

The Bird Flu: A New Emerging Pandemic Threat And Its Pharmacological Intervention

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Abstract:

Bird flu is an infection caused by avian influenza viruses, which are of different types A, B and C. Type A avian influenza viruses are the most frequently associated with avian influenza epidemics and pandemics. There are 16 hemagglutinin (H1 to H16) and 9 neuraminidase types (N1 to N9) identified till date. A peculiar characteristic of influenza A viruses is their propensity for genetic change by two main processes: antigenic drift (small, gradual changes) and antigenic shift (abrupt, major change producing a novel influenza A virus subtype).

There are various modes of transmission of human influenza including inhalation, direct or indirect (fomite) contact etc., can have manifestations ranging from mild to severe or fatal disease, depend on the viral subtype causing the disease. Avian influenza A (H5N1) results in high death rate amongst infants and young children.

The first outbreak of human infection by avian influenza viruses (H5N1) was observed in 1997 in Hong Kong. Since then a large number of outbreaks have been reported in different parts of the world. In fact, the spread of avian influenza H5N1 in various species including humans has lead to a current pandemic threat.

Human avian influenza infections in persons at high risk of exposure can be prevented by adopting a series of protective measures, anti-viral vaccination and health monitoring. Drugs currently available for the treatment or prophylaxis of influenza infections include the adamantanes (amantadine and rimantadine) and the newer class of neuraminidase inhibitors (zanamivir, oseltamivir and peramivir). However, vaccines are considered the first line of defense for reducing the excess morbidity and mortality that invariably accompany pandemics and a number of clinical trials are under way to test them.

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Avian influenza (bird flu), an infection caused by avian influenza viruses has emerged as the primary public health concern of the 21st century. There are three types of influenza viruses, designated A, B and C. Variants of this species are sometimes named according to the species the strain is endemic in or adapted to for example, human flu, swine flu, horse Flu, dog flu etc.

Genomic structure of virus

Influenza virus belongs to a family of viruses called orthomyxoviridae, a group of single stranded minus-sense RNA viruses with a segmented genome. The eight RNA segments of the influenza A virus genome encode 11 viral proteins. These include the polymerase proteins (PB1, PB2, PA, PB1-F2), nucleocapsid protein, hemagglutinin, neuraminidase, matrix proteins (M1, M2), and nonstructural proteins (NS1, NS2).

Hemagglutinin and neuraminidase are the major antigenic determinants of influenza A viruses and serve as the basis for their subtype classification. There are 16 hemagglutinin (H1 to H16) and 9 neuraminidase types (N1 to N9). Hemagglutinin mediates attachment to and entry of the virus into host cells by binding to sialic acid receptors at the cell surface, which partly accounts for the host specificity of the various influenza A virus subtypes. However, a change of one amino acid of the H5 protein is sufficient to change the receptor binding specificity of A/H5N1 viruses. Thus, the barrier to interspecies infection can be overcome easily. Hemagglutinin also forms the main viral target of protective humoral immunity by neutralizing antibody.

Neuraminidase facilitates the spread of the virions in the host by cleaving the glycosidic linkages to sialic acid on host cells and the surface of the viral particles and is the target of neuraminidase inhibitors. M2 is an ion channel crucial for the pH-dependent dissociation of matrix proteins from the nucleocapsid during viral uncoating and pH changes across the trans-Golgi network during maturation of hemagglutinin molecules. M2 is the target of the adamantanes (amantadine and rimantadine). Mutation in the M2 from serine to asparagine at residue 31 invariably confers resistance to adamantanes.

PB1-F2 causes cellular apoptosis by acting on the host mitochondria. The hemagglutinin and PB2 proteins appear to be important in determining host specificity and virulence.⁽¹⁾

Types of bird flu viruses infecting birds and humans⁽²⁾

Influenza A H5: Nine potential subtypes of H5 are known. H5 infections, such as HPAI H5N1 viruses currently circulating in Asia and Europe, have been documented among humans and sometimes cause severe illness or death.

Influenza A H7: Nine potential subtypes of H7 are known. H7 infection in humans is rare but can occur among persons who have direct contact with infected birds. Symptoms may include conjunctivitis and/or upper respiratory symptoms. H7 viruses have been associated with both LPAI (e.g., H7N2, H7N7) and HPAI (e.g., H7N3, H7N7), and have caused mild to severe and fatal illness in humans.

Influenza A H9: Nine potential subtypes of H9 are known; influenza A H9 has rarely been reported to infect humans. However, this subtype has been documented only in a low pathogenic form.

Influenza Type B: These are usually found only in humans. Unlike influenza A viruses, these viruses are not classified according to subtype. Influenza B viruses can cause morbidity and mortality among humans, but in general are associated with less severe epidemics than influenza A viruses. Although influenza type B viruses can cause human epidemics, they have not caused pandemics.

Influenza Type C: viruses cause mild illness in humans and do not cause epidemics or pandemics. These viruses are not classified according to subtype.

Low vs Highly pathogenic avian influenza viruses⁽²⁾

On the basis of specific molecular genetic and pathogenesis criteria that require specific testing, influenza virus A are classified into low pathogenic (LPAIA) and high pathogenic (HPAIA) viruses. However, low pathogenic can evolve into high pathogenic viruses. H5, H7- H5N1, H7N7, H7N3 are HPAIA viruses and human infections with these viruses have ranged from mild (H7N3, H7N7) to severe and fatal disease (H7N7, H5N1). LPAIA viruses causing infection in humans include H7N7, H9N2, H7N2.

A constantly mutating virus: 2 consequences

A notable feature of influenza A viruses is their propensity for genetic change, which occurs by two main processes: antigenic drift and antigenic shift. Antigenic drift refers to small,

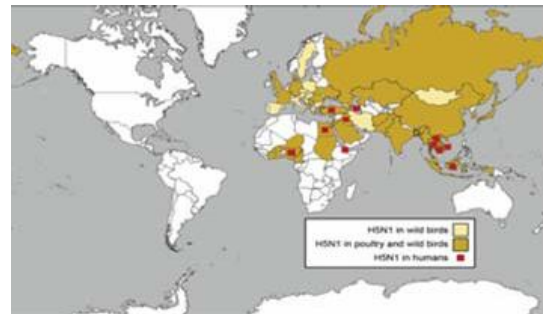
gradual changes that occur through point mutations in the two genes that contain the genetic material to produce the main surface proteins, hemagglutinin, and neuraminidase. These point mutations occur unpredictably and result in minor changes to these surface proteins. Antigenic shift refers to an abrupt, major change to produce a novel influenza A virus subtype in humans that was not currently circulating among people. It can occur either through direct animal (poultry)-to-human transmission or through mixing of human influenza A and animal influenza A virus genes to create a new human influenza A subtype virus through a process called genetic reassortment.⁽²⁾

EPIDEMIOLOGY

Human infections with avian influenza

The first ominous sign that avian influenza viruses (H5N1) could directly infect humans from avian species in a large scale occurred in 1997 in Hong Kong, resulting in 18 documented cases and six fatalities.¹ 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. February 2006 saw outbreaks of bird flu in 13 new countries including many parts of India.⁽⁶⁾ H5N1 is the most virulent subtype in a

long list of highly pathogenic avian viruses that have emerged in recent years.⁽³⁾



Nations with Confirmed Cases H5N1 Avian Influenza (May 2007)⁽¹⁰⁾

Outbreaks of human avian influenza^(3,8)

- H5N1; Hong kong
- H9N2; China
- H9N2; Hong kong
- H5N1; Hong kong, H7N7; Netherlands, H9N2; Hong kong

2004/05 H5N1; H7N3; Canada, H10N7; Egypt

H5N1 in 13 new countries including India
 H5N1 in China, Egypt, Indonesia, Nigeria
 Cumulative Number of Confirmed Human Cases of Avian Influenza A/(H5N1) Reported to WHO⁽¹¹⁾ (as on 11 April 2007)

Country	2003		2004		2005		2006		2007		Total	
	cases	deaths	cases	deaths	cases	deaths	cases	deaths	cases	deaths	cases	deaths
Azerbaijan	0	0	0	0	0	0	8	5	0	0	8	5
Cambodia	0	0	0	0	4	4	2	2	1	1	7	7
China	1	1	0	0	8	5	13	8	2	1	24	15
Djibouti	0	0	0	0	0	0	1	0	0	0	1	0
Egypt	0	0	0	0	0	0	18	10	16	4	34	14
Indonesia	0	0	0	0	20	13	55	45	6	5	81	63
Iraq	0	0	0	0	0	0	3	2	0	0	3	2
Lao People's Democratic Republic	0	0	0	0	0	0	0	0	2	2	2	2
Nigeria	0	0	0	0	0	0	0	0	1	1	1	1
Thailand	0	0	17	12	5	2	3	3	0	0	25	17
Turkey	0	0	0	0	0	0	12	4	0	0	12	4
Viet Nam	3	3	29	20	61	19	0	0	0	0	93	42
Total	4	4	46	32	98	43	115	79	28	14	291	172

Clinical features and prognosis of avian influenza infection in humans

Avian influenza A virus is shed in the feces of healthy-appearing waterfowl (primarily ducks), which in turn infect chickens and other poultry with which they come in contact. Conditions for transmission and jumping species barriers often are ideal in Asia, where poultry, ducks, pigs, and humans live in crowded conditions.⁽³⁾ Human influenza is transmitted by inhalation of infectious droplets and droplet nuclei, by direct contact, and perhaps, by indirect (fomite) contact, with self-inoculation onto the upper respiratory tract or conjunctival mucosa.⁽⁴⁾

The main clinical manifestations of avian influenza infections depend on the viral subtype causing the disease.⁽¹⁾ The incubation period of avian influenza A (H5N1) is quite variable and cases occurring within 2-4 to up to 8-17 days after exposure have been reported. Most patients have initial symptoms of high fever (>38°C) and lower respiratory tract symptoms. Diarrhea, vomiting, abdominal pain, pleuritic pain, and bleeding from the nose and gums have also been reported early in the course of illness in some patients. Infections caused by avian influenza A (H7) viruses also present with conjunctivitis commonly.

Various complications associated with avian influenza include Multi-organ failure with signs of renal dysfunction and cardiac compromise, ventilator-associated pneumonia, pulmonary hemorrhage, pneumothorax, pancytopenia, Reye's syndrome, and sepsis syndrome without documented bacteremia.⁽⁴⁾

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. Deaths occur at an average of 9 or 10 days after the onset of illness and most patients die of progressive respiratory failure.⁽⁵⁾

Laboratory diagnosis

The optimal specimen is a nasopharyngeal aspirate obtained within 3 days of the onset of the symptoms although nasopharyngeal swab may also be obtained. Rapid antigen assays, virus culture, real time polymerase chain reaction (RT-PCR) are various methods available for detection.⁽⁵⁾

Current Pandemic Threat

The current spread of avian influenza H5N1 in domestic poultry flocks and wild birds across the world, as well as the demonstrated ability of this virus to cross the species barrier and infect humans, has lead to a high level of concern that a pandemic may develop. For a pandemic to arise, three pre-requisites have been identified: a new virus subtype to which the population has little or no immunity must emerge; the new virus must be able to replicate in humans and cause serious illness; and the new virus must be efficiently transmitted from one human to another.⁽⁶⁾ Unlike most pandemics, which emerge randomly, H5N1 has been recognized as a likely pandemic candidate for almost 10 years.

Experts from the World Health Organization consider the current pandemic alert level to be stage 3.⁽³⁾

Table (1). World Health Organization (WHO) Classification of Pandemic Stages.

Period	Stage	Description
Inter-pandemic	1	No new influenza virus subtypes have been detected in humans. An influenza virus subtype that has caused human infection may be present in animals. If present in animals, the risk of human infection or disease is considered low.
	2	No new influenza virus subtypes have been detected in humans. However, a circulating animal influenza virus subtype poses a substantial risk of human disease.
Pandemic alert	3	Human infection with a new subtype of influenza occurs, but human-to-human transmission has not been reported (or at most, rare instances of spread to a close contact).
	4	Small clusters of infection with limited human-to-human transmission occur, but the spread of the disease is highly localized, suggesting that the virus is not well adapted to humans.
	5	Larger clusters of influenza infection in humans occur, but human-to-human spread is still localized, suggesting that the virus is becoming better adapted to humans but may not yet to be fully transmissible. Characteristics in this phase pose a substantial pandemic risk.
Pandemic	6	Increased and sustained transmission of the influenza virus occurs in the general population.

Guidance on Public Health Protection ⁽⁷⁾

WHO recommends a series of protective measures aimed at preventing human avian influenza infections in persons at high risk of exposure. These measures are particularly important during veterinary investigations and extensive and urgent culling operations.

Protection of persons at risk of occupational exposure with the help of personal protective equipment like protective clothing, heavy-duty rubber work gloves, standard well-fitted surgical masks, goggles, rubber or polyurethane boots. Pharmaceutical prophylaxis and treatment. Antivirals should be readily available for the treatment of suspected and confirmed cases. Vaccination for public health purposes. Health authorities may consider vaccination against seasonal influenza for persons at risk of occupational exposure to the H5N1 virus. Vaccination against seasonal influenza will not protect people against infection with the H5N1 virus; no vaccine against H5N1 is presently available. Health monitoring. Those at risk of occupational exposure should be aware of the early clinical signs of H5N1 infection, check for these signs (especially fever) each day during potential exposure and for 14 days after last exposure and communicate any symptoms to a designated local physician. Suspected cases should be placed in isolation and managed according to recommended procedures for infection control.

Drug therapy for bird flu Two groups of drugs are currently available for the treatment or prophylaxis of influenza infections: the adamantanes and the newer class of neuraminidase inhibitors.

The adamantanes (amantadine and rimantadine) interfere with viral uncoating inside the cell. They are effective only against influenza A and are associated with several toxic effects and with rapid emergence of drug-

resistant variants. Adamantane-resistant isolates of influenza A are genetically stable, can be transmitted to susceptible contacts, are as pathogenic as wild-type virus isolates, and can be shed for prolonged periods in immunocompromised patients taking the drug. This potential for the development of resistance especially limits the use of the adamantanes for the treatment of influenza, although the drugs still have a place in planning for prophylaxis during an epidemic.

The neuraminidase inhibitors (zanamivir and oseltamivir) interfere with the release of progeny influenza virus from infected host cells, a process that prevents infection of new host cells and thereby halts the spread of infection in the respiratory tract.⁽⁸⁾ These have activity against both influenza A and B viruses. A key advantage of the neuraminidase inhibitors, and a major difference from the adamantanes, is that development of resistance is very rare.

Zanamivir is approved for treatment of influenza among children aged ≥ 7 years.

Oseltamivir is approved for treatment and chemoprophylaxis among persons aged ≥ 1 year. Recommended treatment and chemoprophylaxis dosages of oseltamivir for children vary by the weight of the child.⁽²⁾

Peramivir, a newer agent in clinical trials, has also been shown to be a potent and selective inhibitor of influenza A and B neuraminidases.⁽⁹⁾

Ribavirin, a nucleoside analogue has been used in the treatment of human influenza A virus infections, usually administered orally or by aerosolization, and occasionally by the IV route for severe infections or in immunocompromised hosts. A consistent benefit has not been observed in clinical studies, and currently ribavirin is not considered to be a drug of choice for influenza A infection.⁽¹⁾

Table (2). Different antiviral used in bird flu infections and their important characteristics.

Characteristics	Amantadine	Rimantadine	Oseltamivir	Zanamivir	Ribavirin
Dosage and route of administration	Oral Therapeutic and Prophylactic: 100 mg bid; 100 mg qd for elderly (>65 yr)	Oral Therapeutic: 100 mg bid; 100 mg qd for elderly (>65yr); Prophylactic: 50 – 200 mg/day	Oral Therapeutic: 75 mg po bid; Prophylactic: 75 mg po qd	Inhalation (dry powder) Therapeutic: 2 inhalations (one 5-mg blister per inhalation for a total dose of 10 mg) twice daily; Prophylactic: 2 inhalations once daily for children >5yrs.	6 g/d by aerosolization at 18 h/d; 600 to 2,400 mg/d po in three to four divided doses; 1.5 mg/kg/h continuous infusion for 2 to 6 d
Metabolism	Mainly excreted unchanged in urine	Extensively metabolized in liver	Extensively metabolized in liver	Not significantly metabolized	Partially metabolized in liver
Major route of excretion	Renal	Liver (<1% parent compound excreted unchanged in urine)	Renal	Renal	Renal
Major adverse reactions	Neuropsychiatric	Similar to amantadine but much less common	Few major side effects; well tolerated at up to 1,000 mg single dose or 500 mg bid doses	Few major side effects; may cause bronchospasm in patients with underlying respiratory disease such as asthma and COPD, although not absolutely contraindicated;	Anemia, hyperbilirubinemia, teratogenicity
Important drug interactions	Caution when using other drugs with neurologic toxicity and nephrotoxicity	No clinically significant drug interactions	No clinically significant drug interactions	No clinically significant drug interactions	Antiretroviral agents

Bird Flu Vaccines ⁽⁷⁾

Vaccines are considered the first line of defence for reducing the excess morbidity and mortality that invariably accompany pandemics. Manufacturing capacity for influenza vaccines is overwhelmingly concentrated in Europe and North America. Current production capacity – estimated at around 300 million doses of trivalent seasonal vaccine per year – falls far below the demand that will arise during a pandemic. Also, little knowledge exists to guide formulation of an influenza vaccine that is both effective and economizes on the use of antigen.

However, clinical trials are under way to test different formulations.

Pandemic Preparedness ⁽¹²⁾

WHO has launched a programme “WHO Global Influenza Programme” in order to reduce death and disease due to annual influenza epidemics and prepare for the next influenza pandemic. The objective of this programme is to increase and strengthen global epidemic and pandemic preparedness through:

Improved quality and global coverage of influenza surveillance

Improved understanding of health and economic burden of influenza including benefits from epidemic control and pandemic preparedness

Increased national epidemic and pandemic preparedness including vaccine and pharmaceutical supplies

Expanded use of existing vaccines particularly in developing countries and in high-risk groups and accelerated introduction of new vaccines

More rapid communication and information exchange between WHO Influenza Network Members and key partners and stakeholders.

Conclusion

The bird flue infection in human is recent pandemic threat and introduction of neuraminidase inhibitors was an important step for effective control of infection, however experience from past demand more newer and better drugs to tackle this problem and if possible may be even super-vaccine for future.

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