# EVOLUTION OF AVIAN INFLUENZA AND PUBLIC HEALTH

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**ABSTRACT**

Avian influenza is fast gaining popularity as one of the most important zoonotic disease of 21st millennium. The global existence of diverse viral gene pool exists due to co-circulation of many different avian influenza (AI) viruses. In recent times, human race have came across emergence of novel strains of AI viruses by virtue of genetic reassortment events between viruses or mutation of viral genes. This may lead to possibility of epidemic with unpredictable consequences for animal and human health. This article attempts to describe evolution of AI viruses and its subsequent consequences.

***Key words*:** Bird flu, influenza, emergence, virus, evolution

## Introduction

Avian Influenza (AI), also commonly called 'bird flu' is a viral disease that infects wild birds, shorebirds, waterfowls such as geese, ducks and swans, domestic poultry, turkey, quail and now also has learned to infect other mammals and humans too. It is a complex disease of birds, who's ecological and epidemiology facets have undergone substantial changes over the last decade. However, It has been lacking in public perception that avian influenza viruses have been a part of our ecosystem for long time and well adapted to their natural hosts (primarily wild waterfowl) thereby striking a fine balance between its existence and survivality in host population (Lupiani and Reddy, 2009). This disease is therefore not new for veterinary medicine. New however, is the unprecedented rapid geographic spread of high pathogenic avian influenza virus (HPAIV) and its ability to cross directly from the avian host into humans and others. This results into a serious illness with significant case-fatality ratio approaching that of the most dangerous human pathogens (Mettenleiter, 2009; Galav, 2008). Thus, avian influenza viruses have emerged a serious intimidation not only to poultry farmers, but also to human health on a global scale. This article aims to convey fellow veterinarians and progressive farmers about evolution and emergence of avian influenza viruses and their possible consequences.

## Virus

The influenza virus belongs to family *Orthomyxoviridae* having three genera- A, B and C. Only the Genus A type viruses have been isolated from birds and therefore termed avian influenza viruses (AI) or 'bird flu' viruses. The nomenclature has been based on a combination of two groups of proteins found on their surface: the haemagglutinin or H proteins (18 in numbers) and neuraminidase or N proteins (11 in numbers). Among Influenza-A genera, except subtype H17N10 and H18N11 which have been found only in bats, viruses with 16 haemagglutinin [H1–H16] and all 9 neuraminidase [N1–N9] have been isolated from avian species in all combinations (Tong *et al.*, 2013). Swine is a known natural host for H1 and H3 subtype and this led origin of term 'Swine Flu'.

The abbreviations 'H5N1', 'H7N7', 'H5N2' 'H1N1' etc. have gained much publicity and notoriety with apprehension of a novel flu pandemic with catastrophic consequences. Nomenclature of influenza viruses have described in Fig. 1. As per norms, the H5 and H7 AI types are required to be notified to OIE (World Organization for Animal Health). The H5 and H7 viruses are further divided into two groups based upon ability of the virus to produce disease in poultry: low-pathogenicity avian influenza (LPAI) and high-pathogenicity avian influenza (HPAI). Terming LPAI or HPAI is based on ability of virus (virus used for test: 0.2 ml of a 1/10 dilution of allantoic fluid from embryonated egg passaged virus) to cause mortality in 4 to 6 week-old specific pathogen free (SPF) chickens under laboratory conditions. If six or more chickens out of eight inoculated, die within 10 days, the virus is considered high pathogenic, and if fewer or none die it is considered to be low pathogenic (Anonymous, 2015).

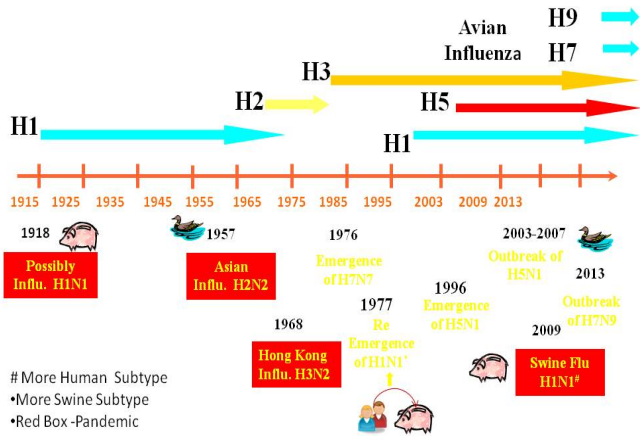


Fig 1: Criteria for Nomenclature of Influenza viruses

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**Evolution and emergence**

The first description of avian influenza dates back to 1878 in Italy, when researchers described a contagious disease of poultry associated with high mortality. The disease, termed 'fowl plague', was initially confused with the acute septicemic form of fowl cholera (Perroncito, 1878), but soon both were differentiated based on clinical and pathological properties in 1880 (Stubs *et al.*, 1943). Later in 1901 etiological agent was found to be a virus (Centanni and Savonuzzi, 1901) and later in 1955 it was demonstrated to be type-A influenza virus based on the presence of type A influenza virus type-specific ribonucleoprotein (Schäfer, 1955). The 1960s and 1970s saw emergence of H5 and H7 subtypes in domestic poultry. The first reported appearance of global zoonotic avian influenza outbreak of HPAI H5N1 type was in 1996 at a goose farm in Guangdong province, China (Tang *et al.*, 1998) and within a year it spread and caused human casualties in Hong Kong (Bender *et al.*, 1999). Since then HPAI H5N1 has spread from Asia to almost all continents including Europe, Middle East and Africa, affecting over 60 countries by mid-2006. During this period, few European countries (prominently Netherlands) also suffered with HPAI H7N7 zoonotic outbreak in 2003 (Elbers *et al.*, 2004).

By early 2013, several new AIV strains have been reported in East and Southeast Asia, threatening both poultry-dependant livelihoods and human health. In March 2013, avian influenza A (H7N9) emerged in China causing a total of 456 human cases and by November 2014 it claimed 172 human lives (Can *et al.,* 2014). This H7N9 type virus is of low-pathogenicity in poultry (no clinical signs are observed in infected birds) but can cause lethal pulmonary infection in mammals without prior trans-species adaptation. Subsequently, H10N8 was also reported in December 2013, causing 3 human cases in China, including two fatalities (Chen *et al.*, 2014) while H5N8 emerged a month after and led to almost 40 poultry outbreaks, mainly in the Republic of Korea, Japan and China (Zhao *et al.*, 2013). These episodes were followed by outbreaks in poultry caused by highly pathogenic H5N6 in China and Lao People's Democratic Republic by May 2014 (Qi *et al.*, 2013).

The timelines of emergence of AIV strains and occurrence of various avian influenza outbreaks have been highlighted in Fig. 2.

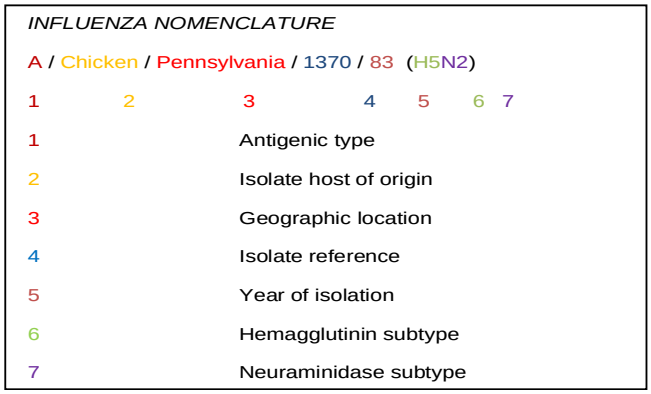


Fig. 2: Emergence of various AIV strains

**Genetic basis/mechanism of evolution**

The diversity in viral gene pool is established through co-circulation of various AI virus strains that may lead to newer strains by virtue of constant evolution. At genetic level, it is attributed to phenomenon of Antigenic DRIFT and Antigenic SHIFT.

*Antigenic DRIFT* is a process of small changes, called point mutations that occur during the normal process of virus replication. Antigenic drift changes the virus just enough that host do not have complete immunity to the new strain after the changes occur but lacks complete change in antigenicity. This occurs frequently but unpredictably and results in minor changes in the shape of virus surface proteins, particularly haemagglutinins (H). This hugely leads to changes in transmissibility and pathogenicity of virus (Webster *et al.*, 1982).

*Antigenic SHIFT* is mechanism that leads to major antigenic changes causing emergence of a new influenza A virus subtype. It may be through *genetic reassortment* (human and animal viruses) or *mutations* (Antigenic Drift) leading to direct animal (poultry) to human transmission (Meena and Cindi, 2011). Occurrence of influenza 'A' viruses of two different subtypes, if simultaneously infects the same host, allows "reassortment," or exchange of viral RNA segments in the host's cells, resulting in a new virus that contains genes from both subtypes. Pigs have been considered effective "mixing vessels" because they contain receptors for both avian and human influenza viruses. Pigs may be infected both by human and avian influenza A viruses at the same time, and a new 'reassorted' virus may emerge that would possibly contain genetic material from both original viruses (Ma *et al.*, 2009). Similarly, the humans may also act as mixing vessels. For this reason, it has been hypothesized that widespread vaccination of human populations with seasonal influenza vaccine might help in reducing circulation of seasonal influenza viruses among humans. Consequently, it will reduce the likelihood of reassortment process of these seasonal viruses within humans.

The existences of H1N1, H2N2, H3N2, H5N1, H7N7, H5N6 etc. are result of *antigenic shift*. For example, a circulating H1N1 virus from 2009 outbreak onwards is the result of mixing different flu viruses-swine influenza, avian influenza and human influenza. This reassortment might retain the transmissibility characteristics of a human seasonal influenza virus and the pathogenicity and virulence characteristics of an avian virus. Direct infections of humans with avian influenza A (H5N1) viruses have occurred and it is attributed to antigenic drift.

At molecular level, researchers have explained evolution by two mechanisms. First one is a known fact that RNA viruses evolve by mimicking some of the features of their host's genes (DNA) or their corresponding mRNAs too. The Influenza A virus - originated from an avian reservoir and replicated in humans over many generations, mimicking of human genes leading to reduction in frequency of CpG dinucleotides in their genome for better adaptation. This is commonly thought to be due to methylation and deamination of Cytosine residues in the dinucleotide (Greenbaum *et al.*, 2008). Second mechanism describes acquiring of additional or replacing the existing amino acids by basic

amino acids in hemagglutinin protein and PB1-F2 proteins that helps in breaking the specie barrier (via receptor binding) and evading host immune response (Horimoto and Kawaoka, 1995; Nelson and Holmes, 2007).

Apart from 'host jumping', another important implication of evolution of avian influenza is capability of developing *drug resistance* to existing antiviral drugs. There are two categories of US-FDA approved anti-influenza viral drugs viz. Neuraminidase Inhibitors {Oseltamivir (Tamiflu®), Zanamivir (Relenza®), Peramivir (Rapivab®)} and Adamantanes (Amantadine and Rimantadine). The mechanism of drugs have been demonstrated pictorially in figure 3.The US-FDA has recently discontinued the use of Adamantanes in United States because of high levels of antiviral resistance to these drugs among circulating influenza viruses including H1N1 (Fiore *et al*., 2011). Oseltamivir is the most common clinical drug for treating influenza as it is effective and easy-to-use (by oral administration). Recent reports of circulating drug-resistant strains of H1N1 and H5N1 indicates grave future threat (Monto, 2009).

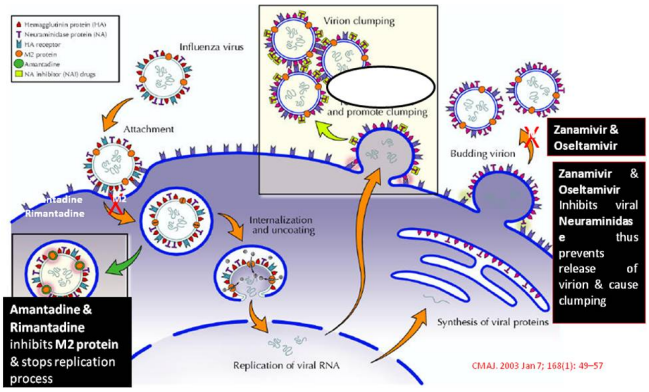


Fig. 3: Pictorial representation of mechanism of action of anti-influenza drugs

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