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Avian influenza in the context of a pandemic challenge

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Abstract

Highly pathogenic avian influenza viruses (HPAIVs) have undergone ecological and evolutionary shifts in recent years, broadening both their host range and geographic distribution. This manuscript explores the emergence and dissemination of HPAIVs, tracing their origins from wild waterfowl reservoirs to domestic poultry, and examining their increasing ability to infect mammalian species, including swine and humans. We detail the molecular transition insights from low pathogenic avian influenza to highly pathogenic avian influenza (HPAI) within poultry populations as drivers of adaptation and enhanced virulence. Key zoonotic episodes involving human and other hosts are reviewed, with attention to the role of viral reassortment and adaptation. Current risk assessments are analyzed, suggesting measures to mitigate the impact of HPAI from a One Health perspective, including public health interventions, coordinated international surveillance, early warning and containment systems, as well as prophylactic and therapeutic options.

Keywords: *Avian influenza. Highly pathogenic avian influenza. Low pathogenic avian influenza. Pandemic. One Health.*

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Introduction

Avian influenza refers to the zoonotic disease caused by a series of strains belonging to multiple subtypes of the Influenza A virus circulating in wild birds as well as domestic poultry. Among these subtypes, H5 and, to a lesser extent, H7 are known for their ability to become highly pathogenic in poultry, referred to as highly pathogenic avian influenza viruses (HPAIVs), presenting a very high death rate in these animals. The virus's genetic features are characterized by a high mutation rate and a segmented RNA genome, which allows for gene reassortment with other influenza virus strains, contributing to its adaptability to infect different species, including mammals and particularly humans.

The study of avian influenza is particularly relevant due to its potential to cause pandemics. While human-to-human transmission of H5 influenza remains limited, the virus has shown the ability to cross species barriers and infect mammals.

Understanding the virology, epidemiology, transmission, and pathogenicity of avian influenza viruses is crucial for developing effective prevention and control strategies. At this time, it is not possible to predict whether a specific avian influenza virus strain will initiate a human pandemic. Therefore, we need constant surveillance and research to prepare contingency measures that can mitigate the threat, including existing improved antivirals and vaccines.

This manuscript provides a comprehensive review of the zoonotic potential of avian influenza viruses, covering key genetic characteristics and mechanisms of mutation, reassortment, and adaptation. It also evaluates their epidemiology and transmission, including their spread in animal populations, potential human infections, and the risk of zoonotic transmission. The review further explores the pathogenesis and clinical impact of avian influenza, focusing on the factors contributing to its high pathogenicity in both animals and humans. Finally, it discusses current preventive and therapeutic measures, including vaccine development, antiviral treatments, and biosecurity strategies to control HPAIV outbreaks.

Transmission and life cycle of avian influenza

Avian influenza viruses naturally circulate among wild waterfowl, such as ducks, geese, and shorebirds, which serve as reservoirs for the virus. Transmission occurs primarily through direct contact with infected birds or exposure to contaminated water, feces, or surfaces. These viruses can spill over into domestic poultry, where the virus spreads rapidly in farms through respiratory secretions, fecal-oral routes, and contaminated equipment, feed, or human handling. Intermediate hosts, such as pigs, have played a key role in previous zoonotic events resulting in human pandemics[1].

Zoonotic transmission for influenza viruses usually refers to the occasional spillover of avian influenza viruses from birds to humans or other mammals, tipically through direct contact with infected animals or their secretions. These infections are typically isolated cases or small outbreaks with limited human-to-human transmission. For sustained human transmission to occur, the virus must require adaptations that enable efficient human-to-human spread, similar to seasonal influenza viruses. So far, HPAIVs have not evolved this capacity, although mutations or reassortment events could potentially facilitate such adaptation. A mink airborne transmission model has identified potential mutations that may predict inter-mammalian transmission[2].

Highly pathogenic avian influenza (HPAI) strains have demonstrated the ability to directly infect mammals, including humans, through direct or indirect contact with infected birds or contaminated fomites. These events typically occur while handling animals in high-risk environments such as live poultry markets and farms, where viral amplification leads to high concentrations of infectious particles in the air and on surfaces, or through handling of infected birds. While human infections remain rare, they can result in severe respiratory illness with higher fatality rates as compared to seasonal influenza. However, underdiagnosis of mild or asymptomatic cases likely contributes to an overestimation of severity, making the true human lethality rate uncertain. Transmission to other mammals, including domestic animals such as cows, cats, and dogs, and wild carnivores such as foxes and seals, among others, has been documented, often due to the exposure or consumption of infected birds[3].

HPAIV virulence hallmarks

Avian influenza viruses are categorized into low-pathogenic avian influenza (LPAI) and HPAI strains based on their severity in poultry. LPAI viruses typically cause mild or no disease in poultry and wild birds, though some can mutate into highly pathogenic forms. In contrast, HPAIV, particularly certain H5 and H7 subtypes, causes severe disease and high mortality in poultry, often reaching 90–100% lethality within

48 hours. While some wild birds can carry HPAI without apparent symptoms, others may suffer severe illness[4].

Specific mutations in viral genes can enhance virulence and potential for zoonotic transmission from birds into mammals. Some of the most significant mutations include hemagglutinin (HA) cleavage site mutations, which allow broader tissue tropism and systemic infection in birds[5].

HA is the receptor-binding protein of the Influenza A virus. The HA is also responsible for the fusion of the viral envelope with cell membranes, leading to viral entry into the infected cell. To acquire its fusogenic properties, a host protease cleavage of HA into two subunits is required. The number of basic amino acids, such as lysines and arginines, present in the HA cleavage site hallmarks HPAI strains and discriminates them from LPAI. The HA protein of HPAIVs has a polybasic cleavage site, consisting of multiple basic amino acids (e.g., R-X-R/K-R). This allows it to be cleaved by ubiquitous furin-like proteases in every tissue, including brain, heart, liver, etc., increasing the viral replication by expanding the virus tissue tropism[6,7]. In contrast, LPAI viruses are restricted to mucosal tissues from the respiratory tract and the intestine that express the more specific HA cleavage proteases (Fig. 1A).

Additional mutations in viral genes have been identified that enhance the ability of avian influenza viruses to replicate efficiently in mammalian hosts. Mutations have been described in the subunits of the viral RNA polymerase complex, which is composed of the PB1, PB2, and PA proteins. Among these, the PB2 E627K substitution is the most frequently observed in HPAI (Fig. 1B). This mutation facilitates viral replication in mammalian cells and is considered a key molecular marker of host adaptation, thereby increasing the risk of adaptation of zoonotic transmission and potential emergence in humans[8]. Adaptation of the PB2 subunit of the influenza polymerase to human hosts may depend on an aspartic acid to lysine substitution, which enhances functional compensation and strengthens interaction with the host factor ANP32A[9,10].

Neuraminidase protein (NA) is, after HA, the second most abundant influenza virion surface glycoprotein. It plays a critical role in the final stage of viral egress by cleaving sialic acid residues that tether newly formed virions to the host cell through HA binding. Amino acid deletions in the stalk region of NA have been associated with increased virulence in poultry by enhancing viral fitness in avian cells[11]. It has been proposed that by reducing the length and the flexibility of the stalk, NA can access more efficiently and cleave sialic acids more efficiently (Fig. 1C).

Strains with life-threatening potential in humans

Different influenza viruses are circulating in animal reservoirs that have been responsible for sporadic human zoonotic infections, leading to a higher mortality rate in humans as compared to seasonal influenza, raising concerns about the possibility that any of these viruses acquire the ability to transmit from human to human in the future.

The HPAI H5 and H7 subtypes can cause mass deaths in poultry populations, posing significant risks to the global food supply and having a considerable economic impact on farming. HPAIVs are derived from LPAI viruses circulating in wild birds that start circulating in domestic poultry, where they have mutated, becoming HPAIVs. Among HPAIVs, H5N1 has spread back into wild bird populations, contributing to the virus's geographic spread through avian migration[8]. Through the years, H5N1 viruses have continued to diversify and to reassort genes with other avian influenza viruses, leading to continuous outbreaks in poultry farms all over the world of H5Nx viruses belonging to different clades and genotypes[12]. Among these, some H5N1, H5N6, and H5N8 viruses have been shown to cause human infections. Although human-to-human transmission is rare, the potential for these viruses to adapt and spread more easily among humans remains a concern, especially in those environments and countries with close contact with domestic and farm animals. In addition, an H7N9 LPAI outbreak in chickens in China was also shown to lead to multiple human infections for several years, fortunately, as with the H5Nx viruses, with no significant human-to-human transmissions[13]. Although some H7N9 viruses became highly pathogenic, the H7N9 viruses disappeared from circulation, most likely helped by a massive campaign of poultry vaccination in China[14].

H5N1 has been a major concern since its emergence in 1997. This HPAIV has caused numerous outbreaks in birds and sporadic but severe infections in humans, with a high mortality rate[15]. Since this year, some recent reports have pointed out a total of 976 human cases with at least 470 deaths, which means nearly 50% of lethality[16]. The virus primarily spreads through direct contact with infected birds or contaminated environments[17].

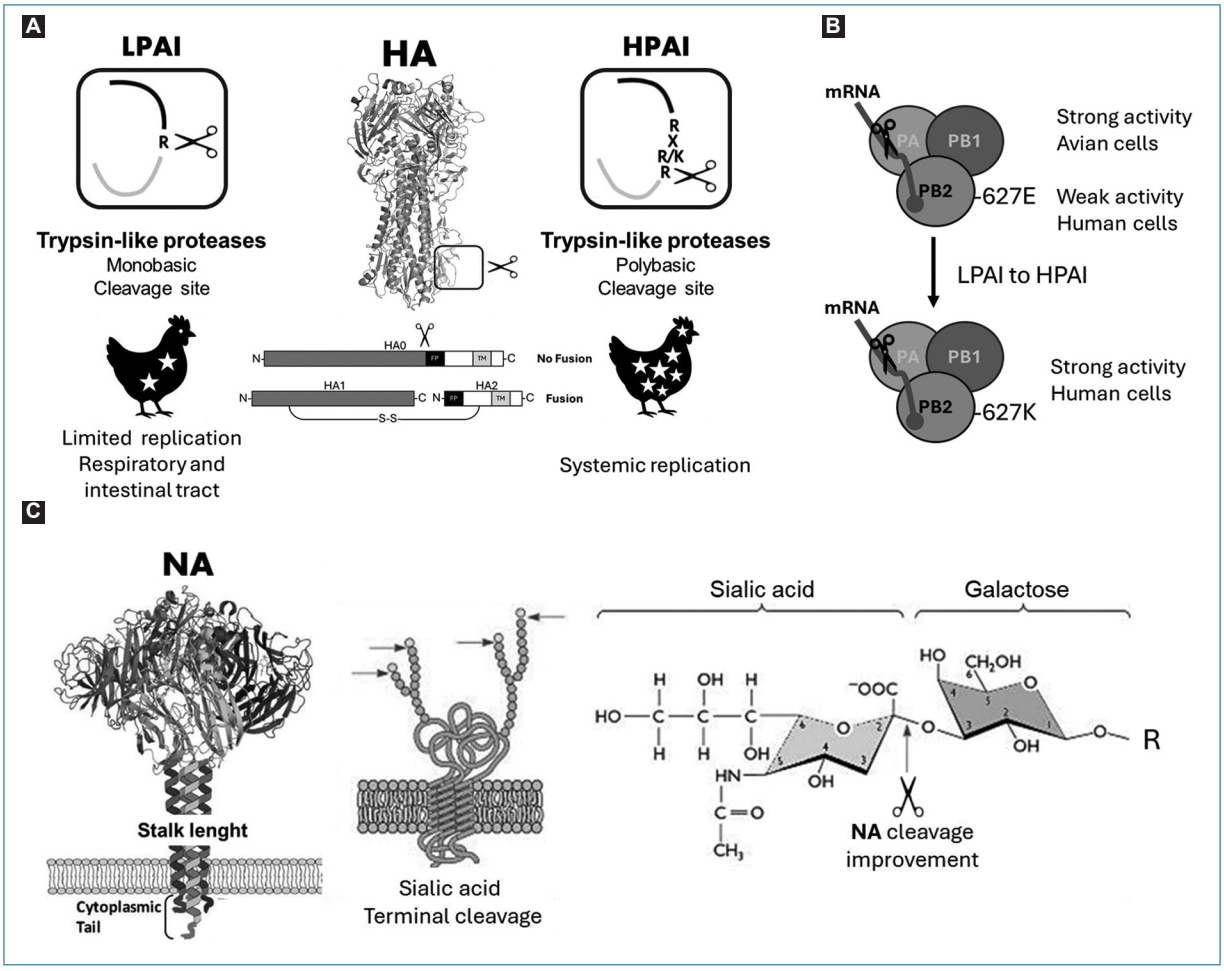

Figure 1. Molecular determinants of pathogenicity and host adaptation in avian influenza viruses. **A:** comparison of hemagglutinin (HA) cleavage sites in low pathogenic avian influenza (LPAI) and highly pathogenic avian influenza (HPAI) strains. LPAI HA contains a monobasic cleavage site restricted to trypsin-like proteases, limiting replication to mucosal tissues. In contrast, HPAI HA features a polybasic cleavage site cleaved by ubiquitous furin-like proteases, enabling systemic infection. **B:** host adaptation through PB2 protein mutation. The E627K substitution enhances polymerase activity in mammalian cells, facilitating cross-species transmission. **C:** structural features of neuraminidase (NA) influencing viral egress and virulence. Shortened stalk regions can improve sialic acid cleavage efficiency, contributing to increased avian host replication.

H7N9 was first detected in humans in China in 2013. This strain has caused severe respiratory illness in humans, with a significant number of cases resulting in death. Most human infections have been linked to exposure to live poultry markets[18].

H5N6 emerged in 2014 and has caused outbreaks in poultry and sporadic human infections, mainly in Asia. The virus has shown genetic reassortment with other influenza viruses, raising concerns about its potential to also adapt to humans. Human infections are rare but can be severe, with a high case fatality rate[19].

H5N8 has primarily affected wild birds and domestic poultry since 2016, causing widespread outbreaks in Europe, Asia, and Africa. While it has not been commonly linked to human infections, its rapid spread in avian populations makes it a major concern for animal health[20]. In 2021, the first human cases of H5N8 were reported in Russia, highlighting the need for ongoing surveillance[21].

Cross-Species transmission and global expansion of avian influenza H5N1

The 2022 outbreak of HPAI H5N1 in the United States was one of the most extensive and costly animal health events in the country's history, affecting over 57 million commercial and backyard poultry across 47 states[22,23]. This outbreak had significant impacts on the poultry

industry, particularly on turkey farms and commercial table egg production[24].

The 2020-2021 outbreak of HPAI H5N8 in Europe caused significant losses in poultry farms across several countries, including Germany, France, and the Netherlands. This outbreak was one of the most devastating HPAI epidemics ever recorded in Europe, affecting numerous poultry farms and wild birds. The outbreak resulted in the culling of millions of poultry birds, leading to substantial economic losses in the poultry sector. In total, around 22,400,000 poultry animals were affected across 28 European countries[25]. Enhanced biosecurity measures were recommended to prevent further spread, including stringent monitoring and reporting of increases in daily mortality and drops in production parameters[26].

Since September 2025, several outbrakes in poultry farms have hitten different countries in Europe including Portugal, Germany, France, Poland, Spain, UK and Hundary, forcing the culling of millions of farm birds. Avian influenza viruses, particularly H5N1, have demonstrated a repeated ability to infect a wide range of species beyond poultry, in addition to humans, pigs, cows, goats, cats, dogs, ferrets, minks, horses, civets, raccoons, seals, sea lions, dolphins, and other terrestrial and aquatic mammals, as well as many different wild birds[27-30]. These cross-species transmission events are shaped by host ecology, viral adaptation, and environmental exposure and have become increasingly relevant in the context of the global spread of HPAIVs from initial waterflow circulating LPAI (Fig. 2).

Among non-avian hosts, swine have long been recognized as critical intermediaries due to their susceptibility to both avian and human influenza A viruses. This dual susceptibility enables genetic reassortment, a process implicated in the emergence of pandemic strains such as H2N2 (1957), H3N2 (1968), and H1N1 (2009)[31,32]. Swine are natural hosts for specific swine influenza-adapted viruses and recipients of human and avian strains[33]. Swine influenza clinical signs include fever, lethargy, anorexia, coughing, sneezing, nasal discharge, and dyspnea. Pregnant sows may abort due to febrile episodes[34]. Transport stress and co-infections further exacerbate transmission and disease severity[35,36].

Dairy cattle have recently emerged as unexpected hosts for H5N1. As of March 2025, infections have been confirmed in at least 16 U.S. states, including California, Colorado, Idaho, Michigan, and Texas[37,38]. Clinical signs are generally mild, like reduced appetite, decreased milk production, and abnormal milk consistency. Viral replication appears concentrated in the mammary glands, with high titers detected in milk[39]. Evidence supports cow-to-cow transmission and spillover to nearby poultry facilities[40].

Companion animals, such as cats and dogs, have also been affected. Infections typically result from contact with infected birds or contaminated environments. Clinical signs include respiratory symptoms, conjunctivitis, fever, lethargy, and in severe cases, neurological manifestations[41]. A notable event occurred in December 2016, when an outbreak of H7N2 among shelter cats in New York City led to the first documented case of cat-to-human transmission[42-44].

Human infections occur primarily through direct or indirect contact with infected birds or mammals, especially poultry and dairy cattle. Mild-to-moderate cases resemble seasonal influenza, while severe cases may progress to pneumonia, acute respiratory distress syndrome, multi-organ failure, and death. In the current U.S. outbreak, 70 human cases have been reported as of March 2025, 41 linked to dairy cows, 24 to poultry, and 5 with unknown or other exposures[45]. Most cases have been mild, with conjunctivitis as the predominant symptom (93%), followed by fever (49%) and respiratory symptoms (36%). Two pediatric cases are suspected of being linked to the consumption of raw milk. A single fatal case occurred in Louisiana in January 2025, involving an elderly individual with previous underlying pathologies likely exposed to infected wild birds or poultry[46]. Other two pediatric cases were recorded during this outbreak but out of the U.S. One of them was in Canada, in a 13-year-old adolescent with mild asthma and elevated body mass index who survived[47], and a 3-year-old girl from Mexico who finally died[48], both cases with unknown animal connection.

Since 2021, the global expansion of H5N1, particularly the clade 2.3.4.4b variant, has intensified concerns. Initially detected in Europe, this strain rapidly spread to Africa, Asia, the Americas, and even Antarctica through migratory birds[49,50]. It has caused mass mortality among wild birds, especially seabirds, waterfowl, and raptors, and large-scale outbreaks in domestic poultry, prompting extensive culling. The virus's broad host range and environmental persistence have facilitated its dissemination and zoonotic potential[51,52].

Recent mammalian outbreaks, including minks, sea lions, and cows, suggest that H5N1 has acquired mutations enhancing replication and transmission in mammals. In particular, the PB2 gene mutations E627K and D701N are associated with increased viral fitness in

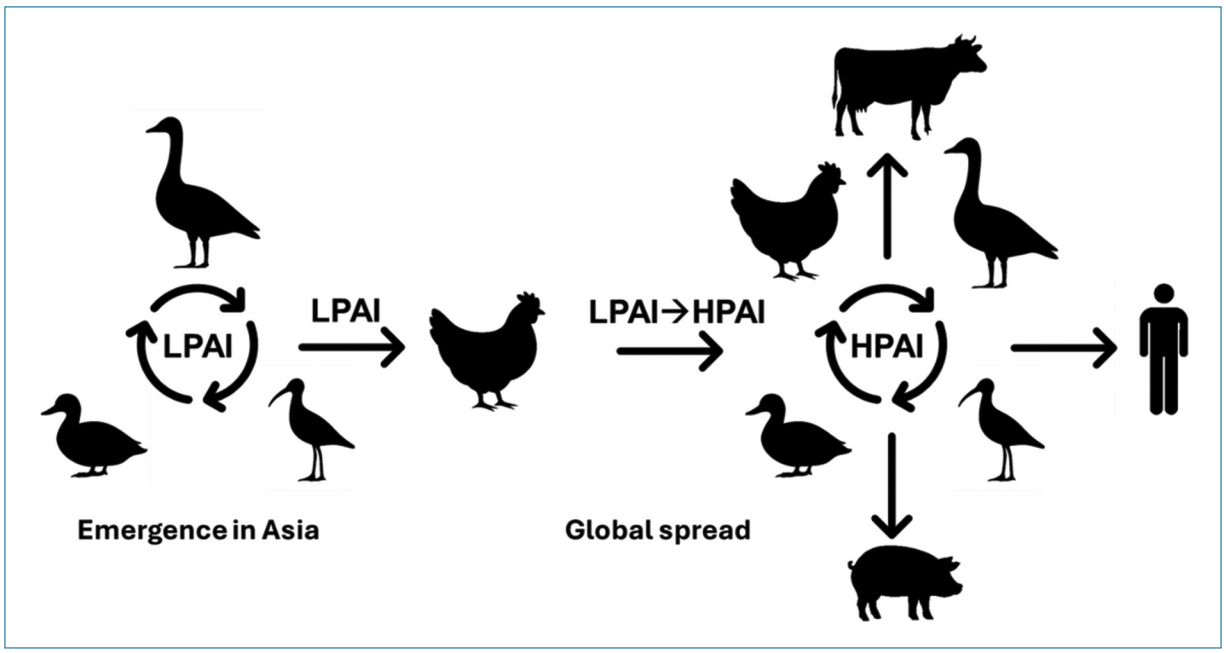

Figure 2. Emergence and interspecies dissemination of avian influenza viruses. The diagram illustrates the initial circulation of low pathogenic avian influenza (LPAI) among wild birds, followed by its evolution into highly pathogenic avian influenza (HPAI). Arrows indicate main transmission pathways across species, including spillovers to mammals such as pigs, cattle, and humans.

mammalian cells and have been detected in multiple species[53]. Although sustained human-to-human transmission has not yet occurred, the accumulation of adaptive mutations and expanding host range underscore the pandemic risk.

Pandemic risk

Although avian influenza H5N1 continues to circulate globally and has demonstrated zoonotic potential, it has not yet acquired efficient human-to-human transmissibility. Consequently, the World Health Organization (WHO) has issued regular risk assessments evaluating the likelihood of an HPAI pandemic. As of August 2025, the primary exposure risk remains concentrated among poultry workers, veterinarians, and individuals handling live or deceased birds. The most recent assessment reaffirms that the risk of transmission from birds to humans and subsequent human-to-human spread remains low[54].

Sustained transmission among mammals remains limited, primarily affecting marine mammals, mink, and dairy cattle. The virus is not currently capable of efficient spread among humans[55]. For this to occur, H5N1 would require further adaptation, which may arise through genetic drift, involving the gradual accumulation of mutations, or through genetic reassortment with mammal-adapted influenza viruses, such as those circulating in swine and humans. Such reassortment may give rise to novel strains with altered virulence, expanded host range, and enhanced transmissibility[56-60].

The adaptation of HA receptor specificity is a critical factor in the transition of avian influenza viruses, such as H5N1, to infect humans efficiently. Avian influenza viruses typically bind to sialic acid residues linked through alpha-2-3 glycosidic bonds (SAα2,3Gal), which are prevalent in the lower respiratory tract of birds. In contrast, human influenza viruses preferentially bind to alpha-2-6-linked sialic acids (SAα2,6Gal), which are abundant in the human upper respiratory tract, facilitating efficient human-to-human transmission[61,62].

Although only a few mutations in HA are needed to alter receptor binding preference, these changes alone seem to be insufficient. Specific mutations in HA can switch the receptor binding preference from avian-type (α2,3-linked sialic acid) to human-type (α2,6-linked sialic acid) receptors. For instance, the Q223R mutation in H1N1 changes the binding preference to avian-type receptors but does not enhance

viral growth in cell culture, suggesting that receptor binding changes alone are not enough for full adaptation[63]. Similarly, the S221P and K216E mutations in H5N1 could enhance binding to human receptors, but models suggest that this does not ensure efficient transmission[64]. Additional concomitant mutations in HA, NA, PB2, possibly PA[65], and yet unidentified, adaptive mutations are likely required to enable sustained human-to-human transmission.

Several factors may signal the emergence of a human influenza pandemic caused by an avian-origin virus. These include genetic changes that enhance human viral infectivity and transmissibility, evidence of sustained human-to-human transmission and increased clinical severity compared to seasonal influenza, and widespread geographic distribution of cases. Monitoring these indicators is essential for early detection and rapid response to mitigate the pandemic risk.

Control measures of avian influenza

Effective prevention and control of avian influenza rely on surveillance and early detection. Surveillance programs in birds, such as those conducted by the USGS National Wildlife Health Center, involve systematic monitoring of wild and domestic bird populations. Diagnostic methods in humans and animals include PCR and serology-based tests with the ability to perform the test at the point of care and in residual waste waters. The integration of these surveillance and diagnostic methods facilitates the understanding of virus circulation, helping to control the spread of avian influenza and mitigate its impact. The WHO and the ECDC have surveillance systems for avian influenza viruses in humans, using existing seasonal influenza surveillance networks, such as the GISRS[66,67], or the European ECDC surveillance[68]. These networks, composed of multiple reference laboratories worldwide, are tasked with promptly forwarding non-subtypable influenza A samples to designated reference centers for identification. In addition, if these regional laboratories have the capacity to identify avian influenza cases by molecular diagnosis, they must immediately report these identifications.

Biosecurity measures are crucial to prevent the spread of avian influenza in poultry farms. Sanitation and quarantine protocols involve regular cleaning and disinfection of facilities and quarantining new birds before introducing them to the flock[69,70]. Movement restrictions on birds and poultry products help prevent the virus from spreading between farms and regions. Eradication strategies during outbreaks include culling infected birds and implementing control zones to contain the virus.

Antiviral medications can play a crucial role in the treatment of avian influenza in humans in the case of an outbreak. They are most effective when administered early in the course of the disease, ideally within 48 h of symptom onset. The most commonly used antivirals are neuraminidase inhibitors, which include NA inhibitors oseltamivir (Tamiflu), zanamivir (Relenza), and peramivir (Rapivab). Oseltamivir and zanamivir are recommended for both treatment and prophylaxis of avian influenza infections[71].

Another antiviral, Baloxavir marboxil (Xofluza), has shown efficacy against avian influenza viruses. Baloxavir inhibits the cap-dependent endonuclease enzyme, which is involved in viral RNA transcription. This newer antiviral offers a different mechanism of action compared to neuraminidase inhibitors and can be used as an alternative or complementary treatment option against H5N1 viruses[72]. The potential appearance of scape mutants could be avoided by the combination of two antivirals against the NA and viral polymerase activities. Novel strategies include the development of long-acting, broad-spectrum antivirals that could serve as immediate prophylactic interventions while a virus-specific pandemic vaccine is being produced.

Vaccines for poultry and humans play a significant role in preventing the disease and reducing complications. While vaccines for humans are not widely available, they can be developed and stockpiled for potential use in a pandemic if the pipeline and industrial procedures are ready and available in case of need. Vaccines targeting animal populations have also been developed and are available to mitigate the impact of farm outbreaks and reduce the risk of zoonotic transmission in alignment with One Health strategies[73]. Timely implementation of H5 vaccination in poultry farms in the context of One Health approach can lessen the impact of HPAI in livestock and reduce the chances of spillover to humans.

Selective breeding of farm animals with reduced susceptibility to influenza A virus and particularly to HPAI represents a potential strategy to mitigate zoonotic risk and enhance biosecurity. Genetic selection of animals with impaired viral entry, replication, or host factor compatibility includes altered sialic acid receptor distribution or modified ANP32A isoforms. Naturally diminished permissiveness to viral infection may allow to establish of livestock populations that act as epidemiological

dead ends, reducing viral amplification and spillover potential.

Finally, it will also be important to continue research focused on developing "universal" influenza virus vaccines able to prevent infection and disease with any influenza virus subtype. Such vaccines are based on the induction of broadly protective immune responses against conserved antigens of the virus, and preclinical results in animal models are very encouraging.

Conclusion

The threat of an avian influenza pandemic remains a significant global health concern. Lessons from the COVID-19 pandemic highlight the need for robust preparedness measures. Effectively addressing challenges related to viral adaptation, surveillance, vaccine development, antiviral resistance, economic impact, public communication, and international cooperation requires a comprehensive, multifaceted approach. By investing in research, strengthening public health infrastructure, and fostering global collaboration, the world can enhance its preparedness and mitigate the risks of a future avian influenza pandemic.

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Conflicts of interest

A. García-Sastre has received research support from Avimex, Dynavax, Pharmamar, 7Hills Pharma, ImmunityBio, and Accurius. A. García-Sastre has consulting agreements for the following companies involving cash and/or stock: Castlevax, Amovir, Vivaldi Biosciences, Contrafect, 7Hills Pharma, Avimex, Pagoda, Accurius, Esperovax, Applied Biological Laboratories, Pharmamar, CureLab Oncology, CureLab Veterinary, Synairgen, Paratus, Pfizer, Virofend, and Prosetta. A. García-Sastre has been an invited speaker in meeting events organized by Seqirus, Janssen, Abbott, Astrazeneca, and Novavax. A. García-Sastre is an inventor on patents and patent applications on the use of antivirals and vaccines for the treatment and prevention of virus infections and cancer, owned by the Icahn School of Medicine at Mount Sinai, New York. J.M. Eiros has participated in training and research projects in collaboration with BioMérieux, Hipra, GSK, Pfizer, Sanofi, and Seqirus.

Ethical considerations

Protection of humans and animals. The authors declare that no experiments involving humans or animals were conducted for this research.

Confidentiality, informed consent, and ethical approval. The study does not involve patient personal data nor requires ethical approval. The SAGER guidelines do not apply.

Declaration on the use of artificial intelligence. The authors declare that no generative artificial intelligence was used in the writing of this manuscript.

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