Avian Influenza

Rebecca M. Wurtz MD, MPH
Charles Schable, MS

Influenza

Influenza is a common viral infection in humans, affecting as much as one-third of the US population during a typical winter influenza season. Although there are 3 types of influenza (A, B and C), all recent human influenza pandemics (1918-19, 1957-58, 1968-69 and 1977-78) have been due to influenza A.

Avian influenza

Many animal species (pigs, horses, marine mammals) can be infected by species-specific strains of influenza (e.g., "swine flu"). In recent years, episodic outbreaks of highly pathogenic avian influenza (AI), a subtype of influenza A, have caused many lethal outbreaks in poultry. Until recently, it was believed that the first cases of AI in humans occurred in 1997 in Hong Kong. However, recent molecular reconstruction of the 1918 flu pandemic virus has shown that it was an AI. This has increased the concern about the likelihood and consequences of a human AI pandemic.

In the interval between 1997 and 2003, several large avian outbreaks involved a small number of associated human cases. However, beginning in late 2003, an AI outbreak spread throughout Southeast Asia involving millions of birds and scores of people. The current widespread H5N1 strain is not highly transmissible from person to person; virtually all human cases have occurred following direct, close contact with infected birds.

In 2005, the avian epizootic spread west to Europe and Asia Minor, northward to Russia, and southward to Indonesia; in 2006, it has spread to Western Europe and Africa. As AI affects birds in more parts of the world, the risk of genetic change and human infection increases.

In addition to the sweep of this particular H5N1 strain, sporadic avian outbreaks of other strains continue to occur, but human infection is rare to non-existent.

Influenza's ability to remake its genome

Influenza is ubiquitous and persistent partly because of its wide host range, and partly because of its extraordinary ability to modify its genome, both by small changes (mutation) and large changes (recombination). Mutations can make a previously mild strain into a virulent strain, and recombination can remake the host range. The ability of influenza to easily "recombine" its genome poses the greatest threat to humans. Each influenza viral particle has 8 separate strands of DNA. If 2 different viruses, avian and human, infect the same host cell, the resulting 16 strands may be re-packaged into

©Scientific Technologies Corporation, 2006, All Rights Reserved

progeny virions in any combination. A virion could leave the host cell as a lethal hybrid: avian pathogenicity plus contagiousness in humans. A recent troubling development has been the recognition that H5N1 avian influenza has evolved into two separate strains or clades. At the 2006 International Conference on Emerging Infectious Diseases, CDC investigators reported that one clade of H5N1 made people sick in Vietnam, Cambodia and Thailand in 2004 and the second clade made people sick in Indonesia in 2005. Fortunately neither clade is transmitted easily from person to person. However this development signals potential control problems since a vaccine must be directed at the specific clade of the virus to be highly effective. Hopefully vaccination with one clade would provide partial immunity against another clade of the virus.

Spread, transmission and pathogenicity of AI in birds

AI's ability to cause rapid, far-flung outbreaks is due to the wide migratory and species range of infected birds, the virus's ability to replicate in birds, and the large quantity of virus shed by infected birds. AI is a common problem among many species of wild birds, particularly waterfowl (gulls, seabirds, shorebirds, and ducks). In the United States, we have seen a well-documented avian dissemination of another viral disease, West Nile Virus, in the last 5 years so the ability of birds to disseminate influenza shouldn't surprise us. However, in contrast to WNV—which usually kills wild birds—avian influenza rarely kills, or even sickens, wild birds. Thus, it does not impair their ability to migrate, resulting in rapid spread of the virus.

In South East Asia, virtually every non-urban household (and many urban households) has poultry in the "backyard." Once domestic flocks are exposed to the virus, usually in fecal material from wild birds, the virus is spread bird-to-bird within flocks, between flocks when they are commingled on the way to market and on feces-contaminated clothing, shoes, and machinery. Carriage by insects and rodents—via contaminated fomites—has also been documented.

Large amounts of virus are shed for 14 days after onset of symptoms (although excretion has been documented at 4 weeks post onset). The virus is secreted in nasal and respiratory secretions and excreted in feces; the most common mode of transmission in poultry is from aerosolized fecal material. Although AI is not a robust virus, it can remain viable in organic material for as long as 105 days.

In general, the infectiousness and mortality in domesticated birds depends on the virus strain, host factors, and stressors. All outbreaks of "highly pathogenic avian influenza" (HPAI)—the most contagious and virulent form of avian influenza—have been caused by H5 and H7 subtypes. Host factors include the host genus: AI is most virulent in chickens and turkeys, although domestic ducks are affected as well. The current outbreak strain replicates unusually well in ducks. Environmental stressors include crowding and cold temperatures.

©Scientific Technologies Corporation, 2006, All Rights Reserved

Spread of the current avian outbreak

The first official report of this H5N1 strain in birds was made by South Korea in December, 2003. Subsequent reports were made by Vietnam, Japan, Thailand, Malaysia, Cambodia, China, Laos, Indonesia, Hong Kong, Mongolia, Taipei, Philippines, Kazakhstan, Turkey, Croatia and Romania.

Diagnosis of AI in birds

Decreased food consumption and egg production are the earliest and most predictable signs of AI in birds. In the setting of mildly pathogenic avian influenza, serologic conversion in flocks *ex post facto* is an epidemiologic diagnostic tool. Serology to diagnose highly pathogenic AI in birds has little utility because most infected birds die before they develop a detectable antibody response. Previously, the standard diagnostic test has been viral culture, which can take as long as 21 days and requires biosafety level 3 laboratory conditions. More recently, laboratory tests have included immuno-fluorescence and PCR tests. Both tests require approximately 4 hours to perform and provide optimal results when done on tissue specimens, so may require a necropsy to obtain specimens.

In the field, a rapid direct antigen detection test can yield results in 20 minutes but is quite expensive (US $12–$15 per test). The test's sensitivity is highest if used on lung fluid from dead birds. Other cheaper tests are being developed but evaluation is pending.

Clearly, in the current epizootic context, specific diagnostic tests for an ill bird or flock are not necessary once the presence of the outbreak strain has been documented in the vicinity.

Control of avian outbreaks

Culling

Slaughter of poultry known or suspected to be infected is the primary control mechanism for AI. Given the high mortality of this isolate in domestic poultry, it has not been difficult to enforce the culling of sick animals, their flocks, and even the entire stock on farms with documented cases. The main controversy has become the culling of poultry not known to be infected within a certain distance of confirmed cases. The *Office International des Epizooties* (*OIE*), the international animal health surveillance agency, calls for the culling of poultry found within a 5-km radius from a confirmed case and restriction of all poultry movement within a 50-km radius. The WHO recommends rapid and aggressive culling, but doesn't recommend a specific geographic range. Culling recommendations are variably implemented, however. Some countries initially tried to control the outbreak with vaccination alone. The Indonesian government did not recommended killing poultry in affected areas, although farmers have culled infected poultry on their own initiative. Chinese authorities have culled poultry found within a 3-kilometer-radius of confirmed cases.

©Scientific Technologies Corporation, 2006, All Rights Reserved

The 1997 Hong Kong AI outbreak ended abruptly after all poultry in Hong Kong were aggressively eradicated. However, the current outbreak is widespread, and widely distributed in wild bird populations, and is difficult to contain despite culling. This has led to reluctance to participate in aggressive slaughter.

Disposal of carcasses must be done in a manner which doesn't spread the infection to humans. People performing culling and post-culling disinfection procedures should have adequate personal protective equipment (including, at a minimum, disposable particulate respirators). Optimal respiratory protection has not been defined. Cullers should be vaccinated against human influenza, to minimize the risk of co-infections and recombination.

Quarantine/Isolation
Poultry which may have been exposed to disease can be quarantined, with culling if any birds show signs of illness. Movement of live poultry should be eliminated, and the practice of marketing live poultry directly to consumers should be discouraged in outbreak areas. Movement of humans and equipment between farms should also be restricted, with only necessary visits by humans and extensive disinfection of equipment before transport. In early February 2004, the USDA and the CDC issued orders banning the import of live birds into the United States from affected countries in Southeast Asia; this ban is still in effect.

Vaccination
The efficacy (and risks) of vaccination of domestic birds in the prevention of disease and transmission of AI is controversial. It is used before an area has infected birds to prevent spread or once an area has infected birds to control spread. The current poultry vaccine is an H5N2-based vaccine; some animal disease experts have commented that mild H5N1 disease will still occur in animals vaccinated with a poor antigenic match and these flocks may potentially serve as covert loci of infection.

Traditional production methods for influenza vaccines are not an option for H5 subtypes because they are rapidly lethal to chick embryos. Other technologies (such reverse genetic plasmid techniques) are being used, but the efficacy of vaccines made in this manner has not been studied.

Antiviral treatment
Avian influenza is routinely resistant to commonly used antiviral antimicrobials. Sequencing and susceptibility testing of the current H5N1 strain confirms that this strain does not respond to amantidine and rimantidine. Antivirals are expensive and not available in the large quantities needed to treat or prophylax poultry in an outbreak of this magnitude, and hence are not a viable option.

Disinfection
Avian influenza, like all influenza viruses, is sensitive to heat, detergents, and drying. However, as noted above, it can survive in organic material (e.g., feces) for months. Organic material should be removed as much as possible before surfaces are disinfected,

©Scientific Technologies Corporation, 2006, All Rights Reserved

including scraping walls, clearing floors, and removing and burying, incinerating, or otherwise isolating manure. Obviously, respiratory protection during cleaning is important. Recommended respiratory protection ranges from N95 and N99 masks, PAPRS if fit cannot be confirmed with particulate respirators, and surgical masks if no higher level of protection is available. Machinery (including rolling stock) should be thoroughly cleaned and disinfected. No new birds should be introduced into the facility for 21 days.

AI in humans

Although dozens of outbreaks of avian influenza around the world have been recorded in the last 35 years, AI didn't grab the public's attention until the first reported human cases occurred in 1997 in Hong Kong. During that outbreak, a total of 18 human cases (and 6 deaths) were reported. The entire chicken population of Hong Kong—1.5 million birds—was culled in 3 days and the outbreak ended. Two human cases of H5N1 influenza occurred in Hong Kong in the spring of 2003, but isolates were genetically different from the current outbreak. In fact, the current H5N1 strain differs significantly from other AI strains in Asia in the recent past. The current strain resembles one first recovered late in 2002 in Penfold Park, Hong Kong.

Transmission, clinical presentation, diagnosis, treatment and prevention of AI in humans

Of the 180+ human cases of laboratory-confirmed AI cases (diagnosed as of early 2006) associated with the current outbreak, almost all have a history of direct contact with poultry, the remainder have a history of close contact with an infected person, and more than half have died. There have been no confirmed cases of transmission to healthcare workers or other casual contacts. The high mortality ratio may be due to a focus on hospitalized, rather than all, patients. It appears that milder cases of avian influenza in humans are possible.

Incubation in humans averages 3 days. The clinical presentation during the current outbreak has included cough, fever, and shortness of breath. Seventy percent have had diarrhea. Chest X-rays from all patients have all been abnormal, with a variety of findings. Most patients have had lymphopenia and thrombocytopenia. (Hien TT, et al. Avian Influenza (H5N1) in 10 patients in Vietnam. NEJM 2004;350:1179-1188; available in electronic form at http://content.nejm.org/cgi/content/abstract/350/12/1179)

Initial screening for AI in humans can be done with the season's influenza A PCR test; the positive predictive value of this test for H5N1 depends on the other types of influenza A circulating in the community, and specific exposure history. H5N1-specific RT-PCR tests are available at WHO and CDC influenza reference labs. Antemortem diagnosis of influenza A (H5N1) has been confirmed by viral isolation, the detection of H5-specific RNA, or both. AI infection in humans may be associated with a higher frequency of virus detection and higher viral RNA levels in pharyngeal than in nasal samples. In one study, the interval from the onset of illness to the detection of viral RNA in throat-swab samples ranged from 2 to 15 days (median, 5.5 days). In Thailand, the results of rapid antigen testing were positive in only 4 of 11 patients with culture-positive AI (36 percent) 4 to 18

©Scientific Technologies Corporation, 2006, All Rights Reserved

days after the onset of illness. Testing of post-mortem lung tissue specimens is sensitive and specific. Again, procedures on potentially infected material should be conducted in Biosafety Level 3 (BSL-3) conditions.

Four antiviral drugs (amantadine, rimantadine, oseltamivir, and zanamivir) are approved by the U.S. Food and Drug Administration (FDA) for the treatment of influenza. The current outbreak strain is resistant to amantadine and rimantidine. Very limited data shows no benefit in human cases from oseltamivir, ribavirin, or steroids. Treatment appears to be mainly supportive.

The possibility of an avian flu pandemic has caused individuals, hospitals, doctors, corporations and countries to "stockpile" oseltamivir for treatment and prophylaxis, but the utility of this drug for those purposes is unknown. The CDC has specifically recommended against stockpiling.

Prevention of AI in humans

Primary prevention is avoidance of infected or potentially infected wild birds and poultry in any setting, including wet markets. Immunization with the current seasonal influenza vaccine and/or giving prophylactic antivirals effective against human influenza strains will minimize concurrent human influenza in people at risk for AI. Amantadine, rimantadine, and oseltamivir are approved by the U.S. Food and Drug Administration (FDA) for the prophylaxis of influenza. Oseltamivir has been shown to be effective in the prophylaxis of H3N2; its efficacy for prophylaxis of avian influenza is unknown.

People at increased risk of occupational exposure include poultry farmers, cullers, and healthcare personnel (HCP), which include staff at acute care hospitals, nursing homes, physician's offices, urgent care centers, outpatient clinics, emergency medical services providers, and home health care providers.

Trivalent inactivated influenza vaccine prevents influenza illness in at least 70% of adults aged 65 years and younger *when* the vaccine and circulating viruses are antigenically similar. However, the annual routine vaccine strains are unlikely to protect against a recombinant avian-human strain or a mutated avian strain and would render vaccination almost useless in controlling the pandemic. Unfortunately, using today's technology, production of a pandemic strain vaccine will take at least 4-5 months and may not be available before the first pandemic wave.

Human travel restrictions

There are currently no human travel restrictions secondary to AI. However, travelers to regions with AI are advised to avoid handling any poultry and to avoid visiting farms or wet markets. Frequent and careful hand washing is a very important practice.

Avian surveillance recommendations

H5N1 has proved to be another example of the importance of animal disease surveillance for human health. Highly pathogenic AI is a "List A" disease on *OIE's* watch list. List A contains the "transmissible diseases that have the potential for very serious and rapid

©Scientific Technologies Corporation, 2006, All Rights Reserved

spread, irrespective of national borders, that are of serious socio-economic or public health consequence and that are of major importance in the international trade of animals and animal products." The *OIE* sets standards for animal surveillance, diagnostic testing and reporting, but participation is voluntary.

The WHO is intensifying its collaboration efforts with animal disease surveillance programs, including the *OIE*.

Human surveillance recommendations

The emergence of SARS in Southeast Asia in 2003 and the resultant heightened surveillance for respiratory illness paved the way for improved detection and communication of the first human cases of H5N1. Although the goal has been "transparency"—an oft-repeated word in recent years—in communications about H5N1, some of the same surveillance and communications problems remain. Governments have denied the presence of AI despite the deaths of tens of thousands of birds, until the evidence was irrefutable.

The WHO is building a single electronic platform, the WHO Communicable Disease Global Atlas, which will bring together standardized data and statistics on a wide range of infectious diseases. FluNet is one of the databases which will allow for data query, interactive mapping and maps and resources.

In areas distant from the current Asian avian outbreak, testing for influenza A should be considered on a case-by-case basis for people with 1) a temperature > 38ºC, 2) a flu-like illness with lower respiratory tract symptoms, 3) history of contact with domestic birds or a known or suspected patient with influenza A in a country affected with H5N1 within 10 days of symptom onset. For example, in 2002, there were 80 live poultry markets in the city of New York, so there is a potential risk of human exposure beyond obvious agricultural and travel exposures.

Pandemic planning

Characteristics of an influenza pandemic that must be considered in preparedness and response planning include: 1) simultaneous impacts in communities across the U.S., limiting the ability of any jurisdiction to provide support and assistance to other areas; 2) an overwhelming burden of ill persons requiring hospitalization or outpatient medical care; 3) likely shortages and delays in the availability of vaccines and antiviral drugs; 4) disruption of national and community infrastructures including transportation, commerce, utilities and public safety; and 5) global spread of infection with outbreaks throughout the world.

Early in a pandemic, especially before vaccine is available or during a period of limited supply, use of other interventions may have a significant effect. For example, antiviral drugs are effective as therapy against susceptible influenza virus strains when used early in infection and can also prevent infection (prophylaxis). Analysis is ongoing to define optimal antiviral use strategies, potential health impacts, and cost-effectiveness of antiviral drugs in the setting of a pandemic. Planning by public and private health care

©Scientific Technologies Corporation, 2006, All Rights Reserved

organizations is needed to assure effective use of available drugs, whether from a national stockpile, state stockpiles or in private sector inventories.

Implementing infection control strategies to decrease the global and community spread of infection, while not changing the overall magnitude of a pandemic, may reduce the number of people infected early in the course of the outbreak, before vaccines are available for prevention. Travel advisories and precautions, screening persons arriving from affected areas, closing schools and restricting public gatherings, and quarantine of exposed persons may be important strategies for reducing transmission. The application of these interventions will be guided by the evolving epidemiologic pattern of the pandemic.

Infection control in occupational and clinical settings
The CDC has made recommendations for people participating in the control of the AI outbreak (including people performing culling and disinfecting activities), including vaccination with the current seasonal influenza vaccine, personal protective gear, and surveillance and monitoring. In addition, the CDC has made recommendations for others who might be exposed to AI in agricultural settings, healthcare professionals and consumers.

Infection control for standard influenza includes: private room or with other flu patients, negative air pressure room or placed with other suspect cases in an area of the hospital with an independent air supply, surgical masks, standard droplet precautions (hand washing, gloves, gown, eye protection).

Healthcare providers should be on the alert for avian influenza in people who present with influenza-like respiratory illness, particularly those who have been exposed to live poultry (in the US or abroad) with known or suspected AI or to contaminated environments. Patients with influenza-like illness should be placed in respiratory isolation, and healthcare workers should wear N95-level masks when entering those isolation rooms. Healthcare workers should be vaccinated with the seasonal influenza vaccine. However, feasibility of these measures in a pandemic setting is questionable since the surge capacity of the nation’s hospital system is limited. Priorities should include droplet transmission precautions (mask and hand hygiene) and cohorting of influenza infected patients.

Economic consequences
Tens of millions of fowl have been culled in the past few years in an effort to control avian flu. Many countries have banned the import of poultry meat from SE Asia, in addition to live birds. This is a devastating economic blow to a region which accounts for 38% (approximately 6 billion) of the world’s chickens and 80% (almost 100 million) of the world’s ducks. Ninety-nine million live chickens were exported from this region in 2002, and poultry meat and eggs accounted for almost 20% of the world exports. Thailand has the fourth largest chicken industry in the world, and it is obviously an important contributor to the gross national product in most of the affected countries. Poultry provides an important source of income and food for small farmers in throughout

©Scientific Technologies Corporation, 2006, All Rights Reserved

Asia. Recovery from this outbreak will require international economic aid to poultry farmers.

Information resources
Comprehensive information on AI, as well as recommendations for surveillance, evaluation of ill persons, personal protective gear, etc can be found at the following websites and in the following articles.

CDC
http://www.cdc.gov/flu/avian/index.html and http://www.pandemicflu.gov

World Health Organization. WHO interim guidelines on clinical management of humans infected by influenza A(H5N1). February 20, 2004.
http://www.who.int/csr/disease/avian_influenza/guidelines/Guidelines_Clinical%20Management_H5N1_rev.pdf.)

OIE
http://www.oie.int/downld/AVIAN%20INFLUENZA/A_AI-Asia.htm

Beigel JH, Farrar J, Han AM, Hayden FG, Hyer R, de Jong MD, Lochindarat S, Nguyen TK, Nguyen TH, Tran TH, Nicoll A, Touch S, Yuen KY and the Writing Committee of the World Health Organization (WHO) Consultation on Human Influenza A/H5. Avian influenza A (H5N1) infection in humans. New Engl J Med 2005;353:1374-85

©Scientific Technologies Corporation, 2006, All Rights Reserved