Bird Migration and Avian Influenza Transmission: Mechanism, Prevention, and Control

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Abstract. Migratory birds have extensive global migration routes and play a crucial role in the intercontinental and cross-species spread of avian influenza virus (AIV). They cause the spread of infection of H3N8, H5N1, and H9N2 in humans worldwide, posing a significant threat to public health. This review explores the transmission pattern by examining the migratory routes of birds and the mechanisms by which viruses are transmitted between birds and mammals. It then delves into the review to elaborate on the infection mechanism that includes the binding of HA and sialic acid on host cells and the mutation strategies of the virus. The research also analyzes limitations of recent prevention and treatment methods, such as defects of inactive vaccines and Oseltamivir. In conclusion, the review proposes future directions, including developing broad-spectrum and T-cell inducible vaccines, exploring the pharmaceutical use value of plant extracts, aiming to provide a basis for establishing precise prevention and control strategies and treating birds and mammals efficiently to safeguard human and ecosystem health.

Keywords: Migratory Birds; AIV; Limitation; Future Prevention and Control System.

1. Introduction

Migratory birds have a broad distribution range, crucial in spreading infectious diseases. There are nine global migratory routes, four crossing China's airspace. Many migratory birds travel back and forth along a fixed path each year. Their long and widespread routes make them the main culprit in the intercontinental spread of the avian influenza virus during specific periods. According to a report released by the World Health Organization, three cases of H3N8 virus infection in China have been reported. The pathologies of H5N1, H9N2, and other viruses infecting humans have also been detected in Asia, Europe, and many other places. This means the natural process of avian influenza spreading by migratory birds poses a potential threat to global public health.

To develop more precise and effective warning, prevention, and treatment systems and solve this essential scientific proposition, it is necessary to sort out the transmission patterns of avian influenza, pathogen infection mechanisms, and deficiencies of existing prevention and care methods. This review begins with migratory birds' migration routes and then summarizes the transmission pattern among birds and from birds to other species, such as mammals. Second, it explains how the mechanism of influenza virus infection of host cells works through binding hemagglutinin with different sialic acids on the surface of the cell membrane, then continuously evolving and mutating to form new strains. By analyzing these two mechanisms and summarizing the defects of existing methods, such as the inactive vaccine's long production period, we can develop new techniques to establish a complete detection and prevention system.

2. Virus Transmission through Bird Migration

2.1 Virus Transmission Through Birds

Anseriformes, such as swans, and Charadriiformes, such as common teals, are major virus carriers. During migration, they release LPAIV efficiently with no clinical symptoms via respiratory particulate matter and feces[2][3]. Anseriformes serve as the natural hosts of all known avian influenza virus subtypes. Given the long-term integration of LPAUVs within the genetic composition of these bird species, the virus exerts minimal influence on its avian hosts. It is capable of prolonged

survival within the host organism, facilitating its transmission and propagation. These birds will congregate along migration routes so the virus can widely spread among different individuals or groups by aerosol droplets, indirect contact via contaminated water sources and formites, direct contact, and vector organisms, including mosquitoes. In 2014 to 2015, highly pathogenic avian influenza H5N8 spread to Europe and North America through East Asia migration routes, but this virus originated in Asia. This is the first record of HPAIV spreading intercontinentally in human history [4]. Then in 2016, humans detected that HPAIV was introduced to Europe again by different routes[5]. And the American lineage's PB1 and PB2 gene segments have been identified in the viruses carried by Chinese migratory birds. During the migration, birds temporarily enter valleys and urban areas for a short time; consequently, the virus can infect poultry and livestock through these pathways, resulting in various outcomes.

2.2 Transmission Between Birds and Mammals

On January 1, 2025, the Louisiana Department of Health, USA, reported the first case associated with the highly pathogenic avian influenza H5N1. The local department of health recognizes that they have detected the D1.1 avian flu virus in a group of cows, and the direct transmission between these cattle and humans resulted in the human infection. In China, the country with the highest number of H9N2 infection cases, researchers found that people who have been to places with a high density of poultry, work in the related sector, or explore the poultry's live environment were most affected by most of the H9N2 infection cases[6]. Moreover, viruses typically require an intermediate step of infecting poultry and livestock before they are transmitted to humans, as people's contact with wild birds is infrequent.

3. AIV Binding Mechanism

3.1 Compatibility of Avian Influenza Virus

The primary infection mechanism of avian influenza virus (AIV) involves binding hemagglutinin (HA) on the viral surface to sialic acid residues on the host cell's surface, which mammal and bird cells have. Upon entry into the host respiratory system via contaminated water or food, the virus binds to receptors containing α-2,3-linked sialic acid [7]. After that, the virus will enter host cells through endocytosis. The human lower respiratory tract and avian intestinal epithelial cells secrete this compound, rendering birds and mammals (including humans) susceptible to AIV" (the human lower respiratory tract. After the virus successfully enters host cells, it will be wrapped by the endoplasmic reticulum. Endosomes are made by Endocytosis, which is mediated by clathrin, and have a pH of around 6.0 to 6.5. This acidic environment will change the HA protein's structure, causing the exposure of the viral fusion peptide [8]. Viral fusion peptide will finally contribute to the envelope between the fusion of the virus and the endosome membrane and help the virus release RNA to host cells, which contain RNA polymers and will form new RNA and mRNA, which can form virus protein by utilizing the nucleotides of the host cells[8]. Once viral replication reaches a critical threshold, the virus either lyses the host cell or exits via budding from the cell membrane to infect other cells. Notably, the biological basis for AIV to achieve cross-species infection lies in its binding to α-2,3-linked sialic acid. At the same time, the conserved replication mechanism ensures the successful completion of its life cycle across multiple species.

3.2 Viral Mutation and Pathogenicity

The core of a virus that produces enormous stress in humans is mutation. Viruses can adapt to the new host environment through ingenious mutation and reassortment and geometrically increase their pathogenicity and transmissibility. For example, to adapt to mammal cells like human cells, AIV will undergo mutation during the self-replication process once it infects humans accidentally. The K356R mutation in the viral polymerase acidic protein (PA) is common in China [6]. When this mutation acts in conjunction with the E627K mutation in the polymerase basic protein 2, the activity of the

virus polymerase will be activated [9]. Besides enhancing activity, some viruses can increase the binding ability to α-2,6-sialic acid by mutations like Q234L and H191N on the HA protein. With this ability, the virus can lead to large-scale influenza. As an aside, the above mutations are all called adaptive mutations[8][10].

The other cunning and dangerous way is called gene reassortment. Suppose AIV and the human influenza virus infect the same host cell simultaneously. In that case, their gene may be communicated and reassorted during the replication process and form a new subtype of virus, like H7N9 AIV. This virus appears in Shanghai, China, and is generated through multiple reassortments between H7, N9, and H9N2 viruses. It has a high fatality rate[11]. Such continuous interspecies spread allows the virus to have toxic genes of AIV and the ability to bind simultaneously with α-2,6-sialic acid, like the human influenza virus. Furthermore, once viruses replicate successfully in the lungs, a highly intense immune response, which causes a cytokine storm, will be stimulated and cause multiple organ failure. This is why the highly pathogenic avian influenza virus (HPAIV) has a high fatality rate[12].

4. Recent Treatment Ways

4.1 Vaccine Prevention

Researchers utilize inactivated vaccines for prevention in China, where H7N9, H9N2, and H5N1 viruses are prevalent. These vaccines typically involve inactivating the virus ex vivo with ultraviolet radiation and chemical agents to reduce its pathogenicity while retaining its immunogenicity [13]. Such an inactive virus will simulate an immune response after entering the human body and prove that B cells differentiate into plasma and memory cells. The pathogen in inactivated vaccines has lost its toxicity and infectivity, thus they pose no infection risk and are suitable for a wide range of people[14]. These vaccines are relatively easy to store and transport and have a mature production process.

Recombinant vaccines represent another common type, but are typically administered to poultry. Its principal mechanism is introducing the gene of the target pathogen into a host cell, and the host cell will express a specific protein and be recognized by the host immune system to simulate an immune response[15]. This type of vaccine also exhibits a high safety profile, as it contains no intact virus and thus cannot cause infection or other adverse effects, and with a versatile manufacturing technology that enables rapid adaptation or development of vaccines in response to sudden influenza outbreaks [16].

4.2 Therapeutic Treatment of AIV

Regarding human infection with AIV, such as H5N1, the World Health Organization suggests that people use Oseltamivir. This medicine blocks the release of viruses from host cells by inhibiting the activity of viral neuraminidase (NA)[17]. This medicine simulates the structure of the natural substrate of NA—sialic acid, which can gather viruses together or prevent viruses from departing from host cells, further restricting the spread of viruses in the host body. Researchers also claim that taking this medicine within 48 hours after being infected with AIV can reduce the fatality significantly.

5. Challenges and Limitations

5.1 Vaccine Prevention

Currently available vaccines for AIV prevention exhibit several limitations. For instance, inactivated vaccines have a lower immune response intensity than live attenuated vaccines, thus requiring repeated or regular booster vaccinations to achieve the desired efficacy. Furthermore, due to the continuous mutation and reassortment of AIV across different species and the long production period of a new vaccine, the update speed often lags behind the virus's mutation speed, which cannot

provide a good prevention effect[13]. This represents the most significant limitation of inactivated vaccines.

Recombinant vaccines face some different problems. Recombinant vaccines have a relatively high cost, need complex technology, and have high requirements for equipment. Compared to traditional vaccines like inactivated vaccines, recombinant vaccines are more in need of multiple vaccinations in certain situations because of their short immune protection period. In poultry immunization, large-scale delivery of recombinant vaccines poses a critical challenge, not to mention that some require additional adjuvants to enhance immune responses [18].

5.2 Therapeutic Treatment of AIV

Although Oseltamivir can inhibit the release of the virus, taking it after two days will cause the treatment effects to decline and may cause symptoms like vomiting and nausea[19]. At the same time, this medicine only acts on NA, so it can't prevent the entire virus replication process. After treatment with this medicine, H7N9 viruses might undergo an R292K mutation in NA and develop drug resistance [20].

This medicine can be used directly on poultry in some situations, such as in an experiment, but it is expensive and unsuitable for large-scale treatment. Moreover, oseltamivir-resistant H5N1 viruses have been detected in poultry [21]. Some substitute medicines like baloxavir, which inhibit viral polymerase 5'cap-dependent endonuclease to restrain the virus, can significantly inhibit the replication and survival of the virus if there is enough dosage. Still, the therapeutic consequences will also decline if medication is delayed.

6. Future Directions

6.1 Developing New Vaccines

The development of broad-spectrum vaccines can address the limitations of inactivated vaccines, such as their inability to keep pace with viral mutation rates and the need for repeated vaccinations. The high cost and need for recombinant vaccine adjuvant can also be solved. Broad-spectrum vaccines can protect against many different subtypes of viruses simultaneously, which means if the virus mutates, the prevention effects of the vaccines will not be reduced. People do not need to reproduce new vaccines [22]. This character is based on the design methods used in the vaccines. Broad-spectrum protection of the host cell records to the conserved region of the virus, like HA stem, NA, etc., even if the head of HA mutates, vaccines still can act on the virus [22]. Right now, a broad-spectrum vaccine is a global research and development hotspot. Linking genes from different viruses to generate a vaccine containing a chimeric antigen—capable of inducing immune responses against various viral types—can reduce costs associated with large-scale vaccination of poultry or mammals. Except for this kind of broad-spectrum vaccine, a T cell-inducible vaccine is also a technical route. This vaccine targets T cells, which have a stronger ability to clean infected cells and have more extended immune memory [22]. T cells can deliver the conserved proteins efficiently and have been proven to significantly reduce the replication ability of H5N1 and H7N9[23].

6.2 Plant Extracts for Pharmaceutical Purposes

Plant extracts come in a wide variety of types and components. Based on this high biocompatibility and the trait of low likelihood to cause adverse effects, they show special advantages in the treatment of avian influenza [24]. For example, in citrus extracts, naringin can interfere with the interaction between viral nucleoprotein and host cells, thereby inhibiting viral replication, hesperidin can regulate the inflammatory response to reduce the damage in the lungs [16,24], and the activity component of nobiletin can block the binding of the cell membrane and viral envelope. Furthermore, numerous other plants contain alkaloids, flavonoids, and other phytochemicals that are key in infection prevention. These secondary metabolites can reduce the activity of RNA polymerase of the virus and stop viruses from replicating themselves [25]. Although a large part of such medicine is still in the

experimental research stage and needs to be optimized, this green drug can break traditional medicine's limitations and play an essential role in future public health.

7. Conclusion

This review focuses on migratory birds, the transmission patterns of AIV, and related prevention and control strategies. Migratory birds are the primary carrier of the cross-regional and cross-species transmission of AIV. The spread pattern of viruses has a close relationship with the viruses' receptor binding, gene mutation, and reassortment. Current prevention approaches exhibit numerous limitations. After a system sort of spread pattern and inflection mechanism, this review aims to provide a scientific basis for formulating targeted prevention strategies. Furthermore, given that vaccines typically lag behind viral mutation rates and the misuse of antibiotics and therapeutic drugs readily induces drug resistance, future research can focus on designing and producing a broad-spectrum, T-cell-induced vaccine, explore the potential of plants extra, and safeguard the health of humans and the ecosystem by optimizing prevention and treatment strategies eventually.

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