



The Alarming Situation of Highly Pathogenic Avian Influenza Viruses in 2019–2023

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Abstract

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- epidemiology
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Avian influenza viruses (AIVs) have the potential to cause severe illness in wild birds, domestic poultry, and humans. The ongoing circulation of highly pathogenic avian influenza viruses (HPAIVs) has presented significant challenges to global poultry industry and public health in recent years. This study aimed to elucidate the circulation of HPAIVs during 2019 to 2023. Specifically, we assess the alarming global spread and continuous evolution of HPAIVs. Moreover, we discuss their transmission and prevention strategies to provide valuable references for future prevention and control measures against AIVs.

Introduction

Avian influenza viruses (AIVs), commonly known as bird flu, were described as influenza type A viruses within the genus *Alphainfluenzavirus* of the family Orthomyxoviridae.^{1,2} They have the potential to cause severe illness in wild birds, domestic poultry, and humans. Over recent years, AIVs have presented significant challenges to global public health systems due to their extensive circulation and notable mortality rates.³ Based on their pathogenicity to chickens (*Gallus gallus domesticus*), AIVs are classified into highly pathogenic AIVs (HPAIVs) and low pathogenic AIVs (LPAIVs).⁴ HPAIVs have been a longstanding concern due to their capacity to induce severe disease and fatalities in various bird species, including ducks and geese,^{5–9} and their ability to spill over into other mammalian species, such as swine, seals, and humans,^{7,10–13} resulting in significant impacts on poultry populations and posing a considerable threat to human health. HPAIVs have been responsible for the loss of approximately 500 million domestic birds and hundreds to thousands of human

infections, with a high case fatality rate of 30 to 50%. Given the substantial economic losses to the poultry industry and the potential for a pandemic, continuous monitoring of HPAIVs is crucial.

AIVs possess segmented, single-stranded, negative-sense RNA genomes, with a length of approximately 13.5 kb.¹⁴ The AIV genome consists of 8 segments: polymerase basic protein 2 (PB2), PB1, polymerase acidic (PA), hemagglutinin (HA), neuraminidase (NA), nucleoprotein (NP), matrix (M), and nonstructural (NS), which encode at least 10 structural and 9 regulatory proteins.^{15–19} The viral genome undergoes continuous antigenic shift and antigenic drift during host infections, leading to the emergence of novel viral strains capable of evading existing host immunity.²⁰ AIVs are further categorized into multiple subtypes based on the antigenicity and genetic variation of the genes encoding the two surface glycoproteins: HA and NA. Presently, there are 16 different HA (H1–16) and 9 different NA (N1–9) subtypes detected in wild bird populations.^{21–23} According to the World Health Organization (WHO), the HA genes of different lineages are

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assigned unified nomenclature to track the evolution of phylogenetically distinct Clades 0–9,^{24,25} with Clade 2 further divided into five subclades, 2.1–2.5.²⁶ These subclades are further subdivided into 2.1.1–2.3.4, respectively. HPAIVs from Clade 2.3.4 have been further categorized into four subclades, 2.3.4.1–2.3.4.4.^{27–29} Due to the global evolution and spread of Clade 2.3.4.4, it has evolved into eight subclades, designated as 2.3.4.4a–2.3.4.4h.³⁰

The majority of current circulating H5 HPAIVs belong to Clade 2. For instance, Clade 2.2 H5N1 HPAIVs of the Guangdong H5 lineage spread from China to Siberia and subsequently to several countries in Asia, Europe, the Middle East, and Africa during the epidemiologic year 2005 to 2006.^{31–33} Since first reported in migratory birds in eastern China in 2013, Clade 2.3.4.4 H5 viruses have caused numerous outbreaks worldwide in both domestic and wild birds. Clade 2.3.4.4a mainly refers to the H5N6 viruses that emerged in China in 2014, while Clades 2.3.4.4b and 2.3.4.4c include the H5N8 viruses associated with intercontinental outbreaks in Asia, Europe, the United States, Canada, and Africa between 2014 and 2018.³⁴ These genetically distinct subgroups emerged and spread along different flyways into Europe, North America, and East Asia, respectively. Clade 2.3.4.4c comprises the H5N8 AIVs responsible for the avian flu outbreak in South Korea in 2014³⁵ and subsequently detected in America and Europe, along with the reassortment of H5N2 viruses, which caused poultry outbreaks in wild waterfowl, backyard, and commercial poultry along the Pacific flyway.³⁶ Clades 2.3.4.4d and 2.3.4.4h consist of H5N6 viruses isolated from samples in China. Clade 2.3.4.4e mainly comprises viruses from South Korea and Japan during 2016 to 2017, while Clades 2.3.4.4f and 2.3.4.4g primarily refer to H5N1 and H5N6 viruses found in China and neighboring southwestern countries, respectively.^{29,37} Moreover, within the current HPAIVs H5 2.3.4.4 clade, some defined subclades have undergone substantial reassortment with LPAIVs of wild birds.³⁸ Additionally, among the various subtypes, sporadic human infections have been reported with H5, H6, H7, H9, and H10 subtypes.^{39,40} The predominant HPAIVs currently identified belong to H5 and H7 subtypes, including H5N1, H5N6, H5N8, H7N3, H7N7, and H7N9.^{41,42}

As pathogens affecting a wide range of species, HPAIVs are perpetuated and circulated not only among avian species but also among other nonavian animals and humans. Wild aquatic birds, including Anseriformes (e.g., geese, ducks) and Charadriiformes (e.g., gulls, shorebirds), are considered the primary reservoirs of these pathogens.³³ Additionally, HPAIVs have been isolated in domestic avian hosts, particularly Galliformes (e.g., chicken, turkey), causing sporadic infections and sustained transmission in domestic poultry.^{43,44} These viruses can devastate poultry populations, resulting in significant economic losses in the agriculture sector. While wild birds and poultry are the primary hosts of HPAIVs, some subtypes can cross species barriers to infect mammals, often with fatal outcomes. Thus, sporadic infections have been reported in mammals, including wild or feral animals (e.g., foxes, seals), stray or domestic animals

(e.g., cats, dogs), and zoo animals (e.g., tigers, leopards).^{45–48} Some mammals are suggested to act as mixing vessels for influenza viruses, potentially leading to the emergence of new viruses with improved infectivity for animals and humans. Human infections with HPAIVs have been reported in numerous countries, particularly in the last 5 years, typically following unprotected exposures to infected poultry or virus-contaminated environments. Although rare, sporadic human infections have occurred. Consequently, as a potential pandemic threat, HPAIVs have garnered significant attention.

HPAIVs can induce a spectrum of symptoms in infected individuals, ranging from none or mild illness to severe disease and fatalities. Reported symptoms in humans include mild upper respiratory tract symptoms, lower respiratory tract disease, severe pneumonia with respiratory failure, encephalitis, gastrointestinal and neurological symptoms, multi-organ failure, and/or death. Since 2016, sporadic human infections with HPAIVs have been reported globally each year. For instance, one case of asymptomatic infection was reported in Vietnam in 2011, and another asymptomatic case occurred in the United Kingdom in late 2021. However, the case fatality rate for some H5 and H7 subtype HPAIV infections among humans has been shown to be higher than that of seasonal influenza infections. For example, among human clinical cases of H5N1 HPAIV reported to date, the case fatality rate exceeds 52%.⁴⁹ Therefore, understanding these viruses is crucial for developing strategies for prevention, treatment, and outbreak containment.

To mitigate the impact of highly pathogenic avian influenza (HPAI) on poultry industries and reduce the risk of human infections, monitoring the spread of avian influenza is essential. Surveillance programs and related organizations, such as the Global Influenza Surveillance and Response System (GISRS) Collaborating Centers for Reference and Research on Influenza developed by the WHO, the World Animal Health Information System (WAHIS) provided by the World Organization for Animal Health (WOAH), the Food and Agriculture Organization of the United Nations (FAO), the Animal and Plant Health Inspection Service (APHIS) by the U.S. Department of Agriculture (USDA), the Public Health Agency of Canada, China's Centers for Disease Control, and the passive surveillance system for testing wild birds found dead or sick for avian influenza in European Union member states since 2005,⁵⁰ serve as early warning systems at both global and regional levels. Recent detections of HPAI highlight the ongoing risk these viruses pose to animal and human health, emphasizing the need for continuous vigilance and research to understand their evolving nature and modes of transmission. Efforts to control avian influenza include promoting transparency, enhancing understanding of HPAIVs, and implementing crucial biosecurity measures to protect the poultry industry and prevent potential human infections.⁴ Given the alarming global spread and continuous evolution of HPAIVs and their impact on the poultry industry and public health, there is an urgent need to review the latest science and evidence on HPAI and control strategies.

Outbreaks and Epidemiology of HPAIVs

Since their first identification in 1996, HPAIVs have spread across multiple continents, resulting in a notable rise in the frequency of avian influenza outbreaks in poultry, other avian species, and mammals in recent years. Consequently, HPAIVs have prompted global concerns due to their high pathogenicity in poultry and elevated fatality rates in humans, particularly during the past 5 years from 2019 to 2023.

The Global Distribution of HPAIVs

According to data from the WAHIS (<https://wahis.woah.org/#/dashboards/qd-dashboard>), a total of 9,498 avian influenza outbreaks caused by various HPAIVs have occurred from 2019 to 2023 (►Fig. 1). These outbreaks have resulted in nearly 60 million cases worldwide, with approximately 24.8 million poultry lost during this period. A wide range of domestic birds and animals, including birds, Anseriformes, Galliformes, have been affected in the past 5 years (►Supplementary Table S1 [online only]).

During the period from 2019 to 2023, a total of 80 countries or regions across five continents—Africa, the Americas, Asia, Europe, and Oceania—reported HPAI outbreaks in both wild birds and poultry to WOA (https://www.who.int/news/item/12-07-2023-ongoing-avian-influenza-outbreaks-in-animals-poses-risk-to-humans). Among these continents, approximately 56.1% of outbreaks occurred in Europe during the recent 5-year period (►Fig. 2). France recorded the highest number of HPAI outbreaks, primarily caused by H5N1 and H5N8 viruses between 2020 and 2023. Other European countries, including Hungary, Poland, and Germany, also reported relatively high numbers of outbreaks caused by H5N1, H5N2, H5N5, and H5N8 viruses. Apart from Europe, avian influenza outbreaks caused by HPAIVs were predominantly reported in various countries across other

continents, including the United States of America in the Americas, Nigeria in Africa, and Indonesia in Asia.

Damage to Animals

The global spread and significant increase in HPAI outbreaks have affected both domestic and wild animals. Over 294 million domestic poultry have been lost due to death or culling in affected areas worldwide. Numerous mass death events have been reported in both terrestrial and aquatic animals, including birds (Anseriformes, Galliformes), cattle, Equidae, sheep, goats, and swine, with at least 13 species affected. It is likely that there are more animals affected by outbreaks that have yet to be detected or reported. In 2021, two European countries—the United Kingdom and Bulgaria—reported outbreaks in wild animals, primarily in Common pheasants and Phasianidae, resulting in the deaths of over 800 animals. This shift in the epidemiology and ecology of HPAIVs has heightened global concern as the spread of these viruses has led to a concerning increase in cases among birds and mammals, posing threats to public health, animal health, food security, and biodiversity.⁵¹

Assessing the Risk to Humans

Sporadic human infection cases by the HPAI influenza virus were reported during 2019 to 2023 but remained very rare. According to information available on WOA, there were 90 human cases confirmed by national authorities or WHO during the past 5 years, including 21 deaths, with a case fatality proportion of approximately 23%. It has been shown that HPAI infections in humans could cause severe disease with a high mortality rate.

Since early 2019, HPAI strains, notably H5N6, H5N1, and H5N8 subtypes, caused significant human infection cases worldwide. The majority of these human infection cases occurred during 2021 to 2023 in Asia and European countries,

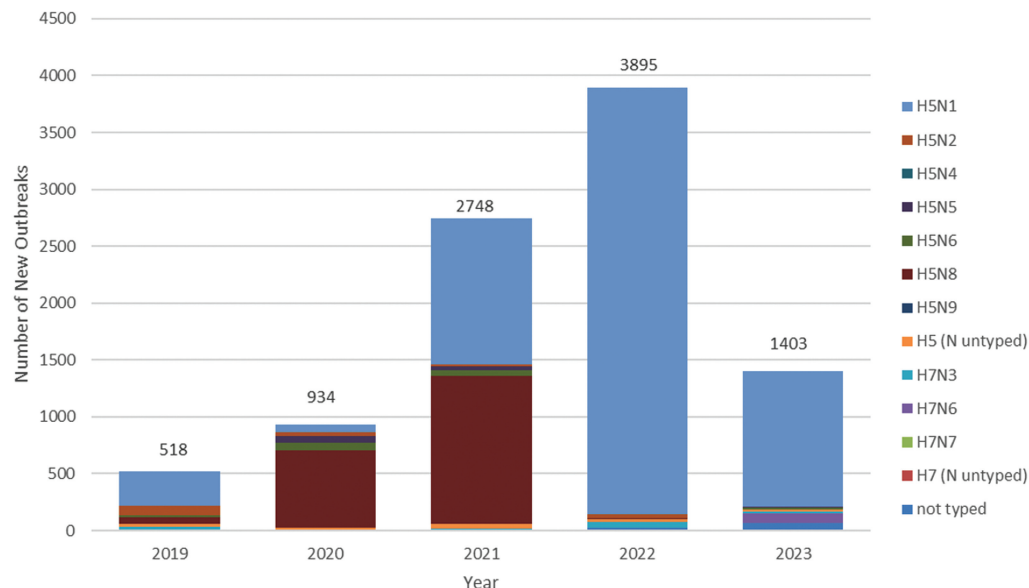


Fig. 1 The avian influenza outbreaks caused by various HPAIVs occurred in 2019 to 2023. HPAIVs, highly pathogenic avian influenza viruses.

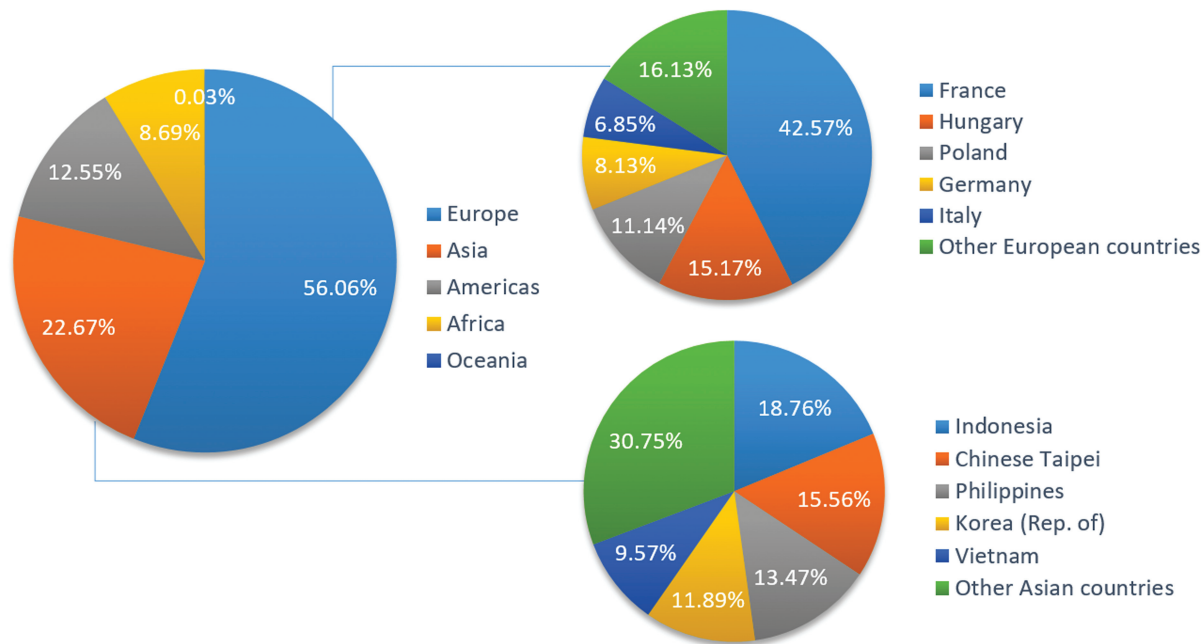


Fig. 2 Global distribution of the HPAIVs outbreaks in 2019 to 2023. HPAIVs, highly pathogenic avian influenza viruses.

including China, Cambodia, the United Kingdom, the Russian Federation, and others. The human cases detected so far are mostly linked to close contact with infected poultry or contaminated environments. A comparison of HA sequences from human- and avian-derived HPAIVs indicated high homology within the same subtype of viruses.⁵²

Based on the information available, the virus does not appear to transmit easily from one person to another. However, studies monitoring the epidemiology and evolution of the HPAIVs, identifying signals of any changes of the HPAIVs that could be more threatening to infect humans, are of significant importance for risk assessment and disease control.

Pathogenesis and Transmission of HPAIVs

HPAIVs have continually caused worldwide outbreaks in wild birds, poultry, and mammals, with some spillover to humans. Most notably, HPAIVs are primarily composed of H5 and H7 viruses, infections with which have resulted in significant mortality within susceptible poultry species and have become a major concern for public health as well.

HPAI H5N1 Viruses

Since first emerging in domestic waterfowl in southern China in 1996, the HPAI H5N1 A/goose/Guangdong/1/1996 lineage has spread widely throughout Asia, followed by Africa, Europe, and the Middle East, leading to several large poultry outbreaks and sporadic human infections. From 2019 to 2023, 6,590 avian influenza outbreaks caused by HPAI H5N1 viruses were reported in several European, American, African, and Asian countries, including France, the United States, Hungary, Nigeria, Indonesia, etc. Migratory birds have been implicated in the dissemination of HPAI H5N1 viruses in Asia and from Asia to Europe.^{53,54} Additionally, according to the information

reported in the WAHIS (<https://wahis.woah.org>), the number of poultry lost in the outbreaks that occurred during these 5 years has been up to 218 million worldwide. Moreover, the first human infections with HPAI A(H5N1) virus were identified in Hong Kong, China in 1997, followed by several years without wide detection until it re-emerged across Asia in 2003. As of December 2023, 882 human cases of H5N1 virus infection and 461 deaths had been reported from 23 countries since 2003, with approximately 52.3% case fatality proportion, according to WHO,⁴⁹ including 14 cases and 6 deaths in 7 countries during 2019 to 2023.

The HPAI H5N1 virus circulating in wild birds and poultry worldwide has undergone genetic variations during the epidemic waves. During 2020, reassortment between poultry and wild bird viruses led to the emergence of a distinct HPAI clade 2.3.4.4b H5N1 viruses with an N1 NA from wild birds.⁵⁵ It was first identified in Europe during the fall of 2020 and spread across Europe and into Africa, the Middle East, and Asia, which has become the predominant subtype of HPAI H5 by the end of 2021.⁵⁶ In late 2021, the H5N1 HPAIV clade 2.3.4.4b was then isolated in poultry and a free-living gull in Canada; the high genetic identity with the wild bird H5N1 virus circulating in northwestern Europe in spring 2021 indicated the transatlantic spread via wild bird migration.^{57,58} In February 2022, according to the USDA's APHIS, an HPAI H5N1 outbreak in turkeys was detected in a commercial poultry facility in the United States.³⁸ This wild-bird-adapted HPAIVs H5N1 have caused sporadic infections in wild birds and outbreaks in commercial and domestic poultry across multiple countries, with occasional spillover to mammals observed.^{59–61}

The detections of HPAI H5N1 virus in various mammals have been reported worldwide. In middle and late 2021, HPAI H5N1 virus clade 2.3.4.4b was detected in two wild red fox

(*Vulpes vulpes*) cubs in the Netherlands and Estonia, respectively.^{62,63} In 2022, Peru reported HPAI H5N1 virus infections in sea lions following the deaths of hundreds of sea lions. Later, HPAI H5N1 viruses of clade 2.3.4.4b also caused infections and some deaths in 10 seals in Maine,⁶⁴ among mink on a farm in northwest Spain, and so on,¹² in bears in Alaska, Nebraska, and Montana.⁶¹ In 2023, HPAIV H5N1 was found to have infected a polar bear, as well as elephant and fur seals in the Antarctic, marking the first HPAI A(H5N1) virus infections in both polar regions. Other animals that have tested positive for HPAI H5 virus include otters, lynx, a polecat, and a badger in Europe, and raccoon dogs and foxes in Japan.⁶⁵

Sporadic infections of HPAI H5N1 virus in humans have also been reported globally. In January 2022, an asymptomatic 80-year-old man who raised ducks in England was reported to have HPAI H5N1 clade 2.3.4.4b virus infection.⁶⁶ The second human case associated with this specific group of H5 viruses was reported in the United States, involving direct exposure to poultry and participation in the culling of poultry with presumptive H5N1 bird flu. In late 2022, Spain reported two human cases of HPAI H5N1 in asymptomatic poultry workers from the same poultry farm with a confirmed outbreak of H5N1. China also reported a human case of HPAI H5N1 virus infection in an adult who developed critical illness and died after poultry exposure. Vietnam reported a case of human infection with HPAI A(H5) virus in a child who became critically ill following exposure to infected backyard poultry. In early 2023, Ecuador reported its first human infection with HPAI A(H5) in a child who became critically ill following exposure to infected backyard poultry. The Cambodia Ministry of Health reported two human infections with HPAI H5N1 virus, including one fatal case. Notably, in contrast to the HPAI H5N1 clade 2.3.4.4b virus circulating in wild birds and poultry in the United States and other countries, the viruses in Cambodia belong to clade 2.3.2.1c.³⁸

HPAI H5N6 Viruses

H5N6 was first documented in Laos during 2013, subsequently spreading to Vietnam and China, as well as other countries via western and eastern routes.^{27,67} Since 2013, HPAI subclade 2.3.4.4 H5N6 virus has been reported in wild birds and poultry in Asia, crossing geographical barriers to emerge in South Korea, Japan, and Europe as well. Phylogenetic analysis has shown that clade 2.3.4.4 H5N6 HPAIVs have continuously reassorted with other subtypes such as H5, H6, and H7N9/H9N2.⁶⁸

During 2019 to 2023, 145 outbreaks led by HPAI H5N6 have been documented by WOAHA, resulting in more than 100,000 cases with more than half deaths in domestic birds, leading to the death or culling of approximately 1.4 million birds. The rise in the frequency of HPAI H5N6 virus infections, especially in 2020 and 2021, has raised serious concerns and posed an alarming threat to public health.⁶⁹ The first detection of HPAIV H5N6 (clade 2.3.4.4b) in Africa was reported in June 2019 in a duck from a live bird market in Nigeria, with the genome closely related to the H5N6 viruses detected in

Europe during 2017 to 2018.⁷⁰ Full-length genome analysis of swab samples collected from live poultry markets in China in 2021 found that the 2.3.4.4b H5N6 viruses were novel reassortants, with the HA and M genes derived from 2.3.4.4b H5N8 viruses of wild-bird origin, whereas other internal genes exhibited several separate clusters.⁶⁹ Additionally, it has been documented that many other subtypes of AIVs from wild birds have donated the internal genes to H5N6 virus, leading to the diversification of this virus in both poultry and humans.^{29,71–75} Transmissibility and receptor binding properties suggest that some H5N6 viruses acquired efficient in-contact transmission in ferrets, as well as binding affinity for human-like SA α 2,6Gal-linked receptors, enabling attachment to human tracheal epithelial and alveolar cells.⁷⁶ Therefore, the high genetic diversity and virulence in mammals of H5N6 viruses pose an increasing threat to public health, necessitating close monitoring of continual adaptation in humans.

Most HPAI H5N6 virus human infection cases were reported in Asia, with almost all confirmed cases occurring in individuals with poultry exposure. By surveying epidemiological, clinical, and genetic data of human infection with H5N6 viruses, Zhu et al found that severe disease occurred in 93.8% of cases, with an estimated case fatality rate of 55.4%.⁷⁵ Since the first human infection case of HPAI H5N6 virus was documented in Sichuan Province, China, in 2014,⁷⁷ human cases have been continuously reported worldwide, caused by H5N6 HPAIVs belonging to clades 2.3.4.4a, 2.3.4.4b, 2.3.4.4d, 2.3.4.4g, and 2.3.4.4h.⁷⁵ During 2019 to 2023, there have been 64 HPAI H5N6 virus human infections documented in China and one case reported in Laos, including 14 human deaths.⁷⁸ The clinical presentations of human infections with HPAI H5N6 virus often begin with fever, upper respiratory tract symptoms, and myalgia, and may rapidly progress to lower respiratory tract illness, resulting in pneumonia, multi-organ failure, acute respiratory distress syndrome, and often death.²⁸ In 2020, five human cases of HPAI H5N6 virus infection were reported in China. In 2021, Laos reported its first human infection with HPAI H5N6 virus in a child who had contact with infected poultry. Additionally, China reported 36 cases of human infection with HPAI H5N6 virus, including 18 deaths. In 2022, China reported 11 cases of HPAI H5N6 virus infection after poultry exposures, with severe or critical illness, including two deaths. Notably, most of these H5N6 HPAIV HA genes in humans during this period originated from subclade 2.3.4.4b.

HPAI H5N8 Viruses

The HPAI H5N8 virus, belonging to H5 clade 2.3.4.4, was first detected in poultry in South Korea in 2014⁷⁹ and has since disseminated to both domestic and wild birds across Asia, Europe, and North America by mid-2015. During the 2020 to 2021 influenza season, novel H5N8 viruses repeatedly entered Europe, Russia, South Korea, and China, causing severe poultry and wild bird outbreaks in several European and Asian countries.^{80,81} More than 2,000 HPAI H5N8 outbreaks have occurred during 2019 to 2023 worldwide, leading to nearly 9 million infection cases in wild and domestic birds

and other animals, with over 4 million deaths. In early 2020, small H5N8 outbreaks were reported across the European poultry sector, followed by the detection of HPAIV H5N8 in poultry in the Republic of Iraq, Russian Federation, Kazakhstan, and the Netherlands since the middle of 2020.⁵⁵ From late 2020 to early 2021, HPAIVs H5N8 were isolated from swans, seals, and a fox in the United Kingdom,⁸² Germany,⁸³ and Denmark.⁸⁴ In December 2020, the first human case of HPAI H5N8 virus infection was reported in an asymptomatic poultry worker in Russia,⁸⁵ suggesting that the H5N8 HPAI virus should be closely monitored for its potential threat to poultry production, food security, and public health.

The rapid global spread of H5N8 HPAIVs has been linked with wild bird migration.^{83,86–89} The co-circulation of H5N8 and other subtypes of viruses in migratory birds has also accelerated the evolution of novel variants. It has been reported that the H5N8 virus reassorted with different viruses and formed several other subtypes of H5 viruses (e.g., the subtypes H5N1, H5N2, H5N3, H5N4, H5N5, and H5N6) in different countries and regions.⁹⁰ Since late 2019 and lasting until June 2020, outbreaks caused by novel HPAI clade 2.3.4.4b H5N8 viruses occurred in Central and Eastern European countries, which were generated by reassortment between H5N8 from sub-Saharan Africa and low-pathogenicity avian influenza (LPAI) viruses from Eurasia.^{89,91} Two genetically distinct HPAI H5N8 viral lineages were detected to cause the outbreaks in Russia during August and September 2020, with one variant represented by viruses of clade 2.3.4.4b isolated in Europe in early 2020 and the other by a novel reassortant between clade 2.3.4.4b and Eurasian LPAI viruses circulating in wild birds, respectively.^{55,92} The Danish H5N8 viruses found in late 2020 were shown to be genetically similar to contemporary European clade 2.3.4.4b H5N8 viruses, possibly new incursions introduced by migrating birds to overwintering sites in Europe.⁸⁴ Meanwhile, the Netherlands HPAI H5N8 detected in mute swans during the same period shared a common ancestor with clade 2.3.4.4b viruses detected in Egypt during 2018 to 2019 with a similar genetic composition, not directly related to H5N8 viruses from Europe detected in early 2020.⁹³ Moreover, in East Asia, HPAI H5N8 virus outbreaks^{81,94–98} from late 2020 to early 2021 shared a recent common ancestor with 2.3.4.4b H5N8 HPAIVs that circulated in Europe in late 2020, whereas some HPAI H5N8 viruses detected in South Korea had a close genetic relationship with the European viruses from early 2020,⁹⁶ indicating the seasonal spread of HPAI virus lineages across the globe.^{92,94,95}

HPAI H7N3 Viruses

Since its first isolation in 2012,⁹⁹ outbreaks of HPAI H7N3 viruses have been documented in various regions, including Mexico, British Columbia, Chile, Italy, and the United Kingdom.¹⁰⁰ Infections of HPAIVs H7N3 have been detected in both wild birds and domestic poultry. From 2019 to 2023, HPAI H7N3 viruses have mostly been isolated from samples in North America. Mexico and the United States have experienced 108 H7N3 HPAI outbreaks, resulting in the death of more than 110,000 domestic birds. During the HPAI H7N3

outbreak in Mexico in June 2022, a total of 2.1 million birds from affected poultry production units and backyard farms were culled.¹⁰¹ In March 2020, an outbreak of HPAI H7N3 occurred on U.S. turkey farms, further emphasizing the global spread and impact of these viruses.¹⁰²

Phylogenetic analyses have indicated that the Mexican H7N3 HPAIV originated from low-pathogenic North American wild bird AIV gene pools, followed by subsequent mutation to a highly pathogenic phenotype with complicated reassortment events.¹⁰³ Thereafter, the H7N3 HPAIVs evolved rapidly and diverged into multiple clusters.^{104,105} Hesterberg et al studied the evolution of AIVs in wild birds, including H7N3, highlighting the complexity of virus evolution in a multi-host ecosystem and underlining the importance of monitoring wild bird populations for a comprehensive understanding of the diversity and evolution of AIVs.³¹ Host adaptation of the Mexican H7N3 HPAI virus indicated high pathogenicity for chickens, whereas a loss of fitness was observed in mallards after circulation.¹⁰⁶ The emergence and selection of the HPAI H7N3 virus in a turkey farm in the Netherlands in 2020 provided direct evidence of LPAI to HPAI virus mutation,¹⁰⁷ potentially caused by the insertion or substitution of basic amino acids at the HA0 cleavage site as suggested in previous studies.^{108,109} An epizootic of highly pathogenic H7N3 avian influenza in an ecologic reserve in Mexico underscores the importance of surveillance and biosecurity measures.¹¹⁰ Understanding the pathobiological origins and evolutionary history of HPAIVs, including H7N3, is crucial for effective control and prevention strategies.¹¹¹ Measures such as culling infected flocks, disinfection of materials, and treatment with antiviral medications like oseltamivir have been used to control outbreaks of H7N3 avian influenza in various countries.¹¹²

Although HPAI H7N3 virus infections have been reported in a small number of people with conjunctivitis since 2004 in Canada and other countries,¹¹³ with some cases resulting in mild symptoms in humans, such as conjunctivitis and mild influenza-like illness, no human infection cases were reported during the recent 5 years. Genetic characterization as well as pathogenesis in both *in vitro* and *in vivo* models of AIV H7N3 isolated from spot-billed ducks in South Korea in early 2019 highlighted the potential for the viruses to mutate and infect humans, emphasizing the importance of routine surveillance.¹¹⁴ Therefore, continued global surveillance of the H7N3 virus in wild birds and poultry populations is essential to understanding its ecology, evolution, and potential threat to humans.

HPAI H7N7 Viruses

Since it was first recorded in 1927, the H7N7 subtype has been commonly isolated in surveillance studies of waterfowl in Europe and other parts of the world.¹¹⁵ HPAIVs of the H7N7 subtype have been a cause of concern due to their virulence and potential to cause severe disease in poultry. During 2019 to 2023, Australia experienced three poultry outbreaks of HPAIVs H7N7 from July to December 2020, resulting in over 255,000 cases reported and the slaughter of more than 433,000 chickens. Scheibner et al¹¹⁶ studied the

virulence of three European H7 viruses in Pekin and Muscovy ducks. All the Muscovy ducklings inoculated with HPAIV H7N7 exhibited mild to severe clinical signs resulting in the death of 2 out of 10, while no impact of the infection route on virulence was observed in Pekin ducklings, indicating the variable virulence of HPAIV H7 in different duck species. Spruit et al.¹¹⁷ studied the N-glycolylneuraminic acid (NeuGc) binding of avian and equine H7 influenza A viruses, highlighting the extinct highly pathogenic equine H7N7 viruses that exclusively bind NeuGc. Vaccination has proven effective in reducing the transmission of H7N7 in chickens and preventing major outbreaks.¹¹⁸ Engineered viral vaccine constructs have been developed to provide dual protection against H7N7 avian influenza and Newcastle disease in poultry.¹¹⁹

The first documented HPAIV H7N7 human infection case occurred in the United States, in 1959, detected in the blood of a man clinically diagnosed with infectious hepatitis.¹²⁰ Since then, H7N7 HPAIV human infections have been reported in England,¹²¹ the Netherlands,¹²² Italy,¹²³ and other countries, associated with exposures during widespread poultry outbreaks. In these cases, mild upper respiratory tract symptoms, lower respiratory tract disease, severe pneumonia with respiratory failure, and multi-organ failure have been reported, including fatal cases. However, no HPAI H7N7 human infection cases were detected during 2019 to 2023. Research on previous H7N7 human cases has investigated the molecular basis of the viruses' pathogenicity to understand differences in virus pathogenicity.¹²⁴ Studies on contemporary North American H7 viruses have shown that they possess human receptor specificity, impacting virus transmissibility.¹²⁵ Additionally, the tropism and innate host responses of H7N7 and other influenza viruses have been studied to understand their pathogenesis in the human respiratory tract.¹²⁶

HPAI H7N9 Viruses

As a newly discovered HPAI subtype with a serious threat to public health and the poultry industry, H7N9 HPAIVs have become a major burden in Asia and raised concerns regarding the potential for a pandemic.¹²⁷ They were first detected in Shanghai and Anhui, China in March 2013,^{128,129} and subsequently spread to over 20 provinces, including Ningxia, Shaanxi, and Shanxi in 2019.

Studies have shown that these viruses have evolved from low pathogenic variants to highly pathogenic strains, with changes in subtypes and genotypes, increasing their pathogenicity in animal models and expanding their host range to include ferrets and mice.^{130,131} The genesis of these H7N9 viruses has been linked to reassortment events between H7 and H9N2 viruses in domestic poultry populations in China. For example, phylogenetic analysis has demonstrated that Tianjin H9N2 isolates belong to the G81 lineage and carry internal genes highly homologous to human H10N8 and H7N9 viruses.¹³² Furthermore, the presence of a polybasic amino acid sequence at the HA cleavage site of some H7N9 viruses suggests high pathogenicity in birds, highlighting the need for enhanced surveillance to monitor the spread of

these viruses.¹³³ In addition to their pathogenicity, HPAI H7N9 viruses have been shown to induce severe inflammation in both poultry and humans, leading to high mortality rates.¹³⁴ Nationwide vaccination of chickens with an H5/H7 bivalent inactivated avian influenza vaccine since September 2017 has successfully controlled H7N9 avian influenza infections in poultry and prevented human infections.⁵¹ Results have indicated a decreased prevalence of low-pathogenic H7N9 strains, while highly pathogenic H7N9 strains have become dominant since the introduction of the vaccine.¹³⁵ Regionally distinct lineages have been established with different genotypes.¹³⁶ Phylogenetic analysis has shown that strains from 2019 formed an independent small branch and were genetically distant from strains isolated in 2013 to 2018.¹³⁵

Human infections with HPAI H7N9 virus were first detected in March 2013 and are characterized by lower respiratory tract disease, which may progress to severe pneumonia with respiratory failure, multi-organ failure, and death in approximately 40% of reported cases.¹³⁷ Furthermore, the detection of virulent mutants of H7N9 in chickens poses an increased threat to human health, emphasizing the importance of controlling and eradicating these viruses to prevent a potential pandemic.¹³⁸ Studies of interferon-induced protein 35 (IFI35) have shown that it does not interact with the NS1 encoded by H7N9, resulting in IFI35 playing an opposite virus-enabling role during HPAIV H7N9 infection.¹³⁴

Overall, H5 and H7 HPAIVs pose a significant threat to public health and the poultry industry. While the increasing numbers of human infections with HPAIVs have raised concerns of a pandemic threat, the implementation of vaccination has been effective in controlling the spread of the virus in poultry and preventing human infections. Further research is still needed to understand the ecology and evolution of related AIVs to develop effective prevention and control measures.

The Spread and Transmission of HPAIVs among Species

The transmission dynamics of HPAIVs among avian species and their potential to cross species barriers to humans have been a subject of significant research interest in recent years. Global outbreaks of HPAIVs have been linked to the transmission of the virus from wild migratory birds to domestic poultry, underscoring the role of wild bird populations in the dissemination of AIVs.^{97,132} Wild birds, particularly migratory species, play a crucial role in spreading HPAI by carrying the virus over long distances and introducing it to new areas through migration.¹³⁹ For instance, the introduction of HPAI H5N1 to North America in 2021 through migratory pathways serves as an example of this pattern.¹⁴⁰ Once introduced, HPAIVs can spread rapidly within domestic bird populations through direct and indirect contact, with infected wild birds transmitting the infection to domestic poultry or contaminating their environments with the virus, thereby facilitating transmission.¹⁴¹ In addition, the high density and close

confinement of domestic poultry make them particularly susceptible to HPAI, exacerbating the spread of the virus within and between flocks.¹⁴² Human activities such as the trade and transportation of poultry and poultry products can also contribute to the spread of HPAI between regions and countries.¹⁴³

Studies have shown that wild birds can carry and transmit AIVs, such as H9N2 and H5N8, to other bird species, including domestic poultry and ostriches.^{97,144,145} The prevalence of the H9N2 avian virus in wild birds has been investigated, with phylogenetic analysis revealing genetic similarities between avian and human influenza viruses.¹⁴⁶ Moreover, the circulation of HPAIVs in resident wild bird populations in northern Europe during the summer months indicates ongoing transmission within both wild and domestic bird populations.¹⁴⁷ The global dissemination of influenza A viruses, driven by wild bird migration through Arctic and subarctic zones, has been identified as a key factor in the geographic spread of low and HPAIVs.¹⁴⁸ The connectivity of different regions, such as Iceland, to viral flow between the eastern and western hemispheres, has been studied to understand inter-species transmission and reassortment dynamics that influence the spread of AIVs.¹⁴⁹ Understanding the transmission patterns of HPAIVs is crucial for implementing effective surveillance, prevention, and control measures to mitigate the impact of HPAI outbreaks on both wild and domestic bird populations.

HPAIVs primarily spread among avian species through direct contact with contaminated excretions from infected birds, such as respiratory secretions or feces.¹⁵⁰ Additionally, airborne transmission can occur, particularly in densely populated poultry environments, where virus-laden droplets can be dispersed over short distances.¹⁵¹ Studies have shown that H5N8 HPAIVs have spread globally via migratory waterfowl, with analysis of viral progeny in terrestrial poultry revealing changes in polymerase and accessory genes, indicating potential differences in transmission dynamics between infected waterfowl and terrestrial poultry.¹⁴⁴ Furthermore, the tropism and infectivity of seasonal HPAIVs H5N1 have been studied in ferret models, showing that the HPAI H5N1 virus primarily infects nonciliated cells.¹⁵² Studies have also evaluated the pathogenicity and transmissibility of HPAI H5N1 viruses in different animal models, such as ferrets, demonstrating fatal disease and transmission between co-housed ferrets.¹⁴⁸

Research has also investigated the potential transmission of HPAIVs from wild mammals to domestic mammalian hosts and humans.¹⁵³ Genomic analysis has been utilized to reveal the transmission and reassortment of wildlife-borne H5N1 HPAIVs among different hosts, such as birds, pigs, and humans.¹⁵⁴ Furthermore, studies have investigated the airborne transmission of highly pathogenic H7N1 influenza virus in ferrets, indicating the potential for AIVs to become capable of airborne transmission among mammals.¹⁵⁵ Evaluations of the pathogenesis and transmission of novel HPAIVs H5N2 and H5N8 in ferrets and mice have highlighted the potential for cross-species infection.¹⁵⁶

In summary, continued research on different HPAIVs is essential to elucidate their modes of transmission among avian species, mammals, and potentially humans.^{157,158} Understanding these transmission dynamics is critical for developing effective prevention and control measures to mitigate the impact of HPAI outbreaks on both animal and human health.

Human infections with avian influenza A viruses are relatively uncommon but can occur sporadically in many countries, typically associated with unprotected exposures to infected poultry or virus-contaminated environments. The primary risk factor for human infection appears to be exposure to infected live or dead poultry or contaminated environments, such as live bird markets.^{159,160} Individuals involved in poultry-related activities, such as slaughtering, defeathering, handling carcasses of infected poultry, and preparing poultry for consumption, especially in household settings, may also be at increased risk of exposure and infection with HPAIVs. Additionally, a small number of human infection cases with HPAIVs have been attributed to exposure to infected wild birds, resulting in a wide range of symptoms and complications.^{161,162}

The pandemic potential of HPAI clade 2.3.4.4 H5 viruses has raised concerns, prompting recommendations for multi-sectoral collaborations to assess the risk of human-to-human transmissibility and develop countermeasures to prevent disease spread.¹⁴⁷ Qualitative risk assessments conducted in live poultry markets in Dhaka City, Bangladesh, have revealed a high prevalence of HPAIVs, posing a plausible risk of transmission between human and poultry species.¹⁴⁵ Specific mutations in the PB2 and PA proteins have been identified that contribute to the efficient replication of H5N1 influenza viruses in human lung cells, highlighting the importance of multisectoral collaborations to prevent disease spread and assess the likelihood of human-to-human transmission.^{147,163} While human-to-human transmission of AIVs is rare, occasional instances of limited nonsustained human-to-human transmission have been reported in a small number of people without poultry exposures.^{164,165}

Overall, current studies underscore the complex dynamics of HPAIVs and emphasize the need for interdisciplinary collaborations to assess and mitigate the risks associated with transmission among avian species and potentially to humans. The different risk factors highlight the importance of preventive measures, such as proper hygiene practices, personal protective equipment, and surveillance, to mitigate the spread of HPAI among humans. Further research is warranted to enhance our understanding of the modes of transmission of these viruses and to develop effective strategies for prevention and control.

Prevention and Control Measures of HPAIVs

The widespread dissemination of HPAIVs across multiple continents in recent years has resulted in numerous economically costly poultry outbreaks and posed continuous risks to public health. Additionally, sporadic human infections with HPAIVs have underscored the potential risk of

these viruses to cross the species barrier. Given the unprecedented spread of HPAIVs, ongoing poultry outbreaks, human exposures, and the potential for a pandemic, it is imperative to enhance constant surveillance of HPAIVs and implement increased protection measures to safeguard humans from possible infections.

Strategies for controlling HPAI in poultry and wild bird populations encompass several key aspects, including: (1) implementation of surveillance programs targeting high-risk avian populations, such as live bird markets and markets selling poultry, as well as fighting cocks.¹⁶⁶ (2) Conducting global avian influenza surveillance, with a focus on wild birds, poultry, related environments, human cases, and high-risk populations.¹⁶⁷ (3) Development of outbreak management strategies, which may involve rapid response measures, culling infected birds, and implementing biosecurity measures.¹⁶⁸ (4) Providing guidance for site managers of areas where significant numbers of wild birds gather, such as islands, shorelines, and wetlands, to mitigate the risk of HPAI spread.¹⁶⁹ (5) These strategies aim to prevent, detect, and control the spread of HPAI in both poultry and wild bird populations, thereby reducing the risk of transmission to humans and other animals.

Global health initiatives and surveillance programs play a crucial role in rapidly detecting, reporting, and responding to animal outbreaks as the first line of defense. Enhanced risk-based surveillance in animals, as well as surveillance for severe acute respiratory infections and influenza-like illnesses in humans, is essential for early detection and investigation of suspected animal and human cases. This is followed by epidemiological, virological investigations, and genetic sequencing analysis around animal outbreaks and human infections.

Several programs and initiatives facilitate the sharing of information on global or local influenza viruses, for example, the Global Program for Avian Influenza and Human Pandemic Preparedness and Response, which aims to minimize the threat posed to humans by HPAI infection through coordinated global efforts,¹⁷⁰ the Global Influenza Program, which provides strategic guidance, technical support, and coordination of activities essential for combating avian influenza and other influenza viruses,¹⁷¹ HPAI Surveillance Programs, which include epidemiologic simulation models to study the spread and control of HPAI among commercial and backyard poultry flocks,¹⁶⁷ and the Global Consultation on Highly Pathogenic Avian Influenza by the Food and Agriculture Organization of the United Nations, which focuses on epidemiology, disease surveillance, diagnostic techniques, prevention, control, and risk reduction strategies.¹⁷² Impact of Surveillance and Control studies the effectiveness of ongoing surveillance and control measures on HPAI, emphasizing the global public health risk and economic impact.¹⁷² These initiatives and surveillance programs aim to prevent, detect, and control the spread of HPAI globally, thereby safeguarding both human and animal health.

Vaccination of poultry has emerged as a crucial tool in complementing disease control measures to prevent avian influenza at its source. The effectiveness of poultry vaccination

relies on robust surveillance and considerations of local factors such as circulating virus strains, risk assessments, and vaccination implementation conditions. Developing effective vaccines against HPAIVs is essential for public health, with an ideal vaccine aiming to reduce virus spread within and between animal flocks to prevent major outbreaks. Several studies have contributed to advancements in vaccine development against HPAIVs. Kingstad-Bakke et al¹⁷³ developed the H5 mosaic (H5M) vaccine antigen, which induced protective levels of humoral immunity against HPAI H5N1 and H5N2 viruses. This research highlights the potential of mosaic-based nanovaccines for avian influenza. Zhang et al¹⁷⁴ discussed the production of high-titer infectious influenza pseudotyped particles with envelope glycoproteins from HPAI H5N1 and avian H7N9 viruses. This experimental approach aids in understanding virus transmission and lethality, emphasizing the importance of vaccine development for epidemic prevention. Wu et al¹⁷⁵ reviewed research progress on human infections with avian influenza H7N9, including key gene mutations, clinical treatment, and vaccine development. Their findings provide a scientific basis for monitoring and preventing H7N9 influenza epidemics. Huang et al¹⁷⁶ assessed the application of a pseudovirus system for re-emerging AIV H5 subtypes in vaccine development. They highlighted the challenges of handling highly pathogenic viruses and the potential of pseudovirus systems in vaccine efficacy and immunogenicity studies. Li and Chen⁵¹ summarized the successful control of H7N9 avian influenza infections in poultry through nationwide vaccination with an H5/H7 bivalent inactivated avian influenza vaccine. This preventive measure not only controlled the virus in poultry but also prevented human infections, demonstrating the importance of vaccination in controlling avian influenza outbreaks.

Overall, the development of effective vaccines against HPAIVs is crucial for preventing potential epidemics and protecting public health. Innovative vaccine technologies, such as mosaic-based nanovaccines and pseudovirus systems, hold promise in enhancing vaccine efficacy and immunogenicity. Additionally, nationwide vaccination efforts have proven successful in controlling avian influenza outbreaks, underscoring the importance of preventive measures in combating infectious diseases. Further research and surveillance are necessary to address the challenges posed by HPAIVs and accelerate vaccine development efforts.

Conclusion

In conclusion, HPAIVs pose a significant threat to both animal and human health. Continued research and vigilance are paramount to effectively monitor and control these viruses, minimizing their impact on global health and economies. Studies on HPAIVs play a crucial role in understanding their epidemiology, transmission, and virulence, exploring their pandemic potential, and guiding the development of vaccines and antiviral strategies. Additionally, they inform public health policies, surveillance strategies, and response plans to mitigate potential outbreaks.

Given the rapid evolution of HPAIVs, continuous surveillance and risk assessment are critical for controlling

outbreaks and reducing impacts on public health and the economy. Early detection of HPAI outbreaks in animals is essential to minimize the risk of transmission to humans and the potential for a pandemic. Furthermore, vigilant field research is necessary to mitigate virological threats to animals raised for food, ensuring food supply security while minimizing transmission risks to humans.

Continued research efforts should focus on exploring passive immunization, assessing pandemic risk associated with HPAI, conducting laboratory studies on altered HPAIVs to understand transmission dynamics, and evaluating various control measures. Mechanistic models used to study HPAI transmission dynamics can contribute to improved strategies for prevention and treatment, ultimately reducing the impact of HPAI on both animal and human health.

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Conflict of Interest

None declared.

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