Pandemic Influenza and the Hospitalist: Apocalypse When?

James C. Pile, MD[1]
Steven M. Gordon, MD[2]

[1] Division of Hospital Medicine, CWRU/MetroHealth Medical Center, Cleveland, Ohio

[2] Chairman, Department of Infectious Diseases, The Cleveland Clinic Foundation, Cleveland, Ohio

Beginning with a cluster of human cases in Hong Kong in 1997, avian influenza (H5N1) has spread progressively through, and beyond, Asia in poultry and other birds; and has resulted in sporadic cases of human disease associated with high mortality. The potential for H5N1 influenza to cause a pandemic of human disease continues to be the subject of intense scrutiny by both the media and the scientific community. While the likelihood of such a prospect is uncertain, the inevitability of future pandemics of influenza is clear. Planning for the eventuality of a virulent influenza pandemic at the local, national and global level is critical to limiting the mortality and morbidity of such an occurrence. Hospitalists have a key role to play in institutional efforts to prepare for a influenza pandemic, and should be aware of lessons that my be applied from both the response to Hurricane Katrina, as well as the severe acute respiratory syndrome (SARS) epidemic. ***Journal of Hospital Medicine*** **2006;1:118–123.** *© 2006 Society of Hospital Medicine.*

KEYWORDS: pandemic influenza, disaster preparedness, emerging infectious diseases, avian influenza.

Background

Influenza viruses are among the most common respiratory viral infections in humans. There are two major types of human influenza viruses, A and B, with influenza A strains responsible for seasonal or pandemic influenza. Influenza illness is characterized by fever, lower respiratory and often upper respiratory symptoms, myalgia, and malaise and occurs seasonally in temperate climates between late fall and early spring. The average "flu season" in the United States is marked by 30,000-40,000 deaths, primarily in elderly patients with significant comorbidity and in the very young. Many of these deaths are caused by secondary bacterial pneumonias. Long "interpandemic" periods, including the current one of almost 40 years, involve minor mutations of the predominant influenza strain from year to year. Typically, adequate time exists to predict the prevailing strain with reasonable accuracy and to tailor a vaccine accordingly. Periodically an influenza pandemic involving a novel influenza strain emerges, attended by greater-than-expected morbidity and mortality.

All influenza viruses are subtyped on the basis of two surface glycoproteins. One of these, hemagglutinin (H), is responsible for viral cell entry; whereas the other, neuraminidase (N), facilitates release of the virus from infected cells, thus allowing perpetuation and amplification of infection. Antigenic drift is the ongoing process of genetic mutations that lead to new strains demonstrating variable change in antigenicity and is the basis for the annual

DOI 10.1002/jhm.81
Published online in Wiley InterScience (www.interscience.wiley.com).

updating of vaccine strains. Antigenic shift is the emergence of a novel influenza A subtype among humans, usually as the result of a recombination event. This radical change is necessary but not sufficient to initiate pandemic influenza, with efficient transmission from person to person also a critical feature. Pandemic influenza strains arise in 1 of 2 fashions. Genetic reassortment may occur when a mammalian host (human or porcine) is infected with both an avian and a human influenza virus, with subsequent dramatic movement into human populations, the source of the 1957 and 1968 pandemics. Alternatively, a novel virus may, after sufficient mutation, move directly from the avian population to humans, as appears to have occurred in 1918.

The 1918-19 Pandemic

Abruptly in 1918, an influenza pandemic of seemingly unprecedented severity swept the world. Although disagreement remains regarding the source of the outbreak (China, the front lines of World War I, and even the United States have all been suggested), within 6-9 months essentially the entire globe had been affected. Unlike more typical influenza seasons, the virus preferentially infected previously healthy young individuals, with those aged 15-40 bearing the brunt of the illness. US military training installations, overcrowded with troops staging for service on the European front, played a particularly ill-fated role in the pandemic as it swept through the United States.

Estimates of the pandemic's worldwide impact on mortality are sketchy at best, but many authorities believe that at least 50 million deaths resulted, with some suggesting a figure as high as 100 million. In the United States the virus was responsible for an estimated 700,000 deaths, with an untold burden of morbidity. Economic and social disruption was the norm in many areas, with widespread closure of businesses and schools and suspension of public gatherings of any kind. Many communities were simply overwhelmed by the sheer numbers of dying individuals. In Philadelphia, steam shovels were used to dig mass graves for influenza victims.[1] The pandemic's effect on the health care system was likewise profound. Most hospitals counted their own physicians and nurses among those who died during the pandemic, and many of the health care workers who succumbed were infected in the course of caring for influenza patients. Overall, an estimated 2%-3% of those infected with the virus died, a far higher percentage than is seen during interpandemic seasons. Strikingly, the vast majority of deaths do not appear to have resulted from secondary bacterial pneumonias, but rather to have been directly virally mediated through ARDS, a necrotizing viral pneumonia, or both.

The mystery of the 1918 pandemic has recently been partially unlocked, with the successful sequencing of the entire RNA genome of strains recovered from pathology tissue of two soldiers, as well as from lung tissue of a victim frozen in Alaskan permafrost since 1918.[2,3] The data suggest that the 1918 virus was derived from an avian source. Notably, some of the same changes in the polymerase proteins have been found in the highly pathogenic H5N1 viruses.

Avian Influenza Viruses

Influenza viruses that primarily infect birds are characterized as avian influenza viruses. These are always type A and are classified as either of low or high pathogenicity on the basis of the severity of the illness they cause in birds. The currently circulating H5N1 avian viruses are highly pathogenic.

Avian influenza viruses do not usually infect humans; however, several instances of human infections have been reported since 1997. The 1997 Hong Kong outbreak of avian (H5N1) influenza in 18 humans resulted in 6 deaths and was a seminal event that provided evidence that avian influenza viruses can infect people. It also provided the epidemiologic link between avian influenza infection in poultry with disease in humans and was proclaimed as a pandemic warning. These sentinel human infections led to the culling of the entire Hong Kong poultry population, with no subsequent human infection reported at that time. In 2003, more than 80 cases of avian influenza A (H7N7) illness occurred in the Netherlands among persons who handled infected poultry. Sustained human-to-human transmission did not occur in this or other outbreaks of avian influenza to date.

Since 2003, sporadic human cases of H5N1 have occurred, most recently reported from Turkey and Iraq. Human cases have also occurred in Vietnam, China, Cambodia, Thailand, and Indonesia, with a total of 173 reported cases and a case fatality rate exceeding 50% as of this writing.[4] This mortality rate may be artificially inflated, as less severe cases have certainly gone unreported. All countries reporting human avian influenza diseases since

2003 have had concurrent epizoonotics in birds (both poultry and migratory birds).

Human cases of H5N1 influenza illness have been characterized by high fever and symptoms in the lower respiratory tract, as would be expected. Less predictable has been the presence of watery diarrhea in many patients and of abdominal and pleuritic pain and bleeding from the nose and gums in some. Sputum production has been variably present, and hemoptysis has been seen in some individuals. Most patients have had clinical and radiological evidence of pneumonia at the time they sought medical care, and progression to ARDS and multiorgan failure has been common. The majority of patients to date have required the initiation of mechanical ventilation early in their hospital course. Laboratory studies have typically shown lymphopenia, thrombocytopenia, and, in many cases, modestly elevated transaminase levels.[5] Notably, the currently predominant strain of H5N1 (Z strain) is resistant to the M2 ion channel inhibitors amantadine and rimantadine but is susceptible to the newer class of neuraminidase inhibitors, zanamivir (Relenza) and oseltamivir (Tamiflu). Neuraminidase inhibitors and corticosteroids have been used to treat patients, although their efficacy in this setting is unclear. To date, virtually all cases appear to have been transmitted directly from poultry, although person-to-person transmission appears likely to have occurred in at least one family in Thailand.[6] A recent study of the 14 clusters of avian influenza among humans emphasized the lack of sustained person-to-person transmission of H5N1 to date.[7]

Three factors are necessary for the emergence of a pandemic influenza strain: the ability to infect humans, a novel genetic makeup, and the ability for sustained transmission between people. A virus that in addition proves highly virulent, as did the 1918-19 H1N1 strain, essentially creates the "perfect storm." H5N1 influenza has currently fulfilled 2 of these 3 criteria. The virus is highly pathogenic, although how much of this "fitness" would be sacrificed with mutation to a more transmissible strain is uncertain. As many have observed, whether there will be another influenza pandemic does not seem in doubt; rather, it is when such a pandemic will occur and whether the pandemic will be caused by H5N1 or another influenza virus, that are the questions.

Potential Effects of the Next Pandemic

The global and national effects of an influenza pandemic will vary in direct proportion to the virulence of the circulating viral strain, but if such a virus is highly virulent, significant and perhaps severe economic and social disruption are likely.

The global economic impact has been estimated to be $800 billion with anticipated quarantines and interruption in global trade. On a national level, it has been estimated that in the United States a pandemic virus whose severity is comparable to that of the 1968 "Hong Kong" influenza pandemic would lead to approximately 200,000 deaths and 700,000 hospitalizations, of which roughly 100,000 would require treatment in intensive care unit settings. A more virulent strain, similar to that of the 1918-19 pandemic, might easily result in 1 million deaths; with the number of patients hospitalized approaching 10 million, well over 1 million of which would require ICU-level care. As an estimated 75% of the 105,000 ventilators in this country are in use at any given time under normal circumstances, the potential for demand to greatly outstrip supply is evident.[8] Depending on the severity of a pandemic, suspension or curtailment of international trade and travel could be reasonably likely. Although the World Health Organization has recommended against closing borders or quarantining countries even in the throes of a pandemic, the prospect of this occurring does not seem implausible. In a worst-case scenario, even the type of national and international chaos envisioned in the "Dark Winter" smallpox planning exercise might occur.[9]

"Fortress America" versus Containment Strategies

Although the pandemic influenza plan calls for stockpiling antiviral drugs and increasing vaccine production capabilities, the most effective plan for pandemic preparedness may involve a surveillance and containment strategy. No country has enough medicines or vaccines to control a widespread outbreak of pandemic avian influenza. The best solution to prevention of a pandemic is stopping any virus from spreading in the first place. Increased surveillance for avian influenza among poultry and migratory birds in key Asian countries, along with provision of funds to compensate farmers for culling of potentially infected flocks, would align incentives for early detection and eradication. Containing an initial outbreak wherever it occurs is the best defense against a pandemic. Notably, China is thought to be a potential "hot zone" for emergence of pandemic avian influenza. China is not only the most populous nation in the world but has one quarter of the world's chickens, two thirds of the world's domesticated ducks, and 90% of the world's domesticated geese.

The challenges of biosecurity (protecting humans against animal-borne diseases such as bird flu) in developing countries include the reality that populations living in close proximity to poultry are also the most illiterate and impoverished, with the most limited access to health care. The recent introduction of H5N1 into Europe has heightened surveillance efforts in the United States. The introduction of H5N1 into the United States may occur through movement of migratory birds and/or importation of exotic birds. The surveillance system has been expanded to include sampling for the influenza virus not only in poultry but also in bodies of water, as the virus is shed in bird feces.

Pandemic Planning

In the setting of a severe pandemic, hospitals will face an enormous burden of patients, with a huge influx of individuals requiring both intensive care unit as well as regular nursing floor care. At the local height of such a pandemic, the ability to successfully discharge every patient whose condition will permit this to the community or elsewhere will be critical, and almost certainly hospitals will need to expand to accept more patients than they are normally configured to hold. Hospitals staffs, particularly nurses and physicians, will be required to handle very large patient censuses. Among medical staffs, emergency physicians, hospitalists, critical care specialists, and infectious disease specialists will certainly be called on to play leading roles, much as they were during and in the aftermath of Hurricane Katrina recently. Despite all of the above, the ability of existing hospitals to accommodate all gravely ill patients may be outstripped, and "auxiliary" hospitals in schools and other public edifices may need to be established. Hospitalists are likely to be called on to play a major role in such temporary "hospitals." The frustration and anguish of not being able to provide a standard level of care to patients (for example, being forced to triage which patients are most deserving of mechanical ventilation) should not be underestimated.

Although characterized by a relatively limited number of patients, the 2003 severe acute respiratory syndrome (SARS) outbreak in Toronto, Ontario, Canada, presented some of the same challenges that will be encountered in a virulent influenza pandemic. These include the need to quickly and drastically modify the usual emergency department and inpatient procedures, as hospitals initially serve to amplify the epidemic, as well as the additional stressor of health care workers becoming ill as a result of work-related exposure. That fewer than 400 cases of SARS pushed the medical system of one of North America's largest cities nearly to its breaking point is both sobering and instructive.[10,11] Interested readers are directed to an excellent summary of lessons learned from the SARS outbreak, most of which are widely applicable to preparations for future infectious epidemics.[12]

Infection Control

Although the CDC and other Web sites currently recommend airborne isolation (respiratory personal protection) for avian influenza in humans, there is not strong epidemiologic evidence of transmission other than via droplets (the transmission mode of human influenza). The emergence of a limited number of cases of avian influenza in the United States would allow employment of airborne isolation measures; but in the event of a larger outbreak, the use of surgical masks and the practice of good hand hygiene would be sufficient by health care workers caring for persons with suspected or proven disease.

The CDC recently released proposed changes to help prevent disease outbreaks from contacts of those exposed to ill persons on airplanes. Proposed guidelines would require airlines to maintain computerized lists of passengers taken at point of departure in order to facilitate tracking of contacts and implementation of quarantine if necessary. These measures are part of pandemic planning and result from problems in tracking passengers on planes with SARS cases. By executive order, imposition of quarantine is limited to 9 diseases: cholera, diphtheria, smallpox, yellow fever, viral hemorrhagic fevers (eg, Ebola), plague, infectious tuberculosis, SARS and influenza caused by new strains with pandemic potential.

What Can Be Done?

Although valuable time has elapsed to prepare for the possibility of an H5N1 influenza pandemic, the US and global communities are presently taking the threat seriously and are engaging in a variety of activities to prepare for such an eventuality. Al-

TABLE 1
Additional Avian Influenza Resources

1. World Health Organization (WHO) Website: http://www.who.int/csr/disease/avian_influenza/en/
2. Centers for Disease Control and Prevention (CDC): http://www.cdc.gov/flu/pandemic/
3. U.S. Government Avian Influenza Website: http://www.pandemicflu.gov
4. U.S. Department of Health and Human Services Pandemic Influenza Plan: http://www.hhs.gov/pandemicflu/plan/
5. Infectious Diseases Society of America (IDSA) Website: http://www.idsociety.org/Content/NavigationMenu/Resources/Avian_Pandemic_Flu/Avian_Pandemic_Flu.htm

though currently available influenza vaccines do not provide any appreciable protection against H5N1, significant work is under way to develop an effective vaccine; with Chiron and sanofi pasteur preparing vaccine trials in association with the National Institute of Allergy and Infectious Diseases. Current influenza vaccine production is hampered by use of obsolete egg-based manufacturing processes requiring 6 months, along with a limited capacity to manufacture adequate vaccine supplies even in many usual influenza seasons. The herculean task of providing hundreds of millions of doses of vaccine as soon as possible after the emergence of a pandemic strain, as daunting as it is, is further complicated by the fact that a successful H5N1 vaccine would not necessarily be effective against a strain that mutated sufficiently to move efficiently from person to person. Nonetheless, even partially solving these problems will pay dividends, whether or not H5N1 proves to be responsible for the next pandemic.

Given these difficulties with vaccine development and production, the backbone of any successful early response to a pandemic in the near future will be development of an adequate stockpile of antiviral medication, accompanied by a successful plan to distribute the drug when and where disease erupts. Despite uncertainties regarding their effectiveness as well as questions regarding optimal dose and duration in the setting of avian influenza, the neuraminidase inhibitors are the current drugs of choice. Of the 2 currently available agents, oseltamivir is the preferred drug for pandemic use, given its oral administration,. Unfortunately, the ability to manufacture the drug in sufficient quantities to stockpile has thus far proved problematic. Roche, the manufacturer of Tamiflu, has recently opened a new manufacturing plant and has stated that it can increase its current production of 55 million doses per year to 300 million doses by 2007. We do not recommend a role for personal stockpiling of neuraminidase inhibitors. Concerns include a shortage of the drug for seasonal influenza, absence of a pandemic at present, ignorance regarding the efficacy and optimal dose for H5N1, inappropriate use by individuals, and inequitable distribution. Recent case reports of oseltamivir resistance emerging during prophylaxis[13] and treatment[14] are of potential concern but do not alter current recommendations.

What can be done locally and specifically, and what can hospitalists do to prepare? First, although we are not sure that Dr Michael Osterholm's goal that "planning for a pandemic must be on the agenda of every public health agency, school board, manufacturing plant, investment firm, mortuary, state legislature, and food distributor. . ."[8] is entirely realistic, every hospital clearly needs to include pandemic influenza as a significant part of its disaster preparedness plan. Such planning will have broad overlap with planning for other potential disasters, including bioterrorist attacks, SARS outbreaks, and others. Hospitals must develop a plan for surge capacity, and such a plan should include not only coordination with other local hospitals, but also planning with local communities to identify sites where temporary "flu hospitals" can be established. Within hospital medicine groups, emergency staffing plans should be established before pandemic influenza (or another disaster) strikes. Such staffing plans need to include the ability to care for a much higher than normal number of patients for an extended period. Conceivably, a large number of patients will need to be manually ventilated for prolonged periods, which of course will tax the resources of any institution. Prompt discharge of all patients stable enough to leave the hospital will be critical, and given the investment of most hospital medicine groups in hospital throughput issues under normal conditions, much of the responsibility for helping to create beds during a crisis will inevitably fall on the shoulders of hospitalists.

Experiences during and shortly after Hurricane Katrina served to underscore that issues such as physical and mental fatigue, concern for the safety of family members, lack of supplies, communication difficulties, and absenteeism all add additional layers of complexity to the task of providing hospital care under extraordinary conditions such as during a natural disaster. These lessons can and should be extended to a major epidemic. This disaster also showed the importance of military involvement in the response to disasters that exceed local and state capabilities. The primary objective of the federal government in responding to disaster is to maintain security and essential services while preventing chaos. A pandemic of virulent influenza will raise the stakes still further, as physicians and nurses become casualties themselves. Despite these challenges, we are confident that the vast majority of hospitalists and other health care workers will rise to the occasion, and just as during the peri-Katrina period, stories of selflessness and heroism will be de rigueur. Appropriate advance planning on all levels will serve to reduce the morbidity and mortality associated with the next pandemic and will help to ensure that health care workers do not sacrifice needlessly.

Address for correspondence and reprint requests: James C. Pile, MD, Division of Hospital Medicine, CWRU/MetroHealth Medical Center, 2500 MetroHealth Drive, Cleveland, OH 44109; Fax: (216) 778-4105; E-mail: jpile@metrohealth.org

Received 30 November 2005; revision received 30 January 2006; accepted 2 February 2006.

REFERENCES

1. Barry JM. The Great Influenza. New York, NY: Viking Penguin, 2004.
2. Taubenberger JK, Reid AH, Lourens RM, Wang R, Jin G, Fanning TG. Characterization of the 1918 influenza virus polymerase genes. *Nature*. 2005;437:889–893.
3. Tumpey TM, Basler CF, Aguilar PV, et al. Characterization of the reconstructed 1918 Spanish influenza pandemic virus. *Science*. 2005;310:77–80.
4. WHO Epidemic and Pandemic Alert and Response. Confirmed cases of avian influenza A (H5N1). Available at http://www.who.int/csr/disease/avian_influenza/country/en/index.html. Accessed on February 28, 2006.
5. Writing Committee of the WHO Consultation on Human Influenza A/H5. Avian influenza A (H5N1) infection in humans. *N Engl J Med*. 2005;353:1374–1385.
6. 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.
7. Olsen SJ, Ungchusak K, Sovann L, et al. Family clustering of avian influenza A (H5N1). *EID*. 2005;11:1799–1801.
8. Osterholm MT. Preparing for the next pandemic. *N Engl J Med*. 2005;352:1839–1842.
9. Center for Biosecurity. Dark Winter overview. Available at http://www.upmc-biosecurity.org/pages/events/dark_winter/dark_winter.html. Accessed November 28, 2005.
10. Borgundvaag B, Ovens H, Goldman B, et al. SARS outbreak in the Greater Toronto Area: the emergency department experience. *CMAJ*. 2004;171:1342–1344.
11. Booth CM, Stewart TE. Severe acute respiratory syndrome and critical care medicine: The Toronto experience. *Crit Care Med*. 2005;33(suppl):S53–S60.
12. Naylor CD, Chantler C, Griffiths S. Learning from SARS in Hong Kong and Toronto. *JAMA*. 2004;291:2483–2487.
13. Le QM, Kiso M, Someya K, et al. Avian flu: Isolation of drug-resistant H5N1 virus. *Nature*. 2005;438:754.
14. de Jong MD, Thanh TT, Khanh TH, et al. Oseltamivir resistance during treatment of influenza A (H5N1) infection. *N Engl J Med*. 2005;353:2667–2672.