

Dissemination of Highly Pathogenic Avian Influenza through Wild Migratory Birds**04**

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ABSTRACT

Avian influenza viruses (AIVs) pose a significant threat to both poultry and human populations due to their ability to cross species barriers. This review explores the genetic diversity and factors influencing the pathogenicity of Influenza A viruses, focusing on the H5N2 subtypes currently circulating in China. The viral subtypes are determined by Neuraminidase (NA) and Hemagglutinin (HA) genes, with H5N2 variants dominating recent outbreaks. The presence of polybasic cleavage sites in the HA molecule is a key indicator of high pathogenicity. Notably, the NP, PB1, and PB2 proteins contribute to increased pathogenicity. Outbreaks are classified based on cytotoxicity and the presence of polybasic cleavage sites in the HA. The dissemination of AIVs is closely linked to wild birds, especially migratory species. HPAI spread through migratory flyways, raising concerns about cross-continental transmission. The study addresses the role of migratory birds, exploring questions regarding their ability to carry infections while migrating and the involvement of illegal exotic bird trade in viral spread. Surveillance measures are crucial for early detection and preparation, necessitating updated kits and knowledge about wild bird behavior. The global impact of AIVs on the poultry industry is profound, affecting both small and large-scale farmers. Economic losses, culling practices, and societal impacts are discussed, emphasizing the vulnerability of small-scale farmers in developing countries. Prevention strategies involve understanding migratory patterns, implementing effective surveillance, and preparing management protocols. Coordination among organizations and heightened situational awareness are vital components of proactive measures against AIV outbreaks.

Key words: Avian influenza, Genetic diversity, Migratory birds, Viral reassortment, Surveillance

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1. INTRODUCTION

The Influenza A virus (IAV) has the broadest range of hosts and carries extraordinary gene diversity compared to the other two influenza virus types (Zhang et al. 2013). The subtypes of influenza viruses are determined by their Neuraminidase (NA) and Hemagglutinin (HA) genes, of which there are 18 and 11 forms, respectively. These viruses have a history of infecting avian hosts, as evidenced by analysis of their viral genomes using phylogenetic link. Although the presence of a site for polybasic cleavage on the HA of H5 viruses is an indicator of their high pathogenicity, experiments in chickens have shown that the introduction of polybasic genes into the LPAIV HA does not necessarily produce a fatal phenotype (Bogs et al. 2010). NP, PB1, and PB2 Influenza proteins may make it more pathogenic to an influenza virus.

Classification of Low pathogenic AIV or High Pathogenic AIV outbreaks in poultry often relates to the cytotoxicity of the infectious agent during illness and if the virus possesses a site for polybasic cleavage in its HA molecule (as mentioned above). However, other proteins, including NA, can increase the virus's pathogenicity. Currently, the H5N6, H5N8, and H5N2 viruses of type H5Nx are the newly circulating AIV strains in China. As a result of these viral re-assortments (Lee et al. 2017). A dominant NA molecule may emerge, increasing the pathogenicity and viral particle release. Viral modifications in the Hemagglutinin proteolytic cleavage site, such as the mutation of numerous non-basic amino acids to basic amino acids, replication of essential amino acids, or mutation with insertion of viral or cellular amino acids, have led to the emergence of high-pathogenic avian influenza (HPAI) viruses from low-pathogenic avian influenza (LPAI) viruses (Swayne et al. 2016). The first cases of the highly pathogenic avian influenza virus in poultry birds were discovered in northern Italy in 1878 (Swayne et al. 2016). Six people died in Hong Kong in 1997 after being infected with the H5N1 strain of the highly pathogenic avian virus (HPAIV), which was first discovered in 1996 in China. The H5 clade 2.3.4.4 (HPAI) subtype H5N8 virus was first identified in chickens in South Korea in 2014. In Europe, North America, and Asia, by the middle of 2015, it has spread to domestic and wild birds (Hall et al. 2015).

2. SUBTYPES

At present, AI viruses can contain surface proteins from any of the nine different neuraminidase subtypes (N1-9) and the 16 different Hemagglutinin subtypes (H1-16) (Swayne et al. 2016).

2.1. AVIAN INFLUENZA A(H5) VIRUSES

There are nine different subtypes of the A (H5) virus including (H5N1), (H5N2), (H5N3), (H5N4), (H5N5), (H5N6), (H5N7), (H5N8) and (H5N9) (Swayne et al. 2016).

2.2. AVIAN INFLUENZA A (H6) VIRUSES

A (H6) viruses have several subtypes, including LPAI A (H6N1) and A (H6N2). The first known human LPAI A (H6N1) virus infection was reported in Taiwan in 2013 (Swayne et al. 2016).

2.3. AVIAN INFLUENZA A (H7) VIRUSES

The nine subtypes of AIV

A (H7N1), A (H7N2), A (H7N3), A (H7N4), A (H7N5), A (H7N6), A (H7N7), A (H7N8) and A (H7N9) are all currently recognized (Swayne et al. 2016).

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2.4. AVIAN INFLUENZA A (H9) VIRUSES:

There are nine recognized subtypes of AIV: A (H9N1), A (H9N2), A (H9N3), A (H9N4), A (H9N5), A (H9N6), A (H9N7), A (H9N8) and A (H9N9). All A (H9) viruses seen in wild birds and poultry across the world are LPAI viruses (Swayne et al. 2016).

2.4.1. AVIAN INFLUENZA A (H10) VIRUSES

A (H10) viruses come in a variety of subtypes, including:

A (H10N3), A (H10N4), A (H10N5), A (H10N6), A (H10N7) and A (H10N8). In 1984, a mink was reported to have A (H10N4), and in 2008, swine (pigs) were found to have A (H10N5). A (H10N3), A (H10N7) and A (H10N8) are the A (H10) virus subtypes reported to have infected humans (Swayne et al. 2016).

3. RECENT OUTBREAKS

When it affects the poultry population, the avian influenza virus (AIV) can lead to severe epidemics (James 2000). However, it occasionally infects people who come into contact with infected birds. A particular illness that has spread beyond its expected endemicity is said to be an epidemic when there are more instances than typical (King et al. 2021). A specific number of cases, meanwhile, is not necessarily required for there to be an epidemic (Bellouet al. 2013). Aside from that, identifying an epidemic also heavily depends on the moment and location of occurrence. So, an epidemic belongs to a particular group of people (community), in a specific place (geographical area) and at a special moment in time (season) (Marchenkoet al. 2011). Since the Gs/GD HPAI viruses first emerged (in 2002), in the outbreaks of HPAI, East Asia has played a significant geographic role that frequently affects aquatic birds in the wild and in captivity (Marchenkoet al. 2015).

Russia, Japan and South Korea are among the nations in East Asia that have frequently been impacted by previous HPAI epidemics in wild birds (Sakodaet al. 2012). In the 20th century, in 1918, 1957, and 1968, three influenza pandemics occurred, resulting in about 0.5 million, 1 million and 05 million fatalities. AIV subtype H5N1 is still the most prevalent subtype. Additionally, the most common region for the geographic scope of epidemics is Asia. A number of the most significant pandemics between 2010 and 2016 were counted in Taiwan, South Korea, China, Japan, India, Israel, and Vietnam. It's due to enhanced clinical and laboratory programs conducted in all of these nations over the past few years, or it may be because these nations have a distinctive environment with plenty of lakes, rivers, creeks, ponds, and creeks that serve as wintering grounds for migratory birds (Jeonget al. 2014).

Cases with a more significant percentage were recorded in Egypt (including Cameroon, Nigeria, Africa, Togo, Libya, Tunisia, Ghana, Burkina Faso, and Cote d'Ivoire). The Spread of the virus in Europe, particularly HPAI H5N8 emergence in Germany, has reinforced the intimate connection between the habitats of wild birds and the pathogen dissemination through their migration (King et al. 2021). The greatest H5N2 epidemic ever documented in the United States occurred between 2014 and 2015, and to stop the expansion of the disease, almost 51 million birds were depopulated. Twenty-five million birds, or 409,836 every day or 284 per minute, were killed between May and June 2015 in the United States (Chatziprodromidouet al. 2018).

The government spent a total of US\$879 million during the 2014–2015 H5N2/H5N8 epidemic, while more than US\$3 billion was paid by the United States egg and poultry industries to stop the disease from infecting poultry. In the USA, this HPAI outbreak was the most expensive. Due to the new wave of HPAI H5N8 viruses in numerous European nations saw severe outbreaks of wild and poultry birds in the first half of 2020 (Jacobs 2022).

ZOONOSIS

There were many bird flu outbreaks reported in Europe before the end of 2020. (HPAI) High-pathogenic avian influenza virus outbreak has been detected in numerous European nations since mid-October, primarily in wild birds, including Germany, France, Belgium, Sweden, Denmark, Ireland, the United Kingdom and Netherlands (Hall et al. 2015). Other poultry and captivity birds tested positive as well. Three different types of Highly pathogenic avian influenza viruses, A(H5N1), A(H5N5), and A(H5N8), were discovered, with H5N8 being the most often found, declared by the European Center for Disease Prevention and Control (ECDC). To stop the H5N8 virus from spreading, 29,000 hens were slaughtered in Germany (Lee et al. 2020).

4. UNITED STATES 2022–23 OUTBREAK

All Health Monitoring Agencies working for the betterment of public health in the United States collaborated and worked on the pandemic wave. Data came on board revealing that a single wave of the viral activity resulting in deaths of many birds following the second wave which came around the end of 2022 which impacted the major Nine areas of the America (Merced-Morales et al. 2021). Despite strict prevention strategies put in place by the sector following the 2015 outbreak, the most recent outbreak has cost about \$661 million to the government, and there is no control to the outbreak in sight (Cox et al. 2000).

4.1. AFRICA 2023 OUTBREAK

In Early December 2020, in the poultry shed rearing, the total number of birds was almost more than 0.1 million. In a small village area of Africa, suddenly, this poultry farm showed numerous mortalities, which created an alarming situation in the Area. The clinical signs and symptoms reported in the birds affected by that infection were swelling of the neck, the pale coloration of the body parts, and congestion in the respiratory (Lo et al. 2022). Given that wild birds in North America that are a carrier of Gs/GD HPAI viruses gives some amount of health danger to people who interact with domestic and wild animals, it is essential for efficient coordination to occur across management organizations and agencies for wildlife, agriculture, and public health (Sleeman et al. 2017).

5. DISSEMINATION THROUGH MIGRATORY BIRDS

In the research and studies conducted on the widespread of highly pathogenic AIV, there is a critical talk about its dissemination through the migratory routes of the wild birds. The burning issue is H5N1 spread to the European countries and is thought to be due to the fly routes of the birds (Kilpatrick et al. 2006). Whenever there is a talk about the pandemic of HPAI strain H5N1 from Asia to the countries of Europe, the only culprit is not the wild birds. We also need to shed a light on the illegal movement of exotic and wild birds and the movement of poultry products through international trade routes (Salzberger et al. 2007). Wild birds, which have the nature of migration in their life from Europe to Asia and other countries like Russia and North America, are the central spreading element of the H5N1 virus in pandemics (Feare 2007; Gauthier-Clerc et al. 2007).

Two significant concerns arise here, which are required to be addressed first, as wild birds are the most discussed element of dissemination for HPAI, but if they get infected with the virus, are they still able to migrate to carry infection? Till now, the answer to this question is not available, as supporting research is silent (Flint 2007). In some studies, it was seen that HPAI infection, especially the Asian strain, does not cause mortality in some wild bird species, like water-fowls (Brown et al. 2006; Keawcharoen et al.

2008). The second question that needs to be answered is that the fly routes of the wild migratory birds are really involved in the dissemination of highly pathogenic types of AIV between the continents and causes pandemics in Europe and North America. There is another point to be noted that many outbreaks of the HPAI virus in wild birds were not the dissemination root cause, which revealed that the new areas where the HPAI pandemic occurs is not linked with the migration behavior of the wild birds which carry H5N1 Infection (Kalthoff et al. 2008).

Various zoonotic infections are disseminated over long distances and change their shape to pandemics through the wild migratory birds when they carry them during their migration from one place to another (Reed et al. 2003). During the regular fly pattern between continents, the most spreading agent is AIV, which is transmitted to long distances via these wild birds (Olsen et al. 2006; Lam et al. 2012).

Low pathogenic type of AIV is usually transferred to long distances during the migration of wild waterfowls (Webster et al. 1992), and these birds carry this low pathogenic strain to other continents like Africa and America (Cappelleet al. 2012). One question still requiring attention: as is there any regional spread of the AIV virus through these wild types of flying birds in the regions? (Normile 2005; Hill et al. 2012). The first case of HPAI was reported in Asia in the last of 1995 (Li et al. 2004), which was then seen to spread through the migration of wild birds in other continents, causing many economic losses and taking human lives as well. It was seen that the rate of transmission of HPAI type of H5N1 from birds to Humans and then its transmission from humans to humans itself was not that significant.

The mortality rate was higher, which is why it was widespread among the wild birds and was a serious issue for the human health committees (Webster et al. 2006). Qinghai Lake was the breeding ground for many wild birds that migrate towards other continents, and that's why the particular strain of HPAI H5N1 transmitted to other areas through the wild birds from the lake area (Brown et al. 2008). It was also noted that many birds, after carrying the infection, sometimes don't show any infection as they migrate and shed the virus without showing any signs and symptoms of H5N1 (Keawcharoen et al. 2008). The take-home message was that large-scale transmission of HPAI infection through migratory birds isn't that easy to detect (Gaidet et al. 2008).

6. INFLUENZA THROUGH WATERBIRDS

Many water birds carry infectious viruses, which may be zoonotic, as dabbling ducks and mallards carry avian influenza virus (Olsen et al. 2006). Almost all the antigenic different types, including Hemagglutinin and neuraminidase, are seen in the dabbling ducks (Fouchier et al. 2005; Olsen et al. 2006; Krauss et al. 2004; Latorre-Margalef et al. 2009). The incidence of occurrence of infection of avian influenza virus in the mallards ranges from 10% in the hot season while it can vary to 60% in the fall season, and this is seen in both nearby continents like Asia and Europe and the northern side of America (Olsen et al. 2006; Krauss et al. 2004; Latorre-Margalef et al. 2009; Wallensten et al. 2007). This kind of variation may be due to many factors which influence the viral spread and its survival. Factors including the breeding season and the other environmental elements which harbour the viral replication and its widespread are made possible (Stallknecht et al. 1990).

6.1. INFLUENZA THROUGH SHOREBIRDS

Charadriiformes is the class of birds which is found to be a habitat on many continents. Which may be many types of birds named as gulls and terns. It is also seen that the frequency and prevalence of the HPAI type of influenza is little different in Charadriiformes than in the Anseriformes (Kawaoka et al. 1998).

The unique point about the Charadriiformes is that two subtypes are only seen in those birds, which are H13 and H16 (Krauss et al. 2004). Another unique point is the shore birds show HPAI infection most of the hot summers (Kawaoka et al. 1998). Ducks have a different pattern of moving to their breeding grounds compared to other shore birds. While most shore birds migrate during the summer, ducks migrate during the fall season. This leads to a higher transmission of infections during this time for ducks (Stallknecht et al., 1988). Hence, the purpose of this talk is the type of birds living in shore areas of the world are seen to be more important in breeding grounds and for longer periods the presence of infection in the wild type of birds may be important as they transmit the infection during their migration to the northern areas of the world in spring (Lee, et al., 2015).

Many studies conducted on the prevalence and frequency of infection in the Charadriiformes and Anseriformes showed different patterns of infection in both (Tian et al. 2015). In a study conducted, a total of 63 subtypes with the HA and NA genes were detected in more than 13 thousand samples of shore birds in almost 15-16 years (Tian et al. 2015). Two different orders of birds including Anseriformes (geese, swans and ducks) and Charadriiformes (gulls and shorebirds), are the names of wild birds. For the low pathogenic type of HPAI virus type A, wild birds are major dissemination elements (Lee et al. 2017). Ruddy shelducks, great black-headed gulls, great cormorants, bar-headed geese, brown-headed gulls, and common coots in Qinghai Lake are common wild birds (Tian et al. 2015).

When the wild birds migrate on their usual fly routes, it is seen that there are some stopover places for their preparation for next migration (Kim et al. 2009), and they seem to get infected in those places by the domestic poultry in nearby places (Tian et al. 2015). Sanmenxia Clade type 2.3.2.1c-like HPAI virus seemed to spread through this way of migration of wild birds (Li et al. 2014). Countries in Europe and Asia, including Japan, China, Korea and Eastern Europe (Eurasia), are best breeding grounds for wild birds like whooper swans (Uchida et al. 2008). Numerous whooper swans which have their breeding ground in China and complete their wintering on that ground (Almost 20,000 birds). More than 10,000 birds from the total during their migration breed on the grounds of Sanmenxia, where ducks of East Asian sides also stay and breed. Their migration isn't complete on those grounds, but after arriving in October on Sanmenxia lake, they fly back to their native grounds in Mongolia and Siberia for next spring breeding (Ao et al. 2020).

In Russia and other neighboring countries like Kazakhstan, Genetic re-assortment of highly pathogenic avian influenza virus created new research grounds that linked the pandemics of the H5N8 virus in Europe (in late and early 2020) with these re-assortment strains (Liang et al. 2021). In Asia the studies show that the spread as the pandemic of HPAI, specially the strain, is due to the wild migratory birds that disseminate the H5N1 strain (Tian et al. 2015), and then these migratory birds take the route to Europe (Xu et al. 2016). Research focusing on the transmission of AIV revealed that the gene flow usually occurs between the routes of the same region, and usual gene flow occurs through them (Lam et al. 2012). In another study, it was seen that migratory flyways of individuals or the partial type may be associated with the gene flow or transmission of AIV through the migration networks (Zhang et al. 2023).

In Early 2015 near the Sanmenxia Lake which is the breeding ground for many migratory wild birds, including whooper swans and other birds, for example ducks from China and nearby countries like Siberia and Mongolia. These birds take their migratory route from Qinghai Lake to Sanmenxia reservoir area. Deaths of more than 100 birds in this area created alarming conditions as it seemed another HPAI virus outbreak, and this outbreak was connected with the fly routes of the following discussed wild birds (Swayne et al. 2020).

In the wake of pandemics, dissemination of the virus through wild birds usually occurs, and it is required to take strict measures about their movement to make surveillance on the virus (Bi et al. 2015). This

kind of early surveillance is helpful in early preparation for such widely spreading viruses. For testing purpose, an updated surveillance kit containing required reagents is needed. Also, new updated knowledge about the wild bird's movement and their virus-shedding behavior can answer the questions about the HPAI ecology, epidemiology, spatial and temporal spread (Fouchier et al. 2005). In a study conducted in 1997, a total of more than 27 thousand samples were collected in the form of cloacal swabs and fresh samples of bird droppings. These samples were tested for the presence of the RNA of HPAI virus type A (Fouchier et al. 2000; Munster et al. 2005). There were two different types of distribution of samples on the basis of the collection as the majority of the samples were taken from the different geographical areas of Sweden and the Netherlands. At the same time, other type of collection was done from the 40 different locations of the world for a pilot study. Wide samples were from the Seagulls, Water geese, Ducks and from shorebirds but these were not the only species as the samples were collected from the 250 different species of birds for HPAI surveillance. Samples from the Greylag Goose, Eurasian Wigeon, Northern Shoveler, Northern Pintail, Common Teal, Black-headed Gull, Mallard, Common Guillemot and Greater White Goose were seen positive. Overall positive surveillance ratio for the HPAI virus was 2.1% in wild birds, but it is noted that it may rise to 60% in the specific geographical areas or the stay points of the wild birds in specific months (Fouchier et al. 2005).

In a study conducted on Northern Pintails (usually takes a fly route between Asia and Northern-areas of America, and it is evident it has shown higher Asian HPAI lineages frequency in areas of Alaska) very little evidence of Asian lineage parts was seen even the study was performed on their areas of breeding (Keawcharoen et al. 2008). It is seen that the genetic base studies done on the Low Pathogenic type of Avian Influenza can be useful for the decision-making in the area wise study or specie-related spread of the Highly Pathogenic type of Avian Influenza. It can be understood that if a route of migration of wild birds or species isn't found to be the culprit for the spread of Avian Influenza of low pathogenic type, it will be very unlikely otherwise for the High Pathogenic type. The same if a species or the migration route seems to support the spread of LPAI, there will be higher Chances of HPAI spread from the same route or the same bird species. Very high chances of genetic re-assortment of two important genes (HA and NA) make it very hard to study the normal pattern. Therefore, the recommended way is complete genetic sequencing, which will open up the surveillance ways for the spread of HPAI pandemics as it will tell us the normal patterns of genetic re-assortment of the LPAI genes (Koehler et al. 2008).

7. GLOBAL IMPACT

The poultry industry as a major part, capturing the 20% share of total protein source in developing countries (Alders et al. 2014). In the recent past, due to the Highly Pathogenic type of Avian Influenza spread across the borders, the killing of millions of birds was practiced to limit the pandemic. Several control measures in Vietnam resulted in the culling and disposal of over 50 million poultry birds in the wake of the HPAI pandemic (McLeod et al. 2005). Economic downfall in the year 2005 estimated by the Food and Agriculture Agency were over billions of Dollars in the East side of the South Asia continent (McLeod et al. 2005). It is seen that these pandemics have great negative impact on both small and large-scale farmers, but small-scale farmers raising poultry in the domestic form in villages are affected greatly than the industrial scale. Industrial-scale farmers face temporary downfall in the form of asset losses or Market worth. The compensation scenario is different in developing and developed countries as many get more than their Market. On the contrary, countries like Cambodia provide no support for affected Farmers (Alders et al. 2014).

In recent past due to the influenza pandemics domestic poultry faced many crises, and the most affected element of the industry was lower-scale poor farmers (Porter 2012). In developing countries

like Vietnam, total losses to the poultry industry, especially to small-scale farmers, were over a hundred Dollars. Production was also hampered for an average of 2-3 months due to the HPAI pandemic in those areas where per-day earning is less than the USA \$2 (McLeod et al. 2005). Stunted growth is a major setback in children seen in those areas of Egypt affected by HPAI pandemics. In many countries, small-scale flocks of poultry are reared by women, and they are impacted by these losses (Bagnol2012). In Turkey, it was noted that due to widespread cases of HPAI, culling practices in small-scale village areas rearing domestic poultry resulted in a lower number of school enrolment for girls (Alders et al. 2014).

8. PREVENTION

Highly Pathogenic avian influenza is reported to spread across borders of Europe to Asia. Due to this widespread circulation, it is necessary to understand the mechanism of its propagation in the form of a pandemic across Eurasia. During their flight from Europe to Asia, many birds gather at different stay points, making these geographic regions hot points (Lee, et al., 2015).

Different management strategies by the agencies dealing in hot areas of migratory birds are necessary to obtain the development and application of action protocols to limit the widespread HPAI outbreak. Managers of these agencies should be well aware of the migratory patterns and the stay behavior of wild birds. They should keep a close eye on the type and number of mortality or morbidity during the migration in order to get prepared for any alarming situation. They should maintain proper surveillance of the health of these birds on a territorial or provincial level (Lee et al. 2017).

A second possible step towards determining whether and how to develop and apply management actions to mitigate damages incurred through the dissemination of HPAI via wild birds is to be prepared. Preparations include numerous elements such as coordination and communication within a management organization and with external agricultural and public health agency partners, consideration of the appropriate use of personal protective equipment (PPE) during outbreak events, determining whether and how to document the geographic extent of HPAI outbreaks in wild birds, evaluation of management options to mitigate the dissemination or effects of HPAI viruses, and elevating situational awareness as determined to be appropriate (Lee et al. 2017).

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