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Review

Pathway of Avian Influenza Virus from Birds to Humans

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ABSTRACT:

Avian Influenza viruses belong to the *Orthomyxoviridae* family and are classified into subtypes based on the hemagglutinin (HA) and neuraminidase (NA) surface glycoproteins. AIV is transmitted via direct contact with infected birds, their droppings, contaminated feed, or water, and can spread through the movement of birds and humans. The pathogenesis of the disease is linked to the viral ability to bind to specific receptors on epithelial cells, especially in the respiratory and gastrointestinal tract, leading to cellular damage and inflammation. Human cases of AIV often result in severe respiratory diseases, including pneumonia and acute respiratory distress syndrome (ARDS), and may lead to mortality. The epidemiology of Avian Influenza is influenced by factors such as host species, migration patterns of wild birds, climate, and agricultural practices. Wild waterfowl, particularly migratory species, are natural reservoirs for low-pathogenic strains of AIV. The effectiveness of vaccines may vary depending on the circulating strains of AIV. While vaccines can reduce the severity of disease and prevent transmission, they are often not a standalone solution and must be combined with other control measures like quarantine, culling, and biosecurity practices. Avian Influenza outbreaks have a substantial environmental and economic impact. The direct economic costs are due to the culling of infected poultry, loss of trade, and disruption to the agricultural sector. Biosecurity is crucial in preventing the of Avian Influenza, particularly in poultry farms and live bird markets. Effective biosecurity measures include controlling access to farms, monitoring and restricting the movement of birds, ensuring proper sanitation and disinfection protocols, and minimizing contact between domestic and wild birds.

Keywords: Pathogenicity, Orthomyxovirus, Haemagglutinin, Neuraminidase.

1. INTRODUCTION:

Avian influenza viruses (AIVs) represent significant challenges to global public health systems due to their widespread circulation and considerable mortality rates. AIVs, which belong to the influenza A genus, have an eight segments genome and encode at least 11 different proteins, including hemagglutinin (HA) and neuraminidase (NA) glycoproteins. HA and NA in avian species are classified into 16 and 9 subtypes, respectively. These two proteins divide and determine distinct serotypes of AIV based on their genetic variations.[1]

Highly pathogenic avian influenza (HPAI) virus was one of the first viral diseases described in poultry. Clinically, HPAI was probably first described by Perroncito in 1878, and the disease was shown to be caused by a filterable agent by several groups in 1901. HPAI has continued to cause serious losses to the poultry industry, and it is defined as a list A disease by the office International des Epizooties. Numerous vaccines against avian influenza have been developed and experimentally shown to be efficacious for the prevention of disease, but the number of HPAI outbreaks in commercial poultry has been increasing rather than being controlled and eradicated.[2]

Several native bird species including wandering albatross (*Diomedea exultant*), macaroni penguins (*Endites cryolathes*), grey-headed albatross (*Thalassic Chrysostom*), and white-chinned petrel (*Procellarid equinoctials*), are listed as either vulnerable or endangered. Iconic long-lived species with late maturity, such as albatross, exhibit low resilience to rapid increases in population mortality. High mortality disease outbreaks

therefore represent a substantial threat to already vulnerable seabird populations. A range of subtypes have since been reported (H1, H3, H4, H5, H6, H7, H9, and H11) including genetic analysis of the influenza virus subtypes H4N7, H5N5, H6N8 and H11N2. In contrast to the more prevalent H11N2 influenza viruses, which likely circulate silently through local populations, H4-H6 subtypes were found to share high sequence similarity with viruses from South America, indicating more recent introduction events.[3]

Avian influenza (AI), also known as "bird flu" is a contagious disease among the poultry population with high avian mortality, causing a decrease in production, generating economic losses, and limiting the circulation of birds, its products, and subproducts. AI is an infection caused by influenza A virus, whose nomenclature has been assigned by the World Health Organization (WHO), the World Organization for Animal Health (WOAH), and the Food and Agriculture Organization of the United Nations (FAO), according to their transmembrane hemagglutinin (HA) and neuraminidase (NA) glycoproteins. Low pathogenic avian influenza (LPAI) is a mild disease, often unnoticed or asymptomatic. In contrast, highly pathogenic avian influenza (HPAI) causes severe systemic affections with high morbidity and mortality rates. The LPAI virus was first identified in poultry in Germany in 1949 as H10N7. The first HPAI virus was identified in 1880 in Northern Italy in domestic birds.[4]

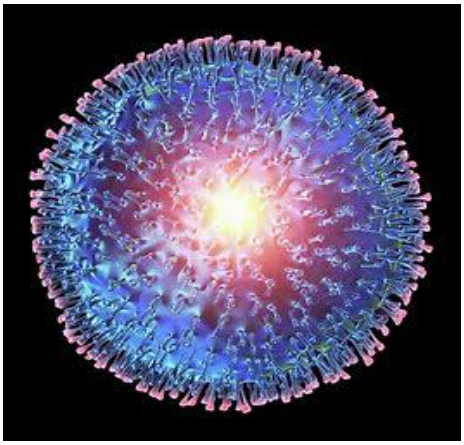

Fig: Avian influenza virus

2. EPIDEMIOLOGY:

In the United States and from 2010 to 2017, the Centres for Disease Control and Prevention (CDC) has estimated that influenza virus infection has resulted in between 9.2 million and 35.6 million illnesses and between 140,000 and 710,000 hospitalizations. In a typical year, 3–5 million cases of severe illness are caused by seasonal influenza virus infection in the world. Children seem to be the main human transmitters of influenza viruses, as illustrated by studies showing that vaccination of children reduces the incidence of severe influenza virus infections in elderly individuals. Incidence of influenza virus infections increases during pandemic years owing to the lack of pre-existing immunity against the new virus, but severity varies depending on the pandemic virus itself, with the 1918 influenza A H1N1 pandemic being the most severe of the past 100 years**.** Influenza A and influenza B viruses cause epidemic seasonal infections, resulting in ~500,000 deaths annually worldwide, with the most recently calculated estimates being 832 deaths per year during the 1999–2015 period. Seasonal influenza virus-associated deaths in the United States range from 5,000 to 52,000 people per year, depending on the year. Several comorbidities are known to increase the risk of lethal influenza virus infection. In addition, pregnancy and age are known risk factors, with very young (<1 year of age) and elderly (>65 years of age) individuals being the most vulnerable populations. Although mortality is low in children >2 years of age and young adults, a substantial number of deaths owing to influenza virus infection have been recorded in young individuals with no known predisposition factors. Approximately 100 children die each year from influenza in the United States; this number has been stabled since 2010**.** Severe disease and/or mortality in patients with influenza virus infection are in general due to either virus-induced pneumonia or secondary bacterial superinfection. Primary viral pneumonia is characterized by high levels of viral replication in the lower respiratory tract accompanied by strong pro-inflammatory responses, also referred to as cytokine storm. Infection of waterfowl with low pathogenic avian influenza A (LPAI) viruses, called as such owing to their lack of lethality in poultry, produces little or no clinical symptoms. However, upon transmission to poultry, LPAI can cause substantial disease symptoms; in addition, viruses with H5 and H7 subtypes can become highly pathogenic (that is, lethal) in poultry. Outbreaks of highly

pathogenic avian influenza A (HPAI) throughout Eurasia and northern Africa are the major influenza disease burden in animals, with >400 million birds killed and economic losses totalling US$20 billion in the first 10 years of the 21st century.[5]

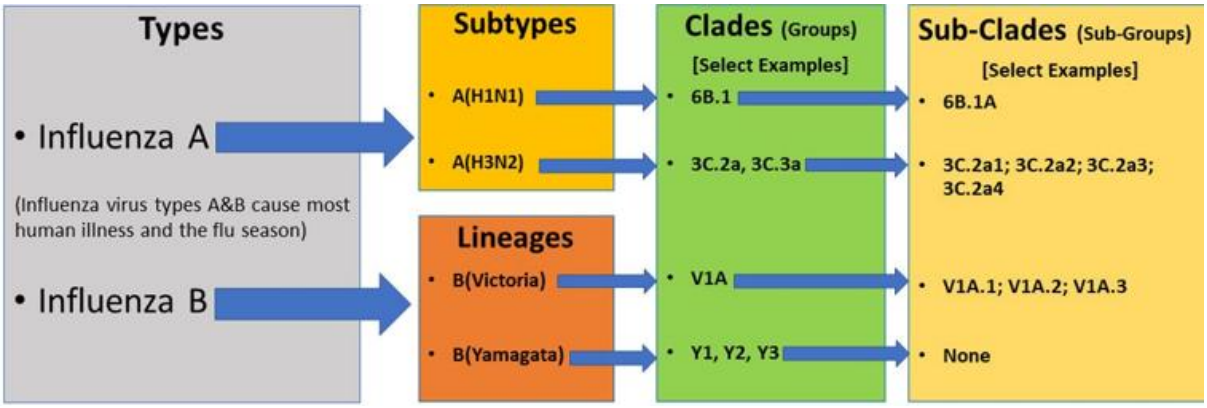

Fig: Types and subtypes of influenza virus

3. ETIOLOGY:

The influenza virus is an RNA virus part of the *Orthomyxoviridae* family with seven genera, namely *Influenzavirus A*, *Influenzavirus B*, *Influenzavirus C*, *Influenzavirus D*, *Togavirus*, and *Isa virus* and *Quarajavirus*, moreover, *Influenzavirus A* has been identified in a wide range of hosts with the highest genetic variability and is the only one capable of infecting birds. Moreover, due to the segmented nature of the viral genome, new strains can emerge through genetic reassortment and antigenic drift, further increasing the difficulty in its control and prevention. The AI virus subtypes depend on the antigen present on the surface of the influenza A virus; there are 16 hemagglutinin subtypes and 9 neuraminidase subtypes. However, recent scientific studies reported new HA subtypes (18 in total) and NA (11 in total), which were isolated in bats.[4]

There are four types of influenza viruses, A, B, C, and D. Influenza types A and B cause human infection annually during the epidemic season. Influenza A has several subtypes according to the combination of hemagglutinin (H) and the neuraminidase (N) proteins that are expressed on the surface of the viruses. There are 18 different hemagglutinin subtypes and 11 different neuraminidase subtypes (H1-18 and N1-11). Influenza A viruses can be characterized by the H and N types such as H1N1 and H3N2. Influenza B viruses are classified into lineages and strains. Influenza B viruses that have circulated in recent influenza seasons belong to one of two lineages, influenza B Yamagata and influenza B Victoria. When this happens, transmission from person to person is usually inefficient. Influenza pandemics like 1918 and 2009 can occur if the transmission from person to person becomes efficient. Avian influenza, or bird flu, is an infectious disease of birds caused by a variety of influenza A viruses, including A(H5N1), A(H5N8), and H7N9 viruses. These viruses are worrisome as they can change to develop the ability for transmissibility from person to person and start a severe pandemic. A good example of animal-origin influenza is the 2009 pandemic influenza, which is an animal influenza virus that likely started in South America in early 2009 and developed the ability to spread from person to person and spread globally.[7]

The H1N1 influenza virus belongs to the orthomyxovirus family and has a single-stranded negative-sense ribonucleic acid (RNA) genome. Its virions typically measure between 80 and 120 nm in diameter, with an RNA genome size of around 13.5 kb. The influenza genome comprises 8 segmented regions that encode a total of 11 different proteins, as mentioned below.

- Envelope proteins: Hemagglutinin (HA) and neuraminidase (NA).
- Viral RNA polymerases: PB2, PB1, PB1-F2, PA, and PB.
- Matrix proteins: M1 and M2.
- Non-structural proteins: NS1 and NS2 (NEP), which are crucial for efficient pathogenesis and viral replication.

The H1N1 strain of influenza A is distinguished from other strains, such as H1N2, based on the surface glycoproteins hemagglutinin and neuraminidase, which exhibit metabolic synergy. Hemagglutinin triggers erythrocyte aggregation by binding to sialic acid and facilitates virus attachment to infected cells, enabling endocytosis. Subsequent fusion with the endosome, mediated by matrix proteins, allows viral RNA-dependent

polymerase to initiate viral replication. Neuraminidase is crucial during viral budding by cleaving sialic receptors and promoting virus spread to neighbouring cells.[8]

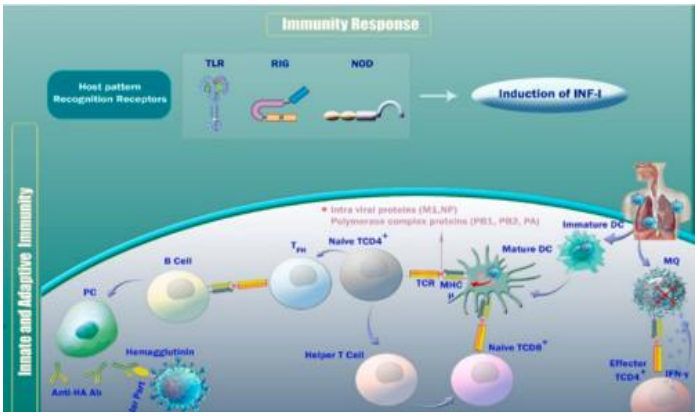

Fig: Immunity response to influenza virus

4. PATHOPHYSIOLOGY:

Human influenza viruses are transmitted through the respiratory route, whereas avian influenza viruses in wild birds are transmitted through the faecal–faecal, faecal–oral or faecal–respiratory routes. Depending on the route of transmission, the virus targets epithelial cells of the respiratory or intestinal tract for infection and productive replication. In addition, some avian influenza A viruses, especially those of the H7 subtype, have been associated with human infections of the eye and conjunctivitis (inflammation of the conjunctiva). Severity of infection in humans is associated with replication of the virus in the lower respiratory tract, which is accompanied by severe inflammation owing to immune cell infiltration.[5]

4.1. Transmission in animals:

The main reservoir of diverse strains and subtypes of influenza A virus is wild birds, especially migratory ducks and geese. Indeed, domestic ducks raised on open ponds are the logical intermediaries between the reservoirs of influenza viruses in wild aquatic birds and other domestic poultry. Transmission between birds can occur directly from contaminated water. Although most of the 16 HA and 9 NA influenza A subtypes cause asymptomatic infections in avian species, H5N*x* and H7N*x* subtypes can evolve into HPAI strains through the acquisition of a novel cleavage site in HA (which enables HA maturation by ubiquitous host proteases and spread of the virus outside the respiratory and intestinal epithelia to multiple organs, including the brain) and can cause lethal infections in chicken, turkey and some breeds of domestic duck. Transmission of influenza viruses to multiple domestic poultry species occurs through so-called backyard farming, whereby species are raised together and in live poultry markets; subsequent transmission to commercial avian farms can occur through the lack of biosecurity (that is, procedures or measures designed to isolate and protect animals and humans from contact with infectious viruses) and because of viral spread through live markets. [5]

Influenza in pigs is a respiratory disease akin to influenza in humans, with high fever and pneumonia caused by influenza A H1N1, H3N2 and H1N2 subtypes. Some strains of influenza A virus have been known to be transmitted by aerosol spread from humans to pigs and vice versa, including the pandemic 2009 influenza A H1N1 strain and the influenza A H3N2 variant that transmits from pigs to children. In horses, infection causes respiratory disease and is spread by aerosol; two lineages of influenza A H3N8 are primarily responsible. In 2004, the equine influenza A H3N8 strain spread to dogs. In 2006 in Asia, an avian H3N2 influenza A virus was also detected as being transmitted to dogs. Influenza A viruses have been found in multiple species all seemingly derived from viral ancestors in wild birds, except for bat influenza-like virus, which is of still uncertain origin. Influenza viruses from wild birds can spill over through water or fomites to marine mammals and to domestic free-range ducks. Transmissions to other avian species (for example, poultry) from domestic ducks or directly from wild birds can also occur from contaminated water. Transmission from ducks to other species occurs through ‘backyard’ farming, whereby the animals are raised together, and in live poultry and/or animal markets. Transmission from backyard to commercial farms can occur via lack of biosecurity and via spread through live markets46. Humans can be infected with poultry and swine influenza viruses through aerosols, fomites or contaminated water. However, in most instances

these infections do not result in subsequent human-to-human transmission. Human-to-human transmission of seasonal or pandemic human viruses can be mediated by respiratory droplets, aerosols or self-inoculation after touching of fomites. Additional virus adaptations would be required for sustainable human-to-human transmission of animal influenza viruses. [5]

4.1.1. Bird-to-Bird Transmission

Wild waterfowl are natural reservoirs of the AI virus and play a role in spreading through their long-distance migratory routes, infecting land birds and domesticated waterfowl via contaminated water sources or food. However, the oral–fecal path is the main transmission route between birds due to the high viral levels in the fecal matter of infected birds, and it can be transmissible for approximately 21 days. Chatziprodromido described proximity to water as a significant risk factor for virus transmission because there may be a close interaction between migratory birds and commercial poultry activities, increasing disease transmission. AI virus can also be transmitted through secretions and body fluids, such as saliva, mucus, and urine. In the production systems, these fluids and feces contaminate the clothing and footwear of operators, cages, implements, and mechanical equipment for egg collection, among others. This route has been considered the principal vehicle for disease dissemination within flocks, making commercial poultry responsible for epidemics registered worldwide. [4]

5.2.2. Zoonotic Transmission

Avian influenza viruses have demonstrated the capacity to cross the barrier between species for multifactorial reasons that have favored transmission. Moreover, host susceptibility, exposure level to infected birds, viral mutations, and favorable environmental conditions form an ideal scenario for the zoonotic transmission of the avian influenza virus. The main route of transmission between birds and humans is direct contact with the feces or secretions of infected animals and exposure to contaminated or virus-infected environments. There is no evidence of human-to-human infection. People within the poultry production chain (from farm to table) are at a higher infection risk than the general population due to prolonged exposure to the infectious agent. [4]

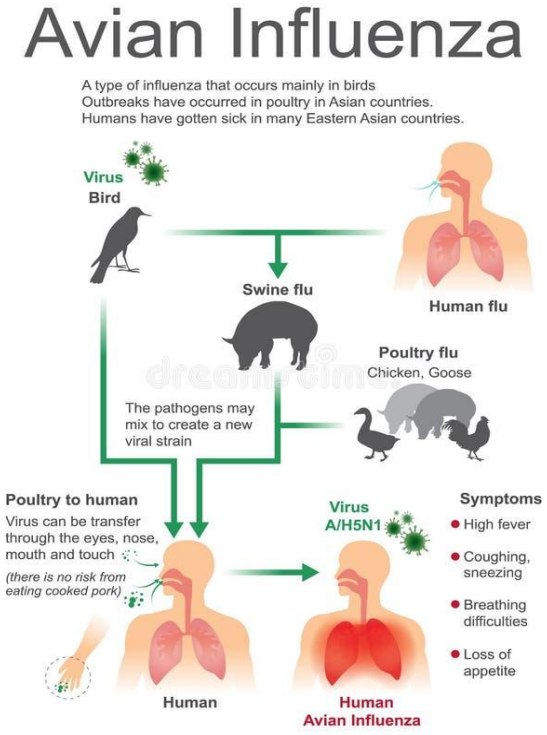

Fig: Zoonotic transmission of avian influenza virus

5. CLINICAL MANIFESTATIONS:

- Myocarditis
- Multi organ failure

- Encephalitis
- Transverse myelitis
- Encephalomyelitis
- Hyperreflexia
- Rhinitis.[10]

6. DIAGNOSTIC TESTS:

1. Rt-pcr test
2. Serologic testing
3. Viral culture test
4. Nucleic acid detection test
5. Elisa test
6. Antigen detection test.[11]

Fig: different types of diagnostic tests for influenza virus

7. TREATMENT:

Treatment with an anti-influenza drug is an option, with the decision to prescribe based on balancing potential benefits, harms, cost, and patient preferences. In otherwise healthy adults and children, the clinical benefit is greatest when treatment is initiated within 24 hours of symptom onset. Although anti-influenza drugs have been approved by the U.S. Food and Drug Administration for use within 48 hours of symptom onset, most clinical trials enrolled patients who had been symptomatic for no more than 36 hours. The primary benefit of treatment is a decrease in symptom duration by approximately 24 hours when treatment is initiated within 36 hours, and a reduction in disease severity. Among adults and children with influenza in the outpatient setting who are treated with an NA inhibitor, systematic reviews of published and unpublished randomized trials found no decrease in hospitalizations or death.[12]

8.1. Anti-viral medications:

These drugs target specific steps of Viral Replication causing the process to get arrested or halted and preventing the formation or release of new viral spores. Three primary classes of drugs include M2 Protein inhibitors, Cap-snatch Inhibitors, and Neuraminidase Inhibitors. Each class has been described in the literature. [13]

8.2.VACCINES:

Vaccination is the primary preventive measure against influenza infection and should be offered during all routine health care visits and hospitalizations at any time during influenza season. Vaccine efficacy is about 60% in a good season, but if the vaccine does not match the current circulating strains of the virus, effectiveness can be as low as 10% to 20%. It is recommended that all people aged 6 months or older receive an annual influenza vaccination unless they have contraindications for the vaccine or any of its components. Ideally, the vaccine should be administered before the end of October because it takes about 2 weeks from vaccination to immunization.

8.2.1. Types of Vaccines:

8.2.1.1. Egg-Based Vaccines:

Most manufacturers use eggs to grow the influenza virus during the development process. People with egg allergies no longer need to be observed for allergic reactions for 30 minutes after administration of the vaccine. However, the CDC provides additional guidance for health care clinicians, especially if the individual has a history of a severe egg allergy.

8.2.1.2. Recombinant Vaccines:

Recombinant influenza vaccines (RIVs) are produced using recombinant technology, which is the process that alters the genetic material to enhance desirable characteristics. The benefits of RIVs over egg-based vaccines are that they can be produced quicker should a pandemic or egg shortage occur and that mutations, which sometimes occur naturally in eggs, can be avoided.

8.2.1.3. Attenuated Vaccines:

The increased risk for Reye's syndrome has been noted in children who receive the live attenuated influenza vaccine and those who take salicylate-containing drugs (eg, aspirin). Therefore, people aged 2 to 17 years with contraindications should avoid the live attenuated influenza vaccine.[14]

8. PREVENTION:

The antiviral drugs amantadine and rimantadine have beneficial effects on cases of influenza involving the type A virus. However, viral resistance to these agents has been observed, thereby reducing their effectiveness. A newer category of drugs, the neuraminidase inhibitors, which includes zanamivir (Relenza), was introduced in the late 1990s; these drugs inhibit both the influenza A and B viruses. It is recommended that children and teenagers with the flu not be given aspirin, as treatment of viral infections with aspirin is associated with Reye syndrome, a very serious illness**.** Advances in scientific understanding of influenza and vaccine technologies enabled the development of a so-called universal influenza vaccine, capable of protecting individuals against a broad range of different influenza subtypes; the vaccine was scheduled for initial testing in clinical trials involving human subjects in 2019. In order to prevent human-infecting bird flu viruses from mutating into more dangerous subtypes, public health authorities try to limit the viral "reservoir" where antigenic shift may take place by ordering the destruction of infected poultry flocks.[15]

Fig: Tips to prevent influenza virus

9. CONCLUSION:

Avian influenza (AI), also known as bird flu, remains a significant concern due to its potential for widespread impact on both animal and human populations. While most strains primarily affect birds, certain variants of the virus, such as H5N1 and H7N9, have demonstrated the ability to infect humans and cause serious illness. The risk of a pandemic is a continual concern due to the virus's ability to mutate and adapt, posing a threat to global health security. Preventive measures, such as surveillance, biosecurity practices in poultry farming, and vaccination of both animals and humans in high-risk areas, are critical to minimizing

the spread and impact of AI. Early detection and rapid response systems, including monitoring wild bird populations, are essential for controlling outbreaks and preventing transmission to humans. Despite significant advancements in research and vaccine development, the ongoing threat of avian influenza underscores the importance of international cooperation, preparedness, and vigilance.

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