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Planning for Avian Influenza

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Avian influenza, or influenza A (H5N1), has 3 of the 4 properties necessary to cause a serious pandemic: It can infect people, nearly all people are immunologically naive, and it is highly lethal. The Achilles heel of the virus is the lack of sustained human–human transmission. Fortunately, among the 124 cases reported through 30 May 2006, nearly all were acquired by direct contact with poultry. Unfortunately, the capability for efficient human–human transmission requires only a single mutation by a virus that is notoriously genetically unstable, hence the need for a new vaccine each year for seasonal influenza. Influenza A (H5N1) is being compared to another avian strain, the agent of the "Spanish flu" of 1918–1919, which traversed the world in 3 months and caused an estimated 50 million deaths. The question is if we are ready for this type of pandemic, and the answer is probably no. The main problems are the lack of an effective vaccine, very poor surge capacity, a health care system that could not accommodate even a modest pandemic, and erratic regional planning. It's time to get ready, and in the process be ready for bioterrorism, natural disasters, and epidemics of other infectious diseases.

In May 1997, a child in Hong Kong died of influenza. The case, in retrospect, seems to have been the first known human infection with influenza A (H5N1), or avian influenza. After 18 cases and 6 deaths in Hong Kong, this virus appeared to be controlled and possibly eradicated by the end of 1997. But it returned in 2003, and it has subsequently continued to evolve and spread. By May 2006, this virus had caused the deaths, from culling or infection, of more than 140 million domesticated birds in 153 countries and infections in 218 patients, with 124 deaths—a mortality rate possibly as high as 55% (1). The poultry infections extended from Asia to Africa, the Near East, Europe, and Eurasia; the human infections have been primarily in Asia but also in Turkey, Egypt, Iraq, and Azerbaijan.

Influenza experts have consistently warned that pandemic influenza is inevitable and historically has occurred at intervals of 11 to 42 years. The worst pandemic in recorded medical history was Spanish flu (H1N1) in 1918 and 1919. The last pandemic was Hong Kong flu (H3N2) 37 years ago in 1968 and 1969. The question now is whether avian influenza will be that next pandemic. The missing link to pandemic spread is lack of sustained person-to-person transmission. The H5N1 influenza virus could acquire property by mutational adaptation of the avian strain, as with the Spanish influenza, or by reassortment through dual infection with human and avian strains as occurred in 1957 (Asian influenza) and 1968 (Hong Kong influenza) (2). Analysis of H5N1 shows that it is avian, and nearly all cases have resulted from direct contact with poultry; human-to-human transmission has been reported but is rare. Those who are skeptical about an H5N1 pandemic point out that genetic changes to facilitate efficient person-to-person transmission are unlikely to occur by either mechanism, since the virus has not acquired this property during 10 years of existence. If they are right, H5N1 will remain primarily an avian pathogen that sporadically causes disease in people, with most cases occurring in those who have close contact with sick poultry.

Should we base our planning on this optimistic scenario? The problem for planners is that a pandemic like that of 1918 has unimaginable consequences, and yet we can't calculate its probability. Most people feel that we should plan for the worst. Complacency is not acceptable. Furthermore, if H5N1 proves to have a limited impact, the planning will improve our preparedness for a future pandemic influenza strain or even another public health disaster, such as SARS (severe acute respiratory syndrome), smallpox, or anthrax.

The experience with the 1918 pandemic influenza is the basis for planning for pandemic avian influenza. The rationale for this strategy is the clinical and virologic similarities between the 2 strains. The 1918 strain traversed the globe in 3 waves and caused an estimated 50 million deaths, including 675 000 in the United States. An unusual feature of the infection was the high mortality rate in healthy persons 15 to 35 years of age (1, 2). By contrast, the annual death toll in the United States for seasonal influenza is about 36 000, and most deaths occur in persons older than 85 years of age. Although some victims of the 1918 pandemic had bacterial pneumonia, most appeared to die of respiratory failure with a characteristic hemorrhagic alveolitis. Dr. Isaac Starr's graphic account of the typical 1918 case is reprinted in this issue: "As their lungs filled with rales the patients became short of breath and increasingly cyanotic. After gasping for several hours they became delirious and incontinent, and many died struggling to clear their airways of a blood-tinged froth that sometimes gushed from their nose and mouth" (3). This course with respiratory failure in young adults sounds similar to the Asian cases of avian influenza, except that many of the patients with avian influenza died despite access to antibacterial agents, antiviral agents, and ventilatory support (4, 5). Despite modern intensive care, the mortality rate for avian influenza is about 20-fold higher than that for the influenza of 1918. The 1918 pandemic and avian influenza also have virologic similarities. Analysis of the reconstructed 1918 pandemic influenza strain shows unusual similarities with H5N1, including the fact that both strains have genes of avian influenza viruses (2, 6, 7).

This issue contains 2 relevant articles on this topic. The first is a summary of the policy monograph of the American College of Physicians addressing the health care response to pandemic influenza (8). The second, quoted in the preceding paragraph, was originally published in *Annals* by Isaac Starr and is a riveting account of his experience as a medical student at the University of Pennsylvania working as a nurse during the 1918 pandemic (3). In this editorial, I describe some of the most important issues about planning for pandemic influenza and appraise the prospects for preparedness (3, 8).

Current planning assumptions are based largely on the anticipated experience if a virus comparable to the 1918 flu strain were to cause a pandemic now. The medical consequences would include the following: 1) The attack rate in the United States would be 30%, causing 90 million cases; 2) of those infected, about 50% would seek medical care; 3) the excess mortality would be 209 000 to 1 903 000 deaths; and 4) the outbreak in a community would last about 6 to 8 weeks.

What Could Be Done To Lessen the Impact of the Disease?

Aside from agricultural intervention to reduce the number of infected birds, the 3 major weapons for controlling person-to-person spread are vaccines, antiviral agents, and social distancing. The College's plan calls for an effective pandemic influenza vaccine (Positions 6 and 7), but several important obstacles stand in the way of success. We will need a vaccine that has a good antigenic match with the epidemic strain and a substantial increase in our vaccine production capacity. The initial attempt with an H5N1 vaccine ("1203 vaccine") required two 90-µg doses to produce a serologic response in about 50% of healthy adults (9). This inoculum is 12-fold greater than the dose for seasonal influenza, which indicates the extent of the challenge to our influenza vaccine production capacity. The worldwide production capacity for this vaccine would be enough to vaccinate a total of 75 million people, which is about one fourth of the U.S. population or 1.25% of the world population (10). Furthermore, using the current H5N1 vaccine as an example, only half of vaccinated healthy persons might be protected against the target virus. Finally, the target virus has already undergone antigenic change to a new clade (10). The College's recommendations for a vaccine supply adequate for the entire U.S. population are clearly not feasible now. The good news is that vaccine producers are pursuing promising new technologies. High-priority research developments include attempts to improve the volume of production with cell cultures, to reduce inoculum size with intradermal injections and use of adjuvants, and to use live attenuated viruses to get a better antigenic response. Thus, the vaccine gap, while large, may be temporary. However, we cannot predict when we will close this gap, nor do we know when we will need a vaccine against pandemic influenza.

Prophylaxis and treatment with neuraminidase inhibitors is another strategy to control pandemic influenza. Oseltamivir and zanamivir are about 60% effective in preventing seasonal influenza, but their effectiveness for preventing pandemic influenza is unknown (11). Clinical trials of neuraminidase inhibitors to treat seasonal influenza have shown modest benefit if therapy is started within the first 48 hours of symptoms (the earlier the start, the greater the benefit). Effectiveness against pandemic influenza is essentially unknown. Oseltamivir had no clear effect on reported avian influenza cases, but the evidence was not strong enough to draw any conclusions, especially since therapy was started late and the dose and duration of the standard treatment regimen may be inadequate for a pandemic strain (5). Despite concern about oseltamivir resistance, which has occurred with both seasonal influenza and avian influenza (12), oseltamivir-resistant strains are infrequent and are generally susceptible to zanamivir. In addition, oseltamivir-resistant strains show reduced fitness for both transmission and pathogenicity in mammalian models (13). The College calls for stockpiling anti-influenza agents in sufficient quantities for 25% of the population (Position 7), although the actual amount necessary could vary substantially depending on use (prophylaxis or therapy) and the dose and duration advocated. The good news is that the drugs' shelf life is 10 years; assuming that the virus remains sensitive, this supply should be good until 2016.

Social distancing appears to be paramount but is not completely understood. A recent model—based on analysis of the 1918–1919 influenza pandemic—estimates that in the United States, one third of transmissions will occur in the household, one third in workplaces and schools, and one third in the general community (14). The largest risk is having a household member with influenza, and one of the most effective containment strategies is early antiviral treatment of the index case and confinement to the home. Therefore, an important containment strategy in an influenza pandemic would use targeted antiviral agents combined with school and business closings (14). The highest priority would be rapid institution of antiviral treatment, preferably within 1 day of symptom onset, and administration of antiviral prophylaxis to exposed persons, especially household members. The antiviral component of this strategy would be vulnerable to infection with drug-resistant strains that retain transmissibility, similar to that of wild-type virus; to date, these strains have not been detected (14).

How Can Hospitals Prepare?

The U.S. health care system is fragmented, is financially distressed, operates with "just-in-time" supplies, and has minimal surge capacity. According to the American Hospital Association, the average proportion of open beds is 4% to 6% of total bed capacity (15), which means that a pandemic will quickly overwhelm hospitals, intensive care units, and emergency departments. A review of hospital preparedness for pandemic influenza by Dr. Thomas Inglesby of the University of Pittsburgh Medical Center for Biosecurity indicated that at its peak, an epidemic comparable to that of 1918 would require 197% of hospital beds, 461% of intensive care unit beds, and 198% of all available respirators (16, 17). The gap between our need for surge capacity in urban areas and our current resources is staggering. Planning to close the gap should occur at the regional level by local providers and public health authorities. The College endorses this strategy (Positions 1 and 8), and it is included in the U.S. Department of Health and Human Services's Pandemic Influenza Plan (18). However, federal funding is woefully inadequate.

Local planners must solve major logistical problems. Requirements include substantial increases in staffed bed capacity, protection for health care personnel, isolation rooms, ventilators, and pharmaceutical caches. Particularly important will be the plans for coordination of activities between hospitals: distribution of resources and patients, enhancement of surge capacity, and creation of a credible communication system for health care workers and the public. The challenge here is collaboration within health care systems and hospitals that are largely private, financially stressed, and historical competitors. Most regions have no administrative structure to plan, to raise money, or to require hospitals to do their share of capacity building.

Health care personnel issues are particularly important. A pandemic may require efficient methods of credentialing and providing liability protection for personnel imported from other states or recalled from retirement. It will also mean foresight in assembling the right mix of expertise. In his review of the 1918 pandemic, Dr. Starr noted a laryngologist "who seeing herpes labialis on a gasping cyanotic patient was much interested in it and prescribed application of guaiac" (3). The greatest need will be providers skilled in primary care, infection control, emergency medicine, pulmonary–critical care, and infectious diseases; nurses; respiratory therapists; pharmacists; and support personnel. However, as in 1918, it may be necessary to take anyone with medical training, including students and retired physicians.

The College's position paper appropriately emphasizes the need to spare hospitals and emergency departments from demands that other organizations could fulfill. Planners must make maximum use of nonhospital resources (such as shelters, schools, nursing homes, hotels, and civic centers) to deliver vaccine and antiviral agents and provide "fever clinics" and resources to deal with other outpatient medical care issues, as in New York City, which established a model program for rapid and efficient delivery of prophylactic antibiotics during the anthrax incident in 2001 (19).

What Are the Risks to Health Care Workers?

Caring for victims of an influenza pandemic will endanger health care workers. The risks involve exposure to H5N1, a virus to which unvaccinated people are considered universally immunologically naive. Health care workers and their families need to receive the highest priority for vaccination, assuming a vaccine exists, and for access to antiviral agents that are active against the epidemic strain. Health care workers should expect hospitals to provide optimal protection, and someone needs to take the lead to resolve the current controversy about the need for negative-pressure rooms and N95 masks or powered air-purifying respirators versus surgical masks.

What are the obligations of health care professionals to care for the sick at great risk to themselves? Historical experience on this point is varied. The Hippocratic Oath is silent on whether physicians are obliged to care for the sick. Many physicians, including Galen and Sydenham, are said to have fled patients with contagious epidemic diseases. But AIDS, SARS, and smallpox have focused attention on the duty to serve, and a consensus has emerged. The American Medical Association Code of Medical Ethics states "that a duty to serve overrides autonomy rights in societal emergencies, even in cases that involve personal risk to physicians" (20). Some states regard the obligation to treat during an emergency as a legal duty punishable by criminal sanctions for failure to act or for abandonment of patients. Some health care contracts specify that health care workers are required to provide services in emergencies. The moral obligation to treat seems obvious, but it has a possibly less obvious reciprocal obligation for institutions to provide maximum available protection, including antiviral agents, vaccines, personal protective equipment, and liability protection.

SARS was a recent prototypic example of an infection that had a high mortality rate and high risk for health care workers, who accounted for more than 20% of cases (21). The health care professions rose to this occasion, and few if any reports of failure to serve exist. A survey of 10 511 health care workers in Singapore during the SARS outbreak confirms this judgment: Seventy-six percent of respondents said that caring for patients with SARS involved great personal risk but was also simply part of their job. Forty-nine percent reported social stigmatization, and 31% reported ostracism by family members (22). The experience in Toronto indicated good participation by health care workers but also a substantial psychological impact (23).

Conclusions

The pandemic influenza of 1918–1919 was a punishing chapter in medical history, with a death toll higher than that of World War I. The potential effect of an avian influenza pandemic has been equated to that of a global tsunami. The United States is leading in the scientific effort to contain pandemic influenza with a vaccine and antiviral agents, although the initial efforts have been disappointing. The federal government has presented a public health plan, which the College has endorsed in general terms. The federal plan is quite similar to European plans in terms of surveillance, use of vaccines and antiviral agents, and implementation of travel restrictions and social distancing (24). One major difference is that the European plans are largely national, in contrast to the U.S. strategy of making operational planning a regional responsibility. The challenge in the United States will be to achieve a coordinated plan in a health care system that is unique among nations in the independence of each unit of service, has an incredibly large shortfall in surge capacity, and currently could not begin to manage the magnitude of the 1918 epidemic in Philadelphia as described by Isaac Starr.

The needs for pandemic influenza preparedness are extensive and expensive. Preparing to meet them will require a major scientific effort to modernize vaccine development, substantial expansion of in-country production capacity for development of antiviral agents and vaccines, effective surveillance systems in agriculture and people, and regional planning for catastrophic health crises. The part of this plan that appears most deficient is the last: regional planning that includes local leadership, surveillance, effective communication systems, methods to expand surge capacity, plans to maintain essential services, identification of health care priorities, and guidelines for care. Most communities haven't begun this work, at least not with an integrated regional plan. For this, there needs to be financial support, a timeline, and public accountability for meeting deadlines. Preevent planning is critical. Once pandemic flu strikes a community, it is likely to be over in 3 to 4 months.

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See also: The Health Care Response to Pandemic Influenza by the American College of Physicians and Influenza in 1918: Recollections of the Epidemic in Philadelphia by I. Starr.

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