The largest, most devastating outbreak of an infectious disease in modern history occurred in 1918, when a highly virulent influenza A (H1N1) virus spread throughout the world and killed between 20 million and 40 million people. Additional epidemics occurred in 1957 (H2N2) and 1968 (H3N2), both originating in Asia and each killing approximately 1 million people. These haunting memories have led to widespread concern about the ongoing outbreak of avian H5N1 influenza in Asia.

Certain parallels between the “Spanish flu” of 1918 and H5N1 justify this concern. Like the 1918 virus, H5N1 influenza has unusually high virulence and can capitalize on an absence of preexisting immunity in humans, at least in certain age groups. Although the two viruses differ in their transmissibility among humans, there is concern that currently circulating H5N1 viruses will evolve into a pandemic strain by adapting to humans through genetic mutation or reassortment with human influenza strains (see diagram). Although it seems that this has not yet occurred, recent studies have demonstrated continued evolution of the virus since the H5N1 outbreak in Hong Kong in 1997. The goose precursor virus of the H5N1 strains that caused that avian influenza outbreak has since evolved into a dominant pathogenic genotype, now endemic among poultry in Asia, with a host range that has expanded to include terrestrial poultry and wild birds. It is this genotype that is implicated in the recent human infections.

Other studies have shown that H5N1 viruses isolated between 1999 and 2002 seemed to acquire the ability to replicate in mammals, possibly as a result of transmission between ducks and pigs. The possibility that the host range of H5N1 has broadened to include mammals is supported by recent reports of H5N1 infections in cats and news reports about tigers in a Thai zoo that have become ill or died after eating raw chicken. In comparison, studies of the 1918 strain indicate that the hemagglutinin protein, although avian in origin, preferentially bound to human receptors, suggesting that it circulated in humans or other species with human-like receptors (e.g., pigs) for long enough to develop this receptor preference. The broadening host range of H5N1 viruses and the recently reported H5N1 infection of pigs, combined with endemicity of contemporary human H3N2 viruses among pigs in southern China and the continuing occurrence of sporadic human H5N1 infections, are obvious concerns; it is possible that the current situation resembles the undocumented events that led to the 1918 pandemic.

Today, modern laboratory techniques, clinical and epidemiologic knowledge, and global communication provide the opportunity to monitor the evolving outbreak and act on it. However, in many of the countries affected by the H5N1 virus, access to these tools is still very limited, severely hampering the ability to track the emergence of pathogens. Despite the decimation of the poultry industry throughout much of Asia and initial optimism that the outbreak had been curbed, new cases of human H5N1 infection have been documented since our report of the first 10 patients. At the time of this writing, there have been a total of 44 proven human H5N1 infections, of which 32 have been fatal, and Cambodia, China, Indonesia, Laos, Malaysia, Thailand, and Vietnam have all reported H5N1 in their poultry. Although human infections have been documented only in Thailand and Vietnam, it seems likely that additional cases have occurred in other countries but have remained unrecognized because of a lack of clinical awareness or diagnostic facilities.

On the basis of the current figures for the reported cases, the mortality associated with human H5N1 infection is remarkably high — 72 percent, as compared with an estimated 2.5 percent for Spanish influenza. However, it is uncertain whether milder cases of human H5N1 infection have occurred. If so, this would be further evidence of the potential for the virus to adapt to humans. Insight into the full clinical spectrum of the illness in humans is critical but requires sustained surveillance, which is not feasible in most affected countries, owing to technical, logistic, and financial constraints. Such surveillance would also yield epidemiologic and virologic data on circulating human influenza.
strains. The absence of such data in many of the affected countries precludes assessment of the risk of reassortment, as well as rational decision making concerning the possibility of vaccinating people against prevailing human influenza strains in an effort to prevent reassortment. Finally, active surveillance in animals and humans would permit close monitoring of the evolution of the current H5N1 viruses, as well as early recognition of other potentially threatening avian viruses.

Fortunately, there has been no direct evidence of efficient poultry-to-human or human-to-human transmission to date. That there have been relatively few cases in humans despite huge numbers of infected poultry seems reassuring. The only documented case of probable human-to-human transmission involved prolonged, unprotected, intimate exposure to a child who was dying of unconfirmed but highly suspected H5N1 infection. Such transmission underscores the importance of infection-control measures in cases of suspected avian influenza. The absence of other secondary cases and the absence of substantial genetic changes in the virus in this case are reassuring, as is the absence of reported illnesses among health care workers involved in the care of patients with H5N1 infection.

In 1997, the H5N1 outbreak in Hong Kong was controlled through the killing of all poultry, a strategy that may prove less successful in the current outbreak, since it is much more extensive and most of the countries involved are less well developed. Furthermore, the potential role of wild birds in maintaining and spreading the virus may be a complicating factor. H5N1 vaccination may be essential for effective control but would require global efforts to ensure sufficient production of vaccine and to address important economic issues related to vaccination (the cost of vaccination and the potential loss of export markets for poultry that tests positive for H5N1 after vaccination).

Long-term solutions for preventing or adequately managing future problems deserve urgent attention. In the era of global travel, the time available for instituting effective public health mea-
Avian Influenza — A Challenge to Global Health Care Structures

PERSPECTIVE

Rationing Influenza Vaccine

Thomas H. Lee, M.D.

It was two days after the presidential election and only a week after the Red Sox won the World Series, but all anyone could talk about at my Boston hospital was influenza shots. I saw 12 outpatients and 1 inpatient that Thursday morning, and all but one asked whether they could get the influenza vaccine. I told them all no. Our hospital, which logged more than 200,000 outpatient visits for primary

sures during an outbreak will be very limited. One of the key lessons of the current H5N1 outbreak is the importance of having in each country the clinical, scientific, and technical capacity to identify a problem and the knowledge necessary to respond to it. Notwithstanding the crucial role played by international and regional centers of excellence in coordinating surveillance and defending against global pandemics, it is people on the ground in affected countries who need to have the necessary infrastructure at their immediate disposal to respond quickly to rapidly evolving epidemics.

In response to the 1997 outbreak, surveillance for influenza in poultry in Hong Kong has been intensified, permitting early recognition of outbreaks of other avian influenza strains; together with other preventive measures, such surveillance has helped to keep Hong Kong free of H5N1 in 2004. This response may serve as a model for currently affected countries, but wider implementation of Hong Kong’s approach will require a global effort.

There are also strong arguments against the artificial separation of the people and institutions that deliver clinical care and those that monitor public health. We believe that uniting these structures in single institutions would enhance cooperation and encourage the interchange of information. In addition, people and countries should be encouraged, through reasonable compensation schemes, to report potential epidemics promptly and honestly.

Few countries or regions in the developed or developing world have responded optimally to recent epidemics and health scares. The continued circulation of H5N1 in poultry in Asia, with sporadic transmission to humans, suggests that we are far from controlling the current epidemic. It is probable that the next influenza virus capable of causing a global pandemic will arise and spread from a developing country in Asia. Further investment in health care infrastructure and consideration of new paradigms for public health are required to address the emergence of such threatening diseases. Considering the potential death toll of a 1918-like influenza pandemic, such collective global investments must be a top priority.

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