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## Avian Influenza: Global Threat

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### INTRODUCTION

Influenza virus has been the cause of human fatalities for many years. In the last 300 years about 10 influenza pandemics have been reported. During 1918 and-1919, this pandemic caused 50 to 100 million deaths worldwide which was a higher rate compared to the number of deaths during the two other pandemics in 1957 and 1968 (1). Similar to the pandemic of 1918, high morbidity and mortality rate has been reported in the pandemics occurring in the years 1830 and 1832 (2).

"Human influenza virus" usually refers to those subtypes that spread widely among humans. It is likely that some genetic parts of current human influenza A viruses originally came from birds. Influenza A viruses are constantly changing, and other strains might adapt over time to infect humans.

The three major influenza pandemics which occurred in 1918, 1957 and 1968 were all caused by a virus with bird source. The genes of viruses responsible for 1957 and 1968 pandemics were shown to carry a segment of the human virus along with the segments of bird virus. It thus seemed that the virus responsible for pandemic arose from the reassortment of a human virus with bird virus in an intermediate host (pig) (3).

However, recent studies indicate that the 1918 virus aroused from a mutation in the genes of the bird virus (4). The risk from avian influenza is generally low to most people, because the viruses do not usually infect humans. However, H5N1 is one of the few avian influenza viruses to have crossed the species barrier to infect humans, and it is the most deadly of those that have crossed the barrier.

Prevalence of avian influenza A virus in Hong Kong and occurrence of limited cases of human infection since 1997 poses an increasing pandemic threat. Moreover, since 2003 there has been a number of evidence suggesting the possibility of pandemic to occur, more than any other time (5).

An important point to be considered is the present population of the world which is about 6.5 billion, being thrice higher than the world population in 1918. Therefore, it is imaginable that even a mild outbreak would be accompanied by a high rate of morbidity and mortality (2).

### *Why the avian influenza A is a pandemic threat?*

The major source of avian influenza A virus is water fowl (6). These birds are contaminated with avirulent or low virulent species. Therefore, infection in these birds is either asymptomatic or associated with minor symptoms. However, these low pathogenic forms after contaminating domestic birds and other intermediate hosts transform into highly

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pathogenic form which are known as the cause of fowl plague (6, 7). This form may cause disease that affects multiple internal organs and has a mortality rate that can reach 90-100%, often within 48 hours.

Infected birds shed influenza virus in their saliva, nasal secretions, and feces and transmit the infection either directly or indirectly. Domesticated birds may become infected with avian influenza virus through direct contact with infected water fowl or other infected poultry, through contact with surfaces (such as dirt or cages) and materials (such as water or feed) that have been contaminated with the virus.

Avian influenza A virus is rarely transmitted from animal to human, as the receptors required for entering and proliferation of the virus are not present (8,9). However since 1997, evidence suggesting transmission of virus from animal to human have been reported, where this virus infected 18 people in Hong Kong, causing 6 deaths. The mortality rate was reported to be higher than 30% (10).

In 1999, H9N2 infections were identified in children in Hong Kong (11), while in 2002 another subtype of this virus, H7N7 occurred in The Netherlands in poultry in several farms. These cases occurred mostly among poultry workers. H7N7-associated illness included cases of conjunctivitis (eye infections), influenza-like illnesses with cough, fever, and muscle aches. Among 89 cases reported, a veterinarian who had visited one of the affected farms and developed acute respiratory distress syndrome and complications related to H7N7 infection, died. (12). In the same year H9N2 subtype was reported in a child in Hong Kong who had presented with influenza symptoms (13). In 2004, H7N3 infections occurred in Canada and 2 diseased cases were detected. The H7N3-associated, mild illnesses consisted of eye infections. At least 10 similar cases were reported among workers of a food corporation who had presented with conjunctivitis and upper respiratory tract symptoms (14). From the beginning of 2004 to August 2005 in 4 countries;

Vietnam, Thailand, Cambodia and Indonesia a total of 112 human cases were reported out of which 57 had died due to this infection (15).

During the 1997 epidemic in Hong Kong, 54 health care workers were evaluated serologically and one showed a high titer of antibody against this virus. This worker was thought to be infected probably through contact with infected patients (16).

Another case of human to human transmission occurred in Thailand in 2004; mother and aunt of a child had been infected due to direct contact with the infected child (17).

Influenza virus is still causing infection in humans all around the world. The latest report showed 12 cases of human infection in east provinces of Turkey and 3 cases in Iraq. To date, a total of 225 human cases infected with this virus has been detected of which 128 had died (table 1).

**Table 1.** Cumulative number of confirmed human cases of avian influenza A/(H5N1) Reported to WHO (2006).

country	2003		2004		2005		2006		Total	
	cases	death	cases	death	cases	death	cases	death	cases	death
Azerbaijan	0	0	0	0	0	0	8	5	8	5
Cambodia	0	0	0	4	4	4	2	2	6	6
China	0	0	0	8	8	5	10	7	18	12
Djibuti	0	0	0	0	0	0	1	0	1	0
Egypt	0	0	0	0	0	0	14	6	14	6
Indonesia	0	0	0	17	17	11	32	26	49	37
Iraq	0	0	0	0	0	0	2	2	2	2
Thailand	0	0	17	5	5	2	0	0	22	14
Turkey	0	0	0	0	0	0	12	4	12	4
Vietnam	3	3	29	20	61	19	0	0	93	42
Total	3	3	46	32	95	41	81	52	225	128

This simultaneity of events reveals that although the transmission of disease from birds to human is

rare but does occur.

Subtypes that have caused widespread illness in people either in the past or currently are H3N2, H2N2, H1N1, and H1N2. H1N1 and H3N2 subtypes also have caused outbreaks in pigs, and H7N7 and H3N8 viruses have caused outbreaks in horses. When human to human transmission occurs, risk of epidemic will be posed.

***How does the avian influenza A virus become capable of transmission from human to human?***

Prior to the 1997 event, the need for specific receptor for being infected with avian influenza A virus was considered as a barrier against human infection. Theoretically, transmission from aquatic birds to human requires an intermediate host like pig that has a specific receptor for both human and bird influenza viruses. However in 1997 it was observed that even poultry may serve as an intermediate host (3).

There are two mechanisms for transmission of avian influenza virus to a virus that is easily transmitted from human to human:

- 1) Reassortment: occurs when the genome is substituted between the avian influenza A virus and human influenza virus through an intermediate host. The intermediate host can be pig, human or poultry.
- 2) Gradual mutation of genes at receptor connection (15).

Of these two mechanisms, mostly mutation is responsible for creation of the new pandemic virus (4). There are evidences showing that more transmissions might occur among humans and the risk of pandemic is impending (table 2).

Recent studies indicates that H5N1 subtype of the virus which presently exists is more virulent and survives longer in environment compared with the previously reported subtypes (5, 18, 19). Moreover, it has also been observed that this virus is virulent in animal species in which it was not virulent before. For instance, there are evidences of severe disease and death in tigers and cats in vitro (20, 21)

Similarities of present situation with 1918 pandemic are:

- 1) Gradual transformation of avian influenza A virus to the human virus.
- 2) Severity of disease
- 3) Accumulation of diseased cases in young healthy people
- 4) Occurrence of primary viral pneumonia in addition to secondary bacterial pneumonia.

**Table 2.** Similarities of present situation with 1918 pandemic.

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## **ROUTES OF TRANSMISSION**

Human influenza is transmitted by inhalation of infectious droplets through direct and perhaps indirect (fomite) contacts, with self-inoculation into the upper respiratory tract or conjunctival mucosa (22, 23). However, the relative efficiency of the different routes of transmission has not been defined yet.

- 1) Animal to human: since 1997 most cases of disease in humans resulted from direct exposure to live infected poultry. Butchering of birds, preparing of diseased birds, handling fighting cocks, consumption of duck's blood or undercooked poultry have also been implicated to be the cause of transmission to human (23,24).
- 2) Human to human: So far, no case of human to human transmission by small particle aerosols has been identified; although human to human transmission has been suggested in several household clusters and in one case of apparent child to mother transmission. In all these cases, intimate contact was reported (17,25)

To date, the risk of nosocomial transmission to health

care workers has been low, even when inappropriate isolation measures were adopted (16).

- 3) Environment to human: Oral ingestion of contaminated water during swimming and direct intranasal or conjunctival inoculation during exposure to water is other potential mode. Furthermore, the widespread use of untreated poultry feces as fertilizer is also a possible risk factor (26)

### **CLINICAL FEATURES**

The incubation period for avian influenza A (H5N1) virus might be longer than for the other known human influenzas. In 1997, most cases occurred within two to four days of exposure. Recent reports also indicate similar intervals but with ranges of up to eight days (10, 25, 27).

Symptoms of avian influenza in humans have ranged from typical human influenza-like symptoms (e.g., fever, cough, sore throat, and muscle pains) to eye infections, pneumonia, severe respiratory diseases (such as acute respiratory distress), and other severe and life-threatening complications. Upper respiratory tract symptoms are present only rarely.

The symptoms of avian influenza may depend on which virus caused the infection. Diarrhea, vomiting, abdominal pain, pleuritic pain and bleeding from the nose and gums have also been reported early during the course of illness in some patients (26). Watery diarrhea appears to be more common in influenza caused by human viruses, and may precede respiratory manifestations for up to one week (28).

Lower respiratory tract manifestations develop early in the course of illness. Respiratory distress, tachypnea and inspiratory crackles are common. Sputum production is variable and sometimes bloody. Almost all patients have clinically apparent pneumonia.

Unlike patients infected by H7N7 subtype, the H5N1 infected cases rarely suffer from conjunctivitis (12).

Radiographic changes include diffuse or

multifocal infiltrates, interstitial infiltrates, lobular or segmental consolidation with air-bronchograms. Pleural effusions are uncommon. Progression to respiratory failure has been seen in most patients associated with diffuse, bilateral, ground-glass infiltrates and manifestations of the acute respiratory distress syndrome (ARDS) (26). Multiorgan failure including renal and cardiac dysfunction has also been reported (25).

It is noteworthy that the clinical spectrum of this disease mentioned above is mostly based on descriptions of hospitalized patients. The frequencies of milder illnesses, sub clinical infections and atypical presentations have not been determined, but case reports indicate that it exists. One such incidence was reported in a brother and sister from Vietnam presented with diarrhea and consequent coma. Both of these siblings had died with the diagnosis of encephalitis. Later, it was revealed that H5N1 virus had been the cause of death. This report demonstrated that avian influenza A virus should be considered as having a wide spectrum of clinical symptoms (29, 30).

The fatality rate among hospitalized patients has been high. Most deaths occur among infants and young children mostly as the result of respiratory failure (26). Common laboratory findings in patients have been leukopenia particularly lymphopenia, mild to severe thrombocytopenia and elevation in hepatic enzymes (elevated aminotransferase levels) (26). Increased risk of death is associated with decreased leukocyte, platelet and particularly lymphocyte counts at the time of admission (25).

### **PATHOLOGIC FINDINGS**

Postmortem autopsy findings indicated diffuse alveolar damage consistent with findings of human influenza cases. Changes include filling of the alveolar spaces with fibrinous exudates and red cells, hyaline-membrane formation, vascular congestion and the proliferation of reactive fibroblasts. Infection of type 2 pneumocytes occurs (26).

## DIAGNOSIS

Laboratory confirmation of influenza A virus requires one or more of the following:

- 1) a positive viral culture
- 2) a positive PCR assay for influenza A (H5N1) RNA
- 3) a positive immunofluorescence test for antigen with the use of monoclonal antibody against H5 antigen.
- 4) At least a fourfold rise in H5-specific antibody titer

All laboratory tests related to H5N1 should be evaluated and approved by WHO (26, 31).

Avian influenza A (H5N1) infection may be associated with a higher frequency of virus detection and higher viral RNA levels in pharyngeal samples rather than in nasal.

Commercial rapid antigen tests are less sensitive in detection of influenza A (H5N1) infections than are RT-PCR assays.

In addition, commercial monoclonal antibody against H1 reacts well. Therefore, for confirmation it is necessary to use monoclonal antibody with WHO provided kit (26, 31).

Among survivors specific humoral immunity responses to influenza A (H5N1) are detectable by micro neutralization assay, 10-14 days after the onset of illness.

Corticosteroid use may delay or blunt these responses (26).

## TREATMENT

Early treatment will provide the greatest clinical benefit, although the use of therapy is reasonable when there is a likelihood of ongoing viral replication (27).

Whenever feasible while the numbers of affected persons are low, patients with suspected or proven influenza A should be hospitalized for clinical monitoring and appropriate diagnostic testing (26).

## ANTIVIRAL AGENTS

Patients with suspected influenza A (H5N1)

should promptly receive a neuraminidase inhibitor depending on the results of diagnostic laboratory testing (26). These viruses are susceptible in vitro to oseltamivir and zanamivir (32, 33).

Recent studies indicate that compared to influenza A (H5N1) strain from 1997, the strain isolated recently requires higher doses and more prolonged administration (34). Inhaled zanamivir has not been studied in cases of influenza A (H5N1) in humans (26).

Oseltamivir is used in higher than usual doses in case of influenza A (H5N1). 75 mg twice daily for five days in adults is reasonable for treating mild cases and higher doses of 150 mg twice daily in adults for 7 to 10 days is a consideration in treating severe infections.

In children weighing 15 kg or less, daily twice doses of 30 mg, 45 mg for those weighing more than 15 to 23 kg, 60 mg for those weighing more than 23 to 40 kg and 75 mg for those weighing more than 40 kg are prescribed (26).

However, the present worry of medical community is the detection of oseltamivir resistant H5N1 variants. Although these variants are less infectious and less transmissible, they can cause complications in treatment (35).

## IMMUNOMODULATORS

Corticosteroids have been used frequently for treating patients infected with influenza A (H5N1) with uncertain effects. Use of other immunomodulator drugs such as interferon might be considered in future, because the interferon possesses both antiviral and immunomodulatory activities (26).

## HOSPITAL INFECTION CONTROL

Influenza is a well recognized nosocomial pathogen (23, 36). Current recommendations are based on efforts to reduce transmission to health care workers and other patients in a no pandemic situation (37).

The efficiency of surgical masks, even multiple

ones is much less than that of N-95 masks, but they could be used if the latter are not available (26,38)

Chemoprophylaxis with 75 mg of oseltamivir, once daily for 7 to 10 days is warranted for persons who have had a possible unprotected exposure.

The use of pre-exposure prophylaxis of oseltamivir warrants consideration if evidence indicates that the influenza A (H5N1) strain is being transmitted from person to person or if there is a likelihood of a high risk exposure e.g. an aerosol generating procedure (39,40).

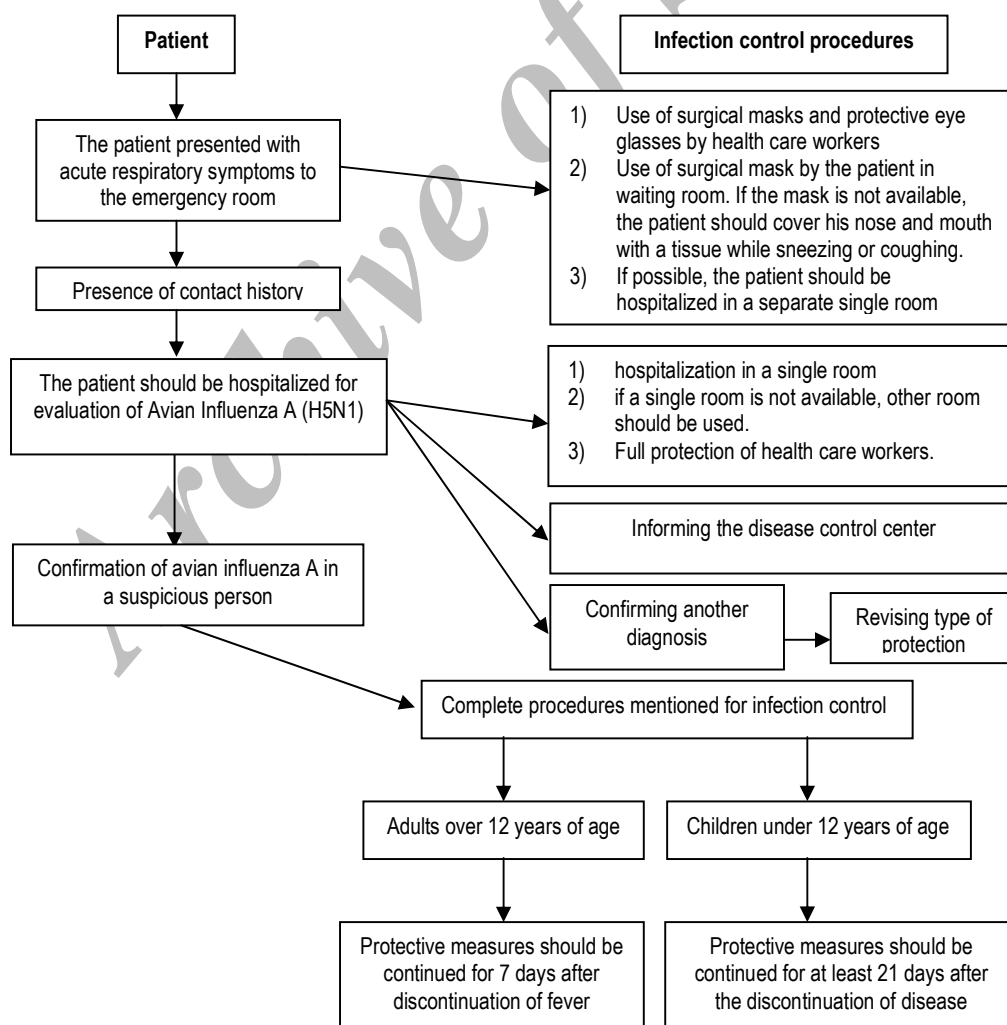
### HOUSEHOLD OR CLOSE CONTACT

Household contacts of persons with confirmed

cases of influenza A (H5N1) should receive post-exposure prophylaxis with oseltamivir. Patients in contact with proven or suspected virus should monitor their temperature and symptoms. Although, to date the risk of secondary transmission has appeared low, self quarantine for a period of one week after the last exposure to infected person is appropriate (26).

For others who have had an unprotected exposure to an infected person or to an environmental source implicated in the transmission of influenza A (H5N1), post exposure prophylaxis with oseltamivir may be warranted (26).

Figure 1. Avian influenza an infection control in medical centers



## PREVENTION

No influenza A (H5) vaccines are currently available for humans (although recently it is revealed that the vaccine produced by segments of virus is effective for immunization) (41).

Generation of vaccine depends on recognition of the pandemic causing species.

After recognition of virus responsible for pandemic, massive production of vaccines takes minimum of 6 months (2).

On the other hand, considering the present ability in vaccine generation industry, during 6 months a maximum of one billion doses will be produced.

Therefore, considering requirement of two doses for prevention, only 500 million people (14% of world population) will have access to the vaccine (2).

Presently, generation of influenza vaccine is egg related. In other words, for making human influenza vaccine in amount of 300 million doses per year, more than 350 million eggs are required. Therefore, it is necessary to create cell culture methods to gain access to more antigens as well as to have quicker process of vaccine generation (2, 26).

Considering the aforementioned facts, although studies in the mentioned fields must be conducted aggressively, we can not count on vaccines for prevention of pandemic.

If the variant responsible for pandemic is resulted from gradual mutations in virus, there would be much more time for vaccine generation and decreasing the size of pandemic.

Furthermore, to decrease the risk of reassortment, it is recommended to prescribe a trivalent human vaccine which is presently available for the people at risk (26).

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