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The pandemic threat of an Avian Influenza Virus: An overview

Amandeep Kaur[1], Ranjeet Kumar[2*], Hardik Kumar[1], Sonakshi Garg[1], Dharmendra Kumar[2]

[1] Research Scholar, Department of Pharmacy Practice, ISF College of Pharmacy, Moga, Punjab, India
[2] Narayan Institute of Pharmacy, Gopal Narayan Singh University, Sasaram, Rohtas, Bihar, India

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Abstract

The worst pandemic in modern history occurred during the 1918 H1N1 Spanish Influenza epidemic. Two additional instances of influenza A (H5N1) viral infection in humans have been disclosed to WHO in the West Pacific Zone between July 12 and July 18, 2024. Merely three HA subtypes, namely H5, H7, and H9, have been identified and observed in domestic fowl across extensive geographic regions. The Asian H7N9 virus and the recently discovered avian-origin H5 A/goose/Guangdong/1/1996 (GsGd) virus have infected hundreds of humans and killed many of them. Although these infectious diseases have not expanded beyond affected individuals, they will start a pandemic if they develop the capacity to travel effectively from person to person, especially through the air. Thus, the focus of this analysis is on the characteristics of the Asian H7N9 and H5 GsGd viruses that facilitate airborne transmission and have recently resulted in zoonotic illnesses. Three waves of outbreaks of influenza have occurred across many continents due to the H5 influenza viruses, which migratory wild birds carry. The third wave of influenza outbreaks began in 2020 and is still underway. China, which produces the majority of the world's poultry, lost very few animals throughout the three phases of H5 avian influenza epidemics and almost completely eradicated the widespread H7N9 viruses that surfaced in 2013. Diverse nations have implemented distinct approaches to manage highly virulent avian influenza. While some countries, like China, have chosen a "cull plus vaccination" approach, many European and North America countries control highly virulent influenza by culling diseased and suspected birds (also known as the stamping-out technique). This paper provides an overview of the avian influenza virus, its management measures, and potential problems associated with an epidemic.

Introduction

The avian influenza virus (AIV) is a serious viral infection that can cause zoonotic illness in birds and poses a constant threat to animal and human health (1). Because it constitutes an RNA virus, reassortments, recombination, and mutations are common (2). This has made it possible to repeatedly convert H5 or H7 subtypes of the lower pathogenic avian influenza (LPAI) viruses to the highly pathogenic avian influenza (HPAI) viruses (3, 4).

***Corresponding author:** *ranjeetkumar2784@gmail.com*
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AIV's potential for a human pandemic, which might happen if the virus manages to spread from person to person, is a serious public health risk (5). The influenza genome Eight gene segments make up a virus: matrix (M), hemagglutinin (HA), nucleoprotein (NP), neuraminidase (NA), basic polymerase 2 (PB2), basic polymerase 1 (PB1), acidic polymerase (PA), and a non-structural protein (NS) (6-8). Each of these regions encodes one to three different proteins. Both antigenic properties associated with HA and NA proteins are used to categorize influenza viruses into distinct subtypes. In avian species, 16 HA subtypes and 9 NA subtypes have currently been identified (9)(10). Since 1918, the H1N1 and H3N2 viruses have been co-circulated in humans worldwide and have been responsible for four influenza pandemics (11, 12). Merely three HA subtypes, namely H5, H7, and H9, have been identified and observed in domestic fowl across extensive geographic regions. Certain strains belonging to the H5 or H7 variants that have the HA gene are extremely pathogenic to chickens and have generated serious issues for the poultry industry worldwide (13) (14). The severity of clinical symptoms is influenced by genetic variations in interferon-induced transmembrane protein 3 (IFITM3). The effects of mutations within the IFITM3 genes on pandemic sickness were initially identified throughout the H1N1 pandemic of 2009. This genetic variation has also been connected to severe disease in certain H7N9 individuals. In comparison to the C/T as well as T/T genotypes, an IFITM3 C/C genotype has been associated with more severe clinical manifestations in H7N9 individuals (15). Additionally, research has linked some host variables—like TMPRSS2, LGALS1, and CD55—to worse outcomes from H7N9 infections (16). Influenza viruses pose a major danger to the health of humanity due to their antigenic diversity and interspecies transmission. They are one of the main causes of respiratory tract infections in humans, leading to seasonal epidemics and sporadic pandemics. Influenza viruses have developed numerous ways to counteract host cells' sophisticated antiviral mechanisms, which depend on recognizing influenza viral items and triggering signaling cascades that result in the secretion of type I IFNs (IFN-α/β). Some of these strategies include inducing host shut-off or controlling the polyubiquitination of popular and host proteins (17).

Epidemiology

During October 2021 and September 2023, the region experienced one of its deadliest avian influenza outbreaks, which resulted in the deaths of millions of bird species and caused 2500 infections on farms across 37 nations. Although the virus that causes H5N1 infection continues to spread to additional animals worldwide, human infections are sporadic. In 1997, there was a significant HPAI H5N1 outbreak in domestic poultry, which coincided with the first known instances of H5N1 illness in people in Hong Kong. This outbreak led to 18 cases of infection in humans, 6 fatalities, and epidemics in chickens in both Italy and Hong Kong. The first H5 influenza A epidemic of this century was brought on by the H5N1 virus and happened in Hong Kong, China in 2002 (18). As a result, in the spring of 2013, the Yangtze River Delta region of China reported the first human illness caused by the LPAI H7N9 viruses (19). In the spring of 2013, the Yangtze River Delta region of China reported the first human illness caused by the LPAI H7N9 viruses (19). Despite the fact that the virus did not infect chickens, most laboratory-confirmed human infections resulted in severe sickness or even death. There were five H7N9 epidemic cycles (20). By the final wave in 2016–2017, the LPAI H7N9 virus transformed into the HPAI H7N9 virus, which not only infected people but also significantly reduced the death rate in chickens. As of September 2019, there have been 1568 laboratory-confirmed cases of H7N9 infection in humans, or around 39% of cases overall (21). All human H7N9 infections originate in China; two cases identified in Canada and Malaysia were connected to Chinese visitors (22).

An H5N1 outbreak in poultry was first documented in South Korea in December 2003 as well as 2004, and it thereafter spread to Vietnam, Thailand, Japan, Laos, Cambodia, Indonesia, China, and Malaysia. Seven confirmed instances of mild illness in poultry employees from a poultry operation in Southern Russia at which epidemics had been recorded marked the first documented human manifestations of HPAI H5N8 in 2021. Chronic lung illness is a major risk factor for H5N1 infection, according to serosurveillance monitoring data collected from people in Egypt who were exposed to poultry (23). As of July 2024, less than 10 human infections had been confirmed from an outbreak among cattle herds in the United States, despite the pandemic still affecting over 100 herds. Different virus subtypes have also been found in recent reports from around the world in human beings. H5N2 has killed one person in Mexico, while Australia has seen the country's first case of less dangerous H5N1 (24, 25).

Two additional instances of influenza A(H5N1) viral infection in humans have been disclosed to WHO in the West Pacific Zone between July 12 and July 18, 2024 (26). 889 cases of human infections with the influenza A(H5N1) virus have been reported worldwide from 23 countries between January 1, 2003, and May 3, 2024. 463 of these 889 instances resulted in death. No new cases of avian influenza A(H5) infection with the virus in humans have been identified by WHO within the Western Pacific Area between July 12 and July 18, 2024. The most recent instance—one case, no deaths—was documented in Vietnam on October 5, 2022 (27).

A person's risk of infection increases when they are exposed to poultry and wild birds at work or during leisure time. Being involved with infected chickens in a commercial chicken farm or owning a backyard flock, fishing, de-feathering, killing infected wild birds along with crazy animals, employing wild birds for conservation, research, or rehabilitating reasons, employed with wild mammals, and going to live bird markets are among the activities that could boost the risk of exposure (28).

Pathogenicity of H5 and H7 Avian Influenza Viruses and Transmission in humans

Depending on how harmful they are to domestic hens, avian influenza virus strains are categorized as either low or extremely pathogenic (29). The majority of avian influenza viruses are categorized as low pathogenic and inflict gastrointestinal infections in birds with few clinical symptoms (30-32). The build-up of many basic amino acids at the HA cleavage site, also known as the polybasic breakage site or polybasic motif, is what causes pathogenicity since it enables the HA molecule to develop beyond the gastrointestinal tract, therefore, cause a systemic infection (29). When chickens are infected with a highly transmissible avian influenza virus, the illness progresses quickly and results in significant fatality rates (33-35).

Significantly, several H5 and H7 viruses, whether highly pathogenic or low-pathogenic, also exhibit virulence in animals. Addeitionally, certain highly pathogenic viruses can infect an animal model systemically (36, 37). Additionally, it is thought that the existence of several basic cleavage sites contributes to mammalian pathogenicity, particularly in conjunction with viral polymerase modifications that facilitate mammalian replication (19, 38-40). Due to little bird interaction between the two continents, influenza viruses in birds of a particular HA subtype have phylogenetically split into two primary lineages: Eurasian and North American (41-43). These lineages have essentially developed independently of one another. Historically, outbreaks in poultry have been generated by low virulent H5 and H7 viruses in both lineages that have evolved to become highly pathogenic (44-47). In the late 1990s, highly pathogenic H5 viruses derived from the A/goose/Guangdong/1/1996 lineage (GsGd) within the Eurasian lineage first appeared. These viruses have been responsible for hundreds of zoonotic infections (48, 49). These migratory birds have

recently brought viruses from this lineage outside of Asia, causing epidemics in North America. Novel H7N9 viruses, which belong to the H7 subtype, first surfaced in China in 2013 and have since been responsible for yearly outbreaks of zoonotic infections.

There is a growing concern that the H5 and H7 viruses, might acquire the ability to spread among people and cause a pandemic because they have both shown a tendency to infect humans (50, 51). The virus most frequently spreads through migrating wild birds, as Figure 1 illustrates Indirect or direct contact with animals that are diseased or with settings and surfaces polluted by excrement is the primary risk factor for the transfer of the disease from birds to people. Risk factors may also include plucking, handling contaminated chicken carcasses, and processing poultry for ingestion, particularly in homes (52).

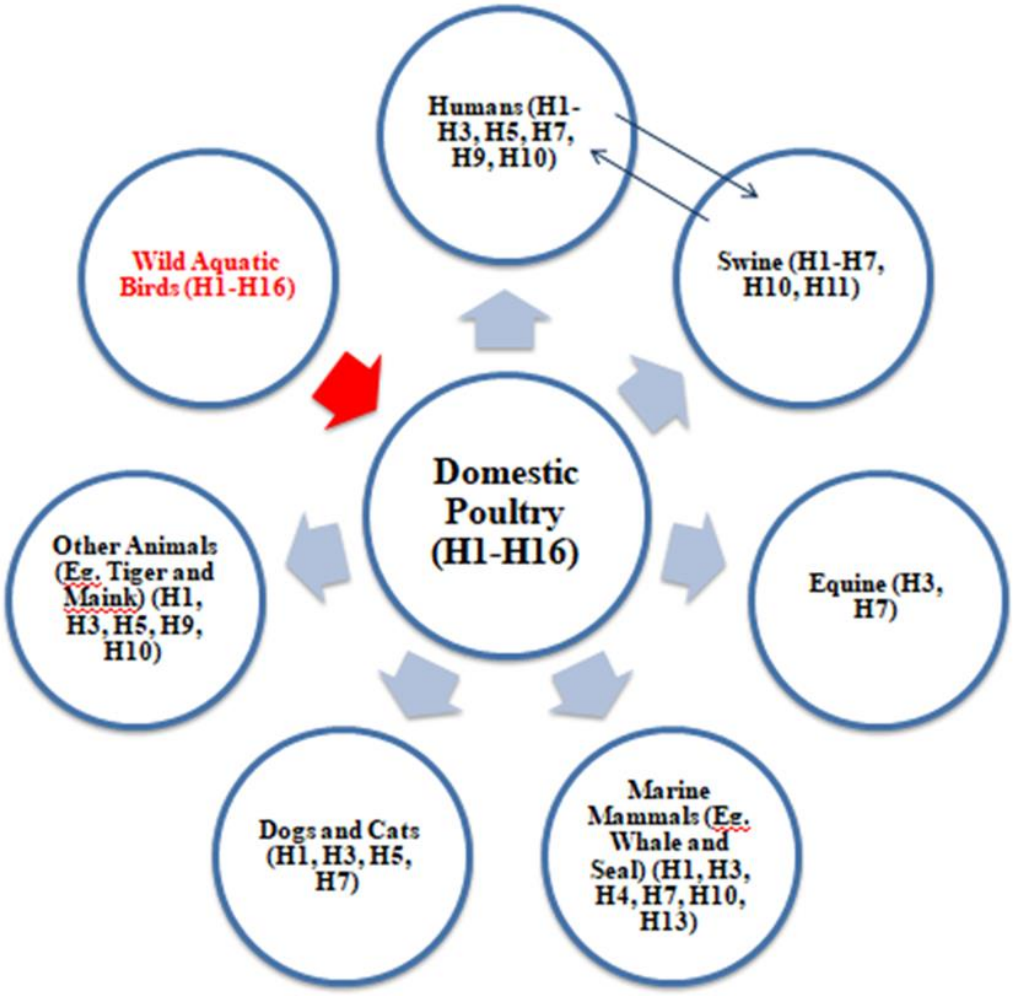

Fig 1: This figure represents the distributed IAV subtypes in several mammalian hosts, as shown in Fig 1. Aquatic wild birds are thought to be the source of the infection that spreads to humans, swine, cats, dogs, marine mammals, and other species. These animals then appear in avian reservoirs and domestic fowl that infect mammalian hosts. Bidirectional arrows relate to possible reverse zoonotic events, or "human-to-animal transmission," after zoonosis, whereas unidirectional arrows allude to the zoonotic possibility of AIVs.

Treatment

Diverse nations have implemented distinct approaches to manage highly virulent avian influenza. While some countries, like China, have chosen a "cull plus vaccination" approach, many European and North American countries manage highly virulent influenza by killing diseased & suspected birds (also known as the stamping-out technique) (53).

Neuramidase inhibitors, such as a drug called, zanamivir, the drug peramivir, and zanamivir, are indicated for the treatment of IAV infections in patients who have a confirmed or suspected infection and who are at risk of developing severe disease. This includes patients with pandemics as well as zoonotic influenza (54, 55). The best results from antiviral therapy are obtained as soon as symptoms appear. Clinical therapy for critically ill hospitalized patients may also involve supportive care for associated problems, such as prolonged organ support for those with serious pneumonia (56). It has been discovered that a bivalent live vaccination, vectored by the duck enteritis virus (DEV), offers quick and comprehensive defense against the very deadly duck enteritis virus and the H5N1 avian virus that causes influenza in ducks (57, 58). Above noteworthy, the DEV-vectored vaccine offered strong cross-protection against viral challenges from several clades. The success of genetically reversed inactivated vaccines in chickens and ducks is well-documented, in contrast to NDV-vectored vaccines, which are only utilized in hens (59).

The H5-Re1 vaccine seed virus was first used in 2004 and offered strong protection against viruses carrying the clade 0 HA, clade 1 HA, clade 2.2 HA, or 2.3.4 HA gene (59). It gets its HA and NA genes from A/goose/Guangdong/1/1996 (H5N1). The A/duck/Anhui/1/2006(H5N1) was the source of the HA and NA genes of the H5-Re5 seed virus, that replaced the H5-Re1 seed virus in March 2008. The H5-Re5 vaccination was used to eradicate the H5N1 viruses carrying the clade 2.3.4 HA gene, and its usage was halted in June 2012 (60). Only the H5-Re13 and H5-Re14 vaccines are currently used to control the local H5 virus-bearing clade 2.3.4.4h HA and worldwide flowing H5 viruses bearing clade 2.3.4.4b HA (61). The vaccine seed viruses H5-Re8, H5-Re11, H5-Re13, and H5-Re14 have been developed to control H5 viruses with different subclades of 2.3.4.4 HA that have emerged in China in recent years. China's widespread use of the trivalent H5+H7 (H5: Re-11; H5: Re-12; H7: Re-2) vaccine significantly contributes to effectively containing influenza virus epidemics (62). The current commercial vaccine, however, is an entirely virus-inactivated vaccine that is produced using fertilized embryonated chicken eggs (ECEs). This has significant drawbacks, such as a lack of fertilized ECEs throughout influenza outbreaks, a lengthy mass production period, endogenous virus contamination, as well as environmental harm from biohazards. In an attempt to produce two antigens in a single viral inoculation, bivalent inactivated vaccines constructed around an influenza virus vector have recently been developed and seem to be immunogenic and effective against both the HP H5N6 and H7N9 viruses in hens (63).

Moreover, due to their potent ability to elicit a broad immune response that includes humoral, and mucosal, along with cellular immunities, non-infectious virus-like particle (VLP) vaccines can offer outstanding defense against homologous, heterologous, as well as heterosubtypic virus infections (59). To produce VLP vaccines for poultry, extensive research has been done. Most of these studies have focused on producing H5 VLP for use in chicken or duck expression systems, such as baculovirus, silkworm pupae, and mammalian 293T cells (64). VLP candidates against additional types, including the H6 and H7 subtypes, were additionally generated for chicken vaccination. This included Escherichia coli, silkworm pupae, and a plant production system for the H6 subtype of VLP. Additionally, chicken H7 VLP was produced using baculovirus. Nevertheless, little information is available at this time about the development of bivalent H5N1 along with H7N9 VLP vaccines for

chickens (59). The CDC has created H5 candidate vaccine viruses (CVVs) that resemble hemagglutinin (HA) proteins of the recently identified clade 2.3.4.4b avian influenza A(H5N1) viral genomes in individuals, birds, and other animals almost exactly or, in many cases, exactly (65).

Conclusion

In conclusion, the H5 and H7 subtypes of avian influenza viruses are causing significant damage to the global poultry industry. Since 2005, over 389 million domestic chickens have died or been destroyed, with 193.9 million of those losses occurring from January 2020 through November 2022. Two additional instances of influenza A(H5N1) viral infection in humans have been disclosed to WHO in the West Pacific Zone between July 12 and July 18, 2024. In addition to posing serious risks to public health, these viruses have resulted in 2634 human cases and over 1000 fatalities. In China, vaccinations have successfully prevented highly pathogenic influenza virus infections in poultry; even though the H5 viruses that are currently circulating worldwide have been found in several wild bird species and occasionally in ducks and geese, these viruses have never caused issues on routinely vaccinated poultry operations in China, and the ubiquitous H7N9 viruses have been all but eradicated there.

In many places around the world, H5N1 viruses with the clade 2.3.4.4b HA genes are causing problems for domestic poultry and are widely circulating among wild birds. Vaccination should be quickly and carefully explored as a control approach, not only in undeveloped countries but also in wealthy ones, to enhance animal welfare, reduce economic losses, and prevent human infections. Any needless barriers to immunization programs must be eliminated right now. In addition to fundamental research, ongoing studies are necessary to produce pandemic influenza vaccines, which might improve our capacity to anticipate and perhaps lessen the impact of an H5 or H7 virus influenza pandemic. Currently, the development of antibodies with a long half-life is a strategically important field of study. The development of such vaccines can be based on conserved influenza viral antigens Conventional methods that use proteins as antigens offer the potential to solve this issue, but they haven't shown very noticeable outcomes yet. The creation of an oligonucleotide vaccine that employs conservative areas of the influenza virus genome as antigens is equally promising. It is reasonable to expect that humans will prevail in the struggle against the virus if influenza vaccinations with an operational term of ten years or more become available.

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Not applicable.

Ethical approval

Not applicable.

Conflict of interest

There is no conflict of interest in conducting this research.

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