

# Emergence of Human Avian-Influenza

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## Abstract

Emerging viral diseases have become major public health problem in the World. Human-avian influenza is one of emerging viral diseases that significantly contribute to the global burden of respiratory diseases. The objective of this review was to discuss the most recent human-avian influenza outbreak documented in 2021. On basis of their epidemiological features, influenza in humans can be classified as seasonal influenza, pandemic influenza and human-avian influenza. Influenza in humans that are caused by avian influenza viruses which are transmitted across species to humans is known as human-avian influenza. So far, three avian influenza viruses have been recognized to cause human-avian influenza, namely, Asian H7N9 viruses, H5N1 viruses and H5N8. The most recent human-avian influenza outbreak was caused by H5N8, which was documented on February 2021 in Russia. The outbreak was associated with contact with H5N8 infected domestic birds. As the influenza viruses constantly evolve, there is possibility of global outbreak of the disease. Thus, it is necessary to take preparedness actions to counter pandemic threats as they are identified.

**Keywords:** Human-avian influenza; Emergence

## Introduction

Influenza (flu) is an acute respiratory disease that is caused by influenza viruses [1]. Influenza significantly contributes to the global burden of respiratory diseases. Each year influenza epidemics kill about half a million people [2]. Human-avian influenza has been recognized as one of the recently emerged viral diseases [3]. The purpose of this review is to discuss the most recent human-avian influenza outbreak.

## Epidemiology of Influenza

### General Epidemiology of Influenza

Influenza has a worldwide distribution involving all age groups, which usually occurs each winter [4]. The virus spreads through inhalation of droplets and aerosols as well as by contact with contaminated objects. The World Health Organization (WHO) estimates that annual influenza epidemics cause 3 to 5 million cases of severe illness, and among them about 290,000 to 650,000 fatalities [5]. In developing countries, 99% of deaths in children under 5 years and older people associated with influenza related lower respiratory tract infections [6]. Influenza is one of the public health problems in Ethiopia, which peaks from November to December [7].

On basis of their epidemiological features, influenza in humans can be classified as seasonal influenza, pandemic influenza and human-avian influenza. Seasonal influenza is caused by both influenza A and influenza B viruses [2]. Whereas, pandemic influenza is only caused by influenza A viruses [4]. Influenza

in humans that are caused by avian influenza viruses which are transmitted across species to humans is known as human-avian influenza [8].

The four influenza pandemics that occurred in the last century were caused by only three subtypes of influenza A viruses (H1N1, H2N2, and H3N2). Annually, seasonal influenza continues to occur in temperate regions of the world by new subtypes of influenza viruses which arises from antigenic drift [4]. Unlike seasonal influenza, the occurrence of pandemic influenza is difficult to predict. Mortality caused during different influenza pandemics varies and it is difficult to predict in advance. During the 1918 pandemic, H1N1 pandemic caused at least 50 million deaths globally. Whereas, during the most recent influenza pandemic (2009), H1N1 pandemic caused 250,000 to 500,000 deaths globally [4]. The evolution of new subtypes of influenza A viruses that caused the four influenza pandemics aroused mainly from antigenic shift that developed by reassortment [4].

In temperate regions, seasonal influenza typically occurs annually in the late winter [9]. Seasonal influenza in Ethiopia occurs from September through January which peaks in November (which is caused by H3N2 and A (H1N1) pdm09) and from November to April (that is caused by influenza B virus, which peaks in March) [7]. According to Centers for Disease Control and Prevention (CDC), in the United States, influenza has resulted in between nine million to 45 million illnesses, between 140,000 to 810,000 hospitalizations and between 12,000 to 61,000 deaths annually since 2010 [10].

The following are avian influenza viruses that have been recognized to cause human-avian influenza: H5N6, H6N1, H7N2, H7N3, H7N4, H7N7, H5N8, H5N1, H5N8, H7N9, H9N2, H10N7 and H10N8 [8,10-12]. Human-avian influenza which is caused by an Asian H7N9 virus was first reported in China in March 2013. But before this time, the virus had seen neither in animals nor in humans. However, since March 2013, human and animal infections with H7N9 have been observed in China. Since the discovery of the virus, Asian H7N9 has caused more than six influenza outbreaks in humans in China [10]. The largest H7N9 outbreak was recorded from October 1, 2016 through September 30, 2017, during which 766 human infection with Asian H7N9 virus was documented [10].

Influenza, which is caused by H7N9 virus, is of concern because it causes severe respiratory illness (e.g., pneumonia) and has high fatality rate. During the past outbreaks, about 39 percent of people confirmed with Asian H7N9 virus infection died. Most human infections with avian influenza viruses in general and Asian H7N9 virus in particular, occur after exposure to infected poultry or contaminated environments, especially markets where live birds have been sold [10].

Human-avian influenza caused by highly pathogenic avian influenza virus of type A of subtype A (H5N1) (HPAI A (H5N1) was first detected in humans in 1997 during a poultry outbreak in Hong Kong [13]. Sporadic human infections with H5N1 have been reported in Asia and later in Africa, Europe, and the Middle East since 2003. Human infections with this virus have been associated with severe disease and death [13]. Today, six countries are endemic for the HPAI H5N1, including China, Egypt, India, Indonesia, Bangladesh, and Vietnam. Canada was the first country in the Americas that reported the first human infection with HPAI Asian H5N1 virus in January 2014. The index case was a traveler who had recently returned from China to Canada [13].

### Epidemiology of H5N8

H5N8 is a subtype of influenza A viruses and highly lethal to poultry and wild birds. The spread of the H5N8 viruses was started in 2014 and caused several waves of disease outbreaks in wild birds and domestic poultry across different continents. In early 2014, novel reassortant H5N8 viruses bearing the subclade 2.3.4.4 HA gene caused multiple outbreaks in migratory birds and domestic ducks in South Korea [14]. During these outbreaks, two distinct groups of H5N8 viruses, Buan2-like and Cochang1-like, were identified. The Buan2-like H5N8 viruses predominated [14], were subsequently spread to Europe, North America, and East Asia by migratory birds, and formed three distinct subgroups [15,16]. In late May 2016, Cochang1-like H5N8 viruses were detected in wild migratory birds at Ubsu-Nur Lake in Mongolia, and then rapidly spread to other European Countries. By August 2017, 1,112 outbreaks in domestic and 955 outbreaks in wild birds in 30 European countries had been reported [17]. In addition, Cochang1-like H5N8 viruses were detected in many countries in Asia and Africa during the second wave of H5N8 outbreaks in 2016–2017 [18–20]. In January 2020, H5N8 viruses caused outbreaks in chickens in Poland and then started a new wave of outbreaks in poultry and wild birds globally [21–23].

The most recent human avian influenza infection was documented in February 2021 in Russia. The outbreak was first detected in farm workers which were found positive for H5N8 infection, who participated in a response operation to contain H5N8 outbreak detected in a poultry farm in the Russian Federation in February 2021. This is the first human infection with H5N8 [3]. H5N8 manifests itself in various ways, from sub-clinical to highly lethal in some population

[24]. H5N8 is a highly pathogenic avian influenza virus with mortality rate of 75% [25].

### Virology

Influenza viruses belongs to the family *Orthomyxoviridae* [26,27]. The Virus family of *Orthomyxoviridae* is characterized by six to eight segments of linear negative-sense single stranded RNA, with a total genome size that ranges from 10,000 to 14,600 nucleotides. The family *Orthomyxoviridae* contains seven genera: *Alphainfluenzavirus*, *Betainfluenzavirus*, *Deltainfluenzavirus*, *Gammainfluenzavirus*, *Isavirus*, *Thogotovirus*, and *Quarantavirus*. The first four genera contain influenza viruses that cause influenza [27].

The size of the virions of influenza viruses ranges from 100 to 120nm in diameter and have a length of up to 20 μm [28,29]. The virions of influenza viruses are similar in composition [30], that are made up of a viral envelope containing the glycoproteins neuraminidase and hemagglutinin wrapped around a central core. The central core contains the viral RNA genome and nucleoprotein as well as other viral proteins that package and protect the RNA [31]. The nucleocapsid consists of helically symmetrical nucleoprotein. Unlike most viruses, influenza viruses have unusually a multipartite genome, which contains seven or eight pieces of segmented negative-sense RNA [30]. For example, Influenza A and B viruses each contain eight segments of single-stranded RNA (for influenza A virus 2341 nucleotides to 890 nucleotides chain length), and influenza C viruses contain seven segments of single-stranded RNA [30].

On the basis of variation in the nucleoprotein antigen, influenza viruses are classified into four types, namely influenza type A, B, C and D. Influenza in human is caused by three types of influenza viruses: A, B, and C [1]. So far, influenza D viruses have not been shown to cause disease in human beings. Influenza D viruses primarily affect cattle. Influenza A and B viruses are the only viruses that have caused seasonal influenza outbreaks (which is also called the flu season). Almost every winter in the United States, Influenza A viruses are the only viruses known to cause influenza pandemics. Influenza type C viruses infect humans, dogs and pigs [32]. This virus causes mild illness and has not shown to cause human flu epidemics [1]. Birds, particularly wild aquatic birds are the natural hosts for large variety of influenza A viruses [33]. Dogs, pigs, horses, bats, and other animals are also infected by influenza A viruses [34]. Humans, Seals and Ferrets, are the only animals known to be infected with influenza B viruses [1,35,36].

Influenza A viruses are further classified into subtypes based on the composition of the two surface proteins (Hemagglutinin (H) and Neuraminidase (N)) of the viruses. There are 18 different Hemagglutinin (HA) subtypes and 11 different Neuraminidase (NA) subtypes (H1 through H18 and N1 through N11, respectively) [37,38]. However, only H1, H2, or H3 combined with N1 or N2 have been commonly found to infect humans. Subtypes are named by combining the H and N numbers. For example, H3N2 represents a virus with Hemagglutinin (H) of type 3 and Neuraminidase (N) of type 2 [37,38].

Influenza A subtypes can be further classified into different genetic clades and sub-clades (which are also known as groups and sub-groups). For example, influenza A subtype A (H1N1) is further divided into the clade A(H1N1) 6B.1 and sub-clade A(H1N1) 6B.1A. Like influenza A viruses, influenza B viruses are also further divided into clades and sub-clades. Influenza B viruses are divided into two clades: lineage B/Yamagata and lineage B/Victoria [1].

One of the major challenges of controlling influenza is the high mutation rate of influenza viruses [39–41], which necessities the

development of new versions of vaccines every year. Both influenza A and influenza B viruses are equally prevalent among human beings. However, the genes of influenza A viruses evolve two to three times faster than the corresponding genes in influenza B viruses [39-41]. The high evolutionary rate of influenza A viruses can be explained by the fact that the human immune system has positive selection for influenza A viruses [42-44]. The low rate of antigenic change coupled with the limited host range of influenza B viruses (which limits cross species antigenic shift) [39-41], reduces the possibility of the occurrence of influenza pandemics caused by influenza B viruses. The currently circulating influenza A subtypes are related to the virus that caused the 2009 flu pandemic [1]. The virus is called A (H1N1) pdm09 virus, and more generally known as 2009 H1N1, which has continued to circulate seasonally since then.

### Clinical Features of Influenza

Clinical features of avian influenza vary from mild to severe depending on the virus subtype and host factors. Hospitalization and death occur mainly among high risk groups. Influenza is characterized by the abrupt onset of fever, runny nose, sore throat, headache, myalgia, malaise, non-productive cough and extreme fatigue [45]. Pneumonia is the most common serious complication of the disease. Influenza may also leads to exacerbations of underlying pulmonary and cardiac diseases [46]. The most frequent serious complications of influenza are pulmonary problems, which are categorized into four groups as follows [46]:

1. Primary influenza pneumonia
2. Secondary bacterial pneumonia
3. Pneumonia that arises from opportunistic pathogens &
4. Exacerbations of chronic pulmonary diseases.

Avian influenza A viruses are designated as Highly Pathogenic Avian Influenza (HPAI) or Low Pathogenicity Avian Influenza (LPAI) based on the ability of the virus to cause severe disease and mortality in chickens in a laboratory setting. HPAI viruses can cause severe respiratory syndromes, pneumonia, and death. There are virtually hundreds of HPAI strains, however, only few that have been shown to cause infection in humans are; H5N1, H5N8, H7N3, H7N7, and H9N2 [47-49]. HPAI viruses have led to significant economic losses due to the death and culling of infected birds, in addition to trade restrictions in order to contain virus outbreaks [50].

The vast majority of reported infections with subtypes other than H5 or H7 were relatively mild, often resulting in upper respiratory symptoms and conjunctivitis [51]. Majority of H5N1 and H7N9 infected patients develop severe symptoms, including inflammation of the lower respiratory tract (e.g. bronchiolitis and pneumonia), respiratory distress and multiple organ dysfunctions [47,48,52]. Notably, high levels of plasma pro-inflammatory cytokines and chemokines are detected in H5N1 and H7N9 infected patients, possibly contributing to pathogenicity in humans [53, 54]. Incubation periods are estimated at 3-5 days [47,48]. The average time from onset of illness to death is commonly 8-12days [49].

### Diagnosis, Treatment and Prevention of Influenza

The most effective approaches in prevention and control against influenza disease are vaccination and antiviral therapy. Vaccination is the best way to protect people against flu and prevent its spread. World Health Organization (WHO) recommends yearly vaccination for nearly all people over the age of six months [55]. Trivalent Inactivated Vaccines (TIV) and Live Attenuated Influenza Vaccine

(LAIV) are developed each year against the strains most likely to cause the disease in the next winter. The Trivalent vaccines are consisted of two influenza A strains and one influenza B strain [56]. In the United States of America in 2012, a quadrivalent LAIV was licensed for intranasal application containing 2 influenza A strains and 2 influenza B strains [55]. In Ethiopia, vaccination against influenza, specifically immunization is done to prevent the spread of H1N1 infection since 2010 [56].

Recent progress on the development of a universal influenza vaccine has shed light on possible strategies to prevent infection with any subtype of influenza viruses in the future. These vaccines are designed to elicit antibodies targeting conserved regions across all known influenza strains and a number of clinical trials are ongoing [57-59].

Diagnostic tests that have been used for the detection of influenza viruses include viral culture, reverse transcription polymerase chain reaction (RT-PCR), rapid antigen testing, and serology [60]. The most common clinical treatments of influenza are neuraminidase inhibitors including, oseltamivir, zanamivir and peramivir [61,62]. The other two older drugs, amantadine and rimantadine, which is Matrix-2(M2) proton channel blockers, have been approved for treatment and prevention of influenza A virus infection [63]. However, many emerged strains of influenza A virus (such as 2009 H1N1 influenza virus) have reportedly shown resistance to these drugs. Accordingly, amantadine and rimantadine are not recommended to be used for current circulating influenza A viruses [64]. Baloxavimmarboxil (Xofluza™) was approved for the treatment of influenza patients in 2018. By inhibiting virus polymerase activity, this antiviral provides a therapeutic option to combat viruses that are resistant to the other currently approved drugs targeting the influenza NA and M proteins [65].

### Conclusion

The most recent human-avian influenza outbreak was associated with contact with H5N8 infected domestic birds. The recent human avian influenza outbreak suggests the possibility of occurrence of human-avian influenza pandemic in the future. Therefore, it is necessary to take preparedness actions to counter human avian influenza pandemic threats. In addition, it is necessary to undertake public education on the different ways of transmission of influenza viruses. Moreover, immunization can be taken for those at high-risk of being infected by the virus as an additional measure of preventing human avian influenza outbreaks in future.

### Conflict of Interest

The authors declare that he has no competing interest.

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