

Avian Flu and Possible Human Pandemic

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Avian flu is affecting the poultry animals world over since first outbreak in 1997 in Hong Kong, and has resulted in 92 human deaths and culling of more than 150 million poultry animals in Asia and Europe. The loss to the economy has also been enormous. 13 new countries, including India, reported occurrence of the disease in poultry animals in February 2006 only, to the World Health Organisation. This rapid rate of spread of virus along with notoriety of the virus for frequent genetic re-assortment, which might enable H5N1 to infect human beings, threatens of possible influenza pandemic since the last pandemic in 1968. The human influenza caused by this subtype of the virus (H5N1) has high case fatality of 54% and majority of affected humans are between the age of 5 to 23 years. Lack of effective vaccine, poor knowledge about treatment, and with scarcity of public health measures in developing countries are major causes of concern. The real threat of impending pandemic can be avoided only if we act immediately on the basis of currently available source of information and apply scientific knowledge rationally for containment and prevention of bird flu and treat human cases promptly.

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Avian influenza is an infectious disease of birds, usually infecting poultry animals and pigs, and is caused by Influenza A (H5N1) virus(1-3). It was first reported in 1997 in Hong Kong(3,4). Year 2003 saw change in the strains of virus, resulting in emergence of 'novel' Z strain and, infection to human beings by this virus, contrary to earlier belief that avian influenza virus can not infect human beings due to differences in receptors(3,5). Vietnam reported first human case due to H5N1(1,6) Avian flu has spread to a number of countries in Asia and Europe with 170 human cases and 92 deaths till February 20, 2006(7). February 2006 saw outbreaks of bird flu in 13 new countries and avian flu became household name in India, when cases of bird flu were reported by media and, later confirmed by Indian government, in Navapur tehsil of Nandurbar district of Maharashtra(8). It was this rate of spread of this virus in poultry animals across the Asian and European countries and observations of newer virus being more similar to 1918 pandemic(9,10) that World Health Organisation (WHO) pronounced world is now closer to another influenza pandemic than at any time since 1968 pandemic(11).

Threat of Human pandemics

Pandemics are the reality of the time; Influenza pandemics have occurred for centuries, thrice in last century only(1). The influenza virus has segmented genome, which undergo continuous mutations and genetic re-assortments. Minor point mutation causing smaller changes (antigenic drifts) enable viruses to evade immune recognition resulting in repeated Influenza outbreaks during Inter-pandemic years(1,11). These pandemics are caused by the most common subtypes of circulating viruses in the community at that time. Currently, circulating avian subtype H5N1 has high fatality rate and has spread to

poultry animals in number of countries. Any virus can cause pandemic if, (a) it has an ability to infect human beings, (b) there is a vulnerable population without innate immunity and, (c) rapid efficient person to person transmission occurs. H5N1 has fulfilled the first two criteria and, any genetic change in H5N1 enabling; human to human transmission, will lead to the pandemic of human influenza. The current situation calls for continued monitoring to identify any increase in viral adaptation to human hosts and enhancement of preventive measures. WHO has put present situation at third phase (*Appendix I*) of pandemic alert plan(9). It is pertinent that India now start containment and control measures of bird flu and be prepared for the management of human cases if that occurs.

Epidemiology of human flu and Avian flu

Human Influenza occurs all over the world with annual global attack rate of 5-15% in adults and 20-30% in children. It is a self limiting illness, lasting for about a week, characterized by mainly upper respiratory tract illness with symptoms like fever or myalgia, headache, malaise or non productive cough. Most people usually recover without requiring any medical treatment. In very young or elderly and, in chronically ill people, infection sometimes leads to the death. Global burden of inter-pandemic influenza is estimated around one billion episodes with 3,00,000-5,00,000 deaths annually(12). Influenza A subtype has caused global pandemics at unpredictable intervals. The 'Spanish flu' in 1918 was the most severe pandemic, causing an estimated 20-40 million deaths world wide while less severe pandemics were occurred in 1957 and 1968 (1,11). Influenza pandemics spread to most countries in the world, within months, requiring universal demand for prevention and control measures(2).

Current outbreaks of avian flu, the biggest in the history, are being caused by Influenza virus A (H5N1) affecting chickens, ducks, geese, turkey, guinea fowls *etc.*(9). These birds suffer from unexplained illness and die in groups. Avian viruses usually do not infect human beings but recently it has become highly pathogenic influenza A (HPIA) with number of outbreaks in poultry animals and a few cases of animal to human transmission also reported(1,11). As of February 20, 2006, 170 laboratory confirmed human cases of H5N1 infections with 92 deaths (Case fatality rate of 54.1%) were reported from 7 countries *viz.*, 93 from Vietnam (42 deaths), 26 from Indonesia (19 Deaths), 22 from Thailand (14 deaths), 12 from China (8 deaths), 12 from Turkey (4 deaths), 4 Cambodia (4 deaths) and, 1 from Iraq (1 death)(7). No human case has been reported from India till now despite continuous surveillance and investigation for suspected cases in affected area(8).

Transmission

Human influenza caused by H5N1 results from inhalation of infectious droplets and nuclei, by direct contact and perhaps, by indirect (fomite) contact(13,14). Avian flu is not transmitted to human beings routinely although human to human and child to mother transmission has also been reported(15,16). Cases of transmission through social contacts (17) or amongst health care workers, risk of nosocomial transmission has been low (18,19). The children between 5 to 9 years typically manifest the highest rates of infection and illness(11). Most patients have been young children and adults with median age being 8, 9 and 12 years in Cambodia, Vietnam and Hong Kong respectively(15,20,21). Thailand reported higher median age of 23 years(22).

Microbiological characteristics

Influenza virus belongs to family

orthomyxoviridae and, is classified into type A, B and C on the basis of core proteins; whereas subtypes of Influenza A virus are determined by envelop glycoproteins possessing either haemagglutinins (HA) or neuraminidase (NA) activity. High mutation rate and frequent genetic re-assortment of these viruses contributes to great variability of the HA and NA antigen.

Type A virus infects mammalian (*e.g.*, pigs and horses) and avian species. Currently, 16 HA and 9 NA subtypes of Influenza A are maintained in wild, aquatic bird population. Humans are generally infected by subtype H1, H2 or H3 and N1 or N2. Animal subtypes of Influenza virus are usually not efficient in infecting humans without virus has been undergoing subsequent antigenic and genetic changes. For example; since 1997 outbreak in Hong Kong, H5N1 subtype has become genetically modified and Highly Pathogenic Influenza A (HPIA) and led to the number of outbreaks in poultry animals with a few human cases(11).

Pathogenesis

The virulence factor of H5N1 is highly cleavable hemagglutinin that can be activated by multiple cellular proteases (23). Virus replicates in the multiple organs of the body and has been detected in blood, cerebro-spinal fluid and stool of the patient (24,25). Whether faeces or blood serve to transmit infection is unknown. Biopsy findings of the specimens have shown reactive histiocytosis with hemophagocytosis in several patients, and lymphoid depletion and atypical lymphocytes have been noted in spleen and lymphoid tissues at autopsy(20,26).

Diagnosis

A great difficulty in clinical diagnosis of Human influenza (H5N1) occurs due to non

specific clinical feature of the disease. Most patients have initial symptoms of high fever (typical temperature of more than 38° C) and an influenza like illness with lower respiratory tract illness(1). Less common modes of presentation are diarrhea, vomiting, abdominal pain and bleeding from nose and gums have also been reported (15,21,22,24). A few cases have been reported without apparent respiratory symptoms(24). Standard case and contact definitions(11) are given in *Appendix II*.

Clinical course

In birds, this virus manifests in form of ruffled feathers, soft shelled eggs, depression, loss of appetite, edema and swelling of the head, eyelid etc. Increased deaths of birds in groups are a cause of suspicion of illness. In humans, the clinical spectrum of influenza (H5N1) varies from milder illness, sub clinical infection to atypical presentation in form of encephalopathy or gastroenteritis(24-27). The incubation period is 2 to 4 days(15,20). Most patients have initial symptoms of high fever and an influenza-like illness with lower respiratory tract symptoms(28). Respiratory distress, tachypnea, and inspiratory crackles develop early in the course of illness(22). Almost all patients have clinically apparent pneumonia; radiographic changes include diffuse, multi-focal, or patchy infiltrates; interstitial infiltrates; and segmental or lobular consolidation with air bronchograms (15,20,21). Multi-organ failure with signs of renal dysfunction and sometimes cardiac compromise, including cardiac dilatation and supra-ventricular tachyarrhythmia, has been common(15,21,22).

Mortality

Avian influenza A (H5N1) results in high death rate amongst infants and young children with case fatality rate at 89% among under 15 years of age(21). Deaths occur at an average of

9 or 10 days after the onset of illness (range, 6 to 30)(15,22) and most patients die of progressive respiratory failure(15,20,22).

Laboratory specimens

The optimal specimen is a nasopharyngeal aspirate obtained within 3 days of the onset of the symptoms although naso-pharyngeal swab may also be obtained(1,28,29). Rapid antigen assays, virus culture, Real Time Polymerase Chain Reaction (RT-PCR) are other methods available. RT PCR assay is more sensitive in virus detection than commercially available rapid antigen tests(1,2,28,29). Leukopenia, particularly lymphopenia; mild-to-moderate thrombocytopenia; and slightly or moderately elevated aminotransferase levels, marked hyperglycemia and elevated creatinine levels are common(15). Laboratory confirmation requires one or more findings of case definition of the four criteria of confirmed case(11,29).

Prevention and Control

(a) Public Health measures

Whenever there is any report of the avian flu in the birds or poultry animals, immediate priority should be on containment of infection. Poultry workers should be screened for illness, along with necessary precautionary information distributed amongst these people.

WHO has suggested some 'signals' to start containment measures for humans in a country *viz.*,

1. Isolation of non-human influenza virus from a human case or
2. Epidemiological evidence of infection from novel influenza virus to 5 secondary cases by 1 index case or
3. Infection transmitted from three or more secondary cases to tertiary cases.
4. Efficient and sustainable transfer of person to person of 'novel' virus.

However, containment would not be tried in case of no confirmation of laboratory report or area being too large or, 6 weeks elapsed after index case.

WHO should be informed within 24 hours of all such occurrences(33). Along with culling of the animals, their feeding stuff, contaminated manure and carcasses should be either destroyed and treated to inactivate the virus. Public need to be educated on initial symptoms of illness and on preventive measures. Regular media briefing should be done to prevent panic in the community(28).

(b) Vaccination

Vaccination is the primary strategy for the prevention of influenza in the community; however, no influenza A(H5) vaccines are currently commercially available for humans. Even for other strains, vaccination may be inadequate during an influenza season due to antigenic drift rendering the vaccines less protective. Besides, in the course of a pandemic, vaccine supplies would be inadequate. Live attenuated, cold-adapted intranasal vaccines are also under development. These have been found protective against human influenza after a single dose in young children(31).

(c) Hospital infection control

Influenza is a well-recognized nosocomial pathogen(13,14). The efficiency of surgical masks is much less than that of N-95 masks, but they could be used if the latter are not available(32). Chemoprophylaxis with 75 mg of oseltamivir once daily for 7 to 10 days is warranted for persons who have had a possible unprotected exposure(32,33).

Management of human cases

The possibility of influenza A(H5N1) should be considered in all patients with severe acute respiratory illness in countries or territories with animal influenza A(H5N1),

particularly in patients who have been exposed to poultry. In addition, Influenza A(H5N1) warrants consideration in patients presenting with serious unexplained illness amongst children (e.g., encephalopathy or diarrhea) in areas with known influenza A(H5N1) activity in humans or animals(24,27).

Whenever feasible, patients with suspected or proven influenza A(H5N1) should be hospitalized in isolation for clinical monitoring, appropriate diagnostic testing, and antiviral therapy. Supportive care with provision of supplemental oxygen and ventilatory support is the foundation of management. Nebulisers and high-air flow oxygen masks should be used only with strict precautions to check nosocomial spread of respiratory infection(28.)

Most hospitalized patients with avian influenza A(H5N1) require ventilatory support and intensive care for multi organ failure. In addition to empirical treatment with broad-spectrum antibiotics, antiviral agents, alone or with corticosteroids, have been used in most, to control secondary infection. Respiratory and blood specimen should be checked for possible bacterial infection(28).

Therapy

Influenza A(H5N1) virus is susceptible to oseltamivir (Tamiflu) and zanamivir (Relenza) (34) but is resistant to amantadine and rimantadine(1,2) Treatment should be started within 48 hours of occurrence of fever, without waiting for laboratory reports(22,35).

Mild cases are treated as given in *Table I*. Higher dose of 150 mg twice daily and treatment for 7 to 10 days is required for treating severe infections(1,28). Salicylate administration should be avoided in children aged less than 18 years to prevent the possibility of Reye's syndrome(28). The effectiveness of zanamivir in reducing the

TABLE I—Dose Schedule for Treatment of Mild Cases (28,37).

S. No.	Age or Weight (Kg)	Oseltamivir dose (5 days)
1.	Age >12 years or weight >40 kg	75 mg BD
2.	Weight >23 to 40 kg	60 mg BD
3.	Weight >15 to <23 kg	45 mg BD
4.	Weight <15 kg	30 mg BD

severity, duration of illness and preventing the complications is proven in children aged 5-12 years(36).

Chemoprophylaxis

Contacts of a patient with proven or suspected virus should monitor their temperature and symptoms. Household contacts of persons with confirmed cases of influenza A(H5N1) should receive post-exposure prophylaxis. Although the risk of secondary transmission has appeared low to date, self-quarantine for a period of one week after the last exposure to an infected person is appropriate(28).

Both oseltamivir and zanamivir are effective in preventing clinical influenza in healthy adults. Close contacts should take 75 mg of oseltamivir for 7 days while community contacts should take same dose till as long as 6 weeks because of continued exposure(28).

Although currently approved only for prophylaxis in children over the age of 13 years, oseltamivir appears to be very effective for post exposure prophylaxis in children as young as 1 year of age (37,38).

Discharge Policy

Infection control measures in adults should remain in place for seven days after resolution of the fever. Children less than 12 years should

be observed for 21 days after onset of illness. Education on personal hygiene and infection control measures should be given to family along with the advice that child should not attend school and to return to health facility immediately if fever recurs(28).

Economic and social impact

Avian flu and flu pandemic has economic aspect also. In India, economic impact will be in form of loss to the poultry industry, which gives employment to 3 million Indian farmers, and is estimated worth 35,000 crores(39). Pandemic flu will also increase the health system burden; from sickness absenteeism and absenteeism of otherwise healthy workers resulting from decreased GDP. While considering social aspect, psychological health of the people should also be kept in the mind which will be affected leading to decreased productivity altogether. Trade and tourism are other sectors which might be greatly affected.

Exact estimates are difficult to assess but Asian Development Bank (ADB) predictions puts this loss between \$9.3-\$33.6 billion (1.8-5.8 percentage points of GDP) for India and at \$99.2-\$382.7 (2.3-6.5 percentage points of GDP) for Asia, depending upon various scenarios of epidemiological uncertainties (severity and impact of disease) and economic uncertainties (how outbreak will affect economy)(40).

Pharmaceutical company may have vested interest for unnecessary upscaling the sale of the drugs for avian flu by lobbying and claiming unjustifiable efficacy of the drugs. However, the efforts of biotechnology industry in developing an 'all powerful flu vaccine' which can be used against majority of strains should be supported by financial aids.

Time to act

The world community has seen the role

of public health measures in successful containment of SARS (Severe acute respiratory syndrome) and its time to apply these measures again. Much before current threat of pandemic, in wake of 1997 outbreak in Hong Kong, an independent research discussed the possibility of influenza pandemic and its effect on health of humans and possible economic burden. This study argued that in such scenario, preventive and containment measures would be cheaper and more effective than treatment. (41) It appears coming true now.

Government agencies and media need to react to outbreaks responsibly and, not by adding unnecessary panic. Transparent act and dissemination of timely and accurate information should be the priority(14). Immediate efforts should be focused on knowledge about avian flu, mode of transmission of virus along with containment and control measures.

Conclusion

The threat of pandemic is real, if not inevitable. Prediction of occurrence and consequences of a new flu pandemic is not possible due to too many unknowns. Despite concerted public health efforts and warnings by international health bodies, i.e. World Health Organisation, the avian flu has spread to many countries in the Asia and Europe. Although, without these efforts situation might have been worse. The definitive economic impact on any country due to trade or travel loss might severely affect many poor and developing countries. The immediate need is of the preventive measures to contain the avian flu and be prepared for the situation with appropriate knowledge if human pandemic starts.

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Appendix I

WHO phases of pandemic alert (9)

Inter-pandemic phase	Low risk of human cases	1
Newer virus in animals, No human case	Higher risk of human cases	2
Pandemic alert	No or very few human cases	3
New Virus causes human cases	Evidence of increased human to human transmission	4
	Evidences of significant human to human transmission	5
Pandemic	Efficient and sustained human to human transmission	6

Appendix-II

Standard case and contact definitions of Influenza A (H5N1)(1,9)

Suspected case

1. Fever (Body temperature of 38 degree Celsius or more); in addition to
2. One of the following symptoms- muscle ache, cough, abnormal breathing (unusual breathing difficulty) or suspected pneumonia by physician, or influenza; in addition to
3. History of direct contact with infected/ dead birds in the past seven days or occurrence of unusual death of the birds in community within past 14 days; or contact with a pneumonia patient or another patient suspected of avian influenza.

Probable case

Above mentioned symptoms of suspected case and:

1. Preliminary test shows infection of influenza group A, but can not yet be confirmed whether its influenza from human or birds
2. Respiratory failure
3. Death

Confirmed case

A confirmed case is an individual, alive or deceased in whom laboratory test shows one or more of the following:

1. Positive viral culture for influenza A/H5
2. Positive RT PCR for influenza A/H5
3. Positive Immunofluorescent Assay using A/H5 monoclonal antibodies
4. A 4-fold rise in influenza A/H5 specific antibody titers.

Contact

A contact of pandemic influenza is a person who had close (*i.e.*, within one meter) contact with an infectious case or who has spent more than 60 minutes in a confined space (such as an aeroplane, or an enclosed room) with an infectious person.

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