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A comprehensive review of the zoonotic potential of avian influenza viruses: a globally circulating threat to pandemic influenza in human

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Abstract

Avian influenza viruses represent a significant zoonotic threat, capable of infecting a variety of avian, animal, and human species. Over recent decades, numerous human epidemic and pandemic flu outbreaks have occurred due to zoonotic avian influenza viruses worldwide. Avian influenza viruses can be transmitted from birds to humans, both directly and indirectly. Waterfowl and domestic birds serve as reservoir hosts for all subtypes of influenza viruses. Pigs and some bird species, like quail, act as mixing vessels, facilitating viral reassortment. Farmers, meat processing workers, and poultry veterinarians are at significant risk of influenza infection due to their frequent contact with ill animals and contaminated environments. As a result, using vaccines and administering efficient antiviral drugs to sick poultry are critical steps for preventing the emergence of future influenza viral pandemics. This review endeavors to furnish a comprehensive exploration of the avian influenza virus and the urgent need for proactive preventive measures.

Introduction

Avian influenza viruses (AIVs), commonly known as bird flu, are a group of viruses that infect domestic poultry, humans, and various animals. These viruses primarily infect birds but have been isolated from a variety of hosts, including humans, horses, pigs, birds, and sea mammals (1). Some strains of AIVs have significant public health importance and can infect humans. All AIV subtypes naturally occur in wild aquatic birds. Wild birds can spread the virus to pigs, people, and domestic fowl through their feces without any clinical symptoms (2). Several variables, like the virus's pathogenicity, virulence, and serotype, as

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well as the age and immunological status of the birds, might affect the severity of clinical symptoms and death rate in poultry (3). AIVs divide into several subtypes based on the variety of two of their surface envelope glycoproteins (hemagglutinin and neuraminidase) that are characterized as HxNy (4). AIVs are divided into two main categories, including highly pathogenic avian influenza (HPAI) and low pathogenic avian influenza (LPAI) viruses. Some LPAI and HPAI viruses are zoonotic agents and cause a wide variety of symptoms in humans, from mild to severe respiratory distress and even death (5). Some AVIs are not infectious to humans, but viruses change genetically, leading to reassortants or hybrid viruses with infectivity for humans (5). Understanding the transmission dynamics, virulence factors, and potential for human infection of avian influenza viruses is crucial for effective surveillance, prevention, and control measures. This review will delve into the characteristics of avian influenza viruses, their zoonotic potential, and their implications for global health.

Influenza virus classification

Influenza viruses belong to the Orthomyxoviridae family with a single-stranded, eight-segmented RNA and negative sense genome. These viruses are divided into 4 types (A, B, C, and D) based on their antigenic properties (6). Influenza A viruses can infect a wide range of hosts, such as humans, birds, horses, pigs, and other animals (7). Influenza B viruses primarily infect humans, but influenza C viruses may infect both people and pigs (2, 8). A new genus of orthomyxoviruses has been discovered recently, named influenza D viruses which are primarily found in cattle and are not known to infect humans. The classification of influenza viruses is important for surveillance, vaccine development, and understanding the potential for outbreaks and pandemics. It allows researchers and public health officials to monitor the circulation of different strains, assess their antigenic properties, and make informed decisions regarding vaccination strategies and pandemic preparedness (7).

Influenza A virus encodes at least eleven proteins, including hemagglutinin (HA), neuraminidase (NA), matrix proteins (M2 and M1), nonstructural proteins (NS1 and NS2), nucleocapsid, and the three polymerases (including the polymerase basic 1 (PB1), polymerase basic 1 (PB2), and polymerase acidic (PA) proteins) (9, 10). Influenza A viruses are further classified based on the combinations of two surface glycoproteins, including HA and NA. The current categorization method divides avian influenza viruses based on 18 hemagglutinin (H1-H16) and H11 neuraminidase (N1-N9), resulting in various subtypes (144 subtypes) (e.g., H1N1, H3N2, H5N1). H17-18 and N10-11 are novel strains found in bat species (9) (Table 1).

AIVs are members of the genus Influenza virus A, which inflict significant economic damage on the poultry industry (11, 12). The severity of AIV influenza infection in birds varies from completely asymptomatic to almost fatal, depending on the virus virulence and pathogenicity, as well as host type and susceptibility (2, 13). AIVs are divided into two groups based on their pathogenicity to chickens: highly pathogenic avian influenza (HPAI) viruses and low pathogenic avian influenza (LPAI) viruses (12). In poultry, LPAI produces mild to moderate clinical signs, and HPAI (H5 and H7) virus infections can induce sickness affecting many organs, resulting in severe disease with mortality rates of up to 90% to 100% within 48 hours (11, 13). However, only some avian influenza A (H5 and H7) viruses are classified as HPAI viruses with severe infectivity. Both the LPAI and HPAI viruses can be zoonotic pathogens (14).

Epidemiology of human infection with AIVs

The history of human infections with AIVs has been an evolving field for several decades (Table 2). Human infection with AIV has been identified commonly as sporadic outbreaks with occasional instances of human-to-human transmission (15). Every year, more than 2,000 ill people are referred

to clinics in the United States just because of influenza viruses, and about 36,000 people die as a result of influenza (9). Some LPAI viruses (such as H7N2, H7N3, H9N2, H7N9, H6N1, H10N7, and H10N8) and some HPAI viruses (such as H5N1, H5N6, H7N7, H7N3, and H7N9) are categorized as zoonotic agents (14, 16). In most of the world, the most common AIV subtypes that cause respiratory symptoms in humans are LPAI H9N2 and HPAI H5N1 (17, 18). It has been proven that H9N2 and H5N1 AIVs occur infrequently in both unvaccinated and vaccinated poultry farms and can be transmitted directly from birds to humans (12). H9N2 and H5Ny AIVs are the two most common circulating subtypes in poultry farms and live-poultry markets (LPMs), while H7N9 and H10N8 viruses are circulating mostly in LPMs. Therefore, H9 and H5 were mostly transmitted from poultry farms to humans, but H7 and H10 are mostly transmitted from birds in LPMs to humans (19). It has been stated that H10N7 AIVs were responsible for mild human infections in Egypt and Australia (20).

The following are some events in the timeline of human infection with AIVs (Table 2):

1. 1957-1958:

The Asian Flu Pandemic (H2N2) in 1965 originated from a reassortment virus from an avian influenza virus with human influenza viruses, resulting in a novel H2N2 subtype. This pandemic caused a globally widespread illness, leading to approximately 1 to 2 million deaths (21).

2. 1968-1969:

The Hong Kong Flu Pandemic (H3N2) emerged in 1968 from another reassortment agent from avian and human influenza viruses. This led to worldwide morbidity and mortality, particularly among older adults (22).

3. 1994-1999:

At this time, it has been the first documented human infection with AIVs. Human infections with H9N2 and H5N1 occurred in Guangdong Province, China, in 1994 and 1996, respectively. Another H5N1 outbreak in Hong Kong in 1997 resulted in six confirmed human cases, with one-third of patients succumbing to the infection. As a result, millions of poultry were culled to control the spread of the virus in these outbreaks (16, 17). In 1997, human infections with H5N1 caused severe pneumonia and respiratory distress syndrome in Hong Kong. In March 1999, AIV subtype H9N2 was identified from the nasopharyngeal swab of two children in London for the first time (10, 16).

4. 2003-2004:

The third human case of H5N1 in Hong Kong was discovered in 2003. H5N1 avian influenza spread in Asia, leading to global outbreaks in 12 countries in poultry and sporadic human cases. The H5N1 virus exhibited high virulence in both birds and humans, with a mortality rate exceeding 50% among reported cases. Avian influenza H9N2 subtypes were identified in 338 poultry workers in India in 2003 (16).

5. 2000 -2010:

Novel H5N1, H5N2, H5N6, and H5N8 HPAI viruses were detected in human infections from 2000 until 2010. H5N6 and H5N8 AIVs were isolated from domestic waterfowl during various years, and H5N6 led to several outbreaks in poultry (23). Therefore, it can be suggested that both waterfowl and chickens are serious hosts for AIV transmission to humans. H5N1 and H5N2 variants are also detected in chickens and waterfowl (17).

6. 2013-2015:

Human infection with a novel avian influenza A (H7N9) virus first appeared in March 2013 in China and was subsequently isolated from an infected human in April 2015. H9N9 was isolated from live poultry markets, causing severe respiratory illness in humans, primarily in eastern China (16). In December 2013, a novel H10N8 LPAIV was documented in China, causing three human infections and two deaths (18). H7N9 and H10N8 LPAI viruses cause mild infection in poultry, but these viruses can lead to severe disease in humans (19). H5N2 played a serious role in the influenza outbreak among chickens in China in 2013, and it is currently a serious problem in the United States

(24). In 2014, several new outbreaks of AIVs killed people in Asia, Vietnam, and Cambodia (25).

7. 2016-2019:

In 2016, the first report of human infections with the H5N8 avian influenza virus was documented in Russia and associated with close contact with infected poultry, leading to mild illness. In 2019, human infections with highly pathogenic H5N1 AIVs were confirmed in 861 cases in 17 countries, resulting in 455 deaths (25) (Table 2).

The severity of infection in humans ranges from mild conjunctivitis to severe influenza-like symptoms, acute respiratory distress syndrome, pneumonia, and encephalitis. Previously, epidemics of the H7N9, H7N7, and H7N3 viruses were observed in a variety of human populations. Although H10 infection is uncommon, human infections with the H10 subtype have been documented in several parts of the world (23, 26). While human-to-human transmission remains limited, ongoing surveillance, research, and preparedness efforts are crucial for mitigating the risk of future outbreaks and pandemics (27). Most of the influenza pandemic in humans with AIVs has been caused by the H7N9 and H5N1 subtypes. Human H5N1 infections have mainly affected young adults, whereas human H7N9 infections have mainly occurred in people older than 60 years of age. The sex ratio of human infections with the H5N1 virus is balanced, but H7N9 AIVs have infected more males than females with a ratio of 2:1 (28).

AIV transmission to human

Humans are infected with AIVs via direct or indirect contact with infected birds or their contaminated environments, like poultry farms and LPMs. Most cases of avian influenza in humans result from exposure to infected birds (2). However, human-to-human transmission has occurred in limited instances (27, 29). Subtypes H5, H7, and H9 were transferred to humans as a result of repeated outbreaks in poultry. H5N1 and H7N9 subtypes have been associated with severe illness and mortality in humans following close contact with infected poultry (30, 31).

Many variables including environmental, viral, and host factors influence AIV transmission from one host to another (32). Several investigations have revealed that crucial elements in virus transmission across hosts are viral surface glycoproteins (especially HA) and their interactions with sialic acid (SA) receptors on host epithelial cells. AIVs must attach to SA receptors on respiratory epithelial cells for cause infection (33). Starting the influenza virus replication cycle in the body depends on the HA surface glycoprotein attaching itself to SA receptors on the surface of susceptible host cells.

Different HA subtypes have different kinds of amino acids in their receptor-binding site of HA glycoprotein (10, 34). Human H1 and H3 virus HA proteins often attach to terminals α-2,6-SA on ciliated cells in the upper respiratory tract (URT). Found on epithelial cells in avian intestines and humans' lower respiratory tracts, AIVS mostly binds to α-2,3-SA (35). Pigs contain α-2,3-SA and α-2,6-SA receptors in their trachea, making them a mixing vessel for the reassortment of human and avian viruses, leading to pandemics (34).

Ducks play a crucial role in the transitory transfer of avian influenza viruses from waterfowl to domestic poultry (36). Given the restricted number of α2.3-SA receptors in human URT, as previously mentioned, AIVs cannot infect humans without adaptation (35). Preferential binding to α2.6-SA can lead to cross-species transmission of human and animal viruses (37). AIVs such as H9N2, H5N1, and H7N9 can bind to both α2.6-SA and α2.3-SA, leading to human infection. Chickens or quail also contain a mix of α2.3-SA and α2.6-SA in the respiratory and intestinal epithelial cells. This can play a significant role in host adaptation to zoonotic influenza viruses (38).

Pigs and wild aquatic birds are the two most common intermediate hosts for AIV reassortment and transmission to humans (39). Although AIV transmission from birds to humans is limited, it is critical to pay attention to this infection for several

reasons, including the unprecedented outbreak, economic impact, expanded range of hosts, market implications, potential for new and dangerous variants, and cross-species transmission. As a result, monitoring and treating AIV infection in poultry is critical to reducing continuing threats to both animal and human health (40).

Routes of influenza virus shedding in birds

AIVs are excreted from a bird's body in a variety of ways, including through feces, and nasal and oral secretions (41). The virus transmission due to nasal and oral secretions is faster than feces (34). Contaminated water and the living environment of birds are common ways for virus transmission among aquatic birds. Aquatic birds act as asymptomatic repositories for LPAI viruses, releasing only viruses into the ecosystem (34).

Pathogenicity of influenza viruses in human

Cleavage of the HA protein is required for the AIVs entrance to cells, pathogenicity, and infection (42). HA is essential in determining host tropism due to its attachment to the terminal α-2,6-linked or α-2,3-linked SA receptor (43). On the other hand, the neuraminidase activity of the NA protein contributes significantly to the destruction of host receptors and virus release from the host cell (44). HA subtypes are classified into two categories based on their structural traits and antigenic features (32). Group 1 includes both human seasonal H1N1 strains and HPAI H5N1 viruses. Group 2 consists of the H3 and H7 branches, which include human H3N2 strains and HPAI H7N7 strains in humans (41).

Amino acid modifications in the HA and NA genes induce antigenic drift, producing a new strain of influenza virus (39). These changes largely overcome existing protection in humans, and the novel strains generate seasonal influenza outbreaks. Further variations in HA subtypes follow from antigenic shifts linked to the advent of pandemic viruses. As a result, HA plays a crucial role in both the influenza virus's life cycle and the changes in its genotypes, making it a key component in determining host vulnerability and pathogenicity (34).

The clinical symptoms of AIV infection in humans vary depending on the virus subtype. Different subtypes of the avian influenza virus can induce single human infections with a variety of clinical symptoms, including conjunctivitis (by H7N2, H7N3, H7N7, and H10N7), moderate respiratory illness (by H9N2, H7N2, H7N3, H7N7, and H10N7), and mortality (by H5N1 and H7N9) (45). Important elements in HPAI H5N1 pathogenesis in severe patients include influenza-related lymphopenia and a reduction in perforin activity in cytotoxic T cells (46). AIV infection in humans normally has a 7-day or shorter incubation period, with an average of 2–5 days (47).

H7N2, H7N3, H9N2, H7N9, and H7N7 subtypes only produce asymptomatic or moderate symptoms in humans, such as conjunctivitis or simple influenza-like disease (e.g., fever and cough) (5). AIV-infected individuals may have headaches, muscular discomfort, and respiratory symptoms such as runny noses, sore throats, and, less occasionally, bleeding gums or conjunctivitis. HPAI H5N1 infects a variety of organs in humans, including the lung, central nervous system (CNS), and digestive system (46). The infected patients' lungs showed diffuse alveolar damage, hemorrhage, hyaline membrane development, lymphocytic infiltration, and fibroblasts (48, 49). In addition to the lung, postmortem findings in deceased patients include myocyte degeneration and edemas in the heart, acute tubular necrosis in the kidney, hepatic central lobular necrosis, cerebral involvement, and disseminated intravascular coagulation (50). Viruses are shed by a variety of means, including respiratory secretions, plasma, cerebrospinal fluid, tissues, and feces (51).

Previous studies have shown that HPAI H5N1 can enter the CNS via the olfactory nerve, resulting in severe meningoencephalitis in humans. CNS involvement and neurological symptoms are important variables in distinguishing AIV infection

from seasonal influenza virus infections in humans (51). In some diseased individuals, HPAI H5N1 infection results in acute respiratory distress syndrome (ARDS), renal failure, pulmonary hemorrhage, pneumothorax, and pancytopenia, followed by hospitalization.

Populations at risk of avian influenza

People who are in contact with infected birds, poultry farms, and processing factory facilities are more at risk of contracting avian influenza infection. Farmers, meat processing workers, and veterinarians are the most at risk for avian influenza viruses (20, 52, 53). Traveling to AIV-infected areas increases the risk of human infection. Farmers, Meat processing workers, and veterinarians also showed higher seropositivity rates for the swine H1N1, H1N2 H3N2 subtypes (19, 54). The elderly have greater levels of antibodies against two swine H1N1 influenza viruses (55).

Influenza virus diagnostic tools

A precise identification of H5N1 infection is crucial for lowering human morbidity and mitigating the risk of a pandemic. The Centers for Disease Control and Prevention (CDC) have offered recommendations on when to do H5N1 virus diagnostic tests on humans (56). Throat swabs, respiratory tissues, rectal swabs, and serum are more common diagnostic samples for influenza infection. However, a combined nasopharyngeal and throat swabs from the same patient is an ideal specimen (57). Rectal swabs and respiratory specimens can identify the H5N1 virus in sick people, but rectal swabs are less sensitive than respiratory specimens (58). Based on some research, viral shedding from fluids and tissues could occur for up to 6 or 7 days. In some studies, viruses have been detected in infected people up to 10 days after the beginning of the disease (59). Molecular methods such as reverse transcription polymerase chain reaction (RT-PCR) and real-time RT-PCR are used for influenza virus diagnosis. Molecular approaches also are important in molecular epidemiology (60).

Another way of detecting AIV infection and epidemiological investigations is the identification of AIV-specific antibodies in collected serum samples. Serological tests like hemagglutination inhibition and enzyme-linked immunosorbent assay are subtype-specific tests (32). Virus isolation in eggs is widely regarded as the gold standard for virus proliferation and detection. In addition, viral isolation in cell culture allows for extremely precise laboratory detection of the virus. Madin-Darby canine kidney (MDCK) cells are the most common cell line utilized to isolate and proliferate human influenza viruses. It should be mentioned that this approach has much higher sensitivity than antigen detection methods (61).

Antigen detection techniques are another approach for detecting the infection. The detection of antigens has a sensitivity of 50–80% and a specificity of 90%. H5N1 antigen can be determined via immunofluorescence approaches (direct and indirect) on collected samples. The reliability of antigenic tests may be influenced by a variety of factors, including specimen type, specimen quality, and specimen collection time (62).

More recently, new approaches have been employed for identifying the influenza virus. The advantages of the new methods compared to the old methods included simplicity, high speed of use, low cost, and high specificity, making them ideal. These approaches include the following: loop-mediated isothermal amplification-based assay (LAMP) (63); reverse transcription loop-mediated isothermal amplification (RT-LAMP); simple amplification-based assay (SAMBA); nucleic acid sequencing-based assay (NASBA); molecular integration with nanotechnology; biosensor development; microchip approaches; and next-generation sequencing (NGS)-based assays (56).

Preventive and therapeutic strategies

Influenza vaccination has been established to promote healthcare worker immunization rates, and it would be a novel approach to public health strategies (56). Vaccination is crucial because antigenic drifting occurs in AIVs, allowing the virus to evade the prior immune response (41). Many efforts have been made to develop a vaccine that protects hosts from all subtypes of avian influenza viruses, known as the universal influenza vaccine, however, this vaccine has yet to be developed. However, if this vaccine is developed in the future, a successful occurrence will avoid the AIV pandemic. A variety of safe and effective medications can be used to treat human and avian influenza infections (64). Some medications, such as M2, neuraminidase, polymerase, and signal-transduction inhibitors like ribavirin, arbidol, and herbs, are used for influenza infection treatment. Several neuraminidase and M2 inhibitors have been authorized for influenza prevention and therapy (65).

M2 inhibitors drugs, such as amantadine and rimantidine, prevent influenza A virus replication by blocking the viral M2 protein ion channel as well as the release of nucleic acid from the infectious virus into host cells, reducing the influenza virus's ability to infect. They have been routinely used for many years to treat both human and avian influenza infections (64).

Neuraminidase inhibitor drugs like zanamavir, oseltamivir, peramivir, and laninamivir inhibit the action of neuraminidase, which blocks the release of progeny virus particles from infected cells, preventing virus spread to other cells. RNA polymerase inhibitor medicines block polymerase activity, reducing AIV replication and inhibiting the virus's pathogenicity. Fluorodeoxycytidine analogs and favipiravir (T705) are two polymerase inhibitors that have been demonstrated to be effective in the treatment of influenza in vitro and in vivo (66).

In general, the protective effectiveness of medications is determined by the severity of the strains, the therapeutic dose, and the timing of treatment initiation (67). The main drugs used to treat influenza are oral oseltamivir and inhaled zanamivir. Two candidates, such as inavir and favipiravir, showed positive effects on treating avian influenza viruses (64). Ribavirin's clinical efficacy against influenza was lower than that of adamantanes or NA inhibitors, and it depended on the administration method (65). In clinical investigations, aerosolized ribavirin effectively eliminated the influenza virus and shortened illness duration, although orally administered ribavirin did not (34, 65).

Prevention strategies include practicing good hygiene, such as hand washing and avoiding close contact with sick birds, as well as vaccination of poultry in endemic areas. Rapid development and distribution of vaccines targeted against emerging AIV strains are also critical for pandemic preparedness (57).

In summary, while human infections with AIVs are relatively rare, they pose a significant public health threat due to their potential for severe illness and limited capacity for human-to-human transmission. Continued surveillance, research, and preparedness efforts are essential for mitigating the risk of future outbreaks or pandemics (46).

Conclusion and future trends

AIVs have a significant role in public health. AIV infections affect a variety of populations, including poultry farmers, meat processing workers, veterinarians, and anyone who comes into contact with wild and domestic birds. AIVs are always a threat to the health of society, and their control is critical. AIV virus mutations may occur at any time, resulting in a new pandemic of viruses that can take place worldwide at any time. Hence, focusing on prevention, using innovative immunization techniques, and developing new drugs are vital to maintaining a healthy society.

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Ethical approval

Not applicable.

Conflict of Interests

There is no conflict of interest.

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