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Review Article

Avian Influenza (H5N1): A Review on Pathogenesis, Transmission, and Control Measures

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Abstract:
H5N1 AI remains the primary cause of serious threats to international economies together with human health while maintaining its position as the most virulent variant of avian influenza. The viruses lead to critical poultry epidemics among domestic birds and they can transmit from birds to humans through zoonotic pathways. The viruses predominate in their natural habitat which consists of wild aquatic birds. The virus employs Hemagglutinin (HA) and Neuraminidase (NA) surface glycoproteins to carry out its infection and multiplication through multiple relationships with host cells. Direct contact with infected birds remains the usual mode of transmission and aside from this transmission route, occasional human-to-human transfer has occurred in minimal cases. Human infections with this virus lead to diverse symptoms ranging between mild flu symptoms to organ failure that ultimately cause fatal pneumonia despite the requirement for molecular testing and viral isolation to confirm diagnosis. Immediate treatment with antiviral drugs zanamivir and oseltamivir provides some therapeutic effect. Prevention methods against bird flu depend primarily on five approaches that combine biosecurity practices, bird vaccinations and the elimination of infected poultry stocks. Economic effects from avian influenza outbreaks result in major poultry sector losses and interruptions to international trading activities. The detection capabilities need improvement alongside readiness levels and additional research about improved vaccines and antiviral treatments stands vital because a pandemic could occur. Global institutions need to continue joint efforts for stopping the expansion of avian influenza and reducing its consequences.
Keywords: H5N1, Avian Influenza, Pathology, Pandemic

Introduction

The natural distribution of Avian influenza viruses (AIVs) can be found in wild aquatic birds that include ducks, geese, swans, gulls, shorebirds and terns. HPAIVs were discovered in Chinese geese during 1996 in Guangdong before they became known as AIVs of subtype H5N1. The small Guangdong village of Sanshui suffered multiple geese outbreaks in its farmed population resulting in excessive fatalities which reached 40 percent (1).

The influenza virus , which is one of the most deadly diseases or asymptomatic infections caused by viruses in the family Orthomyxo viridae, has a genome made up of eight segments of single-stranded negative-sense RNA. AI viruses are subtyped by their surface glycoproteins called Hemagglutinin (HA) and Neuraminidase (NA), which are important factors in determining the pathogenicity, transmission, and adaptation of the AI virus to other species; however, these three characteristics, along with infectiousness, are multi-genic (2).

Researchers discovered two novel HA and NA sub-types in bats thus leading to the total identification of 16 HA sub-types and 9 NA sub-types. HPAI strains fall under this category if they induce death rates above 75% or show IVPI values exceeding 1.2 among chickens tested during a 10-day period. Every strain that meets the HPAI criteria has shown itself to belong to H5 or H7 sub-types. The viruses can lead to restricted pathogenic effects but there are also potential pathogenic consequences (3).

Methodology:

Search strategy:

Data for this review are from publications identified through a systematic search in the Scopus (Elsevier) publication database and PubMed using the key words 'H7N9' during any time period. The search returned over 105 articles. Abstracts of the papers written in English were reviewed for relevance, followed by an examination of the papers referenced in this review. In addition, relevant government and international organization websites like World Health Organization (WHO).

Discussion:

Epidemiology of avian influenza:

Virus nature:

Bird flu represents a highly contagious viral infection which spreads between humans and animals together with poultry in every corner of the world. The majority of human influenza cases were due to viruses of types A and B whereas such infections only occurred in poultry populations through influenza type A. The bird influenza virus demonstrates multiple strains including low pathogenicity and high pathogenicity strains that are detected in farms throughout the world. The discovery of H5N1 virus as type HPAI happened in Chinese geese during 1996. Asian H5N1 appeared for human detection for the first time during Hong Kong's poultry epidemic of 1997. After its initial identification the disease spread across Africa, Asia, Europe, Middle East and was detected in all these regions among humans, poultry and wild birds. The presence of living cells very important for the spread of disease (4).

Replication of avian influenza virus:

The HA protein on the virion's surface identifies and attaches itself to sialic acid on the surface of host cells as it enters the cell. Following binding, receptor-mediated endocytosis allows the virus to enter the cell. Although the precise process of endocytosis is unknown, it has been hypothesized that influenza can enter cells through both clathrin-dependent and clathrin-independent routes.

It is during cellular endosome entry that pH levels start to decrease until the compartment becomes highly acidic. The acid environment triggers the influenza virus HA molecule to transform permanently while making its hydrophobic fusion peptide accessible for exposure. Without the endosomal membrane fusion peptide inserts causes viral membranes to unite with the endosomal boundary. When the M2 viral protein forms tetramers in virions it establishes M2 channel pores through its transmembrane domain.

Because influenza viruses require a cap sequence for RNA polymerase to perform transcription, they are among the few RNA viruses that can replicate in a host nucleus. The M2 protein acts as an ion channel that regulates the intra-virion pH and pumps free hydrogen atoms into the viral core, causing the vRNPs to dissociate from the M1 matrix proteins. This mechanism enables the inner contents of the viral core to be released into the cytoplasm and then enter the nucleus.

Following their dissociation from M1, vRNPs are translocated to the host nucleus, where transcription and viral replication take place. Because the RNA polymerase requires a cap sequence to perform transcription, influenza viruses are one of the few RNA viruses that can replicate in a host nucleus. To accomplish this, the PB1, PB2, and PA components "cap-snatch" host DNA, releasing cap-containing viral mRNA into the cytoplasm for translation by the host ribosome machinery. Surface proteins like HA and NA are translated into the rough endoplasmic reticulum, which is subsequently trans-located into the Golgi apparatus.

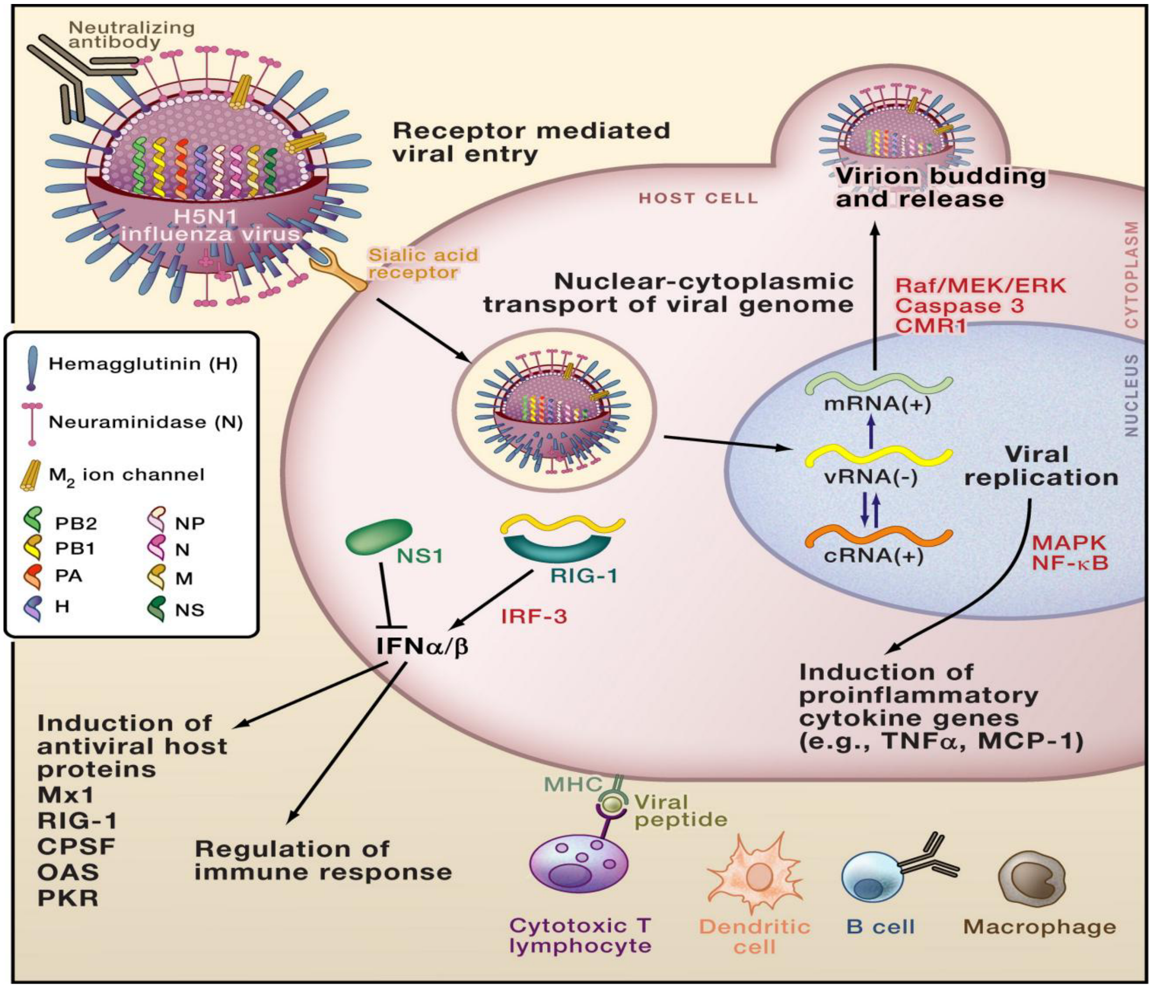

Fig 1: Pathology of H5N1

Transmission pathway:

All birds were domesticated (chicken, duck, and goose), and no transmission from birds in the wild (migrating) or contaminated waterways has been documented. In a few cases, limited human-to-human transmission has been reported among health care workers and family members; in each of these cases, no personal protective equipment was used. Epidemiological investigations of human cases of avian influenza reveal that the virus was acquired by direct contact with infected birds. Influenza A is spread through the fecal-oral and respiratory routes among wild birds and poultry (5).

Until recently, it seemed that the epidemiology of AI was the persistence of LPAI viruses of all H sub-types in wild birds, which occasionally transmitted to poultry but often caused little to no disease. On rare occasions, LPAI viruses of the H5 or H7 sub-type were introduced into poultry, which led to their mutation into virulent viruses that caused HPAI (6).

Transmission from infected poultry birds:

Direct contact with ill or asymptomatic infected poultry poses the greatest risk of human-to-avian influenza virus (AIV) transmission. The precise means of transmission are unclear, however they can happen by ingestion, inhalation, or contact with mucosal membranes. Handling contaminated chicken, going to live poultry markets, and eating raw poultry items like duck blood or raw eggs are all considered high-risk behaviors. Risks from contaminated surfaces or contact with intermediary hosts, such as pigs and cats, are also unknown. There have been no cases linked to eating properly prepared poultry (7).

Pathogenesis of avian influenza in humans:

The pathogenesis of avian influenza, which is caused by the H5N1 virus, is as follows: the virus enters the respiratory tract through inhalation of contaminated air or contact with infected secretions, attaches itself to epithelial cells in the respiratory system, and replicates, causing severe inflammation and damage to the respiratory, digestive, and nervous systems in birds; it can invade deeper lung tissue in humans, causing severe pneumonia and systemic inflammation; the host's immune response may exacerbate tissue damage, leading to complications like acute respiratory distress syndrome (ARDS); it can spread to other organs, causing multi-organ failure; severe cases may result in death, frequently as a result of secondary bacterial infections or complications (8).

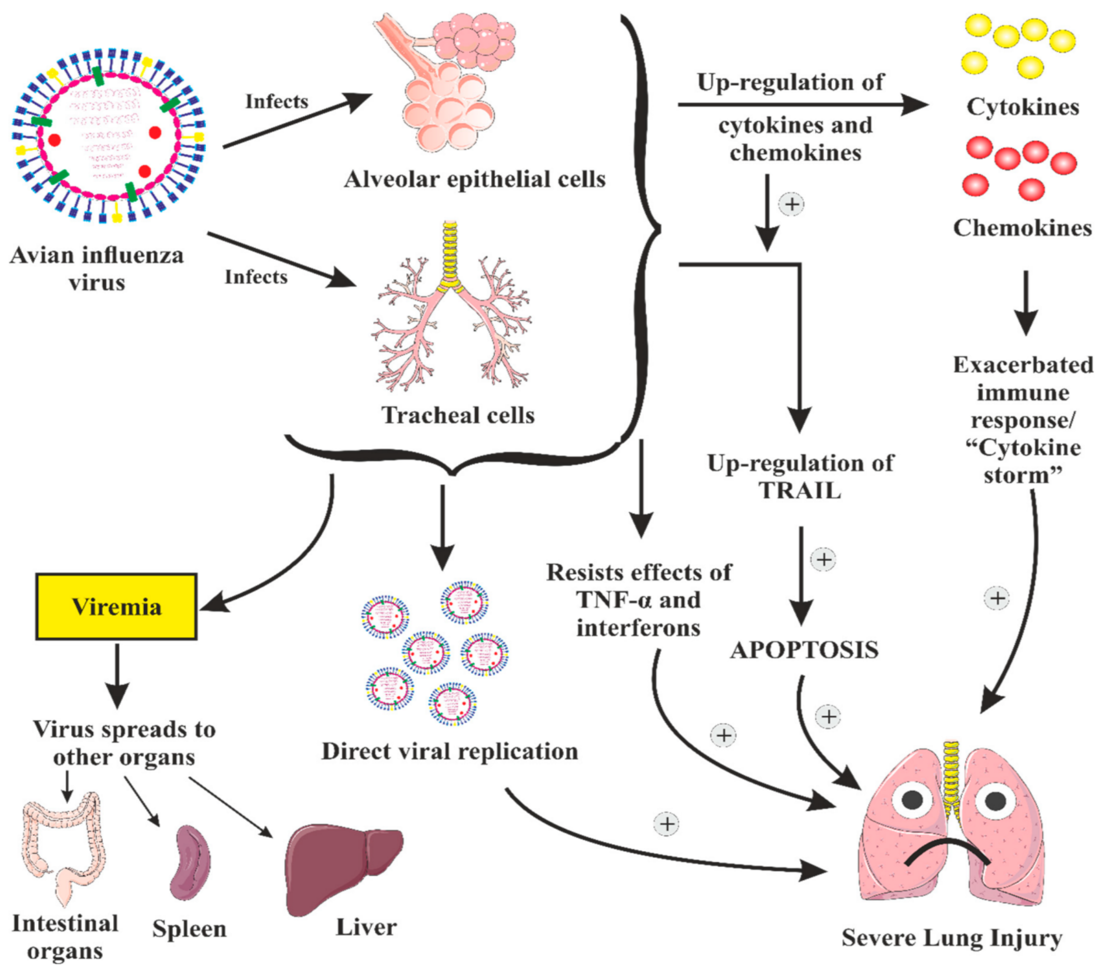

Fig 2:Transmission and Replication of H5N1

Clinical manifestations:

The incubation period for bird flu (avian influenza) ranges from 2 to 5 days but professionals identify a maximum possible duration of 17 days. People show symptoms of bird flu that can vary between light and extensive conditions. The early symptoms will initially appear similar to seasonal flu manifestations which include high temperature along with cough, sore throat and body pain and extreme lack of energy. Eye infections (conjunctivitis), nausea and vomiting together with diarrhea are possible health complications in certain patients. The condition quickly turns into pneumonia when infection progresses to acute respiratory distress syndrome (ARDS) which can result in multi-organ failure and lead to death. Neurological problems including seizures as well as altered mental status have developed in very few people. The illness becomes more serious based on three main elements including virus strain type and patient health status and prompt medical care. People who handle infected birds during their work or while killing or eating infected poultry products become the most vulnerable to infection. Severe cases of infection need early medical diagnosis combined with antiviral drugs for treating complications effectively along with preventing further medical deterioration (9).

Risk factors:

Environmental exposure combined with bird contaminations have raised the H5N1 avian influenza (AIV) risk levels at present in recreational beach areas. The increase in mass bird deaths with recent cases of sea lions requires heightened concern about human exposure to AIV particles that primarily spreads through bird feces and blood as well as mucus. The chance of contacting this virus by consuming water is minimal yet handling infected birds and their environments directly exposes you to substantial risks.

The prevention of infections from bird exposure requires people to keep away from sick animals and deceased specimens and to wear gloves when needed and maintain constant hand care practices. Complete investigations about deceased bird behavior warrant authorities to exercise care during handling procedures while banning beach access to the public. The extended beach surveillance procedures are important because AIV transmission rates remain lower than for poultry farms. Health risks to humans can be assessed through Quantitative Microbial Risk Assessment (QMRA) by studying viral elements together with environmental durability and transmission routes. Available data is insufficient to achieve accurate risk assessment at this present time (10).

Diagnosis and Treatment:

Clinical Diagnosis of Avian Influenza:

The diagnosis of avian influenza presents diagnostic challenges because no specific lesions can be detected during examinations. The virus often spreads through waterfowl without causing disease symptoms because these birds act as carriers. The virus remains present in carriers although they show no clinical indicators because they transmit the infection to various species. Various forms of pathological harm occur inside domestic poultry after virus infection based on the specific viral subtype.

Virus Isolation and Identification:

Medical experts use embryonated egg inoculation as the definitive method for detecting avian influenza virus infections. Highly pathogenic avian influenza viruses need 24 to 48 hours to incubate but low pathogenic avian influenza viruses take a maximum of 21 days. The introduction of the virus occurs mainly in the chorioallantoic sac but researchers sometimes utilize the yolk sac or chorioallantoic membrane for testing purposes.

Serologic Assays:

Poultry disease surveillance together with control programs use traditional serological methods such as agar-gel immunodiffusion and hemagglutination inhibition despite significant progress in direct detection using molecular techniques and antigen capture methods. Competitive ELISA (cELISA) functions as an additional method for selected applications to improve diagnostic precision.

Environmental Sampling:

Testing for Avian influenza (AI) virus requires samples from single birds while pooled specimens together with statistical approaches serve establishments through lower costs. Real-time RT-PCR used with environmental air samples represents a different surveillance method in commercial poultry facilities which provides an efficient non-invasive detection system (11).

Vaccine and anti-viral Treatment:

Antiviral medications successfully prevent the spread of flu virus throughout the body to treat bird flu infections. Medical professionals yield the best results with antiviral procedures if patients start their treatment immediately after the first signs of illness emerge. Medical professionals provide antiviral medications before flu test outcomes become available. The antiviral drugs Tamiflu (oseltamivir) along with Relenza (zanamivir) and Rapivab (peramivir) comprise three main antiviral medications.

Oseltamivir is administered orally, while zanamivir is inhaled using a device similar to an asthma inhaler, and peramivir is given intravenously. If diagnosed with bird flu, it is essential to isolate yourself from others, including household members, to prevent transmission. Avoiding contact with others while awaiting lab results is also recommended. If the infection is confirmed, healthcare providers may recommend testing for individuals who had close contact with you during your symptomatic period. Additionally, antiviral medication may be prescribed to those exposed to bird flu and at high risk of severe illness (12).

Drug resistance in the influenza:

Amantadine and rimantadine, two adamantanes, were first approved in 1966 and 1993, respectively, for the prevention and treatment of influenza A virus (IAV) infections. But beginning with the 1980 outbreak, medication resistance developed, and by 2005–2006, resistance rates had skyrocketed, particularly in the H3N2 subtype. The S31N mutation in the M2 protein was the primary cause of the resistance. Around 45% of IAV subtypes worldwide were resistant to adamantanes by 2013, with resistance being higher in some areas, such as Asia and the Americas.

In order to target the viral neuraminidase enzyme and stop the generation of new viral particles, neuroneuraminidase inhibitors (NAIs) such oseltamivir and zanamivir were developed. However, mutations in the active site of the NA enzyme, such as E119V, H274Y, and R292K, have also led to the development of resistance to NAIs. NAIs are still the principal treatment for IAV in spite of this, although managing resistance requires continued monitoring and the development of novel antivirals.(13)

Control and preventive measures:

Prevention of Avian Influenza:

Direct or indirect contact with infected birds is the main way that avian influenza (AI) viruses are introduced to domestic poultry. Since airborne transmission has not been proven, effective biosecurity measures at the farm level are crucial for preventing AI infections.

Vaccination for Avian Influenza:

Between 1999 and 2003, HPAI outbreaks caused over 50 million birds in the EU to die or be depopulated, resulting in significant economic losses. The preemptive slaughter of infected animals has raised ethical concerns, indicating that the current strategies and control measures for combating AI need to be improved.

Vaccination vs. Preemptive Culling:

AI epidemics can cause significant financial losses, especially in areas with high poultry densities. The density of poultry farms and the difficulties in enforcing strict biosecurity measures increase the risk of major outbreaks. Epidemics in these regions have proven difficult to control despite rigorous eradication efforts, underscoring the need for better control strategies.

Emergency Vaccination:

Recent outbreaks, even in countries with efficient veterinary infrastructure, have resulted in the culling of millions of birds. For instance, major outbreaks in Italy, the US, the Netherlands, and Canada have killed or depopulated millions of birds, despite modern diagnostic (14).

Economic impact on human pandemic:

This discusses the economic impact of a global flu pandemic, which could infect up to 35% of the world's population and cause 1.4 million deaths. Three scenarios were used to simulate the economic effects: less than 1% of GDP loss in a moderate pandemic, a 2% decline in a mild epidemic, and a 5% recession in a severe pandemic, particularly in developing nations (15).

Conclusion:

The current state of global economics together with public health remains vulnerable to avian influenza threats specifically because of highly pathogenic avian influenza (HPAI) viruses like H5N1. Transmission of the virus occurs through direct contact with sick birds while it produces dangerous illnesses that affect humans along with animals. The unpredictable nature of avian influenza together with its rapid mutational ability continues to cause concern even after diagnostic and antiviral advancements and preventive measures like biosecurity and immunization campaigns. A global economic disturbance at all levels affects emerging nations most critically. The importance of monitoring and quick identification and preparedness becomes evident through the potential millions of deaths and severe economic consequences from a pandemic. The essential requirement for controlling this devastating illness demands unified action from international governments alongside organizational bodies and scientific institutions.

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