closely interconnected and should be considered collectively in preparedness planning, in outbreak investigations and when implementing public health actions. Depending on the scenario and overall epidemiological situation, the identified risk area may be more narrowly or broadly defined (e.g. more broadly defined in case of evidence of limited human to human transmission (LHTHT)). The escalation and de-escalation triggers and processes should be included in the operational plan for avian influenza and/or the pandemic influenza plan, whichever the country is implementing.

Preparedness and public health interventions

These actions encompass core public health measures aimed to reduce exposure, limit transmission and mitigate the broader impact of zoonotic influenza outbreaks. Interventions include occupational health and safety (including use of personal protective equipment (PPE)), IPC, vaccination strategies, and the use of antivirals. In addition, they include One Health and international coordination aspects as well as risk communication. These actions are designed to be scalable depending on the context of the outbreak, the level of concern and anticipated severity. Table A2.1 in Annex 2 summarises baseline and escalating national-level public health actions in this domain and links the relevant EU regulations and ECDC guidelines.

One Health coordination and international collaboration

At baseline, strong intersectoral coordination between the animal and human health sectors should be established and sustained. Prompt sharing of sequences in public databases, like GenBank or GISAID and ENA, associated with relevant metadata is critical. A recent joint publication by the EU/EEA and EFSA outlines specific One Health tools for zoonotic avian influenza that should be established at baseline scenario as well as five triggers for One Health investigations with corresponding actions for management of the case(s)/outbreaks [5]. Figure 2 illustrates how the One Health guidance document and the cross-sectoral investigation outcomes link to the current scenario-based framework for response and specific public health actions. The One Health guidance emphasises the importance of clear information flows between veterinary and public health authorities and underscore the need for timely joint risk assessments. A summary of One Health coordination baseline actions is presented in Annex 2 – Table A2.2. In addition to One Health coordination, baseline actions to ensure international collaboration are outlined.

In the event of a human case in the EU/EEA (Annex 2 – Table A2.2 and Annex 3 – Table A3.1), escalating actions should include national authority participation in high-level cross-sectoral meetings with EU/EEA stakeholders (e.g. ECDC, EFSA). It is important to communicate key points on the evolving epidemiological situation across different sectors. In certain scenarios, where there are not just isolated cases, it is important to increase the frequency of rapid joint risk assessments as additional information becomes available to facilitate identification of measures to be taken by the respective stakeholders. In certain scenarios, suggestive of potential HTHT, additional engagement with international stakeholders such as WHO, FAO, and WOAH should be initiated to exchange information and coordinate response strategies. Where markers of mammalian adaptation mutations are detected, real-time communication channels between veterinary and public health sectors that should be in place, should enable timely risk assessment and coordinated monitoring of concerning mutations in animal populations.

Proposed escalating actions are mapped to the different scenarios in Annex 3 – Table A3.1.

Occupational health and safety measures

Occupational health and safety measures to reduce human exposure to zoonotic influenza at the human-animal interface must comply with Directive 2000/54/EC [25] on the protection of workers from the risks of exposures to biological agents and with national legislations (Table 1).

Employers must regularly update the risk assessment taking into account the current epidemiological information provided by health and safety authorities and determine the risk to workers considering the virus classification (group 1, 2, 3 or 4, (art. 2 Directive 2000/54/EC)) as well as the characteristics of the activity in which the worker may be exposed: direct/indirect contact with animals, their fluids, contaminated water, waste or equipment, and exposure time. When the assessment reveals a risk to workers' health and safety, employers must update the prevention plan to implement measures to reduce the risk to as low as possible to protect workers, always taking into consideration vulnerable workers. Escalating occupational safety measures to prevent transmission of zoonotic influenza should focus on strengthening risk assessments, ensuring compliance with Directive 2000/54/EC.

Considerations about vaccination are addressed in the dedicated Section below ('Vaccination').

In the case of an 'intended use of the group 3 and 4 viruses' such as at health and veterinary facilities other than diagnosis, industrial processes (e.g. pharma and biotechnology industries) and laboratories and animal rooms, specific restrictions must be applied including containment measures (Directive 2000/54/EC). Highly pathogenic

avian influenza viruses HPAI (H5), e.g. H5N1, (H7), e.g. H7N7, H7N9, Influenza A virus A/New York/1/18 (H1N1) (Spanish flu 1918), Influenza A virus A/Singapore/1/57 (H2N2), and Low Pathogenic Avian Influenza Virus (LPAI) H7N9 are currently classified in group 3 (Directive 2000/54/EC).

Different scenarios, depending on the specific bird/mammal outbreak context may require an addition and a reinforcement of the implemented prevention measures to ensure tailored and proportionate protection strategies to the risk level. Therefore, risk assessments must be regularly updated according to the latest information and workers should receive continuous training on safe working practices, prevention measures for each activity and risk level, correct use of PPE, and emergency procedures.

Currently, the most likely route of transmission is by breathing droplets generated by infected animals or by contact of mucosa with contaminated dust and water. Highlighted below are some measures that can reduce the transmission of the virus in farms and agricultural settings and should be taken into account in the baseline scenario. This is not a comprehensive list and in the case of an outbreak at the workplace or a release of new information on the epidemiological situation the risk assessment should be revisited, and more strict measures may be needed. All recommendations from the health and safety authorities should be followed. When implementing exposure control measures, the hierarchy of control should be followed in line with Directive 2000/54/EC on the protection of workers from risks related to exposure to biological agents at work and the national legislation implementing it, with the use of technical, collective and organisational measures first and the provision of personal protective equipment (PPE) as a last resource when contact with the source cannot be avoided (i.e. protection of workers health cannot be sufficiently achieved by other means). Specific actions to prevent wildlife access and transmission of the virus, as well as hygienic measures and PPE need to be considered. Workers need to be informed about what to do if they develop symptoms and to report the history of exposure when they seek help.

Actions to prevent transmission of the virus

- Establish protocols for all tasks so they are carried out in a way that minimizes exposure and the generation of dust, including protocols for cleaning and decontamination and the safe collection, storage, transport and disposal of animal waste, contaminated water and equipment.
- Increase air renewal in indoor environments.
- Regularly clean and disinfect premises and equipment. Introduce easy-to-clean surfaces on floors, walls and work equipment (e.g. machines, equipment, production facilities).
- Reduce the number of workers that are in contact with animals or in contaminated environments as well as the contact time.
- Separate contaminated and clean areas to prevent cross-contamination.
- Use of the biohazard sign to signal de-risk.
- Follow national authority regulations for sanitising e.g. manure, slurry and contaminated water.

Hygiene measures

- Clothing management: separate storage should be provided for work and street clothing. Workers must have access to clean, decontaminated clothing at the start of each shift, and contaminated items should be safely stored and handled to prevent cross-contamination.
- Decontamination facilities: employers should provide facilities for washing, which may include eye washes and skin antiseptics. Where advised and in particular in the case of outbreaks, workers should be allowed to shower at the worksite or at nearby decontamination stations at the end of their shifts.

Actions to prevent wildlife access are not discussed in this document.

In escalating situations (Annex 2 – Table A2.1 and Annex 3 – Table A3.2) staff should be limited to essential personnel only, with enhanced disinfection of contaminated areas, strict separation of clean and infected zones, restricted access, and close monitoring of workers exposed to suspected or confirmed infected animals. Agricultural settings should also implement manure and wastewater sanitation and surveillance in line with national recommendations.

Personal protective equipment (PPE)

The use of PPE is the last line of defence in the hierarchy of control measures. When the risk of being exposed through any pathway (inhalation, dermal, ocular) is high (e.g. direct/indirect contact with suspected to be infected animals or their secretions, contaminated objects or working in contaminated environments where there may be air droplets or dust) and cannot be avoided or sufficiently limited by technical means of collective and organisational measures, workers should be provided with appropriate PPE in compliance with Regulation (EU) 2016/425 and any national legislation. The risk assessment should provide information on when PPE is required and what type of PPE should be used. PPE should be properly stored, maintained, disposed, decontaminated if necessary and replaced when defective. It is important to note that the use of PPE can be burdensome (especially respiratory protection equipment) to workers in the field.

Employers should specify procedures for putting on (donning) the PPE on and removing (doffing) it safely and provide training in correct use and storage to workers. Contaminated clothing and PPE should be cleaned, disposed or decontaminated if re-used by the employer according to manufacturer instructions. Fit-testing for respiratory protective masks is highly recommended.

For group 3 and 4 viruses, PPE should include:

- Eye protection, such as goggles or face shield to protect from splashes;
- Respiratory protection, for example fit-tested filtering face piece class-2 (FFP2) mask, air purifying equipment or respirators;
- Impervious gloves (rubber, nitrile, vinyl, no latex);
- Disposable or polycotton coverall with head coverage CE type 5 & 6 that offer protection against dusts, splashes, and liquid sprays; and
- Rubber polyurethane boots.

In escalating situations, personal protective measures must be reinforced, ensuring availability and compliance of PPE under Regulation (EU) 2016/425 [26], with clear protocols for use, storage, disposal, and decontamination. Training and adherence monitoring should be expanded, alongside increased frequency of respirator fit-testing.

Vulnerable workers

Specific protective measures should be in place for at-risk groups, such as pregnant or breastfeeding workers (Directive 92/85/EEC) [27], workers with pre-existing conditions, young workers (Directive 94/33/EC) [28], and inexperienced workers. Employers should provide tailored training and protection for these groups, ensuring their health and safety in high-risk environments. Migrant and temporary workers may face heightened risks due to lack of experience, limited access to information and knowledge of the language or challenging working conditions. Employers should ensure these workers are fully informed and trained in all health and safety protocols, with special attention to language barriers or other communication challenges. The social and infrastructural realities of rural agricultural communities where avian influenza risk is currently concentrated require a specific focus [29].

Health surveillance

Workers in contact with infected or suspected to be infected animals should undergo regular monitoring for influenza-compatible symptoms and/or other health complaints. If a worker is found to be suffering from an infection or illness as a result of exposure, health surveillance (monitoring and testing) potentially should be offered to other workers who have been similarly exposed.

Follow up of exposed workers to suspected to be infected or infected animals is covered under the 'Surveillance' Section below. Health surveillance must be scaled up in escalating situations, including proactive testing of exposed workers regardless of symptoms, vaccination or prophylaxis in line with national guidance, and extending monitoring and follow-up to all potentially exposed colleagues when one worker is found infected.

Targeted surveillance of healthcare workers

If there is potential risk to healthcare staff, testing criteria for HCW caring for hospitalised cases should be re-evaluated, including consideration of regular testing regardless of symptoms. Depending on the testing demands and the laboratory capacity, the use of validated rapid antigen tests may be considered.

Proposed escalating actions are mapped to the different scenarios in Annex 3 – Table A3.2.

Infection prevention and control (IPC)

At baseline, when there are no cases yet in the EU/EEA, healthcare facilities should review and potentially update operational protocols for the appropriate management of suspected cases with minimisation of exposure of healthcare staff and other patients through administrative and environmental controls as well as standard and transmission-based precautions, including use of appropriate PPE, environmental cleaning and disinfection, and waste management procedures (Annex 2 – Table A2.1). National case investigation and management guidance addressing contact tracing, case finding and the duration of isolation of cases and quarantine of contacts should be available to inform healthcare facility protocols (see ECDC Investigation protocol for human exposures and cases of avian influenza in the EU/EEA) [30]. Escalation if there are severely ill patients, and especially if there are clusters of cases with indication of limited human-to-human spread, requires ensuring rapid patient transfer to appropriate treatment/isolation centres, and increased awareness among healthcare workers about updated triage, testing, and patient management protocols, in addition to ensuring the rigorous application of IPC, including PPE use, mentioned above. Healthcare facilities should ensure the provision of sufficient resources and supply chains for adequate PPE to implement emergency procedures in case of escalation.

In the context of clusters when suspected cases of infection may get in contact with any level of care, the relevant IPC operating procedures for emerging viral respiratory infection of pandemic potential or high impact should be activated and standard precautions, including hand and respiratory hygiene, must be rigorously applied

across all levels of care. IPC implementation should be supported by regular refresher training and operational readiness assessments, as well as clear communication and adequate organizational leadership that facilitates adherence to the procedures. Furthermore, it should be noted that increased pathogenicity of a certain influenza virus strain can be linked to specific genetic markers affecting clinical presentation and outcome; in case of an increase in the number of severe cases in clusters of human cases, investigations should also take this into consideration when assessing the risk of severe disease and the escalation of public health actions.

Proposed escalating actions are mapped to the different scenarios in Annex 3 – Table A3.3.

Risk communication and training

Risk communication strategy and relevant operating procedures should be included in the operational plan for zoonotic influenza. Baseline risk communication actions focus on defining and implementing a clear communication strategy defining objectives, key messages, target audience, communication channels, timelines and resources. Objectives should clearly define what the communication aims to achieve (e.g. increased awareness, promote protective behaviour, reduce misinformation). Target audiences should be clearly defined (e.g. healthcare professionals, the general public in affected or at-risk regions, occupational groups at higher risk (e.g. farm workers, cullers, veterinarians) including migrant and temporary workers). Based on this, messaging should:

- issue **targeted prevention messages** based on real-time epidemiological data;
- provide **clear, actionable guidance** on hygiene, food safety (e.g. thorough cooking of poultry), and personal protection; and
- adapt messages using insights from **behavioural and social science research** to increase relevance and effectiveness.

Communication channels to deliver the message should be varied and take the target audience in consideration. Channels can include traditional media (press, radio, TV), digital platforms (web, social media etc.), community engagement and outreach via trusted intermediaries, especially for hard-to-reach groups, or other established channels for engagement with the community of farm workers and cullers, many of whom may belong to migrant communities.

It is important that the messaging is timely and aligned with the epidemiological situation. Messages should be coordinated with other sectors, particularly animal health and relevant SOPs should be in place. Messaging should be formulated and disseminated in line with outbreak phases (preparedness, early detection, escalation, recovery). Multi-disciplinary communication teams (involving technical experts, clinicians, behavioural scientists, risk communicators, press officers, social media managers etc.) should be established during inter-epidemic periods and activated when needed. Training efforts at the national and regional levels, such as workshops and simulation-based exercises, should be implemented to build capacities and identify gaps, involving multiple stakeholders to ensure a coordinated One Health approach.

Escalation of risk communication activities is warranted when there is a significant shift in the epidemiological or virological characteristics (Annex 3 – Table A3.4). In these situations, public health messaging should be intensified and tailored to the specific context following the considerations listed above, with clear guidance for healthcare professionals and high-risk groups, coordinated communication with media and proactive efforts to address misinformation and public concerns. Real-time social listening can be implemented to detect public sentiment, misinformation trends, and information gaps. Messages should be framed to support protective behaviours without creating stigma or panic. Risk communication messages should take into consideration relevant messages across affected EU/EEA countries and neighbouring regions to prevent confusion from inconsistent information. Community engagement activities in the areas where zoonotic influenza outbreaks have been detected and particularly if human cases are suspected or confirmed. For this, engagement with EU-level bodies such as ECDC and EFSA and international partners (e.g. WHO, FAO, WOAH) is recommended to ensure alignment and amplify messages.

Antivirals

Antiviral use for zoonotic influenza involves both treatment and post-exposure prophylaxis (PEP), initially guided by national recommendations for individuals exposed to infected animals, particularly in occupational settings. Baseline actions (Table 1) include ensuring availability for seasonal influenza management purposes (of neuraminidase (NA) inhibitors oseltamivir and/or zanamivir and/or polymerase acidic protein (PA) inhibitor baloxavir marboxil) and applying antivirals for confirmed cases and high-risk exposures taking into consideration potential indications that the circulating virus in animals is more virulent or transmissible in mammals.

Escalation of measures is warranted when there are signals of increased severity in human cases, clusters of infection (with or without known exposure), or the detection of mutations associated with mammalian adaptation – factors that may increase the risk of zoonotic or human-to-human transmission (Annex 2 – Table A2.1 and Annex 3 – Table A3.5). In such scenarios, national recommendations may be expanded to include broader groups for PEP or even consider pre-exposure prophylaxis (PrEP) in targeted populations and securing rapid deployment mechanisms in line with the approved EU label. Depending on the availability of adamantanes (amantadine and rimantadine) they may also be considered in line with national recommendations, in case other antivirals are not effective against the circulation influenza virus strain or are not available, and if it is proven that the circulating zoonotic influenza strain is susceptible to Adamantanes.

According to the label of the EU approved antivirals, the PEP indication (NA inhibitors Tamiflu and Relenza, as well as PA inhibitor baloxavir Xofluza) is broad and includes children and adults; specifically oseltamivir is approved for individuals aged one year and older with contact to a clinically diagnosed influenza case, when influenza virus is circulating in the community, Zanamivir for children aged five years and older after contact with clinically diagnosed influenza case in the household, and baloxavir for individuals aged three weeks and older. In case national recommendations have different recommendations for initiating PEP, then it could be of value to consider expanding PEP use for escalating actions.

The approved labels for influenza antivirals include recommendations for the use of PrEP in exceptional circumstances (e.g. if there is a mismatch between circulating and vaccine virus strains and in a pandemic situation). It can therefore be considered in escalating scenarios when there are human cases in the EU/EEA, especially if there are clusters of cases, according to national recommendations for specific groups (e.g. those workers involved in culling activities of infected animals, household contacts of confirmed human cases or HCWs) according to national recommendations. It should be noted that prolonged use may have implications in safety or resistance emergence. For the antivirals that have an EU-approved PrEP indication at the time of the report the duration of use is for Tamiflu and Ebilfumin up to six weeks (and up to 12 weeks in immunocompromised individuals) and for Relenza (approved by EU MS), up to 28 days [31-33]. As the incubation period of the virus in not yet known, recommendations may need to be adapted when more information becomes available.

In the event of reduced susceptibility to available antiviral drugs, guidance should be adapted to include potential alternative or combination therapies, with consideration of adaptation of vaccination strategies if resistance affects multiple drug classes or if effective antivirals are unavailable during outbreaks of concern. Ensuring access to a range of antiviral agents remains a critical preparedness component.

Vaccination

Vaccination strategies for seasonal, zoonotic and pandemic influenza vaccines are central to preparedness and response measures when zoonotic influenza cases emerge. Seasonal influenza vaccines protect against seasonal influenza virus strains expected to circulate in the population each year, based on global surveillance [34,35]. They reduce the burden of seasonal influenza and – particularly during epidemic periods – may also reduce the hypothetical risk of viral reassortment should individuals become co-infected with both seasonal and zoonotic influenza viruses [23,36]. Zoonotic influenza vaccines are intended to immunise individuals at risk of exposure to animal influenza viruses during outbreaks originating in animals – particularly when there is a risk of human infection or the potential emergence of a pandemic caused by the same or a similar virus strain – in order to protect against severe disease [37]. Pandemic influenza vaccines, by contrast, are developed for use when a novel influenza virus is spreading efficiently among humans, with the aim of providing population-wide protection against severe disease [37].

Vaccination strategies for seasonal and zoonotic influenza form an important part of preparedness and response efforts. At baseline (Annex 2 – Table A2.1), countries may offer seasonal influenza vaccines and, where available, consider the use of zoonotic influenza vaccines for high-risk groups, such as farm workers and culling teams. However, there is currently no real-world evidence on the effectiveness of zoonotic influenza vaccines in preventing severe disease. This is due to limited vaccine deployment, the absence of outbreaks with sufficiently large numbers of both vaccinated and unvaccinated individuals, and the fact that A(H5N1) infections reported globally among occupationally exposed individuals have so far been mild [23,38]. Taken together – in the current baseline scenario and given that no human cases have been detected in the EU/EEA – there is currently insufficient evidence to support a broad recommendation for their use across all EU/EEA countries based on lack

of studies proving clinical effectiveness. Implementation of zoonotic influenza vaccines for occupationally exposed individuals therefore remains an optional measure, to be decided at the discretion of countries [23]. Notably, zoonotic influenza vaccines are intended to complement, not replace, other containment and protective measures, including the use of personal protective equipment (PPE) and the prophylactic use of authorised antivirals. The assessment may need to be updated if the epidemiological situation changes or more information becomes available.

Following a WHO Strategic Advisory Group of Experts on Immunization (SAGE) meeting convened in September 2025, WHO has published provisional updated recommendations. SAGE recommended that countries consider issuing guidance on the use of available licensed influenza A(H5) vaccines during the interpandemic and emergence periods, where this aligns with national public health priorities. Such guidance should be based on a careful review of the evidence, using the WHO evidence-to-recommendations framework. SAGE emphasised that the primary objective of using licensed influenza A(H5) vaccines is to prevent severe disease in individuals at higher risk of infection, with A(H5) vaccination being complementary to other containment and protective measures. Based on existing epidemiological data, SAGE recommended prioritising vaccination for the following groups, according to their risk of exposure: laboratory workers who handle influenza A(H5) viruses; first responders involved in zoonotic influenza outbreaks; health workers who evaluate or manage suspected or confirmed human cases, including potential vaccinators; and people with ongoing contact with animals or their environments in geographic areas where animal or human infections have been reported (Table 1) [39,40].

Table 1. WHO SAGE (interim) decision-aid matrix for determining the use of A(H5) vaccines at country level across four foreseeable situations during the interpandemic and emergence periods

Note the final SAGE update will be published in the Weekly Epidemiological Record in December 2025 [39,40].

Period	Situation	Description	Laboratory workers who handle A(H5) viruses	First responders in zoonotic influenza outbreaks	Health workers involved in treating suspected or confirmed human A(H5) cases	People with ongoing contact with animals or their environments based on local context*
Interpandemic period: no human cases, but animals may be infected	**A**	• No human cases; and • No animal cases	•	–	–	–
	B	• No human cases; but • Animal cases are occurring	•	•	–	•
Emergence or introduction periods: sporadic human cases or clusters of human cases	**C**	• Increasing number of sporadic human cases and/or severity of sporadic human cases; and • Animal cases are occurring	•	•	•	•
	D	• Increasing number of clusters of human cases; and • Animal cases are occurring	•	•	•	•

• = Consider use; if supply allows and based on local context
– = Not recommended
** This could include individuals routinely, occupationally or otherwise exposed to animals, their secretions or contaminated environments, such as poultry/farm workers, veterinarians, zookeepers, backyard bird flock owners, live bird market vendors, people with recreational exposure to animals (e.g., hunters, wild bird watchers).*

When deciding on A(H5) vaccine use during interpandemic or emergence periods, key factors include:

- **Animal**: number of affected animals, extent of detection, availability of preventative and response measures to tackle animal outbreaks, and the species involved (e.g. poultry, dairy cattle, swine), which affect zoonotic risk.
- **Human**: number and trend of cases, source of infection (zoonotic, unknown, or suspected human-to-human), and disease severity.
- **Virological**: match between circulating strains and available A(H5) vaccines, and detection of concerning mutations[40]

Escalating actions (Annex 2 – Table A2.1 and Annex 3 – Table A3.6) can be triggered by clusters of human cases, especially where exposure is unknown or there are signs of possible human-to-human transmission. Measures include continuing seasonal influenza vaccination (preferably inactivated vaccines in pre-pandemic escalating scenarios due to the potential reassortment risk with a live attenuated virus) [38], expanding A(H5) pre-pandemic vaccination to additional high-risk occupational groups, preparing logistics for wider roll-out, and prioritising vaccine allocation based on the concern level.

In scenarios featuring rising human case numbers, severe illness, or widespread antiviral resistance, vaccination may be extended to healthcare workers and other vulnerable populations. Decisions should also consider virological evidence – such as circulating clades and mutations that could increase the risk of spillover events to humans, human-to-human transmission, severity, antiviral resistance or vaccine mismatch. Pandemic vaccine development and deployment strategies for the general population should also be ready for activation in pandemic preparedness plans and remain adaptable in case new evidence becomes available on the pathogen's characteristics, risk groups for severe disease and vaccine effectiveness.

Zoonotic pre-pandemic vaccines are aimed to be used outside of pandemics, i.e. during outbreaks of zoonotic influenza in animals, to protect the most exposed individuals (e.g. occupationally exposed people such as farm workers and veterinarians) or vulnerable populations, or at the early onset of a pandemic if the strain included in the zoonotic vaccine is still able to cross-protect against the pandemic strain in terms of neutralisation and humoral immunity. WHO regularly updates its list of candidate vaccine viruses (CVVs) for zoonotic influenza strains with pandemic potential, based on ongoing global surveillance and genetic, antigenic, and epidemiological data [23,41]. If zoonotic influenza vaccine mismatch is suspected or confirmed, vaccination recommendations may need to be adapted to include the most recently authorised updated zoonotic vaccines or potential use of antivirals as PrEP. Of note, pandemic preparedness vaccines are authorised before an emergency and can be marketed after their composition has been adapted to include the specific virus strain that is responsible, as identified following the declaration of a PHEIC by WHO, and/or the recognition of a public health emergency at Union level by the European Commission. A formal declaration of a pandemic is not a prerequisite under current regulatory frameworks.

Overall, vaccination strategies should be adaptable in order to mitigate transmission and protect vulnerable groups if the epidemiological situation evolves towards more concerning scenarios. When the vaccine is implemented, countries should consider the implementation of real-time vaccine effectiveness studies and adverse event monitoring, as well as sero-epidemiological studies to assess immune responses. Where relevant, countries may also collaborate with EU initiatives such as DURABLE [42], which supports laboratory studies during health emergencies, and the Clinical Trial Coordination Mechanism (CT-CM) [43], which provides coordination support for clinical research. Vaccine monitoring plans should be discussed with EMA and ECDC in the context of the Vaccine Monitoring Platform for coordination across MS [44,45]. Relevant for both seroprevalence and vaccine immunogenicity studies, a key opportunity for research and preparedness in the EU/EEA is the establishment of population-representative studies that leverage biobanking of serum samples. These samples could play an important role in assessing natural or vaccine-induced immune responses to evolving zoonotic influenza strains that emerge over time in different populations.

Surveillance and case/outbreak investigations

A comprehensive approach to signal monitoring and case detection is essential for the early identification of zoonotic influenza cases and timely implementation of appropriate public health measures. Individuals with occupational exposure to infected animals (e.g. farm workers) are at increased risk of zoonotic spillover and surveillance systems should be set up to actively monitor risk groups. Event-based surveillance plays a critical role in detecting unusual signals, with timely notifications from vigilant healthcare workers, whether in primary care, occupational health, or hospital settings, to local public health teams being key to early detection. Event-based surveillance systems should be reinforced, with dedicated communication channels and training mechanisms established to ensure effective engagement with healthcare workers. Additional sources, such as wastewater surveillance in collaboration with the human and animal health authorities [5] and routinely collected respiratory virus data, should also be monitored for signals that could indicate emerging cases of zoonotic influenza. It is essential to ensure adequate capacity, funding and resilience of existing surveillance systems to allow them to adjust accordingly to each outlined scenario. When a signal (e.g. unusual cluster, potential

infection in exposed individual) has been identified within the EU/EEA, rapid and thorough outbreak investigations are essential to ensure timely response. Annex 2 – Table A2.2 summarises all baseline actions within the categories mentioned above and includes important logistical considerations.

Once a case of zoonotic influenza has been identified the EU/EEA, it is important to consider the scenario and the appropriate escalating actions. The baseline actions (Annex 2 – Table A2.2) should be maintained and strengthened as signal monitoring and case detection remain essential. In addition, other surveillance activities should allow us to gain an understanding of:

- characteristics of infection/disease in humans (e.g. describing clinical presentation, identifying risk groups and factors for infection and severe disease);
- changes in the virus (e.g. transmission patterns, further characterisation to identify mutations that might indicate increased mammalian adaptation, antiviral resistance); and
- the potential for increased zoonotic or HTH transmission.

Annex 2 – Table A2.2 and Annex 3 – Table A3.7 summarise all escalating actions for each of the domains: monitoring exposed persons to infected animals, event-based surveillance, outbreak investigation, routine respiratory virus surveillance, reporting, environmental sampling, and monitoring resistance. It is important to carefully consider when and in which area each escalating action is applicable to ensure appropriate use of available resources. For example, enhanced testing strategies should be considered when there is unknown exposure, clusters, evidence of mammalian adaptation (subcategory B) or limited HTHT. A suggestion for escalation is made in Annex 3 – Table A3.7 or the downloadable Excel tool, but for each scenario a risk assessment should guide appropriate public health actions base on the specific epidemiological situation. For example, based on the resources in the scenario (e.g. setting, affected area, number of exposed, testing capacity, etc.), the use of rapid diagnostic tests may be considered in settings with limited laboratory capacity although confirmatory testing of any positive samples and collection of specimens for further characterisation remains essential.

Laboratory preparedness, activities and functions

Laboratory preparedness includes baseline (Annex 2 – Table A2.3) and escalating actions (Annex 2 – Table A2.3, Annex 3 – Table A3.8) for both national reference laboratories and hospital or diagnostic laboratories.

The framework adopts a precautionary, preparedness-oriented approach for escalating scenarios (Annex 2 – Table A2.3 and Annex 3 – Table A3.8) when there are human cases in the EU/EEA and for some actions even those with lower scores - such as isolated cases with known exposure, no severity signals, and no identified mammalian adaptation markers. This approach reflects the importance of initiating early laboratory readiness to enable timely detection and characterisation in the event of additional human cases, supporting rapid response and containment efforts across the EU/EEA.

National reference laboratories

At the national reference laboratory level, actions focus on ensuring diagnostic and confirmatory capacity to detect non-seasonal influenza viruses, conducting genetic virus characterisation, and sharing virus isolates, virus genetic material and/or sequencing data with WHO CC or H5 reference laboratory. Capacity-building through EQAs and trainings, assay maintenance and validation, biosafety procedures, and exploring the potential implementation of laboratory methods for environmental and wastewater surveillance can also be considered. In escalating scenarios, actions expand to validating new specimen types, and securing staff, supplies and reagents for ensuring adequate diagnostic and sequencing capacities.

The laboratories need to be prepared for testing of potential zoonotic influenza cases with testing material and preparing the transportation of specimens. The laboratory assays in the clinical or diagnostic laboratories need to be validated for zoonotic influenza detection and follow the IVD Regulation in the EU/EEA. In the reference laboratories, assays for subtyping and sequencing should be available. In the event of a commercial test not being available, exemptions to the IVDR may be possible and in-house tests be used within individual health institutions and under specific conditions [46]. The detections of zoonotic influenza need to be reported in a timely fashion, and the specimen-sharing also needs to take place in a timely way for confirmatory testing and further virological characterisation at supranational level. Therefore, the material transfer agreements and legal basis for specimen-sharing needs to be prepared in 'peacetime' both for inland and cross-border shipments.

The capacity in the laboratories need to be increased in case of zoonotic influenza clusters and therefore even prior to detected cases, capacity-building, external quality assessments (EQA) and laboratory and bioinformatic trainings need to take place to improve the laboratory preparedness. In the current pre-pandemic scenarios, only a small number of specimens are expected to be received for analysis in the public health. For escalation scenarios, laboratories would need to be prepared to scale up their capacities in testing, typing/subtyping and sequencing in case the situation evolves to a widespread epidemic or pandemic. In the event of a public health need, the respiratory virus EURL may be requested to undertake activities related to any respiratory virus falling within its established remit, including zoonotic influenza. Particular consideration shall be given to existing global structures involved in laboratory activities that are part of influenza surveillance like genetic and antigenic

characterisation of influenza viruses, including the Global Influenza Surveillance and Response System (GISRS), WHO CC, and WHO H5 Reference Laboratories; coordination with these entities, and involving the avian influenza EURL, is essential to ensure alignment and efficiency in response efforts [47]. In low resource settings, WHO CC and the respiratory virus EURL can support with central testing capacity for confirmatory testing, sequencing and further characterisation of the viruses. Where comparable services or activities are already in place to support the countries and ECDC, the respiratory virus EURL shall aim to complement and reinforce these efforts and possible overlap in activities between EURL and other laboratory support activities at supra-national level in the EU/EEA should be avoided whenever possible.

Irrespective of virus characteristics, strict biosafety measures need to be followed in all scenarios. In general, laboratories carrying out work which involves the handling of group 3 biological agents for research, development, teaching or diagnostic purposes must determine the containment measures in accordance with Annex V of the EU Regulation [25] and the risk assessment, in order to minimise the risk of infection. Activities involving the handling of a group 3 biological agent like zoonotic influenza must be carried out only in working areas corresponding to at least containment level 3. Virus isolation and assays requiring handling of live virus is restricted to laboratories equipped with adequate biosafety level (BSL3) and protocols to handle live zoonotic influenza viruses or designated H5 reference laboratories or WHO CCs.

Diagnostic/hospital laboratories

At the diagnostic or hospital laboratory level, baseline preparedness includes maintaining diagnostic capacity, participating in national EQAs, maintaining or establishing specimen referral mechanisms to national reference labs, and ensuring availability of sampling materials. The laboratories need to prepare also for specimen-sharing to national or supranational laboratories (WHO Collaborating Centres for Reference and Research on Influenza (WHO CC) and EU reference laboratory (EURL) for public health in the field of respiratory viruses) [47]. In escalation, this extends to increased testing capacity (staff and materials), improved subtyping and sequencing capabilities in the national and international reference laboratories and support to the diagnostic and hospital laboratories to share their specimens with the reference laboratories, expanded use of POCTs or RADTs, and enhanced reporting of data.

Escalating actions are mapped to the different scenarios in Annex 3 – Table A3.8.

Additional studies and research

Research plays a critical role in characterising and anticipating the evolving zoonotic and pandemic risks posed by zoonotic influenza viruses.

All countries should establish standardised protocols and robust reporting systems that can be rapidly activated in the event of suspected or confirmed zoonotic influenza cases or clusters. These systems should support timely and coordinated investigations to determine routes of transmission, assess transmission dynamics, and characterise the virus involved. A core component of this preparedness is the development of standardised case report forms that capture comprehensive clinical, epidemiological, and microbiological data. This enables systematic documentation and analysis of individual cases and clusters, helping to clarify transmission pathways (e.g. through household transmission studies) and key epidemiological parameters such as secondary attack rates and incubation periods.

In addition, clinical research protocols should be in place to evaluate responses to antiviral therapies and supportive care. These protocols are essential to inform treatment strategies and optimise clinical management during an outbreak.

At baseline (Annex 2 – Table A2.4), countries are encouraged to support sero-epidemiological studies in both occupationally exposed groups and the general population, alongside the genetic characterisation of viruses isolated from human cases. Further virological studies – ideally conducted in collaboration with supranational reference laboratories or WHO Collaborating Centres capable of virus isolation and antigenic characterisation – will be critical for assessing immune escape, mammalian adaptation, and transmissibility

In escalating scenarios, countries are encouraged to initiate or contribute to targeted studies in response to specific signals such as clusters of human cases, novel sources of infection, increased severity, or concerning virological markers (Annex 2 – Table A2.4 and Annex 3 – Table A3.9). Priority epidemiological investigations may include first few (FFX) cases studies, source investigations in coordination with veterinary and environmental sectors, and epidemiological assessments (e.g. attack and secondary attack rates). Furthermore, countries might perform functional virological characterisation and effectiveness evaluations for personal protective equipment (PPE) and antivirals. If vaccination of humans or animals against H5 viruses is introduced, studies on immunogenicity and vaccine effectiveness will also be essential. Research and additional studies will need to be coordinated beyond the national level. Accordingly, coordination with EU-level initiatives should be considered that identify, prioritise, and fund research and clinical trials relevant to preparedness and response. This includes utilising available mechanisms and projects such as the DG HERA and DG RTD Clinical Trials Coordination Mechanism (CT-CM) [43] and DURABLE [42].

National actions when there is a risk of zoonotic influenza virus importation

When human infections with zoonotic influenza viruses are detected outside the EU/EEA, it is essential to assess and respond to the potential risk to the EU/EEA. Similarly, if an outbreak is isolated in a specific area within the EU/EEA or a neighbouring country, the risk to neighbouring areas/countries should be assessed and response actions implemented that aim to avoid or limit the spread. Increasing global connectivity through travel and trade raises the likelihood of introduction. With this in mind, it is important to evaluate the risks associated with specific concerning events in individual countries or areas, in addition to assessing and responding to broader trends in the global epidemiological situation. This section outlines actions in response to these external developments, focusing on mitigating the risk from importation of human cases. This document does not address animal health measures to mitigate risks associated with importation of avian influenza via infected animals or animal products.

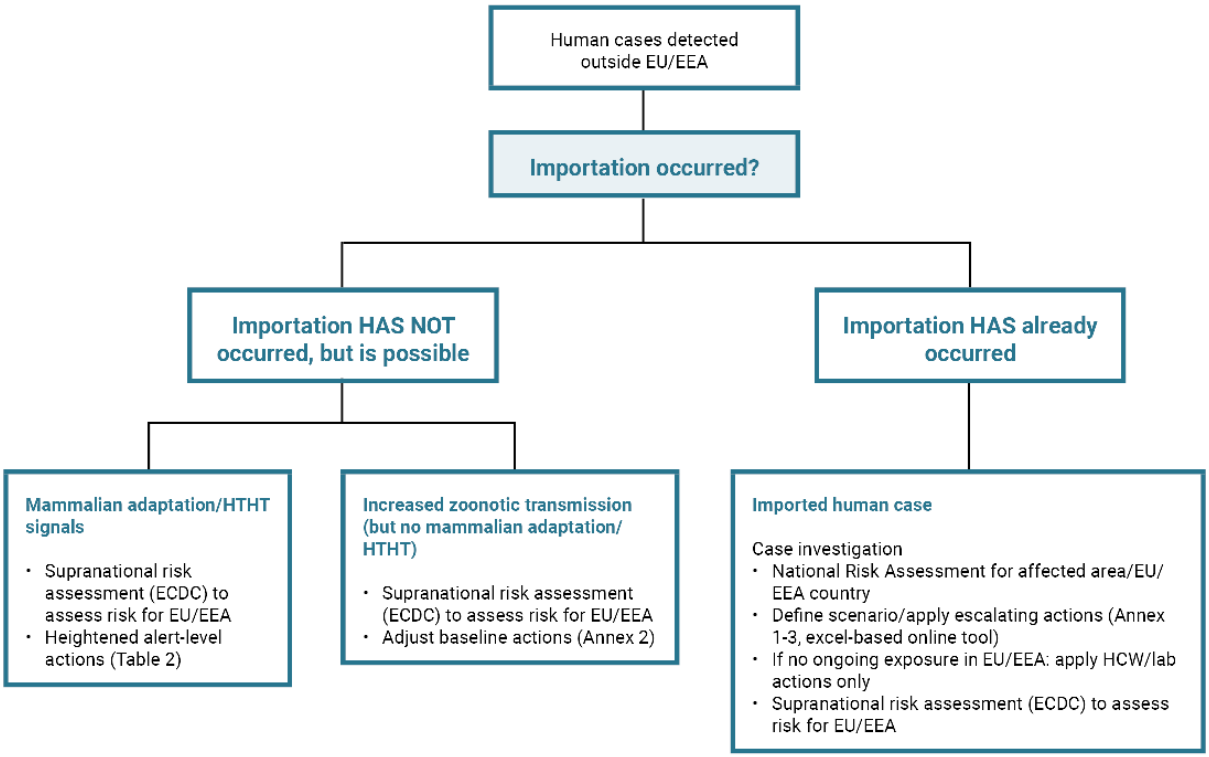
To define the appropriate level for mitigating actions, it is important to consider if (Figure 4):

1. importation has not occurred but is possible; or
2. importation has already occurred.

To make an assessment for the EU/EEA, it is critical to consider the availability of information on the context for exposure and infection for the country where case may originate. **If limited information is available a precautionary approach should be applied.**

Figure 4. Decision tree describing the situation when human cases are detected outside the EU/EEA

The risk assessment should inform decisions on additional public health actions that may be warranted.



1. If importation has *not* occurred *but is possible*:

1a) If scenarios emerge outside the EU/EEA that feature significant mammalian adaptation (equivalent to subcategory B, please refer to the 'Definitions') and/or indications of increased HTHT potential (case clusters or limited HTHT), a supra-national risk assessment should be performed to determine if importation to the EU/EEA is possible or likely. If the risk assessment considers importation into the EU/EEA as possible or likely, heightened alert-level actions (Table 2) may be warranted. Other escalating actions (Annex 2) can also be considered. Assessment and actions should be escalated or de-escalated based on evolving findings.

1b) If scenarios emerge outside the EU/EEA that indicate potential increased zoonotic transmission with no signals of significant mammalian adaptation and/or indications of increased HTHT potential (case clusters or limited HTHT), supra-national risk assessment should be performed to identify which of the baseline actions may need to be adjusted. These could include but are not limited to considerations for surveillance and laboratory preparedness such as:

- Work closely with animal health sector to understand the epidemiological situation in animal populations in the EU/EEA according to a One Health approach;
- Update case definitions and exposure criteria in humans;
- Adapt targeted surveillance for occupationally exposed groups as needed (e.g. surveillance of new occupational groups);
- Consider updating guidance to detect sporadic imported cases if there is risk of importation;
- Ensure diagnostic readiness of national reference laboratories to detect novel strains.

ECDC is monitoring human cases of zoonotic influenza worldwide through event-based surveillance. If importation has *not* occurred and is not considered likely, ECDC will provide a risk assessment for the EU/EEA for zoonotic influenza viruses that cause human cases outside the EU/EEA but are not circulating in animals in the EU/EEA. If the zoonotic influenza viruses causing human cases outside the EU/EEA are circulating in animals in the EU/EEA, ECDC and EFSA will provide a joint risk assessment. The risk assessments in either scenario will advise on any particular public health actions specific for the situation, in addition to the baseline actions that should already be in place.

2. If a human case of avian influenza *has already* been imported:

The epidemiological context (human, animal and environmental factors) in the country where exposure(s) or infection(s) occurred should be assessed. A national risk assessment should be performed for the area in the EU/EEA to which the imported case has arrived (i.e. the affected area) taking into considerations the epidemiological situation in the country of origin. Case investigation of the imported zoonotic human case should be carried out [30]. As part of the risk assessment appropriate escalating actions should be identified. The escalating actions identified in 'National-level actions' can be considered as a list of possible actions to inform decisions. For example:

- If importation is not associated with any ongoing occupational exposure to potentially infected animal in the EU/EEA, only those occupational actions related to clinical management (e.g. HCWs) and diagnostics (e.g. laboratory staff) in contact with the imported case or their diagnostic samples should be applied. Baseline (or current EU/EEA scenario) actions should otherwise continue to apply.
- If on the other hand there is an imported case with limited HTHT potential, then the escalating actions identified in scenarios 13/14 should be applied in the affected area in the EU/EEA.

In addition, a supranational risk assessment is required, to assess the situation for the EU/EEA and identify if there is a change in the epidemiological context. Adjustments may need to be made to the scenario currently applicable in the EU/EEA and, subsequently, in the relevant options for response (public health actions). This includes an assessment of the risk of further importation and the need for heightened alert-level actions (Table 2).

Table 2. Heightened alert-level actions for scenarios with importation risk

Examples of alert-level actions if there is risk of importation to EU/EEA countries due to clusters with significant mammalian adaptation detected and/or potential HTHT to contain and mitigate against possible evolution to a pandemic scenario. Other listed escalating actions (Annex 2) can also be considered.

Preparedness and public health interventions
General: • Assess importation risk via travelling to specific country • Activation of the pandemic influenza plan at the appropriate alert level • Activation of the pandemic influenza coordination committee or other body • Create appropriate situation reports as needed at the appropriate alert level **Occupational health and safety/PPE/IPC:** • Update according to new evidence PPE and IPC guidance for healthcare and occupational settings for preparedness purposes • Assess if there is risk of importation of animal virus with increased zoonotic potential to specific countries, areas, settings or specific facilities • Ensure availability of PPE for agricultural and healthcare workers **Risk communication:** • Issue proactive public messaging to explain the current epidemiological situation, clearly stating what is known, what is unknown, the current risk assessment for the EU/EEA population, and what is being done. • Consider the need for travel advice, depending on the severity, scale and location of human-to-human transmission. If warranted, issue recommendations for travellers such as the need to take precautions, monitor for symptoms after travel and seek medical advice promptly, if symptoms develop. • Outline potential response actions if importation occurs **Antivirals and vaccines:** • Ensure availability of vaccines and antivirals considering national recommendations • May need to activate national preparedness plan (e.g. review countermeasure deployment readiness, vaccine strategies, antiviral distribution, logistics) • Review and update prioritisation/triaging frameworks (e.g. for vaccines and antivirals) • Assess the need for strain-specific vaccines • Secure logistics and supply chains for antivirals, vaccines, PPE
Surveillance
• Heighten clinical awareness among healthcare workers/providers to test symptomatic patients with relevant exposure histories (including but not limited to travel to specific countries) • Consider intensifying surveillance of imported cases (testing at points of entry may be considered e.g. through wastewater surveillance of passenger flights or testing at points of introduction) • If required, update testing algorithms to include novel or adapted strains (e.g. strains that are not usually tested for) or novel sample types (e.g. eye swabs if known symptoms include conjunctivitis).
Laboratory
• Ensure laboratory preparedness for increase of capacity • Ensure genomic surveillance readiness and capability to detect specific mutations • Develop/validate laboratory detection protocols for novel strains and test existing assays for their functionality against novel viruses in silico and in vitro considering the IVDR regulation • Ensure access to diagnostic reagents for diagnostic laboratories and national reference laboratories and sharing of those protocols within the country • Coordinate with WHO, EURL, and supranational laboratories for confirmatory testing and virus characterisation • Assess biosafety protocols in light of novel strains
Research
• Review data gaps on transmissibility, virulence, receptor binding, antiviral susceptibility • Coordinate serology studies and cross-protection assessments • Prepare for biobanking and sample sharing protocols

Supra-national level actions

In line with Regulation (EU) 2022/2371 [6], the European Commission has developed a Union-wide plan for prevention, preparedness, and response. This plan sets out operational measures to support EU/EEA countries in preparing for and responding to serious cross-border health threats. It also defines the roles and responsibilities of each actor – that is, the policy-makers, crisis managers, EU institutions and agencies, EU/EEA countries, and other stakeholders involved in EU health-crisis governance – consistent with their respective mandates [7-9].

In line with the Union plan, ECDC plays a central role in supporting countries in preparing for and responding to zoonotic influenza threats, working closely with the relevant stakeholders and coordination mechanisms outlined in the plan [7-9]. This section mainly focuses on baseline and escalating actions from ECDC's side (Table 3). Examples of collaboration with EU and non-EU supranational actors are provided, although not exhaustively. As a baseline activity, ECDC regularly conducts risk assessments when events involve human cases, including those occurring outside the EU/EEA. Considering the evidence base, in any scenario, ECDC will provide guidance for mitigating the risk, including recommendations for the implementation of public health measures, and promptly inform DG SANTE for further coordination through the Health Security Committee (HSC) and other mechanisms foreseen by the Regulation 2022/2371. Other baseline actions include operational guidance, training, supranational coordination of surveillance and public health laboratory network and developing platforms for this purpose (e.g. the One Health Task Force), as well as facilitating data reporting and performing data analysis to ensure readiness across the public health sector.

Escalating scenarios – such as cases within the EU/EEA, clusters of human cases, increased severity, confirmed mammalian adaptation and/or antiviral resistance – may require enhanced ECDC support. If the epidemiological situations change in the EU/EEA or globally, the national-level actions outlined in this document may need to be adjusted based on the specific situations.

The European Commission (DG HERA) implements several initiatives to strengthen preparedness and response in the area of medical countermeasures (MCM) in EU/EEA countries. At baseline, countries can engage with HERA's initiatives to ensure the availability of MCM in time of crisis (including pre-pandemic and pandemic vaccines, antivirals, diagnostics and PPE), through innovation, joint procurement or stockpiling. They can also engage with the Commission's initiatives to strengthen their surveillance capacities, including sequencing and wastewater surveillance capacities. In escalating scenarios, countries can consider activating or coordinating with EU-level mechanisms that can further support their response, including the RescEU stockpiles, EU-level procurement, and mechanisms to coordinate cross-border studies and clinical trials.

Table 3. ECDC-level baseline and escalating actions

Domain	Baseline actions	Escalating actions
Preparedness and public health interventions	- Provide risk assessment for the EU/EEA for H5N1 and other zoonotic influenza viruses that cause human cases outside the EU/EEA and are *not* circulating in animals in the EU/EEA, even if those don't warrant heightened alert (in the baseline scenario for EU/EEA countries – please refer to the 'Definitions for scenario classification and scoring' for the definition of baseline scenario). - Provide risk assessment for the EU/EEA for H5N1 and other zoonotic influenza viruses that cause human cases outside the EU/EEA and *are* circulating in animals in the EU/EEA. - Provide evidence-based recommendations for public health action. - Supranational coordination (e.g. with EFSA, WHO, other CDCs) during the baseline scenario when there are cases outside the EU/EEA. - Define specific concern levels and scenarios (e.g. expanding clusters, circulation in mammals, antiviral resistance, vaccine escape) that trigger enhanced support from ECDC when there are cases outside the EU/EEA (in the baseline scenario for the EU/EEA). - Provide preparedness guidance and support to countries to develop/update their preparedness and operational plans [22,48-50]. - Provide training to increase capacity and organise Simulation Exercises. - Provide One Health guidance through the OH ECDC task force and assistance in capacity-building through the EU Health Task Force. - Liaise with the European Medicines Agency (EMA) and the Health Emergency Preparedness and Response Authority (HERA) in the event of antiviral resistance emergence or vaccine mismatch.	- Update risk assessment for the EU/EEA. - ECDC may activate its Public Health Emergency (PHE) plan depending on the situation and needs. - Define specific concern levels and scenarios (e.g. expanding clusters, circulation in mammals, antiviral resistance, vaccine escape) that trigger enhanced support from ECDC. - Provide updated guidance regarding the different interventions according to the emerging evidence (e.g. on incubation period, infectiousness, high-risk groups) based on the risk assessment and using the pre-pandemic scenario framework, - Contribute to the assessment of the need for accelerated development and production of strain-specific vaccines. - Continuous information-sharing with EFSA and other European partners including joint risk assessments and communication when needed. - Enhance intelligence-sharing with other international partners WHO, CDCs, FAO, WOAH and affected countries as appropriate. **In events of human cases outside the EU/EEA that warrant heightened alert:** - Joint risk assessments with ECDC, EFSA, and other partners specifically focussed on assessing risk of spread of the virus in animals and/or humans in the EU/EEA and pandemic risk potential. - Liaise with EFSA to assess if there is risk of importation of animal virus with increased zoonotic/pandemic potential. - Assess the importation risk via travel, trade routes, animal movement, food products and risk to public health together with EFSA - Provide regular risk assessments communicated to countries. - Provide preliminary risk characterisation of virus properties: sub- and genotype, transmissibility, virulence, antiviral susceptibility, vaccine match. - Global monitoring coordination: active collaboration with WHO, CDCs, EFSA and affected country authorities (as appropriate). - Coordination with European Commission and EC bodies.
Surveillance	- Provide guidance for event and indicator-based routine respiratory virus surveillance including pathogen-specific and syndromic surveillance. - Collect respiratory virus data at EU-level using different platforms (i.e. EpiPulse Events and Cases, EWRS). - Analyse respiratory virus surveillance data (ERVISS) on a weekly basis. - In collaboration with the animal health sector, EFSA and the avian influenza EURL, provide regular overview of the current epidemiological situation of avian influenza in animals and humans in the EU/EEA and globally, risk assessment for public health, and options for response based on the current situation.	- Adapt existing guidance on national event-based and indicator-based surveillance and provide support as needed. - Adapt EpiPulse reporting as needed to streamline data collection and ensuring relevant epidemiological factors are collected for the specific scenario. - Collect data on cases (EpiPulse) and measures implemented (EWRS) across the EU/EEA and provide an EU/EEA summary. - Analysis of available surveillance data to define key epidemiological indicators/factors to inform the situational and risk assessment.

	- Regularly monitor global sequence data in collaboration with the animal health sector and especially related to new or unusual human or linked animal cases outside of the EU/EEA. - Scan different sources to identify potential signals in media, national public health bulletins, or other sources. - Analyse globally available surveillance data to define key epidemiological indicators/factors (e.g. likely transmission route, associated symptoms, severity measures, risk groups for severe disease, etc.) - Respond to any event reported by the EU/EEA (e.g. suspicion of case) and provide guidance and support where needed. - Strengthen cross-sectoral data integration between animal and human surveillance systems.	- Adjust the frequency of One Health surveillance reports of the epidemiological situation in animals and humans in the EU/EEA and globally according to information needs for informing risk assessments and response actions. **Some of the above actions may be warranted in events of human cases outside EU/EEA that warrant heightened alert.**

Laboratory	- Support to diagnostic/confirmatory capacity.
	- EQAs and bioinformatic ring trials, including troubleshooting and individual feedback.
	- Provide reference material.
	- Provide wet- and dry lab trainings, webinars and self-paced online courses
	- Facilitate sharing of laboratory protocols.
	- Provide technical support for utility of diagnostic assays (RADTs, RT-PCR) for human case investigations.
	- Provide central virus characterisation services and confirmation of subtype:
	  - Genetic (sequencing, bioinformatics analysis and support) in coordination with the respiratory virus EURL
	  - Antigenic (haemagglutination inhibition test, different types of neutralisation assays; availability of wider panel of antisera) in coordination with the respiratory virus EURL
	- Capacity-building (EQAs, trainings, networking).
	- Share data from Epipulse to WHO.
	- Facilitate virus-sharing.
	- Biosafety laboratory maintenance and training.
	- Monitor antiviral susceptibility.
	- Monitor of genetic evolution.
	- Coordinate with international stakeholders, e.g. WHO EURO, WHO HQ, avian influenza EURL, expert groups.
	- Organise of laboratory and expert meetings.
	- Information-sharing.
	- Host reporting systems for virus characterisation data.
	- Support risk assessment by linking regional virological and epidemiological surveillance data.
		- Provide technical support for diagnostics: development and validation of assays (central laboratory, EURL, WHO CC).
		- Provide support to the public health laboratories for aspects related to the IVDR certification.
		- Provide technical support for specimen type validation (saliva, conjunctival, different swabs).
		- Assess biosafety in case of the emergence of HA or other concerning mutations.
		
		In events of human cases outside the EU/EEA that warrant heightened alert:
		- Prepare for detection of the strain of concern in the EU/EEA.
		- Distribute primers/probes and protocols as needed if new strains/subtypes are involved.
		- Support capacity-building for detection and genetic characterisation of new strains/subtypes (e.g. training, EQAs)

Additional studies and research	- Perform systematic reviews on key research questions (e.g. sero-epidemiology, transmission on aircraft (RAGIDA) [51]) - Facilitate outbreak related research, e.g. FFH case, attack rate or risk factor studies	- Activate data collection system for additional epidemiological data and transmission parameters to study R0, attack rate, incubation period, infectious period, serial interval, generation time etc. - Where appropriate, support development of data analysis pipelines that facilitate meta-analytical assessment (e.g. infection severity analysis).

		- Short-term forecasting and mid- to long-term scenario modelling to evaluate possible epidemic trajectories, utilising available data on virus transmissibility, infection severity, population immunity and the effectiveness of interventions. - Facilitate further virological characterisation, such as transmissibility and virulence, through collaboration and coordination between national laboratories with EU initiatives, such as EURLs, DURABLE. **In events of human cases outside the EU/EEA that warrant heightened alert:** - Review data gaps on transmissibility, virulence, receptor binding, antiviral susceptibility

Limitations

- There is uncertainty regarding the significance of the different mutations, especially as the initial virological signals (e.g. mutations potentially affecting previously identified phenotypic traits linked to mammalian adaptation) will precede phenotypic studies that would verify their real-life impact.
- Simultaneous detection of potential mammalian adaptation related phenotypic traits in human and animal origin specimens is not necessarily signalling an increased concern scenario. There is a possibility that the virus evolves while in the human host and acquires mammalian adaptation and human transmissibility-related traits but without further spreading from human-to-human or from human-to-animals.
- The likelihood of each scenario to happen in comparison to other scenarios is not directly calculated and is not presented separately in the algorithm (i.e. the increased likelihood of a mammalian adaptation mutation to emerge and the virus to evolve when there are outbreaks in farmed mammals/humans compared to outbreaks in birds and there is an increased likelihood of human infection when specific mammal species are affected with frequent human contact (e.g. pets or livestock)); however, it is indirectly taken into consideration because a higher scenario score is given depending on the origin of the virus and the frequency of the mutation in human cases.
- The impact of each scenario in public health in terms of healthcare system burden is also not necessarily proportional; a higher scenario score is however given depending on the severity signals of human infections to reflect the significance of this signal and the additional public health measures that will need to be implemented.
- The tool presented in this report aims to provide guidance for a structured approach in public health measure implementation; it may need to be adapted if it is intended to be used as a risk assessment tool.
- For the public health baseline measures that are applicable to each scenario, we have considered an EU/EEA-wide approach; different escalating actions would, however, be applicable if the events occurred in another country within the EU/EEA. We have defined escalating actions based on the affected country or areas with similar risk.
- The list of public health actions by scenario (Annexes 2 and 3) can be used as an example of actions that can be considered; a national and EU-level risk assessment will inform the decisions about response measures in each scenario and additional actions may be needed according to the virological, epidemiological situation and local context.

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Annex 1. Scenario scoring and definitions

a) Scenario scoring

1. Onward human-to-human transmission (HTHT) potential (Score: 1–6)

Case and exposure context	Score
Isolated case (known exposure to animals)	+ 1
Isolated case (unknown exposure)	+ 2
Cluster with suspected common exposure (*excluding* HTHT)	+ 3
Limited HTHT (e.g. household, healthcare setting)	+ 6

2. Virological adaptation to mammals (Score: 1–7)

Includes both the animal origin of the virus and genetic indicators of mammalian adaptation:

Animal origin	Score
Bird origin	+1
Mammal *OR* unknown origin *OR* N/A (LHTHT)*	+2

* N/A - In the context of LHTHT, even if bird origin is suspected for the index case, escalate to +2.

+

Genetic markers for mammalian adaptation	Primary score	Supplementary score** (comparative sequencing)
	Adaptation trait identified in at least one human case isolate Level 'A' < 3 traits Level 'B' ≥3 traits *OR* < 3 traits + other factors (e.g. Concerning new mutations / combinations, new phenotypic data)	Adaptation trait identified in animal isolate(s), where exposure is known *OR* Animal exposure unknown and there is no available animal sequence *OR* Trait in two or more human cases (in clusters)
Mammalian adaptation traits (Annex 3) [23]:		
1. Increasing mammalian specificity of virus receptor attachment	+ 0.5	+ 0.5
2. Increasing HA stability in the mammalian environment	+ 0.5	+ 0.5
3. Increasing activity of viral polymerases in mammalian hosts	+ 0.5	+ 0.5
4. Evasion of innate immunity and mammalian restriction factors	+ 0.5	+ 0.5
5. Disruption of second sialic acid-binding site in neuraminidase	+ 0.5	+ 0.5
OR		
Evidence of virus reassortment	+ 5	

** Additional 0.5 would be added for each phenotypic trait if it is also identified in animals AND/OR unknown origin specimens in terms of lack of sequence information in animals AND/OR if the same mutations occur in specimens from two or more human cases from the same cluster. Evidence of virus reassortment e.g. seasonal ↔ avian, seasonal ↔ swine, avian ↔ swine: +5 (replaces the five genetic adaptation points above).

3. Severity potential (Score: 0 or 2; Scenario modifiers: '-R' and '-V')

Severity signals	Score
Concern about the severity profile of clinical cases (e.g. hospitalisations, deaths)	+ 2

AND

Limitations in available pharmaceutical measures	Scenario modifier
Antiviral resistance	-R
Vaccine mismatch***	-V

*** Refers to anticipated or confirmed antigenic mismatch to EMA-authorised pre-pandemic zoonotic influenza vaccines [37] or available WHO candidate vaccine viruses [41].

Total scenario score: 2–15 +/- scenario modifiers ('-R' and/or '-V')

b) Definitions for scenario classification and public health actions

Baseline scenario

The baseline scenario is the global epidemiological situation as seen/described as of October 2025 (i.e. widespread circulation of avian influenza A(H5N1) but also other subtypes in animals both in the EU/EEA and globally, sporadic human cases outside of the EU/EEA, no significant mammalian adaptation mutations, mild infections in exposed individuals in occupationally settings where organisational, technical and personal protective measures are in place (e.g. during H5 outbreaks in cattle and poultry farms in the US during 2024-2025), sporadic severe infections/deaths usually linked to unprotected exposure to infected animals or their environments) (e.g. H5 cases reported from Asia with close unprotected contact often linked to backyard poultry farms) [3]. Baseline measures therefore cover the pre-spill over scenario in the EU/EEA, given that there are no reported human cases in the EU/EEA yet. If there is a human case detected within the EU/EEA, the scenario framework described in this document in relation to the escalating public health actions can be applied.

It is important to continue to monitor the epidemiological situation outside of the EU/EEA to measure changes to the current baseline scenario. For example, changes to animal and/or zoonotic spillover context observed in a specific area or country may be relevant to the current baseline actions in EU/EEA countries. In this case the baseline actions focusing on minimising animal exposure risk in the EU/EEA need to be adjusted (please refer to the relevant section, National actions when there is a risk of zoonotic influenza virus importation). These adjustments should be identified through risk assessments together with the animal health sector. Please note that this document is not intended to cover aspects of animal health measures to mitigate the risk of importation of animals or animal products or viruses that are circulating in animals outside the EU/EEA. For those aspects other documents can be consulted [15-20].

Affected area

When there are outbreaks of highly pathogenic avian influenza virus in species listed in the EU Commission Implementing Regulation 2018/1882 [52], such as domestic poultry, a restricted zone consisting of at least a three-kilometre protection zone and a 10-kilometre surveillance zone is implemented for at least 21 and 30 days, respectively [53]. A list of restricted zones in place in the EU is regularly amended in the Annex of Commission Implementing Decision 2023/2447 [54]. Healthcare providers with restricted zones in their catchment area should be made aware of the epidemiological situation in animals and potential for human exposure to infected animals. In the event of human cases of zoonotic influenza, the geographical area considered affected for public health purposes, such as enhanced surveillance, as well as awareness raising and vigilance among healthcare providers, may need to be adjusted depending on movement of individuals in the area and the conclusions of the epidemiological investigation. As a result, depending on the scenario and overall epidemiological situation, the identified affected area may be more narrowly or broadly defined geographically (e.g. more broadly defined in case of evidence of LHTHT). Human exposure to infected animals may take place before an outbreak is confirmed in animals. The time window considered for potential human exposures should, therefore, be adapted according to the suspected timing of the start of the outbreak.

Virus origin

For scenario classification, we have categorised the virus origin into two main groups: farmed/domestic birds and farmed/domestic mammals. We acknowledge that other potential sources of the virus, such as wild mammals, fall outside of these two categories. While such scenarios are not explicitly detailed in the framework, the actions outlined here are still broadly applicable. We have included specific considerations in the 'Discussion' for virus origins from certain species (e.g. H5 in swine) as well as from wildlife species in close contact with humans; the specific mammalian species origin is however not captured in the specific scenarios.

Case and exposure context

Cluster of cases with known exposure to infected animals/contaminated environments

As such cluster of human cases are 2 or more cases within a defined setting/geographical area that are temporally linked and share common exposure to animals.

Limited human-to-human transmission (LHTHT)

A cluster where two or more epidemiologically linked human cases of infection occur in the same geographic area, facility or setting (e.g. household, farm, healthcare facility or any other workplace) within 14 days of each other and they share no common environmental or animal exposure. Sequencing can be used to differentiate between HTHT and common source exposure when there is doubt.

Unknown exposure is assigned a +2 score to reflect the heightened uncertainty associated with cases where the source of infection is unclear. This includes the potential involvement of mammals, a novel or unidentified source, and/or undetected community transmission. The scoring follows a precautionary approach, recognising that unknown exposure pathways may signal a greater underlying risk.

Genetic markers for mammalian adaptation

To assess mammalian adaptation based on genetic analysis for scenario's subcategory classification (A or B) and scoring:

- For the interpretation of genetic data it is suggested to use the mutation list included in the ECDC/EFSA Scientific Opinion on Preparedness, prevention and control related to zoonotic avian influenza, which provides a list of 34 mutations (see Annex 4) – categorised across five phenotypic traits linked to mammalian adaptation – that should be monitored in all avian influenza viruses, regardless of subtype [23]. A further refined shortlist of 13 mutations is provided based on the frequency of the genetic markers in the available mammalian and avian sequences. Please note, however, that this list is static and should be constantly updated with new evidence on mutations, new mutations and combinations of mutations. Specific tools like FluMut, a tool for mutation surveillance in A(H5N1) genomes, can be used and this tool is continuously updated [55].
- For all zoonotic influenza sequences, full sequence analysis to identify new, previously uncharacterised mutations should be performed (i.e. comparing each new sequence to the most closely related existing ones to identify amino acid substitutions, regardless of whether their impact is known (e.g. define suspicion that a mutation is likely to affect mammalian adaptation potential)).
- For scenario scoring, a *quantitative approach* can be considered for the number of mutations that are present, i.e. mutations associated with fewer than three phenotypic traits in the same virus could be considered as scenario subcategory A and when three or more traits as scenario subcategory B. It is important to note, however, that quantitative thresholds alone have limitations - as a single mutation (e.g. in HA) or a combination of two mutations could potentially result in increased HTH transmission potential. They may also need to be adjusted according to the emerging evidence (e.g. from phenotypic characterisation studies), the subtype involved and the situation at the time of the event.
- A *qualitative approach* should be considered if there are concerning mutations, for example in HA (e.g. mutation in position 226) that are suspected to alter receptor binding specificity (or if there is a different amino acid substitution in a position previously associated with mammalian adaptation) or other gene mutations that have sufficient experimental data that show that they confer significant mammalian adaptation (i.e. if an experimental study/phenotypic assay performed on the virus under assessment or a genetically closely related virus demonstrated that the mutation confers a significant increase in mammalian adaptation/zoonotic potential), this should be considered as scenario subcategory B irrespective of whether other mutations linked to other phenotypic traits have also been observed in the same virus. For identifying these mutations, please refer to the ECDC/EFSA Scientific Opinion for Preparedness, prevention and control related to zoonotic avian influenza [23]. Accessible tools such as FluMut [55] and FluSurver [56] can support the identification of relevant mutations.
- When looking at genetic markers that might suggest a virus is adapting to mammals, it is important to compare the mutations found in the virus under investigation – for example, from a human case or an exposed animal – with what is commonly seen in viruses circulating in animals globally. Some mutations appear very often in avian viruses across different subtypes and regions. When a mutation is this widespread in birds, it is likely to reflect a stable, conserved part of the virus rather than a sign that the virus is adapting to infect mammals. These kinds of mutations should not be over-interpreted as indicators of zoonotic risk. By contrast, mutations that are found more often in mammalian viruses than in avian ones – and that remain uncommon in birds – are more likely to suggest an advantage for the virus in mammals. These mutations should therefore be treated as more concerning in a qualitative assessment. This comparative, frequency-based approach was also used in the ECDC/European Food Safety Authority Scientific Opinion. That assessment identified an initial list of 34 mutations of interest (those present in fewer than 80% of avian sequences but detected at least once in mammals) and then narrowed this down to 13 priority mutations (those present in fewer than 30% of avian sequences and at least 1% more common in mammals than in birds). These priority mutations are highlighted in Annex 4. For further detail, see Table 3 in the ECDC/EFSA Scientific Opinion on preparedness, prevention and control of zoonotic avian influenza [23].
- In the case of new mutations or of new combinations in the same strain of relevant mutations, it is important to immediately proceed with experimental study/phenotypic assay to investigate their possible impact of the phenotypic characteristics of the virus. It is important to clarify that genomic data are invaluable for promptly flagging candidates with possible increased risk that may warrant proactive public health action; however, they constitute the first step in a risk-based pipeline to identify viruses that warrant, where appropriate, targeted phenotypic studies to substantiate the actual effects of the mutations.

- A case study demonstrating the scenario scoring framework and genetic analysis is described in Annex 5.
- Viruses of different subtypes (e.g. H7N9, H9N2, H5N8, H13N9), circulating in birds and some of which causing infections in mammals with 3 or more traits have been identified in the Scientific Opinion analysis of ~27 000 sequences between from 2000-2024 [23]. A quantitative approach for assignment to level A or level B should be considered if this is the case with the concerning virus. When there is uncertainty or unknowns (e.g. suspicion that a mutation is likely to affect mammalian adaptation potential, paired with unknown exposure and suspected H2H transmission or when the sequencing results/genetic analysis are pending) it is advisable to consider assigning the highest score and then adjusting retrospectively when more information becomes available. A precautionary approach is recommended, especially in the early stages of case detection or limited information and evidence about the real-life phenotypic effects of mutations.

Additional considerations for the acquisition of mammalian adaptation characteristics

It is important to emphasise that the acquisition of mutations for adaptation to humans is thought to be a gradual process, unless reassortment is involved, and while amino acid substitutions are common, the accumulation of multiple mutations and phenotypic traits required to significantly increase zoonotic potential in a single host is considered to be a rare event. It needs to be noted that the circulation of zoonotic influenza viruses in regions with limited surveillance capacity in animals, such as low-income countries, makes it challenging to track their evolutionary steps, potentially leading to gaps in our understanding of these processes [23].

As the acquisition of mutations and phenotypic traits linked to increased zoonotic potential can be a gradual process, effective surveillance systems and preventive measures on the animal and human health sides should be maintained over time. This is reflected in the scoring of each scenario with the score range where higher scores are assigned when significant mammalian adaptations are detected, especially if present in both animal and human isolates or across multiple cases. Both quantitative and qualitative factors must be considered when selecting a scenario subcategory based on the virus genetic characteristics (A or B; see 'Genetic markers for mammalian adaptation' paragraph above).

It also needs to be taken into account that human adaptive mutations may be acquired via reassortment without the need for a gradual adaptation like via point mutations described above; this risk is highest in mammalian hosts that harbour mammalian-adapted influenza viruses (primarily humans and pigs, but also mustelids, dogs and horses). Risks of reassortment should be reduced by preventing co-infections in humans and other mammals. In general, the higher the frequency of spillover events and the longer the transmission chains in mammalian populations, the higher the risk of adaptation of the virus to humans [4]. Genomic surveillance and data-sharing of virus sequences are of utmost importance to enhance preparedness and fill knowledge gaps. Nevertheless, the paucity of genomic data from certain epidemiological settings in some countries limits our capacity to better detect the transmission to new species and geographical spread processes.

Severity signals

This refers to the clinical impact of infection and should be evaluated using a combination of indicators, including indicators of severe disease such as hospitalisation, the need for critical care support (e.g. mechanical ventilation or admission to an intensive care unit), and death.

It is important to note that hospitalisation solely for isolation purposes should not be considered an indicator of severity. In addition to these indicators, clinical symptoms can also provide valuable insight into severity. Manifestations such as encephalitis, respiratory failure or distress, sepsis, or other serious complications directly attributable to the infection should be carefully documented. These clinical features, even in the context where pre-existing co-morbidities are thought to contribute to clinical outcome, can signal a severe disease course and should be considered in the overall assessment.

Overall, we suggest using a precautionary approach when scoring is applied to severity in the scenario framework. However, in scenarios involving isolated human cases or small clusters, measures such as hospitalisation or case fatality rates may be unreliable due to limited sample size. In such cases, it becomes especially important to monitor for changes in the epidemiological profile of cases. For example, attention should be paid to whether severe cases are occurring in occupationally exposed individuals as this group has not typically experienced severe illness (for example taking into account the virus origin – severe cases have not been linked to infections from mammals yet), or if there are unusual clinical presentations such as clusters of cases of encephalitis. If this is the case, even one severe case should be considered as a 'Y' in the 'Severity signals' indicator.

Furthermore, increased pathogenicity of specific influenza strains can also be linked to genetic markers associated with more severe clinical presentation; such findings should be considered when interpreting clusters of severe human cases. While increased severity in mammals (e.g. mass mortality events in a new species of farmed mammals) is not directly incorporated into the scenario algorithm, it should be treated as an indicator

warranting further genetic and phenotypic analyses to assess possible severity signals and their implications for human health.

Additional considerations for population immunity

Population immunity is a key factor in the epidemic potential of zoonotic influenza viruses. However, it is not explicitly included in this framework, which is designed to support early-stage situational awareness and response planning. Data on cross-protection – such as from neuraminidase antibodies or conserved epitopes – are often delayed, uncertain, and not standardised. They are also rarely representative at the population level or across regions with different vaccination and exposure history, limiting their use for early assessments.

Instead, the framework relies on more immediate and standardisable indicators, such as genomic and antigenic characterisation and severity signals, to guide proportionate responses. Notably, population immunity *indirectly* influences indicators such as clinical severity, which *is* included in the document. A population with some degree of pre-existing immunity may experience milder disease outcomes, fewer hospitalisations, or slower transmission – all of which could be picked up through severity signals and inform the scenario classification.

Limitations in available pharmaceutical measures

Antiviral resistance may be inferred with reasonable confidence from genetic analysis alone, particularly when well characterised resistance-associated mutations are identified [55-58]. Confirmation through phenotypic assays demonstrating reduced drug efficacy strengthens this assessment [59]. WHO's Expert Working Group on Antiviral Susceptibility for the WHO GISRS has developed guidelines for development of methods for assessing antiviral susceptibility of seasonal and zoonotic influenza viruses and interpretation of genetic data [60].

Vaccine mismatch is indicated by significant antigenic differences between the circulating virus and existing zoonotic influenza vaccines or available CVVs. This includes changes in key haemagglutinin (HA) epitopes that reduce cross-reactive antibody responses in haemagglutination inhibition (HI) or microneutralisation assays, suggesting diminished vaccine effectiveness and the need for updated CVVs [23,41].

Annex 2. List of national baseline and escalating public health actions and list of relevant resources

Table A2.1. List of national baseline and escalating actions for preparedness and public health interventions and relevant resources

Categories	Baseline actions	Escalating actions	Relevant guidelines and legislation
One Health and international coordination	• Identify stakeholders across sectors for coordinated planning, information-sharing, assessments and outbreak management. • Establish an intersectoral collaboration group in 'peacetime' with regular meetings. • Agree on objectives and procedures for data collection and sharing – this should include the structure of the data to be collected (metadata). • Establish communication channels for rapid information-sharing between veterinary and public health authorities and ensure active information-sharing and coordination between sectors in the management of any relevant incident. • Prepare a checklist/data collection tool for collecting the relevant information on the number of exposed people, their level of exposure and relevant contact details. • Develop and implement joint investigation and response protocols for managing zoonotic spillover events. Train staff and refine established protocols through joint training and simulation exercises to ensure operational readiness. • Establish emergency funding and resource allocation mechanisms for coordinated One Health response, including surge capacity planning. • Ensure legal provisions are in place to enable the implementation of measures according to a One Health approach. • Engage in joint preparedness and response efforts with neighbouring countries and global health agencies. • Strengthen international collaboration for cross-border surveillance and information exchange.	• Conduct high-level cross-sectoral meetings with national and international EU/EEA stakeholders (e.g. ECDC, EFSA). • Communicate key points on evolving epidemiological situation across sectors (e.g. veterinary and environmental sector). • Communicate with veterinary sector to monitor potential spread of concerning (e.g. HA) mutations in animals and consider a joint risk assessment. • Increase the frequency of rapid joint risk assessments to inform response measures. • Conduct high-level cross-sectoral meetings with other international stakeholders (e.g. WHO, WOAH, FAO).	Coordinated One Health investigation and management of outbreaks in humans and animals caused by zoonotic avian influenza viruses Recommendations for preparedness planning for public health threats Preparedness, prevention and control related to zoonotic avian influenza ECDC strategic framework for the integration of molecular and genomic typing into European surveillance and multi-country outbreak investigations Union Civil Protection Mechanism (rescEU) - European Commission rescEU - European Civil Protection and Humanitarian Aid Operations Commission Communication introducing the Union prevention, preparedness and response plan for health crises - Public Health Factsheet - Union prevention, preparedness and response plan for health crises - Public Health

Categories	Baseline actions	Escalating actions	Relevant guidelines and legislation
	• Align national response measures with international guidelines and recommendations. • Conduct joint global genomic monitoring when applicable. For example, when a resistance against treatment or antigenic drift from existing CVVs/vaccines is known to emerge in viruses circulating in animals, sequences should be monitored for the detection and spread of such viruses to be prepared for necessary public health actions.		
Prevention and control measures in workplace	**Any workplace:** • Regularly update the risk assessment in accordance with emerging information, and plan prevention measures following the recommendations from the occupational health authorities to ensure compliance with Directive 2000/54/EC and national occupational health and safety legislation. • Review emergency procedures in case of an outbreak in animals in the workplace. • Ensure you have a supply chain for the provision of personal protective equipment (PPE) and any other materials foreseen in the prevention plan. • Enhance disinfection in all premises. • Develop protocols for the use, storage, disposal and decontamination (if necessary) of PPE. Involve workers in the planning of exposure control measures. • Inform and train all workers on the preventive measures, and on the use, storage and disposal of PPE and emergency plans, and reinforce adherence to procedures. **In the farm setting:** • To prevent human exposures to infected animals and contaminated environments, biosecurity measures should be in place at farms to reduce the risk of introduction and onward transmission of zoonotic influenza viruses [23]. For the early detection of transmission in animal populations and the implementation of stricter protective measures in workers, animals should be monitored for clinical signs of infection and surveillance should be carried out in	**Actions to prevent transmission of the virus:** • Regularly update the risk assessment in accordance with current scenario and planned prevention measures following the recommendations from the occupational health authorities to ensure compliance with Directive 2000/54/EC and national occupational health and safety legislation. The updates of the risk assessment should always consider vulnerable workers. • Inform and train workers on the application of measures, including emergency procedures, to reduce the risk of infection according to the new scenario, use of PPE, and reinforce adherence to implemented measures. Vulnerable workers will require special protection measures. • Limit the number of staff to the minimum required to undertake activities that involve contact with animals, their fluids, contaminated water or dust aerosols. • Enhance disinfection in all premises as needed. Workers working in contaminated areas should follow disinfection procedures. • Restrict access to nominated workers. • Closely monitor workers in contact with infected or suspected infected animals. • Follow recommendations by health authorities for sanitising, e.g. manure, slurry and contaminated water. • In farms and agricultural settings, the monitoring of wastewater can be effective to monitor the presence of the virus.	**National and EU occupational health and safety legislation and guidance** Directive 2000/54/EC on the protection of workers from risks related to exposure to biological agents at work and national legislation implementing it 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 Preparedness, prevention and control related to zoonotic avian influenza **PPE:** Investigation protocol of human cases of avian influenza virus infections in EU/EEA Testing and detection of zoonotic influenza virus infections in humans in the EU/EEA, and occupational

Categories	Baseline actions	Escalating actions	Relevant guidelines and legislation
	susceptible species with epidemiological links to infected animals [23]. • Review procedures to minimize exposure of workers to animals and their secretions and reduce contact time during tasks. • Separate physically areas with infected animals or with potential contamination of the virus from clean areas.	• Monitor adherence to procedures and provide refresher trainings. **Personal protective equipment (PPE)** • Ensure the availability of appropriate PPE and respiratory protection equipment (RPE) in compliance with Regulation (EU) 2016/425 and any national legislation. • Adapt and reinforce adherence to procedures about the use, storage and disposal of PPE. • Increase the frequency of PPE fit-testing, especially respiratory protective equipment. **Health surveillance** • If a worker is found to be suffering from an infection or illness as a result of exposure, health surveillance should be offered to other workers who have been similarly exposed. • Follow vaccination and the provision of prophylaxis recommendations according to national health authorities' guidelines. • Evaluate testing criteria for HCW caring for hospitalised cases, including consideration of regular testing regardless of symptoms	safety and health measures for those exposed at work Regulation (EU) 2016/425 on personal protective equipment Considerations for infection prevention and control practices in relation to respiratory viral infections in healthcare settings WHO guidelines on Infection prevention and control of epidemic- and pandemic-prone acute respiratory infections in health care WHO Laboratory biosafety manual. 4th edition Laboratory biosafety manual, 4th edition: Personal protective equipment
Infection prevention and control measures in healthcare settings	• Ensure awareness among healthcare workers and administration at all levels of care. • Ensure that the pandemic response plan includes clear procedures for communication and coordination among public health, primary care, emergency care, ambulance services and healthcare facilities, addressing also reference facilities for the management of patients. • Ensure an adequate number of healthcare facilities that will serve as reference treatment centres, that these facilities can rapidly activate plans for receiving severely ill patients with zoonotic influenza and that the healthcare workers involved in the management of these patients are adequately trained on the required IPC measures and procedures for the safe	**Quarantine of contacts** • Consider self-quarantine for healthcare staff with high level of exposure to confirmed human cases. • Asymptomatic healthcare staff with high level (unprotected) exposure to confirmed human cases should wear an FFP2 respirator or surgical face mask for 14 days after exposure, if not self-quarantining. **Isolation** • Patients with probable or confirmed infection should wear a surgical mask, unless not tolerated, when they are out of an isolation room • The decision for discontinuation of isolation should be based on resolution of fever and improvement of	Considerations for infection prevention and control practices in relation to respiratory viral infections in healthcare settings WHO guidelines on Infection prevention and control of epidemic- and pandemic-prone acute respiratory infections in health care Health emergency preparedness for imported cases of high-consequence infectious disease

Categories	Baseline actions	Escalating actions	Relevant guidelines and legislation
	management of these patients, including with simulation exercises. • Require healthcare facilities to review (or establish if not available) their plans and operating procedures for the identification and management of suspected and confirmed cases of emerging viral respiratory infection of pandemic potential or high impact, addressing roles and responsibilities, screening and triage, patient placement, transfer, and movement within the facility and plan for simulation exercises. • Require healthcare facilities to ensure the availability of refresher training plan for healthcare workers on IPC for emerging viral respiratory infections of pandemic potential or high impact that can be rapidly deployed and has allocated human and material resources. • Develop guidance/protocol for self-isolation and monitoring based on national policy of probable human cases until zoonotic influenza is ruled out (see also below in Surveillance, Monitoring). • Initiate identification of contacts of probable cases and inform about monitoring of symptoms. Self-quarantine of close contacts (e.g. household) may be implemented depending on national policies.	respiratory tract symptoms and signs, and can be supported by negative nucleic acid tests on respiratory tract samples. • Self-isolation of probable/confirmed cases not requiring hospitalisation. • Consider using dedicated facilities for the isolation of probable/confirmed human cases not requiring hospitalisation (including hospitalisation not due to severity but for isolation purposes). • Isolate severely ill patients requiring hospitalisation ideally in airborne infection isolation rooms with negative pressure or, if not available, well-ventilated single rooms with private bathroom. • Minimise visits to patients and set up clear procedures for visitors. **Other IPC measures in healthcare facilities** • Activate, monitor, review and update (if necessary) operational protocols for case management and ensure the availability of case investigation and management guidance according to the present scenario. • In hospital rooms, it is recommended that the floor is cleaned regularly and that frequently-touched surfaces are cleaned and disinfected using hospital disinfectants active against viruses. • Decontamination of non-single use medical devices should be carried out in accordance with the manufacturer's instructions. Use of dedicated equipment should be considered. • Waste should be treated as infectious clinical waste Category B (UN3291) and handled in accordance with healthcare facility policies and local regulations. • Staff engaged in cleaning and waste management should be trained and provided with appropriate PPE. **Enhanced preparedness in case of clusters** • Activate the plans and operating procedures for the identification and management of suspected and confirmed cases of emerging viral respiratory infection of pandemic potential or high impact • Strengthen the application of standard precautions in primary, emergency and hospital care	

Categories	Baseline actions	Escalating actions	Relevant guidelines and legislation
		• Ensure the provision of sufficient resources and supply chains	
Communication and training	**Risk communication** • Define and implement a clear communication strategy defining objectives, key messages, target audience, communication channels, timelines and resources. • Adapt messages using insights from behavioural and social science research to increase relevance and effectiveness. (applies to all scenarios). • Consider establishing multi-disciplinary risk communication team (involving technical experts, clinicians, behavioural scientists, risk communicators, press officers, social media managers etc.). • Conduct interdisciplinary risk communication workshops and scenario-based simulation exercises at national and regional levels, involving both animal and public health sectors. • Community engagement in the areas where avian influenza outbreaks are occurring. • Issue targeted advice for e.g. hunters, farmers (including backyard), veterinarians, pet owners, and animal handlers regarding protective measures and monitoring for symptoms. • Raise awareness among HCWs and frontline testing laboratories on when to suspect and how to test AI cases, and on managing suspected or confirmed AI cases. • Engage with EU-level bodies such as ECDC and EFSA and international partners. **Raising awareness among occupationally exposed and healthcare professionals** • In areas where outbreaks of avian influenza in birds or mammals have occurred, public health authorities should communicate the current epidemiological situations with public health professional. As part of the messaging, the need for overall vigilance and increasing testing for influenza, typing and subtyping should be communicated.	**Risk communication** • Develop clear and timely public health messaging to address misinformation and concerns. • Coordinate with media and stakeholders to ensure consistent and evidence-based messaging across all communication channels. • Establish channels for engagement with the community of animal workers and cullers; many of which may belong to migrant communities. • Implement real-time social listening to detect public sentiment, misinformation trends, and information gaps (less important for lower concern scenarios). • Activate national multi-disciplinary risk communication teams (depending on resources, less important for lower concern scenarios). • Adapt targeted advice for e.g. hunters, farmers (including backyard), veterinarians, pet owners, and animal handlers regarding protective measures and monitoring for symptoms. • Reinforce awareness among HCWs on when to suspect and how to test AI cases, and on managing suspected or confirmed AI cases. • Issue advice to public on food consumption according to new evidence and joint risk assessment with animal health sector (for example to avoid raw milk and raw dairy products in case of suspected spread of AI in cattle). • Provide clear, actionable guidance on hygiene, food safety (e.g. thorough cooking of poultry), and personal protection. • Issue targeted prevention messages based on real-time epidemiological data. **Training** • Provide targeted training for healthcare workers to ensure consistent and informed messaging to patients. • Provide targeted training for healthcare workers to raise awareness for testing needs and exposure	WHO guidance on risk communication

Categories	Baseline actions	Escalating actions	Relevant guidelines and legislation
	Training to strengthen preparedness and communication effectiveness • Conduct interdisciplinary workshops and scenario-based simulation exercises at national and regional levels, involving both animal and public health sectors. • Provide targeted training for healthcare workers to ensure consistent and informed messaging to patients. • Provide trainings for workers with animal species where zoonotic influenza has been detected (i.e. farmers, animal care technicians, zookeepers, workers at rehabilitation centres, etc). • Encourage workers to disclose their occupation or animal exposure when seeking medical treatment for respiratory or usual symptoms to ensure quick and appropriate treatment.	risks (incl. to collect history of exposure) to help identify cases in the community.	
Antivirals	• Treatment of influenza A positive patients that are occupationally or otherwise exposed to infected animals according to national recommendations. • Post-exposure prophylaxis according to national recommendations. • Ensure availability of antivirals for seasonal influenza outbreaks (that should cover the potentially increased need in pre-pandemic scenarios).	• Develop mechanisms for early deployment of antivirals in suspected outbreak areas. • Consider pre-exposure prophylaxis (PrEP) for those occupationally or otherwise routinely exposed to infected animals or human cases according to national guidance. Approved label for exceptional circumstances. • Consider expanding post-exposure prophylaxis (PEP) to other groups according to the scenario. **If there is antiviral resistance:** • Adapt recommendations for alternative therapies and/or combination therapies if there is resistance emergence • Consider adapting recommendations to international guidelines (i.e. WHO, EMA, ECDC). • Ensure availability of alternative antiviral drug options and/or other therapeutics. • If national guidance exists for H5 vaccine use, widespread antiviral resistance or limited availability – especially amid increased zoonotic transmission potential (e.g. mammalian adaptation, human clusters) and/or higher severity – may justify re-evaluating or adapting H5 vaccine recommendations.	Investigation protocol of human cases of avian influenza virus infections in EU/EEA EMA - antivirals WHO tables for amino acid substitutions

Categories	Baseline actions	Escalating actions	Relevant guidelines and legislation
Vaccines	• Consider offering seasonal influenza vaccine to all occupationally exposed to zoonotic influenza according to national recommendations. • Consider offering zoonotic influenza vaccine (when available) to people occupationally exposed to infected animals and other relevant groups exposed to zoonotic influenza according to national recommendations. • Ensure national pandemic vaccination strategies for general population immunisation are included in preparedness plans.	• Depending on existing national guidance, consider expanding zoonotic influenza vaccination to additional high-risk occupational groups (e.g. farm workers, veterinarians, culling teams, laboratory workers). • Prepare logistics for broader vaccination campaigns (procurement, cold chain, distribution, administration). • Establish risk-based prioritisation for vaccine allocation. • Consider adapting recommendations for use according to international guidelines (i.e. WHO, ECDC). • Consider expanding recommendations for use to additional groups when there are clusters of human cases with potential human-to-human transmission, depending on the situation/setting. • Consider expanding zoonotic influenza vaccination to high-risk occupational groups, as well as additional relevant groups when there are severity signals (e.g. HCWs). • Consider adapting/expanding zoonotic influenza vaccination to relevant high-risk occupational groups when there is widespread antiviral resistance. **If there is vaccine mismatch with the pre-pandemic vaccine:** • Consider adapting recommendations for antiviral use when there is vaccine mismatch to the vaccine that is being/is planned to be used. • Consider adapting recommendations for use of the zoonotic influenza vaccine if the vaccine is being used and there is mismatch with circulating strains.	ECDC/EFSA Scientific Opinion on Preparedness, prevention and control related to zoonotic avian influenza Considerations for use of avian influenza A(H5) vaccines during the interpandemic and emergence periods: report of a WHO virtual scientific consultation, September 2024 Union Civil Protection Mechanism (rescEU) - European Commission rescEU - European Civil Protection and Humanitarian Aid Operations

Table A2.2. List of national-level baseline and escalating actions for surveillance and case/outbreak investigations and relevant resources

Category	Baseline actions	Escalating actions	Relevant guidelines
Monitoring of exposed persons to infected animals with zoonotic influenza	• Preferably actively follow up moderate to high-risk exposures for 10–14 days. • Monitor (passively or actively) exposed individuals to infected animals with low level exposure (adequately protected). • Follow up (preferably actively) individuals who are asymptomatic, occupationally or otherwise exposed to AIV-infected animals and have inconclusive RT-PCR result. • If exposed individuals develop symptoms, they should self-isolate and be tested immediately • Asymptomatic persons exposed to infected animals or their environments should be tested on a case-by-case basis according to the level of exposure.	• Actively monitor all exposed individuals to infected animals due to increased zoonotic transmission potential. • Increase testing of asymptomatic persons with exposure to infected animals or their environments. • Consider use of validated rapid antigen tests to test exposed individuals.	ECDC Investigation protocol for human exposures and cases of avian influenza in the EU/EEA ECDC/EFSA/EU-OSHA Testing and detection of zoonotic influenza virus infections in humans in the EU/EEA, and occupational safety and health measures for those exposed at work ECDC Considerations for infection prevention and control practices in relation to respiratory viral infections in healthcare settings
Event-based surveillance	• Monitor for any unusual epidemiological patterns or reported signals from respiratory disease surveillance data. • Establish event-based surveillance systems that enable regional healthcare centres and occupationally exposed individuals to report signals early. Ensure prompt reporting of any clusters of severe or unusual respiratory symptoms or other unexplained neurological symptoms. • Clusters of severe respiratory infections requiring hospitalisation should be investigated thoroughly.	• Strengthen event-based surveillance for unusual patterns of respiratory or unexplained illness. Any identified clusters of severe respiratory illness should be investigated, especially if influenza A is detected but cannot be subtyped. • Enhance vigilance and local data monitoring among healthcare professions as needed to ensure the investigation and reporting of any unusual/unexpected signals. • Investigate all clusters of unusual respiratory illness in any setting, test for influenza A, and followed up by subtyping of influenza A positive samples.	ECDC Investigation protocol for human exposures and cases of avian influenza in the EU/EEA

Category	Baseline actions	Escalating actions	Relevant guidelines
Wastewater surveillance and environmental sampling	• Wastewater surveillance can be used as a complementary system for the early identification of zoonotic influenza viruses in specific areas and establishing and monitoring wastewater system should be considered in the current baseline scenario. According to the latest JRC Monthly Bulletin, wastewater surveillance for influenza A is currently being conducted in five EU/EEA countries, although it is not clear if subtyping is routinely being performed to differentiate between seasonal and zoonotic influenza viruses. • If established, monitor wastewater surveillance or other environmental testing methods for unusual signals. It is essential to establish the origin of the zoonotic influenza virus detected in wastewater prior to taking any action as outlined further in other documents.	• Enhance environmental sampling and testing as needed.	ECDC Investigation protocol for human exposures and cases of avian influenza in the EU/EEA The European Wastewater Surveillance Dashboard
Routine (indicator-based) respiratory virus surveillance	• Ensure adequate capacity, funding and resilience of existing surveillance systems to allow it to adjust accordingly to emerging or re-emerging pathogens. • Collect exposure history during patient consultation. This is especially important in areas with known ongoing zoonotic influenza outbreaks in birds or mammals. • Ensure that clinicians are aware of unusual presentation linked to zoonotic influenza outbreaks. • Maintain year-round monitoring of respiratory symptoms in secondary care (severe acute respiratory infections, SARI) and in primary care level (ILI/ARI). • Test all specimens collected from patients meeting ILI/ARI case definitions at sentinel sites for influenza and subtype an adequate level of positive influenza A cases.	• Adjust testing algorithm if needed. • Test all hospitalised patients with zoonotic influenza compatible symptoms for influenza A and subtype all positive influenza A specimens, irrespective of exposure history within affected area. • Communicate with clinicians in primary care to lower threshold for testing for influenza in primary care settings and ensure that capacity is in place for increase testing within affected area. • Subtyping all Influenza-A positive in specimens within affected area.	ECDC Operational considerations for respiratory virus surveillance in Europe ECDC Surveillance and targeted testing for the early detection of zoonotic influenza in humans during the winter period in the EU/EEA ECDC Enhanced influenza surveillance to detect avian influenza virus infections in the EU/EEA during the inter-seasonal period

Category	Baseline actions	Escalating actions	Relevant guidelines
	• Any patient with unusual presentation or exposure history, or specimens from clusters during the interseason, should be tested for influenza and all influenza A positive specimens should be subtyped. • Test all patients admitted to hospital (including SARI hospital) with respiratory or other compatible symptoms for influenza. When feasible, subtype all positive influenza A (especially outside of the seasonal influenza epidemic periods). A more targeted approach can be taken when respiratory virus activity is elevated during the season such as limiting this to area with the highest zoonotic spillover risk. • Identify samples that test positive for influenza A in routine respiratory pathogen testing but yield inconclusive subtyping results for known seasonal influenza viruses (excluding those with poor sample quality), and ensure these samples are referred for further testing (see laboratory domain below). • Monitor routine surveillance data for unusual signals (e.g. unusual or non-seasonal patterns in syndromic data in areas with known animal outbreaks).		
Case/outbreak investigation	• Prepare necessary tools for potential human zoonotic influenza outbreak investigation (e.g. prepare case identification form, potential outbreak teams, inter-agency communication and data-sharing mechanisms). • Investigate any suspicion or clusters identified through event or indicator-based surveillance.	• Timely and thorough case investigation (including case confirmation and active case finding, epidemiological investigation, contact tracing and monitoring, and other public health actions). • Test all symptomatic individuals identified through contact tracing or with history of exposure to identified animals should be tested. • Test asymptomatic contacts depending on the epidemiological situation. • Consider use of validated rapid antigen tests for identified outbreak settings.	ECDC Investigation protocol for human exposures and cases of avian influenza in the EU/EEA WHO Surveillance for human infections with avian influenza A(H5) viruses
Logistical considerations	• Ensure sufficient specimen collection material is available. Local health authorities and occupational health providers could maintain additional materials for fast distribution if needed to avoid any delays. • Ensure specimen collection can be performed in different healthcare settings as well as by the	• Adjust planning as required based on the epidemiological situation.	ECDC Investigation protocol for human exposures and cases of avian influenza in the EU/EEA

Category	Baseline actions	Escalating actions	Relevant guidelines
	outbreak investigation teams following biosafety procedures. • Ensure there is a process for packaging and transport of specimens and ensure specimen shipment process is in place. Please refer to the laboratory section for further details.		
Reporting	• Defined reporting mechanisms and structures at national and supranational level.	• Ensure timely reporting of relevant data (e.g. reassortment, swine, avian influenza) at national and supranational level in accordance with national, international, and EU/EEA legislation established reporting protocols.	ECDC Reporting protocol for zoonotic influenza virus
Evaluation	• Assess the capacities, infrastructures, and interoperability of different surveillance systems to detect and adjust to different scenarios. • Assess and test the tools in place for outbreak (including clusters) investigation.		One Health fact-finding visit to Finland (ec.europa.eu/food/audits-analysis/audit-report/download/16774) ECDC Public Health Emergency Preparedness Assessments (PHEPA)

Table A2.3. List of national-level baseline and escalating actions for laboratories and relevant resources

Category	Baseline actions	Escalating actions	Relevant guidelines
Diagnostic/hospital laboratories			
Diagnostic capability and capacity	• Prepare detection capacity for at least H5 influenza viruses by ensuring used diagnostic influenza A tests detect H5 viruses or that diagnostic laboratories have a subtyping test for H5 for use in case suspected human cases arise in the area. • Consider participating in capacity-building exercises (participation to national EQAs and trainings). • Ensure sampling kits and transport media are available for sampling. • Determine a process for shipment of clinical specimen and virus genetic material to national reference labs for additional subtyping and virus characterisation. • Prepare documentation for transportation of the specimens. • Ship to NRL/NRC: Influenza A positive specimens that are subtype negative on tests designed to provide influenza subtyping H1/H3 result or if there is exposure to potentially infected animals and results are inconclusive. • Ensure reporting is in place to report results to national authorities.	• Improve specimen referral pathways for rapid confirmatory testing at national reference laboratories and upscale virus or clinical specimen-sharing with national reference laboratories. • Increase influenza A subtyping capability. • Enhance real-time reporting to national (and international) surveillance systems. • Increase diagnostic testing and subtyping capacity in hospital settings. • Increase overall capacity for testing (human resources and equipment, including training). • Increase sequencing capability/capacity in key diagnostic laboratories to improve timeliness of results. • Expand access to point-of-care testing (POCTs) and rapid antigen detection tests (RADTs) for outbreak settings. • Ensure supply chain resilience for critical diagnostic materials (reagents, consumables, equipment, and PPE).	WHO guidance, Apr 2025: Surveillance for human infections with avian influenza A(H5) viruses: objectives, case definitions, testing and reporting ECDC/EFSA/EU-OSHA 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 Directive in 2019 eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:32019L1833 Case definitions, WHO, IHR WER8407_52-56.PDF Directive 2008/68/EC on the inland transport of dangerous goods WHO Surveillance for human infections with avian influenza A(H5) viruses: objectives, case definitions, testing and reporting
National reference laboratories			
Diagnostic/ confirmatory capacity	• Develop and ensure capacity to accurately detect and subtype relevant zoonotic influenza viruses, also ensuring detection assays are updated for currently circulating strains of non-seasonal subtypes or zoonotic viruses. • Ensure valid specimen types: validation of specimen types for specific assay types (saliva, conjunctival, different swabs, environmental samples) and advise the diagnostic laboratories accordingly. • For specimens that need further result validation, timely share the related clinical specimens, virus isolate or virus genetic material from specimens of detected unsubtypeable (those attempted to be subtyped and turned negative for H1pdm09 and H3) influenza A or zoonotic influenza viruses with the future respiratory virus EURL and WHO	• Increase diagnostic testing /(sub)typing capacity for influenza A viruses and support diagnostic/hospital laboratories to increase subtyping capacity. • Upscale virus-sharing with supranational reference laboratories. • Diagnostics; Develop, validate, and implement existing and new assays, including POCTs and RADTs, in line with IVDR and share test protocols with diagnostic laboratories.	WHO Operational Guidance on Sharing Influenza Viruses with Human Pandemic Potential (IVPP) under the Pandemic Influenza Preparedness (PIP) Framework Case definitions, WHO, IHR WER8407_52-56.PDF Directive 2008/68/EC on the inland transport of dangerous goods ECDC/EFSA/EU-OSHA Testing and detection of zoonotic influenza virus infections in humans in the EU/EEA, and occupational safety and health measures for those exposed at work ECDC Survey report on laboratory capacity for molecular diagnosis and characterisation of zoonotic influenza viruses in human specimens in EU/EEA and the Western Balkans

Category	Baseline actions	Escalating actions	Relevant guidelines
	Collaborating Centre or H5 reference laboratory (for H5 viruses).		ECDC Reporting protocol for zoonotic influenza virus WHO guidance, April 2025: Surveillance for human infections with avian influenza A(H5) viruses: objectives, case definitions, testing and reporting EC Directive 2019/1833 WHO Surveillance for human infections with avian influenza A(H5) viruses: objectives, case definitions, testing and reporting
Virus characterisation	• Develop and maintain capability and capacity for sequencing and bioinformatic analysis. • Develop capability and capacity for genotypic antiviral drug susceptibility assessment if markers for genotypic antiviral susceptibility have been defined. • Assays that require handling of live virus, e.g. antigenic characterisation (e.g. haemagglutination inhibition test) and phenotypic antiviral susceptibility testing for zoonotic influenza viruses from human specimens should be performed only at laboratories equipped with adequate biosafety level facilities and protocols.	• Restrict virus isolation of zoonotic influenza viruses to laboratories equipped with adequate biosafety level (BSL3) and protocols to handle live zoonotic influenza viruses or in designated H5 reference laboratories or WHO CCs (e.g. WHO H5 Reference laboratory in Pasteur Institute France or Crick Institute, London, UK). • Increase virus isolation and characterisation capacity of national reference laboratories, incl. Antigenic and antiviral susceptibility properties [involvement of supranational reference laboratories and WHO CC]. • As part of surveillance activities, monitor antigenic and antiviral susceptibility geno- and phenotypic characteristics of the viruses.	ECDC Investigation protocol for human exposures and cases of avian influenza in the EU/EEA – Annex 3 Biosafety and biosecurity guidance and regulations WHO laboratory biosafety manual, 4th edition Directive 2000/54/EC on the protection of workers from the risks related to exposure to biological agents at work WHO 11 April 2025 document Surveillance for human infections with avian influenza A(H5) viruses: objectives, case definitions, testing and reporting
Capacity-building	• Participate in ECDC/WHO laboratory networks. • Participate in international external quality assessments and improve tests accordingly. • Organise EQAs for national laboratories. • Participate in ECDC/WHO trainings and provide trainings to local and regional laboratories. • Consider developing wastewater surveillance laboratory protocols and methods including sequencing for H5 or other zoonotic influenza viruses for early identification of zoonotic influenza viruses from the environment or humans. • Ensure biosafety laboratory maintenance and training. • Ensure sampling kits and transport media are available.	• Increase overall capacity for testing (human resources and equipment, including training). • Increase sequencing capacity. • Enhance capacity for bioinformatic analysis as needed. • Enhance capacity for data management as needed.	

Category	Baseline actions	Escalating actions	Relevant guidelines
	• Ensure supply chain resilience for critical diagnostic materials. • Prepare legal basis and documentations for transportation of the specimens. • Prepare for using conjunctival swaps if needed (paired with lower and/or upper respiratory tract specimens). • Establish biobanking of clinical samples for retrospective analysis. • Ensure analysis capacity, e.g. sequence analysis (bioinformatics expertise). • Ensure information management systems that allow capacity for crisis time data management in the laboratories.		
International tasks and networking	• Ensure data-sharing to national and international databases (reporting of data including sequencing data and sharing laboratory protocols). Promptly deposit and share sequences in public databases, such as GenBank or GISAID and ENA, associated with relevant metadata. • Ensure cross-border shipment legal basis is in place for both clinical specimens or viral genetic material and viral isolates. • Specimen-sharing (for confirmatory testing and for additional research needs with WHO CC taking into consideration legislative aspects/PIP). • Ensure Material Transfer Agreements are in place for shipment of specimens to WHO and EU reference laboratories if needed (e.g. GISRS PIP, Nagoya protocol, national regulations). • Share laboratory protocols nationally and internationally.	• Take part in international training activities and simulation exercises as requested/provided. • Participate in national and international outbreak management meetings and expert groups and inform national laboratories of key laboratory findings.	WHO Operational Guidance on Sharing Influenza Viruses with Human Pandemic Potential (IVPP) under the Pandemic Influenza Preparedness (PIP) Framework WHO Surveillance for human infections with avian influenza A(H5) viruses: objectives, case definitions, testing and reporting Case definitions, WHO, IHR WER8407_52-56.PDF Directive 2008/68/EC on the inland transport of dangerous goods ECDC/EFSA/EU-OSHA 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

Table A2.4. List of national-level baseline and escalating actions for additional studies and research and relevant resources

Baseline actions	Escalating actions	Relevant guidelines
• Establish standardised, ready-to-activate protocols and reporting systems to enable timely investigation and characterisation of zoonotic influenza cases and transmission. • Conduct sero-epidemiological studies (occupationally exposed, community), and where possible biobanking of serum samples collected to assess responses to circulating zoonotic influenza strains that may emerge over time in different populations, which may be antigenically different. • Ensure capacity is in place to perform special studies (e.g. FFX studies, cohort studies) when required (including building relationships with key research groups). • Conduct immunogenicity and vaccine effectiveness studies when vaccine introduced, including biobanking of samples collected for immunogenicity assessment to facilitate assessment of heterologous cross-protective immune responses in the event that zoonotic influenza strains emerge that differ to vaccine strains. • Consider engaging with EU initiatives (such as the DG HERA and DG RTD Clinical Trials Coordination Mechanism mechanism) for the prioritisation and coordination of clinical trials and studies.	• Conduct specific studies to address key questions depending on epidemiological situation (e.g. primary transmission route, HTH transmission parameters, risk factors for severe disease) where applicable. • Conduct genotypic and phenotypic studies to assess antiviral resistance (in collaboration with supranational reference laboratories or WHO CCs). • Prepare new CVVs as needed (if there is antigenic mismatch) (with shipments to supranational reference laboratories or WHO CCs). • Conduct studies on mammalian adaptation and transmissibility (in collaboration with supranational (e.g. WHO or EU) reference laboratories and EU-level initiatives). • Advance functional characterisation: focus on critical traits/experiments, e.g. infectivity, receptor binding specificity, viral load, immune evasion (in collaboration with supranational (e.g. WHO or EU) reference laboratories and EU-level initiatives). • Support investigations into the risk of human infection from food sources, particularly consumption of raw/unpasteurised milk or dairy products contaminated with avian influenza virus. • Explore new potential sources of infection, including new species or new potential environmental reservoirs of zoonotic influenza and their role in transmission. • Conduct studies on effectiveness of PPE. • Implement FFX studies for early assessment of transmission dynamics (in collaboration with supranational (WHO/EU) initiatives). • Conduct studies on duration of infectivity and risk factors for prolonged shedding (to inform duration of isolation). • Conduct studies on risk factors for transmission to healthcare workers (e.g. inadequate PPE, viral load, high-risk procedures, proximity to the patient and duration of contact).	ECDC Investigation protocol of human cases of avian influenza virus infections in EU/EEA ECDC/EFSA Scientific Opinion on Preparedness, prevention and control related to zoonotic avian influenza WHO Influenza Investigations and Studies (Unity Studies) protocols DG HERA and DG RTD Clinical Trials Coordination Mechanism Adopted opinion on prioritised clinical studies and their funding addressing highly pathogenic avian influenza H5N1

Annex 3. National-level escalating actions applicable for each scenario

X: applicable (+/- R or V scenarios); R: applicable in scenarios with +R (antiviral resistance); V: applicable in scenarios with +V (vaccine mismatch); Actions: Escalating actions for affected area and areas with similar risk in the EU/EEA

Table A3.1. National-level escalating actions for One health coordination and international collaboration applicable for each scenario

DOMAIN	One Health and international coordination																											
Animal origin	Birds												Mammals or unknown												N/A			
Cases in humans	Isolated cases (known exposure)				Isolated cases (unknown exposure)				Cluster				Isolated cases (known exposure)				Isolated cases (unknown exposure)				Cluster				Limited HTHT			
Severity signals	N		Y		N		Y		N		Y		N		Y		N		Y		N		Y		N		Y	
Mammalian adaptation potential	A	B	A	B	A	B	A	B	A	B	A	B	A	B	A	B	A	B	A	B	A	B	A	B	A	B	A	B
Actions	1A	1B	2A	2B	3A	3B	4A	4B	5A	5B	6A	6B	7A	7B	8A	8B	9A	9B	10A	10B	11A	11B	12A	12B	13A	13B	14A	14B
Conduct high-level cross-sectoral meetings with national and international EU/EEA stakeholders (e.g. ECDC, EFSA).	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Communicate key points on evolving epidemiological situation across sectors (e.g. veterinary and environmental sector).	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Communicate with veterinary sector to monitor potential spread of concerning (e.g. HA) mutations in animals and consider a joint risk assessment.	R/V	X	R/V	X	R/V	X	R/V	X	R/V	X	R/V	X	R/V	X	R/V	X	R/V	X	R/V	X	R/V	X	R/V	X	R/V	X	R/V	X
Increase the frequency of rapid joint risk assessments to inform response measures.									X	X	X	X									X	X	X	X	X	X	X	X
Conduct high-level cross-sectoral meetings with other international stakeholders (e.g. WHO, WOAH, FAO).										X		X										X		X	X	X	X	X

Table A3.2. National-level escalating actions for prevention and control measures in the workplace applicable for each scenario

DOMAIN	Prevention and control measures in workplace																											
Animal origin	Birds												Mammals or unknown												N/A			
Cases in humans	Isolated cases (known exposure)				Isolated cases (unknown exposure)				Cluster				Isolated cases (known exposure)				Isolated cases (unknown exposure)				Cluster				Limited HTHT			
Severity signals	N		Y		N		Y		N		Y		N		Y		N		Y		N		Y		N		Y	
Mammalian adaptation potential	A	B	A	B	A	B	A	B	A	B	A	B	A	B	A	B	A	B	A	B	A	B	A	B	A	B	A	B
Actions	1A	1B	2A	2B	3A	3B	4A	4B	5A	5B	6A	6B	7A	7B	8A	8B	9A	9B	10A	10B	11A	11B	12A	12B	13A	13B	14A	14B
Regularly update the risk assessment in accordance with current scenario and planned prevention measures following the recommendations from the occupational health authorities to ensure compliance with Directive 2000/54/EC and national occupational health and safety legislation. The updates of the risk assessment should always consider vulnerable workers.									X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Inform and train workers on the application of measures, including emergency procedures, to reduce the risk of infection according to the new scenario, use of PPE, and reinforce adherence to implemented measures. Vulnerable workers will require special protection measures.	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Limit the number of staff to the minimum required to undertake activities that involve contact with animals, their fluids, contaminated water or dust aerosols.			X	X			X	X	X	X	X	X			X	X			X	X	X	X	X	X	X	X	X	X
Enhance disinfection in all premises as needed. Workers working in contaminated areas should follow disinfection procedures.	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Restrict access to nominated workers.									X	X	X	X									X	X	X	X	X	X	X	X
Closely monitor workers in contact with infected or suspected infected animals.	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Follow recommendations by health authorities for sanitising, e.g. manure, slurry and contaminated water.	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
In farms and agricultural settings, the monitoring of wastewater can be effective to monitor the presence of the virus.					X	X	X	X	X	X	X	X					X	X	X	X	X	X	X	X	X	X	X	X
Monitor adherence to procedures and provide refresher trainings.			X	X	X	X	X	X	X	X	X	X			X	X	X	X	X	X	X	X	X	X	X	X	X	X
Ensure the availability of appropriate PPE and respiratory protection equipment (RPE) in compliance with Regulation (EU) 2016/425 and any national legislation.	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Adapt and reinforce adherence to procedures about the use, storage and disposal of PPE.	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Increase the frequency of PPE fit-testing, especially respiratory protective equipment.									X	X	X	X									X	X	X	X	X	X	X	X
If a worker is found to be suffering from an infection or illness as a result of exposure, health surveillance should be offered to other workers who have been similarly exposed.	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Follow vaccination and the provision of prophylaxis recommendations according to national health authorities' guidelines.	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Evaluate testing criteria for HCW caring for hospitalised cases, including consideration of regular testing regardless of symptoms.			X	X			X	X			X	X			X	X			X	X			X	X	X	X	X	X

Table A3.3. National-level escalating actions for infection prevention and control (IPC) applicable for each scenario

DOMAIN	Infection prevention and control measures in healthcare settings																											
Animal origin	Birds												Mammals or unknown												N/A			
Cases in humans	Isolated cases (known exposure)				Isolated cases (unknown exposure)				Cluster				Isolated cases (known exposure)				Isolated cases (unknown exposure)				Cluster				Limited HTHT			
Severity signals	N		Y		N		Y		N		Y		N		Y		N		Y		N		Y		N		Y	
Mammalian adaptation potential	A	B	A	B	A	B	A	B	A	B	A	B	A	B	A	B	A	B	A	B	A	B	A	B	A	B	A	B
Actions	1A	1B	2A	2B	3A	3B	4A	4B	5A	5B	6A	6B	7A	7B	8A	8B	9A	9B	10A	10B	11A	11B	12A	12B	13A	13B	14A	14B
Consider self-quarantine for healthcare staff with high level of exposure to confirmed human cases.	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Asymptomatic healthcare staff with high level (unprotected) exposure to confirmed human cases should wear an FFP2 respirator or surgical face mask for 14 days after exposure, if not self-quarantining.	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Patients with probable or confirmed infection should wear a surgical mask, unless not tolerated, when they are out of an isolation room.	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
The decision for discontinuation of isolation should be based on resolution of fever and improvement of respiratory tract symptoms and signs, and can be supported by negative nucleic acid tests on respiratory tract samples.	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Self-isolation of probable/confirmed cases not requiring hospitalisation.	X		X		X		X		X				X		X		X		X		X							
Consider using dedicated facilities for the isolation of probable/confirmed human cases not requiring hospitalisation (including hospitalisation not due to severity but for isolation purposes).		X				X				X	X	X		X				X				X	X	X	X	X	X	X
Isolate severely ill patients requiring hospitalisation ideally in airborne infection isolation rooms with negative pressure or, if not available, well-ventilated single rooms with private bathroom.			X	X			X	X			X	X			X	X			X	X			X	X			X	X
Minimise visits to patients and set up clear procedures for visitors.			X	X			X	X			X	X			X	X			X	X			X	X			X	X
Activate, monitor, review and update (if necessary) operational protocols for case management and ensure the availability of case investigation and management guidance according to the present scenario.		X	X	X		X	X	X		X	X	X		X	X	X		X	X	X		X	X	X	X	X	X	X
In hospital rooms, it is recommended that the floor is cleaned regularly and that frequently-touched surfaces are cleaned and disinfected using hospital disinfectants active against viruses.		X	X	X		X	X	X		X	X	X		X	X	X		X	X	X		X	X	X	X	X	X	X
Decontamination of non-single use medical devices should be carried out in accordance with the manufacturer's instructions. Use of dedicated equipment should be considered.		X	X	X		X	X	X		X	X	X		X	X	X		X	X	X		X	X	X	X	X	X	X
Waste should be treated as infectious clinical waste Category B (UN3291) and handled in accordance with healthcare facility policies and local regulations.		X	X	X		X	X	X		X	X	X		X	X	X		X	X	X		X	X	X	X	X	X	X
Staff engaged in cleaning and waste management should be trained and provided with appropriate PPE.		X	X	X		X	X	X		X	X	X		X	X	X		X	X	X		X	X	X	X	X	X	X
Activate the plans and operating procedures for the identification and management of suspected and confirmed cases of emerging viral respiratory infection of pandemic potential or high impact.											X	X											X	X		X	X	X
Strengthen the application of standard precautions in primary, emergency and hospital care.											X	X											X	X		X	X	X
Ensure the provision of sufficient resources and supply chains.											X	X											X	X		X	X	X

Table A3.4. National-level escalating actions for risk communication and training applicable for each scenario

DOMAIN	Communication and training																													
Animal origin	Birds												Mammals or unknown												N/A					
Cases in humans	Isolated cases (known exposure)				Isolated cases (unknown exposure)				Cluster				Isolated cases (known exposure)				Isolated cases (unknown exposure)				Cluster				Limited HTHT					
Severity signals	N		Y		N		Y		N		Y		N		Y		N		Y		N		Y		N		Y			
Mammalian adaptation potential	A	B	A	B	A	B	A	B	A	B	A	B	A	B	A	B	A	B	A	B	A	B	A	B	A	B	A	B		
Actions	1A	1B	2A	2B	3A	3B	4A	4B	5A	5B	6A	6B	7A	7B	8A	8B	9A	9B	10A	10B	11A	11B	12A	12B	13A	13B	14A	14B		
Develop clear and timely public health messaging to address misinformation and concerns.	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Coordinate with media and stakeholders to ensure consistent and evidence-based messaging across all communication channels.	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Establish channels for engagement with the community of animal workers and cullers; many of which may belong to migrant communities.	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Implement real-time social listening to detect public sentiment, misinformation trends, and information gaps (less important for lower concern scenarios).	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Activate national multi-disciplinary risk communication teams (depending on resources, less important for lower concern scenarios).	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Adapt targeted advice for e.g. hunters, farmers (including backyard), veterinarians, pet owners, and animal handlers regarding protective measures and monitoring for symptoms.		X	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X						
Reinforce awareness among HCWs on when to suspect and how to test AI cases, and on managing suspected or confirmed AI cases.			X	X	X		X	X	X	X	X	X			X	X	X		X	X	X	X	X	X	X	X	X	X		
Issue advice to public on food consumption according to new evidence and joint risk assessment with animal health sector.													X	X	X	X	X	X	X	X	X	X	X	X						
Provide clear, actionable guidance on hygiene, food safety (e.g. thorough cooking of poultry), and personal protection.										X		X										X		X	X	X	X	X		
Issue targeted prevention messages based on real-time epidemiological data.										X		X										X		X	X	X	X	X		
Provide targeted training for healthcare workers to ensure consistent and informed messaging to patients.	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Provide targeted training for healthcare workers to raise awareness for testing needs and exposure risks (incl. to collect history of exposure) to help identify cases in the community.	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		

Table A3.5. National-level escalating actions for antivirals applicable for each scenario

DOMAIN	Antivirals																											
Animal origin	Birds												Mammals or unknown												N/A			
Cases in humans	Isolated cases (known exposure)				Isolated cases (unknown exposure)				Cluster				Isolated cases (known exposure)				Isolated cases (unknown exposure)				Cluster				Limited HTHT			
Severity signals	N		Y		N		Y		N		Y		N		Y		N		Y		N		Y		N		Y	
Mammalian adaptation potential	A	B	A	B	A	B	A	B	A	B	A	B	A	B	A	B	A	B	A	B	A	B	A	B	A	B	A	B
Actions	1A	1B	2A	2B	3A	3B	4A	4B	5A	5B	6A	6B	7A	7B	8A	8B	9A	9B	10A	10B	11A	11B	12A	12B	13A	13B	14A	14B
Develop mechanisms for early deployment of antivirals in suspected outbreak areas.		X	X	X		X	X	X	X	X	X	X		X	X	X		X	X	X	X	X	X	X	X	X	X	X
Consider pre-exposure prophylaxis (PrEP) for those occupationally or otherwise routinely exposed to infected animals or human cases according to national guidance. Approved label for exceptional circumstances.	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Consider expanding post-exposure prophylaxis (PEP) to other groups according to the scenario.		X	X	X		X	X	X	X	X	X	X		X	X	X		X	X	X	X	X	X	X	X	X	X	X
Adapt recommendations for alternative therapies and/or combination therapies if there is resistance emergence	R	R	R	R	R	R	R	R	R	R	R	R	R	R	R	R	R	R	R	R	R	R	R	R	R	R	R	R
Consider adapting recommendations to international guidelines (i.e. WHO, EMA, ECDC).	R	R	R	R	R	R	R	R	R	R	R	R	R	R	R	R	R	R	R	R	R	R	R	R	R	R	R	R
Ensure availability of alternative antiviral drug options and/or other therapeutics.	R	R	R	R	R	R	R	R	R	R	R	R	R	R	R	R	R	R	R	R	R	R	R	R	R	R	R	R
If national guidance exists for H5 vaccine use, widespread antiviral resistance or limited availability - especially amid increased zoonotic transmission potential (e.g. mammalian adaptation, human clusters) and/or greater severity - may justify re-evaluating or adapting H5 vaccine recommendations.	R	R	R	R	R	R	R	R	R	R	R	R	R	R	R	R	R	R	R	R	R	R	R	R	R	R	R	R

Table A3.6. National-level escalating actions for zoonotic and pandemic influenza vaccination applicable for each scenario

DOMAIN	Vaccines																											
Animal origin	Birds												Mammals or unknown												N/A			
Cases in humans	Isolated cases (known exposure)				Isolated cases (unknown exposure)				Cluster				Isolated cases (known exposure)				Isolated cases (unknown exposure)				Cluster				Limited HTHT			
Severity signals	N		Y		N		Y		N		Y		N		Y		N		Y		N		Y		N		Y	
Mammalian adaptation potential	A	B	A	B	A	B	A	B	A	B	A	B	A	B	A	B	A	B	A	B	A	B	A	B	A	B	A	B
Actions	1A	1B	2A	2B	3A	3B	4A	4B	5A	5B	6A	6B	7A	7B	8A	8B	9A	9B	10A	10B	11A	11B	12A	12B	13A	13B	14A	14B
Depending on existing national guidance, consider expanding zoonotic influenza vaccination to additional high-risk occupational groups (e.g. farm workers, veterinarians, culling teams, laboratory workers).									X	X	X	X									X	X	X	X	X	X	X	X
Prepare logistics for broader vaccination campaigns (cold chain, distribution, administration).									X	X	X	X									X	X	X	X	X	X	X	X
Establish risk-based prioritisation for vaccine allocation.									X	X	X	X									X	X	X	X	X	X	X	X
Consider adapting recommendations for use according to international guidelines (i.e. WHO, ECDC).																									X	X	X	X
Consider expanding recommendations for use to additional groups when there are clusters of human cases with known exposure/potential human-to-human transmission, depending on the situation/setting.																									X	X	X	X
Consider expanding zoonotic influenza vaccination to high-risk occupational groups, as well as additional relevant groups when there are severity signals (e.g. HCWs).			X	X			X	X			X	X			X	X			X	X			X	X	X	X	X	X
Consider adapting/expanding zoonotic influenza vaccination to relevant high-risk occupational groups when there is widespread antiviral resistance.									R	R	R	R									R	R	R	R	R	R	R	R
Consider adapting recommendations for antiviral use when there is vaccine mismatch to the vaccine that is being/is planned to be used.	V	V	V	V	V	V	V	V	V	V	V	V	V	V	V	V	V	V	V	V	V	V	V	V	V	V	V	V
Consider adapting recommendations for use of the zoonotic influenza vaccine if the vaccine is being used and there is mismatch with circulating strains.	V	V	V	V	V	V	V	V	V	V	V	V	V	V	V	V	V	V	V	V	V	V	V	V	V	V	V	V

Definitions: ***Zoonotic influenza vaccines*** *are intended for the immunisation of individuals at risk of exposure to animal influenza viruses during outbreaks originating in animals, including situations where public health authorities anticipate a potential pandemic caused by the same or a similar virus strain.* ***Pandemic influenza vaccines****, by contrast, are developed for use once a novel influenza virus is spreading efficiently among humans, in order to support population-wide protection.* ***Vaccine mismatch*** *refers to anticipated or confirmed antigenic mismatch to EMA-authorised pre-pandemic zoonotic influenza vaccines [37] or available WHO candidate vaccine viruses [41].*

Table A3.7. National-level escalating actions for surveillance applicable for each scenario

DOMAIN	Surveillance and case/outbreak investigations																											
Animal origin	Birds												Mammals or unknown												N/A			
Cases in humans	Isolated cases (known exposure)				Isolated cases (unknown exposure)				Cluster				Isolated cases (known exposure)				Isolated cases (unknown exposure)				Cluster				Limited HTHT			
Severity signals	N		Y		N		Y		N		Y		N		Y		N		Y		N		Y		N		Y	
Mammalian adaptation potential	A	B	A	B	A	B	A	B	A	B	A	B	A	B	A	B	A	B	A	B	A	B	A	B	A	B	A	B
Actions	1A	1B	2A	2B	3A	3B	4A	4B	5A	5B	6A	6B	7A	7B	8A	8B	9A	9B	10A	10B	11A	11B	12A	12B	13A	13B	14A	14B
Actively monitor all exposed individuals to infected animals due to increased zoonotic transmission potential.	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Increase testing of asymptomatic persons with exposure to infected animals or their environments.		X		X	X	X	X	X	X	X	X	X		X		X	X	X	X	X	X	X	X	X	X	X	X	X
Consider use of validated rapid antigen tests to test exposed individuals.		X		X	X	X	X	X	X	X	X	X		X		X	X	X	X	X	X	X	X	X	X	X	X	X
Strengthen event-based surveillance for unusual patterns of respiratory or unexplained illness. Any identified clusters of severe respiratory illness should be investigated, especially if influenza A is detected but cannot be subtyped.	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Enhance vigilance and local data monitoring among healthcare professions as needed to ensure the investigation and reporting of any unusual/unexpected signals.	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Investigate all clusters of unusual respiratory illness in any setting, test for influenza A, and followed up by subtyping of influenza A positive samples.						X		X	X	X	X	X						X		X	X	X	X	X	X	X	X	X
Enhance environmental sampling and testing as needed.					X	X	X	X	X	X	X	X					X	X	X	X	X	X	X	X	X	X	X	X
Timely and thorough case investigation (including case confirmation and active case finding, epidemiological investigation, contact tracing and monitoring, and other public health actions).	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Test all symptomatic individuals identified through contact tracing or with history of exposure to identified animals should be tested.	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Test asymptomatic contacts depending on the epidemiological situation.		X		X		X		X		X	X	X		X		X		X		X		X	X	X	X	X	X	X
Consider use of validated rapid antigen tests for identified outbreak settings.									X	X	X	X									X	X	X	X	X	X	X	X
Adjust testing algorithm if needed.	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Test all hospitalised patients with zoonotic influenza compatible symptoms for influenza A and subtype all positive influenza A specimens, irrespective of exposure history within affected area.	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Communicate with clinicians in primary care to lower threshold for testing for influenza in primary care settings and ensure that capacity is in place for increase testing within affected area.					X	X	X	X	X	X	X	X					X	X	X	X	X	X	X	X	X	X	X	X
Subtyping all Influenza-A positive in specimens within affected area.						X		X		X		X						X		X		X		X	X	X	X	X
Adjust planning as required based on the epidemiological situation.	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Ensure timely reporting of relevant data (e.g. reassortment, swine, avian influenza) at national and supranational level in accordance with national, international, and EU/ EEA legislation established reporting protocols.	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

Table A3.8. National-level escalating actions for laboratory preparedness, activities and functions applicable for each scenario

DOMAIN	Laboratories																											
Animal origin	Birds												Mammals or unknown												N/A			
Cases in humans	Isolated cases (known exposure)				Isolated cases (unknown exposure)				Cluster				Isolated cases (known exposure)				Isolated cases (unknown exposure)				Cluster				Limited HTHT			
Severity signals	N		Y		N		Y		N		Y		N		Y		N		Y		N		Y		N		Y	
Mammalian adaptation potential	A	B	A	B	A	B	A	B	A	B	A	B	A	B	A	B	A	B	A	B	A	B	A	B	A	B	A	B
Actions	1A	1B	2A	2B	3A	3B	4A	4B	5A	5B	6A	6B	7A	7B	8A	8B	9A	9B	10A	10B	11A	11B	12A	12B	13A	13B	14A	14B
Increase diagnostic testing /(sub)typing capacity for influenza A viruses and support diagnostic/hospital laboratories to increase subtyping capacity.	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Upscale virus-sharing with supranational reference laboratories.	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Diagnostics; Develop, validate, and implement existing and new assays, including POCTs and RADTs, in line with IVDR and share test protocols with diagnostic laboratories.		X		X		X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Restrict virus isolation of zoonotic influenza viruses to laboratories equipped with adequate biosafety level (BSL3) and protocols to handle live zoonotic influenza viruses or in designated H5 reference laboratories or WHO CCs (e.g. WHO H5 Reference laboratory in Pasteur Institute France or Crick Institute, London, UK).	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Increase virus isolation and characterisation capacity, incl. Antigenic and antiviral susceptibility properties [involvement of supranational reference laboratories and WHO CC].									X	X	X	X									X	X	X	X	X	X	X	X
Monitor antigenic and antiviral susceptibility geno- and phenotypic characteristics of the viruses	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Increase overall capacity for testing (human resources and equipment, including training).									X	X	X	X		X	X	X		X	X	X	X	X	X	X	X	X	X	X
Increase sequencing capacity.				X				X	X	X	X	X		X		X		X		X	X	X	X	X	X	X	X	X
Enhance capacity for bioinformatic analysis as needed.				X				X	X	X	X	X		X		X		X		X	X	X	X	X	X	X	X	X
Enhance capacity for data management as needed.									X	X	X	X									X	X	X	X	X	X	X	X
Take part in international training activities and simulation exercises as requested/ provided.	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Participate in national and international outbreak management meetings and expert groups and inform national laboratories of key laboratory findings.	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Improve specimen referral pathways for rapid confirmatory testing at national reference laboratories and upscale virus or clinical specimen-sharing with national reference laboratories.	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Increase influenza A subtyping capability.	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Enhance real-time reporting to national (and international) surveillance systems.	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Increase diagnostic testing and subtyping capacity in hospital settings.				X			X	X	X	X	X	X				X			X	X	X	X	X	X	X	X	X	X

Increase overall capacity for testing (human resources and equipment, including training).									X	X	X	X									X	X	X	X	X	X	X	X
Increase sequencing capability/capacity in key diagnostic laboratories to improve timeliness of results.									X	X	X	X									X	X	X	X	X	X	X	X
Expand access to point-of-care testing (POCTs) and rapid antigen detection tests (RADTs) for outbreak settings.									X	X	X	X									X	X	X	X	X	X	X	X
Ensure supply chain resilience for critical diagnostic materials (reagents, consumables, equipment, and PPE).	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

Table A3.9. National-level escalating actions for additional studies and research applicable for each scenario

DOMAIN	Additional studies and research																											
Animal origin	Birds												Mammals or unknown												N/A			
Cases in humans	Isolated cases (known exposure)				Isolated cases (unknown exposure)				Cluster				Isolated cases (known exposure)				Isolated cases (unknown exposure)				Cluster				Limited HTHT			
Severity signals	N		Y		N		Y		N		Y		N		Y		N		Y		N		Y		N		Y	
Mammalian adaptation potential	A	B	A	B	A	B	A	B	A	B	A	B	A	B	A	B	A	B	A	B	A	B	A	B	A	B	A	B
Actions	1A	1B	2A	2B	3A	3B	4A	4B	5A	5B	6A	6B	7A	7B	8A	8B	9A	9B	10A	10B	11A	11B	12A	12B	13A	13B	14A	14B
Conduct specific studies to address key questions depending on epidemiological situation (e.g. primary transmission route, HTH transmission parameters, risk factors for severe disease) where applicable.	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Conduct genotypic and phenotypic studies to assess antiviral resistance (in collaboration with supranational reference laboratories or WHO CCs).	R	R	R	R	R	R	R	R	R	R	R	R	R	R	R	R	R	R	R	R	R	R	R	R	R	R	R	R
Prepare new CVVs as needed (if there is antigenic mismatch) (with shipments to supranational reference laboratories or WHO CCs).	V	V	V	V	V	V	V	V	V	V	V	V	V	V	V	V	V	V	V	V	V	V	V	V	V	V	V	V
Conduct studies on mammalian adaptation and transmissibility (in collaboration with supranational (e.g. WHO or EU) reference laboratories and EU-level initiatives).		X		X		X		X	X	X	X	X		X		X		X		X	X	X	X	X	X	X	X
Advance functional characterisation: focus on critical traits/experiments, e.g. infectivity, receptor binding specificity, viral load, immune evasion (in collaboration with supranational (e.g. WHO or EU) reference laboratories and EU-level initiatives).		X		X		X		X	X	X	X	X		X		X		X		X	X	X	X	X	X	X	X
Support investigations into the risk of human infection from food sources, particularly consumption of raw/unpasteurised milk or dairy products contaminated with avian influenza virus.									X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Explore new potential sources of infection, including new species or new potential environmental reservoirs of zoonotic influenza and their role in transmission.					X	X	X	X									X	X	X	X					X	X	X	X
Conduct studies on effectiveness of PPE.									X	X	X	X									X	X	X	X	X	X	X	X
Implement FFX studies for early assessment of transmission dynamics (in collaboration with supranational (WHO/EU) initiatives).																									X	X	X	X
Conduct studies on duration of infectivity and risk factors for prolonged shedding (to inform duration of isolation).									X	X	X	X									X	X	X	X	X	X	X	X
Conduct studies on risk factors for transmission to healthcare workers (e.g. inadequate PPE, viral load, high-risk procedures, proximity to the patient and duration of contact).																									X	X	X	X

Annex 4. Mammalian adaptation traits identified by ECDC/EFSA

The European Centre for Disease Prevention and Control (ECDC) and the European Food Safety Authority (EFSA) have conducted a structured mutation analysis to assess the zoonotic risk of avian influenza viruses (AIVs). Viral sequences from 2000 to 2024 were systematically screened to identify mutations associated with adaptation to mammalian hosts. Using a four-step methodology, the analysis produced a final shortlist of 34 key mutations that should be monitored in all avian influenza viruses, regardless of subtype, grouped into five functional traits [23]. The 13 **bolded** mutations represent those that appear far more frequently in mammalian influenza viruses than in avian ones, while remaining relatively uncommon in birds. Because this pattern suggests a potential selective advantage in mammalian hosts, these mutations are of higher concern in qualitative assessments of zoonotic risk. For further detail, see Table 3 in the ECDC/EFSA Scientific Opinion on preparedness, prevention and control of zoonotic avian influenza [23].

Trait 1: increasing mammalian specificity of virus attachment to receptor

7 unique mutations:
HA:156A, HA:156V, HA:186D,221D (186D in conjunction with 221D), HA:186V, HA:221D, **HA:222L**, HA:224S

Trait 2: increasing HA stability in mammal's environment

Repeats a mutation also present in Trait 1:
HA:222L

Trait 3: increasing activity of viral polymerases in mammalian hosts

17 unique mutations:
PA:356R; PA:552S; PA:85I; PA:97I; PB1-F2:66S; **PB2:271A**; **PB2:292V**; **PB2:526R**; PB2:588I; **PB2:588V**; **PB2:591K**; PB2:591R; **PB2:627K**; **PB2:627V**; **PB2:631L**; **PB2:701N**; PB2:702R

Trait 4: evasion of innate immunity and counteraction of mammalian restriction factors

8 unique mutations:
MP1:95K; NP:100I; NP:100V; NP:283P; NP:313V; NP:313Y; NP:52H; **NP:52N**

Trait 5: disruption of the second sialic acid binding site (2SB) in neuraminidase

2 unique mutations:
NA:399R; NA:432E

While these findings support targeted surveillance and preparedness strategies as part of a One Health approach to early detection and pandemic prevention, it is important to note, that this list is static and should be regularly updated as new evidence emerges regarding individual mutations and their combinations. Tools such as FluMut, which supports mutation surveillance in A(H5N1) genomes, are continuously updated and can assist in maintaining up-to-date assessments [55].

Annex 5. Case study

Background

This case study adapts elements of a true zoonotic influenza case reported in Canada in 2025 [61], to demonstrate how – should such a similar case arise in the EU/EEA – the epidemiological and virological characteristics can be scored and mapped to the scenario framework.

Scenario description

Clinical presentation and management

- A 13-year-old female presents to the emergency department with fever, cough and severe respiratory distress, requiring inpatient admission.
- An initial nasopharyngeal sample tests positive for influenza A, but H1/H3 negative following RT-PCR, with a Ct value of 27 indicating high viral load. RT PCR specific for influenza A(H5) is positive.
- She is treated with oseltamivir – later supplemented with amantadine and baloxavir – and managed with full airborne/droplet/contact precautions.
- She develops respiratory failure, with haemodynamic instability and acute kidney injury, requiring ICU admission, intubation and venovenous extracorporeal membrane oxygenation (vv-ECMO).
- Following a six-week course of clinical care, she is stabilised and later discharged.

Epidemiological context

- Epidemiological investigation does not identify any known animal exposures or potential animal sources for infection, with no known contact with potentially infected animals or environments in the 14 days prior to presentation.
- Contact tracing identifies no symptomatic contacts, with all asymptomatic household contacts testing negative for influenza following nasopharyngeal sampling.

Virological context

- Following sequencing, the isolated virus is confirmed as influenza A/H5N1 clade 2.3.4.4b (genotype D1.1) – matching the clade contained in a zoonotic influenza vaccine authorised in the EU – and is most closely related to viruses detected in wild birds sampled in the region.
- No evidence of antiviral resistance is detected via genomic or phenotypic testing.
- The viral genome sequence was typed as clade 2.3.4.4b, genotype D1.1,4 most closely related to viruses detected in wild birds in the region. Markers of mammalian adaptation were detected in aspirates collected during admission. Based on raw sequence data, the E627K mutation was detected (52% allele frequency) in the polymerase basic 2 (PB2) gene product, with analysis of the H5 hemagglutinin (HA) gene yielding ambiguous calls in the codons for amino acid residues E186 (E190 according to H3 numbering; 28% allele frequency) and Q222 (Q226 to H3 numbering; 35% allele frequency).

Genetic markers for mammalian adaptation

Text with a light green background indicates the appropriate scoring for each domain for the case study.

Consensus sequence

Sequence data (GISAID ID: **EPI_ISL_19548836**; A/British_Columbia/PHL_2032/2024) were obtained from the GISAID EpiFlu™ database [62]. We gratefully acknowledge the authors and the originating and submitting laboratories.

Mammalian adaptation traits identified by ECDC/EFSA

Analysis date: 2025-09-05

Tool(s): FluMut v.0.6.4, FluMutDB v.6.4, FluMutGUI v.3.2.0 [55]

Mutations identified in **two traits**:

Trait 1: increasing mammalian specificity of virus attachment to receptor (n=1): HA:156A

Trait 2: increasing HA stability in mammal's environment (n=0)

Trait 3: increasing activity of viral polymerases in mammalian hosts (n=2): PB1-F2:66S; PB2:627K

Trait 4: evasion of innate immunity and counteraction of mammalian restriction factors (n=0)

Trait 5: disruption of the second sialic acid binding site (2SB) in neuraminidase (n=0)

Additional qualitative scoring

In avian influenza viruses, the E627K mutation in PB2 is typically not present in the viral population infecting birds. When found at intermediate frequencies in a human case, it suggests the mutation may have arisen during replication and adaptation within the human host.

While the virus consensus sequence scores for Trait 1 (HA:156A) and Trait 3 (PB1-F2:66S; PB2:627K) – i.e. fewer than three traits – it is initially scored as Level A. However, the presence of the E627K mutation in the PB2 gene at a substantial allele frequency (52%) raises concern for ongoing mammalian adaptation within the host. Furthermore, low-frequency variants at key haemagglutinin receptor-binding residues – E186D (28%) and Q222H (35%) in H5 numbering, corresponding to E190D and Q226H in H3 numbering – suggest early, further emergence of mutations associated with increased human receptor affinity. Together, these findings support evidence of progressive intra-host adaptation and warrant heightened surveillance and consideration of increased public health risk, resulting in escalation to **Level B**.

This case highlights the value of using raw sequence data to identify ambiguous calls, as consensus sequences may mask minority variants below the set threshold. It also underscores the importance of cross-referencing H5 and H3 numbering systems, since H5-specific screening tools may otherwise miss relevant mutations when residues are reported using H3 numbering, due to positional differences between subtypes.

Scenario scoring

1. Onward human-to-human transmission (HTHT) potential (Score: 1–6)

Case and exposure context	Score
Isolated case (known exposure to animals)	+ 1
Isolated case (unknown exposure)	+ 2
Cluster with suspected common exposure (*excluding* HTHT)	+ 3
Limited HTHT (e.g. household, healthcare setting)	+ 6

2. Virological adaptation to mammals (Score: 1–7)

Includes both the animal origin of the virus and genetic indicators of mammalian adaptation:

Animal origin	Score
Bird origin	+1
Mammal *OR* unknown origin *OR* N/A (LHTHT)*	+2

** N/A - In the context of LHTHT, even if bird origin is suspected for the index case, escalate to +2.*

+

Genetic markers for mammalian adaptation	Primary score Adaptation trait identified in at least one human case isolate Level 'A' < 3 traits Level 'B' ≥3 traits *OR* < 3 traits + other factors (e.g. Concerning new mutations / combinations, new phenotypic data)	Supplementary score** (comparative sequencing) Adaptation trait identified in animal isolate(s), where exposure is known *OR* Animal exposure unknown and there is no available animal sequence *OR* Trait in two or more human cases (in clusters)
Mammalian adaptation traits (Annex 3) [23]:		
1. Increasing mammalian specificity of virus receptor attachment	+ 0.5	+ 0.5
2. Increasing HA stability in the mammalian environment	+ 0.5	+ 0.5
3. Increasing activity of viral polymerases in mammalian hosts	+ 0.5	+ 0.5
4. Evasion of innate immunity and mammalian restriction factors	+ 0.5	+ 0.5
5. Disruption of second sialic acid-binding site in neuraminidase	+ 0.5	+ 0.5
OR		
Evidence of virus reassortment	+ 5	

*** Additional 0.5 would be added for each phenotypic trait if it is also identified in animals AND/OR unknown origin specimens in terms of lack of sequence information in animals AND/OR if the same mutations occur in specimens from two or more human cases from the same cluster. Evidence of virus reassortment e.g. seasonal ↔ avian, seasonal ↔ swine, avian ↔ swine: +5 (replaces the five genetic adaptation points above).*

3. Severity potential (Score: 0 or 2; Scenario modifiers: '-R' and '-V')

Severity signals	Score
Concern about the severity profile of clinical cases (e.g. hospitalisations, deaths)	+ 2

AND

Limitations in available pharmaceutical measures	Scenario modifier
Antiviral resistance	-R
Vaccine mismatch***	-V

******** *Refers to anticipated or confirmed antigenic mismatch to EMA-authorised pre-pandemic zoonotic influenza vaccines [37] or available WHO candidate vaccine viruses [41].*

Total scenario score: 7

Scenario summary

Case and exposure context: *Isolated case, unknown exposure*

Animal origin: *Bird*

While the isolated virus is related to viruses detected in wild birds sampled in the region, there is no known contact with potentially infected animals or environments.

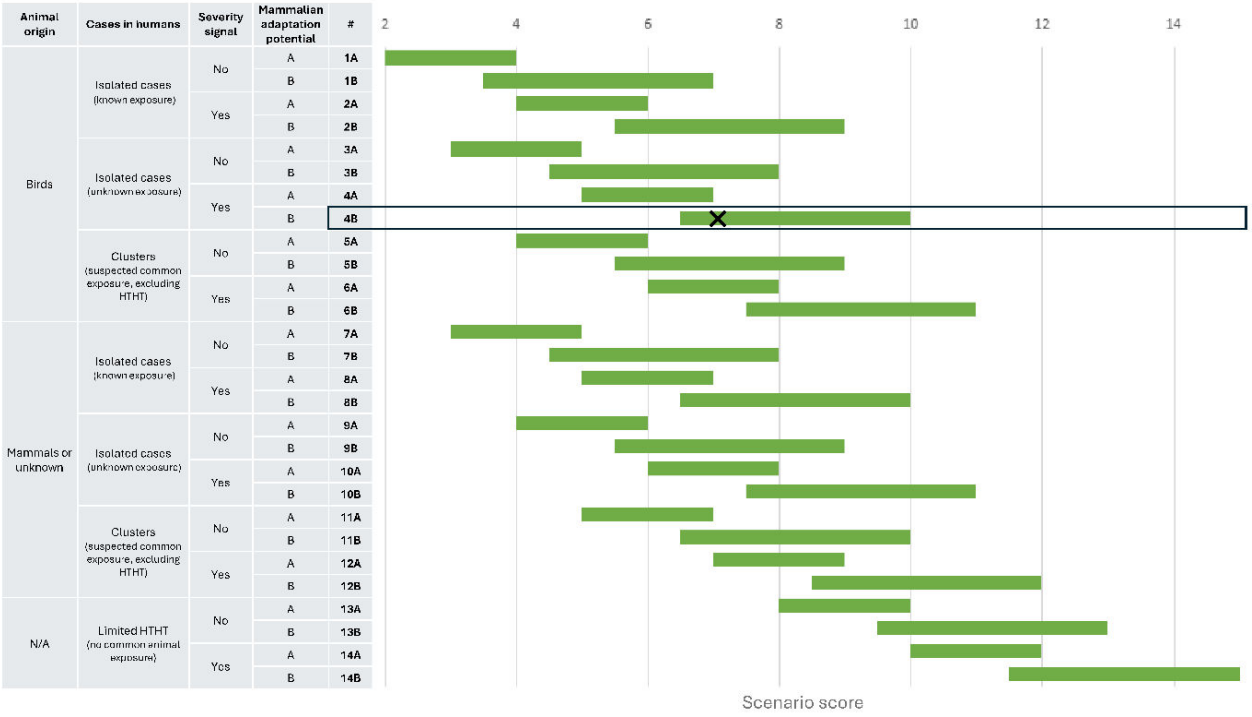
Severity signals: *Yes*

Genetic markers for mammalian adaptation: *Level B*

Antiviral resistance: *No genetic or phenotypic evidence of antiviral resistance*

Vaccine mismatch: *No*

Scenario assessment: *4 B; concern score 7/15*



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