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SCIENTIFIC REPORT

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

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Abstract

Avian influenza viruses (AIV) remain prevalent among wild bird populations in the European Union and European Economic Area (EU/EEA), leading to significant illness and mortality of birds. Transmission between bird and mammal species has been observed, particularly in fur animal farms, where outbreaks have been reported. While transmission from infected birds to humans is rare, there have been instances of exposure to these viruses since 2020 without any symptomatic infections reported in the EU/EEA. However, these viruses continue to evolve globally, and with the migration of wild birds, new strains carrying potential mutations for mammalian adaptation could be selected. If avian A(H5N1) influenza viruses acquire the ability to spread efficiently among humans, large-scale transmission could occur due to the lack of immune defences against H5 viruses in humans. The emergence of AIV capable of infecting mammals, including humans, can be facilitated by various drivers. Some intrinsic drivers are related to virus characteristics or host susceptibility. Other drivers are extrinsic and may increase exposure of mammals and humans to AIV thereby stimulating mutation and adaptation to mammals. Extrinsic drivers include the ecology of domestic and wild host species, human activities like farming practices and the use of natural resources, climatic and environmental factors. One Health measures to mitigate the risk of AIV adapting to mammals and humans focus on limiting exposure and preventing spread. Key options for actions include enhancing surveillance targeting humans and animals, ensuring access to rapid diagnostics, promoting collaboration between animal and human sectors, and considering the implementation of preventive measures such as vaccination of poultry. Effective communication to different target audiences should be emphasised, as well as strengthening veterinary infrastructure, enforcing biosecurity measures at farms, and reducing wildlife contact with domestic animals. Careful planning of poultry and fur animal farming, especially in areas with high waterfowl density, is essential for effective risk reduction.

KEYWORDS

highly pathogenic avian influenza, humans, mammals, pandemics, poultry, zoonotic virus

*The report was developed jointly by the two agencies and both parties equally contributed.

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KEY MESSAGES

Summary of the current situation

- In the European Union and European Economic Area (EU/EEA) avian influenza viruses (AIV) continue to be widespread in wild bird populations, causing high morbidity and mortality in wild birds. This also spills-over to wild and domestic mammals, cause outbreaks in poultry and occasional outbreaks in fur animal farms.
- Transmission from birds to different mammalian species has been observed. Transmission between mammals has been suggested based on the epidemiological investigations, especially in fur animal farm settings.
- Transmission from infected birds to humans remains a rare event. Transmission from an infected mammal to humans has not been observed. Despite many human exposure events to avian influenza (AI) A(H5N1) clade 2.3.4.4b viruses since 2020, no symptomatic or productive infection in a human has been identified in the EU/EEA.
- Viruses continue to diversify globally, and with the migration of wild birds, other AIV strains currently circulating outside Europe and carrying potential mutations of mammalian adaption could enter the EU/EEA.
- Should avian A(H5N1) influenza viruses acquire the ability to spread among humans, large-scale transmission could occur, given the naïve immune status of humans to H5 viruses.

Drivers for viral evolution and adaptation:

Drivers that increase exposure of susceptible mammals to AIV and the chance of spill-over events could facilitate the emergence of virus mutations and adaptations to mammals. These can be intrinsic such as host susceptibility and the characteristic of the virus or extrinsic such as human activities, and environmental and climatic factors.

Virus characteristics

- The A(H5N1) virus of the Gs/GD lineage, which is the lineage to which currently circulating 2.3.4.4b clade viruses belong, has demonstrated the ability to take some evolutionary steps towards adaptation to mammals and a propensity to reassort. To date reassortments have only occurred only among viral subtypes of avian origin and no reassortment events with influenza viruses circulating in humans or pigs have been reported in nature.
- The necessary accumulation of different gene mammalian adaptation mutations would likely only occur through a gradual and lengthy process, although, specific single mutations in the haemagglutinin (HA) gene could alter the receptor binding leading to viruses better adapted to bind to human receptors. Such mutations associated with mammalian adaptation have been indicated in previous influenza pandemic strains. After almost three decades of exposure of humans to the Gs/GD lineage, the virus has not acquired the mutations required for airborne transmissibility between humans. However, the current global spread of the virus in birds and its presence in areas with heterogeneous poultry livestock systems in terms of varying levels of surveillance in third countries compared to the European Union (EU) and infection control in both domestic and wild animals make it difficult to predict the evolutionary direction the virus will take in the future.
- Previous influenza pandemics were driven by reassortment between viruses originating from different species (human-like, avian-like and swine-like). These viruses possessed characteristics enabling replication in humans and the ability to transmit to and between humans. They had antigenic properties which rendered the affected populations immunologically naïve. Reassortment processes could potentially lead to significant genetic shifts in a short period of time and represent the highest risk for pandemic viruses to emerge.
- During the seasonal influenza season where there is high influenza circulation among the human population, there is a continued risk of a reassortment event. In particular, if mammals (animals as well as humans) are coinfected with a seasonal and AIV. Critical settings are fur animal farms and other settings where AIV may circulate in mammalian hosts that are also susceptible to other influenza viruses, for example, minks, cats, pigs and ferrets. These mammalian hosts could potentially serve as a 'mixing vessel'.

Susceptibility of farmed animals and farming practices

- Carnivore-susceptible animal species can be infected by highly pathogenic AIV (HPAIV) by eating feed that contains raw carcasses from infected birds. Among these, certain species of farmed fur animals (e.g. mink and foxes) have higher susceptibility to influenza viruses, which represents a driver for viral adaptation to mammals.
- Field and experimental evidence indicates that the infection of pigs with certain AIV is possible and generally of a subclinical nature, leading this species to possibly play a role in the acquisition of mammalian-like adaptations and in the emergence of reassortant zoonotic viruses.
- The probability of virus introduction from the wild bird reservoir into farms is higher in water bird-rich areas and in farms with outdoor production systems and/or poor external biosecurity. The probability of introduction is associated with poultry type, with decreasing probability from ducks to turkeys, to layers and broilers.
- Selection pressure on virus evolution increases with different susceptible species present in the same farm. These can include different poultry species, but also mixed farming of poultry and fur animals or poultry and pigs which could further increase the risk.

- The probability of continued virus evolution following ongoing spread between farms increases with regional farm density, especially between those with low biosecurity.

Susceptibility of companion animals

- Susceptible companion animals such as cats living in households with access to outdoor roaming can have a higher chance of being exposed to dead infected birds, other companion animals, feral cats as well as humans. Therefore, they represent a possible vehicle for transmission, in particular if they live in areas with high density of wild birds and/or poultry farms, where AI outbreaks are detected.

Epidemiological role of wildlife

- Wild mammals, especially synanthropic and peri-urban species, might serve as bridge hosts between wild birds, domestic animals and humans, facilitating viral evolution.
- When there is an increased number of reported AI outbreaks in wild mammals, this may suggest mammal-to-mammal transmission as a possible route of spread; nevertheless, further investigations both at the genomic and epidemiological levels are necessary to confirm this.

Environmental and climatic drivers

- Several environmental and climatic factors such as extreme weather events, climate change and habitat destruction can directly or indirectly influence the ecology and demography of wild birds, and, consequently, highly pathogenic AI (HPAI) infection dynamics, which could contribute to virus evolution.

Options for One Health risk mitigation measures:

The risk mitigation measures for the emergence of AIV adapted to mammals and humans should aim at limiting the exposure of mammals, including humans, to AIV and preventing its spread. The main measures are listed below.

- Surveillance targeting humans and animals should be enhanced, together with genomic analysis and the sharing of sequence data. Animals targeted should include wild birds, poultry, captive birds and the most susceptible domestic mammals (e.g. fur animal farms, mixed farms of poultry and fur animals or poultry and pigs, and cats) as well as susceptible wild mammals, especially peri-urban and peri-domestic mammals.
- Access to rapid, sustainable and cost-effective diagnostic processes, including genomics, for AIV screening of relevant animal (both domestic and wild) populations is imperative, and need to be maintained in resource-limited settings as well.
- Strong collaboration between animal and human sectors and the involvement of authorities for occupational safety and health (in settings where workers are involved) is paramount. Other preventive measures should focus on minimising exposure, ensuring correct use of appropriate personal protective equipment and hygiene measures, reducing environmental contamination and enhancing biosafety and biosecurity measures, as necessary.
- Individuals who are occupationally exposed to animals infected with AI can be offered vaccination against seasonal influenza and/or influenza A(H5) virus for protection and to minimise the risk of reassortment between avian and human seasonal influenza strains. Specific vaccination recommendations are under the remit of national authorities. Antivirals can be used to treat infected persons or as post-exposure prophylaxis when there are contacts of human cases.
- Vaccination of animals is an additional prevention strategy of AI infection at farms, complementary to stamping-out policies applied to control the infection. Vaccination should be coupled with surveillance to monitor the evolution of the field virus and identify any possible antigenic changes, including possible vaccine-induced mutations.
- It is important for public health authorities to communicate to the public about the possibility of human infection by AI. Awareness-raising programmes should target multiple audiences under a co-ordinated One Health prevention and control plan. Main target groups include the agricultural community in collaboration with occupational safety authorities, stakeholders connected to wildlife (e.g. hunters, researchers and managers), pet keepers and the general public.
- Preparedness and capacity of the veterinary infrastructure and of other relevant competent authorities including those responsible for wildlife in at-risk and affected countries should be increased, to mitigate the risk of a large spread of HPAI viruses in domestic and wild animals.
- Biosecurity should always be in place at farms to limit exposure of domestic animals to infection and its spread, including preventing direct or indirect contact of farmed animals with wild birds and other wildlife, contaminated fomites or feed (e.g. dead wild birds or raw poultry meat), and avoiding farming multiple susceptible species at the same high-risk location.
- Actions should be taken to reduce the contact and risk of transmission between (synanthropic) wildlife and poultry or other domestic animals. This can be achieved by making sure wildlife and companion animals are kept out of farm facilities that there is, proper waste and wildlife carcass removal and, if possible, limiting outdoor access for companion animals in risk areas.

- Careful planning and reorganisation of poultry and fur animal farming is essential, particularly regarding i) the location and density of poultry farms, especially those in high-risk areas close to wetlands with a high density of waterfowl and ii) farming highly susceptible species kept outdoors at high density.

1 | SCOPE OF THIS DOCUMENT

The document considers the pandemic potential of currently circulating A(H5N1) viruses in the European Union and European Economic Area (EU/EEA) and at the global level. It focuses on potential events such as reassortment, mutation and adaptation of AIV to mammals including humans. The drivers contributing to viral evolution and adaptation of currently circulating A(H5N1) viruses to mammals including humans are described and discussed. This includes the implications of the co-circulation of human influenza viruses alongside the current AI A(H5N1) strains in mammals. To reduce the risk to human health at the national and EU level, potential prevention and mitigation measures following a One Health approach are presented.

2 | TARGET AUDIENCE

This report provides guidance for public health authorities in EU/EEA countries on how to interpret the current situation of AI A(H5N1) outbreaks in animals. It also addresses which One Health mitigation measures could be implemented in animals and humans to reduce the risk to human health. It is intended as a reference for public health authorities in animal and human sectors dealing with surveillance, preparedness and response to zoonotic influenza infections.

3 | DATA AND METHODOLOGY

To compile this report, the European Centre for Disease Prevention and Control (ECDC) and European Food Safety Authority (EFSA) utilised a non-systematic literature review, outbreak data reported to World Organisation for Animal Health and World Health Organization (WHO), and expert knowledge.

4 | BACKGROUND

AI, commonly known as bird flu, is caused by influenza type-A viruses with the capability to infect a diverse array of bird species, including wild birds, domestic birds and poultry (WHO, 2018). The primary reservoir for these viruses is wild waterfowl, and they can cause spillover infections in other species (ECDC, 2022a).

AI A viruses are classified based on their levels of pathogenicity to chickens or cleavage site composition, resulting in designations as either low pathogenic avian influenza (LPAI) or HPAI. However, these classifications do not align with the severity of illness they might induce in humans. Certain low pathogenicity avian influenza viruses (LPAIVs), particularly those of subtype A(H5) and A(H7), have the potential to evolve into a HPAI form, displaying a heightened ability to cause severe disease and death in infected poultry, mainly chickens and turkeys. Of these subtypes, the A/Goose/Guangdong/1/1996 (Gs/GD) lineage A(H5N1) viruses of clade 2.3.4.4b are currently the most widespread of the HPAI strains in bird populations (CDC, 2022).

In the summer of 2020, the A(H5N8) 2.3.4.4b clade viruses reappeared in central Asia after a previous intercontinental incursion in 2016 and spread to Europe, Africa and Eastern Asia. A few months later, an A(H5N1) 2.3.4.4b clade virus emerged through reassortment in Europe and started spreading among both wild and farmed birds globally, causing an outbreak that has continued up to date and resulted in high mortality in wild birds and culling of millions of poultry globally (WAHIS, 2023; WHO, 2023a).

Since it was first detected in 1996, the HA gene of the Gs/GD-like A(H5N1) has continually evolved both through accumulation of mutations which have resulted in the emergence of multiple HA genetic clades and subclades (0–9) and through reassortment with other AIV that have produced countless genotypes. The viruses of the Gs/GD lineage stand apart from other HPAI viruses due to their ability to infect wild birds, which are normally recognized as reservoirs of LPAIVs only. Multiple clades of the Gs/GD lineage have caused five intercontinental epidemic waves by infecting wild birds and using their migratory routes: in 2005 clade 2.2; in 2008–2010 clade 2.3.2.1; in 2014–2015 clades 2.3.4.4c and 2.3.2.1; in 2016–2017 clade 2.3.4.4b; in 2020–2023 clade 2.3.4.4b. However, only clade 2.3.4.4b has become endemic in the wild bird populations of multiple regions including Europe and the Americas and has spread to all the continents, apart from Oceania (EFSA, ECDC, EURL, 2023b).

While the primary mode of transmission predominantly occurs among birds, transmission to mammals, including humans, can occur. Spillover infections to wild and domestic mammals were observed in Europe, North and South America and Asia, with a growing number of different species affected, among them wild birds and mammals, farmed fur animals and a limited number of household pets (Abbasi, 2023; Aguero et al., 2023; Domanska-Blicharz et al., 2023; Puryear et al., 2023; Rabalski et al., 2023; TSLN, online). The first documented human infection with an older A(H5N1) strain dates back to 1997 in Hong Kong, marked by an outbreak that resulted in 18 human cases, of which six were fatal (Uyeki, 2009). The WHO has registered almost 900 human cases of A(H5N1) infections in 23 countries since January 2003 (WHO, 2024b). There have been no reported human cases with confirmed infection in the EU/EEA.

5 | CURRENT SITUATION

Epidemiological situation of AI A(H5N1) clade 2.3.4.4b

AIV of A(H5N1) clade 2.3.4.4b cause infection and disease in animals and continue to circulate in Europe and globally. The situation with 2.3.4.4b clade H5 viruses is comparable in all affected regions globally, with large numbers of spillover events from infected (mostly wild) birds to different terrestrial as well as marine mammals, but very few, sporadic infections in humans. Symptomatic infection with A(H5N1) clade 2.3.4.4b virus in humans has been reported in Asia, and North and South America (Bruno et al., 2023; Castillo et al., 2023; WHO, 2022). Most of these human cases had been in direct contact with infected poultry or exposed to a contaminated environment. No human infection with confirmed symptomatic disease of this clade has been reported in the EU/EEA. Investigations and testing of workers involved in culling operations during AI outbreaks on farms in Spain resulted in positive polymerase chain reaction signals. The United Kingdom also reported such cases. On further investigation, all but one were considered most likely to be from mucosal contamination through environmental exposure rather than infection, and the remaining one was inconclusive (Aznar et al., 2023; UKHSA, 2024; WHO, 2024a).

Despite the large number of AIV transmission events from wild birds to different terrestrial and marine mammalian species since 2020, no transmission from infected mammals to humans has been confirmed. No human infection was identified when several domestic cats with severe respiratory and neurological signs were confirmed to be infected with A(H5N1) in Poland (Domanska-Blicharz et al., 2023; Rabalski et al., 2023). Also, during the large outbreaks in Finnish fur farms where different breeds (fox, mink and raccoon) were affected by AI A(H5N1), no human infection was observed (Lindh et al., 2023).

An outbreak in a mink farm in Spain in 2022 (Aguero et al., 2023) and outbreaks in farmed fur animals during 2023 in Finland (Lindh et al., 2023) have indicated that transmission of AI might occur among these animals in these specific settings and conditions. During the outbreaks, mutations related to mammalian adaptation have been identified in the virus sequences from infected mammals mostly related to an enhancement of the replication in the mammal host (Plaza et al., 2024). Transmission between different animal species kept in mixed fur farms cannot be excluded (Lindh et al., 2023). Transmission between farmed fur animals as well as other mammals is of concern and needs to be closely monitored.

Immunological situation in humans

There is lack of data on population immunity. Neutralising antibodies against A(H5) are rare in the human population, as H5 never circulated in humans. This means that any transmissible A(H5) virus with a basic reproduction number (R0) > 1 will spread. Antibodies against seasonal N1 influenza viruses might provide some level of cross–reactivity to A(H5N1) clade 2.3.4.4b through neuraminidase (NA) inhibition (Daulagala et al., 2024; Kandeil et al., 2023), but systematic data are not available. Therefore, if A(H5) viruses were to acquire the ability to transmit between humans, it would imply the presence of a highly susceptible and naïve human population with potential for extensive spread of infection.

Assessment of the risk of infection with A(H5N1) clade 2.3.4.4b to humans

ECDC assesses the risk of human infection with A(H5N1) clade 2.3.4.4b viruses currently circulating in Europe as low for the general public and low-to-moderate for those occupationally or otherwise exposed to animals infected with AI (ECDC, 2023b; EFSA, ECDC, EURL, 2023a, 2024).

Future sporadic transmissions from animals to humans and related severe disease in individuals cannot be excluded. With the high number of infected birds and mammals, ongoing outbreaks in poultry and fur farms, and small holdings such as backyard farms with no or low biosecurity measures, as well as a high environmental contamination with AIV, sporadic human infections with AIV may occur in people not wearing personal protective equipment who are in contact with infected animals. In regions with AI outbreaks where there is dense poultry or fur farming or people living in close proximity to birds or susceptible mammals, humans have an elevated risk of zoonotic transmission, due to prolonged or frequent contact between humans and potentially infected birds, mammals and environmental contamination.

While at present there are no indicators of increasing risk for transmission to humans, the risk assessment requires regular review during this time of unusually high levels of transmission in birds and mammals, especially in susceptible farmed mammals such as mink and other fur production animals. ECDC, EFSA, WHO and other stakeholders constantly monitor the situation, including screening published sequences of A(H5N1) strains for markers for mammalian adaptation.

6 | DRIVERS OF THE CURRENTLY CIRCULATING INFLUENZA A VIRUSES THAT CAN LEAD TO VIRAL EVOLUTION AND ADAPTATION TO MAMMALS, INCLUDING HUMANS

There is a continued risk of a new epidemic or pandemic in environments where viruses evolve and spread. These new strains may carry mutations of mammalian adaptation, show enhanced polymerase activity and replication in mammals, increased virulence, increased binding to human-like receptors, as well as the evasion of human BTN3A3, a protein involved in immune response regulation. If viruses are given opportunities to evolve under continuous selection pressure

(e.g. when virus spreads in mammals that are kept in high numbers in close proximity), this could facilitate the emergence and spread of isolates with the accumulation of such mutations. This is, however, a gradual process that would likely require a more extended time period and repeated opportunities to evolve within mammalian species. Below, the contributing drivers leading to a greater likelihood of influenza A(H5N1) viruses adapting to mammals and humans are presented and discussed.

Drivers that can lead to virus evolution could be events or conditions that may increase exposure of mammals or humans to AIV leading potentially to spillover transmission and further spread and thus increased chance of adaptation of avian virus to mammals. Spill-over events are common events in nature and more than two thirds of human viruses have a zoonotic origin (Rosenberg, 2015). Spill-over of pathogens occurs when a pathogen in a reservoir population comes into contact with a novel host population and 'spills over' to that. It may or may not spread further, and at different scales, within the novel host population, depending on the degree of adaptation of the pathogen to the new host population and the susceptibility of the latter (Woolhouse et al., 2012). Due to several changes that have occurred in the last decades in the environment and in host interactions, mostly due to human activity, the risk of viral spill-over and the risk of the further spread of pathogens in novel populations are predicted to increase significantly (Wolfe et al., 2007). The latter two phenomena are considered potential risk factors for the occurrence of large-scale epidemics or pandemics. In general terms, and at the global level, not only related to influenza pandemics, some of those drivers have been recognised as playing a major role through: (1) increasing human demand for animal protein; (2) agricultural and animal farming intensification; (3) increased use, trade and exploitation of wildlife; (4) unsustainable use of natural resources accelerated by urbanisation, deforestation, land use change and extractive industries; (5) increased travel and transportation; (6) changes in food supply; (7) climate change; (8) the critical health and economic situation for people living in emerging infectious disease hotspots (UNEP & ILRI, 2020; Vora et al., 2022).

Drivers for viral evolution and adaptation can be intrinsic, such as host susceptibility and the characteristic of the virus, or extrinsic, meaning all external conditions, such as ecological features of different animal species, human activities and environmental factors, that may increase exposure of mammals/humans to AIV. Below some of the main drivers for viral evolution and adaptation of influenza A(H5N1) viruses to mammals are described.

6.1 | Potential implications of co-circulation of seasonal influenza strains, AI and other animal influenza viruses

There is a continued risk of a new pandemic following an antigenic shift event, that is, reassortment between seasonal and avian and/or other animal influenza viruses in 'mixing vessels' such as pigs, minks, seals, other mammals and also humans. The risk of a reassortment event is proportional to the number of hosts coinfected with viruses of different origin (e.g. avian, swine and human origin; Ferguson et al., 2004); moreover, the higher the frequency of inter-species passage of the viruses, the higher the risk of humans becoming suitable hosts and a pandemic strain emerging. Unlike the gradual changes seen with antigenic drift, reassortment could potentially lead to significant genetic and antigenic shifts in a short period of time, as a single accidental coinfection event can produce a new strain with pandemic potential if the right genetic combination arises. Therefore, the emergence of a pandemic strain through reassortment can be swift and unpredictable as observed in the 2009 A(H1N1) pandemic.

With co-circulation of different influenza viruses, the characteristic segmented influenza RNA genome allows the reassortment and creation of newly composed influenza viruses deriving from different influenza viruses. Such reassortment events were the driver of the influenza pandemics in the past. Gene segments from the 1918 pandemic virus that caused the 'Spanish flu' had a nucleotide composition and a high guanosine–cytosine content like those influenza A viruses that (then and now) circulate in wild waterfowl, and are unlike influenza A virus strains adapted to humans (Dunham et al., 2009; Greenbaum et al., 2008; Rabadan et al., 2006). This indicates that, with or without adaptation in intermediate hosts such as pigs, the 1918 virus was likely derived from a waterfowl influenza A virus. The 1957 H2N2 'Asian' pandemic virus can be traced back as the direct descendant of the 1918 H1N1 pandemic virus. It acquired three novel gene segments through reassortment with an unidentified avian virus. The gene segments encoding HA and NA were replaced by an avian-like H2 subtype HA and an N2 subtype NA (Scholtissek et al., 1978), respectively, with the other five gene segments retained from the 1918-derived H1N1 lineage. The gene segment encoding the PB1 polymerase was also replaced with an avian-like gene segment (Kawaoka et al., 1989). Similarly, the 1968 H3N2 'Hong Kong' pandemic was caused by a reassortment event between a circulating human H2N2 virus and an AI A virus, acquiring novel HA (H3 subtype) and PB1 gene segments (Kawaoka et al., 1989; Scholtissek et al., 1978). The remaining six gene segments, including the NA gene segment, were retained from the 1957 H2N2 virus (including five segments PB2, PA, NP, M and NS – retained from the 1918 H1N1 lineage). The most recent influenza pandemic was caused by a novel triple reassorted H1N1 virus which emerged in 2009 in Mexico. Whole-genome sequencing and phylogenetic analysis revealed that the 2009 H1N1 virus was the result of reassortment between an H1N1 Eurasian swine lineage virus and a H1N1 virus from the triple reassortant swine lineage that is found mostly in North America (Neumann & Kawaoka, 2011). This is how the term 'Swine Flu' emerged for the 2009 pandemic. The triple reassortant virus contained gene segments from an unidentified subtype of avian virus, a human seasonal H3N2 virus and a virus from the classic swine H1N1 lineage.

Since the emergence of the Gs/GD lineage in 1996, there have been no reported cases in nature of reassortment of A(H5N1) viruses with human influenza viruses. However, clade 2.3.4.4 H5 viruses are of particular concern because of the

high frequency of genotype turnover driven by virus reassortment. The propensity of clade 2.3.4.4 H5 viruses to reassort and form novel genotypes, possessing different NAs; e.g. N1, N2, N6 or N8) and internal genes acquired from LPAIVs co-circulating in avian species, has also characterised the evolutionary pattern of its descendent clade 2.3.4.4b. Since 2020, such events have been occurring with high frequency among clade 2.3.4.4b viruses leading to the emergence of high genetic diversity among the circulating viruses. Of note, the reassortments of the NA gene, which were frequently detected until mid-2021, became extremely rare starting from autumn 2021, and the A(H5N1) subtype is now the dominating subtype. The occurrence of these reassortment events has led to the emergence of new genotypes with characteristic features in terms of host range and pathogenicity. Genotypes capable of infecting new species of wild birds have thus emerged, with an inevitable impact on the temporal and spatial distribution of the virus (e.g. BB genotype infecting seabirds and causing spillover in kept mammals; EFSA, ECDC, EURL, 2023b). Although the ability of clade 2.3.4.4b H5N1 viruses to reassort with human influenza viruses has yet to be ascertained, the potential of reassortment of previously circulating Gs/GD A(H5N1) viruses and A(H3N2) or A(H1N1) human viruses has been demonstrated through in vitro and in vivo studies (Jackson et al., 2009).

6.2 | Characteristics of the currently circulating A(H5N1) virus

Even though the Gs/GD-like viruses (A/Goose/Guangdong/1/96 (Gs/GD)-like H5N1 HPAI viruses) have been circulating for 28 years, the key genetic changes in the HA gene known to induce a complete switch of the receptor specificity from avian to human receptors have not yet been identified. Several adaptive mutations in the receptor-binding site of avian HAs have been shown to cause a switch of binding specificity, exemplified by E190D/G225D and A138S in H1 HA and Q226L/G228S in the HAs of H2 and H3 subtypes (Shi et al., 2014). These mutations enhance the virus' ability to bind to the human receptor while diminishing its affinity for the avian receptor. In addition, as a prerequisite for a pandemic virus to emerge, other amino acid substitutions will also be needed in the HA, to help HA stabilisation and make the viruses more transmissible through the air (Long et al., 2019). Outside Europe, the sporadic detection of the mutation Q226L, which is one of the mutations associated with the switch in the receptor specificity from avian-type to human-type receptor (Long et al., 2019), has been reported. In particular, this substitution was identified in A(H5N6) viruses of clade 2.3.4.4b in two human cases in China in 2021, in a farmed dog in China in 2023 (Yao et al., 2023; Zhu et al., 2022) and in two A(H5N1) viruses of clade 1 collected from human infections in Cambodia in 2013 (Rith et al., 2014). Few mutations in the HA protein, which have proven to increase in vitro binding to human-type receptor (i.e. S133A, S154N, T156A), have been identified in the majority of the A(H5N1) viruses of the 2.3.4.4b clade circulating in Europe since October 2022, while others (i.e. D94N, S155N, T188I, Q192R, V210I) have only been sporadically observed (Suttie et al., 2019). The impact of these HA mutations on the biological characteristics of the circulating viruses is still unknown and more studies are needed. However, none of them have caused a shift from avian-like to human-like receptor-binding preference; the circulating viruses remain avian-like and preferentially bind to alpha-2,3 sialic acid.

The virus has demonstrated the potential to readily acquire mutations in the polymerase complex that confers an increased ability to replicate in mammalian cells (i.e. E627K, D701N or T271A in the PB2 protein) once introduced in mammalian hosts. Indeed, these mutations have been identified but only sporadically in avian species infected by the 2.3.4.4b clade A(H5Nx) viruses in the EU/EEA, while more than half of the viruses sequenced from mammals in the same region presents these adaptation markers. However, it is worth noting that the sampling of these mammals is not random, but mainly focussed on dead animals or animals showing clinical signs.

When AIV crosses the species barrier, the functional balance between HA and NA needs to be adjusted to the sialoglycan repertoire of the novel host species in the second sialic acid-binding site (2SBS) in NA (Du et al., 2021). Mutations in the 2SBS of the NA, which can affect the binding and cleavage of receptors and the virus replication in mammalian hosts (S369I, I396M/V, K432E, N1 numbering), have been identified among H5N1 viruses detected in EU/EEA over the last 3 years. Mutations I396M/V and K432E have been rarely detected, while S369I has been observed in all the H5N1 viruses belonging to the BB genotype, and mainly detected in seabirds. This virus has caused spillover events in fur farms since late 2022.

Another important factor to consider is the potential of the Gs/GD-like H5 viruses, including those of the 2.3.4.4b clade, to overcome the human/mammal antiviral response. Indeed, certain 2.3.4.4b clade viruses detected in the EU/EEA present mutations that allow the evasion of the antiviral activity of the human butyrophilin subfamily 3 member A3 (BTN3A3) protein (i.e. A(H5N1) viruses of the BB genotype have acquired the mutation NP-Y52N/H; EFSA, ECDC, EURL, 2023a, EFSA, ECDC, EURL, 2023c).

Unique ecological and epidemiological features characterise the 2.3.4.4b clade viruses, namely: (i) the continuous geographical expansion resulting in a panzootic event of unprecedented proportions that reached the avian population in all continents except for Oceania; (ii) the increasingly wide host range, with infections and deaths reported in a variety of wild bird species (356 species belonging to 21 orders; Klaassen & Wille, 2023) and in mammals, with sporadic episodes and field data suggesting a potential mammal-to-mammal transmission, as reported not only in Spain and Finland (Aguero et al., 2023; Lindh et al., 2023) but also in other countries outside Europe (Leguia et al., 2023); (iii) the ability to generate an unprecedented number of genotypes through reassortment events; and (iv) the endemicity of the virus in wild bird population in Europe with viral persistence throughout the summer season (EFSA, ECDC, EURL, 2023c; Youk et al., 2023).

To date, the currently circulating A(H5N1) clade 2.3.4.4b virus has caused only a few cases of human infection. However, the high number of infections and transmission events between different animal species increases the likelihood of the

viral reassortment and/or the acquisition of mutations that may improve the ability of newly emerging influenza viruses to efficiently infect, replicate, and transmit to and between mammals.

None of the pandemic events of the last 106 years have been caused by highly pathogenic viruses of the influenza A H5 subtype, but have involved viruses of the H1, H2 and H3 subtypes.

Concluding remarks

- The A(H5N1) virus of the Gs/GD lineage has demonstrated the ability to take some evolutionary steps towards adaptation to mammals. Specifically, the ability: (1) to acquire mutations that make its replication more efficient in mammalian cells and (2) to evade certain components (BTN3A3) of the mammalian host's antiviral response. In addition the virus has a significant propensity to reassort, although to date reassortments have occurred only among viral subtypes of avian origin and not with swine or human influenza viruses.
- After almost three decades of exposure of humans to the Gs/GD lineage, the virus has not acquired the mutational changes needed for a complete switch in specificity to human receptor-binding patterns. However, the current global spread of the virus and its presence in areas with heterogeneous poultry and livestock systems in terms of varying degrees of development in surveillance and infection control in both domestic and wild animals, make it difficult to predict the evolutionary direction the virus will take in the near future.
- The accumulation of mutations in AIV causing mammalian adaptation, the possibility of reassortment with other animal influenza viruses and the use of vaccines warrants enhanced surveillance including continuously monitoring the properties of the circulating viruses, early detection, and swift response from the animal and public health side.

6.3 | Susceptibility of farmed mammals

Fur animals

Among farmed mammal animals susceptible and reported to be infected by influenza A(H5N1), fur animals (Mustelidae and Canidae) are the most relevant group of species. Among these, A(H5N1) cases have been reported in farmed mink in Spain in 2022 (Aguero et al., 2023) and in Finland in summer 2023 (Lindh et al., 2023) in American mink (*Neogale vison*), Arctic fox (*Vulpes lagopus*), common raccoon dog (*Nyctereutes procyonoides*) and red fox (*Vulpes vulpes*).

Furthermore, a large number of reports have been published that describe the circulation of different seasonal, avian and swine influenza A viruses in farmed mink and other fur animals in different countries globally (Englund, 2000; Gagnon et al., 2009; Graaf et al., 2023; Meseko et al., 2018; Mok & Qin, 2023; Peng et al., 2015; Qi et al., 2009; Rosone et al., 2023; Sun et al., 2021; Tremblay et al., 2011; Yong-Feng et al., 2017; Yu et al., 2020):

- Serological evidence of AI H7 and H9 in China;
- H9N2 causing respiratory disease in mink farm (and foxes, raccoon dogs), contact transmission, virus shedding (6–8 dpi) and seroconversion;
- H9N2 mink adapted virus-enhanced virulence in mice;
- H5N1, H10N4/N7, infections detected in mink, raccoon dogs, foxes;
- H5N6, H7N9, H9N2 seropositive (including possible coinfection) mink;
- Swine H1N2, swH3N2, swH3N2/pH1N1 virus isolation in mink;
- Seasonal H1N1pdm09, H3N2 detected in mink.

In the outbreak in Finland, direct contact with wild birds (gulls) was the suspected source of introduction, although most of the A(H5N1) viruses collected from fur farms were highly related to each other and to viruses collected from gulls in the same geographic area, making it difficult for most of the cases to assess the virus origin (wild birds vs. other fur farms vs. within-farm virus transmission). Genetic analysis revealed that the virus belonged to the BB genotype (the same as in the outbreak in mink farm in Spain in 2022) and about 43% of the characterised viruses contained at least one of the adaptive markers associated with increased virulence and replication in mammals in the PB2 protein (E627K, D701N, T271A or K526R), which have rarely been identified in HPAI A(H5) bird isolates of clade 2.3.4.4b in Europe since 2020. This may suggest that these mutations with potential public health implications have likely emerged upon transmission to mammals. No human infections related to the AI detections in animals in fur farms in Finland have been detected (EFSA, ECDC, EURL, 2023a, 2023b, 2023c).

American mink is highly susceptible to influenza viruses, and can be infected with avian and human influenza viruses, with a strong likelihood of coinfections, thus they could serve as 'mixing vessels', as do pigs, for the generation of novel reassortant viruses.

Aerosol transmission among mink can occur for human influenza viruses, not avian viruses, suggesting that mink are similar to ferrets, which are considered the 'gold standard' animal model to study influenza, as they are conducive hosts for human influenza virus replication (Sun et al., 2021).

Fur animal farms usually host several thousands of animals (e.g. 5000–20000) with high animal density: this provides ideal conditions for virus replication and transmission, therefore increasing the risk of virus evolution (EFSA, ECDC, 2021).

Moreover, farmed mink and other fur animals are generally farmed in open housing systems in contiguous wire netting cages, which may allow close contact between caged animals and other wild or domestic animals approaching these facilities, which, if they are susceptible, may acquire viruses if mink are infected.

Concluding remarks

- The intrinsic susceptibility of farmed fur animals, such as mink, to influenza viruses coupled with the risk derived from the farming system with high animal density and promiscuity among animals of the same and of other species require that biosecurity (e.g. avoiding feeding with raw poultry meat, limiting access to wild birds to fur farms) and surveillance of influenza viruses in mink farms should be constantly implemented both in animals and exposed humans.

Pigs

Inter-species transmission of influenza viruses from other mammalian and avian species to pigs has been extensively documented. Accumulating knowledge therefore suggests that pigs are indeed a mixing vessel with the potential for reassortments of influenza A viruses from mammalian and avian species, and that the directional flow of virus goes both ways (i.e. to and from pigs; Abdelwhab & Mettenleiter, 2023; Arruda et al., 2024; Ma et al., 2009).

However, it is worth noting that the susceptibility of pigs to AIV is similar to humans, with the predominant sialic acid linkage being α2-6 sialic acid. Furthermore, AIV replication is restricted in swine cells in the same manner as it is in human cells because swine acidic leucine-rich nuclear phosphoprotein 32 family member A (ANP32A) does not possess the avian-specific gene duplication necessary to facilitate the activity of avian virus polymerase (Long et al., 2019; Moncorge et al., 2013).Therefore, the concept of pigs as a mixing vessel hinges more on favourable circumstances, such as close interactions between infected birds, swine and humans, rather than purely physiological factors. These circumstances include dense housing on pig farms allowing for close-contact transmission events and opportunities for reassortment (Long et al., 2019).

Transmission of AIV to pigs has been sporadically reported in the last two decades, with most events reported in Asia. Distinct AIV subtypes have been identified in the swine population including highly pathogenic H5N1 and H7N9, and low pathogenic H3N3, H4N1, H4N6, H4N8, H5N2, H6N6, H7N2, H9N2 and H10N5 viruses. However, evidence on the role of pigs as a 'mixing vessel' for Gs/GD H5 viruses and in particular for Clade 2.3.4.4b A(H5N1) is lacking. A study carried out in 2022 in Germany to investigate the susceptibility of pigs against experimental infection with a A(H5N1) Clade 2.3.4.4b virus identified in poultry resulted in marginal viral replication, without inducing any clinical manifestation or pathological changes (Graaf et al., 2023). Low susceptibility to infection and disease, replication mainly restricted to the lower respiratory tract and the absence of transmission have been demonstrated in other experimental studies conducted infecting pigs with Gs/GD H5 viruses belonging to clades different from the 2.3.4.4b (Kaplan et al., 2017; Lipatov et al., 2008). However, the susceptibility of swine may vary in the case of infection with A(H5N1) viruses characterised by the presence of mammalian-adaptive mutations. Indeed experimental infection of swine with the mink-derived clade 2.3.4.4b A(H5N1) virus (Aguero et al., 2023) resulted in productive virus replication and seroconversion in all the infected pigs, despite a lack of transmission to contact sentinel pigs. In addition, mammalian-like mutations such as PB2-E627K and HA-Q222L emerged at low frequencies in clinical samples and tissues derived from infected pigs (Kwon et al., 2023).

Reported cases of pigs infected with Gs/GD H5 viruses have been sporadic and mostly subclinical in field studies. Indeed, seroconversion of backyard pigs against HPAI H5N1 2.3.4.4b clade virus has been demonstrated in France (Hervé et al., 2021) and Italy (Rosone et al., 2023). So far, no pigs tested positive for clade 2.3.4.4b H5 viruses have been reported in EU/EEA. However, surveillance in pigs in China in 2014 identified individuals of this species infected with 2.3.4.4 clade A(H5N6) viruses. In addition, Gs/GD H5 viruses belonging to clades which are not circulating in the EU/EEA, namely clade 7, 2.3.4, 2.3.2.1c, 2.1.3 and 2.1.3.3, have been identified in the Asian and African swine population (Chauhan & Gordon, 2022). Pigs raised in mixed poultry-pig farms or kept near an area in which an influenza A(H5N1) outbreak among poultry were found to be at a higher risk of contracting the infection.

Concluding remarks

- The available scientific information suggests that the current 2.3.4.4b H5 strains are poorly adapted to pigs. However, field and experimental evidence indicates that infection in this species is possible and generally of a subclinical nature. Active surveillance should be routinely implemented in pigs exposed to or in proximity of either HPAI infected poultry or wild birds or other mammals, given the important role played by this species in the emergence of reassortant zoonotic viruses.
- Considering the plethora of new H5N1 genotypes which have emerged in the last 3 years and the ability of these viruses to acquire mutations that confer an increased adaptation to mammals, a periodic reassessment of the permissiveness of pigs to emerging HPAI H5N1 viruses is needed.

6.4 | Susceptibility of companion animals

The H5N1 virus was also detected in companion mammal animals such as domestic (and feral) cats, dogs and ferret in the EU and other countries (Briand et al., 2023; CFIA, 2023; Domanska-Blicharz et al., 2023; Moreno et al., 2023; Rabalski et al., 2023; Račnik et al., 2022).

All known cases of infected companion animals, which often displayed severe clinical symptoms including death, were linked to contact with infected birds (predation or contact with dead birds) or bird product (e.g. consumption of raw poultry meat), and were also often characterised by viruses with mutations related to mammalian adaptation.

These were mostly single cases at household level. However, it is worth noting that an H5N1 outbreak in cats occurred in Poland, where 25 out of 46 tested cats were infected with the CH genotype (H5N1 A/Eurasian wigeon/Netherlands/3/2022-like). Genomic sequencing confirmed that the virus was very similar among the cat isolates indicating one common source of infection, suspected to be poultry meat, but not confirmed. This genotype was already responsible for several poultry outbreaks in Poland, but the virus from the cat isolates possessed two amino acid substitutions in the PB2 protein (526R and 627K) which are two molecular markers of virus adaptation in mammals.

Feral cats have also been reported as susceptible to infection, with cases documented in the United States and the EU (EFSA, ECDC, EURL, 2023a, 2023b, 2023c). In Spain, where HPAI virus detections in wild birds were reported, a serological study revealed four seropositive feral cats out of 183 tested (2.2%). Similarly, feral cats with access to infected sources, such as infected poultry or fur farms, may represent a risk of transmission to both the feral cats and household cats population as they would encounter both (Amman et al., 2022).

Ferrets, which are also kept as companion animals and are very popular in some Member States (e.g. Slovenia), have been also reported to be infected in the EU (EFSA, ECDC, EURL, 2023a, 2023b, 2023c). Ferrets have intrinsic high susceptibility to avian, swine and human influenza A viruses and clinical signs are similar to those in humans. Because of that, they are one of the best animal models for studying pathogenesis of influenza viruses. Current experimental data demonstrate that clade 2.3.4.4b viruses can be highly virulent in mice and ferrets but do not transmit to exposed ferrets through respiratory droplets (Kobasa et al., 2023; Maemura et al., 2023).

Concluding remarks

- Companion animals living in households and with access to outdoor roaming have a high risk of being exposed to dead infected birds, other companion animals as well as feral cats and humans. Therefore, they represent a possible vehicle for transmission, in particular if they are in areas with a high density of wild birds and/or poultry farms where AI outbreaks are detected.

6.5 | Farming practices

Farming practices that influence virus evolution can be categorised into those associated with (1) the probability of virus introduction from wild birds into farmed animals (mostly poultry, but may also be mammals), (2) the propagation of the virus once it has been introduced into a farm (within-farm transmission, including potential of prolonged spread), (3) inter-species transmission in a farm and (4) onward spread to other farms. Points 1 and 3 require a host species switch that serves as a bottle neck for virus evolution, points 2 and 4 result in virus amplification allowing for continued virus circulation and exposure to other farms and species, and, consequently, continued virus evolution.

1. Farming practices associated with the probability of introduction

Farming practices that increase the probability of introduction are linked to the exposure of virus in the surroundings of a farm and the external biosecurity of the farm. Farms located in areas with water bodies (or have them on the premises) and high densities of water birds are more at risk of virus introduction than those located in dryer areas (Schreuder et al., 2022).

Besides the location, the type of poultry and the lack of external biosecurity are the most important risk factors associated with the probability of introduction. From examining epidemiological data from affected farms in Europe, duck farms appear to be associated with the highest probability of virus introduction, followed by turkey farms and chicken farms; with layers being more at risk than broilers (Health et al., 2017).

Outdoor housing farming practices create the highest risk of introduction as shown for LPAIV (sixfold increase, (Bouwstra et al., 2017)). This also implies that increasing the percentage of organic poultry farms – a goal in the Farm to Fork strategy of EU – may increase the number of outbreaks given the same exposure and absence of risk mitigation measures (e.g. vaccination).

In addition, general biosecurity weaknesses play a role such as (a) farm premises attractive for wild (water) birds (water, feed present outside the poultry houses), etc.), (b) lack of an adequate biosecurity infrastructure (clothing, boots, hygiene locker, shower, truck cleaning and disinfection, etc.), (c) absence of biosecurity protocols and (d) inadequate compliance to biosecurity (behaviour; Health et al., 2017).

The wild bird virus reservoir seriously challenges biosecurity, because wild birds can fly over the fence surrounding a farm, making adequate biosecurity measures at each poultry house crucial (WOAH, 2023a). Under the assumption that

each bird in a flock has the same probability of infection by environmental exposure, farm size would be a risk factor for virus introduction. Nevertheless, this (theoretical) association may not take place in practice due to on average better biosecurity practices in large farms than in smaller ones (Ssematimba et al., 2013).

Although the susceptibility of mammals for H5N1 is lower than for poultry, it seems likely that the same risk factors for the introduction from wild birds apply. As for the species, farmed fur animals will have a higher risk of introduction than pig farms. In pigs, outdoor farming is expected to increase the risk of virus introduction (dead wild birds in the outdoor area will be eaten by the pigs). Although fur animals do not have outdoor areas, the houses/sheds are usually open and easily accessible for birds, and the wire netting cages where mink are kept allow exposure of mink to other wild or domestic in-contact animals.

Feeding could also be a driver for the introduction of AI into farms and mammal companion animals. Carnivores that are fed feed containing material from carcases of infected birds can be infected with HPAIV (Frymus et al., 2021; Keawcharoen et al., 2004). Feed containing raw poultry meat is often fed to fur animals (by product of poultry slaughterhouses), and also to cats or dogs by some pet owners (e.g. biologically appropriate raw food diet). Animals in the wild can be exposed by eating animals that have died from HPAIV.

2. Farming practices associated with virus propagation

In the current production system, discovering the extent of within-farm transmission in poultry farms is dependent on the early detection of the disease through passive surveillance in the most, and the ability of the farmer to quickly recognise the first signs of an outbreak. In chickens and turkeys, rapid detection is common due to very high case fatality (EFSA AHAW Panel, 2023). However, in ducks, where the clinical manifestation may be less clear, detection and reporting could be delayed (Briand et al., 2018). In the absence of early detection, farm size/number of flocks is a risk factor since more animals can become infected resulting in more virus produced. Animal density is also a risk factor for the transmission rate of HPAIV on a farm; however, it is unclear whether this plays a relevant role in the range of densities present in the current farming practices. Lack of biosecurity between poultry houses poses a risk for virus propagation, whereas good biosecurity measures could slow down the spread of infection between houses. Moreover, by applying all-in-all-out, the farm is emptied and disinfected, so the virus transmission stops, whereas farms where animals are always present on the same premise (animals of multiple ages) could create a reservoir of virus. This is not very likely for HPAI in naïve chickens and turkeys, where the disease if present is usually clinically manifested, but may be a risk factor in ducks (and vaccinated poultry and for LPAIV; Jacquinet et al., 2022).

3. Farming practices associated with inter-species transmission

Housing multiple poultry species on the same premises likely results in transmission between bird species and the associated selection pressure on the virus while going from one bird species to another (Health et al., 2017). The risk of virus evolution increases if poultry and potentially susceptible mammals are farmed on the same premises. From the mammals reported above, fur animals seem to have the highest risk of infection. Consequently, a combined poultry—fur animal farm could be considered a high-risk farming practice. The risk of virus evolution on such farms further increases, because fur farms are often visited by stray cats (because of the feed) and the example of SARS-CoV-2 showed that viruses can be readily transmitted between mink and cats (van Aart et al., 2022). Mixed poultry-pig farms are also considered a farming practice with increased risk, because pigs have been a mixing vessel for avian and mammalian viruses for a long time. Although the currently circulating A(H5N1) virus can infect pigs, it is poorly adapted to this species (Graaf et al., 2023), yet this could change in the future, given the high reassortment rate of the virus among wild birds. It is known that several (reassortants of) swine influenza viruses are circulating abundantly on pig farms (Henritzi et al., 2020) creating a chance of a novel reassortant should H5N1 be introduced to a pig population.

4. Farming practices contributing to between-farm spread

Risk factors for between-farm spread are the movement of animals and the density of farms (and farm types) in the area (Boender et al., 2007). In addition, the movement of visitors, trucks and contaminated material play a role (Ssematimba et al., 2013). However, in Europe primary introductions from wild water birds cause the majority of outbreaks, between-farm spread remains important in regions with a high density of poultry farms, in particular if these are ducks/geese or turkeys.

5. Farming practices increasing the risk of human exposure

When humans are in a house with infected poultry, they are exposed to the virus, but no evidence has been found for farming practices increasing the risk of human H5N1 exposure. For HPAIV H7N7, it was observed that persons doing screening activities in infected areas had a 7.6% probability of contracting infection and persons doing culling activities had a 6.2% probability of infection (Bos et al., 2010). No association was observed between housing systems (caged or loose housing), poultry type (chicken, turkey, duck) or farm size in that study. Additionally, oseltamivir showed a 79% protective effect, while the use of respirators and protective glasses showed no demonstrable effect (te Beest et al., 2010).

Concluding remarks

- Farming practices that influence virus evolution can be distinguished in those associated with (1) virus introduction (2) the propagation of the virus once it has been introduced into a farm, (3) inter-species transmission in a farm and (4) onward spread to other farms.
- The probability of virus introduction from the wild bird reservoir is higher in water (bird)-rich areas and in farms with an outdoor production system and/or poor external biosecurity. The probability of introduction is associated with poultry type with decreasing probability from ducks to turkeys, to layers and broilers.
- Selection pressure on virus evolution increases with different susceptible species on a farm, these can be different poultry species, but combinations of poultry and fur animals or poultry and pigs could further increase the risk.
- The probability of continued virus evolution following ongoing spread between farms increases with regional farm density.
- Carnivores can be infected by eating feed that contains raw carcases from HPAIV-infected birds. Therefore, it is recommended not to feed raw poultry to farmed or companion animals.

6.6 | Role of wildlife

AI is mainly found in birds, but recently, there has been a notable increase in AI infections in mammals, mainly wild mammals, including cases with varying severity from asymptomatic to mass mortalities, alongside some human infections.

Large number of species of wild mammals have been reported to be infected with A(H5N1) clade 2.3.4.4b viruses to date: European otter, North American river otter, marine otter, European badger, skunk, Virginia opossum, Amur leopard, Amur tiger, mountain lion, fisher, European polecat, lynx, bobcat, red fox, coyote, raccoon, raccoon dog, South American bush dog, American black bear, brown Bear, grizzly bear, Kodiak bear, grey seal, harbour seal, fur seal, sea lion, porpoise, bottlenose dolphin, short-beaked common dolphin, white sided dolphin, dogs, Japanese raccoon dogs, Beech marten, Caspian seals, Asiatic black bear, Chilean dolphin and Burmeister's porpoise.

Particularly concerning are instances of H5N1 infections in dolphins in South America, and harbour and grey seals in New England (US; EFSA, ECDC, EURL, 2023a). These outbreaks coincided with avian infections in the respective regions and mass mortalities of sea lions and southern elephant seals in Argentina, Brazil and Uruguay. Although evidence suggests the adaptations of the virus to mammals, the precise transmission routes and pathogenesis in mammalian hosts remain unclear.

A thorough literature review about the epidemiological role of mammals, specifically wild mammals, in AI maintenance, spread, pathology and virology has been conducted and the main findings are reported below (ENETWILD Consortium, 2024).

Influenza A subtype H5N1 was most frequently found in wild mammals compared to other subtypes of interest: H7Nx, H10Nx, H3N8 and H9N2. This may be due to a report bias since H5N1 is more pathogenic so more visible and detectable by passive surveillance.

Most studies reported isolated cases of infection in Carnivora, suggesting a connection between predation and scavenging behaviour and AI infection (from wild birds).

In captive settings, even in taxa with high reported infections, such as tigers and mustelids, the most frequent subtypes were H5N1 and H9N2. In these cases, the source of infection was generally identified as feeding on raw chicken meat from infected poultry.

Carnivores were more exposed if they had access to shared resources with migratory or synanthropic birds, such as aquatic mammals, companion mammals, fur farmed carnivores or found at wildlife–livestock interface.

The greater the number of infection records in a particular species, the higher the diversity of subtypes recorded. This finding might suggest a higher probability of exposure to a wider range of subtypes from multiple sources due to species ecology and distribution (e.g. scavenging habits), or a higher susceptibility of those species to be infected with different AIVs (e.g. immunity features).

Host features that seemed to favour infection were scavenging feeding habits, for example, those of generalist mesopredators[1] such as red foxes and mustelids, which often inhabits urban and peri-urban settlement with exposure to other domestic mammals (e.g. cats and dogs) and humans, and in general carnivores were more exposed to infection and displayed more viral mammalian adaptations.

Harbour seals, grey seals and red foxes were reported to be infected with more subtypes. Infection risk factors identified for these species include: a high probability of coming into contact with potentially infected bird species (i.e. aquatic, migratory and peri-domestic), scavenging habits (especially for the fox, although also seals do feed on dead birds), and contact with guano, water and other contaminated environmental resources.

Sustained mortality events due to H5N1 have so far only been reported in seals and foxes, with evidence suggesting transmission from infected wild birds. However, the several mass mortality events that have occurred in pinnipeds in Latin America suggest that mammal-to-mammal transmission may be a possible route of viral spread. However, this needs to be confirmed by further investigations with larger sampling sizes, and more in-depth genomic analysis associated with more detailed epidemiological information to better understand the dynamics of virus transmission in these populations. The

[1]A mesopredator is a predator that occupies a mid-ranking trophic level in a food web. Mesopredators are usually medium-sized carnivorous or omnivorous animals, such as raccoons, foxes or coyotes, usually preying prey on smaller animals. They are often defined by contrast from apex predators in a particular food web.

high likelihood of continuous contact of this species with potentially infected birds requires ongoing vigilance, as this increases potential opportunities for further reassortment or adaptation of these viruses to mammalian hosts.

Different human activities may increase the risk of infection for sea animals. Fishing waste disposed by fishermen can attract seabirds and sea mammals that come to feed, increasing the chance of infection exposure. In South America in many places along the Pacific coast, seabirds and sea lions are artificially fed on docks as a tourist attraction, generating large congregations of wild animals that increase contact chance among those and with humans.

Also, semiaquatic animals, such as certain mustelid species like mink and otter, which are intrinsically susceptible to AI viruses, may have greater exposure to waterfowl through predation and scavenging and become at risk for infection.

Concluding remarks

- While there is an increased number of reported infections in wild mammals, there is no hard evidence of mammal-to-mammal transmission in the wild, an event that needs to be proven by further investigation, at both genomic and epidemiological level. So far experimental evidence suggests it is possible for some viral genotypes but it is not very effective.
- Wild mammals, especially synanthropic and peri-urban species, might serve as bridge hosts between wild birds, domestic animals and humans, facilitating viral evolution.
- Subclinical infections are crucial for virus maintenance, especially in wild mammals, although surveillance mainly focuses on mass mortality events in marine mammals. Limited evidence exists regarding species-specific susceptibility and morbidity/mortality of viral genotype-host combinations.
- Active monitoring is recommended to detect AIV mutations or adaptations favouring spread in mammals, including humans.

6.7 | Environmental and climatic drivers

Several environmental and climatic factors can directly or indirectly influence HPAI infection dynamics, especially in wild birds, and consequently in domestic poultry and mammals, thereby representing drivers for virus evolution. Among these, weather events, especially if extreme or sudden, climate change and habitat destruction can impact wild bird ecology, demography, biodiversity and migration and bring the virus to new areas and/or closer to domestic poultry or mammals (Gilbert et al., 2008). A few reported examples are found below.

Droughts, which are currently intensified events due to climate change and global warming, could result in reduction of wetlands, which reduces the food and shelter availability for wild waterfowl. This can affect waterfowl ecology in many ways, (i) leading to weaker birds, (ii) higher density of birds in fewer and smaller areas, thus increasing chance of virus spread, (iii) movement of waterfowl to other habitats, such as agricultural areas where contacts with domestic poultry can increase and (iv) the movement of waterfowl to other wetlands beyond their normal ranges, which could potentially introduce AIV to new places (Wang et al., 2023).

On the contrary, the intensification of localised rainfall may lead to the creation of provisional new wet areas that attracts wild waterfowl, thus potentially spreading HPAI virus to new areas. In certain dry areas with erratic rainfalls, for example, Australia, it was observed that the risk of AIV outbreaks in poultry increases after a period of high rainfall (Ferenczi et al., 2021). This was presumably due to increased breeding events of wild waterfowl at temporary wetlands and increased proportions of immunologically naïve juvenile birds entering the population after major rainfall events, with aggregation near permanent water bodies when the landscape dries out.

Other environmental drivers for infection spread and consequent evolution pressure on HPAI virus may be triggered by AI infection of guano sea birds. In certain islands and guano headlands in South America, not only do large colonies of sea lions and seabirds cohabitate, but indirect transmission may also occur through guano runoff into the surrounding waters. Similarly, guano may be a vehicle to agricultural areas and domestic poultry, since guano is often used as crop fertiliser (Leguia et al., 2023).

7 | ONE HEALTH RISK MITIGATION MEASURES AND ACTIONS TO REDUCE THE RISK TO HUMAN HEALTH

In this chapter, the main possible risk mitigation measures for the prevention and control of infection in humans and animals under a One Health perspective are presented.

7.1 | Enhanced surveillance and data sharing

Surveillance of human influenza A should be enhanced especially in the areas where detections in animals have occurred. ECDC has published technical reports on 'Enhanced surveillance of severe avian influenza virus infections in hospital settings in the EU/EEA' and 'Targeted surveillance to identify human infections with avian influenza virus during the influenza season 2023/24, EU/EEA (ECDC, 2023c, 2023d). All viruses of non human origin detected in humans need to be further characterised genetically and antigenically.

The persistent circulation of the HPAI A(H5N1) virus in wild birds on several continents and the increased frequency of virus transmission to domestic animals and wild mammals require the strengthening of AI surveillance in animals. Surveillance should encompass wild birds, poultry, captive birds and susceptible domesticated mammals (e.g. fur animal farms). Additionally, well-structured surveillance systems should be designed and implemented in wild mammal species where incursions of HPAI A(H5N1) virus have been detected with increasing frequency in recent years (ENETWILD Consortium, 2024). International guidelines should be established to standardise surveillance systems for wild terrestrial and aquatic mammal populations at HPAI risk.

To closely monitor the evolution of the HPAI A(H5N1) virus in animal populations, international networks of AI laboratories should be strengthened to ensure regular genomic analysis of HPAI viruses detected through AI surveillance plans, with the rapid global sharing of viral sequences. Depositing genetic data in publicly accessible platforms (e.g. Global Initiative on Sharing All Influenza Data, European Nucleotide Archive) and interpretation in conjunction with epidemiological information should be done as soon as possible after a human case or a report of an outbreak . This would support and accelerate the advancement of knowledge on the zoonotic and pandemic risk linked to influenza viruses.

7.2 | Health monitoring, rapid testing and quarantine

People exposed to infected animals should be monitored (actively or passively) for 10–14 days from their last exposure, with testing and self-isolation (quarantine) initiated immediately should they develop symptoms (respiratory, gastrointestinal and others). Testing should include seasonal influenza. The testing and management of potential human cases and their contacts is outlined in other documents (ECDC, 2022b, 2023a).

7.3 | Strengthening laboratory capabilities and capacities

Technically capable and well-equipped public health laboratories are essential for testing and diagnosis, surveillance and response to potential human cases of AI. National influenza centres should participate in the WHO Headquarters and ECDC external quality assessment and training activities and prepare for detecting and handling potential human cases of AI.

Similarly in animals, access to rapid, sustainable and cost-effective diagnostic procedures for AIV screening of large susceptible populations, such as poultry and wild birds, are imperative and need to be assured in resource-limited settings.

In remote areas, where laboratory facilities are lacking and cold chain maintenance is difficult, tools to preserve the quality and integrity of biological samples during transportation are needed and/or commercial courier systems to rapidly move samples from field to diagnostic laboratories.

To monitor the emergence of zoonotic mutations and identify reassortment events, laboratories must be equipped with or have access to genetic sequencing platforms, and the generation of the complete genomes of identified AIV must be part of the diagnostic process.

To expand epidemiological investigations and better address public health and food safety issues, it would be beneficial to have available validated rapid diagnostic tests for field use as well as cost-effective sampling methods and diagnostic screening tools validated on environmental matrices and poultry-derived products.

In addition, to identify potential host species such as birds and mammals that could survive HPAI infections and might be overlooked in passive surveillance programme, it is crucial to develop and validate serological assays. These assays should offer expanded diagnostic capabilities by encompassing several HA and NA subtypes, and they should be economically feasible to implement with a flexible testing schedule.

7.4 | Health care system readiness

Healthcare system readiness is important, especially in areas where there are outbreaks in animals. It can include healthcare worker training to recognise signs and symptoms of the disease, how to use personal protective equipment (PPE) to protect themselves and prevent spread, and how to care for patients. Healthcare systems should be prepared and able to handle patients. They should also be prepared to detect and report new cases swiftly.

More information on infection prevention and control and preparedness for COVID-19 in healthcare settings that would be relevant for the management of other respiratory viruses can be found in the ECDC document (2021) and more information on occupational safety and health measures for those exposed at work can be found in (ECDC, 2022b). ECDC has also published an investigation protocol of human cases of AIV infections in EU/EEA (ECDC, 2023a). WHO has also published a guidance with key resources and information on the topic (WHO, 2023b).

7.5 | Personal protection measures

The general public should minimise contact with animals or potentially contaminated surfaces in areas with known outbreaks (e.g. farms). Information is core to those potentially at risk of infection either through occupational or during leisure

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

7.6 | Occupational health and safety

Since exposure is likely in workplaces where animal contact cannot be avoided, occupational health and safety measures should be taken at such premises and enhanced where occupational cases have been identified. Ensuring a safe workplace and being protected from AIV while performing work duties are important for people occupationally in contact with infected poultry (like poultry farm workers), potentially infected wild birds, or other animals, for example, backyard farmers, breeding-site managers and bird ringers. The availability, training and use of appropriate PPE help protect people from getting infected with an AIV. The requirement to wear face masks/respirators (e.g. FFP2 or 3) in routine duties, for example, for mink and other fur animal farm workers, should only be considered as last line when all other measures to protect workers have been implemented. In an outbreak situation, contact with infected animals by individuals should be limited and they should wear appropriate PPE according to national recommendations, usually including face mask or respirator, goggles, disposable gloves, protective clothing, and boots or boot covers. Further information on occupational health and safety is provided in the joint document of ECDC, EFSA, EU-OSHA and the European reference laboratory for AI '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, 2022b).

7.7 | Communication, awareness raising and public education

It is important to inform the public about the risk of infection and ways of transmission of AIV to humans. Given the global scale of the AI epidemic and the diverse range of hosts and sectors affected, it is crucial to inform and involve a broad audience across multiple sectors in a co-ordinated One Health prevention and control strategy. A key step in this effort is to implement awareness-raising campaigns aimed at early detection, prevention and control of AI infections. Target audiences include:

- Individuals within the agricultural community, such as farmers, agricultural workers, animal transporters, slaughterhouse personnel and veterinarians: it is important to provide regular reminders about how AI spreads among animals and how to prevent infections. It is crucial to emphasise the importance of biosafety practices (e.g. use of personal protective equipment) and to reinforce biosecurity measures on farms to prevent AI outbreaks. Authorities and industry should disseminate information and operating instructions through various channels to farm personnel, including translations for workers from diverse backgrounds. Moreover, awareness should be raised regarding the risk of disease transmission from humans to animals, emphasising the importance of staying at home when feeling sick;
- Hunters, wildlife managers, wildlife researchers: people regularly coming in contact with wildlife and carrying animals (e.g. hunting dogs) in the wild should be informed about the potential risks of exposure to e.g. infected waterfowl for themselves and their animals. They should be educated on how to respond if they encounter dead wild birds and prevent their dogs from scavenging on carcasses to minimise the risk of disease transmission;
- Pet keepers and shelter personnel: pet owners should be advised and encouraged to take precautions to protect their pets, such as refraining from feeding pets with any raw meat from game birds or poultry, preventing pets from coming into contact with dead wild birds found outside, and reporting any signs of illness in pets to veterinarians;
- The general population: should be educated about avoiding close contact (e.g. touching) with poultry and wild birds, especially in areas with known outbreaks.

7.8 | Disease control to avoid further spread

It is crucial to strengthen the preparedness and capacity of the veterinary infrastructures in at-risk and affected countries to mitigate the risk of a massive spread of HPAI viruses in domestic animals. Fully operational emergency plans, along with adequate early detection and surveillance systems, need to be adopted globally to ensure the timely application of effective control policies in the event of HPAI outbreaks.

Given the current epidemiological situation, there is a need to explore additional control strategies, such as vaccination, complementary to stamping-out policies applied to eradicate the infection.

7.9 | Biosecurity at farm level and whole production chain

To reduce the probability of HPAIV outbreaks in farmed animals, risk-mitigating measures are recommended in regions with high exposure, for example, regions with a high density of wild water birds and during periods of high exposure, where keeping birds and other susceptible animals indoors is an effective risk mitigation measure.

In addition, since there have been many outbreaks in farms with indoor housing, adequate external biosecurity is crucial. Because the yard can be contaminated with bird faeces, measures should prevent contaminated material entering each poultry house present, including change of footwear at the entrance, a proper hygiene locker, no pets in the poultry house, etc.

To reduce the risk of interspecies virus transmission, housing multiple HPAIV susceptible species on a single farm should be discouraged, combinations of susceptible poultry and mammals in particular.

The risk associated with feeding HPAIV-contaminated feed can be mitigated by not feeding farmed carnivore animals feed that contains products from fresh poultry meat or game birds.

7.10 | Land management

Given the large scale of the avian flu epidemic in domestic poultry in Europe and worldwide, medium-term and long-term mitigation strategies to prevent AI should be primarily implemented in densely populated poultry areas. Along side appropriate biosecurity and surveillance along the whole value chain, the location of poultry farms should also be properly planned: the reduction of the density of commercial poultry farms primarily in areas close to wetlands (high density of waterfowl) should be considered, and the reorganisation of certain poultry production systems, especially those that involve highly susceptible species, kept outdoor at high density and moved along the production process (EFSA, ECDC, EURL, 2021).

7.11 | Wildlife management

Increasing global surveillance for influenza infection in wild mammals, particularly carnivores, is essential to monitor virus adaptation and assess the risk of zoonotic transmission. Serological testing can provide valuable insights into the circulation of AI subtypes in the wild.

Additionally, cases of AI in zoo animals highlight the conservation concerns for endangered wild carnivores. Efforts to understand and mitigate the impact of AI on wildlife populations are crucial for both animal and human health.

Active surveillance at wildlife–livestock interfaces, particularly investigating peri-urban and peri-domestic mammals (e.g. rodents, fox, mustelids) and birds, and pandemic preparedness efforts, including monitoring multiple AIV subtypes, are essential for mitigating the risk of AIV transmission to humans.

Monitoring of seabird breeding colonies for unusual mortality will allow for the early detection of HPAI viruses and, if appropriate, the removal of carcasses for the reduction of environmental contamination and therefore reduced mortality and transmission to other species.

Management actions to reduce the risk of transmission between synanthropic wildlife and poultry and other domestic animals at farm level could include removing and/or reducing wildlife attractants elements such as ponds, standing water, feed sources and waste/carcasses; preventing wildlife access to poultry facilities; increasing wildlife deterrents (Shriner et al., 2016). In urban and peri-urban settings, management actions could include proper waste removal and disposal and limiting outdoor access to companion animals especially in area with AI outbreaks in poultry and in high-risk period.

Capacity building in disease prevention, outbreak investigations and controlling the spread of disease in wildlife should be priorities (e.g. through carcass removal). Preparedness plans for carcass removal and other control measures should be in place, particularly in areas of high density of waterfowl or seabird colonies and aquatic mammals, where AI outbreaks are expected and/or where mass mortality events occur.

7.12 | Seasonal influenza vaccination

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

7.13 | Avian influenza vaccination

Immunisation against H5 of individuals that are occupationally exposed to AIV infected animals could be considered for personal protection and to potentially minimise the risk of disease in humans, virus reassortment and appearance of

human-adapted mutations. Specific vaccination recommendations are the responsibility of national authorities. Candidate vaccine viruses remain antigenically similar to currently circulating strains, but constant monitoring of circulating viruses for potential vaccine escape, other mutations and reassortment is essential.

7.14 | Vaccination of animals

Vaccination of poultry against HPAIV is a potential measure to reduce the overall circulation of AI and therefore reduce human exposure to HPAIV (EFSA AHAW Panel, 2023). The rules for implementation of vaccination in birds against HPAI and enhanced surveillance, and risk mitigation measures following vaccination are strictly regulated by Delegated Regulation (EU) 2023/361 for harmonised implementation in all EU Member States.

HPAI vaccination in poultry is meant to complement other preventive and control measures such as infection monitoring in wild birds, early detection and biosecurity (WOAH, 2023b), to reinforce their impact to prevent and control HPAI introduction and spread.

The impact of poultry vaccination on the risk of human exposure is still controversial (Yamaji et al., 2020). When AI vaccines are antigenically similar to the field virus and properly applied alongside effective eradication measures, they can significantly reduce overall virus circulation. Conversely, inadequate or improper poultry vaccination may hinder HPAI eradication efforts.

Currently circulating AIV in animals are considered antigenically similar to the proposed candidate vaccine viruses and to the virus included in the recently approved vaccine for human use in EU/EEA. Nevertheless, under the implementation of vaccination in poultry, continuous surveillance of circulating AIV is needed to monitor the evolution of the field virus and identify any possible antigenic changes, including possible vaccine induced mutants, that would require the update of the vaccine to match the circulating virus strain (EFSA AHAW Panel, 2023).

Such vigilance ensures that the vaccine remains effective and contributes to preventing the unintended generation of more virulent or resistant strains. This monitoring would also guarantee that the candidate vaccine viruses for human use remain antigenically similar to the circulating AIV in animals. Experiences on HPAI vaccination outside the EU in China, Mexico, Egypt are described in (EFSA AHAW Panel, 2023).

7.15 | Use of antivirals

AIV are susceptible to antivirals. Treatment of humans infected with AIV should be initiated as soon as possible after the onset of symptoms. However, even when treatment is initiated beyond the initial 48-h window, it has been demonstrated to reduce the mortality risk in severely ill patients (Muthuri et al., 2013). Post-exposure prophylaxis can also be considered for persons exposed to infected animals and for contacts of probable or confirmed human cases.

In animals, antivirals against influenza virus infection are not authorised in the EU and their use is prohibited by the EU legislation (i.e. Article 4 of Delegated Regulation (EU) 2023/361).

Moreover, the potential use of antivirals for influenza outbreaks in poultry or other farmed animals, particularly mammals, raises several concerns because it may contribute to the emergence of drug-resistant strains (Parry, 2005), making it not only more difficult to treat an individual infection but also potentially reducing the effectiveness of these drugs overall and limiting the available treatment as well as prophylaxis options during a potential pandemic.

No resistance has been observed for NA inhibitors (oseltamivir/zanamivir) and baloxavir marboxil in the EU/EEA and very few viruses identified sporadically globally have so far shown resistance. Almost 6% of A(H5N1) virus detections in animal species in EU/EEA countries in the last year contained sporadic mutations such as S31N in the M2 gene which are associated with resistance to M2 blockers (amantadine/rimantadine).

ABBREVIATIONS

AI	avian influenza
AIV	avian influenza virus
ECDC	European Centre for Disease Prevention and Control
EU/EEA	European Union and European Economic Area
HA	haemagglutinin
HPAI	highly pathogenic avian influenza
HPAIV	highly pathogenic avian influenza virus
LPAI	low pathogenic avian influenza
LPAIV	low pathogenicity avian influenza virus
NA	neuraminidase
PPE	personal protective equipment
WHO	World Health Organization

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AMENDMENT

A number of minor editorial amendments were carried out, including in the author list and references. The sentence on page 5 was reworded to 'Careful planning and reorganisation of poultry and fur animal farming is essential, particularly regarding i) the location and density of poultry farms, especially those in high-risk areas close to wetlands with a high density of waterfowl and ii) farming highly susceptible species kept outdoors at high density.' The editorial correction does not materially affect the contents or outcome of this scientific output. To avoid confusion, the original version of the output has been removed from the EFSA Journal, but is available on request.

CONFLICT OF INTEREST

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ANNEX 1

Terms of reference and their interpretation

Terms of reference as received from the European Commission:

- Setting out the risk assessment of the pandemic potential of the current EU/EEA and global situation; this risk assessment should consider the risks associated with the co-circulation of human influenza viruses and currently circulating influenza A(H5N1) viruses among mammals while analysing existing evidence on risk factors that support viral evolution and adaptation to mammals, increasing relevance of those viruses for public health.
- Based on the risk factor analysis, propose potential prevention and risk mitigation measures and a list of potential actions to implement them (including those addressing jointly humans and animals following a One Health approach) to reduce risk to human health (reference to Regulation (EU) 2022/2370 on setting-up a European Centre for Disease Prevention and Control, Art. 5 Prevention Framework). Suggested actions and measures should be for implementation at national and EU level. The global perspective should also be provided to the extent possible.

The deadline for this request is 15 March 2024.

Interpretation of the terms of reference:

The virus considered in this report is influenza A(H5N1) of clade 2.3.4.4b although the possible role of other influenza A(H5N1) clades or other AIV for epidemics/pandemic are mentioned.

Tor 1 is about the pandemic potential of currently circulating A(H5N1) viruses in EU/EEA and at global level. The crucial aspect of this is the risk of reassortment, mutation and adaptation of AI viruses to mammals and humans. The drivers that may lead to viral evolution and adaptation of the currently circulating influenza A(H5N1) viruses to mammals and humans are described and discussed, including the co-circulation of human influenza viruses and currently circulating influenza A(H5N1) viruses in animals.

Tor 2 will be addressed by listing and describing the possible prevention and risk mitigation measures for both human and animal health under a One Health approach, at national and EU/EEA level, as well as highlighting those measures applicable at global level.