

Review Article: Avian Influenza Infections in Human

Rangsima Lolekha, M.D.*

Tawe Chotpitayasunondh, M.D.**

Somsak Lolekha, M.D.***

ABSTRACT

Avian influenza (AI) viruses do not commonly infect human. Human infections with AI A (H5N1, H9N2, H7N7 and H7N2) viruses have been reported in Hong Kong, the Netherlands, Vietnam, Thailand, Canada and the US since 1997. The H7-type AI viruses are less virulent than the H5-type strain, and usually associate with conjunctivitis and mild influenza-like illness in humans. The H5-type strains usually associate with respiratory distress with high fatality. Tests for diagnosing all influenza strains of animals and humans are rapid and reliable. Antiviral drugs used for treatment and prevention are clinically effective against influenza A virus strains in healthy adults and children, but they are still expensive and supplies are limited. Experience in the production of influenza vaccines is also considerable, particularly as vaccine composition changes each year to match changes in circulating virus due to antigenic drift. A least four months would be needed to produce a new vaccine capable of conferring protection against a new virus subtype. At present, human-to-human transmission of AI virus was limited. However, it is of particular concern because AI mutates rapidly and has a documented propensity to acquire genes from viruses infecting other animal species. If the host is concurrently infected with human and AI strains which can be served as the “mixing vessel” for the emergence of a novel subtype that can infect human, this could lead to the start of an influenza pandemic. The world needs to be better prepared to respond to the next influenza pandemic. Improved influenza surveillance, good public health network, antiviral agents and vaccine development are important for preparedness of the next pandemic. (*J Infect Dis Antimicrob Agents* 2004;21:99-110.)

INTRODUCTION

Since mid December, 2003 the avian influenza (AI) outbreaks remind us that an influenza pandemic is possible and imminent as long as the virus remains present in poultry or the environment. This article reviews a recent knowledge about AI infections in humans.

Basic knowledge

Type A influenza viruses can infect several animal species, including birds, pigs, horses, seals and whales. Influenza viruses that infect birds are called “avian influenza viruses”. The AI viruses are genetically different from influenza viruses that usually infect people. There are many subtypes of AIA viruses which

*Thailand MOPH-US CDC Collaboration DDC, 7 Building, 4th Floor, Ministry of Public Health, Soi 4, Nonthaburi 11000, Thailand.

**Infectious Disease Unit, Department of Pediatrics, Queen Sirikit National Institute of Child Health, Bangkok 10400, Thailand.

***Infectious Disease Unit, Department of Pediatrics, Ladproa General Hospital, Bangkok, Thailand.

Received for publication: June 24, 2004.

Reprint request: Ransima Lolekha, M.D., Thailand MOPH-US CDC Collaboration DDC 7 Building, 4th Floor, Ministry of Public Health, Soi 4, Nonthaburi 11000, Thailand.

Keywords: Avian influenza, influenza, H5N1, H9N2, H7N7, H7N2

are classified on the basis of their surface proteins, hemagglutinin (HA) and neuraminidase (NA). There are 15 known H subtypes and 9 known N subtypes. While all subtypes can be found in birds which are considered the natural hosts for influenza A viruses, only 3 subtypes of HA (H1, H2 and H3) and two subtypes of NA (N1 and N2) are known to have circulated extensively in humans.¹ AI viruses do not usually infect human, however, several instances of human infections with outbreaks have been reported since 1997.^{2,3}

Characteristics of AI in birds⁴

AI viruses can be distinguished as “low pathogenic (LPAI)” and “high pathogenic (HPAI)” forms based on genetic features of the virus and the severity of the illness they cause in poultry. AI usually does not make wild birds sick, but can make domesticated birds very sick and even kill them. The most common route of introduction of AI viruses into an poultry area is by wild birds, usually through waterfowl, but also by gulls and shorebirds. Very virulent HPAI viruses can lead to mortality in poultry as high as 100 percent. LPAI viruses cause a much milder disease, with few clinical signs and mortality is

much lower. Sometimes secondary bacterial infections or some unknown environmental conditions may cause exacerbation of LPAI infections leading to more serious disease. Certain AI virus subtypes of low pathogenicity may circulate for some time in a poultry population, and mutate into a HPAI virus strain. Birds that are infected with AI viruses shed virus in saliva, nasal secretions and feces. Contact with feces or respiratory secretions is important in the transmission of infection among poultry. Between flocks, infection usually spreads through movement of infected birds and the actions of humans in moving feedstuff, personnel, equipment, and vehicles into and from premises that are contaminated with infected feces or respiratory secretions. AI virus infections in human is shown in Table 1.

The first human outbreak of highly pathogenic AIA (H5N1) virus infections resulted in 18 hospitalizations and six deaths among Hong Kong residents during 1997.^{3,5-7} The H5N1 outbreak during 2003-2004 in Thailand and Vietnam resulted in 19 confirmed cases and 14 deaths in Vietnam⁷ and 12 confirmed cases and 8 deaths in Thailand.⁸ All genes of AI viruses which infected human are of bird origin. This means that the virus has not acquired genes from human influenza

Table 1. Confirmed instances of avian influenza viruses infecting humans since 1997-May 2004.¹

Year	Country	Subtypes	Infected/Death cases	Remarks
1997	Hong Kong	H5N1	18/6	1.5 million chickens were culled
1999	Hong Kong	H9N2	2/0	
2003	Hong Kong	H9N2	2/1	Another family member died of a respiratory illness in China, but no testing was done
2003	Netherlands	H7N7	89/1	1 patient died (in a 57-year-old veterinarian who had visited an affected farm)
2003	Hong Kong	H9N2	1/0	
2004	Vietnam	H5N1	22/14	
2004	Thailand	H5N1	12/8	
2004	USA	H7N2	1/0	

viruses, however this development would make person-to-person spread more likely. There are different variations of AI viruses circulating in each outbreak for example the genetic sequencing of virus samples from South Korea and Vietnam show that the viruses in these two countries are slightly different.⁹ All influenza viruses can mutate, so it is possible that an AI virus could mutate so that it could infect humans and spread easily from person to person. Because these viruses do not commonly infect humans, there is little or no immune protection against them in the human population. If an AI virus was able to spread easily from person to person, an “influenza pandemic” could begin.

AI A virus strains isolated in humans have been H5N1, H7N7 and H9N2. Recently, there is a report of an isolated case of human influenza caused by A/H7N2 from a patient in New York State.¹⁰ The patient’s acute symptoms resolved after hospitalization. Family members reported no respiratory illnesses and were tested seronegative for antibodies against H7 viruses. The source of this infection is unknown.¹⁰

Transmission of AI infections in human

Most cases of AI infection in humans have resulted from closed contact with infected poultry or contaminated materials. Other means of transmission are possible, such as the virus becoming aerosolized and landing on exposed surfaces of the mouth, nose, or eyes, or being inhaled into the lungs.

Symptoms and signs of AI in human

The reported symptoms of AI in humans have ranged from typical influenza-like symptoms (e.g. fever, cough, sore throat and muscle aches) to eye infections, pneumonia, acute respiratory distress and other life-threatening complications. Symptoms of AI in humans are shown in Table 2.

Table 2 demonstrates that H7-type AI viruses

reported from the Netherlands are less virulent in humans than the H5-type strain that occurred in Southeast Asia in 2004. Other H7-type strains were responsible for outbreaks in Canada (H7N3) during 2004 and in the Netherlands in 2003 (H7N7). The H7-type strain is usually associated with conjunctivitis and mild influenza-like symptoms while H5N1 causes very severe disease in humans, with a high fatality. H5N1 infection affects more body organs and systems than normal influenza, and respiratory symptoms are dominant. Factors associated with severe disease in Hong Kong outbreak in 1997⁷ include older age, delay in hospitalization, lower-respiratory-tract involvement and a low total peripheral white blood cell count or lymphopenia. In 2004, an outbreak in Thailand, most severe diseases occurred in children.¹⁴

Human-to-human transmission

A case-control study identified recent exposure to live poultry as an important risk factor for H5N1 infection¹⁶, and cohort studies suggested that human-to-human transmission of H5N1 virus is very limited.^{17,18} In 1999, AI A (H9N2) viruses were not transmitted from two infected children to household members, relatives or health care workers (HCWs) in Hong Kong.¹⁹

The absence of human-to-human transmission of avian H9N2 viruses and the low transmissibility of avian H5N1 viruses among humans has several explanations.^{17,18} The genomes of the H9N2 and H5N1 strains isolated from humans are derived entirely from AI viruses, and thus no reassortment with circulating human influenza A viruses occurs. It is possible that the AI genome limits viral spread among humans. The transmission of influenza virus among humans and other species remains poorly understood. However, following the infection of an AI virus in human cell, alterations in HA receptor-binding specificity would be required for effective human-to-human transmission.²⁰ In addition,

Journal reported	Causative agents	Age/sex	History of contact sicked poultry	History, symptoms, signs on admission	Laboratory studies	Clinical course	Treatment and outcome
MMWR ¹⁴ Feb 13, 2004 Thailand	H5N1	5 cases: 4 male (age 6-7 years) and 1 female (age 58 years)	4 patients report death in poultry owned by the patient's family and 2 reported touching poultry.	Patients reported to hospitals 2-6 days after onset of fever and cough. Fever (5), sore throat (4), rhinorrhea (2) and myalgia (2), dyspnea on day 1-5 after symptom onset. CXR: patchy infiltrates (4) and interstitial infiltrates (1).	Peripheral leukocytes were normal (2) or decreased (3), lymphopenia (<1,000/ L) (4), thrombocytopenia (2). Mild-to-moderate elevations in hepatic transaminases (4).	All patients had respiratory failure, pneumothorax (2), required inotropic support for decreased cardiac function (3), renal impairment (2). None had documented evidence of secondary bacterial infection.	Oseltamivir in 3 patients. All died on day 8-29.
NEJM ¹⁵ March 18, 2004 Vietnam	H5N1	10 cases: 6 males and 4 females with mean age of 13.7 years (range, 5 to 24).	8/9 patients, in whom a history could be obtained, had history expose to sick poultry in the week before the onset of illness. The median time between exposure and the onset of illness was 3 days (range, 2 to 4).	The median time between the onset of illness and hospitalization was 5.9 days (range, 3 to 8). All patients presented with fever, shortness of breath, and cough. Sputum production (5), and in three of these patients, the sputum was bloodstained. Pleuritic pain (2). Diarrhea (7),	The median total leukocyte count on admission was 2,100/mm ³ (range, 1,200-3,400). The median total lymphocyte count was 700/mm ³ (range, 250-1,100). The median platelet count was 75,500/mm ³ (range, 45,000-174,000). Mild-to-moderate elevations in transaminases (5/6) and marked hyperglycemia (3). CXR: extensive infiltration bilaterally, lobar collapse, focal consolidation or air bronchograms.	All patients had dramatic worsening of findings on chest radiography-pneumothorax (2), inotropic support for decreased cardiac function (2), gastro-intestinal hemorrhage (1). major sequelae, 8 patients died, and 1 patient is recovering. The median time to death from the onset of illness was 9 days (range, 6-17).	Oseltamivir in 5 patients. Ribavirin in 2 patients. 1 patient survived with no major sequelae, 8 patients died, and 1 patient is recovering. The median time to death from the onset of illness was 9 days (range, 6-17).

WBC = leukocytes; AST = aspartate aminotransferase; CXR = chest X-ray; U/A = urinalysis; NP = nasopharyngeal; RT-PCR = Reverse transcriptase polymerase chain reaction

the patients may not have shed H5N1 and H9N2 virus in titers sufficient to facilitate transmission to other persons.

Case management in patients who live or travel in area that has reported HPAI or H5N1 infection in poultry is as follows:

1. Identification of suspected AI infection in humans as follows:^{21,22}

1.1) Any individual presenting with fever (temperature >38 °C) and one or more of the following symptoms: cough sore throat, shortness of breath and one or more of the followings:

- Contact with a confirmed case of influenza A/H5 while this case was infectious during the 7 days prior to the onset of symptoms.
- Contact with birds, including chickens that have died of an illness during the 7 days prior to the onset of symptoms.
- Work in a laboratory during the 7 days prior to the onset of symptoms where there is processing of samples from persons or animals suspected of having highly pathogenic AI (HPAI) infection.

1.2) Any individual who died from an unexplained acute respiratory illness

All suspected cases as above should be monitored under closed clinical observation. If clinically indicated, they should be hospitalized under appropriate infection control precautions. If a case does not require hospitalization, he or she and his or her family should be educated on personal hygiene and infection control measures (e.g. hand-washing, use of a paper or surgical mask by the ill person and restriction of social contacts), and he should be promptly sought to medical care if his condition worsens. As resources permit, non-hospitalized patients should be followed up by home visits or telephone contact.²²

2. All suspected cases should have diagnosis confirmed by respiratory and blood specimens for influenza and other infections as clinically indicated.

Assays available for the diagnosis of influenza A virus infections include:²³

- 2.1) Rapid antigen detection. Results can be obtained in 15-30 minutes.
- 2.2) Virus culture. Provides results in 2-10 days. Both shell-vial and standard cell culture methods may be used to detect clinically important respiratory viruses. The virus is identified by immunofluorescence or haemagglutination-inhibition assay.

3. Polymerase chain reaction. Primer sets specific for the haemagglutinin (HA) gene of currently circulating influenza A/H1, A/H3 and B viruses are becoming more widely used. Results can be available within 24 hours. Any specimen with a positive result for influenza A virus should be further tested to identify the type of influenza. In a situation where laboratories cannot perform specific influenza A/H5 identification, the procedures are required to:

- 3.1) Forward specimens to a national influenza centre or to other recommended reference laboratories for further identification or characterization.
- 3.2) Inform the relevant WHO country office, WHO regional office or U.S. CDC office that specimens or isolated virus are being forwarded to other laboratories for further identification or further characterization.

4. Serological identification of influenza A/H5 infection. Serological tests available for the measurement of influenza A-specific antibody include the haemagglutinin inhibition test, the enzyme immunoassay, and the virus neutralization tests. Paired serum should be obtained from the patient on first week of illness and 2 weeks later.

A confirmed case of influenza A/H5 infection is an individual whose laboratory testing demonstrates **one or more** of the followings:²³

- Positive viral culture for influenza A/H5;
- Positive polymerase chain reaction (PCR) for influenza A/H5;
- Positive immunofluorescence antibody (IFA) test for H5 antigen using H5 monoclonal antibodies;
- 4-fold rise in H5-specific antibody titer in paired serum samples.

5. Treatment options for highly suspicious cases are as follows:

5.1) Specific treatment: antiviral agents for influenza

Studies to date suggest that the prescription medications approved for human influenza strains would be effective in preventing avian influenza infection in humans, however, sometimes influenza strains can become resistant to these drugs and so they may not always be effective. Genetic sequencing of A (H5N1) virus samples from human cases in Vietnam and Thailand show antiviral resistance to amantadine and rimantadine⁷, two of the antiviral drugs commonly used for influenza. Oseltamivir and zanamavir are effective against this strain of H5N1, and treatment should be initiated early.²² The effectiveness of antiviral drugs against H5N1 infections and the period after which these drugs will provide little or no benefit is not fully known. The dose of oseltamivir recommended for children below 15 kg is 30 mg twice a day. For children who weigh between 15-23 kg, the dose is 45 mg twice a day. For children who weigh between 23-40 kg, the dose is 60 mg twice a day. And for children who weigh more than 40 kg and adult, the dose is 75 mg twice a day.²⁴ The oseltamivir (Tamiflu[®]) is available in 2 preparations including 75 mg capsule and oral suspension which is packaged with a dispensing syringe calibrated with graduation of 30, 45 and 60 mg.

Ribavirin is another potential antiviral drug which efficacy against AI virus is still under investigated. It can cause adverse reactions especially severe anemia.²²

A more detailed understanding of the pathogenesis is needed to direct therapeutic approaches such as the use of immunomodulating drugs and steroid. It still needs further study.²²

5.2) Supportive treatment²²

- Patients with respiratory distress should be monitored oxygen saturation, and supplemental oxygen should be given as required. Nebulizers and high-air-flow oxygen masks have been potentially implicated in the nosocomial spread of severe acute respiratory syndrome, so these devices should only be used if clinically justified and strict infection control should be applied.
- Respiratory and blood specimens should be taken serially to check for possible bacterial infection.
- Intravenous antibiotic therapy should be used to control secondary bacterial infections.
- Avoid administration of salicylates (such as aspirin) in children less than 18 years of age because of the risk of Reye syndrome. Use paracetamol or ibuprofen, either orally or by suppository, for management of fever as clinically indicated.

6. Discharge policy²²

Studies are required to provide better understanding of viral excretion patterns in humans infected with the influenza A (H5N1) viruses associated with the current outbreaks in Thailand and Vietnam. Until further evidence is available, WHO recommends that infection control precautions for adult patients remain in place for 7 days after the fever has resolved. Previous studies have indicated that children younger than 12 years can shed virus for up to 21 days after the onset of illness, therefore, infection control measures should remain in place for 21 days. Where this is not

feasible (because of a lack of local resources), the family should be educated on personal hygiene and infection control measures (e.g. hand-washing and use of a paper or surgical mask by a child who is still coughing). Children should not attend school during this period.

Prevention of AI infection in hospitals

The recommendations by CDC and WHO are based on what are deemed optimal precautions for protecting individuals involved in the response to an outbreak of high pathogenic AI from illness and the risk of viral reassortment (i.e. mixing of genes from human and avian viruses). The health risk to humans from LPAI viruses is less well established, but is likely to be lower. Nonetheless, it is considered prudent to take all possible precautions to the extent feasible when individuals have contact with birds infected by any AI virus as part of control and eradication activities.

Basic infection control ⁽²¹⁾

- Transmission of human influenza is by droplets and fine droplet nuclei (airborne). Transmission by direct and indirect contact is also recognized. However, during the 1997 influenza A (H5N1) outbreak in humans in Hong Kong, droplet and contact precautions successfully prevented nosocomial spread of the disease. So far there is no evidence to suggest airborne transmission of the disease in the current outbreaks in Thailand and Vietnam. Nevertheless, because of the high mortality of the disease and the possibility of the virus mutating to cause efficient human-to-human transmission, WHO recommends the use of high-efficiency masks, in addition to droplet and contact precautions. In addition, a negative pressure room if available is recommended, and the patient should be isolated in a single room. If a single room is not available, cohort patients separately in designated multi-bed rooms or

wards; beds should be placed more than 1 metre apart and preferably be separated by a physical barrier (e.g. curtain, partition). Reinforce standard precautions with droplet and contact precautions. Educate workers about the importance of strict adherence to and proper use of hand hygiene after contact with infected or exposed poultry, contact with contaminated surfaces, or after removing gloves. Hand hygiene should consist of washing with soap and water for 15-20 seconds or the use of other standard hand-disinfection procedures.

- Ensure personnel have access to appropriate personal protective equipment (PPE). All those entering patients' rooms should use mask (high efficiency mask if available or surgical mask), gown, face shield or goggles and gloves. Instructions and training in PPE use and respirator fit-testing.
- Limit the number of HCWs who have direct contact with the patient(s); these HCWs should not look after other patients. The number of other hospital employees (e.g. cleaners, laboratory personnel) with access to the environment of these patients should also be limited. Designated HCWs should all be properly trained in infection control precautions. Restrict the number of visitors and provide them with appropriate PPE and instruct them in its use.

Personal protective equipment (PPE)²¹

- Disposable gloves made of lightweight nitrile or vinyl or heavy duty rubber work gloves that can be disinfected should be worn. A thin cotton glove can be worn inside the external glove to protect against dermatitis, which can occur from prolonged exposure of the skin to moisture in gloves caused by perspiration.

Gloves should be changed if torn or otherwise damaged. Remove gloves promptly after use, before touching non-contaminated items and environmental surfaces.

- Protective clothing, preferably disposable outer garments or coveralls, an impermeable apron or surgical gowns with long cuffed sleeves, plus an impermeable apron should be worn.
- Disposable protective shoe covers or rubber or polyurethane boots that can be cleaned and disinfected should be worn if available.
- Safety goggles should be worn to protect the mucous membranes of eyes.
- Disposable particulate respirators (e.g. N-95, N-99 or N-100) are the minimum level of respiratory protection that should be worn. This level or higher respiratory protection may already be in use in poultry operations due to other hazards that exist in the environment (e.g. other vapors and dusts). Workers must be fit-tested to the respirator model that they will wear and also know how to check the face-piece to face seal. Workers who cannot wear a disposable particulate respirator because of facial hair or other fit limitations should wear a loose-fitting (i.e. helmeted or hooded) powered air purifying respirator equipped with high-efficiency filters.
- Disposable PPE should be properly discarded, and non-disposable PPE should be cleaned and disinfected as specified in state government, industry or USDA outbreak-response guidelines. Hand hygiene measures should be performed after removal of PPE.

Administration of antiviral drugs for prophylaxis²¹

- If possible, workers should receive an influenza antiviral drug daily for the duration of time during which direct contact with infected

poultry or contaminated surfaces occurs. The choice of antiviral drug should be based on sensitivity testing when possible. In the absence of sensitivity testing, a neuraminidase inhibitor (oseltamavir) is the first choice since the likelihood is smaller that the virus will be resistant to this class of antiviral drugs than to amantadine or rimantadine. However, countries where antiviral agents are limited, the chemoprophylaxis for workers is less necessary than appropriate PPE practices

Surveillance and monitoring of workers²¹

- Instruct workers to be vigilant for the development of fever, respiratory symptoms, and/or conjunctivitis (i.e. eye infections) for one week after last exposure to AI-infected or exposed birds or to potentially AI-contaminated environmental surfaces.
- Individuals who become ill should seek medical care and prior to arrival, notify their health care provider that they may have been exposed to avian influenza. In addition, employees should notify their health and safety representative.
- With the exception of visiting a health care provider, individuals who become ill should be advised to stay home until 24 hours after resolution of fever, unless an alternative diagnosis is established or diagnostic test results indicate the patient is not infected with influenza A virus.
- While at home, ill persons should practice good respiratory and hand hygiene to lower the risk of transmission of virus to others.

Evaluation of Ill workers²¹

- Workers who develop a febrile respiratory illness should have a respiratory sample (e.g. nasopharyngeal swab or aspirate) collected.

- The respiratory sample should be tested by RT-PCR for influenza A, and if possible for H1 and H3. If such capacity is not available in that area or if the result of local testing is positive, then local CDC should be contacted and the specimen should be sent for further testing.
- Virus isolation should not be attempted unless a biosafety level 3+ facility is available to receive and culture specimens.
- Optimally, an acute- (within one week of illness onset) and convalescent-phase (after three weeks of illness onset) serum sample should be collected and stored locally in case testing for antibody to the AI virus should be needed.

Vaccination with seasonal influenza vaccine²¹

Selected groups to be immunized²⁵

- All persons who are expected to be in contact with poultry or poultry farms suspected or known to be affected with AI (H5N1), especially (a) cullers involved in destruction of poultry, and (b) people living and working in poultry farms where H5N1 has been reported or is suspected or where culling takes place.
- HCW involved in the daily care of known or confirmed human cases of influenza H5N1.
- Given sufficient supplies of vaccine, HCW in emergency care facilities in areas where there is confirmed occurrence of influenza H5N1 in birds.

The selected groups described above should receive the current season's influenza vaccine. The vaccine will not protect humans from infection with avian H5N1 influenza rather, it reduces the possibility of dual infection with avian and human influenza viruses. There is a small possibility that dual infection could occur and result in reassortment. The resultant hybrid virus could be highly transmissible among people and lead to widespread

infections. Vaccination of all residents of affected areas is not supported by current epidemiologic data. And there are no specific influenza vaccination requirements for international travelers with respect to the current outbreaks of AI in poultry.

Vaccination for prevent AI in human²⁶

Prevention on influenza H5N1 requires the development of a vaccine based on the viruses that are currently circulating. The existence of a large number of virus subtypes together with the known variation of different strains within a subtype pose serious problems when selecting strains to produce influenza vaccines and to use vaccination as a routine tool for disease prevention. Current viruses are genetically distinct enough from the viruses identified from the last outbreak so a new vaccine should be produced based on current virus's strain. The best-case scenario for having a virus available for a vaccine for the human population is several months from now. This means that if, for instance, an explosion of human cases were to occur tomorrow, that vaccine would not be an option. What we have seen in prior pandemics in the last century is that the second wave of disease, which usually occurred a few months after the first wave, tended to be the worst wave.²⁶ So even if a vaccine for influenza H5N1 is not available for several months, it could actually be useful for the second wave of pandemic.

In conclusion, AI infection in humans reminds us that an influenza pandemic is possibly imminent. The world needs to be better prepared to respond to the next influenza pandemic. Improved influenza surveillance, good public health network, antiviral agents and vaccine development are important for preparedness of the next outbreak.

References

1. Centers for Disease Control and Prevention (CDC). Basic information about avian influenza (Bird Flu)

- [online]. January 29, 2004 [cited 2005 Feb 28]. Available from: URL: <http://www.cdc.gov/flu/avian/facts.htm>.
2. Chan PK. Outbreak of avian influenza A (H5N1) virus infection in Hong Kong in 1997. *Clin Infect Dis* 2002;34 (Suppl 2):S58-64.
 3. Centers for Disease Control and Prevention. Update: isolation of avian influenza A (H5N1) viruses from humans--Hong Kong, 1997-1998. *MMWR Morb Mortal Wkly Rep* 1998;46:1245-7.
 4. Centers for Disease Control and Prevention (CDC). Interim guidance for protection of persons involved in U.S. avian influenza outbreak disease control and eradication activities [online]. February 17, 2004 [cited 2005 Feb 28]. Available from: URL: <http://www.cdc.gov/flu/avian/protectionguid.htm>.
 5. Claas EC, Osterhaus AD, van Beek R, et al. Human influenza A H5N1 virus related to a highly pathogenic avian influenza virus. *Lancet* 1998;351:472-7.
 6. Lee SY, Mak KH, Saw TA. The avian flu (H5N1): one year on. Department of Health, Hong Kong Special Administrative Region of China. *Public Health and Epidemiology Bulletin* 1999;8:1-7.
 7. World Health Organization. Avian influenza A (H5N1) - update 22: First data on patients from Viet Nam, Clinical data from Hong Kong 1997, Susceptibility of H5N1 viruses to antiviral drugs [online]. February 12, 2004 [cited 2005 Feb 28]. Available from: URL: http://www.who.int/csr/don/2004_02_12a/en/.
 8. Department of Disease Control Ministry of Public Health. Avian influenza in human surveillance summary 26 March 2004 [online]. 2003 [cited 2005 Feb 28]. Available from: URL: http://www-ddc.moph.go.th/bird_flu_sit.html.
 9. Centers for Disease Control and Prevention (CDC). Bird Flu Fact Sheet [online]. February 4, 2004 [cited 2005 Feb 28]. Available from: URL: <http://www.cdc.gov/flu/avian/outbreak.htm>.
 10. Centers for Disease Control and Prevention (CDC). Interim report: Human infection with avian H7 influenza viruses, North America [online]. April 5, 2004 [cited 2005 Feb 28]. Available from: URL: <http://www.cdc.gov/flu/avian/interim-report.htm>
 11. Yuen KY, Chan PK, Peiris M, et al. Clinical features and rapid viral diagnosis of human disease associated with avian influenza A H5N1 virus. *Lancet* 1998;351: 467-71.
 12. Fouchier RA, Schneeberger PM, Rozendaal FW, et al. Avian influenza A virus (H7N7) associated with human conjunctivitis and a fatal case of acute respiratory distress syndrome. *Proc Natl Acad Sci USA* 2004;101: 1356-61.
 13. Peiris M, Yuen KY, Leung CW, et al. Human infection with influenza H9N2. *Lancet* 1999;354: 916-7.
 14. Centers for Disease Control and Prevention (CDC). Cases of Influenza A (H5N1)---Thailand, 2004. *MMWR Weekly* [online] February 13, 2004 [cited 2005 Feb 28];53(05):100-3. Available from: URL: <http://www.cdc.gov/mmwr/preview/mmwrhtml/mm5305a2.htm>
 15. Tran TH, Nguyen TH, Nguyen TL, et al. Avian influenza A (H5N1) in 10 patients in Vietnam. *N Engl J Med* 2004;350:1179-88.
 16. Mounts AW, Kwong H, Izurieta HS, et al. Case-control study of risk factors for avian influenza A (H5N1) disease, Hong Kong, 1997. *J Infect Dis* 1999;180:505-8.
 17. Bridges CB, Katz JM, Seto WH, et al. Risk of influenza A (H5N1) infection among health care workers exposed to patients with influenza A (H5N1), Hong Kong. *J Infect Dis* 2000;181:344-8.
 18. Katz JM, Lim W, Bridges CB, et al. Antibody response avian influenza A (H5N1) viruses and detection of anti-H5 antibody among household and social contacts. *J Infect Dis* 1999;180:1763-70.
 19. Uyeki TM, Chong YH, Katz JM, et al. Lack of evidence for human-to-human transmission of avian influenza A (H9N2) viruses in Hong Kong, China 1999. *Emerg Infect Dis* 2002;8:154-9.
 20. Matrosovich M, Zhou N, Kawaoka Y, Webster R. The surface glycoprotein of H5 influenza viruses isolated from humans, chickens and wild aquatic birds have

- distinguishable properties. *J Virol* 1999;73:1146-55.
21. Centers for Disease Control and Prevention (CDC). Outbreaks of avian influenza A (H5N1) in Asia and interim recommendations for evaluation and reporting of suspected cases--United States, 2004. *MMWR Morb Mortal Wkly Rep* 2004;53:97-100.
 22. World Health Organization. WHO interim guidelines on clinical management of humans infected by influenza A (H5N1)[online]. March 2, 2004 [cited 2005 Feb 28]. Available from: URL: http://www.who.int/csr/disease/avian_influenza/guidelines/en/avian_labtests.pdf http://www.who.int/csr/disease/avian_influenza/guidelines/clinicalmanage/en/, 2 March 2004
 23. World Health Organization. Recommended laboratory tests to identify influenza A/H5 virus in specimens from patients with an influenza-like illness [online]. February 19, 2004 [cited 2005 Feb 28]. Available from: URL: http://www.who.int/csr/disease/avian_influenza/guidelines/en/avian_labtests.pdf
 24. Bridges CB, Harper SA, Fukuda K, Uyeki TM, Cox NJ, Singleton JA. Prevention and control of influenza. Recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR Recomm Rep* 2003;52(RR-8):1-34.
 25. World Health Organization. Guidelines for the use of seasonal influenza vaccine in humans at risk of H5N1 infection [online]. January 30, 2004 [cited 2005 Feb 28]. Available from: URL: http://www.who.int/csr/disease/avian_influenza/guidelines/seasonal_vaccine/en/
 26. Harper S. Clinician outreach & communication activity conference call. Avian Influenza Update [online]. January 30, 2004 [cited 2005 Feb 28]. Available from: URL: <http://www.indianaruralhealth.org/Conference%20Call-Influenza%20Update-02-05-04.htm>