Avian/bird flu: Epidemiology, clinical features & current management

Abstract
Epidemics and pandemics of influenza have been documented throughout history, the mechanisms underlying these are still poorly understood. Experts agree that another influenza pandemic is inevitable and possibly imminent. A number of Asian countries have been currently affected by avian/bird flu infecting their poultry stocks. The diagnosis of influenza is usually confirmed by isolation of virus or from serological results. As production of potential and effective antiviral agent for human are hazardous and inadequate so prevention of adaptive mutation or reassortment is the key to control the situation which could be achieved by depopulation of commercial poultry and improved hygiene. Prevention of the spread of bird flu is multifaceted, focusing on the health of both birds and humans including broad surveillance, cluster investigation, contact tracing, target use of antivirals, continued vaccine and travel restriction.

Introduction
Avian influenza or bird flue refers to an infection caused by a large group of different influenza viruses that primarily affect birds. Wild birds worldwide carry the viruses, but usually do not get infected by them. However, bird flu is very contagious among birds and can produce the disease to some domesticated birds, including chickens, ducks, and turkeys\(^1\). On rare occasions, these bird viruses can infect some other species, including pigs and humans. The vast majority of avian influenza viruses do not infect humans\(^2\). Influenza pandemic happens when a new subtype emerges that is not previously known to cause human diseases\(^2\). A number of Asian countries have been currently affected by avian/bird flu infecting their poultry stocks. In some of these countries, a small number of people have also contracted the virus from chickens. Scientists are concerned by these events because it is feared that the avian flu virus could merge with a human flu virus and could evolve as a new virus, which would be transmitted rapidly from person to person with potentially devastating results. As avian H5N1 is a strain with pandemic potential, since it might ultimately adapt into a strain that is contagious among humans and is highly infectious and rapidly fatal\(^2\). To control the outbreak of avian flu virus many of these Asian countries are culling their poultry stocks.

History
Influenza pandemic is one of the rare but recurrent events. Three pandemics has occurred in the previous century, in 1918 "Spanish influenza", in 1957 "Asian influenza" and in 1968 "Hong Kong influenza."
Amongst them the “Spanish influenza”\(^2,3,4\) pandemic was the deadliest one. Over 18 months the flu caused an estimated 400 million people became infected of whom an approximately 40-50 million people died all over the world\(^2,3,4,5\). Subsequent pandemics were much milder, with an estimated 2 million deaths in 1957 and 1 million deaths in 1968\(^6\).

Recently in 1997 documented infection of humans with an avian influenza virus occurred in Hong Kong, where the H5N1 strain caused severe respiratory disease in 18 humans, of whom 6 died\(^6\). The infection coincided with an epidemic of highly pathogenic avian influenza, caused by the same strain, in the country's poultry population\(^6\). Alarm mounted again in February 2003, when another outbreak of H5N1 avian influenza was reported from Hong Kong\(^6\). In January 2004, laboratory tests confirmed the presence of H5N1 avian influenza virus in human cases caused severe respiratory disease in the northern part of Vietnam\(^6,7,8\). Again in 29th November 2005, WHO has officially recognized 133 human cases infected by H5N1 influenza virus, of whom 68 deaths have been reported from Vietnam, Thailand, Cambodia, Indonesia, and China. Two other avian influenza viruses have recently caused illness in humans. Amongst them an outbreak of highly pathogenic H7N7 avian influenza was first documented in the Netherlands in February 2003 and mild cases of avian influenza H9N2 in children occurred in Hong Kong in 1999 and in mid-December\(^4,6\).

**Epidemiology**

Every winter, an average of 36,000 people die of influenza in the United States. Every century, flu pandemic sweeps the globe three or four times claiming millions of lives\(^9\). A pandemic occurs when a new influenza virus emerges and starts spreading like normal influenza virus by coughing and sneezing. As the virus is new, the human are nonimmune to it, causes the rapid spread of the virus, that in turn causes pandemic influenza that is experienced as more fatal disease than the normal one\(^2\). Health experts have been monitoring a new and extremely severe influenza virus the H5N1 strain for almost eight years\(^7\). The virus has, however, shown an ability to jump species, infecting cats, pigs, tigers, and leopards in recent years. A recent study proved that the virus was causing increasingly severe disease when injected into laboratory mice\(^7\). In August 2005, H5N1 was confirmed in Vietnam\(^7,8\). The event alarmed public health authorities, as it marked the first time that an avian influenza virus was transmitted directly to humans and caused severe illness with high mortality\(^9,10\). Most cases have occurred in previously healthy children and young adults. Fortunately, the virus does not jump easily from birds to humans or spread readily among humans.

**Virology**

Influenza viruses belong to orthomyxoviridae family and the genus is Influenza\(^7\). The virion of the virus is 80 to 120 nm in diameter and may be filamentous. Eight different segments of negative-stranded RNA are present; which allows genetic reassortments in single cells infected with more than one virus and may result in multiple strains that are different from the initial ones\(^1,4,7,9\). Type designation of the virus is based on the antigenic character of the virus envelope protein or M-protein and the nucleoprotein within the virus particle\(^7,9\). The virus envelope glycoproteins have hemagglutinin (HA) and neuraminidase (NA) activity\(^7,11\). Depending on these characteristics the virus is divided into three types - A, B or C\(^1,4,7,9,12\). Type A is responsible for lethal influenza pandemics whereas type B causes smaller, localized outbreaks. The type C strains are more stable but less common and produce milder symptoms. Influenza B and C are usually found only in humans. But type A influenza infects human and animals\(^1,4,9,12\). Fifteen distinct HA subtypes and nine NA subtypes exist for influenza virus A, but they can
combine to form a number of other subtypes like H1N1, H1N2, H1N3, H7N7, H3N8 etc. At least 15 flu subtypes affect birds, the most virulent of which is H5N1,13. The ability of influenza viruses to change their genetic makeup and to swap genes indiscriminately makes them so unpredictable and potentially deadly. The change takes place in two ways:

Antigenic drift: These are small, permanent, ongoing alterations in the genetic material of a virus. Because viruses aren't able to repair genetic errors that take place as they reproduce, new strains are continually replacing old ones.6,9,11,14,15

Antigenic shift: This occurs when influenza A subtypes from different species trade and merge genes. The result is an entirely new strain, different from either of the parent viruses. Because no natural immunity to the new strain exists, it can spread quickly, causing widespread illness and death. And when one of the original subtypes is a human influenza virus, the new virus has the ability to spread easily from person to person and the potential to become a global epidemic.6,9,12,14,15 Conditions favorable for the emergence of antigenic shift have long been thought to involve humans living in close proximity to domestic poultry and pigs. Because pigs are susceptible to infection with both avian and mammalian viruses, including human strains, they can serve as a "mixing vessel" for the exchange of genetic material from human and avian viruses, resulting in the emergence of a novel subtype.6,14,15

Transmission
Migratory waterfowl, most notably wild ducks are the natural reservoir and carrier of avian influenza viruses, and these birds are also the most resistant to infection. The virus causing bird flu spreads by faeco-oral route among the birds.16 Infected birds shed the virus in their droppings, saliva and nasal secretions. Domestic poultry become infected from contact with these birds or with contaminated water, feed or soil. They may also catch the disease the same way humans contract conventional flu, by inhaling the airborne virus. Bird flu spreads quickly and lethally within a flock and is transported from farm to farm on tractors and other equipment, on cages, and on workers' shoes and clothing.6,9 Though heat destroys the virus, but it can survive for a long time in cool temperatures. Open-air markets where eggs and birds are often sold in crowded and unsanitary conditions are hotbeds of infection and spread the disease into the wider community. Humans may pick the virus through close contact with sick birds, contaminated surfaces or by airborne spread or direct contact of the infected people.6,15 Scientists do not think that migratory birds are carrying the virus from continent to continent because outbreaks have not followed traditional flyways.9

Clinical features
The incubation period of the virus is usually two days, but it can vary from one to five days and the symptoms of the disease usually lasts for five to seven days. Most people with bird flu have signs and symptoms of conventional influenza-dry cough, muscle pains, sore throat, elevated temperature (which may not be present in elderly people), headache, fatigue and tiredness. Some of the complications of flu are otitis media, primary influenza, pneumonia, secondary bacterial bronchitis, exacerbations of chronic respiratory disease, croup and bronchiolitis in infants and young children, febrile convulsions, toxic shock syndrome, Reye's syndrome, myositis and myoglobinuria, myocarditis, neurological sequelae - including Guillain-Barre syndrome, transverse myelitis, encephalitis, and worsening or destabilization of pre-existing diseases, such as cardiac failure and diabetes. There is a possibility of increased incidence of schizophrenia if exposure is in utero during second trimester.15
Limited information about the clinical course of human infection with H5N1 avian influenza in the 1997 Hong Kong outbreak was published in which patient suffering from avian flu developed the symptoms of fever, sore throat, cough and, in several of the fatal cases, severe respiratory distress secondary to viral pneumonia and some with chronic medical conditions.

**Diagnosis**

The diagnosis of influenza is usually confirmed by isolation of virus or from serological results. As influenza is mainly a droplet infection so high titres of virus is shed by the patients with symptoms. Influenza A and B virus replicate in several primary kidney cell lining, and influenza may be shown in tissue culture by adsorption of guinea pig erythrocytes. Serological tests include complement fixation and haemagglutination inhibition. These tests provide useful epidemiological information but will only confirm a diagnosis after the patient has recovered from the acute illness. Rapid diagnostic techniques of influenza include gene amplification and antigen detection by immunofluorescence or enzyme linked immunosorbent assay (ELISA). Immunofluorescence is comparatively inexpensive but less sensitive compared to standard tissue culture. A capture ELISA has been described for the influenza antigen detection that uses a monoclonal antibody to nucleoprotein and is high sensitive and specific. The polymerase chain reaction has recently been used to identify influenza virus genome in clinical material, and several methods have been described. The procedure uses reverse transcriptase and type specific primers based on highly conserved sequences. It is also highly sensitive and gives result within 24 hours. Influenza primers may be combined with specific primers for a range of other respiratory viruses in a more comprehensive assay known as a multiplex polymerase chain reaction.

**Management**

The management of influenza includes relief of symptoms, treatment of complications, and specific antiviral treatment. The clinical severity of influenza is variable, and most patients with uncomplicated infection will require symptomatic treatment alone.

**Antiviral drugs:** Amantadine and its analogue rimantadine have been used for both treatment of and prophylaxis against influenza A and is believed to inhibit all subtypes of influenza A but have little action against influenza B or C. They have a tricyclic chemical structure with an amine side chain and a cage-like configuration, and they are believed to act by inhibiting virus uncoating. The recommended dose of amantadine is 200 mg daily, which is reduced to 100 mg in people over 65 years. There are few serious adverse effects, although epilepsy has been reported in patients with underlying cerebral disease. More common problems include headache, light headedness, dizziness, difficulty in concentrating, and insomnia. These effects occur in 5-29% of patients.

Unfortunately the 2004 H5N1 strain is resistant to amantadine and rimantadine, complicating treatment and prophylaxis.

The neuraminidase inhibitors that works by preventing the virus from escaping its host cell are generally effective against influenza A and may be useful in treatment of and prophylaxis against H5N1 influenza, although the clinical utility of neuraminidase inhibitors in treating patients with H5N1 influenza is not yet known. Oseltamivir (Tamiflu) is approved for treatment of influenza in persons aged 1 year and older and approved for prophylaxis of influenza in persons aged 13 years and older. In Southeast Asia, resistance against the drug is developing quickly. Zanamivir is approved for treatment of influenza in persons 7 years and older but is not approved for prophylaxis. Another antiviral flu drug, Relenza, may be an alternative.
Vaccines: Salk first described the use of killed influenza vaccine in 1945. Early virus vaccines contained intact, formalin-inactivated virus and were associated with many adverse effects. Modern subunit vaccines are well tolerated and evoke a good serological response. Two forms of subunit vaccine are available; split virus vaccine containing disrupted virus particles partially purified by extraction with organic solvents, and surface antigen vaccine composed of highly purified haemagglutinin and neuraminidase antigens. Current commercial influenza vaccines are usually trivalent, containing two influenza A subtypes and influenza B. Over a period of three to six months the antibody titer induced by the vaccine declines. So annual vaccination is recommended but the effect of repeated annual vaccination has been questioned as the efficacy of a vaccine is also dependent on the degree of antigenic similarity between strains of vaccine and circulating strains of influenza.

Other than killed influenza vaccines there are recombinant fusion proteins and live attenuated vaccines. Live attenuated influenza virus vaccines have been investigated extensively in the former Soviet Union and in the United States and were proved as well tolerated. The advantages of these vaccines over inactivated vaccines include good immunogenicity in children, induction of nasopharyngeal IgA, and a longer lasting antibody response. Again live attenuated vaccines also need to be updated regularly along with antigenic changes.

One way of protecting against all types of influenza, including emerging pandemic strains, would be a universal flu vaccine that would not have to be reengineered each year. In the early August 2005, the British company Acambis announced that they has developed such a vaccine that is on trial. The vaccine would focus on the M2 viral protein, rather than the surface hemagglutinin and neuraminidase that (M2 protein) do not change. The universal vaccine is made through bacterial fermentation technology, which would greatly speed up the rate of production. Further the vaccine could be produced continuously, since its formulation would not change. Still, such a vaccine is years away from full testing, approval, and use.

Prevention
Prevention of the spread of bird flu is multifaceted, focusing on the health of both birds and humans including broad surveillance, cluster investigation, contact tracing, target use of antivirals, continued vaccine and travel restriction.

Measures to control the virus among domestic poultry: First-line defense against avian flu virus is to destroy the exposed and affected birds. Since 1997, when the first human cases of bird flu appeared, hundreds of millions of sick or exposed birds have been destroyed. In many cases, affected farms were also quarantined. Many birds were burnt or buried alive. Though the methods used to cull birds and the wholesale slaughter was questioned. Some nations have instituted strict vaccination and surveillance programs for poultry farms and markets, taken steps to prevent bird smuggling, and put quarantine programs for new birds. Further more many countries have banned or restricted the import of birds and eggs from bird flu epidemic areas.

Recommendations for health professionals: Recently, WHO developed guidelines on infection control for management of patients with H5N1 avian influenza by implementing standard precautions, droplet precautions, contact precautions and by airborne precautions (including use of high-efficiency masks and negative-pressure rooms if available). For adults and children over 12 years of age, these precautions should be implemented at the time of admission and maintained until 7 days after resolution of fever. For children of 12 years and under,
Precautions should be continued until 21 days lapsed from onset of illness. The WHO guidelines also recommend that all healthcare workers who may come into contact with the H5N1 virus or with infected patients should be vaccinated with the current WHO recommended vaccine. Although this will not protect against H5N1 influenza A, it will help avoid simultaneous infection with other influenza strains and may thereby decrease the risk of genetic reassortment.

Recommendations for travelers: Travelers traveling to any region with bird flu outbreaks should avoid rural areas, small farms and especially any close contact with domestic birds. Open-air markets are dreadful places because they are often breeding grounds for disease. The simplest and the best way to prevent infections are washing hands properly. Alcohol-based hand sanitizers are good for the purpose. Young children who are likely to put their hands in their mouths and who may not wash thoroughly should be cared. Heat destroys avian influenza virus so poultry should be cooked properly. Eating raw or undercooked eggs or any products containing them should be avoided and cutting boards, utensils and all surfaces that have come in contact with raw poultry should be washed with hot, soapy water. Specific prophylaxis should be taken that is advised by the expert.

Conclusion
Although epidemics and pandemics of influenza have been documented throughout history, the mechanisms underlying these are still poorly understood. Experts agree that another influenza pandemic is inevitable and possibly imminent. An outbreak of avian influenza is ravaging the poultry industry in South East Asia. This carries a devastating economic toll. Though the current H5N1 strain circulating in Asia appears to be highly pathogenic for humans still there is no pandemic. It is thought to be due to the prompt culling of Hong Kong's entire poultry population in 1976. However if the virus continues to circulate widely among poultry it has a greater potential to infect humans and other animals where genetic re-assortment could take place and may create a new pandemic. As production of potential and effective antiviral agent for human are hazardous and inadequate so prevention of adaptive mutation or re-assortment is the key to control the situation which could be achieved by depopulation of commercial poultry and improve hygiene. The 1918 global flu pandemic spread in the age of horse, boat and train and at a time when the world population was only a third of today. If such a virus re-emerges, perhaps as a mutant, it could spread far faster and the severity will markedly be increased. It is the high time to adopt prompt control measures to avert the pandemic that is knocking at the door.

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