

# Systematic Literature Review of Avian Influenza Virus Prevalence in Birds and Humans Globally from 1918 to 2018

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# ABSTRACT

Avian influenza viruses are now widely recognized as important threats to agricultural biosecurity and public health, and as the potential source for pandemic human influenza viruses. Human infections with avian influenza viruses have been reported from Asia (H5N1, H5N2, H9N2), Africa (H5N1, H10N7), Europe (H7N7, H7N3, H7N2), and North America (H7N3, H7N2, H11N9). Direct and indirect public health risks from avian influenza are not restricted to the highly pathogenic H5N1 "bird flu" virus, and include low pathogenic as well as high pathogenic strains of other avian influenza virus subtypes, e. g., H1N1, H7N2, H7N3, H7N7, and H9N2. Research has shown that the 1918 Spanish Flu pandemic was caused by an H1N1 influenza virus of avian origins, and during the past decade, fatal human disease and human-to-human transmission has been confirmed among persons infected with H5N1 and H7N7 avian influenza viruses. Our ability to accurately assess and map the potential economic and public health risks associated with avian influenza outbreaks is currently constrained by uncertainties regarding key aspects of the ecology and epidemiology of avian influenza viruses in birds and humans, and the mechanisms by which highly pathogenic avian influenza viruses are transmitted between and among wild birds, domestic poultry, mammals, and humans.

Keywords: Avian influenza; Human influenza; Epidemiology; Virus

### INTRODUCTION

Avian influenza or bird flu is a highly contagious acute viral disease that can occur in epidemics and cross-border forms in poultry. Influenza A viruses are the etiological agent of avian influenza and belong to the Orthomyxoviridae family. Influenza viruses also includes types B, C, and D viruses; however, there is no evidence that type B, C, and D can infect avian species. The natural reservoir of influenza A viruses are avian species within the orders Anseriformes and Charadriformes. At least 16 of the 18 known haemagglutinin subtypes (H1-H16) and 9 of the known neuraminidase (N1-N9) subtypes have been identified in avian species. Additionally, influenza A viruses can also infect different mammal species including humans, horses, pigs, cats, dogs, and even some marine mammals.

Furthermore, a new lineage of influenza A viruses have been recently identified in bats in Guatemala and Peru, suggesting the existence of other natural reservoirs of the virus. Nevertheless, the mechanisms that allow some influenza A viruses to cross the interspecies barrier

are not clearly understood. Influenza A viruses are pleomorphic, enveloped, and contain 8 genomic segments of negative- sense single strand RNAs (-ssRNA). The high genetic variability of this virus is the result of its mutagenic capacity (antigenic drift) and its potential to exchange genetic segments when two or more viruses infect the same cell (antigenic shift) [1]. These mechanisms of viral diversification have allowed the emergence of new variants, some with zoonotic and pandemic potential, hindering prevention, control, and treatment. Additionally, these genetic changes may be associated with patterns of infection (e.g., epidemic or pandemic) and the course of the disease (morbidity and mortality rates).

The current widespread outbreaks of avian influenza among domestic fowl throughout eastern Asia have reawakened concern that avian influenza viruses may again cross species barriers to infect the human population, either directly or via intermediate hosts, and thereby initiate a new influenza pandemic comparable to the great pandemics of 1918 ("Spanish flu"), 1957 ("Asian flu"), 1968 ("Hong Kong flu"), and 1977 (H1N1 virus). A recent survey of influenza A viruses isolated from feral Canadian ducks over a

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period of 17 years confirmed the stability of the gene pool and, at the same time, revealed that extensive reassortment of genes was occurring more or less at random, so that all combinations of H and N antigen subtypes were present [2].

#### Human-to-human transmission

Human-to-human transmission has been documented for H5N1 and H7N7 avian influenza viruses, and human-to-human transmission of an H7N2 avian influenza virus may have occurred during a May 2007 outbreak in the United Kingdom. Human-tohuman transmission of an H5N1 HPAI virus was first documented during the 1997 outbreak in Hong Kong, and subsequent instances of probable human-to-human transmission of H5N1 viruses have been reported from Thailand, Vietnam, Indonesia, and Pakistan. Human-to-human transmission of highly pathogenic H7N7 virus was documented in conjunction with a widespread series of outbreaks of a highly pathogenic H7N7 virus among poultry farms in the Netherlands during March–May 2003, in which there was at least one human fatality from this virus among the 89 cases diagnosed at the time of the outbreak [3].

#### Prevention and control

On April 27, 2007, the United States of America Food and Agriculture Administration (FDA) authorized the first HPAIV H5N1 vaccine to humans for the protection of groups at high risk. The Food and Agriculture Organization of the United Nations published the list of the manufacturers of poultry influenza vaccines (FAO, 2012a). Vaccinations may reduce the risk of infection and lower virus output, with birds representing a lower sanitary risk, and may be used for poultry surrounding outbreaks zones. The three categories of strategies proposed for vaccination by FAO are: (1) Response to an outbreak, employing perifocal vaccination (ring vaccination) or vaccination only of domestic poultry at high risk, in combination with the destruction of infected domestic poultry; (2) Vaccination in response to a "trigger", upon the detection of the disease by surveillance studies, in areas where biosecurity is difficult to be implemented (e.g., high density of poultry farms); and (3) Preemptive baseline vaccination of chickens and other avian species when the risk of infection is high and/or the consequences of infection are very serious (Figure 1).



After the influenza outbreaks in poultry and the potential pandemics threat to humans caused by the HPAIV of the H5N1 subtype, improvements in biosecurity and the use of inactivated vaccines are the two main options for the control of the disease.

Vaccines against avian influenza are designed to induce the protection of flocks, preventing outbreaks, and can be used as tool in perifocal vaccinations to fight isolated episodes of the disease Although in the United States the control of the HPAIV was obtained by eradication programs, strategies were also employed against the velogenic and mesogenic strains of the Newcastle disease virus. On April 27, 2007, the U.S. Food and Drug Administration (FDA) approved the first vaccine against HPAIV H5N1 for use in humans at high risk of infection. A model plan for human influenza pandemics preparedness was published in Ireland.

### MATERIALS AND METHODS

Data used from WHO, the Hong Kong Centre for Health Protection of the Department of Health of the Government of Hong Kong SAR and Jiang et al. globally. All cases occurred in mainland China. According to an article in 2017, 12 deaths due to A(H5N6) have been reported since 2014. The latest case was reported in January 2018 with disease onset on 19 December 2017. Data used from WHO, the Hong Kong Centre for Health Protection of the Department of Health of the Government of Hong Kong SAR [4].

Number of human cases due to A(H5N6), clade 2.3.4.4, infection by year of onset, 2014-2018 (n=19) HPAI A(H5N6) virus of clade 2.3.4.4 from South Korea showed a higher pathogenicity and viral replication in the upper respiratory tract in ferrets than a HPAI A(H5N8) virus. HPAI A(H5N6) was transmitted between ferrets through direct contact, whereas HPAI A(H5N8) did not transmit between ferrets. Both viruses had strong  $\alpha$ -2,3 syliac acid receptor specificity with low  $\alpha$ -2,6 syliac acid receptor specificity indicating an avian receptor preference. Unlike HPAI A(H5N8), the HPAI A(H5N6) virus had a NA stalk deletion and an 80 to 84 residue deletion in the NS1 gene. This study indicates a higher potential for HPAI A(H5N6) than for A(H5N8) to infect humans. Experiments with AI H5Nx viruses of clade 2.3.4.4 suggested that the lack of glycosylation could be involved in the induction [5]. A T160A mutation in the HA protein, which exhibits binding to the α-2,3 and  $\alpha$ -2,6 receptors (Figure 2).



# Signs and symptoms of avian influenza a virus infections in humans

Signs and symptoms may depend on which avian influenza A virus caused the infection. Low Pathogenic Avian Influenza (LPAI) A virus infections of humans have been associated with generally mild, non-fatal illness. The reported signs and symptoms of LPAI A virus infections in humans have ranged from conjunctivitis to influenza-like illness (e.g., fever, cough, sore throat, muscle aches) to lower respiratory disease (pneumonia) requiring hospitalization.

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On the other hand, Highly Pathogenic Avian Influenza (HPAI) A virus infections of humans have been associated with a wide range of illness. Illness has ranged from conjunctivitis only, to influenza-like illness, to severe respiratory illness.

# **RESULTS AND DISCUSSION**

### Prevention and control

On April 27, 2007, the United States of America Food and Agriculture Administration (FDA) authorized the first HPAIV H5N1 vaccine to humans for the protection of groups at high risk. The Food and Agriculture Organization of the United Nations published the list of the manufacturers of poultry influenza vaccines (FAO, 2012a). Vaccinations may reduce the risk of infection and lower virus output, with birds representing a lower sanitary risk, and may be used for poultry surrounding outbreaks zones. The three categories of strategies proposed for vaccination by FAO. Response to an outbreak, employing perifocal vaccination (ring vaccination) or vaccination only of domestic poultry at high risk, incombination with the destruction of infected domestic poultry. Vaccination in response to a "trigger", upon the detection of the disease by surveillance studies, in areas where biosecurity is difficult to be implemented (e.g., high density of poultry farms) and Pre-emptive baseline vaccination of chickens and other avian species when the risk of infection is high and/or the consequences of infection are very serious [6]. After the influenza outbreaks in poultry and the potential pandemics threat to humans caused by the HPAIV of the H5N1 subtype, improvements in biosecurity and the use of inactivated vaccines are the two main options for the control of the disease (Figure 3).



The early serologic data suggested that many older adults had some cross-reactive immunity to the pH1N1 due to prior infection with antigenically related strains, while children and most young adults were immunologically naive.

# Highly versus low pathogenic avian influenza viruses (HPAIV vs. LPAIV)

AIV are typed according to their pathogenicity in chickens into Low Pathogenic (LP) and Highly Pathogenic (HP) strains. LPAIVs are maintained in wild aquatic birds almost without developing severe clinical signs of the disease. The clinical signs in domestic poultry induced by LPAIVs include a body weight reduction and/ or a slight drop in egg production in layers poultry. In contrast to LPAIV, the HPAIV phenotype is restricted to H5Nx, H7Nx, and H9N2 subtypes that carry a multibasic cleavage site in their HA protein [7-10].

## CONCLUSION

There are two main types of influenza, influenza A and influenza B. Influenza A viruses are divided into subtypes based on the Hemagglutinin (H) and Neuraminidase (N) proteins on their surfaces. Influenza A viruses infecting humans have been primarily subtypes H1, H2, and H3 while influenza A subtypes H1 through H17 can infect birds and other animals such as pigs. There are in addition ten different neuraminidase surface proteins. Reservoirs for influenza A viruses include humans, swine, poultry and other birds and mammals. Humans are the primary reservoir for influenza B. Seasonal influenza viruses spread person-to-person primarily through large-particle respiratory droplet transmission (e.g., when an infected person coughs or sneezes near a susceptible person). Transmission via large-particle droplets requires close proximity between source and recipient persons because droplets do not remain suspended. In the air and generally travel only a short distance (<6 feet). Other possible routes of influenza transmission are mucosal inoculation from hands touching contaminated surfaces and airborne transmission. The relative contribution of each type of transmission has not been defined but for airborne transmission is thought to be small. Avian and swine influenza viruses are generally less transmissible from person-to-person than seasonal influenza viruses. These viruses are primarily transmitted from animals to humans directly or through environmental contamination. However, limited person-to-person transmission has been described with these viruses.

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