Avian influenza virus and human: pandemic concern and threat?

Type A influenza viruses cause natural infections in human and other animals especially in birds. Wild aquatic birds are the natural hosts for all known influenza type A viruses. Avian type viruses are divided into two groups: highly pathogenic avian influenza (HPAI) and low pathogenic avian influenza (LPAI). HPAI virus is very dangerous but LPAI virus is much weaker. Two forms of mutations have been recognized for antigenic changes in influenza viruses: drift and shift. Antigenic shift is responsible for producing re-assortment viruses with a potentiality to be transmissible to human and possibly resulting in pandemic. A new species of viruses, the loss of previous immunity in human population and the ability for influence and transmission from human to human are three major conditions needed for occurrence of influenza pandemic in human. When pandemic happens, public health is a major concern due to probability of high case fatality rate and other socioeconomic consequences.

**Keywords:** influenza A virus, Human, Pandemics

**Introduction**

The influenza A virus has a membrane and consists of 8 pieces of RNA. The virus is a member of the family Orthomyxoviridae. Type A is responsible for recurrent epidemics almost every year and also is responsible for pandemics, which have high mortality in human. Spanish flu in 1918, Asian flu in 1957 and Hong Kong flu in 1968 are examples of such pandemics. It is told that Spanish flu in 1918 have killed nearly 40 million, the pandemic between 1957 and 1968 is also responsible for respectively 4 and 1 million deaths (1,2). 8 pieces of RNA produce about 10 proteins: Neuramynidaze (NA), hemagglutinin (HA), matrix protein M1 and M2, non-structural protein NS2 and NS1, nucleocapsid protein and three polymerase: PB1, PB2 and PA. Lately, some influenza virus PB1 gene expresses protein known as PB1-F2 (3). Type A influenza virus containing HA and NA antigens. Mutations in the viral antigens leads to regular changes over time will and called antigenic drift. In this
circumstance only minor antigenic changes will be occurred. The other antigenic change called antigenic shift is responsible for rapid and dangerous variation of the virus (recombinant or reassortment), that if occur, is the major cause of epidemics and pandemics. This phenomenon occurs when two (or more) influenza viruses infect the same cell (1). Currently 16 H and 9 N types have been identified. Clinical and pathogenic H5N1 human infections in comparison with seasonal influenza are different (4). H5N1 influenza infection may be clinically caused diarrhea, liver and kidney failure and severe pneumonia. All of these effects related to systemic conditions (sepsis like syndrome), respectively. For example, in some cases after being infected with the virus, no viruses directly enter into the liver cells and liver inflammation can caused by kupfer cells (4-6). Based on some of the tests after death, evidence of viral response in organs outside the lungs or intestines has been reported. For verifying that other organs are also involved by infection, more investigations are needed. In some patients with H5N1 virus that cause CSF inflammation and no other complications, the virus has been isolated from the cerebrospinal fluid (4, 6, 7). The range of age for the H5N1 disease has been classified between 3 months to 75 years with an average of 18 years. The first signs of the disease appears after 2 to 4 days from the last contact with infected poultry. At this time it is not been determined how much virus can enter the body. The majority of patients with H5N1 influenza have symptoms such as fever, cough, shortness of breath and signs of pneumonia (1, 8-11). Infection is limited to the lungs and no evidence of bacterial infection is found. Non-respiratory symptoms often include diarrhea, vomiting and abdominal pain have been reported. H5N1 virus also can enter into the cerebrospinal fluid and infect the central nervous system (CNS). Although the norotrophic tendency of H5N1 virus in many mammals, such as rats and cats have been observed, the involvement of CNS in human is very rare. The important point is that seasonal influenza virus rarely may lead to diseases of the CNS. Diseases related to the deadly H5N1 virus during pregnancy have been
reported, but the possibility of infection of the fetus is not yet certain. Mild cases of H5N1 will appear as flu like syndrome as reported in Hong Kong in 1997. The clinical course of human H5N1 virus is often started with rapid progression of infection to respiratory disease in the lower respiratory tract (LRT). Ordinary course for transmission of virus to patients in hospital is 4 days and the time for probable death is 9 days. Acute Respiratory Disease Syndrome (ARDS) is the outcome. Failure of many organs, especially kidneys and heart, Reye's syndrome, pneumothorax and pulmonary hemorrhage should be considered as its complications. Also the virus infected cells maybe undergo the energy depletion. The effect of human Influenza A Virus (IAV) on mitochondrial showed decrease in cell respiration (19).

In most cases, sudden death due to acute respiratory failure has been reported. Approximately more than half of patients are under 20 years and 89% of patients are under 40 years. The mortality rate of H5N1 in age from 10 to 19 years old is reached to highest level (76%) (4,12-14). For diagnosis purposes, in areas where prevalence of the disease is unusual, experimental observations can be strong reason for presence of avian influenza virus. The accuracy of the results is still under discussion. It requires a complete list of all suspected factors (which are interfering in the test results) and needs using very sensitive methods including viral culture, revealing the antigens, nucleic acid detection by RT-PCR, and detection of antibodies. As a matter of principle in areas where the flu virus is active, Patients with severe pneumonia should be evaluated in terms of virological assay for detection of influenza virus and in case of positive result other species of H5 Should be studied and appropriate treatment, care and epidemiological control measures should be considered (14,15). In severe cases lymphopenia, thrombocytopenia, and in some cases increasing the amount of albumin and lactate dehydrogenase and creatinekinase will also be occurred. In acute cases cytokines and chemokines are also increased. Rapid culture decreased the time required but has low sensitivity. Serological diagnostic tests for severe cases of the disease are not useful for rapid
RT-PCR testing is very reassuring and studies in Hong Kong have shown a sensitivity of 100%. Rapid antigen tests for the detection of H5N1 virus do not have much credibility (positive 33% in Vietnam and 86% in Hong Kong) (15). Microneutralization evaluation test is more sensitive than inhibitor Hemaglutination (HI), although it consumes time for about 96 hours and laboratory biosafety class 3 is required. Microneutralization test has a sensitivity of 88-100% in children and 96-80% in adults (17, 18). Similar to H1N1 flu, the cytopathic effect (CPE) of H5N1 flu virus is detectable easily after 4 or 5 days of viral culture using madin-darby canine kidney cell (MDCK) (16,19).

Literature review

In most rural areas of Asia, domestic birds are kept in unsanitary conditions. This and other health problems make it difficult to know the prevalence of the disease. In some places stores that sell live chickens are opened overnight, and are suitable places for the progress and development of avian influenza virus. However, these places also help the virus survive. This virus enters from an infected chicken into the store, where they spread in the environment. The transmission can be reached to zero in rest-day (the day when the store is completely empty of birds) (20-24). In dead-up day (the day that chickens are killed) all birds are killed but the virus can still be transmitted. Personnel that have direct contact with birds or infected poultry materials are in danger (25,22, 23). Studies in Hong Kong and South Asia have shown that chicken shops can be considered as a key factor in the survival of the virus. In countries such as Indonesia and Vietnam there have week evidence of the role of the shops in transmission of the virus. But if so, the health intervention can prevent effective transmission (26-28). After infection with H5N1 HPAI up to 17 days, birds may show no symptoms to transfer it to others (29-31). Following entering chicken cells the virus can undergo antigenic variation even in the first turn of replication (29). In some parts of Asia birds are in farmland and can transmit the virus to other birds, and other domestic animals (32,33). According to
studies conducted in Thailand, it can be said that the increase number of chickens can result in increased risk factors for the spread of HPAI virus (32,34,20). Local or cross-border transport and mobility in increasing of transmission and spread of the virus also cannot be ignored. A standard principle for business related to birds and their products can also help to more prevention of viral transmission. Birds and fowl to be exported in bulk in international trading typically may be a major case for transmitting HPAI H5N1 virus. The use of chicken feces is also an important rout for transmitting the virus (35,26). Even with the wide range of genetic differences of H5N1 virus in Asia, only a small spectrum of the disease can spread to Europe and the South West towards India (36). While the displacement of birds and their products cannot be fully contributed to the spread of H5N1 virus, epidemic, biological and genetic evidence shows that the geographical spread of the virus in 2005 has increased because of the migrating birds and movement of poultry in local or regional area or their products. It is estimated that the displacement of birds and their products is a major factor in the H5N1 outbreaks, although this has certainly not been established (37). It is claimed that non-domesticated birds are also the source HPAI H5N1 virus (38,35). Tiger, leopard, cats and birds also can be infected by feeding of infected birds or infected carcasses. On the basis of serological evidence pigs are accidently infected. Although it seems that this virus will not become epidemic among pigs, but what is empirically proven is that vaccination of pigs results in infection of the pigs but no pig to pig transmission. Taken as a whole, the probable role of mammals is their potentiality as an intermediate host in the transmission of H5N1 to humans. The importance of this transmission would be more clear when a person without having a history of contact with infected birds becomes ill (39, 40,34 ,10,14). In 1997, the first report of human infection of H5N1 virus in Hong Kong was reported, with 18 cases and 6 deaths. The source and origin of the disease was in poultry where chickens, ducks, geese and other species of small birds are kept alive, and they sold for human consumption
In February 2003, when the world was faced with the disease so called SARS, Hong Kong H5N1 virus was detected in a father and son. However, at that time there was no clear data for ability of virus for human to human transmission. Spring and winter are the months for outbreak of human cases. Many organs of infected birds with HPAI H5N1 virus are the source of virus. Consumption of raw poultry or poultry products, including blood is dangerous. Because the symptoms of infection in many cases are not detected (especially ducks), the birds infected without symptoms are important factors for the spread of infection. Factors such as wet environment and climate and geographical conditions can be an important cause for rapid transmission. Contaminated things, such as water and chicken compost are the sources for the release of H5N1 virus in among people who apparently have no direct contact with birds. The virus is imported through the respiratory, gastrointestinal tract or conjunctiva of the birds and is transmitted to humans. There are reports of diarrhea in patients with H5N1 that result in intestinal infection in humans. Despite the high prevalence of the virus in birds in populated areas and high chance of exposure to humans, H5N1 has only been reported in a few populations. Influenza pandemics occurred in 1889, 1918, 1957, 1968, and 1977 are noticeable examples of pandemics in the past. Also recently the word faced with another influenza pandemic so called swine flu. For occurrence of a pandemic 3 conditions would be needed: 1) a new species of HA (and probably NA), 2) the loss of previous immunity in the human population, and 3) the viral ability for easily transmission from human to human. Fortunately, the virus has not yet shown this ability. Ecological factors affect the probability of pandemic. Of course, an increase in mobility (travel) and international trading play an important role in acceleration of the pandemics. It is not certainly clear whether access to anti-viral and health care in particular, can play a role in reducing the likelihood of pandemics. It is very difficult to predict what type of virus would be responsible for the pandemic. In fact,
genetically, the H5N1 virus is always modified among birds and the causative virus is endemic among them. The H5N1 may appear in an intermediate host, such as pigs but cannot leads to epidemic among them. However interaction between pigs and birds can result in transmission of the virus from pigs to poultry and from poultry to humans (48,49). Pandemics of 1957 and 1968 were related to HPAI viruses. Probably the next pandemic may be occurred by an LPAI virus that is already circulating among poultry or other domesticated birds without symptoms, for example H9N2 which also has the ability to infect pigs. Furthermore human cells may have susceptible receptors for the virus and thus as a matter the H9N2 virus could perhaps be considered for the next pandemic (48,43).

Conclusion
The logical explanation for fearing of H5N1 virus is not only the probability of pandemic but what is certain is the severe impact on humans. Virus transmission to human directly or through genetic changes can cause a hazard to humans. Although there is low probability of outbreak of H5N1, but serious risks occur in human societies. The effects on food supplies, economic losses and killing animals, especially birds are the serious outcome and impact of the virus on human populations. Despite all studies, what is clear so far is that the causes of prevalence of the disease in birds are still unclear. For more clarifications further studies needs to be done.

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References


