Research and Reviews: Journal of Microbiology and Biotechnology e-ISSN:2320-3528
p-ISSN:2347-2286

A Systematic Review of Avian Influenza Virus Transmission, Epidemiology and Pathogenesis

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Review Article

Received: 05/08/2021
Accepted: 19/08/2021
Published: 26/08/2021

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Keywords: Avian influenza; LPAI; HPAI; H5N1; Mutation

ABSTRACT

Avian influenza virus belongs to family Orthomyxoviridae, genus Influenza virus A is a public health risk with pandemic potential of spread. Mortality caused by H5 and H7 group of Influenza virus, designated as high pathogenic is upto 100%. Other groups cause mild respiratory infection and are designated as Low pathogenic. The aim of the present review was to investigate avian influenza virus, transmission, epidemiology, pathogenesis, clinical manifestations, and diagnosis of disease caused by this virus. Prevention, control and eradication strategies are also reviewed. The data were collected from previously reported article. Genetic changes can arise to turn low pathogenic viruses to high pathogenic viruses. The exact mechanism involved in this process is not well known. But, it is assumed that more the virus circulates in poultry, more it becomes prone to genetic mutations. Avian influenza virus A H5N1 is a threat to public health as it causes severe illness and death in human.

INTRODUCTION

Avian Influenza virus belongs to family Orthomyxoviridae and known as avian influenza virus type A. It is also known as bird flu virus, avian flu virus and fowl plague virus. Avian influenza virus is enveloped, pleomorphic virus. It have segmented, negative sense and ribonucleic acid genome. Its size ranges from 80-120nm. These viruses are classified into seven genera, of which three (A, B and C) infects vertebrates. The classification is based upon the antigenic differences in their matrix protein and nucleoproteins which can be detected by using the serological test AGID test. Avian influenza virus of type-A influenza viruses infect a broad range of animals like chickens, pigs, horses, seals, wild ducks and humans. Other type of viruses B and C infect infrequently pigs and only humans. For naming of influenza virus standard nomenclature is followed. The name of newly isolated virus includes type of influenza, isolation place, designation of strain, and year of isolation are included in it [1].

For example, A/Hong Kong/165/97 is taken as influenza type A, isolated in Hong Kong, strain 165, isolated in 1997. For the first time, Avian Influenza appeared in Italy in 1878 and was termed as Fowl Plague. Later on, this disease was reported in other European countries, in some parts of Southeast Asia, United States of America, Egypt, South America and Russia. According to European Union, Avian Influenza is respiratory disease of poultry that causes respiratory distress and other complications in 1 to 2 month old chicken. The Influenza virus also infects the human infants with a very high rate of mortality, while in adults, it causes chronic illness resulting into mortality. In US, 200,000 patients infected with Influenza virus were registered and admitted to hospital, resulted into 360,00 deaths, rendering it as a threat to public health. There are many subtypes of avian influenza virus but only five of them infect humans and that are H5N1, H7N9, H9N2, H7N3, H7N7.

LITERATURE REVIEW

Avian influenza virus cannot directly infect human. The host specie barrier for Influenza virus is explained as the specifity of hemeagglutinin protein for binding to sialic acid receptors. It is very specific phenomenon as Human influenza viruses bind favorably to sialic acid receptors having galactose α-2-6 linkages in the respiratory epithelial cells of respiratory tract, while avian viruses have tendency to bind with sialic acid receptors having galactose α-2-3 linkages in the epithelial cells of intestine. Pig is intermediate host between these two species as tracheal epithelium of pig both of these linkages i.e. linkage α-2-3 and α-2-6 and act as an intermediate host for changing the virus genome as so, the new virus types emerge out.

Specification of the etiological agent

Ten different proteins encoded by eight gene segments present in the type-A influenza virus. These proteins can be further divided into exterior (surface proteins) and interior (internal proteins). The internal proteins have the complex of polymerase along with the non-structural proteins 1 and 2, the nucleoprotein, the matrix 1 protein, and the three polymerase proteins PB1, PB2 and PB3. On the other hand haemagglutinin HA, neuraminidase NA and two matrix proteins are the part of surface proteins. These proteins basically provide the antigenic sites for neutralizing the antibodies and for the stimulation of the defensive immune response. Due to the variety of the HA and NA subtypes, there is a lot of variation in antigenic sites [2]. Fifteen subtypes of HA and NA have been recognized on the basis of the neuraminidase inhibition test and haemagglutination inhibition test.

Epidemiology

In May 1997 the first case of H5N1 was identified in human. For six months there was not any case but then in November and December 1977, the second case of an epidemic was seen an added to it 17 other cases were also reported. These cases were spread in different areas. From these 18 cases of individual confirmed with H5N1 infection, 10 were female and 8 were male ant the range of age is from 1 to 60 years and some of them are less than 12 years of age. Twelve of them made a full recovery and six of them died. Molecular and epidemiological evidence shows that the source of the H5N1 outbreak in 1997 was poultry in humans. In recent times, an outbreak of high path avian H7N7 influenza in the Netherlands in 2003 caused conjunctivitis in 349 humans and the death of a veterinarian.

In February 2004, humans were infected by H7N3 viruses in Canada. Furthermore, recent avian H6N1 viruses were recognized to have internal genes which were similar genetically to those of human H5N1 and H9N2 influenza viruses, giving the suggestion that H6N1 viruses could become new human pathogens. Chicken to human transmission was identified that it was the source of human infection basically although H5N1 could also be transmitted from human to human which was a source of concern as it could be able to lead the emergence of new pandemic virus. Mostly this infection is maintained in a population of wild birds. Waterfowl is considered as the major cause of spreading this virus to domestic birds. Ducks particularly juveniles, mostly get infected but rarely show clinical signs of illness. As the replication of this virus occurs in the intestinal tract so virus shed in feces. Contaminated equipment and live-bird markets contribute to the spread of infection.

Influenza viruses have negative sense and segmented RNA core. A lipid envelope surrounds this core. The virion of influenza A virus contains neuraminidase NA and hemagglutinin HA along with a membrane protein M2. A ribonucleoprotein having RNA segments that are connected with PA, PB1, PB2 polymerase proteins and nucleoprotein (NP). These three polymerase proteins are further connected with the viral RNA. These proteins have a basic role in transcription and translation. The morphology of influenza virus is pleomorphic with filamentous or

spherical form and sometimes it can be a mixture of both. The form of HA spikes is rod-shaped and NA spikes have a mushroom-like shape with slender stalks. The range of these HA and NA molecules is from 10 to 12 nm.

Influenza A viruses have eight RNA segments that are single-stranded and each encodes one protein. Their genome is 13.6 kb long, and it is comprised of 8 segments which code for 11 proteins. The viral genome is 2 percent that is present in the total mass of the virion. In the eight RNA segments, there is a conserved region having promoter activity and this conserved region is due to the first 12 nucleotides present at the 3' end and the last 13 at the 5' end. A Mostly single protein is encoded by viral genes but nonstructural NS and M genes of the influenza viruses are some exceptions. A 26 kDa NS1 protein obtained in result of unspliced mRNA and 14 kDa NS2 protein from spliced mRNA both are encoded by the NS gene of influenza type A virus. Consecutive nine amino acids and same initiation codon shared by these proteins. M1, M2 proteins from unspliced and mRNA 3 from spliced RNAs also produced from the M gene of the influenza type a virus.

Avian influenza viruses are able to produce a variable type of disease, infection, and death in different bird species. There are two different groups on the basis of its pathogenicity. The virulent viruses that cause fowl plaque are now called highly pathogenic avian influenza [HPAI]. The mortality rate of this group is almost 100% and this group is restricted to H5 and H7. Other viruses that cause mild respiratory diseases are called as Low Pathogenic Avian Influenza [LPAI]. The factors that cause the conversion of virus from LPAI to HPAI are not well known. In some circumstances, the mutation appears to take place swiftly after an introduction from the wild birds. While, in other cases, the LPAI virus, before mutating, circulate in the poultry for months [3].

So, it cannot be predicted what time this mutation will happen. Anyhow, we can rationally assume that more is the circulation of LPAI in poultry, greater is the chance that mutation will occur to HPAI. The glycoprotein i.e. haemagglutinin is produced for influenza viruses which act as a precursor HA0 and which requires cleavage by proteases of the host before it becomes functional and then virus particles act as infectious particles. Type of proteases in a given tissue and the structure of the haemagglutinin molecule of the virus are important for the spread of the influenza virus. Post-translational cleavage of the haemagglutinin HA0 which act as a precursor is break down into HA1-HA2 dimer and this dimer is disulfide linked to become the functional and then it gets full biological power. In most of the cases, the trypsin-like enzymes only present in the epithelial cells of the digestive and respiratory tract cleave the haemagglutinin. Arginine and lysine are the basic amino acids present at the cleavage site that make it susceptible to cleavage by intracellular proteases of host and thus infection occur.

Avian influenza viruses which infect humans/ belong generally to H5 and H7 subtypes. But, in some cases, sporadic cases and death have been reported after H6, H9 and H10 infections. H5N1 (High path) and H7N9 AI viruses (low path) can cause high fatality rates in humans while most other strains like H5 and H7 strains cause mild illness or conjunctivitis. An H7N7 (high path AIV) outbreak occurred in 2003 in Netherland, and 89 humans were infected.

Lowly Pathogenic Avian Influenza Viruses

In avian influenza viruses of low pathogenesis, the HA0 precursor protein contains single arginine at the cleavage site and at position -3 or -4 from the cleavage site there is another basic amino acid. In these viruses, the cleavage is limited by extracellular host proteases like trypsin and thus the replication is limited to only to specific sites such i.e. respiratory and intestinal tracts.

Respiratory signs produced by LPAI in poultry are sneezing, coughing and nasal discharge. Sinusitis is mutual in quails, domestic ducks, and turkeys. The respiratory tract, lesions, and typical signs are also produced like congestion and inflammation of the lungs and trachea. Decreased egg production or loss of fertility, rupture of ova, reduction in mucosal fluid and inflamed exudates in the lumen of oviduct are also included in typical signs. Visceral urate deposition and acute renal failure may also occur in some layer and few breeders. Usually, morbidity and mortality rate is less but can be increased in case of secondary viral or bacterial infections or by environmental stress. LPAI viruses can produce some occasional infections, but in Asia, Middle East, North Africa H9N2 LPAI is very common.

In avian influenza viruses of high pathogenicity, the HA0 precursor protein has multibasic amino acids (lysine and arginine) at the cleavage site. The cleavage in these viruses can be done by ubiquitous protease-like furin. Thus these viruses are can replicate and damage any vital organ or tissues to the bird.

Sometimes there is an absence of secondary infections. Even in the absence of secondary pathogens, HPAI causes severe systemic disease in turkeys, chickens, and other gallinaceous poultry and it leads to high mortality. It can cause high mortality such as 100% in some days. Clinical signs and lesions are removed before death in peracute cases. In acute cases, bluish discoloration of the skin and mucous membrane, head edema, comb, wattle and snood included in lesions. In the case of subcutaneous hemorrhages, edema, red discoloration of shanks and feet occur. Pinpoint hemorrhages appear on visceral organs. Strictly affected birds are suffered by greenish diarrhea. Some birds have a peracute infection and they developed CNS problems like paralysis, incoordination torticollis and also wings droppings. Microscopic lesions vary and may consist of hemorrhages, edema, and also necrosis of multiple visceral organs CNS and skin.

Avian influenza virus can be transmitted by two ways one is through the intermediate host or directly through birds. H5N1 can mutate and can adapt or reassert the segments of genes to allow the effective transmission during the infection of mammals with human influenza virus and after reassontment can lead to the emergence of a new virus that may be transmissible from person to person and become more lethal. It is just like a theory of mixing vessel i.e. double reassortant (avian/human; human/swine) and triple reassortant (human/avian/swine), these influenza A viruses isolated from pigs in China or the United States. It is stated by a few authors that influenza virus is obtained by huge droplet transmission which is its pre-eminent mode [4].

Hence in the light of this conclusion for influenza, shielding against infectious mists is usually ignored, present in the context of influenza pandemic readiness. For instance, the Canadian Pandemic Influenza Plan and the US Department of Health and Human Services Pandemic Influenza Plan prescribe surgical covers, not N95 respirators, as a feature of individual defensive equipment for routine patient care. This condition negates the information on flu infection transmission gathered in the previous quite a few years. Certainly, aerosols are mentioned as an essential mode of transmission of influenza.

Clinical Signs and Symptoms

The incubation period is variable e.g. in naturally infected birds is up to 3 days and in the whole flock is 14 days. Virus and route of infection have a great influence on the incubation period. Clinically the disease may not appear by signs and symptoms, mild or may severe having high mortality rate. Highly pathogenic strains cause extreme outbreaks with high mortality rate. There is a dramatic drop in egg production when infection occurs in laying birds. Diarrhea, edema (an excessive accumulation of serum in tissue spaces or a body cavity) in the cranial part, cyanosis, sinusitis (inflammation of paranasal sinuses), respiratory problems and lacrimation are some signs of clinical presentation. Chickens and turkeys that show clinical signs with highly pathogenic avian influenza are dead. The clinical signs were shown other than laziness, anxiety and coma state.

The appearance of clinical signs depends on the age of the birds. The more age of the birds the more the chances of clinical signs appearance before death. Drop in egg production is also an important clinical sign in laying chickens and breeders. Diarrheas with loose droppings mixed with mucus also occur. In addition to all these signs and symptoms, respiratory signs have also be seen like coughing, sneezing, and tough breathing. These signs were reported with highly pathogenic avian influenza (HPAI). But these signs are most common in case of LPAI.

During the time of replication, the complex of RNA polymerase of influenza virus does not show assuring activity. This is the main reason the influenza virus gather point mutation. The rate of mutation of their genes is very high. Change in amino acids of surface glycoproteins due to mutation is probably beneficial for strains of the virus because it avoids previous immunity. Infection is caused by HA molecule as they bind to receptors present on host cells. Against HA protein, antibodies are formed that stop binding of these molecules with receptors and also stop the reoccurrence of infection. The NA and HA can elude formerly obtained immunity by two methods. One is an antigenic drift in which mutations prevent the attachment of antibody and second method is by an antigenic shift in which reassortment occur between two viruses of influenza A and the virus obtain HA of the new emerging subtype.

After inoculation in the nasopharynx, the replication of influenza A virus become on peak after the incubation of almost 48 hours. Some of the viruses also shed after five to six days. The virus can replicate in both tracts upper respiratory tract as well as in the lower respiratory tract. The viral antigen can be detected in secretions and cells of infected patients. The influenza virus can be diagnosed by culturing virus, by demonstrating the viral antigen or by its viral genetic material. A sequential strategy is necessary for the diagnosis of any disease:

- Suitable sample collection and its prevention for laboratory confirmation are necessary. Feces, cloacal swab, tracheal swabs etc. are included.
- The suspension is inoculated in embryonated eggs. Other culture systems can also be used according to feasibility. Harvesting of allantoic fluid after the incubation of 4 to 7 days is used the further testing i.e. haemagglutinating activity.
- Immunodiffusion can also be used for the confirmation of influenza A virus by taking a suspension of a chorioallantoic membrane from the eggs
- Genomic sequencing in which components of the amino acid at the cleavage site of the haemagglutinin is determined/ can also be done
- Serological tests (agar gel immunodiffusion test, haemagglutination inhibition test, and competitive ELISA) are used also
- A test is developed to distinguish infected from vaccinated individuals is Neuraminidase inhibition test based on the DIVA (differentiating infected from vaccinated animals) strategy.
- Vaccines
- Two vaccine methods had been used to control or for the removal of HPAI, are given below:
- Whole virus vaccine in the inactivated form
- A fowlpox vaccine in the recombinant form

The whole virus inactivated vaccines have been used abundantly in Mexico and Pakistan during the recently happened outbreaks having H5 and H7 HPAI viruses. The fowlpox vaccine in recombinant form was used in Mexico to control plan against MPAI (H5N2). Other methods are also trying for future purpose, containing deoxyribonucleic acid and subunit HA protein vaccines.

The HA protein evokes the basic defensive immunity in poultry, but in addition to this NA also play a role in protection. These vaccines provide protection in chickens and one HA homologous type provide protection against one challenge virus means H5 vaccine will provide immunity against H5 targeted virus and will not provide protection against H7 challenge virus.

Prevention, control, and eradication

Outbreaks can be controlled by slaughtering infected flocks, implementation of effective disinfectants, quarantine the imported birds and by providing the bird proof buildings to the poultry. Vaccination is usually used. Inactivated oil emulsion vaccines and recombinant haemagglutinin vaccine [5].

As there are new emerging subtypes so vaccine effective against one particular subtype may not be effective against another one. Due to reversion live vaccine cannot be used however attenuated, reassortant influenza virus vaccine and cold-adapted vaccine have been producing good results. A few techniques have been used for the prevention and eradication of avian influenza from all around the world. Many different countries have chosen different prevention techniques to meet the increasing demands of indigenous requirements. So the implementations of international rules and standardization of sanitary health requirements have accomplished the demands. Actions that are used to control prevent and eradicate avian influenza will depend upon the following:

- Types of birds that are affected
- Pathogenicity (highly pathogenic avian influenza or low pathogenic avian influenza)
- Distribution of the birds that are infected geographically
- A demand for indigenous and global markets
- The financial repute of nation (Halvorson, 1995)

With all these implementations of international rules and standardization, continual improvement is necessary for complete eradication of the virus otherwise it may emerge in the form of a new virus. For the effective control and prevention against LPAI and HPAI, some plans should be followed that have some salient features given below:

- Complete, incorporated countrywide surveillance and diagnostic program.

- Better biosecurity practiced at all stages of production and processing by means of all employees of corporations, diagnostic laboratories and authorities groups which have contact with rooster or system from poultry operations.
- Schooling of poultry farmers and different people about AI manage and sharing of records on surveillance and management techniques at all degree within the production methods
- Quarantine or controlled motion of A1-infected poultry
- Stamping-out or slaughter program for all HPAI and some H5 and H7 MPAI outbreaks
- A vaccine was as one element of a comprehensive manipulate program and under particular conditions with countrywide authorities control.

CONCLUSION

Influenza viruses contain single-stranded RNA which is a negative sense. These viruses belong to the genus Influenzavirus A, of the family Orthomyxoviridae and cause multiple manifestations ranging from respiratory signs to severely generalized septicemia. Their genome is 13.6kb long, and it is comprised of 8 segments which code for 11 proteins. They infect a broad range of animals like chickens, pigs, horses, seals, wild ducks and humans. Anyhow, there are some subtypes of them which are specific to certain species, but birds are known to be the host to all identified subtypes of influenza A viruses. AI viruses are categorized as low pathogenic (LPAIV) or high pathogenic (HPAIV). It is observed that if, in wild birds, LPAIV generally cause infections which are asymptomatic i.e., subclinical infections restricted to the respiratory tract. But, infections may lead to clinical signs and lesions which reflect path physiological damage to the respiratory and other systems, when introduced in the domesticated birds. The HPAIV have been observed to be primarily in the gallinaceous poultry and cause systemic infections thus produce high morbidity and high mortality. Presently, the influenza A subtypes that are circulating in humans are H3N1 and H1N1. Antigenic drift can occur in all subtypes of influenza A viruses, but most often it occurs generally in the human influenza virus. Mutation in influenza A virus proteins such as NA and/or HA can result in immune escape by the virus. The viral antigen is detected in secretions and cells of infected patients. Diagnosis can be done by culturing the virus or by serology. Both HA and NA can evoke the immune response when used as a vaccine. Prevention and control of disease is the major challenge as it is a highly mutating virus.

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