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Special report

# Avian flu (H5N1): its epidemiology, prevention, and implications for anesthesiology

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**Abstract** Avian flu, influenza A subtype H5N1, is an emergent and virulent disease that poses a threat to the health and safety of the world community. Avian flu is 1 of more than 25 influenza A viruses that reside primarily in birds but also infect humans and other mammals. Avian flu is responsible for the current outbreak in Asia; H5N1 has now displayed probable human-to-human transmission; it could be a harbinger of a global epidemic. Anesthesiologists are exposed to a risk for infection when they are involved in airway instrumentation of infected patients. Given the evidence of emerging resistance to common antiviral agents used to treat H5N1 influenza virus and limited supply of H5N1 vaccine, prevention is our best protection. The following article will detail the virology and preventive public health practices for H5N1. This knowledge can also be used to define and prevent other yet unidentified infectious threats.

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## 1. Introduction

Avian flu (H5N1) and severe acute respiratory syndrome (SARS) are the latest communicable diseases to come to our attention [1–3]. Avian flu (H5N1) is particularly important currently because of the following findings:

1. evidence of probable person-to-person transmission [1];
2. recent spread to poultry outside Southeast Asia [4];
3. increasing mammalian pathogenicity;
4. transmission through an intermediary host, the pig.

Avian flu (H5N1) was thought to be transmitted only through direct contact with infected birds. However, these recent findings make it a disease of potential global significance. Understanding how to contain and prevent an

avian flu (H5N1) epidemic is critical to the health and safety of anesthesiologists who care for patients with avian flu.

To aid our understanding and prevention of emerging viral diseases, this article describes basic principles of epidemiology: outbreak and epidemic analysis, common epidemiological statistics, and primary prevention. Web-based references are also provided for quick access to current public health information, practices, and policies. Knowledge of these basic public health principles can be applied not only to preventing these diseases, but also to other yet unknown emerging infectious diseases that may threaten the health and safety of all, including anesthesiologists.

## 2. Epidemiology of avian flu

Most subtypes of influenza A viruses cause only minor illness in humans. However, they can lead to severe cases of

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pneumonia or death, as was the case in the 1918 pandemic of the Spanish flu subtype (H1N1). The influenza A virus, with 27 known subtypes that range from low to high pathogenicity in the bird population, also infects humans and other mammals. Subtype H5N1, currently known as avian or bird flu, is of particular interest because of its increasing pathogenicity and ability to form a new viral subtype to which there is no native immunity in human hosts.

Avian flu is distinct from SARS. Like avian flu (H5N1), SARS was initially thought to be caused by an influenza virus. However, SARS atypical pneumonia results from infection with a novel, mutant RNA coronavirus, SARS-cornovirus [5], which does not belong to the influenza family. Coronaviruses are known to infect birds, mammals, and humans in species-specific fashion. Most cause only minor illness in humans, with symptoms of an upper respiratory tract infection.

After exposure to avian flu (H5N1), the incubation time (time between exposure and onset of illness) is approximately 4 days. The patient's illness typically lasts 5 to 24 days. Avian flu infections present with fever, sore throat, malaise, nonproductive cough, and occasionally conjunctivitis and diarrhea. Symptoms can intensify to include chest pain and dyspnea [2,6], frequently resulting in patients seeking medical attention at the peak of their infectivity. Transmission remains sporadic among humans, and true incidence is unknown at the present time. However, if individuals are infected, the current case-fatality rate for avian flu is thought to be greater than 50% in humans [2] and greater than 90% in birds and other mammals. It is unknown if preexisting comorbidities such as age (>60 years), diabetes, renal disease, and hypertension can heighten the case fatality rate, as what happens with a SARS infection.

Genetic reassortment, or spontaneous mutations of the virus during replication, may cause new, more dangerous subtypes. Although human-to-human transmission of the H5N1 virus remains sporadic [7,8], the virus has the potential to transform itself into subtypes for which little immunity exists. Genetic reassortment can also occur when one individual is simultaneously infected with both the rare H5N1 virus and with another, more common human subtype. The result is a subtype that lacks innate immunity but possesses a high degree of transmissibility to humans. Although H5N1 has shown no human reassortment to date, the potential for pandemic spread exists if more effective, sustained human transmission occurs. Similar scenarios were seen in the other influenza pandemics: Asian flu (H2N2) in 1957 and Hong Kong flu (H3N2) in 1968, whose combined death toll was greater than 100 000 deaths in the United States alone [9].

### 3. Prevention and treatment of avian flu (H5N1)

The key to addressing the threat of avian flu in all populations, including anesthesiologists, is prevention of the

disease and containment of its spread through traditional, public health preparedness: basic hygiene, Universal Precautions, and special procedures designed to prevent exposure and contain infection in health-care settings. Currently, avian flu is treated with varying efficacy, using between 1 and 4 different antiviral drugs: amantadine, rimantadine, oseltamivir, and zanamivir. However, H5N1 has now shown resistance to both amantadine and rimantadine, rendering treatment less predictably effective [10]. Although production of an effective vaccine for avian flu is now in progress, worldwide distribution would require costly global efforts and would likely be too late to prevent significant disease if a pandemic were to occur [7]. In addition, pandemics, which typically last much longer than other public health threats, can reappear in "waves" as the agent is spread to new locations or with induction of a newly resistant strain. Severe acute respiratory syndrome and avian flu are models for primary prevention methods. Indeed, traditional public health measures of surveillance and quarantine contributed greatly to halting the SARS epidemic [11].

The major tools of primary prevention, preventing the disease from occurring in the first place, include surveillance, threat identification, reporting, and containment. Collection of surveillance data varies from location to location. In the United States, individual states are responsible for collecting surveillance data about various infectious diseases that, by law, must be reported by health-care providers and public health facilities. The Council of State and Territorial Epidemiologists determines the list of diseases selected for reporting, but individual states determine the extent of information beyond the mere number of new cases that is collected and reported. Every week, the National Notifiable Disease Surveillance System indexes cases collected from state health reporting. Compiled by the Centers for Disease Control, this information may be accessed by the public through a variety of sites, including *Morbidity and Mortality Weekly Report*, *Morbidity and Mortality Weekly Report Surveillance Summaries*, *Reports and Recommendations*, and *The Annual Summary of Reportable Disease*.

Surveillance in the United States and in most developed countries is extensive and easily accessible. This is not always the case in developing countries. Full and complete epidemiological information depends on the quality of the information sources, processing, and availability.

Like any emerging disease, avian flu is first reported as a group of cases commonly referred to as an outbreak or cluster.<sup>1</sup> *Outbreak* is defined as "an epidemic limited to a *localized* [emphasis added] increase in the incidence of a disease" [12]. *Epidemic* is a broader term describing any disease, infectious or not, whose frequency is greater than expected. Avian flu was first reported in an isolated human

<sup>1</sup> Technically, *cluster* is used in reference to noninfectious diseases such as a cluster of cases of newly diagnosed leukemia in children who live near high-voltage power lines, but several publications have identified *clusters* of SARS cases.

case in 1997 in Hong Kong. The first cluster of avian flu has appeared in 2 sisters in 2004.

### 3.1. Threat identification

The threat can be identified by laboratory identification of the infectious agent or, as initially was the case with SARS, by case definition, the constellation of signs and symptoms displayed by patients. Although we have identified the genetic structure of the H5N1 virus, the case definition of avian flu remains an important surveillance tool for identifying threats, especially in the main rural regions of Southeast Asia, where H5N1 appears to be the most prominent but also where ready access to diagnostic laboratory examination does not exist. Common signs and symptoms include fever, headache, malaise, sore throat, cough, and rhinitis. Although less common, conjunctivitis and gastrointestinal symptoms have also been reported. Finally, is the reporting of recent contact with poultry, especially sick birds, or travel within 10 days to countries with recent avian flu activity.

### 3.2. Containment

Recommended containment methods are the same for both avian flu and SARS [13]. All personnel who have had contact with patients who possibly have or are proven to have avian flu should use Universal Precautions, have good hand-washing, and use personal protective equipment (PPE): gloves, a protective suit rather than gown, and eye protection if within 3 feet of the patient. In addition, anesthesiologists who expect to be exposed to respiratory secretions during airway interventions should use disposable or specially handled stethoscopes and blood pressure cuffs and wear tight-fitting N95 micropore facemasks [13].

With epidemic or pandemic spread, environmental containment is also vital. In Singapore, at the height of the SARS epidemic, medical providers modified their infection-control procedures to better contain nosocomial spread of the virus [14]. In addition to wearing standard PPE, providers wore disposable hats, disposable shoe covers, and positive air-powered respirators. Staff were trained on the need for this awkward uncomfortable equipment. Operating suites were also specially modified to decrease the spread of the infection, and traffic flow was reduced by cancelled elective surgeries. Operating rooms (ORs) with positive pressure and at least 25 exchanges per hour were designated to be used. Whenever possible, ORs with separate air-conditioning and humidification systems were selected. Airflow outside these rooms was limited; all doors except for one were closed and sealed with tape to minimize personal movement. After each procedure with a known infectious patient, the OR was decontaminated and the air was allowed to circulate for at least 1 hour. All nondisposable equipment was double-bagged, with the inner biodegradable bag inserted directly into the sterilizer.

Finally, specialty-specific prevention measures were necessary. Anesthesiologists performed intubations in a

manner that maximally decreases the spread of respiratory droplets. The most senior anesthesiologist inserted tracheal tubes. In all cases, muscle relaxants were used to minimize the duration of the procedure and the risk for further spreading infected secretions by coughing [15]. The use of regional anesthesia and avoidance of airway manipulation in the case of infected patients requiring surgical procedures are also recommended [16]. When general anesthesia was required, hydrophobic filters were placed on both the inspiratory and expiratory limbs of the anesthesia circuit. These filters, the gas, or end-tidal carbon dioxide sampling line, and the trap were discarded after each case. Instrumentation of the airway, if necessary, was performed using either a cuffed endotracheal tube or a laryngeal mask airway [16]. In the Toronto outbreak of SARS, anesthesiologists also used mechanically powered, air-purifying respirators and double-gloving techniques with decontamination between removals of each layer of PPE. Some infection-control questions were not specifically addressed but deserve consideration. Should rolls of tape be disposed between cases? What are the proper procedures to disinfect touch-screen monitors and equipment? What personal items, beepers, laptops, PDAs, pens, etc, are allowed in a contaminated OR? What have we learned from the recent epidemics?

Infectious agents continuously evolve and coevolve with their hosts. Coevolution is inevitable because no species lives in isolation from others. Three categories of events, genetic, ecological, and opportunistic, can initiate coevolutionary change in either the host or the pathogen.

### 3.3. Genetic coevolution

Coevolution occurs when the host populations diverge and pathogens mutate in response. For example, 2 distinct species of *Plasmodium* (*falciparum* and *vivax*) have evolved because the human populations of East and West Africa have genetically diversified.

### 3.4. Ecological coevolution

Ecological changes in the host may also trigger evolutionary changes in the pathogen. As the host enters any new ecological equilibrium, an otherwise unknown and non-host-specific pathogen can mutate and cross species.

### 3.5. Opportunistic coevolution

Coevolution can also occur in response to a new opportunity. A pathogen may selectively evolve in response to altered immune mechanisms in the host. The overuse of antibiotics could also have prompted virulent coevolution of viruses. "Nature is opportunistic, so whenever a new niche is created, emergent and old disease will inevitably seek to exploit the new opportunities. The fact that pathogens are able to maximize their potential very quickly following the opening of a new niche clearly serves as a warning of the power of humans as a selective force shaping disease diversity" [17].

Both avian flu and SARS-cornovirus may have followed any of these 3 evolution cues. For whatever reason, we appear to have overcome the SARS epidemic, but avian flu may be waiting in the wings to emerge on a worldwide scale. The World Health Organization has designated avian flu in the fourth of six phases of pandemic spread. Clearly, the public health measures are the first-line defenses for containing these new viruses. “Only careful and rapid application of knowledge and reason through a variety of public health measures has been effective in minimizing the spread and severity of the epidemic. More information and data generated from the studies of the epidemic are needed immediately to save lives and to prevent fear and disease, both in China and elsewhere in the world” [18].

## References

- [1] Ungchusak K, Auewarakul P, Dowell SF, et al. Probable person-to-person transmission of avian influenza A (H5N1). *N Engl J Med* 2005;352:333-40.
- [2] Avian influenza infection in human. <http://www.cdc.gov/flu/avian/gen-info/avian-flu-humans.htm> [accessed 10/02/05].
- [3] Li KS, Guan Y, Wang J, et al. Genesis of a highly pathogenic and potentially pandemic H5N1 influenza virus in eastern Asia. *Nature* 2004;430(6996):209-13.
- [4] Avian influenza—situation in Indonesia—update 31. [http://www.who.int/crs/don/2005\\_08\\_18/en/index.htm](http://www.who.int/crs/don/2005_08_18/en/index.htm) [accessed 09/25/05].
- [5] Drosten C, Gunther S, Presiser W, et al. Identification of a novel corona virus A (H5N1) in patients with severe acute respiratory syndrome. *N Engl J Med* 2005;352:333-40.
- [6] Chotpitayasunouh T, Ungchusak K, Hanshaoworakul W, et al. Human disease from influenza A (H5N1), Thailand 2004. *Emerg Infect Dis* 2005;11:201-9.
- [7] Barclay WS, Zambon M. Pandemic risks from bird flu. *BMJ* 2004;328:238-9.
- [8] Recent avian influenza outbreaks in Asia. <http://www.cdc.gov/flu/avian/outbreaks/asia> [accessed 09/15/05].
- [9] Information about influenza pandemics. <http://www.cdc.gov/flu/avian/gen-info/pandemics.htm> [accessed 10/01/05].
- [10] Evolution of H5N1 avian influenza viruses in Asia. <http://www.cdc.gov/ncidod/EID/vol11no10/pdfs/Vol11No10.pdf> [accessed 10/01/05].
- [11] Svoboda T, Henry B, Shulman L, et al. Public health measures to control the spread of severe acute respiratory syndrome during the outbreak in Toronto. *N Engl J Med* 2004;350:2352-61.
- [12] Brownson R, Pettiti D. *Applied epidemiology: theory to practice*. Oxford (UK): Oxford Press; 1988. p. 71.
- [13] Interim recommendations for infection control in health-care facilities caring for patients with known or suspected avian influenza. <http://www.cdc.gov/flu/avian/professional/infect-control.htm> [accessed 10/01/05].
- [14] Chee V, Khoo M, Lee S, Lai Y, Chin N. Infection control measures for operative procedures in severe acute respiratory syndrome-related patients. *ASA Newsletter*, vol. 100. Park Ridge (Ill): American Society of Anesthesiologists; 2004. p. 1394-8.
- [15] Peng P, Wong D, Bevan D, Gardam M. Infection control and anesthesia: lessons learned from the Toronto SARS outbreak. *Can J Anaesth* 2003;50:989-97.
- [16] Outbreak of severe acute respiratory syndrome in Singapore and modifications in the anesthesia service. *ASA Newsletter*, vol. 100. Park Ridge (Ill): American Society of Anesthesiologists; 2004. p. 1629-30.
- [17] Greenblatt C, Spigelman M. *Archaeology, ecology, and evolution of infectious diseases*. Oxford (UK): Oxford Press; 1988. p. 73.
- [18] Gopalakrishna G, Choo P, Leo YS, et al. SARS transmission and hospital containment. *Emerg Infect Dis* 2004;10:395-400.