

Influenza A (H5N1): Will It Be the Next Pandemic Influenza? Are We Ready?

Influenza experts have predicted the next pandemic flu for many years. What they fear most is an event like the Spanish flu of 1918 to 1919—the largest outbreak of fatal infectious disease during the past century. Avian influenza (influenza A [H5N1]) appears to have that potential. Dramatic response strategies have been undertaken in some countries, but the response in others has been far more measured. For example, the United Kingdom has committed to stockpile enough oseltamavir to treat 25% of its population in an effort to be prepared; the United States has enough in its Strategic National Stockpile for less than 1% (1). So how real is this risk?

Most influenza viruses occur in birds, particularly the aquatic waterfowl that are their natural reservoir. Only a few types of influenza virus have circulated widely in humans. “Bird flu” refers colloquially to both influenza in birds and to instances when these avian viruses jump the species barrier to cause human disease. The influenza A genome encodes 2 major surface glycoproteins, the hemagglutinin (H) and neuraminidase (N) proteins. The subtypes of these proteins are antigenetically distinct, having 16 H subtypes and 9 N subtypes. All of these subtypes may be found in birds, but only H1, H2, and H3 have caused pandemics and epidemics in people. Influenza viruses are constantly evolving into new antigenic variants, which accounts for vulnerability and the need for annual vaccination. Minor changes, or “drifts,” are the rule; major changes, or “shifts,” represent new hemagglutinin with or without new neuraminidase proteins that result in a novel virus for which the population lacks specific immunity.

As noted, “Spanish flu,” involving influenza A (H1N1), was the largest rapidly fatal pandemic in human history. The virus traversed the world in less than 1 year, causing at least 40 million deaths. We are accustomed to influenza-associated morbidity and mortality. In the United States, the usual influenza season brings 30 000 to 40 000 deaths, but most of these occur in frail persons described as the “elderly elderly,” meaning those older than 85 years of age, or patients with serious comorbid conditions. The 1918 influenza pandemic was distinctly different—most of the victims were young, previously healthy adults at an average age in the 30s. That pandemic reduced life expectancy in the United States by an astonishing 13 years. Many people died within a few days of the onset of symptoms. Autopsies often showed a characteristic hemorrhagic, necrotizing viral pneumonia—not a bacterial superinfection that might now respond to antibacterial agents. Of note, the average time to death in 1918 was about 7 to 9 days after the onset of illness (2), an interval that might allow for intervention with specific antiviral therapy, if available. Subsequent studies of the 1918 strain showed

that it had a constellation of genes that account for this unique virulence (3), although recent studies have pointed to a unique virulence related to the hemagglutinin of the 1918 strain (4).

Since 1918, there have been 2 other influenza pandemics representing antigenic shifts of influenza A. In 1957 to 1958, “Asian flu,” involving influenza A (H2N2), caused about 70 000 deaths in the United States, and in 1968 to 1969, “Hong Kong flu,” caused by influenza A (H3N2), caused 34 000 deaths in the United States. Both of these more recent pandemics involved influenza A strains with gene combinations from human influenza strains and avian influenza strains.

In 1997, a cluster of avian influenza due to influenza A (H5N1) occurred in people in Hong Kong (5). This outbreak was unique and alarming because it was the first recognized direct transmission of influenza from birds (poultry) to people, it involved a unique strain (H5N1), and it was highly fatal: Six of 18 (33%) recognized case patients died. To cause a global influenza pandemic, the virus needs 3 properties: 1) ability to infect people, 2) substantial antigenic novelty naiveté, and 3) efficient person-to-person transmission. Investigation of the Hong Kong outbreak showed that H5N1 clearly had the first 2 properties, but only minimal evidence of human-to-human transmission was noted (6, 7). Nevertheless, the decision was made to cull all chickens and other poultry in Hong Kong. Many view this to be a heroic, albeit temporizing, decision.

In late 2003 and early 2004, new outbreaks of influenza A (H5N1) in poultry occurred in 8 Asian countries: China, Cambodia, South Korea, Thailand, Vietnam, Japan, Indonesia, and Laos. Over 100 cases of this infection have been reported in patients in Thailand, Cambodia, and Vietnam. The alarming fact of the disease in humans is that the overall mortality rate is approximately 50%, far higher than the 2% mortality rate of Spanish flu (8), and that, like Spanish flu, most of the deaths have occurred in young, previously healthy adults or children. Autopsies also show a similar hemorrhagic, necrotizing pneumonia, and genetic and structural studies show that the hemagglutinin of influenza A (H5N1) has some of the characteristics of the Spanish flu strain (9). Of note, only 2 amino acid changes in the receptor-binding pocket of H5 lead to a virus that efficiently recognizes receptors on human cells (10). Attempts to control this virus include widescale culling—over 100 million birds have now either died of H5N1 infection or have been killed in the attempt to control the epidemic—and immunization of poultry in some countries. Despite these attempts, many authorities now feel H5N1 is enzootic in much of the bird population of

Table. Avian Influenza Infections in Humans, 1997–2005

| Strain | Location | Date | Findings in Patients |
|--------|-----------------------------|----------------|---|
| H5N1 | Hong Kong | 1997 | 18 flu cases; 6 deaths |
| H9N2 | China | 1999 | Two nonfatal flu cases in children |
| H7N2 | Virginia | 2002 | 1 asymptomatic case |
| H7N7 | The Netherlands | 2003 | 78 cases of conjunctivitis and 7 flu cases; 1 death |
| H5N1 | Hong Kong and China | 2003 | 2 flu cases; 1 death |
| H5N1 | Thailand, Vietnam, Cambodia | 2003–June 2005 | 88 flu cases; 50 deaths |
| H9N2 | Hong Kong | 2003 | 1 nonfatal flu case |
| H7N2 | New York | 2003 | 1 nonfatal flu case |
| H7N3 | Canada | 2004 | Conjunctivitis |

Asia, in areas that account for about one third of the global human population.

Influenza scientists have been predicting another pandemic for years. It is believed not to be a question of whether a pandemic will occur but when, and H5N1 has made these predictions particularly worrisome. Efforts to prepare for a global pandemic of H5N1 have included the use of reverse genetics to produce seed virus for a live-virus vaccine (11). This vaccine is currently in human trials, although there is some concern that the necessary studies of safety and efficacy may require an extended amount of time. Consequently, the virus is likely to traverse the globe before the vaccine could be mass produced. Furthermore, earlier studies of candidate human H5 vaccines found that this hemagglutinin was a poor immunogen (12–14).

Oseltamivir and zanamivir, but not rimantadine or amantadine, are active against H5N1 in vitro and in animal models of influenza (15–17). However, clinical utility of these drugs for treatment or prevention of H5 disease has not been rigorously studied, the supply is inadequate for a global pandemic, and antiviral resistance occurs in N1-containing viruses during oseltamivir treatment (18).

How concerned should we be? As noted, a flu pandemic requires human-to-human transmission. This currently seems to be the Achilles' heel of H5N1. There is one apparently confirmed case (19), but to date, no human genes indicating reassortment have been detected in the analyses of H5N1 strains and sustained human-to-human transmission has not occurred. Indeed, some would speculate that, with this much disease in poultry over 9 years, if a pandemic were to happen it would have happened already (8). Also, some have reported serologic evidence of avian influenza antibodies (H5, H7, H10, and H11 strains) in 2% to 38% of humans, suggesting that bird flu infections involving multiple strains have gone on for years but have only recently been reported (3, 20, 21).

Despite these reassurances, we must not ignore the possibility of an H5N1 pandemic. Even if it does not materialize, the planning and development of effective interventions will provide the necessary preparations in the event that another avian strain jumps the species barrier (Table) or a known human pathogen like H2N2, to which large segments of the population lack immunity, re-emerges. One of the most important and relevant observa-

tions made in recent years is that the number of avian strains now recognized as human pathogens is relatively large (Table). Preparation for the next pandemic will enhance our ability to cope with annual epidemics and their substantial toll. Conversely, wider use of vaccines and antiviral drugs during the interpandemic period will provide the foundation for responding to the next pandemic. In this regard, greatly expanding national, health care institutional, and perhaps even personal stockpiles of antiviral agents makes good sense in the near term, especially until an immunogenic H5 vaccine for humans has been developed. The Infectious Diseases Society of America has recommended that the United States have sufficient oseltamivir to treat up to 50% of the population (22); at present, we are not even close to that goal.

The available evidence indicates that influenza A (H5N1) is enzootic in poultry in Asia and has caused influenza with an alarming mortality rate, mostly in young adults and children. If a pandemic were to occur, it could easily dwarf all previous epidemics, with mortality estimates ranging from 2 to 50 million (23). On the other hand, the virus may stay primarily in birds and cause only sporadic illness in people. But the defense prepared for H5N1 should have salutary benefits that extend far beyond the particular virus to cover pandemics or epidemics of other strains—events that seem to be unpredictable, as indicated by the recent experience with the severe acute respiratory distress syndrome (SARS) and West Nile virus.

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